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Targeting integrin pathways: mechanisms and advances in therapy

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Integrins are considered the main cell-adhesion transmembrane receptors that play multifaceted roles as extracellular matrix (ECM)-cytoskeletal linkers and transducers in biochemical and mechanical signals between cells and their environment in a wide range of states in health and diseases. Integrin functions are dependable on a delicate balance between active and inactive status via multiple mechanisms, including protein-protein interactions, conformational changes, and trafficking. Due to their exposure on the cell surface and sensitivity to the molecular blockade, integrins have been investigated as pharmacological targets for nearly 40 years, but given the complexity of integrins and sometimes opposite characteristics, targeting integrin therapeutics has been a challenge. To date, only seven drugs targeting integrins have been successfully marketed, including abciximab, eptifibatid, tirofiban, natalizumab, vedolizumab, lifitegrast, and carotegrast. Currently, there are approximately 90 kinds of integrin-based therapeutic drugs or imaging agents in clinical studies, including small molecules, antibodies, synthetic mimic peptides, antibody–drug conjugates (ADCs), chimeric antigen receptor (CAR) T-cell therapy, imaging agents, etc. A serious lesson from past integrin drug discovery and research efforts is that successes rely on both a deep understanding of integrin-regulatory mechanisms and unmet clinical needs. Herein, we provide a systematic and complete review of all integrin family members and integrin-mediated downstream signal transduction to highlight ongoing efforts to develop new therapies/diagnoses from bench to clinic. In addition, we further discuss the trend of drug development, how to improve the success rate of clinical trials targeting integrin therapies, and the key points for clinical research, basic research, and translational research.

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INTRODUCTION

Integrins have emerged as cell adhesion transmembrane receptors that serve as extracellular matrix (ECM)-cytoskeletal linkers and transduce biochemical and mechanical signals between cells and their environment in a wide range of states in health and diseases since their discovery in the 1980s^{1–3} (Fig. 1). In mammals, each integrin heterodimer comprises an α -subunit and a β -subunit in a noncovalent complex, and 18 α - and 8 β -subunits create 24 functionally distinct heterodimeric transmembrane receptors.⁴ Each α or β subunit contains a large ectodomain, a single-span helical transmembrane domain, and a short cytosolic tail, with the exception of $\beta 4$.⁵ The majority of integrin heterodimers contain the $\beta 1$ subunit and αv subunit. The $\beta 1$ subunit can form heterodimeric complexes with 12 α -subunits, but $\beta 4$, $\beta 5$, $\beta 6$, and $\beta 8$ only interact with one α -subunit. Most α -subunits only form one kind of complex with one β -partner, while $\alpha 4$ and αv interact with more than one β -partner, including $\alpha 4\beta 1$, $\alpha 4\beta 7$, $\alpha v\beta 1$, $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 6$, and $\alpha v\beta 8$.

The “integrin” terminology originates from its function as the integral membrane protein complex bridging the ECM to the cytoskeleton.⁶ The first integrins discovered were isolated based on their binding ability to fibronectin.¹ Typically, integrins can interact with a plethora of ECM proteins, and most of them

contain small peptide sequences as integrin recognition motifs.^{7,8}

The targeting integrin sequences can be as simple as the Arg–Gly–Asp (RGD) or Leu–Asp–Val (LDV) tripeptides or more complex as GFOGER peptide.^{9–11} According to the different binding characteristics of integrins, integrins can be divided into four types: leukocyte cell-adhesion integrins, RGD-binding integrins, collagen (GFOGER)-binding integrins, and laminin-binding integrins.¹² Classically, there are eight members in the RGD-binding family of integrins: $\alpha v\beta 1$, $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 6$, $\alpha v\beta 8$, $\alpha 8\beta 1$, $\alpha 5\beta 1$, and $\alpha 11\beta 3$. The RGD peptide is the common binding motif of these RGD-binding integrins in the ECM (e.g., fibronectin, osteopontin, vitronectin, and fibrinogen).¹³ Leukocyte cell-adhesion integrins consist of eight members, including $\alpha 4\beta 1$, $\alpha 9\beta 1$, $\alpha L\beta 2$, $\alpha M\beta 2$, $\alpha X\beta 2$, $\alpha D\beta 2$, $\alpha 4\beta 7$, and $\alpha E\beta 7$. Integrins $\alpha 4\beta 1$, $\alpha 4\beta 7$, $\alpha 9\beta 1$, and $\alpha E\beta 7$ also recognize short specific LDV peptide sequences, and an LDV motif is also present in fibronectin. $\beta 2$ is the most common integrin that mediates leukocyte adhesion and migration, which is characterized by sites within ligands that are structurally similar to the LDV motif.¹⁴ The four collagen-binding integrins ($\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$, and $\alpha 11\beta 1$) recognize the triple helical GFOGER sequence in the major collagens, but their binding ability *in vivo* depends on the fibrillar status and the accessibility of interactive domains.¹² Four non- αI domain-containing laminin-

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Historical milestone for the discovery of integrins and their crucial inhibitors

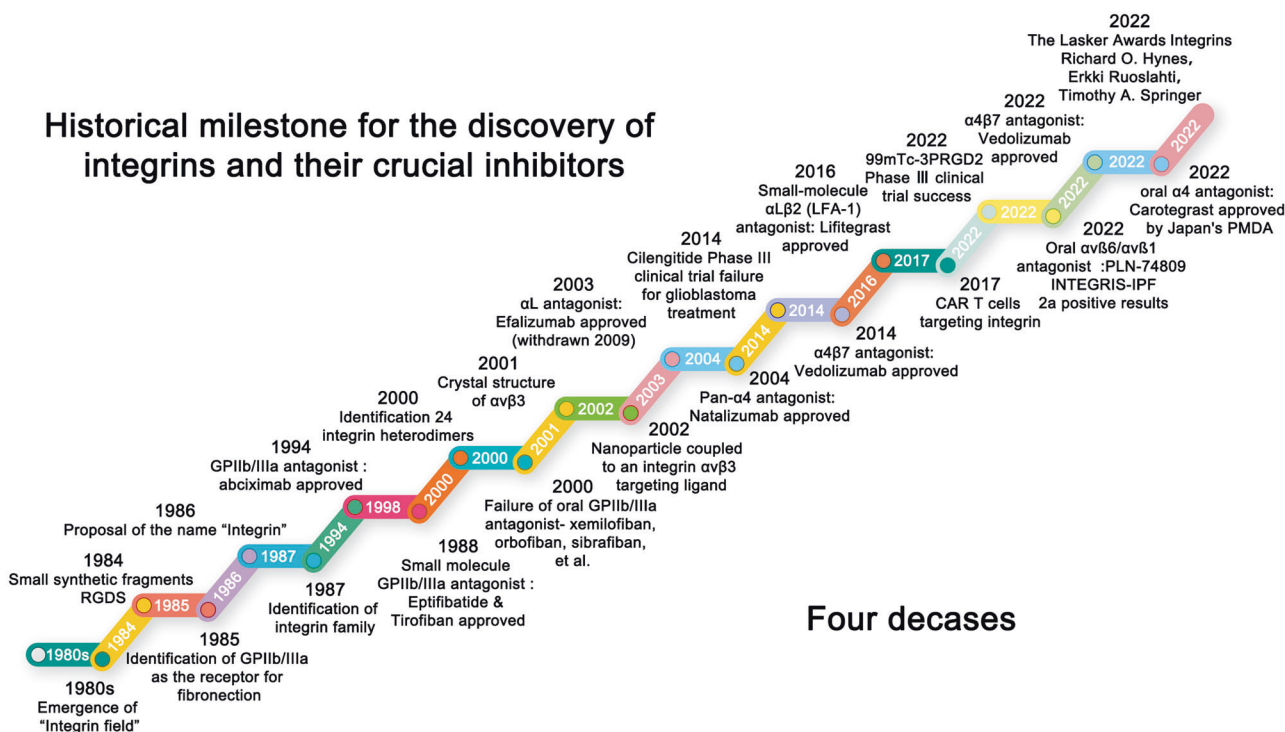


Fig. 1 Timeline of the historical milestone for the study of integrin receptors and their main antagonists and agents in the past four decades

binding integrins ($\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 7\beta 1$, and $\alpha 6\beta 4$) can bind with laminins. In addition, three α I domain-containing integrins ($\alpha 10\beta 1$, $\alpha 2\beta 1$, and $\alpha 1\beta 1$) can form a distinct laminin/collagen-binding subfamily. The expression of these integrin isoforms is tissue-specific and developmentally regulated; however, a full understanding of their role is still lacking. Beyond classical ECM mediators, integrins are also reported to interact with a diversity of non-ECM proteins on the surfaces of prokaryotic, eukaryotic, and fungal cells, as well as a range of viruses.^{15,16} In addition, integrins can also be exploited as cell-surface receptors for growth factors, hormones, and polyphenols.¹⁷

The wide range of ECM and non-ECM molecules makes integrins integral mediators of cell biology in mass. Integrin functions are dependable on a delicate balance between active and inactive status via multiple mechanisms, including protein-protein interactions, conformational changes, and trafficking.⁴ These processes are triggered through “inside-out” signals and “outside-in” signals, resulting either from interacting with proteins such as α -actinin, talin, vinculin, and paxillin to the cytoplasmic β -integrin tail or from binding to ECM ligands and recruiting adhesion complexes.^{18,19} Upon adhesion, cytoskeletal proteins are linked to the integrin β -subunit cytoplasmic tail.²⁰ Most integrin adhesion complexes (IACs) include focal adhesions (FAs), fibrillar adhesions, immunological synapses, and podosomes.²¹ The primary intracellular downstream signaling mediators of integrins refer to focal adhesion kinase (FAK), Src-family protein tyrosine kinases, and integrin-linked kinase (ILK).²² Integrins transduce mechanical and biochemical signals to promote cell proliferation, adhesion, spreading, survival, and ECM assembly and remodeling.

Due to their exposure on the cell surface and sensitivity to molecular blockade, integrins have been investigated as pharmacological targets for nearly 40 years, and a certain amount of current efforts involving integrin therapeutics continues to surprise (Fig. 1). In 2022, the Lasker Prize in Medicine was awarded to Richard Hynes, Erkki Ruoslahti, and Timothy Springer for groundbreaking research in the discovery of integrins, which aroused great concern about the field of integrins. The integrin

discovery history started in the 1980s. The first identification of integrin family member is α IIb β 3, and the first integrin-targeting drug was Abciximab, approved in 1994 as an α IIb β 3 antagonist.²³ Intravenous α IIb β 3 inhibition has been a major success in the treatment of coronary artery disease, but current oral α IIb β 3 antagonists have failed to achieve endpoints but potentially induce a direct toxic effect with prothrombotic mechanisms.²⁴ In 2003, a nanotherapeutic agent, a nanoparticle coupled to an α v β 3-targeting ligand for delivering genes, was first reported to selectively target angiogenic blood vessels in tumor-bearing mice.²⁵ In 2003, the α L antagonist Efalizumab was approved but withdrawn in 2009 due to the adverse effect of progressive multifocal leukoencephalopathy. In 2004, the pan- α 4 antagonist natalizumab was approved for multiple sclerosis. Then, there is a real gap in the market for targeting integrins. The failure of cilengitide in clinical trials on glioblastoma treatment had a huge impact on targeting α v-integrin drug discovery.²⁶ To date, there are no approved drugs targeting α v-integrin. In 2014 and 2016, vedolizumab and lifitegrast, targeting α 4 β 7 and α L β 2 for the treatment of inflammatory bowel disease and dry eye disease, respectively, were approved. In 2017, CAR T cells targeting integrin were investigated.²⁷ In 2022, there will be a large breakthrough targeting integrin, including the phase III clinical trial success of the 99m Tc-3PRGD2 imaging agent, the approval of Carotegrast, as the first oral anti-integrin drug, by Japan’s Pharmaceuticals and Medical Devices Agency (PMDA), and the phase IIa positive results of the oral α v β 6/ α v β 1 antagonist PLN-74809. To date, the U.S. Food and Drug Administration (FDA) has approved a total of seven drugs targeting integrins.²⁸ Currently, there are approximately 90 kinds of integrin-targeting therapies in clinical trials, including integrin antagonists and imaging agents, including small molecules, antibodies, synthetic mimic peptides, antibody-drug conjugates (ADCs), CAR T-cell therapy, imaging agents, etc. A serious lesson from past integrin drug discovery and research efforts is that successes rely on both a deep understanding of integrin-regulatory mechanisms and unmet clinical needs.

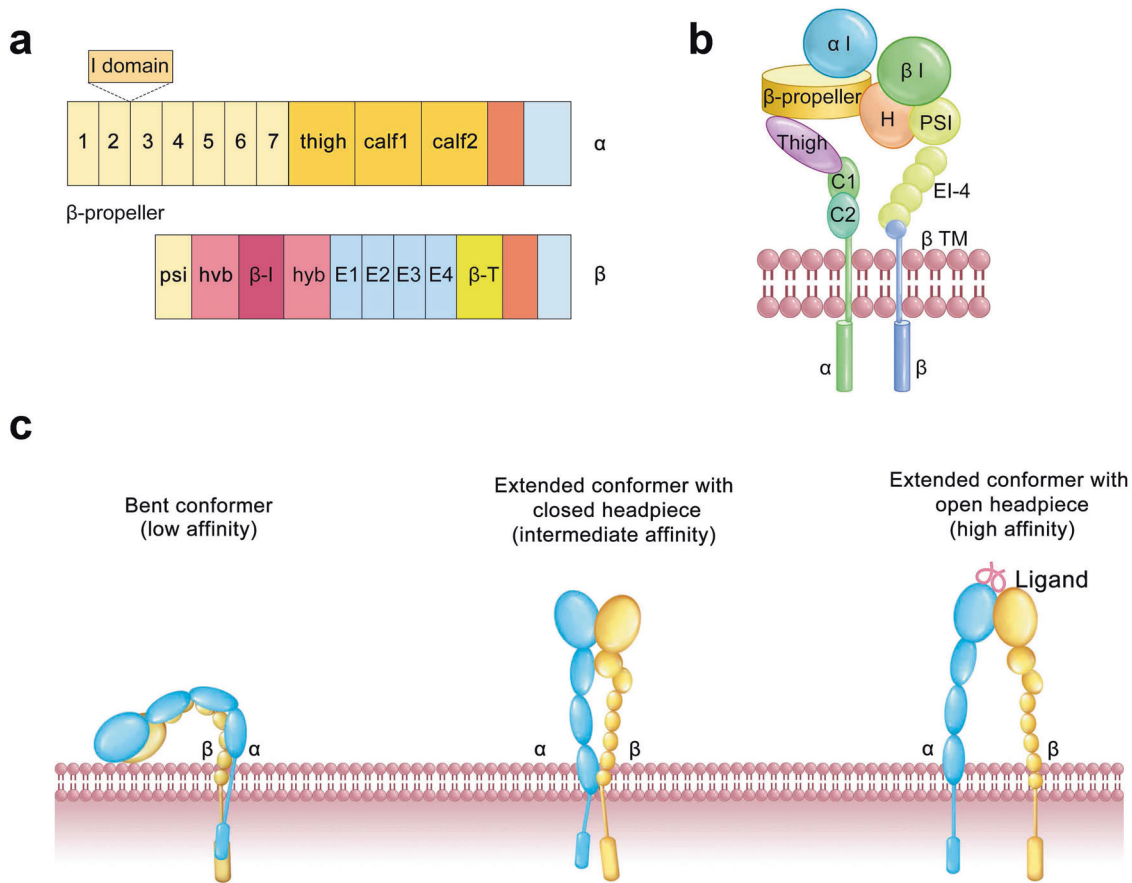


Fig. 2 The primary structure and representative conformations of integrins. **a** Organization of domains within the primary structures. **b** Arrangement of domains within the representative 3D crystal structure of integrins. **c** Conformational change of integrins: bent closed, extended–closed, and extended open conformations

Several recent reviews have analyzed the details of both biochemical and mechanical integrin regulation, integrin structure, integrin roles in cancer and fibrosis disease, RGD-binding integrin drug discovery, especially small-molecule inhibitors of the α_v integrins, the mechanism of endocytosis, exocytosis, intracellular trafficking, and mechanotransduction.^{3,4,28,29} Herein, we attempt to provide a systematic and complete review of all integrin family members and integrin-mediated downstream signal transduction to highlight ongoing efforts to develop new therapies/diagnoses. Furthermore, we also provide insight into the trend of drug development, how to improve the success rate of clinical trials of integrin-targeting therapies, and the key points for clinical research, basic research, and translational research.

STRUCTURE AND FUNCTION OF THE INTEGRIN FAMILY

Since the crystal structure of $\alpha_v\beta_3$ was available in 2001, conformational changes in integrin ectodomains have been illustrated. The ectodomain of an α -subunit contains four extracellular domains: a seven-bladed β -propeller, a thigh, and two calf domains (Fig. 2a, b). The common structure of different α -subunits present in their extracellular domain are seven repeat motifs, which fold into a seven-bladed propeller structure on the upper surface, and on the lower surface of blades 4–7, divalent cation-binding sites are located (Fig. 2a, b). Half of the integrin α subunits (i.e., α_1 , α_2 , α_{10} , α_{11} , α_D , α_X , α_M , α_L) contain a domain of 200 amino acids, known as the inserted (I) domain or α_A domain, which is located between blades 2 and 3 of the β propeller. Integrins with an α I domain bind to ligands through this domain.³⁰ The structure of an α I domain contains a metal ion-

dependent adhesion site motif (MIDAS), which is the major ligand-binding site.³¹

The crystal structure of the α I domain suggests three distinct conformations, termed bent closed, extended–closed, and extended open conformations³² (Fig. 2c). They differ not only in the coordination of the metal in the MIDAS but also in the arrangement of the $\beta F-\alpha 7$ (F/ $\alpha 7$) and the disposition of the $\alpha 1$ and $\alpha 7$ helices.^{32,33} In the active state of the α I domain, a C-terminal glutamate from the α I domain ligates the β I MIDAS and further stabilizes the high-affinity conformations.³⁴ The ectodomain of the β -subunit comprises seven domains with complex domain insertions (Fig. 2a, b): a β I domain with insertion in the hybrid domain, plexin-semaphorin-integrin (PSI), four cysteine-rich epidermal growth factor (EGF) modules, and a beta-tail domain (β TD) domain.³⁵ The integrin β subunit I domain is homologous to the α I domain. Resting integrins exist in a bent–closed conformation, which is unable to bind ligand, and Integrins can extend and form a high-affinity conformation with an open headpiece.^{36,37} The open headpiece conformation is induced with binding ligands, and this activated state possesses a high binding affinity. Ligand binding further provides the energy for conformational change triggering outside-in signaling. In addition, for induction of the high-affinity state, the open headpiece conformation could be produced artificially by mutations.³⁸ For example, it was reported that mutations in β TD residues in CD11b/CD18 integrins could lead to constitutive activation and outside-in signaling responses.³⁵

All α I domain-less integrins bind to the ligand directly using a binding pocket that is formed by the β -propeller/ β I domain interface.²¹ In this ligand-binding pocket, three divalent metal ion-

binding sites are concentrated on the ligand-binding sites of the β I domain in a linear arrangement.³⁹ The middle site, like the α I domain, called MIDAS, whose metal ion directly coordinates the side chain of the acidic residue characteristic of the integrin ligands, and the two outer sites, adjacent metal ion-dependent binding site (ADMIDAS) and ligand-associated metal binding site (LIMBS) or synergistic metal ion-binding site (SyMBS),^{40,41} can also bind Mn^{2+} , Mg^{2+} and Ca^{2+} , sharing some coordinating residues in common with MIDAS.^{42–44} The divalent metal cation on MIDAS is essential for the binding of integrin ligands. Some studies have shown that after the metal ions in MIDAS are removed by residue mutations, the ligand fails to bind to integrins, which suggests that MIDAS is critical for coordination and binding.⁴³

The first crystal structure of $\alpha v\beta 3$ bound to a mutant of fibronectin revealed the structural basis underlying pure antagonism, a central π - π interaction between Trp1496 in the RGD-containing loop of the high-affinity form of the 10th type III RGD-domain of fibronectin (FN) (hFN10) and Tyr122 of the $\beta 3$ -subunit that blocked conformational changes triggered by a wild-type form (wtFN10) and trapped hFN10-bound $\alpha v\beta 3$ in an inactive conformation.⁴⁵ Then, the cyclic peptide CisoDGRC and small-molecule antagonists of $\alpha IIb\beta 3$ and $\alpha v\beta 3$ were reported to retain high affinity without apparently inducing the conformational change in $\alpha v\beta 3$ by the same mechanism, interacting with $\beta 3$ Tyr122 on the $\beta 1$ - $\alpha 1$ loops and preventing its movement toward MIDAS, which is a key element in triggering conformational change.^{46–48} Recently, Lin et al.⁴⁹ proposed that the water molecule between the Mg^{2+} ion and the MIDAS serine side chain is also important for the integrin conformational change, and expulsion of this water is a requisite for the transition to the open conformation. Therefore, direct evidence for distinct functional roles for conformational change is still acquired for integrin-targeting drug development.

RGD-binding integrins

RGD-binding integrins refer to a class of integrins that bind with the tripeptide motif Arg–Gly–Asp in ECM proteins, including $\alpha v\beta 1$, $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 6$, $\alpha v\beta 8$, $\alpha 5\beta 1$, $\alpha 8\beta 1$, and $\alpha IIb\beta 3$ ^{50,51} (Fig. 3).

Integrin $\alpha v\beta 1$ primarily binds with transforming growth factor- β (TGF- β), fibronectin, osteopontin, and neural cell-adhesion molecule L1.⁵² In fibroblasts, such as hepatic stellate cells and pulmonary fibroblasts, integrin $\alpha v\beta 1$ -induced TGF- β activation is important in ECM accumulation.^{53,54} It also mediates the adhesion of osteoblasts to connective tissue growth factor, which induces cytoskeleton reorganization and cell differentiation.⁵⁵ Recently, integrin $\alpha v\beta 1$ was identified as a regulator that mediates the vascular response to mechanical stimulation.⁵⁶

Integrin $\alpha v\beta 3$ is one of the earliest integrins to be studied. Because of its specific binding with vitronectin, integrin $\alpha v\beta 3$ was originally called the vitronectin receptor. However, further studies found that integrin $\alpha v\beta 3$ also binds with many other ligands, such as TGF- β , fibronectin, osteopontin, neural cell adhesion molecule L1, fibrinogen, von Willebrand factor, thrombospondin, fibrillin, and tenascin.⁵² It is widely expressed in mesenchyme and blood vessels, smooth muscle cells, fibroblasts, and platelets.⁵⁷ Integrin $\alpha v\beta 3$ participates in angiogenesis, ECM regulation, vascular smooth muscle cell migration, and osteoclast adhesion to the bone matrix.⁵⁷ In addition, integrin $\alpha v\beta 3$ expressed in leucocytes participates in regulating monocyte, macrophage, and neutrophil migration and dendritic cell and macrophage phagocytosis, which regulates inflammation progression.^{58,59}

Integrin $\alpha v\beta 5$ binds with TGF- β , osteopontin, vitronectin, bone sialic protein, thrombospondin, and nephroblastoma overexpressed (NOV, also known as CCN3).⁵² Integrin $\alpha v\beta 5$ -induced TGF- β activation is involved in various physiological processes, such as wound healing mediated by myofibroblasts,⁶⁰ matrix molecule synthesis by airway smooth muscle,⁶¹ and type I procollagen expression in skin fibroblasts.⁶² The binding of

integrin $\alpha v\beta 5$ with vitronectin is essential for cerebellar granule cell precursor differentiation by regulating axon formation.⁶³ In addition, integrin $\alpha v\beta 5$ is highly expressed in mature intestinal macrophages and mediates macrophage phagocytosis of apoptotic cells.^{64,65}

Integrin $\alpha v\beta 6$ primarily binds with TGF- β , fibronectin, osteopontin, and a disintegrin and metalloproteinase (ADAM).^{52,66} It is an important activator of TGF- β , which regulates innate immunity and anti-inflammatory surveillance in the lungs, junctional epithelium of the gingiva, skin, and gastrointestinal tract.^{67–69} In addition, it participates in the process of tooth enamel formation.⁶⁸ Studies have reported that $\beta 6$ subunit of $\alpha v\beta 6$ -integrin (ITGB6) knockout significantly increases the risk of emphysema,⁷⁰ causes hypomineralized amelogenesis imperfecta,⁷¹ promotes skin inflammation and hyperplasia,⁶⁸ and accelerates skin wound repair.⁷²

Integrin $\alpha v\beta 8$ is a receptor for TGF- β , which activates TGF- β signal transduction by binding with TGF- β .⁷³ Integrin $\alpha v\beta 8$ -mediated TGF- β activation is involved in regulating neurovascular development, immune cell recruitment and activation, and stem cell migration or differentiation (such as neuroblast chain and neural stem cell migration, nonmyelinating Schwann cell, and mesenchymal stem cell differentiation).⁷⁴

Integrin $\alpha 5\beta 1$ binds with numerous ligands, such as fibronectin, fibrinogen, fibrillin, osteopontin, and thrombospondin.⁷⁵ Owing to its diversity of ligands, integrin $\alpha 5\beta 1$ is involved in numerous physiological processes, including promoting cell migration,⁷⁶ invasion,⁷⁷ proliferation,⁷⁸ and aging.⁷⁹ The normal function of T cells is also inseparable from the participation of integrin $\alpha 5\beta 1$, which affects the inflammatory process. In addition, integrin $\alpha 5\beta 1$ is adverse for the formation of bone tissue, and upregulation of integrin $\alpha 5\beta 1$ causes the loss of bone tissue-forming capacity in adipose-derived stromal/stem cells.⁸⁰

Integrin $\alpha 8\beta 1$ binds with TGF- β , tenascin, fibronectin, osteopontin, vitronectin, and nephronectin.⁵² It is highly expressed in contractile cells, such as vascular smooth muscle cells, neuronal cells, and mesangial cells.⁸¹ Integrin $\alpha 8\beta 1$ functions as a cell migration regulator that promotes or inhibits cell migration according to the differentiated state of cells.⁸¹ It promotes the migration of cells that are not initially contractile (such as mesangial cells, vascular smooth muscle cells, and hepatic stellate cells) and inhibits the migration of cells that are differentiated for contractile function (such as neural cells).^{81,82}

Integrin $\alpha IIb\beta 3$ is primarily expressed in platelets and their progenitors.⁸³ It binds with fibrinogen, fibronectin, thrombospondin, vitronectin, von Willebrand factor, and so on.⁵² Integrin $\alpha IIb\beta 3$ plays a central role in maintaining platelet adhesion, spreading, aggregation, clot retraction, and thrombus consolidation, resulting in platelet activation and arterial thrombosis.⁸⁴

Leukocyte cell-adhesion integrins

Leukocytes constitutively express several types of integrins, including $\alpha 4\beta 1$, $\alpha 9\beta 1$, $\alpha L\beta 2$, $\alpha M\beta 2$, $\alpha X\beta 2$, $\alpha D\beta 2$, $\alpha 4\beta 7$, and $\alpha E\beta 7$ ⁸⁵ (Fig. 3). Among them, integrins containing the $\beta 2$ subunit are most abundant in leukocytes; therefore, integrin $\beta 2$ is also called a leukocyte integrin.⁸⁶

Leukocyte cell-adhesion integrins are primarily involved in the regulation of inflammation. When infection occurs, leukocytes, such as neutrophils, eosinophils, and basophils, are carried close to the site of infection by blood flow.^{87,88} Selectins expressed on leukocytes then bind with their ligands on vascular endothelial cells, which makes leukocytes adhere to the vascular endothelium and start fast rolling.⁸⁶ This process provides enough time for integrins to bind with their ligands. Integrins $\alpha L\beta 2$ (bound to intercellular adhesion molecule [ICAM]-1), $\alpha M\beta 2$ (bound to ICAM-2), and $\alpha 4\beta 1$ (bound to vascular cell-adhesion molecule [VCAM]-1) are activated, slowing the rolling of leukocytes.⁸⁶ As leukocytes stop in the vascular endothelium, active integrin $\alpha L\beta 2$ and $\alpha M\beta 2$

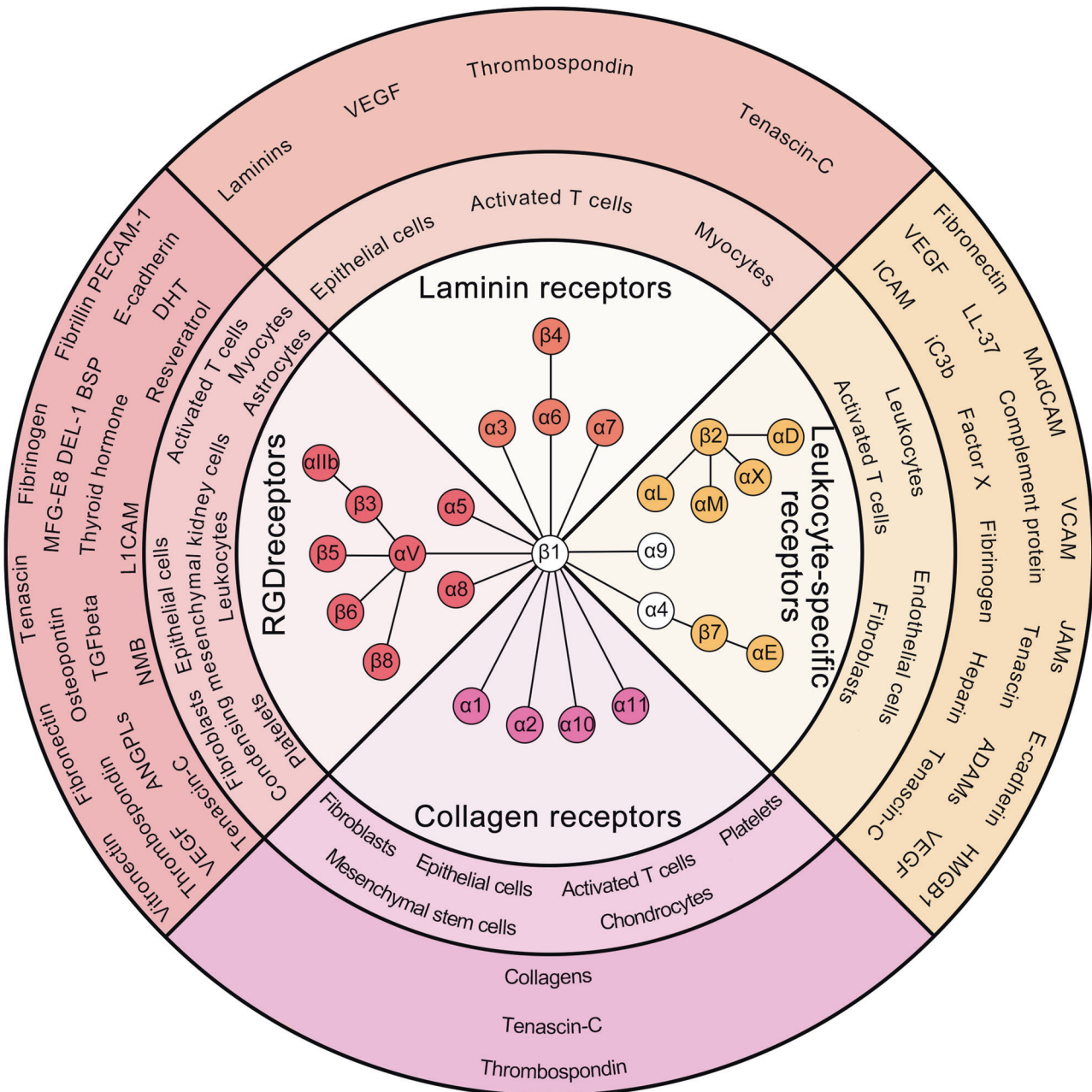


Fig. 3 Classification, distribution, and ligands of integrins. The inner ring shows the 24 integrins that are composed of 17 α subunits and 8 β subunits. They are divided into four categories, namely, RGD-binding integrins, leukocyte cell-adhesion integrins, collagen-binding integrins, and laminin-binding integrins, according to their distribution, ligand specificity, and functions. The middle ring shows the distribution of integrins in different cell types. The outer ring indicates the ligands bound by different types of integrins

induce leukocyte spreading and crawling toward infection.⁸⁹ Leukocytes that reach the site of infection cross the vascular endothelium and enter infected tissue with the participation of integrin $\alpha 6 \beta 1$, thereby mediating the inflammatory response.^{86,89} In addition, integrin $\alpha L \beta 2$ is also involved in enhancing the phagocytosis of bacteria by neutrophils.⁹⁰ It was reported that an integrin $\alpha L \beta 2$ antibody effectively inhibited the phagocytosis of *Streptococcus pyogenes* by neutrophils.⁹¹ Integrin $\alpha M \beta 2$ was proven to be important in neutrophil phagocytosis, reactive oxygen species (ROS) formation, neutrophil extracellular traps (NETs), apoptosis, and cytokine production, thereby regulating inflammation and defending against microbial infection.⁹⁰ Integrins $\alpha X \beta 2$ and $\alpha M \beta 2$ are homologous adhesion receptors that are expressed on similar types of leukocytes and share many

receptors.⁹² It plays a central role in regulating the anti-inflammatory function of macrophages.⁹² Deficiency of integrin $\alpha X \beta 2$ results in the loss of antifungal activity of macrophages by eliminating its recruitment and adhesion function⁹² and disturbs dendritic cell recruitment to the infection site.⁹³ Integrin $\alpha D \beta 2$ is highly homologous to integrin $\alpha M \beta 2$ and $\alpha X \beta 2$. It binds with ICAM-1, ICAM-3, and VCAM-1, thereby playing an important role in regulating inflammation and microbial infection.^{90,94} Integrin $\alpha E \beta 7$ is mainly expressed in lymphocytes of intestinal, lung, and skin epithelial tissues as well as in conventional dendritic cells of mucosa and dermis.⁹⁵ The interaction between integrin $\alpha E \beta 7$ and E-cadherin mediates lymphocyte attachment to intestinal and skin epithelial cells.⁹⁵ In human hematopoietic stem cells and progenitor cells, integrin $\alpha 1 \beta 9$ regulates cell

adhesion and differentiation in the endosteal stem cell niche, thereby regulating hematopoietic processes.⁹⁶ In addition, integrin $\alpha 1\beta 9$ is also involved in the regulation of cell adhesion and migration in numerous organs, such as the skin, liver, and spleen.⁹⁷ Integrin $\alpha 4\beta 7$ specifically binds VCAM-1 and mucosal address in cell-adhesion molecule-1 (MAdCAM-1) to regulate lymphocyte migration, which mediates the homing of lymphocytes to gut tissues.^{98,99}

Collagen (GFOGER)-binding integrins

Collagen-binding integrins refer to a class of integrins that bind with GFOGER-like sequences in collagen, including $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$, and $\alpha 11\beta 1$ ¹⁰⁰ (Fig. 3).

Integrin $\alpha 1\beta 1$ was first identified in activated T cells.¹⁰¹ It is also expressed in connective tissue cells (such as mesenchymal stem cells and chondrocytes) and cells that are in contact with basement membranes (such as smooth muscle cells, pericytes, and endothelial cells).¹⁰² Integrin $\alpha 1\beta 1$ binds with collagens I, III, IV, IX, XIII, XVI, and collagen IV chain-derived peptide arrest.^{102,103} In leukocytes, integrin $\alpha 1\beta 1$ functions as a promoter of T cells in inflammatory responses^{104,105} and mediates monocyte transmigration by binding with collagen XIII.¹⁰⁶ In bone, integrin $\alpha 1\beta 1$ plays an important role in damage repair processes. It has been reported that knockout of integrin $\beta 1$ (ITGB1) results in slowed proliferation of mesenchymal stem cells and inhibition of cartilage production, thereby hindering fracture healing and promoting osteoarthritis.^{107,108}

Integrin $\alpha 2\beta 1$ is expressed in fibroblasts, T cells, myeloid cells, megakaryocytes, platelets, keratinocytes, epithelial cells, and endothelial cells.^{100,109} Integrin $\alpha 2\beta 1$ binds with collagens I, III, IV, V, XI, XVI, and XXIII.¹⁰⁹ It also binds with lumican and decorin, which are proteoglycans.^{110,111} In platelets, integrin $\alpha 2\beta 1$ participates in stabilizing thrombi by binding with collagen I.^{112,113} In T helper cell 17, integrin $\alpha 2\beta 1$ cooperates with interleukin 7 receptor to mediate bone loss.¹¹⁴

Integrin $\alpha 10\beta 1$ is expressed in fibroblasts, chondrocytes, chondrogenic mesenchymal stem cells and cells lining the endosteum and periosteum.¹¹⁵ It primarily binds with collagens II and is essential in cartilage production and skeletal development.^{115,116} Integrin $\alpha 10\beta 1$ is regarded as a biomarker of chondrogenic stem cells.¹¹⁵ A previous study revealed that integrin $\alpha 10\beta 1$ deficiency resulted in cartilage defects and chondrodysplasia.¹¹⁷

Integrin $\alpha 11\beta 1$ is expressed in fibroblasts, mesenchymal stem cells, and odontoblasts.^{100,118} It is important in tooth eruption, wound healing, and fibrosis.^{119,120} The osteogenic differentiation of mesenchymal stem cells is driven by integrin $\alpha 11\beta 1$.¹²¹ Studies have shown that integrin $\alpha 11\beta 1$ deficiency results in incisor tooth eruption defects in mice.¹¹⁸ In addition, integrin $\alpha 11\beta 1$ also promotes myofibroblast differentiation, which accelerates dermal wound healing.¹¹³ Knockout of integrin $\alpha 11\beta 1$ reduced granulation tissue formation in mice.¹²²

Laminin-binding integrins

Laminin-binding integrins are a group of integrins that bind with laminins.¹²³ Laminins are macromolecular glycoproteins located in the ECM.¹²⁴ As the main component of the basement membrane, laminins play critical roles in regulating cell adhesion, proliferation, migration, and survival.¹²⁵ Laminins consist of various α , β , and γ subunits,^{126,127} which constitute 16 different laminin isoforms.^{126,127}

Integrins that have been identified as binding with laminins include $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 10\beta 1$, $\alpha 6\beta 4$, $\alpha 7\beta 1$, and $\alpha \nu \beta 3$ ^{128–130} (Fig. 3). Integrins $\alpha 1\beta 1$ and $\alpha 2\beta 1$ bind with the N-terminal domain of laminin $\alpha 1$ and $\alpha 2$ chains.^{131–133} Integrins $\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 6\beta 4$, and $\alpha 7\beta 1$ bind with the C-terminal domain of laminins.^{128,134} Integrin $\alpha \nu \beta 3$ binds with the L4 domain of the laminin $\alpha 5$ chain.¹²⁹ However, the physiological effects of the

binding of $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$, and $\alpha \nu \beta 3$ with laminins are very limited, so we generally classify integrins $\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 6\beta 4$, and $\alpha 7\beta 1$ as laminin-binding integrins.^{134,135} Integrins $\alpha 1\beta 1$, $\alpha 2\beta 1$, and $\alpha 10\beta 1$ have been classified as collagen-binding integrins, and integrin $\alpha \nu \beta 3$ has been classified as an RGD-binding integrin (as described above).

Integrin $\alpha 3\beta 1$ is mainly expressed in the lung, stomach, intestine, kidney, bladder, and skin.¹²⁵ It mainly binds with laminin-332 and laminin-511 to mediate cell adhesion to the basement membrane and cell-to-cell communication.¹²⁵ Studies have found that integrin $\alpha 3\beta 1$ plays a crucial role in the development of the brain, lung, liver, kidney, skin, muscle, and other organs.^{136–140} Deficiency in integrin $\alpha 3\beta 1$ causes symptoms such as skin blisters,¹⁴¹ disorganization of neurons in the cerebral cortex,¹⁴² fragmentation of the glomerular basement membrane,¹³⁹ and death in neonatal mice within 24 h of birth.¹³⁹

Integrin $\alpha 6\beta 1$ is primarily expressed in platelets, leukocytes, gametes, and epithelial cells.¹²⁵ Laminin-111, laminin-511, and laminin-332 are the most highly affiliative ligands.¹⁴³ In the brain, integrin $\alpha 6\beta 1$ may be involved in nervous system development.¹⁴⁴ In the ovary, the interaction of integrin $\alpha 6\beta 1$ with laminins could inhibit progesterone production, thereby regulating luteal formation and follicle growth.¹⁴⁵ Moreover, integrin $\alpha 6\beta 1$ in pericytes acts as a regulator of angiogenesis by controlling the structure of platelet-derived growth factor (PDGF) receptor (PDGFR) β and the basement membrane.¹⁴⁶

Integrin $\alpha 6\beta 4$ is expressed in subsets of endothelial cells, squamous epithelia, immature thymocytes, Schwann cells, and fibroblasts in the peripheral nervous system.^{147,148} Both laminins and epidermal integral ligand proteins are ligands of integrin $\alpha 6\beta 4$.¹²⁵ Integrin $\alpha 6\beta 4$ binds with laminins and mediates epithelial cell adhesion to the basement membrane, thus maintaining the integrity of epithelial cells.¹²⁵ In addition, integrin $\alpha 6\beta 4$ binds with bullous pemphigoid (BP) antigen 1-e (BPAG1-e) and BP antigen 2 (BPAG2) to form hemidesmosomes (HDs), where the extracellular domain of integrin $\alpha 6\beta 4$ binds with laminins and the intracellular domain of integrin $\alpha 6\beta 4$ interacts with the actin cytoskeleton. This structure links the intracellular keratin cytoskeleton to the basement membrane and plays a critical role in regulating the stability of epithelial cell attachment.^{149–151} In mice, integrin $\alpha 6\beta 4$ deficiency results in reduced skin adhesion properties and extensive exfoliation of epidermal and other squamous cells, accompanied by loss of HDs on the basement membrane of keratinocytes.^{147,149} These findings suggested that integrin $\alpha 6\beta 4$ might be involved in epidermolysis bullosa.^{149,152} In addition, integrin $\alpha 6\beta 4$ is also involved in cell death, autophagy, angiogenesis, aging and differentiation regulation and plays a regulatory role in cancer, respiratory diseases, and neurological diseases.^{153,154}

Integrin $\alpha 7\beta 1$ is mainly expressed in cardiac and skeletal muscles. It binds with laminin-211 and laminin-221 to mediate the binding of muscle fibers with myotendinous junctions. It has been found that integrin $\alpha 7\beta 1$ deficiency may be one of the important causes of congenital myopathy,¹⁵⁵ as integrin $\alpha 7$ (ITGA7) knockout mice develop muscular dystrophy.¹⁵⁶ In addition, integrin $\alpha 7\beta 1$ participates in vascular development and integrity. Studies have revealed that integrin $\alpha 7\beta 1$ deficiency causes abnormalities in the recruitment and survival of cerebral vascular smooth muscle cells, leading to vascular damage.¹⁵⁷

INTEGRIN-MEDIATED SIGNAL TRANSDUCTION

Inside-out signaling

Integrins act as adhesion and signaling receptors by bidirectionally transducing mechanotransduction and biochemical signals across the plasma membrane, which requires the engagement of extracellular ligands by the integrin extracellular domains and recruits additional adaptor, cytoskeletal proteins, and signaling

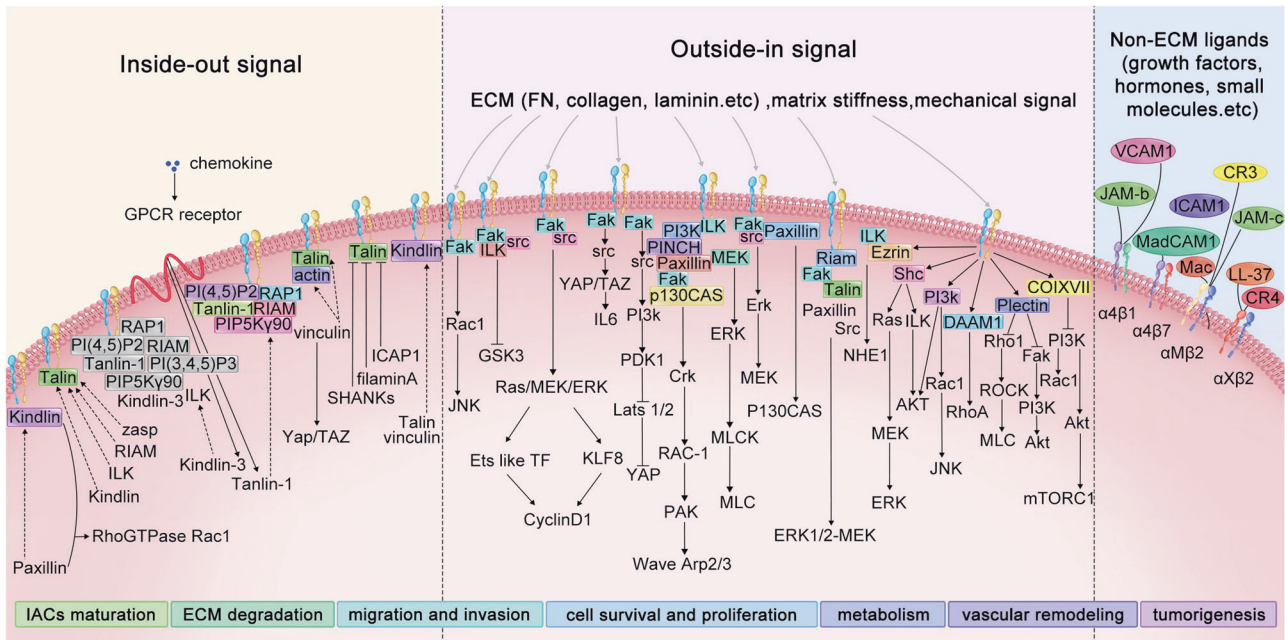


Fig. 4 Schematic overview of integrin activation-associated signaling cascades. Integrin activation is regulated by multiple external signals, such as ECM, mechanotransduction or signaling from non-ECM ligands, including growth factor receptors, hormones, and small molecules, which is termed the “outside-in” mechanism. ECM or non-ECM ligand binding and force application results in integrin clustering and initiates downstream signaling to the actin cytoskeleton through recruited talin and vinculin, where actin can simultaneously pull on integrins and further in turn promote force generation. The “outside-in” mechanism then triggers various signaling cascades that ultimately result in cell survival, proliferation, cell spreading, and even tumorigenesis and metastasis. On the plasma membrane, there is also an “inside-out” mechanism, which regulates the displacement of intracellular integrin inhibitors and allows talin or kindlin binding to integrin β -tails, controlling integrin affinity for ECM components. For example, in neutrophils, both Talin-1 and Kindlin-3 are rapidly recruited to activate $\beta 2$ integrins induced by extracellular chemokines binding to GPCR (G-protein-coupled receptor). Solid arrows indicate recruiting, and the solid blunt end arcs indicate inhibitory effects

molecules to their cytoplasmic tails.^{8,158} The 3D structure of integrins determines their functional state. There are three basic conformations for integrin: a bent conformation, a medium-affinity conformation, and a high-affinity conformation^{8,159} (Fig. 2c). Integrin activity corresponds to the integrin conformation: a bent conformation is associated with a ligand with low affinity, whereas a high affinity is associated with an extended conformation. In the bent conformation, both α and β subunits of the integrin are in a folded state, assuming a compact V-shaped conformation with the headpiece folded over the tailpiece, such that the ligand-binding site of the head is close to the proximal membrane end of both “legs”. The affinity of integrin for extracellular ECM and integrin-mediated downstream events are regulated by the dynamic equilibrium between these conformations. The bent conformation is commonly maintained by endogenous inhibitory proteins. For example, shank-associated RH domain-interacting protein (SHARPIN) in leukocytes and mammary-derived growth inhibitor (MDGI) suppress integrin activity by binding directly to the cytoplasmic tail of integrin α -subunit cytoplasmic tails.^{160,161} In addition, SHARPIN directly binds to integrin $\beta 1$ cytoplasmic tails, and kindlin-1 can significantly enhance this interaction.¹⁶² Integrin cytoplasmic-associated protein-1 (ICAP1) acts as an inhibitor of $\beta 1$ activation, which can be antagonized by Krev/Rap1 Interaction Trapped-1 (KRIT1).¹⁶³ Immunoglobulin repeat 21 of filamin A (FLNa-Ig21) not only binds directly to the integrin $\beta 3$ cytoplasmic tail but also interacts with the N-terminal helices of the $\alpha 11b$ and $\beta 3$ cytoplasmic tails to stabilize the bent conformation.¹⁶⁴

In contrast, integrin-binding adaptor proteins inside the cell, including talins (talin-1 and talin 2), kindlins (kindlin-1, kindlin-2, and kindlin-3), vinculin, paxillin, FAK, and others binding to the integrin cytoplasmic domain, trigger high-affinity extended integrin conformational changes. The extension of the

extracellular domain, the separation of heterodimeric subunits from transmembrane parts in the membrane, and the rearrangement of the $\alpha \beta$ interface in the ligand-binding domain release integrins from a compact bent conformation to an open conformation, and the ligand-binding affinity increases. Then, integrins may cluster into many different types of adhesive complexes. This activation multistep process is called activation or inside-out signaling,¹⁶⁵ while the signal transmission direction of outside-in is the opposite¹⁶⁶ (Fig. 4). Talin is a main focal adhesion binding protein that initiates inside-out signaling by disrupting the interactions of the α and β subunits, known as the inner membrane clasp.¹⁶⁷ The head of talin consists of binding sites for phosphoinositides, rap1 GTPases, F-actin, and attaches to a rod comprising binding sites for integrin, vinculin, actin, KANK, and others, many of which are mechanosensitive and can only be exposed by tensile forces.¹⁶⁸ The association of the transmembrane domain (TMD) of $\alpha 11b$ and $\beta 3$ is maintained by specific helical packing TMD interactions near the outer membrane clasp,¹⁶⁹ which could be disrupted by talin by altering the topology of the $\beta 3$ TMD.^{167,170} The direct experimental evidence suggested that talin binding to $\beta 3$ integrin could change the membrane embedding and therefore the topology of integrin $\beta 3$ TMD.¹⁷⁰ Proline-induced kink in $\beta 3$ -TMD could break the continuity of the helix and replace the inner membrane clasp interaction,¹⁶⁷ which exerts crucial effects on regulating the TMD topography. Similarly, proline-induced kink can also impair talin-mediated $\alpha 4 \beta 7$ activation.¹⁷¹ The $\beta 2$ cytoplasmic tail binding to talin-1 can induce a conformational change and result in a change in the angle of the $\beta 2$ TMD, which is further transmitted to the extracellular domain and leads to an extension conformation.¹⁷² Recent studies have indicated that introducing the proline mutation L697P kink into the $\beta 2$ TMD can completely affect the change in the extracellular domain of $\beta 2$ conformation and

prevent $\beta 2$ integrin extension. Talin-mediated integrin activation is sufficient for inside-out signaling, which could be interfered with by α -actinin in a type-specific way. α -actinin plays opposite roles in controlling the activation of $\alpha 1 \beta 3$ versus $\alpha 5 \beta 1$ integrin by regulating the conformation of TMD.¹⁷³ It was reported that α -actinin could impair integrin signaling by competing with talin for binding to the $\beta 3$ -integrin cytoplasmic tail and further inducing a kink in the TMD of $\beta 3$ -integrin, whereas it could promote talin binding to $\beta 1$ integrin by restricting cytoplasmic tail movement and reducing the binding entropic barrier.¹⁷⁴ Unlike talin binding to the membrane-proximal NPXY (Asn-Pro-x-Tyr) motif of the β subunit tail, kindlin binds to the membrane distal NXXY motif and facilitates the recruitment of the integrin-linked pseudo kinase-PINCH-parvin complex, paxillin and the Arp2/3 complex to integrins.²⁰ Kindlins seem to be regulated by oligomerization but not conformational autoinhibition,¹⁷³ while vinculin is an autoinhibited adaptor protein with multiple binding sites for other adhesion components, such as talin, IpaA, β -catenin, paxillin, PIP2, and F-actin. Activated vinculin is rapidly recruited to the actin-binding layer from a membrane-attached integrin signaling layer and recruits additional proteins.^{175,176} Paxillin is a key adaptor protein regulated by phosphorylation, which contains binding sites for adhesion, including parvin, Src, FAK, actopaxin, vinculin, talin, and ILK.¹⁷⁷ FAK is a cytoplasmic tyrosine kinase that is activated by disruption of an autoinhibitory intramolecular interaction and phosphorylates substrates such as paxillin, promoting additional protein docking sites regulating downstream events.¹⁷⁸ The “inside-out” pathway receives priming signals from adhesion molecules, chemokine receptors and other intracellular signals. Integrin activation involves various intracellular signaling proteins described above and with other proteins, including spleen tyrosine kinase (SYK), Bruton’s tyrosine kinase (BTK), phosphoinositide 3-kinase (PI3K), Rap1-interacting adaptor molecule (RIAM), and associated interacting adapter molecules, allowing subsequent downstream signal transduction.¹⁷⁹ For example, in neutrophils, chemokine attachment with G-protein-coupled receptors (GPCRs) causes heterotrimeric G-proteins to divide into G_{α} and $G_{\beta\gamma}$, which initiates phospholipase C (PLC) activation to activate calcium and DAG signals and then promotes PI (4,5) P2 binding to activated RAP1 and RIAM via the PKC-phospholipase D (PLD)-Arf6 axis. This process induces the recruitment of talin-1 and subsequently Kindlin-3 in combination with $\beta 2$ integrin.¹⁸⁰ Activated talin is recruited to the cell membrane and binds to induce integrin activation by stimulation with T-cell receptor (TCR) or chemokine receptors, which conduct receptor signaling to downstream cellular events such as migration and chemotaxis.¹⁸¹

Outside-in signaling

Transmembrane connections and mechanotransduction. Cell invasion and migration induced by integrin-mediated adhesion complexes are involved in disease states such as tumor metastasis, autoimmune diseases, and other important physiological processes.^{182–185} Before adhesion formation, integrins first form tiny clusters at the junction of the cell–ECM. This is sometimes due to the transverse interaction of certain integrins across the membrane domain. These formed and dissolved clusters are regulated by the cell microenvironment.¹⁸⁶ Through activation of specific integrin receptors, key adaptor, cytoskeleton and kinase assemble at the cell membrane to form adhesion complexes that transduce signals from the ECM to the interior of the cell. Following integrin activation, the protein complexes consisting of integrin, adaptors, scaffolding molecules, structural proteins, protein kinases, phosphatases, and GTPases are termed IACs.^{186,187} The proteomic differences between active and inactive IACs show a striking 64% similarity.¹⁸⁸ Active IACs have stable microtubules that participate in FA disassembly and inhibit their oligomerization. However, inactive IACs have a large number of Ras homology (Rho) and Ras

GTPase family proteins, which activate myosin contractility, promoting FA maturation.¹⁸⁹ Further analysis identified 60 core proteins in IACs, termed the “consensus adhesome”, comprising four potential axes viz. FAK-paxillin, ILK-PINCH-kindlin, α -actinin-zyxin-vasodilator-stimulated phosphoprotein (VASP), and talin-vinculin.^{6,22,190,191} However, Kank2-paxillin and liprin-b1-kindlin have been revealed as new associations. In parallel studies, Kank1 was localized to the periphery of mature IACs by binding talin, coordinating the formation of cortical microtubule stabilization complexes, including ELKS, liprins, kinesin family member 21A (KIF21A), LL5b and cytoplasmic linker-associated proteins (CLASPs), which in turn led to IAC instability.^{192,193} Thus, Kank proteins are also considered possible core adhesome components. IACs are heterogeneous without uniform standard definition. According to size, composition, lifetime, cellular distribution, and function, IACs have been classified as nascent adhesions, focal complexes, FAs, invadosomes (podosomes and invadopodia), and reticular adhesions.¹⁸⁷ Among them, FAs and FA-like structures are the most representative and well-studied. According to the different stages of cell adhesion to the ECM, classical FAs are preceded by focal complexes and followed by fibrillar adhesions with different molecular compositions.^{194–196} “Nascent adhesions” or “focal complexes” are the earliest FA-like structures visible under the light microscope and consist of fewer proteins, such as talin, paxillin, α -actinin and kindlin-2, than typical FAs.¹⁹⁷ The actin polymerizes in nascent adhesions cause retrograde actin flow, starting centripetal from the lamellipodium, which generates force in the opposite direction of the nascent adhesions triggering molecular events involving talin and vinculin that strengthen the integrin-cytoskeleton bonds leading to focal complex formation. This “molecular clutch” is essential for adhesion maturation and eventually cell migration and mechanotransduction.^{198–201} It should be noted that although myosin II is not required for the formation of adhesions, its contractility plays an important role in the maturation of the same.^{200,202}

The formation and maturation of FAs require the participation of various proteins in different physiological and pathological contexts. Cooperation between $\alpha v \beta 3$ and $\alpha 5 \beta 1$ integrins has been shown to play a role in FA maturation and cell spreading.²⁰³ The binding of Talin to cell membranes has been proven to be essential for integrin activation and FA formation.²⁰⁴ Talin, ILK, and the type Iy phosphatidylinositol 4-phosphate [PI(4)P] 5-kinase (PIP5K) play a role in polarized FA assembly.²⁰⁵ The binding of proteins such as paxillin, vinculin, VASP and zyxin to FAs depends on the orientation and locations of FAs.²⁰⁶ This means that FA composition is dynamic, depending on the cellular microenvironment and that many proteins are regulated by the phosphorylation pathway.^{189,198,207,208} As IACs mature, they either disassemble or undergo changes to their protein composition and signaling activity induced by force.^{209,210} In addition to adhesion to ECM ligands, non-ECM ligands or counterreceptors on adjacent cells, integrins serve as transmembrane mechanical junctions that contact the cytoskeleton inside cells from those extracellular.²¹¹

Mechanotransduction is known as the process by which cells sense mechanical stimuli and translate them into biochemical signals and is central to the processes, primarily myosin motors, which exert forces on actin filaments anchored to cell–cell or cell–matrix adhesions and mechanosensors. Mechanosensing interacts with tyrosine kinases, and other signaling pathways play a key role in cancer, cardiovascular diseases and other diseases.²¹² Integrin-ligand bonds and even all of the above interactions are transient in nature. Some nascent adhesions quickly disperse, while others persist and are trapped in the retrograde actin flow resulting from a combination of actin polymerization, contractile forces applied by myosin II motors and leading-edge membrane tension. Thus, integrin-mediated adhesions link the rearward-flowing actin cytoskeleton to the extracellular environment, allowing cells to exert and experience mechanical forces. This

assembly is termed the molecular clutch.^{213,214} The tensile stress caused by actin flow and integrin attachment to the ECM leads to conformational changes that result in exposure of cryptic binding and phosphorylation sites, which allows the recruitment and activation of additional proteins to further regulate downstream signaling pathways.²¹⁵ Talin and vinculin are two very important mechanosensitive proteins that regulate the link between integrins and actin. The application of force results in integrin clustering and initiates integrin downstream signaling through the coupling of integrins via talin and vinculin to the actin cytoskeleton. In turn, actin can pull on integrins, further promoting force generation. The N-terminal FERM domain of Talin binds directly to the NPXY motif at the proximal tail membrane of β -integrin. After subsequent attachment to F-actin, talin is stretched to cause a conformational change that exposes the first cryptic vinculin binding site in its rod R3 domain.²¹⁶ Vinculin interacts with talin and actin to unfold its closed, autoinhibited conformation,²¹⁷ which permits transmission and distribution of mechanical force through the cytoskeleton. Vinculin and talin coordinate to stabilize each other's extended conformational states. Vinculin allows more force to be applied to Talin by linking it to actin, thereby exposing additional binding sites reciprocally.^{216,218} Among these interactions, the Ras-family small GTPase Rap1 and the Rap1 effector RIAM play a role in recruiting talin to the membrane and facilitating the conformational activation of talin.²¹⁹ The Talin rod, rather than vinculin unfolding induced by mechanical force, inhibited the Talin-RIAM interaction, suggesting that force may be a molecular switch regulating the interaction between vinculin-RIAM and talin.²²⁰ In addition, Yes-associated protein-1 (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) signaling has recently been recognized as an important mechanotransducing hub that contributes to integrating cellular and tissue mechanics with metabolic signaling, allowing transcriptional responses.²²¹

Integrin-mediated downstream events. As the transmembrane connection of integrins has been characterized, integrin signaling has been reported to not only modulate IACs formation and actin cytoskeletal rearrangements but also regulate intracellular pathways in response to the ECM or other ECM that triggers "outside-in" signals that serve to modulate gene expression, proliferation, survival/apoptosis, polarity, motility, shape, and differentiation.¹⁶⁶ Integrins engage with extracellular activators such as divalent cations, endogenous agonists, activating antibodies, and ligand-mimicking molecules,^{222–225} and their subsequent clustering leads to the activation of SYK, FAK and Src-family kinases (SFKs), regulating integrin downstream signaling pathways.²²⁶ In addition, mechanical forces can also trigger integrin conformational changes downstream.^{39,227–230} Integrin ligation triggers the upregulation of P53 activation, BCL-2 and FLIP pro-survival molecules,^{231,232} and the activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway, PI3K/AKT pathway, JNK16 signaling, and stress-activated protein kinase (SAPK) or nuclear factor κ B (NF- κ B) signaling.^{233–235} In fibroblasts, integrin-mediated adhesion activates FAK as well as the sodium-proton antiporter and protein kinase C (PKC),²³⁶ and recruitment of FAK to integrins has been considered to precede talin recruitment.²³⁷ Integrin-FAK signaling is required for microtubule stabilization,²³⁸ leading to anoikis resistance in normal cells and metastasis of independent anchorage growth in tumor cells.²³⁹ FAK interacts with a scaffolding protein, and the hematopoietic PBX-interacting protein (HIP/PBXIP1) in FAs leads to MAPK activation, which leads to Talin proteolysis and contributes to the regulation of cancer cell migration.^{187,240–244} In autosomal dominant polycystic kidney disease, increased ECM fibrosis activates the mechanistic target of rapamycin (mTOR) pathway through the ILK/PINCH/ α Parvin/FAK complex, further accelerating the repair of EMT and cell migration.²⁴⁵ The activation

of Src-family kinases is one of the earliest stages of "outside-in" signaling.²⁴⁶ Interaction of integrins with urokinase plasminogen activator receptor (uPAR) activates Rho GTPase to promote cell migration and invasion. α subunit of α v β 3 coupled to Fyn and Yes. Fyn and Yes activate FAK, which is a necessary element in Src homology and collagen homology (SHC) activation. SHC combined with Ras/ERK/MAPK are activated from α v β 3/receptor tyrosine kinase (RTK) receptor combinations, thus activating matrix metalloproteinases (MMPs). Neuropilins (NRPs), vascular endothelial growth factor (VEGF) receptors known as therapeutic targets of tumor growth and metastasis, promote tumorigenesis in breast cancer cells by localizing to FAs and binding to α 6 β 1 integrin to activate FAK/Src.²⁴⁷ FAs regulate turnover and cell mobility through microtubules, and autophagy and ubiquitination are equally important for their role as biosensors of the cellular microenvironment and for migration.¹⁸⁹ Hypoxia induces anoikis resistance by regulating activating transcription factor 4 (ATF4) and autophagy genes via the integrin signaling pathway. Cell separation from the ECM also triggers integrin signaling via the eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3)-reactive oxygen species (ROS)-ATF4 axis, promoting autophagy and developing anoikis resistance.²⁴⁸ RIAM-VASP relays integrin complement receptors in outside-in signaling driving particle engulfment by determining ERK phosphorylation and its kinetics.²⁴⁹ In tandem with the ERK1/2 and c-Jun N-terminal kinase (JNK)1/2 pathways, β 1 integrin/FAK/Cortactin pathway signals in FA disassembly and turnover, leading to cell survival and therapeutic drug resistance.^{250,251} Specific mechanical cues, such as rigid environments, lack of spatial constraints, and tensile loading, promote YAP/TAZ nuclear translocation and transcriptional activity.²⁵² Hippo-YAP signaling depends on the Enigma protein family and FAK, which signal to Hippo through the PI3K pathway.²⁵³ Similar to the biophysical cues required for YAP/TAZ activation, myocardin-related transcription factor (MRTF) achieves transcriptional regulation of serum response factor (SRF) by translocating to the nucleus. Mechanistically, MRTFs respond to the G/F-actin ratio because G-actin binds MRTFs to promote nuclear export and sequester the protein in the cytoplasm.²⁵⁴ Notably, different integrins regulate downstream signaling pathways through divergent binding mechanisms, such as latent TGF- β (L-TGF- β), a latent form of TGF- β , binding to α v β 6 integrin triggers a conformational change from extended-closed to extended open, which allows actin cytoskeletal force to be transmitted through the β subunit to release mature TGF- β from its latent complex,²⁵⁵ while the α v β 8 has a distinct cytoplasmic domain without interacting with the actin cytoskeleton, and α v β 8-mediated TGF- β activation directs TGF- β signaling to the opposing L-TGF- β /glycoprotein A repetitions predominant (GARP)-expressing cell through the formation of a large multicomponent cell-cell protein complex.²⁵⁶ A schematic overview of integrin activation-associated signaling cascades is shown in Fig. 4.

INTEGRIN ROLES IN PHYSIOLOGY AND PATHOLOGY

Integrin roles in cancer

Integrins regulate cell proliferation, adhesion, migration, and survival, and tumors can hijack integrin-facilitated biological signaling to participate in every step of cancer progression, including tumor initiation and proliferation, invasiveness, circulating tumor cell survival, metastatic niche formation, immunosuppression, and colonization of the new metastatic site and support multiple therapy resistance.²⁵⁷ Integrins are considered therapeutic targets in multiple cancers. The expression of integrins can vary considerably between normal and tumor tissue and is also associated with cancer types and organotrophic metastasis. For example, integrins α v β 3, α v β 6, and α 5 β 1 are usually expressed in most normal epithelia at low or undetectable levels but can be highly upregulated in multiple tumors.²⁵⁸ The overexpression of

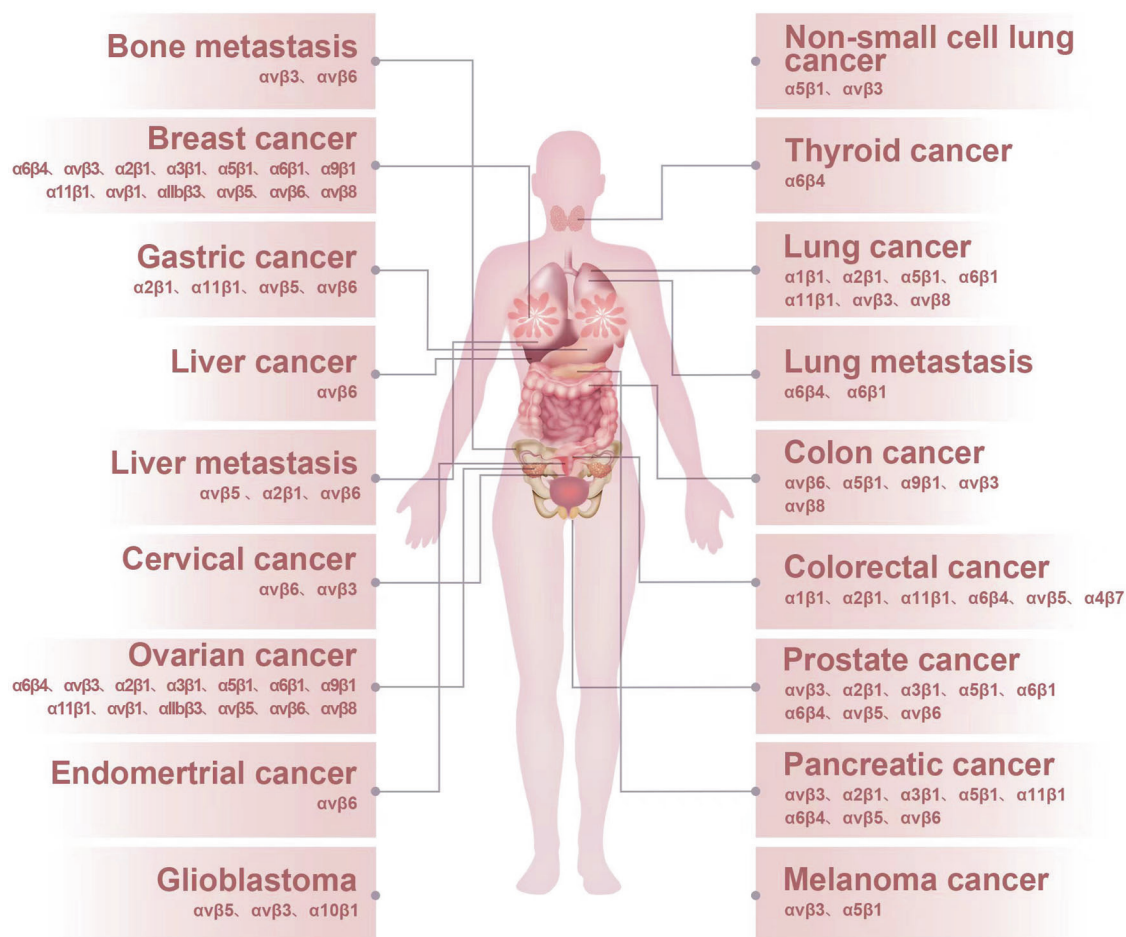


Fig. 5 The expression and function of major integrins and their related cancer types and metastatic sites. The expression of integrins can vary considerably between normal and tumor tissue and is also associated with cancer types and organotrophic metastasis

the integrins $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 6$, $\alpha 5\beta 1$, $\alpha 6\beta 4$, and $\alpha 4\beta 1$ promotes cancer progression in various cancer types. The expression and function of major integrins and their related cancer types and metastatic sites are shown in Fig. 5, which indicates the applicability of these integrin receptors as therapeutic targets and underlines the requirement for patient stratification in future clinical studies. Herein, we summarize the recent progress in the engagements of integrins and integrin-regulated mechanisms in different cancers.

Integrin and tumorigenesis. Most integrins act as tumorigenesis promoters in multiple solid tumors, but some integrins also act as suppressors in tumor tumorigenesis.²⁵⁷ The $\beta 1$ integrin family has heterogeneity in tumor initiation and progression.^{259,260} Several studies have suggested a beneficial role for the inhibition of $\beta 1$ integrin or deletion of the $\beta 1$ gene, including reversion of the malignant phenotype in breast cancer and reduction of drug resistance and metastasis in gastric, ovarian, and lung cancer.^{261–264} $\alpha 2\beta 1$ integrin is highly expressed on normal breast epithelium, and $\alpha 2\beta 1$ integrin is reported to be a metastasis suppressor in mouse models and human breast cancer.¹²⁵ Other studies, however, suggested integrin $\alpha 2$ or $\alpha 2\beta 1$ as a key regulator of hepatocarcinoma cell invasion and conferring selective potential for the formation of hepatic metastasis.²⁶⁵ In addition, many studies have also proven that laminin-binding integrins ($\alpha 3\beta 1$ and $\alpha 6\beta 4$) exert opposing effects (tumor-promoting and suppressive) on tumor development and progression.¹²⁵ Integrins may act as tumor suppressors by activating TGF- β and exerting

anti-proliferative effects in the early stage of tumor formation until cancer becomes refractory, and the inhibitory effect of TGF- β on tumor cell proliferation will decrease or even disappear; then, the same integrins can drive tumor progression.^{266,267} $\beta 1$ integrin expression and function are associated with metabolic reprogramming. An array of studies has suggested that glycolytic enzymes affect $\beta 1$ integrin expression, which produces a vicious cycle for promoting cancer progression.²⁶⁸ In colon cancer cells, the glycolytic enzyme pyruvate kinase M2 induces metabolic reprogramming, positively affecting the overexpression of enhanced $\beta 1$ integrin expression and increasing cell migration and adhesion.²⁶⁹ Inhibition of glycolytic enzymes could decrease integrin $\beta 1$ expression and proliferation in breast cancer cells.^{268,269}

Integrins also play an important role in regulating immune response during tumor development.²⁷⁰ Importantly, as a gut-tropic molecule, integrin $\alpha 4\beta 7$ plays a profound role in regulating the progression of colorectal cancer (CRC).²⁷¹ $\alpha 4\beta 7$ mediates the recruitment of IFN- γ -producing CD4 + T cells, cytotoxic CD8 + T cells, and NK cells to the CRC tissue where they exert effective anti-tumor immune responses.²⁷¹ Higher $\beta 7$ expression levels are correlated with longer patient survival, higher cytotoxic immune cell infiltration, lower somatic copy number alterations, decreased mutation frequency of APC and TP53, and better response to immunotherapy.²⁷¹

Integrins have been reported to sustain intratumoral cancer stem cell (CSC) populations depending on tumor type. Prospective identification studies suggested that integrin $\alpha v\beta 3$, $\alpha 6\beta 1$, and

$\alpha 6 \beta 4$, which are overexpressed in CSCs, promote the sustainability of self-renewal and the expansion of CSCs for tumor initiation.²⁷² Actually, the $\alpha 6$ and $\beta 3$ subunits are regarded as a signature of luminal precursor cells in the mammary ductal epithelium,²⁷³ and the $\alpha 6$ and $\beta 4$ subunits are generally applied as markers to identify bipotential progenitors in normal prostate and prostate cancer in mice.^{274,275} Deletion of the signaling domain of $\beta 4$, which also pairs with $\alpha 6$, decreases the self-renewal ability of prostate tumor progenitors.²⁷⁵

Integrins play key regulatory roles in neovascularization. Endothelial cells highly express a diverse repertoire of $\alpha 1 \beta 1$, $\alpha 2 \beta 1$, $\alpha \nu \beta 3$, $\alpha 5 \beta 1$, and $\alpha \nu \beta 5$.^{276,277} In particular, $\alpha \nu \beta 3$ is expressed on quiescent endothelial cells at very low levels but is markedly increased during tumor angiogenesis.²⁷⁸ Therefore, integrin $\alpha \nu \beta 3$ antagonists can induce endothelial cell apoptosis in neovascularization without affecting the normal vasculature, which leads to many peptide-based integrin inhibitors and antibodies developed in clinical trials for cancer treatment. Integrin $\alpha \nu \beta 3$ and VEGF have a synergistic signaling connection during the activation of endothelial cells and vascularization induced by interplay between VEGF and ECM molecules.²⁷⁹ The anti-integrin $\alpha \nu \beta 3$ antibody BV4 inhibits the phosphorylation of VEGFR2,²⁷⁹ and the VEGFR2-specific inhibitor SU1498 inhibits the complex interaction between VEGFR2 and integrin $\beta 3$.²⁸⁰ FAK-Src signaling is important in both $\alpha \nu \beta 3$ and VEGF-associated tumor angiogenesis.²⁴³ The crosstalk of integrin $\alpha \nu \beta 3$ and VEGFR2 could be regulated by Src. Src inhibitors not only block both the phosphorylation of integrin and VEGFR2 but also complex formation between VEGFR2 and integrin $\beta 3$.²⁸¹ The interplay of integrin $\alpha \nu \beta 3$ in VEGFR signaling should be considered in anti-angiogenesis drug development.

Integrin and metastatic cascade. Metastasis causes 90% of cancer deaths.²⁸² The “seed-and-soil” hypothesis provides insight into organ-specific metastasis. Integrins engage in the metastatic cascade, which is dependent on tumor type, stage, metastatic site, and microenvironmental influences. For breast, prostate, and lung malignancies, the most frequent metastasis site is bone. The correlative evidence suggests that the role of integrins (e.g., $\alpha \nu \beta 3$, $\alpha 2 \beta 1$, $\alpha 4 \beta 1$, $\alpha 5 \beta 1$) mediates the interactions of tumor cells with the bone microenvironment. $\alpha \nu \beta 3$ has been studied most as an important integrin for bone metastasis.²⁸³ Integrin $\alpha \nu \beta 3$ was expressed at higher levels in breast cancer patients with bone metastases than in their primary tumors.²⁸⁴ Tumor-specific $\alpha \nu \beta 3$ participates in breast cancer spontaneous metastasis to the bone by mediating chemotactic and haptotactic migration towards bone factor.²⁸⁵ Functional modulation of $\alpha \nu \beta 3$ is also required for prostate cancer within bone metastasis and for tumor-induced bone gain.²⁸⁶ In addition, $\alpha \nu \beta 3$ activation depends on the recognition of specific bone-specific matrix ligands.²⁸⁶ $\alpha \nu \beta 3$ could be a potential marker for bone metastasis, and treatment with $\alpha \nu \beta 3$ antagonists can reduce the capacity of tumor cells to colonize bone.²⁸⁷

In recent years, exosomes have been recognized as the “primers” of the metastatic niche.²⁸⁸ Integrins, as the most highly expressed receptors on exosomes, are major players in mediating exosome functions and especially exert important effort in guiding exosomes to spread into the prime long-distance organs to form a premetastatic niche and further support organ-specific metastasis.²⁸⁹ A comprehensive proteomic investigation suggested diverse exosome-carrying integrins derived from different types of primary tumors.²⁹⁰ Most notably, lung-tropic cancer cells predominantly secreted $\alpha 6 \beta 1$ integrins and $\alpha 6 \beta 4$ integrin-positive exosomes, while liver-tropic cancer cells mainly shed exosomes with a high enrichment of $\alpha \nu \beta 5$ integrin.²⁹⁰ Targeting exosome uptake of integrins $\alpha 6 \beta 4$ and $\alpha \nu \beta 5$ can reduce lung and liver metastasis, respectively.²⁹⁰ In prostate cancer, $\alpha \nu \beta 6$ is not detectable in the normal human prostate but is highly expressed in primary prostate cancer.²⁹¹ It was reported that $\alpha \nu \beta 6$ is

packaged into exosomes secreted by prostate cancer cells and transferred into $\alpha \nu \beta 6$ -negative recipient cells, which contributes to enhancing cell migration and metastasis in a paracrine fashion.²⁹¹ $\alpha \nu \beta 3$ -expressing exosomes are highly enriched in the plasma of prostate cancer patients; in addition, the levels of $\alpha \nu \beta 3$ remain unaltered in exosomes isolated from blood from prostate cancer patients treated with enzalutamide.²⁹² Exosome-carrying integrin $\alpha \nu \beta 3$ is transferred to nontumorigenic recipient cells and promotes a migratory phenotype.²⁹³ Exosome-carrying integrin $\alpha 3$ (ITGA3) and ITGB1 from urine from prostate cancer with metastasis are more abundant than those from benign prostate hyperplasia or primary prostate cancer.²⁹⁴ In pancreatic cancer, numerous lines of evidence suggest that exosomal integrins also play key roles in exosome-mediated tumor progression and metastasis; for example, exosome-carrying $\alpha \nu \beta 5$ released by primary tumor cells in the pancreas tends to metastasize to the liver, whereas $\alpha 6 \beta 4$ and $\alpha 6 \beta 1$ tend to metastasize to the lung.²⁹⁵ In future studies, the general applicability of exosome integrin-mediated organ-specific metastasis remains to be validated in vivo models and in other cancer types.

Integrin and drug resistance. Tumor metastasis and therapeutic resistance together determine a fatal outcome of cancer. Interactions between cell-surface integrins and ECM components have been found to be responsible for intrinsic and acquired therapy resistance, which is named cell-adhesion-mediated drug resistance (CAMDR).^{282,288} Generally, integrins are involved in resistance to most first-line therapies in the clinic, such as radiotherapy,²⁸⁹ chemotherapy,²⁹⁰ angiogenesis,²⁹¹ endocrine therapy,²⁹² and immunotherapy.²⁹³ The mechanism of integrin-induced primary and adaptive drug resistance is variegated. In various cancers, $\beta 1$ integrin-interacting matrix molecules promote primary radiotherapy resistance by activating DNA repair and prosurvival signaling through the engagement of FAK, SRC, PI3K-AKT and MAPK signaling.^{294–297} In addition, integrin-mediated reprogramming also induces radiosensitization.²⁸⁹ The interaction of Integrin with ECM by activating ATP binding cassette (ABC) efflux transporters enhances the intracellular drug concentration and promotes chemoresistance to doxorubicin and mitoxantrone.²⁹⁸ Cluster of differentiation-44 (CD44), alone or together with MET receptor, also participates in the upregulation of P-glycoprotein (P-gp) expression and promotes chemoresistance.²⁹⁹ In xenograft models and patient specimens, Arman et al. found that c-Met replaced $\alpha 5$ integrin from $\beta 1$ integrin and formed the c-Met/ $\beta 1$ complex during metastases and invasive resistance, and decoupling the crosstalk in the c-Met/ $\beta 1$ complex may have therapeutic implications for antiangiogenic drug resistance.³⁰⁰ The interaction of integrin $\alpha \nu \beta 3$ with osteopontin engages in acquired epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) resistance by activating the downstream FAK/AKT and ERK signaling pathways in EGFR mutant non-small cell lung cancer.³⁰¹ Integrins are involved in invasion, angiogenesis, bone metastases and anti-androgen resistance in prostate cancer.²⁹² The mechanism of resistance to androgen ablation is not well understood. In our previous study, we found that the integrin-ECM interaction promotes enzalutamide (anti-androgen drug) resistance in castration-resistant prostate cancer (CRPC) via the PI3K/AKT and ERK1/2 pathways.³⁰² $\alpha \nu \beta 3$ and $\alpha \nu \beta 6$ expression are required for prostate cancer progression, including CRPC. Integrin $\alpha \nu \beta 6$ can induce androgen receptor (AR)-increased activity in the absence of androgen via activation of JNK1 and further upregulation of survival.³⁰³ In mouse melanoma and breast cancer models, Tregs expressing integrin $\beta 8$ (ITGB8) are the main cell type in the tumor microenvironment, which activates TGF- β produced by cancer cells and promotes immune escape, and ITGB8 ablation or anti-ITGB8 antibody treatment could improve cytotoxic T-cell activation.²⁹³ In triple-negative breast cancer (TNBC), integrin $\alpha \nu \beta 6$ on the surface of tumor cells activates

TGF- β , and upregulating SRY-related HMG box (SOX) 4 transcription factor contributes to immunotherapy resistance. An integrin α v β 6/8-blocking monoclonal antibody can inhibit SOX4 expression and sensitize TNBC cells to programmed cell death ligand 1 (PD-1) blockade.³⁰⁴ Therefore, targeting integrin is regarded as a promising therapeutic opportunity for overcoming multiple drug resistance.

Integrin roles in fibrotic diseases

Fibrosis refers to chronic inflammation or injury induced by various factors, resulting in an increase in fibrous connective tissue and a decrease in parenchymal cells. It causes abnormal structural changes and functional abnormalities in injured organs, which is an abnormal manifestation of excessive damage repair.³⁰⁵ Fibrosis occurs in almost any organ, especially the liver, lung, and kidney. Fibrosis diseases are difficult to detect in the early stages, and most are found to have progressed to organ sclerosis, which can be life-threatening for patients.³⁰⁵ Currently, therapies for fibrosis disease are still limited, and organ transplantation is the only effective treatment option for end-stage fibrosis diseases.³⁰⁶ However, due to the limited number of donor organs and their high price, replacement therapy has not been widely used. It is particularly important to develop new antifibrotic drugs from the pathogenesis of fibrosis.

TGF- β 1 plays a critical role in the pathogenesis of fibrosis and has been considered a therapeutic target for fibrotic diseases.^{307–309} Unfortunately, both preclinical and clinical trials have shown that direct targeting of TGF- β 1 for fibrosis disease treatment is not feasible.³⁰⁸ TGF- β 1 is involved in the regulation of the immune system and plays important anticancer and cardiac function maintenance roles.^{308,310,311} Global inhibition of TGF- β 1 leads to serious multiple organ dysfunction.³⁰⁸

Encouragingly, researchers have found that blocking the interaction between integrins (especially integrins rich in α v subunits) and TGF- β 1 showed an efficient antifibrosis effect without causing TGF- β 1 dysfunction-induced adverse effects.³⁰⁵ Integrins are receptors by which cells adhere to the ECM.³¹² Several integrins have been confirmed as activators of TGF- β 1,³¹² and antagonists of α v β 1⁵⁴ and α v β 6^{313,314} have shown considerable inhibitory effects in experimental animal models of liver, lung, and renal fibrosis. In fact, in recent years, several integrin inhibitors have been developed and evaluated in phase II and III clinical trials in fibrotic diseases, such as PLN-74809, IDL-2965, GSK-3008348, and STX-100.³¹⁵ These findings revealed the promise of integrin inhibitors in the treatment of fibrotic diseases. In the following, we focus on nonalcoholic steatohepatitis (NASH), pulmonary hypertension (PH), and autosomal dominant polycystic kidney disease (ADPKD), the diseases that usually cause fibrosis, and discuss the role of integrins in fibrotic processes (Fig. 6).

NASH. NASH, a chronic liver disease that develops from nonalcoholic fatty liver disease (NAFLD), is one of the most common chronic liver diseases in patients without a history of alcohol abuse.^{316,317} Approximately 30–40% of NASH patients develop fibrosis, and 10% develop cirrhosis.³¹⁸ The prognosis of NASH depends on histological severity, especially hepatic fibrosis.³¹⁹ Therefore, preventing the progression of NASH to liver fibrosis is of great importance in NASH treatment. Despite the increasing incidence of NASH-related liver fibrosis, which currently kills 2 million people worldwide each year,^{320–322} there are no approved drugs. Most drugs in clinical trials target the early stages of steatosis/hepatitis other than fibrosis itself, which generally result in inadequate outcomes.^{323,324} This dilemma provides an opportunity for integrin inhibitors to be applied in the treatment of liver fibrosis.²⁸ Several integrins have been identified to inhibit the progression of NASH to liver fibrosis, including α v β 3, α 4 β 7, α 9 β 1, and α 8 β 1 (Fig. 6).

Integrin α v β 3 is expressed in hepatic stellate cells (HSCs),³²⁵ which are considered key mediators of fibrotic responses.³²⁶

Generally, integrin α v β 3 induces myofibroblast cells to express α -smooth muscle actin (α -SMA), leading to excessive production of ECM.^{327,328} It has been reported that integrin α v β 3 and α v β 5 bind with secreted osteopontin in the liver of NAFLD mice, which inhibits autophagosome-lysosome fusion and promotes lipid accumulation.³²⁹ Application of osteopontin antibody not only suppressed hepatic steatosis but also attenuated liver fibrosis,³²⁹ indicating a functional role of integrin α v β 3 and α v β 5 in inhibiting the progression of NASH to liver fibrosis. Moreover, in high glucose-induced human liver sinusoidal endothelial cells (HLSECs) (an *in vitro* model of NAFLD), integrin α v β 3 antibody (clone LM609) significantly downregulated the expression of laminin and suppressed fibrosis.³³⁰ In fact, numerous studies have confirmed the efficacy of integrin α v β 3 as a predictor of fibrosis in experimental NASH models.^{325,328,331} However, no integrin α v β 3 inhibitors have been evaluated in clinical trials to investigate their inhibitory effect on the progression of NASH to liver fibrosis. It is waiting to be explored.

Integrin β 7 expressed in leukocytes is regarded as an important receptor that binds to MAdCAM-1 and induces homing of leukocytes to gut-associated lymphoid tissue.³³² Integrin β 7 pairs with other integrin α subunits, including α 4 and α E,³³² in which α 4 β 7 affects the progression of NASH to liver fibrosis.^{332–334} At first, researchers focused only on the role of integrin β 7 in NASH-induced liver fibrosis. Knockout of integrin β 7 (ITGB7) significantly promoted inflammatory cell infiltration and fibrosis in the livers of NASH mice.³³² In contrast, MAdCAM-1 knockout showed anti-inflammatory activity.³³² Later, integrin α 4 β 7 was found to play an important role in the progression of NASH to liver fibrosis. The abnormality of gut microbiota in NASH mouse models promoted the expression of MAdCAM-1 in the liver, which recruited α 4 β 7-positive CD4 T cells to the liver and induced inflammation and fibrosis.³³⁴ Blocking integrin α 4 β 7 has shown promising therapeutic effects on fibrosis in NASH,³³⁴ indicating its great potential as a therapeutic target for NASH-induced liver fibrosis.

Integrin α 9 β 1 plays an important role in lipotoxic hepatocyte-induced hepatic recruitment of monocyte-derived macrophages (MoMFs), which promotes the progression of NASH to fibrosis.³³⁵ Integrin α 9 β 1 expressed in hepatocytes could be activated by hepatocyte lipotoxicity and endocytosed by hepatocytes.³³⁵ Extracellular vesicles are formed and secreted by hepatocytes, which are further captured by MoMFs.³³⁵ Integrin α 9 β 1 mediates MoMF adhesion to liver sinusoidal endothelial cells by binding to VCAM-1, which induces inflammation.³³⁵ Blocking integrin α 9 β 1 significantly reduced liver injury, liver inflammation, and liver fibrosis,³³⁵ indicating that it is a therapeutic target for fibrosis in NASH. In addition, it has also been reported that anti-mouse osteopontin mouse IgG (35B6) inhibits the cell adhesion of mouse and human osteopontin to Chinese hamster ovary (CHO) cells expressing integrin α 9, which suppresses liver inflammation and fibrosis in NASH mice.³³⁶ All these findings revealed the therapeutic potential of integrin α 9 β 1 inhibitors in liver fibrosis induced by NASH.

Integrin α 8 β 1 is expressed in smooth muscle cells, HSCs, and fibroblasts.³³⁷ It was upregulated in patients with NAFLD and liver fibrosis.^{82,338} In NASH, the activation of HSCs expressing the integrin α 8 subunit has been proven to be an agonist of latent TGF- β , which participates in promoting fibrosis.⁸² A previous study showed that inhibiting the integrin α 8 subunit with an integrin α 8 antibody significantly improved liver fibrosis in a NASH mouse model.⁸² In addition, miR-125b-5p silencing caused by NAFLD also downregulated integrin α 8, which inhibited the RhoA signaling pathway and promoted fibrosis.³³⁸ These results implied the functional role of integrin α 8 β 1 in promoting liver fibrosis induced by NASH.

Moreover, other integrins have also been proven to be involved in liver fibrosis. Integrins containing the α v subunit have received the most attention due to their activating activity on TGF- β , including α v β 1, α v β 5, α v β 6, and α v β 8.^{306,327} In addition, integrins

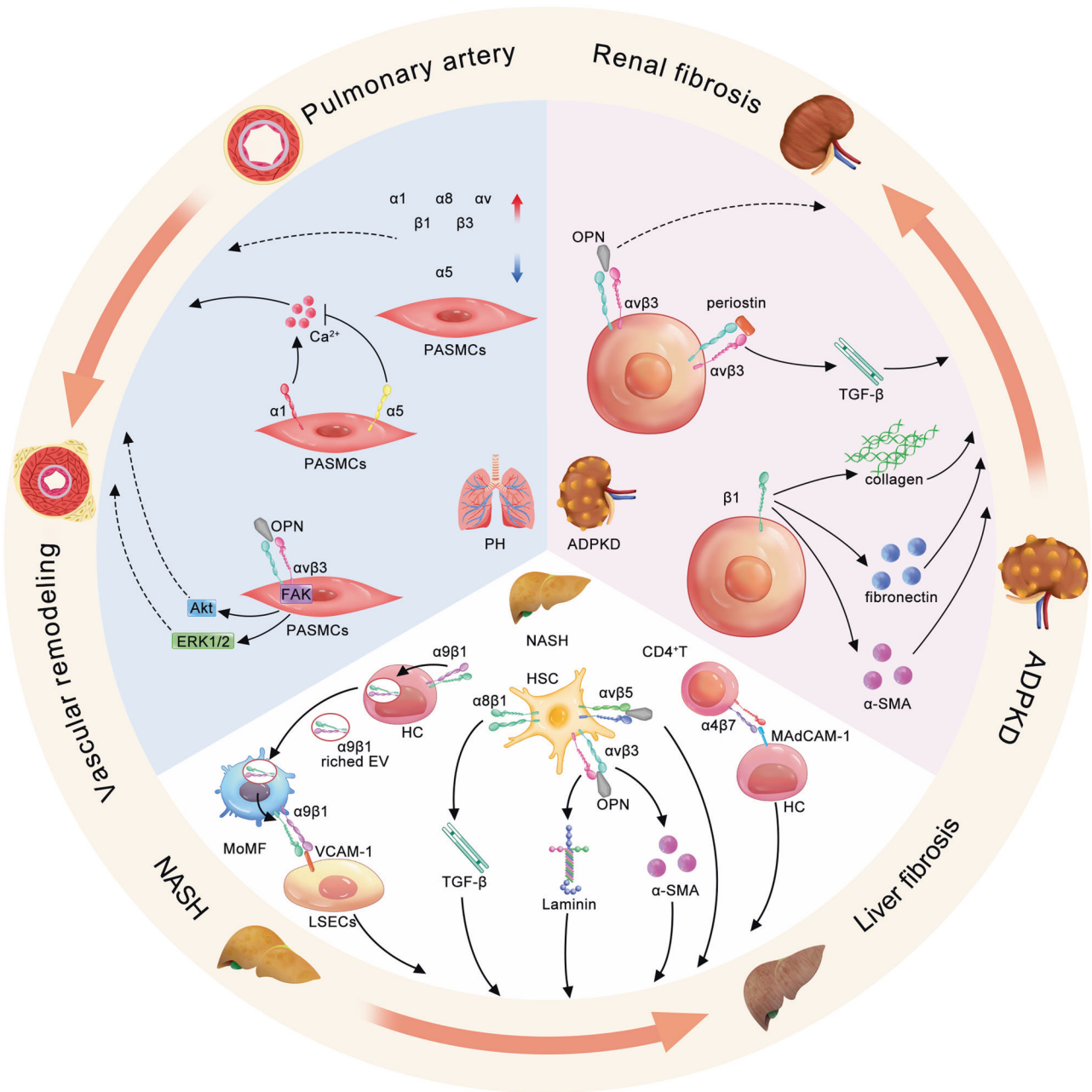


Fig. 6 Roles of integrins in fibrosis processes in NASH, PH, and ADPKD. The lower part of the circle shows the role of integrins in liver fibrosis in NASH. In hepatic cells (HCs), activated integrin $\alpha 9 \beta 1$ is endocytosed by hepatocytes and secreted in the form of extracellular vesicles (EVs), which are further captured by MoMFs. Captured integrin $\alpha 9 \beta 1$ mediates MoMF adhesion to liver sinusoidal endothelial cells (LSECs) by binding to VCAM-1, which accelerates liver fibrosis. In HSCs, integrin $\alpha 8 \beta 1$ promotes liver fibrosis by activating TGF- β . The binding of integrin $\alpha \nu \beta 3$ with OPN could promote laminin and α -SMA expression, which causes ECM accumulation and fibrosis progression. Integrin $\alpha \nu \beta 5$ also binds with OPN and enhances liver fibrosis, but the underlying mechanism still needs to be clarified. In CD4+ T cells, the adhesion between integrin $\alpha 4 \beta 7$ and HC expressing MAdCAM-1 recruits CD4+ T cells to the liver, which induces liver inflammation and fibrosis. The left part of the circle shows the role of integrins in intimal fibrosis in PH. In the progression of PH, integrin $\alpha 1$, $\alpha 8$, $\alpha \nu$, and $\beta 3$ are upregulated, and $\alpha 5$ is downregulated in PSMCs. Integrin $\alpha 1$ increases and $\alpha 5$ decreases the concentration of Ca^{2+} , promoting intimal fibrosis. The binding between integrin $\alpha \nu \beta 3$ and OPN activates FAK signal transduction, which might be involved in the processes of vascular remodeling. The right part of the circle shows the role of integrins in renal fibrosis in ADPKD. Integrin $\alpha \nu \beta 3$ expressed in renal tubular epithelial cells binds with periostin, activating TGF- β and promoting renal fibrosis. Binding between integrin $\alpha \nu \beta 3$ and OPN is also involved in the renal fibrosis process, but the underlying mechanism is unclear. Renal tubular epithelial cells expressing integrin $\beta 1$ enhance the expression of collagen, fibronectin, and α -SMA, which promote renal fibrosis

$\alpha 11$ and RGD-recognizing integrins (such as $\text{a11b}\beta 3$ and $\alpha 5 \beta 1$) are also important regulators of liver fibrosis.³³⁹ Integrin inhibitors such as IDL-2965 and PLN-74809 have been investigated in clinical trials to evaluate their therapeutic effect on liver fibrosis.³³⁹ However, none of their roles in fibrosis induced by NASH have been

elucidated. It may be a promising direction for the treatment of NASH-derived liver fibrosis.

PH. PH is a disorder of the pulmonary vasculature defined by increased pulmonary vascular resistance ≥ 3 Wood units.³⁴⁰ It is

characterized by excessive pulmonary vasoconstriction and vascular remodeling resulting in persistent elevation of pulmonary arterial pressure.³⁴¹ PH causes right ventricular hypertrophy, right heart dysfunction, and even right heart failure, threatening up to 100 million people worldwide.^{340,342} Pulmonary vascular remodeling in PH involves the processes of endothelial injury, endothelial cell abnormality, excessive vascular smooth muscle cell proliferation, invasion of the intima by (myo)fibroblast-like cells and, especially, intimal fibrosis.³⁴³ Increased deposition of interstitial ECM components, including collagen, elastin, tenascin-C, and fibronectin, has been demonstrated in human patients and animal models.^{341,344–346} As the receptor for ECM proteins, integrins play important roles in maintaining vascular remodeling.³⁴⁷

Pulmonary vasculature expresses several types of integrins, including $\alpha 1$, $\alpha 2$, $\alpha 3$, $\alpha 4$, $\alpha 5$, $\alpha 7$, $\alpha 8$, $\alpha \nu$, $\beta 1$, $\beta 3$, and $\beta 4$ ^{12,348,349} (Fig. 6). Studies revealed that in the pulmonary arteries (PAs) of chronic hypoxia and monocrotaline-treated PH rat models, integrin $\alpha 1$, $\alpha 8$, and $\alpha \nu$ were upregulated, and integrin $\alpha 5$, $\beta 1$, and $\beta 3$ were downregulated significantly.^{347,350} Integrin $\alpha \nu$ activates TGF- $\beta 1$ and TGF- $\beta 3$, which are critical to vascular homeostasis. TGF- β regulates PH through multiple signaling pathways, including upregulation of endothelial nitric oxide synthase, stimulation of VEGF and endothelin-1, alteration of bone morphogenetic protein (BMP) signaling, and anaplastic lymphoma kinase (ALK)-1–ALK-5 signaling in endothelial cells.^{351–353} Integrins $\beta 1$ and $\beta 3$ have been reported to regulate cell proliferation by interacting with activated ILK, a pro-proliferative protein kinase. ILK is activated by integrins in response to growth factors and cytokines, which in turn trigger downstream signals, including activation of Akt and inhibition of the growth suppressor HIPPO.^{354–356} ILK1 is upregulated in pulmonary artery vascular smooth muscle cells (PAVSMCs) of human pulmonary arterial hypertension (PAH) and experimental models and is required for increased cell proliferation, survival, pulmonary vascular remodeling, and overall PH, and inhibition of ILK reverses experimental PH in male mice.³⁵⁵ Researchers believe that integrin $\alpha 1$ and $\alpha 5$ may participate in regulating ECM, as they are expressed in the smooth muscle cells of PAs (PASMCS).³⁴⁷ In these processes, integrin $\alpha 1$ -ligand collagen IV expands, while integrin $\alpha 5$ -ligand fibronectin suppresses chronic hypoxia treatment-induced FAK phosphorylation.³⁴⁷ The regulatory effects of integrin $\alpha 1$ and $\alpha 5$ on FAK phosphorylation then react to Ca^{2+} signaling, which may be involved in intimal fibrosis.³⁴⁷

In addition, integrin $\beta 3$ may function as an inhibitor of fibrosis and vascular remodeling in PH. It has been reported that silencing integrin $\beta 3$ (ITGB3) significantly improves chronic hypoxia-induced pulmonary hemorrhage, pulmonary vascular remodeling, and pulmonary fibrosis in rats.³⁵⁰ These effects may come from the interaction between integrin $\beta 3$ and ECM. However, the underlying mechanism still needs to be clarified. The role of integrin $\alpha \nu$ in regulating PH-induced fibrosis has attracted little attention. However, the interaction between $\alpha \nu \beta 3$ and osteopontin has been confirmed, which activates FAK and AKT, promoting the proliferation of PASMCS and enhancing vascular remodeling.^{357,358}

ADPKD. ADPKD is an autosomal dominant kidney disease caused by polycystic kidney disease-1 (PKD1) or polycystic kidney disease-2 (PKD2) gene mutations. It is the fourth leading cause of the end-stage renal disease (ESRD), with an incidence of $\sim 1/2500$ to $1/1000$.^{359,360} ADPKD is characterized by progressive growth of multiple renal tubules and collecting duct-derived cysts in bilateral kidneys, which compress the renal parenchyma and cause nephron loss.³⁶¹ Fibrosis is an important pathophysiological change of ADPKD that directly leads to renal dysfunction and induces ESRD.³⁵⁹ Therefore, antifibrosis is important in the treatment of ADPKD. However, apart from replacement therapies, there is no clinical solution that could effectively prolong the lifespan of ADPKD patients, which makes it urgent to develop new drugs.³⁶²

In recent decades, research on integrin function in fibrotic kidney diseases has achieved exciting results. A growing number of integrins have been found to play regulatory roles in the progression of fibrosis in renal dysfunction and show great potential as therapeutic targets for renal disease. In particular, integrin $\alpha \nu \beta 3$ ²⁴⁵ and $\beta 1$ ³⁶³ are promising antifibrotic targets in ADPKD treatment (Fig. 6).

As an important activator of latent TGF- $\beta 1$, integrin $\alpha \nu \beta 3$ enhances TGF- β /small mothers against decapentaplegic (SMAD) signaling pathways, which induces ECM production, promoting renal fibrosis in ADPKD.²⁴⁵ Periostin is a ligand of integrin $\alpha \nu \beta 3$, which binds to integrin $\alpha \nu \beta 3$ through its fasciclin 1 (FAS1) domains and promotes the release of TGF- β from latent TGF- β -binding protein.²⁴⁵ Periostin (Postn) has been confirmed as a profibrotic factor and was upregulated in ADPKD.³⁶⁴ Studies reported that global knockout of postn in pcy/pcy mice, an ADPKD mouse model, significantly inhibited renal cyst development and renal fibrosis.³⁶⁵ In contrast, overexpression of periostin obtained the opposite results.³⁶⁶ All these effects of periostin on fibrosis in ADPKD were thought to be mediated by integrin $\alpha \nu \beta 3$.^{364–366} Recently, osteopontin was reported as a urinary biomarker for predicting ADPKD progression.³⁶⁷ Since osteopontin is another ligand that activates the interaction between integrin $\alpha \nu \beta 3$ and TGF- $\beta 1$, this study seems to confirm the profibrotic effects of integrin $\alpha \nu \beta 3$ in ADPKD.

Integrin $\beta 1$ is the most prevalent β -chain integrin subunit expressed in the kidney.³⁶⁸ It has been reported that knockout of ITGB1 significantly ameliorates renal fibrosis by suppressing the expression of α -smooth muscle actin (α -SMA), fibronectin, and collagen in the kidneys of PKD1 knockout mice.³⁶³ Several integrins that contain the $\beta 1$ subunit have been identified as regulators of renal fibrosis, including $\alpha 1 \beta 1$,³⁶⁹ $\alpha 2 \beta 1$,³⁷⁰ $\alpha 5 \beta 1$,³⁷¹ and $\alpha \nu \beta 1$.³⁷² Although whether these integrins function in the fibrotic process of ADPKD has not been fully elucidated, their great potential to be developed as an antifibrotic target for ADPKD treatment could not be neglected.

In addition, integrins contain $\alpha \nu$ subunits (such as $\alpha \nu \beta 5$ ³⁷³ and $\alpha \nu \beta 6$ ³⁷⁴), and integrin $\alpha 3$ ³⁷⁵ also participates in promoting renal fibrosis. However, the roles they play in ADPKD are unclear. However, there is no integrin inhibitor that undergoes a clinical trial to evaluate its therapeutic effects on renal fibrosis. In future studies, the profibrotic mechanism of integrins in ADPKD and evaluating their therapeutic effect on ADPKD are expected to disperse the dimness brought by ADPKD.

Integrin roles in cardiovascular diseases

Atherosclerosis. Atherosclerosis (AS) is the fundamental pathological process of vascular diseases. The rupture of atherosclerotic plaques and secondary thrombosis are the most common causes of severe vascular events. The alteration of integrin signaling pathways can affect multiple aspects of AS, such as endothelial dysfunction and activation, leukocyte homing to the plaque, leukocyte function within the plaque, smooth muscle recruitment and fibroproliferative remodeling, and thrombosis.³⁷⁶ In view of the crucial role of integrins in the occurrence and development of AS, we review the integrin regulation of AS and the potential of integrins as therapeutic targets. The model for atherosclerotic plaque development and the main roles of integrins in the process of AS are shown in Fig. 7.

Oxidized low-density lipoproteins (Ox-LDL) and shear stress generated by blood flow lead to endothelial cell dysfunction, which in turn promotes inflammatory cell homing and infiltration. Monocytes migrate into the subendothelium, transform into macrophages and initiate AS. Ox-LDL can activate $\alpha 5 \beta 1$ and induce $\alpha 5 \beta 1$ -dependent signal transduction, thereby activating the FAK/ERK/p90 ribosomal S6-kinase (p90RSK) pathway to induce NF- κ B signaling.³⁷⁷ Shear stress activates provisional matrix-binding integrins ($\alpha 5 \beta 1$ and $\alpha \nu \beta 3$), and some studies have

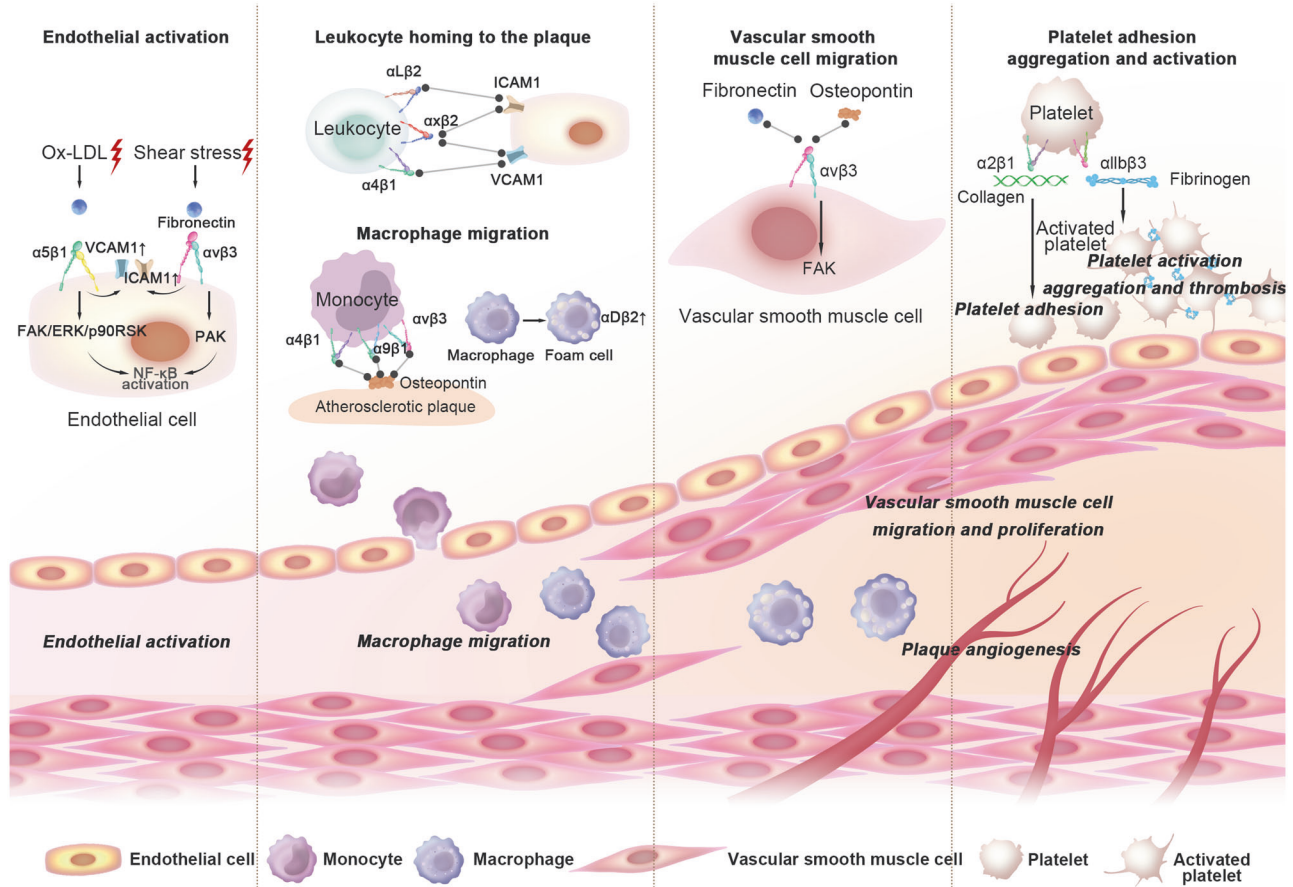


Fig. 7 Main roles of integrins in the process of AS. Integrin signaling can affect multiple processes in AS, including endothelial dysfunction and activation, leukocyte homing to the plaque, smooth muscle cell migration, and thrombosis. In the process of endothelial cell activation, ox-LDL activates $\alpha 5 \beta 1$, induces the FAK/ERK/p90RSK pathway and promotes NF- κ B signaling. Shear stress can activate $\alpha \nu \beta 3$ and induce PAK activation by binding to fibronectin, thereby promoting NF- κ B activation. Both ox-LDL and shear stress generated by blood flow mediate the increased expression of proinflammatory genes (ICAM-1 and VCAM-1) after integrin ligation. During the process of leukocyte homing to plaques, $\alpha \nu \beta 2$ and $\alpha 4 \beta 1$ interact with VCAM-1 on the endothelial cell surface, and $\alpha \nu \beta 2$ and $\alpha \nu \beta 2$ interact with ICAM-1 to promote leukocyte adhesion. Integrins $\alpha 4 \beta 1$, $\alpha 9 \beta 1$ and $\alpha \nu \beta 3$ on the surface of monocytes interact with osteopontin, which is expressed in atherosclerotic plaques, to promote monocyte migration and survival. Integrin $\alpha D \beta 2$ is upregulated during macrophage foam cell formation. During vascular smooth muscle cell migration, $\alpha \nu \beta 3$ binding with fibronectin, osteopontin, etc., mediates FAK activity and drives migration. In the process of thrombosis, integrins $\alpha 2 \beta 1$ and $\alpha I I b \beta 3$ on platelets are involved in platelet adhesion, activation, aggregation, and thrombosis

reported that $\alpha \nu \beta 3$ inhibition is sufficient to prevent NF- κ B activation involving p21-activated kinase (PAK) signaling on fibronectin.^{378,379} In addition, proinflammatory gene expression (ICAM-1 and VCAM-1) also increases after ox-LDL and shear stress-induced ligation of provisional matrix-binding integrins.^{377,380}

Leukocytes express integrins that mediate interactions with cell-adhesion molecules on endothelial cells. Several studies have shown that $\alpha 4 \beta 1$ and various $\beta 2$ integrins play vital roles in the formation of atherosclerotic plaques. $\alpha 4 \beta 1$ is the major leukocyte VCAM-1 receptor.³⁸¹ $\alpha \nu \beta 2$ and $\alpha 4 \beta 1$ can bind VCAM-1 cooperatively to promote leukocyte adhesion.³⁸² In addition, $\alpha \nu \beta 2$ and $\alpha \nu \beta 2$ interact with ICAM-1/2 on the surface of endothelial cells. A deficiency of α integrin significantly reduces monocyte recruitment and AS development in apoE^{-/-} hypercholesterolemic mice.³⁸³ Monocyte integrins $\alpha 4 \beta 1$, $\alpha 9 \beta 1$, and $\alpha \nu \beta 3$ interact with osteopontin, which is expressed in atherosclerotic plaques, to promote monocyte migration and survival.³⁸⁴ Integrin $\alpha D \beta 2$ shows prominent upregulation during macrophage foam cell formation.³⁸⁵ Meanwhile, ligation of specific macrophage integrins (e.g., $\alpha M \beta 2$, $\alpha \nu \beta 3$) may affect various aspects of macrophage function in AS,³⁷⁶ including macrophage clearance of local lipid deposits,^{386–388} phagocytosis of apoptotic cell debris^{389,390} and the ability to promote local proinflammatory

gene expression.³⁹¹ Recently, nexinhib20, a neutrophil exocytosis inhibitor, has been confirmed to inhibit exocytosis and neutrophil adhesion by limiting $\beta 2$ activation,³⁹² which sheds new light on targeting integrin $\beta 2$ therapy.

Vascular smooth muscle cells (VSMCs) are vital in the progression of AS because they can transdifferentiate into proliferative and migratory phenotypes. Current studies support the key role of $\alpha \nu \beta 3$ signaling in smooth muscle proliferation and migration. Both $\alpha 5 \beta 1$ and $\alpha \nu \beta 3$ bind to fibronectin, and their inhibitors reduce atherosclerotic plaque formation, but only $\alpha \nu \beta 3$ inhibition reduces fibrous cap formation incidence.^{378,393} Ligation of $\alpha \nu \beta 3$ and $\alpha \nu \beta 5$ integrins mediates FAK activity³⁹⁴ and causes VSMC migration by AKT and paxillin phosphorylation.^{395–397}

The rupture of an atherosclerotic plaque is the primary trigger for arterial thrombosis. Platelets express integrins of the $\beta 1$ and $\beta 3$ families ($\alpha 2 \beta 1$, $\alpha 5 \beta 1$, $\alpha 6 \beta 1$, $\alpha \nu \beta 3$, and $\alpha I I b \beta 3$), whose main ligands are collagen, fibronectin, laminins, vitronectin, and fibrinogen, respectively.³⁹⁸ Platelet adhesion promoted by $\alpha 2 \beta 1$ induces $\alpha I I b \beta 3$ activation by the phospholipase C-dependent stimulation of the small GTPase Rap1b.³⁹⁹ Inactive $\alpha I I b \beta 3$ on resting platelets is conformationally converted into active to bind fibrinogen, triggering platelet aggregation and augmenting thrombus growth.

Although integrin signaling has been found to be involved in multiple developmental stages of AS, there are still a wide range of pathological processes that need to be further explored. Future studies should focus on more selective integrin inhibitors and explore better ways to target integrin inhibitors to specific cell types to establish the worth of integrins as therapeutic targets for reducing AS and its complications.

Thrombosis. Thrombosis can occur in the arterial or venous circulation and has become a major health issue associated with high morbidity and mortality.⁴⁰⁰ Arterial thrombosis caused by rupture of atherosclerotic plaque has been mentioned above.

α IIb β 3 is the most abundant integrin in blood platelets⁴⁰¹ and is critical for arterial thrombosis.⁴⁰² It binds to fibrinogen by the HHLGGAKQAGV sequence in the C-terminus of the fibrinogen γ chain and RGD sequences in the α chain.³⁹⁸ Inside-out signaling activates α IIb β 3, which contributes to platelet adhesion and aggregation. Outside-in signaling mediates platelet spreading and amplifies platelet thrombi.^{403–406} Therefore, α IIb β 3 antagonists, which are designed to block the ligand binding function of α IIb β 3, are able to treat thrombosis, such as three current FDA-approved antiplatelet agents (abciximab, eptifibatid, and tirofiban). Numerous oral compounds (orbofiban, sibrafiban, xemilofiban, lefradafiban, and roxifiban) have undergone substantial research. Because of adverse effects such as increasing cardiovascular events, oral active antagonists have not yet received approval.²⁴

Compared to α IIb β 3, α v β 3 is widely expressed in tissues in addition to platelets.⁴⁰⁷ A growing number of studies have shown that integrin α v β 3 is essential for mediating the adhesion of monocytes, platelets, and endothelial cells. One of the key regulators of pathological angiogenesis and endothelial function is generally α v β 3 integrin.^{408–410} In vivo, it is expressed at low levels on quiescent endothelial cells but is markedly increased during wound angiogenesis, inflammation, and tumor angiogenesis.²⁷⁹ In vitro, α v β 3 mediates the adherence of platelets to osteopontin and vitronectin.⁴¹¹ It is also involved in the regulation of endothelial cell function,^{412,413} platelet aggregation and thrombosis.^{414,415} Moreover, clinical studies suggest that genetic variants of integrin β 3 may be used to predict venous thromboembolism in colorectal cancer patients.⁴¹⁶ Therefore, integrin α v β 3 is an emerging approach for the identification and treatment of thrombotic-related diseases. Further research is still required to determine its reliability and specific mechanism.

In addition to integrins expressed on platelets, α 9 β 1, which is highly expressed in neutrophils, is also involved in thrombosis via several mechanisms.^{417–419} α 9 β 1 is upregulated during neutrophil activation and interacts with VCAM-1 and polymeric osteopontin to mediate neutrophil chemotactic activity and stabilize adhesion to endothelial cells, leading to an increased risk of thrombosis.^{420,421} Moreover, apoptosis of neutrophils is inhibited by α 9 β 1 through the PI3K and ERK signaling pathways.⁴²² Integrin α 9 can also modulate arterial thrombosis by enhancing NETosis. Treatment with anti-integrin α 9 antibody in wild-type mice inhibits arterial thrombosis, thereby revealing a novel role for integrin α 9 in the modulation of arterial thrombosis.⁴²³ Due to the importance of both neutrophils and neutrophil extracellular traps for deep vein thrombosis and chronic thrombosis,^{424–426} it may be a promising line of research to explore the role of α 9 β 1 in venous thrombosis.

Cardiac hypertrophy. Cardiac hypertrophy is defined as an increase in the size of cardiomyocytes. It is initially an adaptive response to physiological and pathological stimuli, but pathological hypertrophy usually progresses to heart failure.⁴²⁷ Hypertrophy is directly related to β 1 integrin, including β 1A and β 1D.^{428,429} Deficiency of integrin β 1 induces hypertrophic changes with reduced basal contractility and relaxation⁴³⁰ and increases myocardial dysfunction after myocardial infarction.⁴³¹ A previous

study showed a correlation between the expression of integrin β 1 and angiotensin II type 1 (AT₁) receptor. An AT₁ blocker could promote the regression of cardiac hypertrophy by reducing integrin β 1 expression.⁴³² Moreover, a β 3 integrin/ubiquitination (Ub)/NF- κ B pathway has been identified to contribute to compensatory hypertrophic growth.⁴³³ FAK plays a key role in further proceeding the intracellular signals after integrin activation.^{434,435} Moreover, melusin, a muscle-specific integrin β 1-interacting protein, is important in protecting cardiac hypertrophy.^{436,437} ILK also emerges as a crucial player in mechanotransduction by integrins.^{438,439}

Cardiac hypertrophy is not autonomous and is entirely dependent on events occurring in muscle cells. Macrophages can also potentially contribute to the pathogenesis of cardiac hypertrophy. Integrin β 2 contributes to the adhesion of macrophages to endothelial cells, and β 2 blockade attenuates cardiac hypertrophy in mice.⁴⁴⁰ The mechanism of integrins in cardiac hypertrophy needs to be further understood and explored, such as differences in signaling pathways that initiate compensatory and decompensated cardiac hypertrophy. Targeting integrins and signaling pathways may be novel strategies to control cardiac hypertrophy and prevent heart failure.

Integrins play vital roles in myocardial fibrosis. The expression and function of integrins are altered in the diseased heart.⁴⁴¹ Targeting integrins and their associated proteins can be a potential therapeutic target for myocardial fibrosis. Scar tissue size following heart injury is an independent predictor of cardiovascular outcomes.⁴⁴² The differential expression of integrins α v β 3 and α v β 5 in cardiac fibroblasts of collagen V-deficient mice drives myofibroblast differentiation, and a specific inhibitor, cilengitide, can rescue the phenotype of increased postinjury scarring.⁴⁴³ Integrins are also involved in aneurysms. The expression of both α 5 and α v subunits in VSMCs plays an important role in assembling ECM within the vessel wall, and the loss of these two integrins leads to the formation of large aneurysms within the brachiocephalic/carotid arteries.⁴⁴⁴ Thoracic aortic dissection (TAD) is also associated with integrins. Macrophage-derived legumain binds to integrin α v β 3 in VSMCs and blocks it, thus attenuating Rho GTPase activation, down-regulating VSMC differentiation markers, and ultimately exacerbating the development of TAD.⁴⁴⁵

Integrin roles in infectious diseases

SARS-CoV-2 infection. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a dimeric virus in the *Betacoronavirus* genus.⁴⁴⁶ The viral genome consists of four structural proteins, namely, spike (S), envelope (E), membrane (M), and nucleocapsid (N). The envelope, membrane and nucleocapsid are integrated into the viral envelope. A growing number of studies have focused on the integrin-mediated regulation involved in virus entry and spread (Table 1). α v β 6 integrin has been reported to be of interest in inhibiting SARS-CoV-2 entry and treating coronavirus disease 2019 (COVID-19)-related diseases.⁴⁴⁷ SARS-CoV-2 acts on human cells through angiotensin converting enzyme II (ACE2), and recent studies suggested that integrins might be the cell receptors for SARS-CoV-2.⁴⁴⁸ The association between the S protein of SARS-CoV-2 and the ACE2 receptor has been established, but the S1 subunit contains a solvent-exposed RGD-binding motif. It is recognized by integrins, particularly α 5 β 1 and α v β 3.^{449,450} Moreover, the SARS-CoV-2 S protein was reported to interact with integrins independent of the RGD sequence, which helps to explain how SARS-CoV-2 and other viruses evolved to interact with integrins.⁴⁵¹ Viruses bind cell-surface integrins via RGD. In vitro studies have provided evidence of cognate binding interactions between SARS-CoV-2 S proteins, integrin β 1^{452,453} and integrin β 3.^{454,455} Some drugs or methods that target integrins have been shown to have effects on infection. One study suggested that the ATN-161 molecule inhibited the S

Table 1. Integrins expression involved with SARS-CoV-2 infection

Subtype of integrins	Characteristics	Potential role in infection of SARS-CoV-2
$\alpha v \beta 3$	Expressed throughout the host, particularly in the endothelium.	SARS-CoV-2 caused vascular dysregulation in vitro during COVID-19 via major endothelial integrin $\alpha v \beta 3$ to. ⁴¹³
$\alpha v \beta 6$	A molecular target and an epithelium-specific cell-surface receptor, that is upregulated in injured tissues, including fibrotic lung.	$\alpha v \beta 6$ Integrin, an intriguing target for both the inhibition of SARS-CoV-2 entry and the diagnosis/treatment of COVID-19-related fibrosis. ⁴⁰⁶ PET/CT images using the integrin $\alpha v \beta 6$ -binding peptide (18F- $\alpha v \beta 6$ -BP), as an approach to identify the presence, persistence, and progression of lung damage. ⁴¹⁶
$\alpha v \beta 8$	Expressed via epithelial cells and fibroblasts in the lung.	The high expression of integrin in the lung and its high binding affinity to viral RGD motif ($\sim KD = 4.0$ nM) may be the possible reasons for the high infectivity of SARS-CoV-2. ⁴¹⁷
$\alpha IIb \beta 3$	Expressed on the surface of platelets, and it plays an important role in platelet aggregation and blood clotting.	The integrin $\alpha IIb \beta 3$ -based platelet activation status declined in nonsurvivors compared to survivors in COVID-19 patients. ⁴¹⁸
$\alpha 5 \beta 1$	Expressed in the fetal lung mesenchyme.	Blockade of SARS-CoV-2 binding to integrins $\alpha 5 \beta 1$ and $\alpha v \beta 3$ by the small peptides ATN-161 and Cilengitide reduced viral infectivity and attenuate vascular inflammation. ⁴¹⁹ The S protein of SARS-CoV-2 induces endothelial inflammation by signaling of integrin $\alpha 5 \beta 1$ and NF- κB . ⁴²⁰
$\alpha 4 \beta 7$	Expressed on memory CD4 ⁺ T cells.	COVID-19 is associated with a decrease of the key gut-homing marker $\alpha 4 \beta 7$ in circulating adaptive immune cells. ⁴²¹

protein interaction with $\alpha 5 \beta 1$ integrin, and the interaction of $\alpha 5 \beta 1$ integrin and ACE2 represents a promising approach to treat COVID-19.⁴⁵³ Mn^{2+} accelerates the cell entry of SARS-CoV-2 by inducing integrin extension and binding to high-affinity ligands.⁴⁵⁶ In addition, integrins found on the surfaces of pneumocytes, endothelial cells and platelets may be vulnerable to SARS-CoV-2 virion binding. Below, we summarize six known integrins and their potential roles in SARS-CoV-2.

Although several approaches to integrin delivery to SARS-CoV-2 host cells have been discussed in the current literature, data from peer-reviewed experiments on this topic are still scarce. More data on integrin involvement and integrin ligands in SARS-CoV-2 infection, disease progression, and recovery are needed before clinically relevant imaging or therapeutic approaches can be realized.

Human immunodeficiency virus (HIV). Monocytes/macrophages play an important role in HIV transmission in all stages of HIV infection and disease. Adhesion molecules, including integrins, are recognized as the main factors that influence HIV viral replication. Previous studies proved that blocking αv and integrin binding triggered a signal transduction pathway, which inhibited the transcription of NF- κB -dependent HIV-1.⁴⁵⁷ Inhibition of β integrins (specific monoclonal antibody, small RGD mimetic compounds, and RNA interference) proved that integrin $\beta 5$ mainly contributed to the blockade of HIV-1 replication.⁴⁵⁸ Other integrins, such as $\alpha v \beta 3$ and $\alpha 4 \beta 7$, have also been proven to be associated with HIV. For example, the transactivating factor of HIV-1 binds to integrin $\alpha v \beta 3$, prompting neovascularization.⁴⁵⁹ $\alpha 4 \beta 7$, as a structurally dynamic receptor, mediates outside-in signaling to cells. The HIV envelope protein GP120 binds to and signals by $\alpha 4 \beta 7$ ⁴⁶⁰; thus, targeting $\alpha 4 \beta 7$ might be a new therapeutic method to prevent and treat HIV infection.⁴⁶¹

Other infectious diseases, such as the West Nile virus, enter cell entry by using the integrins $\alpha v \beta 1$ and $\alpha v \beta 3$.^{462,463} Ebola is related to integrin $\alpha 5 \beta 1$, and herpes simplex virus type 1 (HSV-1) interacts with $\alpha v \beta 3$.^{464,465} Moreover, in immunized mice, the increased frequency of circulating integrin $\alpha 4 \beta 7^+$ cells is correlated with protection against *Helicobacter pylori* infection.⁴⁶⁶ $\beta 2$ integrin is important in the recruitment of dendritic cells to the infection site and may affect the initiation of innate immunity.⁴⁶⁷ The over-expression and suppression of integrin $\alpha 6$ increases and decreases

stemness phenotypes of HPV^{+ve} head-neck squamous cell carcinoma (HNSCC) cells, respectively.⁴⁶⁸ Severe anti-programmed death-1 (PD-1)-related meningoencephalomyelitis can be treated with anti-integrin $\alpha 4$ therapy.⁴⁶⁹ Studies of murine and human cells expressing RGD-binding integrins proved that $\alpha v \beta 6$ and $\alpha v \beta 8$ heterodimers were involved in M1 and M3 infections.⁴⁷⁰ These targets are of great significance for the mechanistic exploration and treatment of HIT and other infectious diseases, and more research data are needed in the future.

Integrin roles in autoimmune diseases

Integrins participate in the immune response against autoimmune diseases such as inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, which induces strong adhesion between lymphocytes, endothelial cells and epithelial cells by binding to ECMs and specific receptors. Many integrins are expressed in T cells, B cells, neutrophils, natural killer (NK) cells, monocytes, dendritic cells, macrophages, and platelets.⁴⁷¹

Inflammatory bowel disease (IBD). IBD comprises a series of chronic recurrent intestinal diseases, including ulcerative colitis (UC) and Crohn's disease (CD).⁴⁷² The pathogenesis of IBD has not yet been clearly elucidated, and genetic predisposition, dysregulation of gut microbiota, or environmental factors cause an inappropriate and persistent immune response triggering impaired intestinal barrier function and stenosis.^{473–476} Evidence suggests that IBD and its associated complications are not only modulated by sustained inflammation but also maintained by inflammation-independent mechanisms.⁴⁷⁷ Integrins have been considered to be involved in both inflammatory and inflammation-independent mechanisms due to their important roles in immune cell recruitment and cell-ECM interactions in intestinal diseases.^{478,479}

Integrins $\alpha 4 \beta 7$, $\alpha 4 \beta 1$, and $\alpha E \beta 7$ are mainly involved in mediating lymphocyte homing to the intestinal mucosa. Integrin $\alpha 4 \beta 7$ is specifically expressed on lymphocytes in the gastrointestinal tract and mediates the motility and adhesion of lymphocytes when inactive and activated, respectively.^{480–483} Integrin $\alpha 4 \beta 7$ highly expressed on CD4⁺ memory T cells interacts with MAdCAM-1 expressed in intestinal inflammatory foci and regulates the homing of activated T cells during

inflammation.^{484–486} In addition, $\alpha 4\beta 7$ expression promotes the infiltration of regulatory T cells into the gut, whereas blockade reduces enteric homing of regulatory and effector T cells.⁴⁸⁰ $\alpha 4\beta 1$ integrins (found on most leukocytes) are highly expressed in lymphoid tissues of the gut and interact with VCAM-1 expressed on the endothelium.^{487–489} Adoptive transfer of $\alpha 4$ null T cells inducing defective homing of T cells to the inflamed tissues in immunodeficient mice significantly alleviated chronic colitis.⁴⁹⁰ Blocking $\alpha 4$ -integrin prevents immune infiltration of the activated T-cell populations driving IBD.^{488,491} Integrin $\alpha E\beta 7$ is mainly expressed on the surface of $CD8^+$ T cells, Treg cells, $CD69^+\alpha E^+$ intestinal tissue-resident memory T (TRM) cells, TH9 cells, and mucosal DC subsets, allowing them to adhere to the layer of the intestinal epithelium as a result of interacting with its ligand E-cadherin.^{492–498} $CD8^+$ T cells remain within the intestinal epithelium by downregulating $\alpha 4\beta 7$ and upregulating $\alpha E\beta 7$ to bind E-cadherin.^{499,500} Proinflammatory $CD4^+$ T cells displaying Th17 and Th1 inflammatory phenotypes highly express $\alpha E\beta 7$ in the colon and reduce the expression of associated genes, including inducible costimulator (ICOS), cytotoxic T-lymphocyte antigen (CTL-4), interleukin-10 (IL-10), and forkhead box protein P3 (FOXP3).⁴⁸⁹ A subset of $CD4^+$ T cells with the natural killer group 2D (NKG2D) receptor also express integrin $\alpha E\beta 7$, which is characterized by inflammatory and cytotoxic effects.⁵⁰¹ Th9 $CD4^+$ and $CD8^+$ cells expressed increased $\alpha E\beta 7$ compared with $\alpha 4\beta 7$ expressed by Th17 and Th2 T cells.⁴⁹⁶ In the colon of UC patients, the ability of αE^+ dendritic cells (DCs) to generate regulatory T cells is attenuated and induces a Th1/Th2/Th17 phenotype in $CD4^+$ effector T cells.⁵⁰² The frequency and tolerogenic functionality of αE^+ DCs are altered in the inflamed intestinal mucosa.⁵⁰³ In addition to being physically retained in the intestinal epithelium, T lymphocytes expressing $\alpha E\beta 7$ have direct cytotoxic activity against epithelial cells,^{489,504} and αE expression on a subset of resident memory $CD4^+CD69^+$ T cells accumulated in the mucosa of IBD patients predicts the development of flares.⁴⁹⁵ Blockade of $\beta 7$ integrin inhibits lymphocyte migration to gut-associated lymphoid tissue (GALT) and persistently suppresses adaptive immune-mediated IBD.^{505–507} In addition, integrin $\alpha v\beta 5$ is highly expressed on mature intestinal macrophages but not other immune cells in the mouse intestine, acts as a receptor for apoptotic cell uptake and promotes tissue repair by regulating the homeostatic properties of intestinal macrophages, such as angiogenesis and ECM remodeling.⁶⁴ Integrin $\alpha v\beta 6$ is expressed only in epithelial cells and is mainly regulated by the integrin $\beta 6$ (ITGB6) gene, which can increase integrin-ligand expression, macrophage infiltration, proinflammatory cytokine secretion, and signal transducer and activator of transcription 1 (STAT1) signaling pathway activation. ITGB6 transgenic mice were found to have increased susceptibility to both acute and chronic dextran sulfate sodium-induced colitis, and $\alpha v\beta 6$ induces intestinal fibrosis through the FAK/AKT pathway.^{508,509}

Anti-inflammatory treatment is ineffective in the development of fibrosis in IBD, a consequence of chronic inflammation. The mechanism of fibrosis is thought to be a continuous interaction between the stiffened ECM matrix resulting from the aberrant release of ECM components and cellular compartments.⁵¹⁰ During tissue injury, matrix deposition and turnover are highly disrupted, resulting in dysregulated matrix stiffness in the ECM.^{511,512} Increased matrix stiffness triggers colonic myofibroblast activation to produce a fibrogenic phenotype and autopropagate fibrosis.⁵¹³ The expression of genes related to inflammatory and fibrogenic remodeling was significantly increased, suggesting the presence of both fibrosis and inflammation in CD strictures. Interstitial ECM is the most fundamental in the process of fibrosis, including the latent state of TGF- β , EGF, fibroblast growth factor (FGF) and other molecular fibrotic mediators.⁵¹⁴ αv and $\beta 5$ are the major integrin isoforms in intestinal fibrosis, and their main function is to activate

TGF- β . $\alpha v\beta 8$ binds to a linear RGD motif of latent TGF- β , which subsequently recruits MMP14 and then releases TGF- β through proteolytic cleavage. $\alpha v\beta 8$ can also activate TGF- β independently from cytoskeletal forces without release from latent peptide.²⁵⁶ In vivo studies have shown that overexpression of $\alpha v\beta 6$ in the epidermis activates TGF- $\beta 1$, resulting in chronic ulcers and fibrosis.⁵¹⁵ Latent TGF- $\beta 1$ was also activated through integrin $\alpha v\beta 3$ expressed in human and rat intestinal smooth muscles,⁵¹⁶ leading to the production of collagen I and fibrosis in CD.⁵¹⁷ The elevated expression of $\alpha 3\beta 1$ can enhance the expression level of MMP9 in keratinocytes through the TGF- β pathway.⁵¹⁸

Natalizumab (anti- $\alpha 4$ antibody) and vedolizumab (anti- $\alpha 4\beta 7$ antibody) have been approved for maintaining clinical remission in patients with IBD.^{519,520} Natalizumab was the first drug approved for the treatment of Crohn's disease, but its use has been limited because of its risk of progressive multifocal leukoencephalopathy.^{521,522} Compared with natalizumab, vedolizumab acts specifically on $\alpha 4\beta 7$ to selectively inhibit the trafficking of lymphocytes in the intestine. It has been approved for the treatment of IBD with few systemic adverse effects.^{523,524} Currently, several anti-integrin drugs are undergoing more clinical trials. Abrilumab, a fully human monoclonal IgG2 antibody against the $\alpha 4\beta 7$ integrin heterodimer, shows encouraging results in two phase II studies on moderate to severe CD and UC (CD: NCT01696396, UC: NCT01694485),^{525,526} while no phase III clinical trial registration information has been found to date. Etrolizumab is a monoclonal antibody that specifically targets the $\beta 7$ subunit of $\alpha 4\beta 7$ and $\alpha E\beta 7$ integrins to block their interaction with MAdCAM-1 and E-cadherin, respectively, which is in an ongoing robust phase II study on UC and a phase III study on CD. Notably, a phase I study of etrolizumab to evaluate its pharmacokinetics, pharmacodynamics and safety in pediatric patients 4 to <18 years of age with moderate to severe ulcerative colitis (UC) or with moderate to severe CD has been registered. AJM300, an oral $\alpha 4$ integrin antagonist characterized by mild adverse effects sharing a similar mechanism with natalizumab^{527,528} is currently in a phase III study of patients with active UC (NCT03531892).

Multiple sclerosis (MS). MS is an autoimmune disease driven by agnogenic chronic inflammation in the central nervous system (CNS). It is characterized by inflammation in the brain and spinal cord that causes the demyelination of neurons, which blocks nerve signal transmission.⁵²⁹ MS patients show sensory disorders, motor dysfunction, optic neuritis, and other physical and cognitive disorders.⁵²⁹ Currently, there are approximately 2.5 million people with MS worldwide,⁵³⁰ which is a huge burden to society. The infiltration of autoreactive immune cells from peripheral circulation into the brain is the core pathogenesis of MS.⁵³¹ Preventing the infiltration processes of leukocytes into the CNS is an effective way to curb the progression of MS. Therefore, the adhesion molecules involved in leukocyte activation and mediating leukocyte migration to the CNS have received extensive attention. Among them, leukocyte integrins, as mentioned above, play important roles in regulating leukocyte function. In fact, in recent years, studies on the role of integrins in MS have yielded exciting results. In particular, integrin $\alpha 4$. Integrin $\alpha 4$ pairs with integrin $\beta 1$, $\beta 2$, or $\beta 7$, of which integrin $\alpha 4\beta 1$ is regarded as an important therapeutic target for MS. Integrin $\alpha 4\beta 1$ is also called very late antigen-4 (VLA-4), which binds primarily to VCAM-1 and ECM ligand fibronectin deposited in inflamed tissues. The interaction between integrin $\alpha 4\beta 1$ and VCAM-1 promotes the homing of leukocytes into the CNS, which accelerates the progression of MS. Disturbing the interaction between integrin $\alpha 4\beta 1$ and VCAM-1 has been shown to effectively retard the progression of MS. As early as 1992, Yednok et al. demonstrated that inhibiting integrin $\alpha 4\beta 1$ could effectively suppress the accumulation of leukocytes in the CNS, and they recommended anti-integrin $\alpha 4\beta 1$ antibody as therapeutic for MS.⁵³² Natalizumab, a humanized IgG4 antibody

that recognizes integrin $\alpha 4$, has been confirmed to significantly reduce the risk of the sustained progression of disability and the rate of clinical relapse in patients with relapsing MS. It could also enhance the therapeutic effect of interferon- β 1 α (IFN- β 1 α) on MS when combined with it. However, it has been reported that long-term use of natalizumab may cause serious infection complications, such as progressive multiple leucoencephalitis (PML). Therefore, there is still a long way to go for the treatment of MS by targeting integrin $\alpha 4\beta 1$. Novel integrin $\alpha 4\beta 1$ inhibitors may be the key to overcoming MS in the future.

Rheumatoid arthritis (RA). RA is a chronic and systemic autoimmune inflammatory disease that is characterized by synovial hyperplasia, articular inflammation, and synovial invasion into adjacent cartilage.⁵³³ Integrins play an important role in the pathophysiology of RA, such as promoting communication between ECM proteins and rheumatoid cells and facilitating angiogenesis. $\alpha \nu \beta 3$ and $\alpha 5\beta 1$ are expressed on synoviocytes, including chondrocytes, fibroblasts, and endothelial cells, and synovial-infiltrated cells, including T cells, neutrophils, B cells and macrophages, which promote binding to cartilage-pannus junctions and fibroblast invasion.^{534–536} Fibronectin upregulated in inflamed articular tissues is a ligand of $\alpha \nu \beta 3$ and $\alpha 5\beta 1$.⁵³⁴ $\alpha 5\beta 1$ promotes the proliferation of naive T cells and memory T cells by binding to fibronectin.⁵³⁴ In RA, osteoclasts express $\alpha \nu \beta 3$ at high levels, and $\alpha \nu \beta 3$ promotes bone resorption because of osteoclast migration by recruiting c-Src kinase.⁵³⁷ Macrophages and Th cells expressing $\alpha \nu \beta 3$ and $\alpha 5\beta 1$ produce IL-17, IL-1, and tumor necrosis factor (TNF)- α , which lead to the activation of synovial fibroblasts.^{538,539} Neutrophils express $\alpha \nu \beta 3$ and $\alpha 5\beta 1$, which contribute to neutrophil migration and mediate cell adhesion to neutrophil extracellular traps (NETs).⁵³⁶ $\alpha \nu \beta 3$ expressed by Th17 cells enables them to adhere to osteopontin, which serves as a costimulator of IL-17.⁵⁴⁰ Inhibition of $\alpha \nu \beta 3$ prevents osteoclast-mediated bone destruction by reducing Th17 activation and receptor activator of nuclear factor- κ B ligand (RANKL) levels.⁵⁴⁰ In addition, integrins in RA could promote new vascularization, accumulation of synovial cells, and the secretions lead to hypoxia-inducible factor 1 (HIF-1) release, which acts as a stimulator of VEGF, PDGF and fibroblast growth factor 2 (FGF-2). These growth factors induced overexpression of $\alpha \nu \beta 3$ and $\alpha 5\beta 1$ in smooth muscle cells, endothelial cells, and platelets. Upregulated $\alpha \nu \beta 3$ and $\alpha 5\beta 1$, in turn, further activate proinflammatory cytokine production, which mediates smooth muscle cell and endothelial cell proliferation and migration and platelet activation.^{541–543} Furthermore, $\alpha 9$ is reported to be overexpressed both in animal models of arthritis and in RA patients, and increased $\alpha 9$ expression precedes the onset of arthritic symptoms. Blocking $\alpha 9$ inhibits fibroblast-like synoviocyte (FLS) activation against arthritis through a nonimmune-mediated mechanism.⁵⁴⁴

In addition to the abovementioned diseases, integrins and their ligands are also involved in the progression of other autoimmune diseases. Multiple sclerosis is a demyelinating and inflammatory disorder of the CNS. Integrins such as $\alpha 4\beta 7$, $\alpha E\beta 7$, and $\alpha 4\beta 1$ and their ligands are involved in the progression of multiple sclerosis by modulating the processes of immune cells.⁵⁴⁵ B cells, neutrophils, and macrophages express high amounts of $\alpha M\beta 2$, and systemic lupus erythematosus (SLE)-IgG enhances $\alpha M\beta 2$ -mediated adhesion to fibrinogen in systemic lupus erythematosus.⁵⁴⁶ Inhibition of the $\alpha 1\beta 1$ interaction with collagen leads to reduced accumulation of epidermal T cells, and the presence of anti- $\alpha 6$ -integrin autoantibodies due to altered laminin integrity has been observed in psoriasis.^{547,548}

Integrin roles in other diseases

In addition to the above reports of integrin-related diseases, integrins also contribute to eye development and pathological processes, including the healing process of keratoconus injuries,

allergic eye disease, cornea, lens opacification, diabetic retinopathy, glaucoma, eye infection, axon degeneration in the optic nerve, and scleral remodeling in high myopia.⁵⁴⁹ For example, $\alpha 5\beta 1$ integrin participates in anchoring or integrating transplanted stem cells to the trabecular meshwork in the eye for regeneration, and this might be a way for stem cell-based therapy for glaucoma.⁵⁵⁰ Vitronectin/ $\alpha \nu$ -integrin-mediated NF- κ B activation has been proven to induce inflammatory gene expression in bone marrow-derived macrophages. This will be an important step in the inflammatory process of dry eye disease (DED).⁵⁵¹ In addition, drug discovery focused on integrin $\alpha \nu \beta 2$, providing a marketed small molecule, LifiteGrast, for the topical treatment of DED.⁵⁵² For ophthalmic diseases, integrin inhibitors were proven to be effective in several preclinical models and have reported promising results in clinical trials.⁵⁵³

Integrins are also promising antiresorptive therapeutic targets.⁵⁵⁴ Osteoactivin promotes integrin $\beta 1$ expression and leads to ERK activation. The expression of several genes upstream of osteoactivin was blocked, and the mRNA and protein levels of osteoactivin were decreased by dexamethasone. This ultimately inhibits integrin $\beta 1$ -ERK activation, resulting in reduced osteogenesis.⁵⁵⁵ In addition, $\alpha \nu \beta 3$ integrin participates in osteoclast differentiation and resorption, and $\alpha \nu \beta 3$ -integrin antagonists are considered to be effective drugs for postmenopausal osteoporosis.⁵⁵⁶ L-000845704, as an $\alpha \nu \beta 3$ -integrin antagonist, was reported to inhibit bone resorption and improve bone mass in women with postmenopausal osteoporosis. A phase II clinical trial of 227 postmenopausal women with osteoporosis showed that L-000845704 could decrease the bone absorption marker carboxyterminal telopeptides of type I collagen (CTX) and increase the bone mineral density of the lumbar spine and femoral neck.⁵⁵⁷

Alzheimer's disease (AD), characterized by cognitive decline, is a neurodegenerative disorder and is associated with amyloid- β ($A\beta$) plaque deposition, neuronal loss, and hyperphosphorylation of tau protein. Astroglial-associated AD is known to be caused by the interaction of amyloid β oligomers with $\beta 1$ integrin. This enhanced $\beta 1$ integrin and NADPH oxidase (NOX) 2 activity by NOX-dependent mechanisms.⁵⁵⁸ In transgenic AD models, neutrophil depletion or inhibition of neutrophil trafficking by lymphocyte function-associated antigen (LFA)-1 blockade can reduce AD-like neuropathology and improve memory in mice showing cognitive dysfunction.⁵⁵⁹ The counter ligand of VCAM-1- $\alpha 4\beta 1$ integrin, expressed by a large proportion of blood CD8⁺ T cells and neutrophils, was abundant on circulating CD4⁺ T cells in AD mice.⁵⁶⁰ This suggested that $\alpha 4$ integrin-dependent leukocyte trafficking promoted cognitive impairment and AD neuropathology. Thus, the blockade of $\alpha 4$ integrins might be a new therapeutic method for AD. Recently, compared to isotype control injections without changing amyloid- β plaque load in a mouse model of AD, an antibody recognizing $\alpha 4$ -integrin therapy reduced astroglial, microglial, and synaptic changes in APP/PS1 mice.⁵⁶¹

CHALLENGES AND OPPORTUNITIES: INTEGRIN-TARGETING DRUG DISCOVERY FROM BENCH TO CLINICAL

Integrins have historically been promising and challenging targets for the treatment of multiple diseases. The targeting integrin-related indications are summarized in Table 2, referring to cancer, fibrotic diseases, cardiovascular disease, viral infections, autoimmune diseases, and so on. The ongoing clinical studies of integrin-targeting drugs intended as disease therapies are summarized in Table 3 (from 2019 to 2022). Currently, there are ~90 kinds of integrin-targeting therapies in clinical trials, including integrin antagonists and imaging agents (search at <https://www.clinicaltrials.gov>, <https://www.clinicaltrials-register.eu>, <https://www.australianclinicaltrials.gov.au>, <http://www.chictr.org.cn> using the search term "integrin") (Table 4). Among them, approximately

Table 2. The targeting integrin-related indications in clinical trials

Indication	Target in clinical research
Ulcerative colitis and Crohn's disease	$\alpha 4\beta 7$; $\alpha 4\beta 1$; $\alpha E\beta 7$; $\alpha 2\beta 1$
Multiple sclerosis	$\alpha 4\beta 7$; $\alpha 4\beta 1$; $\alpha 2\beta 1$
Acute coronary syndrome and thrombotic cardiovascular events	$\alpha IIb\beta 3$; $\alpha 4\beta 1$
Plaque psoriasis	$\alpha v\beta 3$; Integrin α ; $\alpha 4\beta 1$; $\alpha L\beta 2$
Rheumatoid arthritis	$\alpha 1\beta 1$; $\alpha 9\beta 1$; $\alpha v\beta 3$
Cancers	Pan- αv ; $\alpha 5\beta 1$; $\alpha 2$; $\alpha L\beta 2$; $\alpha 4\beta 1$; $\beta 6$; $\alpha 3\beta 1$; $\beta 7$
Diabetic nephropathy	$\alpha v\beta 3$
Interstitial fibrosis and tubular atrophy; idiopathic pulmonary fibrosis	Pan- αv
HIV	$\alpha 4\beta 7$; LFA-1A; $\alpha 4\beta 1$
SARS-CoV-2	$\alpha v\beta 1$; $\alpha v\beta 6$
Dry eye disease	LFA-1; $\alpha 4$
Symptomatic focal vitreomacular adhesion; diabetic macular edema; non-proliferative diabetic retinopathy; non-exudative macular degeneration; age-related macular degeneration	Pan- αv ; $\alpha 2\beta 1$; $\alpha 4\beta 1$; $\alpha 5\beta 1$
Patellar osteoarthritis involving both knees; patellofemoral osteoarthritis involving both knees	Pan- αv ; $\alpha 4\beta 1$
Asthma	$\alpha 4\beta 1$; $\alpha 4\beta 7$
Imaging agent	$\alpha v\beta 3$; $\alpha v\beta 5$; $\alpha v\beta 6$; $\alpha 6$; $\alpha IIb\beta 3$;
Leukocyte adhesion deficiency-I	$\beta 2$

two-thirds of drugs or imaging agents are being studied in Phase I to Phase III, and nearly one-third of integrin-targeting therapies are terminated, withdrawn or no progression. The related reasons are manifold, including delayed and difficult enrollment, lack of efficacy, safety concerns, commercial decision making, and lack of funding. In 2022, the positive results in clinical trials show the new dawn of integrin-targeting therapies. For example, carotegrast (AJM300) is an oral, targeting $\alpha 4$ -integrin small-molecule antagonist, and the phase III study results showed that carotegrast was well tolerated and induced a clinical response in patients with moderately active ulcerative colitis who had an inadequate response or intolerance to mesalazine. Carotegrast, as the first oral anti-integrin drug, was approved by Japan's PMDA on March 28, 2022, for moderate ulcerative colitis (only when 5-aminosalicylic acid preparations are not adequately treated).⁵⁶² Pliant Therapeutics, Inc. (PLRX) reported positive results for PLN-74809, the oral dual $\alpha v\beta 1/\alpha v\beta 6$ inhibitor, in the INTEGRIS-IPF Phase IIa study, which met its primary and secondary endpoints, demonstrating that PLN-74809 was well tolerated over the 12-week treatment period and showed a favorable pharmacokinetic profile. Herein, we summarize the main progression of small molecules, synthetic mimic peptides, antibodies, ADCs, peptide drug conjugates (PDCs), nanotherapeutic agents, CAR T-cell therapy, and imaging agents.

Small-molecule compounds and peptides

Small-molecule drugs accounted for the largest part of the ongoing clinical trials given their cost advantage, safety perspective, pharmacokinetic profiles, administration route, etc., compared with antibodies or larger conjugate molecules. Historically, many RGD-binding integrin drug discovery initiatives have been carried out to target the orthosteric binding sites, but most of

these drug discoveries have not been successful due to the potential binding-induced conformational shifts of integrin from a low-affinity to a high-affinity state.²⁸ These reactions have been found for $\alpha IIb\beta 3$ RGD mimetics such as eptifibatide and $\alpha v\beta 3$ -integrin RGD mimetics cilengitide, which shows direct agonist and proangiogenic effects at low doses.

In light of this potential effect, some research groups switched to identify non-RGD or pure small-molecule integrin antagonists and inhibitors binding allosterically. Another problem for drug discovery based on RGD-integrins is the undesirable physico-chemical properties due to zwitterionic or amphoteric design. Therefore, novel chemotypes that are nonzwitterionic would be beneficial for oral bioavailability.²⁸ One of the first breakthroughs of non-RGD mimetics is RUC-1 and its more potent derivatives RUC-2 and RUC-4, targeting $\alpha IIb\beta 3$ outside-in signaling pathways, which do not induce integrin activation.^{563,564} A phase I, dose-escalation study showed that RUC-4 administered subcutaneously provided rapid, high-grade inhibition of platelet aggregation and that it is also safe and well tolerated and has the potential to be used at the point of first contact before primary coronary intervention.⁵⁶⁵ RUC-4 was designed as a nonzwitterionic chemotype that does not potentially induce conformational shifts, which provides a promising approach for the discovery of αv -containing integrin antagonists. Other $\alpha v\beta 3$ small-molecule pure antagonists, TDI-4161 and TDI-3761, have been designed and proven to not induce the conformational change tested by cryogenic electron microscopy imaging of integrin conformations.⁵⁶⁶ Recent studies have shown that failed integrin small-molecule inhibitors in clinical trials are capable of stabilizing the extended open conformation with high affinity.⁴⁹ Closing inhibitors show a simple chemical feature with a polar nitrogen atom that stabilizes integrins in their bent-closed conformation by intervening between the serine residue and MIDAS.⁴⁹

The rational design of molecules that bind to integrin outside the ligand binding site, the allosteric site, could prevent integrin activation by sealing the orthosteric site or by keeping or promoting the conformation at a low-affinity state.²⁸ There are only reported some antibodies targeting the allosteric site, such as natalizumab.⁵⁶⁷ In recent years, novel chemotypes with high-quality orally bioavailable inhibitors have made large breakthroughs, such as carotegrast,⁵⁶² PLN-74809,⁵⁶⁸ and PTG-100.⁵⁶⁹ Although PTG-100, an oral $\alpha 4\beta 7$ antagonist peptide, initially did not meet the primary endpoint in a phase IIa study, it showed proof-of-concept efficacy in patients with moderate-to-severe active UC, and the related data also suggested that local gut activity of an oral $\alpha 4\beta 7$ inhibitor is important for efficacy for UC treatment, which is different from full-target engagement in blood. Other orally bioavailable inhibitors under ongoing clinical studies include IDL-2965 and MORF-057, developed by EA Pharma, Pliant, Protagonist, Indalo, and Morphic, respectively (Table 4).

Antibodies, ADCs, and PDCs

Many monoclonal antibodies (mAbs) targeting integrins are now available as research tools or life-changing therapeutics and are classified into three groups: inhibitory mAbs acting as antagonists, stimulatory or activation-specific mAbs, and nonfunctional mAbs.⁵⁷⁰ Anti-integrin mAbs are essentially competitive inhibitors, and most act as allosteric inhibitors, recognizing various parts of the ectodomain of subunit- or conformation-specific integrins.⁵ Abciximab, an antibody against integrin $\alpha IIb\beta 3$, has undergone extensive clinical studies (EPIC, EPILOG, CAPTURE)⁵⁷¹ and has been approved for use during PCI or in patients with unstable angina/non-ST-elevation myocardial infarction that did not respond to traditional treatment.⁸⁴ The integrin $\alpha 4$ antibody natalizumab has shown considerable therapeutic effects on multiple sclerosis.⁵⁶² Vedolizumab, an integrin $\alpha 4\beta 7$ antibody, was used to treat Crohn's disease and ulcerative colitis.⁵⁶² Recently, abrilumab (Amgn), also called AMG-181, targeting the integrin $\alpha 4\beta 7$ heterodimer, showed

Table 3. Recent integrin-targeting drugs intended as disease therapies in ongoing clinical studies (2019–2022)

Disease	Targeted integrins	Drug name	Source	Drug types	Time (first posted)	Study status
Ulcerative colitis and Crohn's disease	$\alpha 4\beta 7$	MORF-057	NCT05291689	Small molecule	2022-03-23	Phase II
		PN-10943	NCT04504383	Small molecule	2020-08-07	Phase II
Solid tumors	$\alpha v\beta 3$	Antiangiotide	CTR20150368; CTR20200847	Peptide	2015-07-20 2020-08-28	Phase I
		BGC-0222	CTR20221496	Peptide drug conjugate	2022-06-16	Phase I
		ProAgio	NCT05085548	Novel proteins synthesized by computer simulation	2021-10-20	Phase I
	$\alpha v\beta 5$	CEND-1	NCT05042128; NCT05052567; NCT05121038; CTR20212588	Peptide	2021-09-13 2021-09-22 2021-11-16 2021-10-22	Phase II
	Pan- αv	HYD-PEP-06	CTR20220769	Small molecule	2022-04-14	Phase II
	$\alpha L\beta 2$; $\alpha 4\beta 1$;	7HP-349	NCT04508179	Small molecule	2020-08-11	Phase I
	$\beta 6$	SGN-B6A	NCT04389632	Antibody drug conjugate	2020-05-15	Phase I
	$\alpha 3\beta 1$; $\alpha 5\beta 1$	ABBV-382	NCT04554966	Antibody	2020-09-18	Phase I
	$\beta 1$	OPC-415	NCT04649073	CAR T-cell therapy	2020-12-02	Phase II
	$\beta 7$	MT-1002	NCT04723186	Peptide	2021-01-25	Phase II
Relapsed and/or refractory multiple myeloma						
Acute coronary syndrome patients with PCI	$\alpha II\beta 3$	Zalunfiban	NCT04825743	Small molecule	2021-04-01	Phase III
		AXT-107	NCT04697758; NCT04746963	Peptide	2021-01-06 2021-02-10	Phase I/II
Diabetic macular edema/neovascular age-related macular degeneration/dry eye disease	$\alpha v\beta 3$; $\alpha 5\beta 1$	THR-687	NCT05063734	Small molecule	2021-10-01	Phase II (Terminated)
		pan- αv ; $\alpha 5\beta 1$	AG-73305	Fusion protein	2022-03-31	Phase II
		LFA-1A	VVN-001	Small molecule	NCT04556838; CTR20211530	2020-09-21 2021-07-01
Imaging diagnosis	$\alpha v\beta 3$	99mTc-3PRGD2	CTR20191465; NCT04233476	Imaging agent	2019-07-30 2020-01-18	Phase III
		Alfatide[18F] [68Ga]-FF58	CTR20213024 NCT04712721	Imaging agent Imaging agent	2021-12-10 2021-01-15	Phase III Phase I
	$\alpha v\beta 3/\alpha v\beta 5$	99mTc- RWY	NCT04289532	Imaging agent	2020-02-28	Early Phase I
	$\alpha 6$	[18F]FBA- A20FMDV2	NCT04285996	Imaging agent	2020-02-26	N/A
	$\alpha v\beta 6$	(68)Ga-RGD	NCT05275699	Imaging agent	2022-03-11	Phase I
	$\alpha v\beta 3$	PLN-74809	NCT04072315; NCT04396756; NCT04480840; NCT04565249	Small molecule	2019-08-28 2020-05-21 2020-07-21 2020-09-25	Phase II
Primary sclerosing cholangitis/idiopathic pulmonary fibrosis/acute respiratory distress syndrome	$\alpha v\beta 1$; $\alpha v\beta 6$	BIIB-107	NCT04593121	Small molecule	2020-10-19	Phase I
HIV	$\alpha 4\beta 7$	OS2966	NCT04608812	Antibody	2020-10-29	Phase I
Multiple sclerosis	$\alpha 4$	Pagantangentide	CTR20210520	Small molecule	2021-04-01	Phase I

encouraging results in a phase II study on moderate to severe CD and UC.⁵⁶² AJM300 is an oral antagonist of integrin $\alpha 4$, which is currently in a phase III study of patients with active UC.⁵⁶² Integrin αv mAbs have a range of selectivity profiles, which are beneficial in the validation of integrin targets in disease, but highly selective αv small-molecule inhibitors are unavailable.⁵⁷² Currently, an example is P5H9 (MAB2528) for $\alpha v\beta 5$.⁵⁷³ Currently, the antibody in the highest clinical trial stage is Etrolizumab, targeting integrin $\beta 7$, which recently carried out a head-to-head comparison, phase III study, with infliximab, approved anti-TNF- α antibody, for the treatment of moderately to severely active ulcerative colitis (GAEDENIA).⁵⁷⁴ Overall, the GARDENIA study demonstrated that etrolizumab and infliximab achieved the same efficacy and safety endpoints at weeks 10 and 54.⁵⁷⁵ This head-to-head comparison

also shows that the safety of the two in long-term results at 1 year is comparable.

Integrins, as cell-surface receptors, are overexpressed in specific diseased tissues, which makes them design ADCs and PDCs to conjugate integrin-binding antibodies and peptides to bioactive moieties. Indeed, recent clinical trials (NCT04389632) and (CTR20221496) have been initiated to investigate an ADC and PDC that selectively recognize $\beta 6$ and $\alpha v\beta 3$, respectively, to target solid tumors.

Nanotherapeutic agents

Integrins have been considered potential targets for cancer treatment for a long time, but there are no approved anticancer drugs targeting integrin. Nanotherapeutics approaches applied in

Table 4. Integrin-targeting therapies in clinical trials

Drug name	Source	Sponsor	Drug types	Time (first posted)	Target	Indication	Dose	Delivery route	Study status
Natalizumab biosimilar	NCT04115488	Polpharma Biologics S.A.	Antibody	2019-10-04	$\alpha 4\beta 1; \alpha 4\beta 7$	Relapsing-remitting multiple sclerosis	300 mg every 4 weeks	IV	Phase III
Etolizumab	Ulcerative colitis: NCT02100696; NCT02118584; NCT02136069; NCT02165215; NCT02163759; NCT02171429; Crohn's disease: NCT02394028; NCT02403323;	Hoffmann-La Roche	Antibody	UC: 2014-04-01 2014-04-21 2014-05-12 2014-06-17 2014-06-16 2014-06-24 CD: 2015-03-20 2015-03-31	$\alpha 4\beta 7; \alpha E\beta 7$	Ulcerative colitis and Crohn's disease	Ulcerative colitis: 105 mg Q4W Crohn's disease: 210 mg at Weeks 0, 2, 4, 8, and 12 /105 mg Q4W	SC	Phase III
SAN-300	NCT02047604	Bausch Health Americas, Inc.	Antibody	2014-01-28	$\alpha 1\beta 1$	Rheumatoid arthritis	0.5 mg/kg QW 1.0 mg/kg QW 2.0 mg/kg QOW 4.0 mg/kg QOW 4.0 mg/kg QW	SC	Phase II
Abrilumab	NCT01694485; NCT01696396; NCT01959165;	AstraZeneca	Antibody	2012-09-27 2012-10-01 2013-10-09	$\alpha 4\beta 7$	Ulcerative colitis	21 mg, 70 mg or 210 mg (on day 1, week 2, week 4, and every 4 weeks thereafter until week 24)	SC	Phase II
Abituzumab	NCT01008475; NCT01360840; NCT02745145;	EMD Serono Research & Development Institute, Inc.	Antibody	2009-11-05 2011-05-26 2016-04-20	pan- αv	K-ras wild-type metastatic colorectal cancer; metastatic castrate-resistant prostate cancer; systemic sclerosis-associated interstitial lung disease;	K-ras Wild Type Metastatic Colorectal Cancer: 250 mg IV for 1 h Q2W; Metastatic Castrate-resistant Prostate Cancer (PERSEUS): 750 mg IV for 1 hour Q3W; Systemic Sclerosis-associated Interstitial Lung Disease: 500 mg/1500 mg IV for 1 hour Q4W;	IV	Phase II
Etaracizumab	NCT00192517	Medimmune Lic	Antibody	2005-09-19	$\alpha v\beta 3$	Plaque psoriasis	4 mg/kg	SC	Phase II
VPI-2690B	NCT02251067	Vascular Pharmaceuticals, Inc.	Antibody	2014-09-26	$\alpha v\beta 3$	Diabetic nephropathy	6 mg, 18 mg, 48 mg QOW	SC	Phase II

Table 4. continued

Drug name	Source	Sponsor	Drug types	Time (first posted)	Target	Indication	Dose	Delivery route	Study status
Intetumumab	NCT00246012; NCT00537381;	Centocor, Inc.	Antibody	2005-10-30 2007-10-01	pan- αv	Melanoma; metastatic hormone refractory prostate cancer;	Melanoma: 3 mg/kg, 5 mg/kg or 10 mg/kg Q3W Metastatic Hormone Refractory Prostate Cancer: 10 mg/kg QW for initial 6 weeks, then Q3W	IV	Phase II
ASP-5094	NCT03257852	Astellas Pharma Inc	Antibody	2017-08-22	$\alpha 9\beta 1$	Rheumatoid arthritis	Not mentioned	IV	Phase II
Volociximab	NCT00099970; NCT00100685; NCT00278187; NCT00369395; NCT00401570; NCT00516841;	Abbott Laboratories/ Facet Biotech	Antibody	2004-12-22 2005-01-05 2006-01-18 2006-08-29 2006-11-20 2007-08-16	$\alpha 5\beta 1$	Non-small cell lung cancer; pancreatic cancer; epithelial ovarian cancer or primary peritoneal cancer; renal cell carcinoma; melanoma;	Non-Small Cell Lung Cancer: IV over 30 min QOW; Metastatic Pancreatic Cancer: 10 mg/kg or 15 mg/kg QW or QOW; Advanced Epithelial Ovarian Cancer or Primary Peritoneal Cancer: 15 mg/kg QW; Metastatic Renal Cell Carcinoma : 10 mg/kg QOW /15 mg/kg QW; Metastatic Melanoma:5 mg/kg QW	IV	Phase II (terminated)
BG-00011	NCT00878761; NCT01371305; NCT03573505;	Stromedix, Inc.; Biogen;	Antibody	2009-04-09 2011-06-10 2018-06-29	$\alpha v\beta 1; \alpha v\beta 6$	Renal transplant patients with biopsy proven interstitial fibrosis and tubular atrophy; idiopathic pulmonary fibrosis;	Renal Transplant Patients With Biopsy Proven Interstitial Fibrosis and Tubular Atrop: 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg or 1 mg/kg; Idiopathic Pulmonary Fibrosis: 56 mg QW	SC	Phase II (terminated)
Vatelizumab	NCT01659138; NCT01861249; NCT02222948; NCT02306811;	Sanofi	Antibody	2012-08-07 2013-05-23 2014-08-22 2014-11-03	$\alpha 2\beta 1$	Multiple sclerosis; ulcerative colitis;	Not mentioned	IV	Phase II (terminated)
ABBV-382	NCT04554966	AbbVie	Antibody	2020-09-18	$\alpha 4\beta 7$	HIV	Not mentioned	IV or SC	Phase I
MINT-1526A	NCT01139723	Genentech, Inc.	Antibody	2010-06-08	$\alpha 5\beta 1$	Solid tumors	Not mentioned	IV	Phase I
OS2966	NCT04608812	OncoSynergy, Inc.	Antibody	2020-10-29	$\beta 1$	Glioma	Not mentioned	Intratumoural infusion	Phase I
Anti-GPIIb/IIIa chimeric	CXSL0500115	Shanghai Yalian Antibody	Antibody	2006-03-13	$\alpha IIb\beta 3$	Venous thrombosis	Not mentioned	Not mentioned	Phase I

Table 4. continued

Drug name	Source	Sponsor	Drug types	Time (first posted)	Target	Indication	Dose	Delivery route	Study status
monoclonal antibody Flab'2		Pharmaceutical Co., Ltd.							
Recombinant anti-CD11a humanized monoclonal antibody	CXSL0500018	Sansheng Guojian Pharmaceutical (Shanghai) Co., Ltd.	Antibody	2005-10-25	LFA-1A	Psoriasis	Not mentioned	Not mentioned	Phase I
Anti-CD8 monoclonal antibody	NCT01048372	CytoDyn, Inc.	Antibody	2010-01-13	LFA-1A	HIV infections	Not mentioned	Not mentioned	Phase I
PF-4605412	NCT00915278	Pfizer	Antibody	2009-06-08	$\alpha 5 \beta 1$	Solid tumors	7.5 mg IV for 2 h every 4 or 2 weeks	IV	Phase I (terminated)
Cilengitide	NCT00689221	EMD Serono	Peptide	2008-06-03	$\alpha v \beta 3; \alpha v \beta 5$	Glioblastoma and methylated gene promoter status	2000 mg twice weekly over 1 h	IV	Phase III (terminated)
batifiban	CTR20130809; CTR20130814;	BIO-THERA	Peptide	2018-05-02 2013-10-23	$\alpha IIb \beta 3$	Acute coronary syndrome and thrombotic cardiovascular events	bolus 220ug/kg (0.11 ml/kg) for 1-2 min, IV 2.5ug/kg/min for 24h	IV	Phase III
MT-1002	NCT04723186	Shaanxi Micot Technology Limited Company	Peptide	2021-01-25	$\alpha IIb \beta 3$	Acute coronary syndrome patients with PCI	0.9 mg/kg loading dose + 1.8 mg/kg/h for 4h; 1.2 mg/kg loading dose + 2.3 mg/kg/h for 4h; 0.6 mg/kg loading dose + 1.2 mg/kg/h for 4 h	IV	Phase II
Risuteganib	NCT02153476; NCT02348918; NCT02435862; NCT03626636;	Allegro Ophthalmics	Peptide	2014-06-03 2015-01-28 2015-05-06 2018-08-13	$\alpha v \beta 3; \alpha v \beta 5; \alpha 2 \beta 1; \alpha 5 \beta 1$	Symptomatic focal vitreomacular adhesion; diabetic macular edema; non-proliferative diabetic retinopathy; non-exudative macular degeneration	Symptomatic focal Vitreomacular Adhesion: 2.0 mg; Diabetic Macular Edema: 0.5 mg, 1.0 mg, 2.0 mg or 3.0 mg; Non-Proliferative Diabetic Retinopathy: 1.0 mg, 2.0 mg or 3.0 mg; Non-Exudative Macular Degeneration: 1.0 mg	injected intravitreally	Phase II
Antiangiotide	CTR20150368; CTR20200847;	Inner Mongolia Tianqi Mongolian Medicine Group Co., Ltd.; China Pharmaceutical University;	Peptide	2015-07-20 2020-08-28	$\alpha v \beta 3$	Solid tumors	7.5, 15, 30, 45, 60, 75 mg/m ² QD or twice weekly	IV	Phase I
CEND-1	NCT05042128; NCT05052567; NCT05121038; CTR20212588;	Australasian Gastrointestinal Trials Group; Qilu Pharmaceutical Co., Ltd; Anup Kasi;	Peptide	2021-09-13 2021-09-22 2021-11-16	$\alpha v \beta 5$	Pancreatic ductal adenocarcinoma; colon and appendiceal cancers;	3.2 mg/kg	IV	Phase II

Table 4. continued

Drug name	Source	Sponsor	Drug types	Time (first posted)	Target	Indication	Dose	Delivery route	Study status
Dentonin	NCT01925261; NCT02837900;	Cend Therapeutics, Inc.; Orthotrophix Inc	Peptide	2021-10-22 2013-08-19 2016-07-20	Integrin	Patellar osteoarthritis involving both knees; patello-femoral osteoarthritis involving both knees;	Patellar Osteoarthritis Involving Both Knees: 200 mg 4 times weekly; Patello-Femoral Osteoarthritis Involving Both Knees: 20 mg/50 mg/100 mg/200 mg	Intra-articular Injections	Phase II
Valtegrast Hydrochloride	NCT00048009; NCT00048022;	Hoffmann-La Roche	Peptide	2002-10-25 2002-10-25	$\alpha 4\beta 1$; $\alpha 4\beta 7$	Asthma	Not mentioned	not mentioned	Phase II
Pegylated recombinant human endostatin	NCT01527864	Protgen Ltd	Peptide	2012-02-07	$\alpha 5\beta 1$	Non-small cell lung cancer	10 mg/m ² QW	IV	Phase II
AC-PHSCN-NH2	NCT00131651	Attenuon Llc	Peptide	2005-08-19	$\alpha 5\beta 1$; $\alpha v\beta 3$	Renal cell cancer	three times weekly by short (10 min) IV infusion at 1 of 3 dose levels (20, 100, and 600 mg).	IV	Phase II (terminated)
AXT-107	NCT04697758; NCT04746963;	AsclepiX Therapeutics, Inc.	Peptide	2021-01-06 2021-02-10	$\alpha v\beta 3$; $\alpha 5\beta 1$	Diabetic macular edema; neovascular age-related macular degeneration	0.1 mg, 0.25 mg, or 0.5 mg	Intravitreal injection	Phase I/II
JSM-6427	NCT00536016	Jerini Ophthalmic	Peptide	2007-09-27	$\alpha 5\beta 1$; $\alpha v\beta 6$; $\alpha v\beta 8$	Age-related macular degeneration	1.5 mg/ml, 3 mg/ml, 7.5 mg/ml 15 mg/ml QW	intravitreal injections	Phase I
Pury Peptide	CTR20170691; CTR20181547;	Shaanxi Mccoot Technology Co., Ltd.	Peptide	2017-07-26 2019-10-22	$\alpha 11\beta 3$	Acute coronary syndrome with PCI	360ug/kg bolus + 5ug/kg/min IV for 6 h; 400ug/kg bolus + 7.5ug/kg/min IV for 6 h; 400ug/kg bolus + 10ug/kg/min IV for 6 h; 400ug/kg bolus + 13ug/kg/min IV for 6 h; 400ug/kg bolus + 16ug/kg/min IV for 6 h; 400ug/kg bolus + 20ug/kg/min IV for 6 h	IV	Phase I
PTG-100	NCT02895100	Protagonist Therapeutics	Peptide	2016-09-09	$\alpha 4\beta 7$	Ulcerative colitis	150, 300 or 900 mg tid	Oral	Phase II
99mTc-3PRGD2	CTR20191465; NCT04233476;	Peking University; Foshan Ridio Pharmaceutical Co. Ltd.; Institute of Biophysics, Chinese	Imaging agent	2019-07-30 2020-01-18	$\alpha v\beta 3$	Diagnosis for the lymph node metastasis in lung tumors	0.3 mCi/kg	IV	Phase III

Table 4. continued

Drug name	Source	Sponsor	Drug types	Time (first posted)	Target	Indication	Dose	Delivery route	Study status
Alfatide[18 F]	CTR20213024	Academy of Sciences; RDO Pharm.; Jiangsu Shimeikang Pharmaceutical Co., Ltd.; Taizhou Qirui Pharmaceutical Technology Co., Ltd.;	Imaging agent	2021-12-10	$\alpha v \beta 3$	Diagnosis for the lymph node metastasis in non-small-cell lung carcinoma	no more than 10 mL within 90 s, (0.1~0.15) ± 0.015 mCi/kg	IV	Phase III
¹⁸ F-FPPRGD2	NCT01806675; NCT02995642;	Stanford University	Imaging agent	2013-03-07 2016-12-16	$\alpha v \beta 3$	Cancer; vascular inflammation	10 mCi	IV	Phase II
⁹⁹ mTc-rBitistatin	NCT00808626	Temple University	Imaging agent	2008-12-16	$\alpha IIb \beta 3$	Venous thrombosis	10 mCi, 0.1 ug/kg	IV	Phase II (terminated)
Flotegatide-F18	NCT00988936; NCT01602471; NCT02325349;	Siemens Molecular Imaging	Imaging agent	2009-10-02 2012-05-21 2014-12-25	$\alpha v \beta 3$	Metastatic breast cancer/metastatic colon/rectum cancer/non-squamous non-small cell lung cancer; lung or head and neck cancers; lymphoma; carotid artery stenosis	Lung or Head and Neck Cancers: 2-4MBq/kg	IV	Phase II (terminated)
AH111585 (18 F)	NCT00918281	GE Healthcare	Imaging agent	2009-06-11	$\alpha v \beta 3$; $\alpha v \beta 5$	Solid tumors	Not mentioned	IV	Phase II
(68)Ga-RGD	NCT05275699	Peking Union Medical College Hospital	Imaging agent	2022-03-11	$\alpha v \beta 3$	Keloid	111 MBq	IV	Phase I
[⁶⁸ Ga]-FF58	NCT04712721	Novartis Pharmaceuticals	Imaging agent	2021-01-15	$\alpha v \beta 3$; $\alpha v \beta 5$	Solid tumors	3 MBq/Kg (+/- 10%). no lower than 150 MBq or higher than 250 MBq	IV	Phase I
⁶⁸ Ga-NOTA-3PTATE-RGD	NCT02817945	Peking Union Medical College Hospital	Imaging agent	2016-06-29	$\alpha v \beta 3$	Lung cancer; neuroendocrine neoplasm	111-185 MBq	IV	Phase I
⁶⁸ Ga-NOTA-BBN-RGD	NCT02747290; NCT02749019;	Peking Union Medical College Hospital	Imaging agent	2016-04-21 2016-04-22	$\alpha v \beta 3$	Prostate cancer patients; Breast cancer patients	111-148 MBq	IV	Phase I
⁶⁸ Ga-BNOTA-PRGD2	NCT01527058; NCT01542073; NCT01656785; NCT01801371; NCT01940926; NCT02511197;	Peking Union Medical College Hospital	Imaging agent	2012-02-06 2012-03-01 2012-08-03 2013-02-28 2013-09-12	$\alpha v \beta 3$	Lung injury and pulmonary fibrosis; glioma; stroke; lung cancer; myocardial infarction; rheumatoid arthritis	111 MBq ($\leq 40 \mu\text{g}$ BNOTA-PRGD2)	IV	Phase I

Table 4. continued

Drug name	Source	Sponsor	Drug types	Time (first posted)	Target	Indication	Dose	Delivery route	Study status
Ga-68 NODAGA-RGD	NCT02666547	University of Lausanne Hospitals	Imaging agent	2015-07-29	$\alpha v\beta 3$	Pathological angiogenesis	200 MBq	IV	Phase I
[18F]FP-R01-MG-F2	NCT02683824; NCT03183570;	Stanford University	Imaging agent	2016-02-17 2017-06-12	$\alpha v\beta 6$	Idiopathic pulmonary fibrosis; primary sclerosing cholangitis; Covid-19 pneumonia; pancreatic cancer	7 mCi (range 6-9 mCi)	IV	Phase I
[18F] $\alpha v\beta 6$ -BP	NCT03164486	Julie L. Sutcliffe, Ph.D	Imaging agent	2017-05-23	$\alpha v\beta 6$	Multiple cancers	up to 10 mCi	IV	Early phase I
99mTc- RWY	NCT04289532	Peking University	Imaging agent	2020-02-28	$\alpha 6$	Breast cancer	11.1 MBq/kg	IV	Early phase I
[18F]FBA-A20FMDV2	NCT04285996	Queen Mary University of London	Imaging agent	2020-02-26	$\alpha v\beta 6$	Cancer	Not mentioned	Not mentioned	N/A
Zalunifiban	NCT04825743	Celecor Therapeutics	Small molecule	2021-04-01	$\alpha IIb\beta 3$	ST-elevation myocardial infarction	0.11 mg/kg; 0.13 mg/kg	SC	Phase III
Firategrast	NCT00097331; NCT00101946; NCT00395317; NCT00469378;	GlaxoSmithKline	Small molecule	2004-11-23 2005-01-19 2006-11-02 2007-05-04	$\alpha 4\beta 1$	Multiple sclerosis; Crohn's disease	Multiple Sclerosis: 900 (females) or 1200 (males) mg bid	oral	Phase II
MORF-057	NCT05291689	Morphic Therapeutic	Small molecule	2022-03-23	$\alpha 4\beta 7$	Ulcerative colitis	Not mentioned	Oral	Phase II
TRK-170	NCT01345799	Toray Industries, Inc	Small molecule	2011-05-02	$\alpha 4\beta 7$	Crohn's disease	Not mentioned	Not mentioned	Phase II
AJM-347	NCT03133468	EA Pharma Co., Ltd.	Small molecule	2017-04-28	$\alpha 4\beta 7$	Unknown	Not mentioned	Oral	Phase I
PN-10943	NCT04504383	Protagonist Therapeutics	Small molecule	2020-08-07	$\alpha 4\beta 7$	Ulcerative colitis	150 mg /450 mg BID	Oral	Phase II
E-7820	NCT00309179; NCT01133990; NCT01347645; NCT05024994;	Eisai Inc.	Small molecule	2006-03-31 2010-05-31 2011-05-04 2021-08-27	$\alpha 2$	Bone marrow cancers; colorectal cancer; rectal cancer; solid tumors	Myeloid: 100 mg QD; Colon or Rectal Cancer: 40 mg/day, 70 mg/day, and 100 mg/day	Oral	Phase II
AXR-159	NCT03598699	Axerovision	Small molecule	2018-07-09	$\alpha 4$	Dry eye disease	Not mentioned	Topical	Phase II
VVN-001	NCT04556838; CTR20211530;	VivaVision Biotech, Inc	Small molecule	2020-09-21	LFA-1A	Dry eye disease	1% or 5% solution 1 drop in each eye every 12 h	Topical	Phase II

Table 4. continued

Drug name	Source	Sponsor	Drug types	Time (first posted)	Target	Indication	Dose	Delivery route	Study status
HYD-PEP-06	CTR20220769	Jilin Hayi University Pharmaceutical Co., Ltd.	Small molecule	2021-07-01 2022-04-14	Pan- α v	Colorectal cancer	3.75 mg/kg QD for 14 days	IV	Phase II
GB-1275	NCT04060342	Gb006 Inc	Small molecule	2019-08-19	Integrin	Solid tumors	Not mentioned	Oral	Phase II
BIRT-2584-XX	NCT00333411	Boehringer Ingelheim GmbH	Small molecule	2006-06-05	Integrin α	Psoriasis	100, 300 and 500 mg QD	Oral	Phase II
Milategrast	NCT03018054	EA Pharma Co., Ltd.	Small molecule	2017-01-11	Integrin	Ulcerative colitis	30 mg or 60 mg QD after breakfast	Oral	Phase II
MIK-0429	NCT00533650	Merck Sharp; Dohme LLC;	Small molecule	2007-09-21	Pan- α v	PostMenopausal osteoporosis	Not mentioned	Not mentioned	Phase II
SF-0166	NCT02914613; NCT02914639;	OcuTerra Therapeutics, Inc.	Small molecule	2016-09-26 2016-09-26	α v β 3; α v β 6; α v β 8	Age-related macular degeneration; diabetic macular edema	5% solution twice a day	Topical	Phase II
AS-101	NCT00418249; NCT00788424; NCT00927212; NCT00926354; NCT01010373; NCT01555112; NCT01943630; NCT03216538;	Biomax; Rabin Medical Center;	Small molecule	2007-01-04 2008-11-11 2009-06-24 2009-06-23 2009-11-10 2012-03-15 2013-09-17 2017-07-13	α 4 β 1; α v β 3	Age-related macular degeneration; atopic dermatitis; chemotherapy-induced thrombocytopenia; HIV; psoriasis; myelodysplastic syndrome; acute myeloid leukemia; external genital warts; female androgenetic alopecia	External Genital Wart: 15% gel QD; MDS&AML: 3 mg/m ² three times per week; AMD: 1% oral solution 0.4 ml QD; Psoriasis: 4% AS-101 Cream on the psoriatic lesions BID; Atopic Dermatitis: 2% /4% ointment, topical application bid; Chemotherapy induced thrombocytopenia: 3 mg/m ² twice a week; Female Androgenetic Alopecia: Topical use	Topical/ IV/ Oral	Phase II (terminated)
zaurategrast	NCT00484536; NCT00726648;	UCB Pharma	Small molecule	2007-06-11 2008-08-01	α 4 β 1	Multiple sclerosis	1000 mg QD for 4 weeks; 100 mg bid for 4 weeks; 500 mg bid for 4 weeks; 1000 mg bid for 4 weeks	Oral	Phase II (terminated)
THR-687	NCT05063734	Oxurion	Small molecule	2021-10-01	pan- α v; α 5 β 1	Diabetic macular edema	2.5 mg	intravitreal injections	Phase II (terminated)
RO-0506997	NCT00104143	Hoffmann-La Roche	Small molecule	2005-02-24	α 4	Multiple sclerosis	20 mg, 80 mg or 300 mg, bid	Oral	Phase II (terminated)
BMS-587101	NCT00162253	Bristol-Myers Squibb	Small molecule	2005-09-13	α L β 2	Psoriasis	Not mentioned	Not mentioned	Phase II (terminated)
PLN-74809	NCT04072315; NCT04396756;	Pliant Therapeutics	Small molecule	2019-08-28 2020-	α v β 1; α v β 6	Primary sclerosing cholangitis; idiopathic pulmonary	Primary Sclerosing Cholangitis:40 mg, 80 mg or 160 mg	Oral	Phase II

Table 4. continued

Drug name	Source	Sponsor	Drug types	Time (first posted)	Target	Indication	Dose	Delivery route	Study status
LLP2A	NCT04480840; NCT04565249;			05-21 2020-07-21 2020-09-25		fibrosis; acute respiratory distress syndrome; SARS-CoV-2;			
alendronate	NCT03197623	Nancy E. Lane, MD	Small molecule	06-23	$\alpha 4\beta 1$	Osteopenia secondary to glucocorticoids	50, 150, 400, 750 or 1200 $\mu\text{g}/\text{kg}$	IV	Phase I
GLPG-0187	NCT00928343; NCT01313598; NCT01580644;	Galapagos NV	Small molecule	2009-06-25 2011-03-14 2012-04-19	pan- αv ; $\alpha 5\beta 1$;	Solid tumors	Not mentioned	IV/Oral/SC	Phase I
7HP-349	NCT04508179	7 Hills Pharma LLC	Small molecule	2020-08-11	$\alpha \text{L}\beta 2; \alpha 4\beta 1$;	Solid tumor	Not mentioned	Oral	Phase I
HYC-11395	CTR20182266	Hefei Heyuan Pharmaceutical Co., Ltd.; Nanjing Heqi Pharmaceutical Technology Co., Ltd.;	Small molecule	2018-11-28	$\alpha \text{IIb}\beta 3$	Acute coronary syndrome and thrombotic cardiovascular events	1 $\mu\text{g}/\text{kg}$	IV	Phase I
Lefradafiban	NCT02264106; NCT02264119; NCT02265289;	Boehringer Ingelheim GmbH	Small molecule	2014-10-15 2014-10-15 2014-10-15	$\alpha \text{IIb}\beta 3$	Thrombosis	30 mg Tid	Oral	Phase I
BIIB-107	NCT04593121	Biogen	Small molecule	2020-10-19	$\alpha 4$	Multiple sclerosis;	Not mentioned	SC	Phase I
IDL-2965	NCT03949530	Indalo Therapeutics	Small molecule	2019-05-14	pan- αv	Idiopathic pulmonary fibrosis; nonalcoholic steatohepatitis	Not mentioned	Oral	Phase I
Pegantangentide	CTR20210520	Jiangsu aodexin Bio-pharmaceutical Technology Co., Ltd.; China Pharmaceutical University;	Small molecule	2021-04-01	$\alpha\text{v}\beta 3$	Rheumatoid arthritis	0.2 mg~4 mg	SC	Phase I
ELND-002	NCT01144351; NCT01318421;	Elan Pharmaceuticals	Small molecule	2010-06-15 2011-03-18	$\alpha 4$	Multiple sclerosis	Not mentioned	SC	Phase I (terminated)
GSK-3008348	NCT02612051; NCT03069989;	GlaxoSmithKline	Small molecule	2015-11-23 2017-03-03	$\alpha\text{v}\beta 6$	Idiopathic pulmonary fibrosis;	1 to 3000 ug	Topical	Phase I (terminated)
OPC-415	NCT04649073				$\beta 7$			IV	Phase II

Table 4. continued

Drug name	Source	Sponsor	Drug types	Time (first posted)	Target	Indication	Dose	Delivery route	Study status
Marnetragene autotemcel	NCT03812263	Otsuka Pharmaceutical Co., Ltd.	CAR T-cell therapy	2020-12-02		Relapsed and/or refractory multiple myeloma	up to 1×10^7 cells/kg On 2 days		
BA 015 gene therapy	NCT01764009	Rocket Pharmaceuticals Inc	Cell- based therapy	2019-01-23	$\beta 2$	Leukocyte adhesion deficiency-I	at least 2×10^6 total CD34 + cells/kg	IV	Phase II
CAR- T therapy	NCT03778346	Onxeo	Gene therapy	2013-01-09	$\alpha 5\beta 1; \alpha v\beta 3$	Melanoma	0.25 mg, 1 mg and 4 mg	IV	Phase II (terminated)
AG-73305	NCT05301751	The Sixth Affiliated Hospital of Wenzhou Medical University	CAR T-cell therapy	2018-12-19	$\beta 7$	Relapsed/refractory multiple myeloma	10^6-10^7 /Kg	IV	Phase I
Targeted NIF-hirulog hybrid	CXSL0600027	Allgenis Biotherapeutics Inc	Fusion protein	2022-03-31	Integrin	Diabetic macular edema	0.5 mg/ 1 mg/ 2 mg/ 3 mg	intravitreal	Phase II
ATL-1102	ACTRN12608000226303; ACTRN12618000970246; Therapeutics	Chongqing Fujin bio-pharmaceutical Co., Ltd.	Fusion protein	2006-06-07	Integrin	Stroke	Not mentioned	Not mentioned	Phase I
IMGN 388	NCT00721669	Immunogen Inc	Antisense oligonucleotide	2005-02-19	$\alpha 4$	Duchenne muscular dystrophy; multiple sclerosis	Not mentioned	Not mentioned	Phase II
SGN-B6A	NCT04389632	Seagen Inc.	Antibody drug conjugate	2008-07-24	$\alpha v\beta 3$	Solid tumors	Not mentioned	IV	Phase I
BGC-0222	CTR20221496	Gao Ruiyao Ye (Beijing) Technology Co., Ltd.	Antibody drug conjugate	2020-05-15	$\beta 6$	Solid tumors	Not mentioned	IV	Phase I
ProAgio	NCT05085548	ProDa BioTech, LLC	Peptide drug conjugate	2022-06-16	$\alpha v\beta 3$	Solid tumors	Not mentioned	IV	Phase I
			Novel proteins synthesized by computer simulation	2021-10-20	$\alpha v\beta 3$	Pancreatic cancer; solid tumor	3.2–36.8 mg/kg	IV	Phase I

targeting integrin therapies probably overcome the limitations of conventional therapies used in cancer treatment to achieve more precise, safer, and highly effective therapeutics. Integrins, overexpressed on the surface of cancer cells, are viewed as beneficial targets for the preferential delivery of genes or drugs into cancer cells.⁵⁷⁶ The delivery of RGD-based peptides to integrin receptors could be helpful for the binding and liberation of drugs in the tumor vasculature. The majority of nanoparticles (NPs) modified with RGD peptide and loaded with nucleotides or drugs have been developed in preclinical studies. For example, $\alpha v\beta 3$ -integrin-targeting NPs obtained by coupling RGD ligands to the surface of PEGylated chitosan-poly(ethylene imine) hybrids showed high gene silencing efficiency and facilitated efficient siRNA delivery.⁵⁷⁷ The RGD motif was also used to connect to PEG-PLA and loaded with paclitaxel (PTX) and its derivative docetaxel (DTX) to avoid their disadvantages of low solubility and dose-limiting toxicity.⁵⁷⁸ The cyclopeptide isoDGR is found in aged fibronectin, where it is formed by deamidation of Asn in an asparagine-glycine-arginine (NGR) site, which is a new $\alpha v\beta 3$ -binding motif with high affinity and does not induce integrin allosteric and activation.^{579,580} Therefore, in future studies, isoDGR-based nanotherapeutic agents have potential applications in cancer treatment.

CAR T-cell therapy

Integrins are also used in immunotherapy by conjugating to CAR T cells. Currently, there are two kinds of CAR T-cell therapies in clinical studies. OPC-415 targeting $\beta 7$ and Marnetegrane autotemcel targeting $\beta 3$ were developed by Otsuka and Pocket, respectively. The active conformer of integrin $\beta 7$ served as a novel multiple myeloma (MM)-specific target, and MMG49, in the N-terminal region of the $\beta 7$ chain, derived CAR showed good anti-MM effects without normal hematopoietic cell damage.²⁷ Currently, OPC-415 targeting $\beta 7$ CAR T-cell therapy is in a phase II study. Integrin $\alpha v\beta 3$ - and $\alpha v\beta 6$ -CAR T cells also show therapeutic potential in solid tumors, such as melanoma, triple-negative breast cancer, and cholangiocarcinoma.^{581,582}

Imaging agent

Molecular imaging is an important part of precision medicine and plays an important role in the early diagnosis, staging, prognostic evaluation, individualized treatment and efficacy monitoring of major diseases such as cancers. 2-Deoxy-2-[¹⁸F]fluoro-d-glucose ([¹⁸F]FDG) positron emission tomography combined with low-dose computed tomography ([¹⁸F]FDG-PET/CT) is currently the gold standard for the clinical imaging diagnosis of various malignant tumors. However, in recent years, the development of clinical application of PET imaging has entered a bottleneck period, mainly due to the complex preparation of positron-electron drugs and the high imaging cost. Compared with PET technology, single photon emission computed tomography (SPECT) has lower equipment and drug costs, a higher clinical penetration rate and a better application foundation. However, the lack of effective imaging agents, such as ¹⁸F-FDG, limits the SPECT technology to play a greater role in tumor diagnosis and efficacy evaluation. Currently, SPECT imaging agents in the clinical phase mainly focus on integrin $\alpha v\beta 3$ due to its overexpression on the surface of tumor neovascular endothelial cells and many tumor cells and the high affinity of polypeptides containing RGD sequences. Therefore, targeting $\alpha v\beta 3$ SPECT imaging agents has been developed. ^{99m}Tc-3PRGD2 is the first broad-spectrum SPECT tracer developed by Peking University targeting integrin $\alpha v\beta 3$ for detecting tumors, imaging angiogenesis, and evaluating tumor response to therapy.⁵⁸³ The phase III study showed the good efficacy of ^{99m}Tc-3PRGD2 for the evaluation of lung cancer progression. $\alpha v\beta 6$ integrin also serves as a promising target for cancer imaging. ¹⁸F-FP-R₀1-MG-F₂ is an integrin $\alpha v\beta 6$ -specific PET imaging agent developed by Stanford University. The pilot-phase PET/CT study showed good safety and radiation dose performance

in pancreatic cancer patients.⁵⁸⁴ Except for pancreatic cancer, the potential indications include idiopathic pulmonary fibrosis (IPF), primary sclerosing cholangitis, and COVID-19 pneumonia.

CONCLUSIONS AND PERSPECTIVES

Decades of the investigation into the biological functions of integrins have suggested that integrins exhibit roles in the regulation of many aspects of human health and disease, and their molecular mechanisms and signal transduction are also strikingly complex. Considering the width and feasibility of therapeutic options, targeting integrins is an important avenue to explore. In recent decades, targeting integrin drug discovery has continued to move forward with its twists and its turns. Many of the lessons learned from the past are also valuable to achieve a heavy bomb in this field. We give the perspective from three aspects: basic research, clinical research, and translational research.

For basic research, research on integrins is quite mature but also a newly reawakened field. It is important to validate the function of integrin targets in clinically predictive disease models and analyze the expression landscape in a large-scale cohort in different diseases and states, which contributes to success in clinical trials. Notably, current studies of integrin-targeted strategies are focused not only on extracellular but also on intracellular targets that involve both inside-out and outside-in signaling pathways. Several adapters are known to interact with the cytoplasmic tails of β -integrins, including G α 13, focal adhesion kinase, ILK, and Syk, Src-family kinases. For example, G α 13 binds directly to the ExE motif in the cytoplasmic domain of the integrin β subunits, and this binding occurs only during early outside-in signaling. A myristoylated ExE motif peptide selectively inhibits outside-in signaling, platelet spreading and the second wave of platelet aggregation by selectively inhibiting G α 13-integrin interaction. This strategy to inhibit outside-in signaling not affect primary platelet adhesion and aggregation, but limit the size of a thrombus to prevent vessel occlusion.^{398,585} 14-3-3 ζ synergizes c-Src to $\beta 3$ -integrin, and forms the 14-3-3 ζ -c-Src-integrin- $\beta 3$ complex during platelet activation. Interference with the formation of complex by myristoylated-KEATSTF-fragment (KF7) and 3',4',7'-trihydroxyisoflavone (THO) is a strategy to selectively inhibit outside-in signaling without disrupting the ligand binding of integrins.⁵⁸⁶ Targeting intracellular targets via outside-in signaling pathways may provide new sights for avoiding the formation of potentially undesired conformational states. Considering the substantial clinical failure in targeting integrin in the orthosteric binding sites due to activation of integrin signaling, identification of other allosteric sites is urgently needed to develop candidates that target integrin at other sites. Clearly, the conformational states shift exists in $\alpha v\beta 3$ and $\alpha ll\beta 3$ induced by their inhibitors, but it is not clear to other RGD-binding integrins or leukocyte cell-adhesion integrins, collagen-binding integrins, laminin-binding integrins. Crystallographic structural analysis would be helpful to reveal the conformational change mechanism. Considering the width and complexity of biological function and signaling within the integrin family, whereas only a small part of integrin biology is known, further research is required to explore the much unknown field.

For clinical research, targeting integrin therapeutics may have their greatest utility as combination therapies with other agents considering the potential function of integrin inhibition in overcoming acquired resistance to chemotherapy, radiotherapy, targeted therapy (including VEGFR inhibitors) or therapy targeting the immune microenvironment. Currently, due to the complexity of solid tumors, the combination therapy of anti-tumor drugs with different mechanisms or targets is the mainstream strategy in the clinic to improve anti-tumor efficacy and overcome or delay drug resistance. The identification of robust biomarkers and imaging

technology applications are required to find patients with tumors whose progression is driven by integrin signaling or to measure specific integrin expression levels in the recruited subjects, which could guide the best clinical use of integrin inhibitors. In addition to focusing on the efficacy of integrin antagonists, we should also pay special attention to the adverse effects of integrin antagonists in clinical applications or clinical trials. For example, the oral α IIb β 3 antagonists were associated with increased mortality compared to intravenous administration.²⁴ One explanation could be that some of the drugs have agonist-like activity, which may trigger “outside-to-inside” signals within the receptor-cell membrane complex, affect receptor conformational status and competency, membrane fluidity, and calcium metabolism,⁵⁸⁷ and potentially activate GPIIb/IIIa receptor, maintain procoagulant activity and P-selectin expression.^{588,589} Moreover, progressive multifocal leukoencephalopathy (PML), a rare but serious opportunistic infection of the central nervous system, is the most concerning adverse event of integrin antagonists. Currently approved α 4 integrin antagonist, natalizumab, is at high risk of developing PML.⁵⁹⁰ Efalizumab, an α L β 2 integrin antagonist previously approved for the treatment of plaque psoriasis,^{591,592} was also withdrawn from the market due to the incidence of PML.⁵⁹³ A restricted risk management plan is necessary to help reduce the potential risk of PML in clinical practice and clinical trials.⁵⁹⁴ For example, patients with any neurologic symptoms, immunocompromised conditions, or those receive concurrent immunosuppressive therapy or anti-TNF α antibodies should be precluded.^{527,594} Therefore, these related adverse effects should be taken into consideration in ongoing clinical trials and systematic post-marketing surveillance will contribute to the success of translational research and drug discovery of targeting integrin therapeutics.

For translational research, developing small molecules with new chemotypes, high affinity, and good pharmacokinetic profile for oral dosing is challenging but has a huge market. The identification of novel non-RGD or pure antagonist chemotypes via high-throughput screening and targeting integrin and ECM interactions are important drug discovery directions. In addition, given the multifaceted roles of integrins as signaling molecules, dual-target drug development and multi-indicative simultaneous development will improve the efficiency and success rate. Dual-target novel agents may overcome resistance compared with single-target drugs and often improve treatment outcomes, and have more predictable pharmacokinetics profiles than combination therapies. The development of dual-target inhibitors has become an attractive research field for human cancer treatment and may provide synergistic anticancer effects. For example, integrins combined with other cell-adhesion molecules, such as CD44 and dual-target inhibitors of tubulin and α v-integrin, for cancer treatment are an untapped research field. Currently, for cardiovascular diseases and ulcerative colitis treatment, anti-integrin therapeutics have been a major success. In the future, targeting integrin drug discovery is gradually going forward to unmet medical needs, such as IPF, NASH, aggressive or resistant malignancy, etc. Based on robust target validation, integrins will provide new significant opportunities for a variety of indications.

In summary, integrins play a crucial role in human health and disease due to their expression in multiple cell types and widespread involvement in cellular processes. Knowledge of integrins in various diseases is progressing, but the drug discovery process is less than satisfactory. We hope the progression in basic research, clinical research, and translational research will establish realizable access for developing effective drugs for unmet medical needs.

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AUTHOR CONTRIBUTIONS

X.P. and Y.C. conceived and organized the manuscript. X.P., Q.X., X.H., Z.Q., H.Z., Z.L., and Y.G. wrote the manuscript, prepared the figures and contributed to the discussion. R.X. and N.Z. researched data and prepared the table. All authors have read and approved the article.

ADDITIONAL INFORMATION

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REFERENCES

- Hynes, R. O. & Yamada, K. M. Fibronectins: multifunctional modular glycoproteins. *J. Cell Biol.* **95**, 369–377 (1982).
- Hynes, R. O. The emergence of integrins: a personal and historical perspective. *Matrix Biol.* **23**, 333–340 (2004).
- Kechagia, J. Z., Ivaska, J. & Roca-Cusachs, P. Integrins as biomechanical sensors of the microenvironment. *Nat. Rev. Mol. Cell Biol.* **20**, 457–473 (2019).
- Moreno-Layseca, P., Icha, J., Hamidi, H. & Ivaska, J. Integrin trafficking in cells and tissues. *Nat. Cell Biol.* **21**, 122–132 (2019).
- Zheng, Y. & Leftheris, K. Insights into protein-ligand interactions in integrin complexes: advances in structure determinations. *J. Med. Chem.* **63**, 5675–5696 (2020).
- Winograd-Katz, S. E., Fassler, R., Geiger, B. & Legate, K. R. The integrin adhesome: from genes and proteins to human disease. *Nat. Rev. Mol. Cell Biol.* **15**, 273–288 (2014).
- Ezraty, E. J., Bertaux, C., Marcantonio, E. E. & Gundersen, G. G. Clathrin mediates integrin endocytosis for focal adhesion disassembly in migrating cells. *J. Cell Biol.* **187**, 733–747 (2009).
- Takagi, J., Petre, B. M., Walz, T. & Springer, T. A. Global conformational rearrangements in integrin extracellular domains in outside-in and inside-out signaling. *Cell* **110**, 599–511 (2002).
- Xiong, J. P. et al. Crystal structure of the extracellular segment of integrin α V β 3 in complex with an Arg-Gly-Asp ligand. *Science* **296**, 151–155 (2002).
- van der Flier, A. & Sonnenberg, A. Function and interactions of integrins. *Cell Tissue Res.* **305**, 285–298 (2001).
- Attwood, S. J. et al. Measurement of the interaction between recombinant I-domain from integrin α 2 β 1 and a triple helical collagen peptide with the GFOGER binding motif using molecular force spectroscopy. *Int. J. Mol. Sci.* **14**, 2832–2845 (2013).
- Humphries, J. D., Byron, A. & Humphries, M. J. Integrin ligands at a glance. *J. Cell Sci.* **119**, 3901–3903 (2006).
- Xiao, T. et al. Structural basis for allostery in integrins and binding to fibrinogen-mimetic therapeutics. *Nature* **432**, 59–67 (2004).
- Tselepis, V. H., Green, L. J. & Humphries, M. J. An RGD to LDV motif conversion within the disintegrin kistrin generates an integrin antagonist that retains potency but exhibits altered receptor specificity. Evidence for a functional equivalence of acidic integrin-binding motifs. *J. Biol. Chem.* **272**, 21341–21348 (1997).
- LaFoya, B. et al. Beyond the matrix: the many non-ECM ligands for integrins. *Int. J. Mol. Sci.* **19**, 449 (2018).
- Hussein, H. A. et al. Beyond RGD: virus interactions with integrins. *Arch. Virol.* **160**, 2669–2681 (2015).
- Davis, P. J. et al. Small molecule hormone or hormone-like ligands of integrin α v β 3: implications for cancer cell behavior. *Horm. Cancer* **4**, 335–342 (2013).
- Critchley, D. R. et al. Integrin-mediated cell adhesion: the cytoskeletal connection. *Biochem. Soc. Symp.* **65**, 79–99 (1999).
- Harburger, D. S. & Calderwood, D. A. Integrin signalling at a glance. *J. Cell Sci.* **122**, 159–163 (2009).
- Sun, Z., Costell, M. & Fassler, R. Integrin activation by talin, kindlin and mechanical forces. *Nat. Cell Biol.* **21**, 25–31 (2019).
- Campbell, I. D. & Humphries, M. J. Integrin structure, activation, and interactions. *Cold Spring Harb. Perspect. Biol.* **3**, a004994 (2011).
- Humphries, J. D., Chastney, M. R., Askari, J. A. & Humphries, M. J. Signal transduction via integrin adhesion complexes. *Curr. Opin. Cell Biol.* **56**, 14–21 (2019).

23. Hamm, C. W. Anti-integrin therapy. *Annu. Rev. Med.* **54**, 425–435 (2003).
24. Chew, D. P., Bhatt, D. L., Sapp, S. & Topol, E. J. Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists: a meta-analysis of phase III multicenter randomized trials. *Circulation* **103**, 201–206 (2001).
25. Hood, J. D. et al. Tumor regression by targeted gene delivery to the neovasculature. *Science* **296**, 2404–2407 (2002).
26. Stupp, R. et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* **15**, 1100–1108 (2014).
27. Hosen, N. et al. The activated conformation of integrin $\beta(7)$ is a novel multiple myeloma-specific target for CAR T cell therapy. *Nat. Med.* **23**, 1436–1443 (2017).
28. Slack, R. J. et al. Emerging therapeutic opportunities for integrin inhibitors. *Nat. Rev. Drug Discov.* **21**, 60–78 (2022).
29. Nolte, M. A., Nolte-t Hoen, E. N. M. & Margadant, C. Integrins control vesicular trafficking; new tricks for old dogs. *Trends Biochem. Sci.* **46**, 124–137 (2021).
30. Luo, B.-H., Carman, C. V. & Springer, T. A. Structural basis of integrin regulation and signaling. *Annu. Rev. Immunol.* **25**, 619–647 (2007).
31. Lee, J. O., Rieu, P., Arnaout, M. A. & Liddington, R. Crystal structure of the A domain from the alpha subunit of integrin CR3 (CD11b/CD18). *Cell* **80**, 631–638 (1995).
32. Arnaout, M. A., Mahalingam, B. & Xiong, J. P. Integrin structure, allostery, and bidirectional signaling. *Annu. Rev. Cell Dev. Biol.* **21**, 381–410 (2005).
33. Saggiu, G. et al. Cis interaction between sialylated Fc γ RIIA and the α -domain of Mac-1 limits antibody-mediated neutrophil recruitment. *Nat. Commun.* **9**, 5058 (2018).
34. Adair, B. D. et al. Three-dimensional EM structure of the ectodomain of integrin $\{\alpha\}V\{\beta\}3$ in a complex with fibronectin. *J. Cell Biol.* **168**, 1109–1118 (2005).
35. Gupta, V. et al. The beta-tail domain (betaTD) regulates physiologic ligand binding to integrin CD11b/CD18. *Blood* **109**, 3513–3520 (2007).
36. Fan, Z. et al. High-affinity bent $\beta(2)$ -integrin molecules in arresting neutrophils face each other through binding to ICAMs in cis. *Cell Rep.* **26**, 119–130.e115 (2019).
37. Fan, Z. et al. Neutrophil recruitment limited by high-affinity bent $\beta(2)$ integrin binding ligand in cis. *Nat. Commun.* **7**, 12658 (2016).
38. Sen, M., Yuki, K. & Springer, T. A. An internal ligand-bound, metastable state of a leukocyte integrin, $\alpha\beta(2)$. *J. Cell Biol.* **203**, 629–642 (2013).
39. Zhu, J. et al. Structure of a complete integrin ectodomain in a physiologic resting state and activation and deactivation by applied forces. *Mol. Cell* **32**, 849–861 (2008).
40. Xiong, J. P. et al. Crystal structure of the extracellular segment of integrin $\alpha V\beta(3)$ in complex with an Arg-Gly-Asp ligand. *Science* **296**, 151–155 (2002).
41. Xiong, J. P. et al. Crystal structure of the extracellular segment of integrin $\alpha V\beta(3)$. *Science* **294**, 339–345 (2001).
42. Humphries, M. J., Symonds, E. J. & Mould, A. P. Mapping functional residues onto integrin crystal structures. *Curr. Opin. Struct. Biol.* **13**, 236–243 (2003).
43. Chen, J. F., Salas, A. & Springer, T. A. Bistable regulation of integrin adhesiveness by a bipolar metal ion cluster. *Nat. Struct. Biol.* **10**, 995–1001 (2003).
44. Mould, A. P. et al. Role of ADMIDAS cation-binding site in ligand recognition by integrin $\alpha(5)\beta(1)$. *J. Biol. Chem.* **278**, 51622–51629 (2003).
45. Van Agthoven, J. F. et al. Structural basis for pure antagonism of integrin $\alpha V\beta(3)$ by a high-affinity form of fibronectin. *Nat. Struct. Mol. Biol.* **21**, 383–388 (2014).
46. Li, J. et al. Novel pure $\alpha V\beta(3)$ integrin antagonists that do not induce receptor extension, prime the receptor, or enhance angiogenesis at low concentrations. *ACS Pharmacol. Transl. Sci.* **2**, 387–401 (2019).
47. Spitaleri, A. et al. Structural basis for the interaction of isoDGR with the RGD-binding site of $\alpha V\beta(3)$ integrin. *J. Biol. Chem.* **283**, 19757–19768 (2008).
48. Nardelli, F. et al. Succinimide-based conjugates improve IsoDGR cyclopeptide affinity to $\alpha V\beta(3)$ without promoting integrin allosteric activation. *J. Med. Chem.* **61**, 7474–7485 (2018).
49. Lin, F. Y. et al. A general chemical principle for creating closure-stabilizing integrin inhibitors. *Cell* **185**, 3533–3550.e3527 (2022).
50. Ludwig, B. S., Kessler, H., Kossatz, S. & Reuning, U. RGD-binding integrins revisited: how recently discovered functions and novel synthetic ligands (Re-) shape an ever-evolving field. *Cancers* **13**, 1711 (2021).
51. Sun, C. C., Qu, X. J. & Gao, Z. H. Arginine-glycine-aspartate-binding integrins as therapeutic and diagnostic targets. *Am. J. Ther.* **23**, e198–e207 (2016).
52. Takada, Y., Ye, X. & Simon, S. The integrins. *Genome Biol.* **8**, 215 (2007).
53. Han, Z. et al. Integrin $\alpha V\beta(1)$ regulates procollagen I production through a non-canonical transforming growth factor beta signaling pathway in human hepatic stellate cells. *Biochem. J.* **478**, 1689–1703 (2021).
54. Reed, N. I. et al. The $\alpha V\beta(1)$ integrin plays a critical in vivo role in tissue fibrosis. *Sci. Transl. Med.* **7**, 288ra279 (2015).
55. Hendsi, H. et al. Integrin mediated adhesion of osteoblasts to connective tissue growth factor (CTGF/CCN2) induces cytoskeleton reorganization and cell differentiation. *PLoS ONE* **10**, e0115325 (2015).
56. Yamashiro, Y. et al. Matrix mechanotransduction mediated by thrombospondin-1/integrin/YAP in the vascular remodeling. *Proc. Natl Acad. Sci. USA* **117**, 9896–9905 (2020).
57. Kokubo, T., Uchida, H. & Choi, E. T. Integrin $\alpha(v)\beta(3)$ as a target in the prevention of neointimal hyperplasia. *J. Vasc. Surg.* **45**, A33–A38 (2007).
58. Bishop, G. G. et al. Selective $\alpha(v)\beta(3)$ -receptor blockade reduces macrophage infiltration and restenosis after balloon angioplasty in the atherosclerotic rabbit. *Circulation* **103**, 1906–1911 (2001).
59. Guernonprez, P. et al. Antigen presentation and T cell stimulation by dendritic cells. *Annu. Rev. Immunol.* **20**, 621–667 (2002).
60. Porte, J., Jenkins, G. & Tatler, A. L. Myofibroblast TGF-beta activation measurement in vitro. *Methods Mol. Biol.* **2299**, 99–108 (2021).
61. Tatler, A. L. et al. Integrin $\alpha V\beta(5)$ -mediated TGF-beta activation by airway smooth muscle cells in asthma. *J. Immunol.* **187**, 6094–6107 (2011).
62. Asano, Y. et al. Involvement of $\alpha V\beta(5)$ integrin in the establishment of autocrine TGF-beta signaling in dermal fibroblasts derived from localized scleroderma. *J. Invest. Dermatol.* **126**, 1761–1769 (2006).
63. Oishi, Y. et al. Vitronectin regulates the axon specification of mouse cerebellar granule cell precursors via $\alpha V\beta(5)$ integrin in the differentiation stage. *Neurosci. Lett.* **746**, 135648 (2021).
64. Kumawat, A. K. et al. Expression and characterization of $\alpha V\beta(5)$ integrin on intestinal macrophages. *Eur. J. Immunol.* **48**, 1181–1187 (2018).
65. Schiesser, J. V. et al. Integrin $\alpha V\beta(5)$ heterodimer is a specific marker of human pancreatic beta cells. *Sci. Rep.* **11**, 8315 (2021).
66. Koivisto, L., Bi, J., Hakkinen, L. & Larjava, H. Integrin $\alpha V\beta(6)$: structure, function and role in health and disease. *Int. J. Biochem. Cell Biol.* **99**, 186–196 (2018).
67. Madala, S. K. et al. Inhibition of the $\alpha V\beta(6)$ integrin leads to limited alteration of TGF-alpha-induced pulmonary fibrosis. *Am. J. Physiol. Lung Cell Mol. Physiol.* **306**, L726–L735 (2014).
68. Ansar, M. et al. Expansion of the spectrum of ITGB6-related disorders to adolescent alopecia, dentogingival abnormalities and intellectual disability. *Eur. J. Hum. Genet.* **24**, 1223–1227 (2016).
69. White, J. B., Hu, L. Y., Boucher, D. L. & Sutcliffe, J. L. ImmunoPET imaging of $\alpha V\beta(6)$ expression using an engineered anti- $\alpha V\beta(6)$ Cys-diabody site-specifically radiolabeled with Cu-64: considerations for optimal imaging with antibody fragments. *Mol. Imaging Biol.* **20**, 103–113 (2018).
70. Morris, D. G. et al. Loss of integrin $\alpha(v)\beta(6)$ -mediated TGF-beta activation causes Mmp12-dependent emphysema. *Nature* **422**, 169–173 (2003).
71. Wang, S. K. et al. ITGB6 loss-of-function mutations cause autosomal recessive amelogenesis imperfecta. *Hum. Mol. Genet.* **23**, 2157–2163 (2014).
72. Xie, Y., Gao, K., Hakkinen, L. & Larjava, H. S. Mice lacking $\beta(6)$ integrin in skin show accelerated wound repair in dexamethasone impaired wound healing model. *Wound Repair Regen.* **17**, 326–339 (2009).
73. Zhou, M. et al. Integrin $\alpha V\beta(8)$ serves as a novel marker of poor prognosis in colon carcinoma and regulates cell invasiveness through the activation of TGF-beta1. *J. Cancer* **11**, 3803–3815 (2020).
74. McCarty, J. H. $\alpha V\beta(8)$ integrin adhesion and signaling pathways in development, physiology and disease. *J. Cell Sci.* **133**, jcs239434 (2020).
75. Hou, J. et al. The roles of integrin $\alpha(5)\beta(1)$ in human cancer. *Oncotargets Ther.* **13**, 13329–13344 (2020).
76. Renner, G. et al. Expression/activation of $\alpha(5)\beta(1)$ integrin is linked to the beta-catenin signaling pathway to drive migration in glioma cells. *Oncotarget* **7**, 62194–62207 (2016).
77. Lv, X. et al. Porcine hemagglutinating encephalomyelitis virus activation of the integrin $\alpha(5)\beta(1)$ -FAK-cofilin pathway causes cytoskeletal rearrangement to promote its invasion of N2a cells. *J. Virol.* **93**, e01736–18 (2019).
78. Oh, S. H. et al. The extracellular matrix protein Edil3 stimulates osteoblast differentiation through the integrin $\alpha(5)\beta(1)$ /ERK/Runx2 pathway. *PLoS ONE* **12**, e0188749 (2017).
79. Lopez-Luppo, M. et al. Cellular senescence is associated with human retinal microaneurysm formation during aging. *Invest. Ophthalmol. Vis. Sci.* **58**, 2832–2842 (2017).
80. Di Maggio, N. et al. Extracellular matrix and $\alpha(5)\beta(1)$ integrin signaling control the maintenance of bone formation capacity by human adipose-derived stromal cells. *Sci. Rep.* **7**, 44398 (2017).
81. Zargham, R. Tensegrin in context: dual role of $\alpha(8)$ integrin in the migration of different cell types. *Cell Adh. Migr.* **4**, 485–490 (2010).
82. Nishimichi, N. et al. Induced hepatic stellate cell integrin, $\alpha(8)\beta(1)$, enhances cellular contractility and TGFbeta activity in liver fibrosis. *J. Pathol.* **253**, 366–373 (2021).

83. van den Kerkhof, D. L., van der Meijden, P. E. J., Hackeng, T. M. & Dijkgraaf, I. Exogenous integrin alphallbeta3 inhibitors revisited: past, present and future applications. *Int. J. Mol. Sci.* **22**, 3366 (2021).
84. Huang, J. et al. Platelet integrin alphallbeta3: signal transduction, regulation, and its therapeutic targeting. *J. Hematol. Oncol.* **12**, 26 (2019).
85. Mitroulis, I. et al. Leukocyte integrins: role in leukocyte recruitment and as therapeutic targets in inflammatory disease. *Pharmacol. Ther.* **147**, 123–135 (2015).
86. Guenther, C. beta2-integrins-regulatory and executive bridges in the signaling network controlling leukocyte trafficking and migration. *Front. Immunol.* **13**, 809590 (2022).
87. McEver, R. P. & Zhu, C. Rolling cell adhesion. *Annu. Rev. Cell Dev. Biol.* **26**, 363–396 (2010).
88. Muller, W. A. Getting leukocytes to the site of inflammation. *Vet. Pathol.* **50**, 7–22 (2013).
89. Schenkel, A. R., Mamdouh, Z. & Muller, W. A. Locomotion of monocytes on endothelium is a critical step during extravasation. *Nat. Immunol.* **5**, 393–400 (2004).
90. Yuki, K. & Hou, L. Role of beta2 integrins in neutrophils and sepsis. *Infect. Immun.* **88**, e00031–20 (2020).
91. Schnitzler, N. et al. A co-stimulatory signal through ICAM-beta2 integrin-binding potentiates neutrophil phagocytosis. *Nat. Med.* **5**, 231–235 (1999).
92. Jawhara, S. et al. Distinct effects of integrins alphaXbeta2 and alphaMbeta2 on leukocyte subpopulations during inflammation and antimicrobial responses. *Infect. Immun.* **85**, e00644–16 (2017).
93. Guenther, C. et al. beta2-integrin adhesion regulates dendritic cell epigenetic and transcriptional landscapes to restrict dendritic cell maturation and tumor rejection. *Cancer Immunol. Res.* **9**, 1354–1369 (2021).
94. Miyazaki, Y. et al. Integrin alphaDbeta2 (CD11d/CD18) is expressed by human circulating and tissue myeloid leukocytes and mediates inflammatory signaling. *PLoS ONE* **9**, e112770 (2014).
95. Fukui, T. et al. Pivotal role of CD103 in the development of psoriasiform dermatitis. *Sci. Rep.* **10**, 8371 (2020).
96. Schreiber, T. D. et al. The integrin alpha9beta1 on hematopoietic stem and progenitor cells: involvement in cell adhesion, proliferation and differentiation. *Haematologica* **94**, 1493–1501 (2009).
97. Xu, S. et al. Integrin-alpha9beta1 as a novel therapeutic target for refractory diseases: recent progress and insights. *Front. Immunol.* **12**, 638400 (2021).
98. Li, H. et al. alpha4beta7 integrin inhibitors: a patent review. *Expert Opin. Ther. Pat.* **28**, 903–917 (2018).
99. Arthos, J. et al. The role of integrin alpha4beta7 in HIV pathogenesis and treatment. *HIV/AIDS Rep.* **15**, 127–135 (2018).
100. Zeltz, C. & Gullberg, D. The integrin-collagen connection—a glue for tissue repair? *J. Cell Sci.* **129**, 653–664 (2016).
101. Hemler, M. E. et al. VLA-1: a T cell surface antigen which defines a novel late stage of human T cell activation. *Eur. J. Immunol.* **15**, 502–508 (1985).
102. Gardner, H. Integrin alpha1beta1. *Adv. Exp. Med. Biol.* **819**, 21–39 (2014).
103. Hamaia, S. W. et al. Mapping of potent and specific binding motifs, GLOGEN and GVOGEA, for integrin alpha1beta1 using collagen toolkits II and III. *J. Biol. Chem.* **287**, 26019–26028 (2012).
104. Kriegelstein, C. F. et al. Collagen-binding integrin alpha1beta1 regulates intestinal inflammation in experimental colitis. *J. Clin. Invest.* **110**, 1773–1782 (2002).
105. Suzuki, K. et al. Semaphorin 7A initiates T-cell-mediated inflammatory responses through alpha1beta1 integrin. *Nature* **446**, 680–684 (2007).
106. Dennis, J. et al. Collagen XIII induced in vascular endothelium mediates alpha1beta1 integrin-dependent transmigration of monocytes in renal fibrosis. *Am. J. Pathol.* **177**, 2527–2540 (2010).
107. Ekholm, E. et al. Diminished callus size and cartilage synthesis in alpha 1 beta 1 integrin-deficient mice during bone fracture healing. *Am. J. Pathol.* **160**, 1779–1785 (2002).
108. Zemmyo, M. et al. Accelerated, aging-dependent development of osteoarthritis in alpha1 integrin-deficient mice. *Arthritis Rheum.* **48**, 2873–2880 (2003).
109. Madamanchi, A., Santoro, S. A. & Zutter, M. M. alpha2beta1 Integrin. *Adv. Exp. Med. Biol.* **819**, 41–60 (2014).
110. Zeltz, C. et al. Lumican inhibits cell migration through alpha2beta1 integrin. *Exp. Cell Res.* **316**, 2922–2931 (2010).
111. Fiedler, L. R. et al. Decorin regulates endothelial cell motility on collagen I through activation of insulin-like growth factor I receptor and modulation of alpha2beta1 integrin activity. *J. Biol. Chem.* **283**, 17406–17415 (2008).
112. Grenache, D. G. et al. Wound healing in the alpha2beta1 integrin-deficient mouse: altered keratinocyte biology and dysregulated matrix metalloproteinase expression. *J. Invest. Dermatol.* **127**, 455–466 (2007).
113. Zweers, M. C. et al. Integrin alpha2beta1 is required for regulation of murine wound angiogenesis but is dispensable for reepithelialization. *J. Invest. Dermatol.* **127**, 467–478 (2007).
114. El Azreq, M. A. et al. Cooperation between IL-7 receptor and integrin alpha2-beta1 (CD49b) drives Th17-mediated bone loss. *J. Immunol.* **195**, 4198–4209 (2015).
115. Lundgren-Akerlund, E. & Aszodi, A. Integrin alpha10beta1: a collagen receptor critical in skeletal development. *Adv. Exp. Med. Biol.* **819**, 61–71 (2014).
116. Camper, L. et al. Distribution of the collagen-binding integrin alpha10beta1 during mouse development. *Cell Tissue Res* **306**, 107–116 (2001).
117. Bengtsson, T. et al. Loss of alpha10beta1 integrin expression leads to moderate dysfunction of growth plate chondrocytes. *J. Cell Sci.* **118**, 929–936 (2005).
118. Popova, S. N. et al. Alpha11 beta1 integrin-dependent regulation of periodontal ligament function in the erupting mouse incisor. *Mol. Cell. Biol.* **27**, 4306–4316 (2007).
119. Barczyk, M. M. et al. A role for alpha11beta1 integrin in the human periodontal ligament. *J. Dent. Res.* **88**, 621–626 (2009).
120. Erusappan, P. et al. Integrin alpha11 cytoplasmic tail is required for FAK activation to initiate 3D cell invasion and ERK-mediated cell proliferation. *Sci. Rep.* **9**, 15283 (2019).
121. Kaltz, N. et al. Novel markers of mesenchymal stem cells defined by genome-wide gene expression analysis of stromal cells from different sources. *Exp. Cell Res.* **316**, 2609–2617 (2010).
122. Schulz, J. N. et al. Reduced granulation tissue and wound strength in the absence of alpha11beta1 integrin. *J. Invest. Dermatol.* **135**, 1435–1444 (2015).
123. Barczyk, M., Carracedo, S. & Gullberg, D. Integrins. *Cell Tissue Res.* **339**, 269–280 (2010).
124. Durbeej, M. Laminins. *Cell Tissue Res.* **339**, 259–268 (2010).
125. Ramovs, V., Te Molder, L. & Sonnenberg, A. The opposing roles of laminin-binding integrins in cancer. *Matrix Biol.* **57–58**, 213–243 (2017).
126. Aumailley, M. The laminin family. *Cell Adh Migr.* **7**, 48–55 (2013).
127. Domogatskaya, A., Rodin, S. & Tryggvason, K. Functional diversity of laminins. *Annu. Rev. Cell Dev. Biol.* **28**, 523–553 (2012).
128. Belkin, A. M. & Stepp, M. A. Integrins as receptors for laminins. *Microsc. Res. Tech.* **51**, 280–301 (2000).
129. Sasaki, T. & Timpl, R. Domain IVa of laminin alpha5 chain is cell-adhesive and binds beta1 and alphaVbeta3 integrins through Arg-Gly-Asp. *FEBS Lett.* **509**, 181–185 (2001).
130. Munksgaard Thoren, M. et al. Integrin alpha10, a novel therapeutic target in glioblastoma, regulates cell migration, proliferation, and survival. *Cancers* **11**, 587 (2019).
131. Calderwood, D. A. et al. The integrin alpha1 A-domain is a ligand binding site for collagens and laminin. *J. Biol. Chem.* **272**, 12311–12317 (1997).
132. Colognato, H., MacCarrick, M., O’Rear, J. J. & Yurchenco, P. D. The laminin alpha2-chain short arm mediates cell adhesion through both the alpha1beta1 and alpha2beta1 integrins. *J. Biol. Chem.* **272**, 29330–29336 (1997).
133. Desban, N. & Duband, J. L. Avian neural crest cell migration on laminin: interaction of the alpha1beta1 integrin with distinct laminin-1 domains mediates different adhesive responses. *J. Cell Sci.* **110**, 2729–2744 (1997).
134. Yamada, M. & Sekiguchi, K. Molecular basis of laminin-integrin interactions. *Curr. Top. Membr.* **76**, 197–229 (2015).
135. Genersch, E. et al. Integrin alphavbeta3 binding to human alpha5-laminins facilitates FGF-2- and VEGF-induced proliferation of human ECV304 carcinoma cells. *Eur. J. Cell Biol.* **82**, 105–117 (2003).
136. Kreidberg, J. A. Functions of alpha3beta1 integrin. *Curr. Opin. Cell Biol.* **12**, 548–553 (2000).
137. Couvelard, A. et al. Expression of integrins during liver organogenesis in humans. *Hepatology* **27**, 839–847 (1998).
138. Lora, J. M. et al. Alpha3beta1-integrin as a critical mediator of the hepatic differentiation response to the extracellular matrix. *Hepatology* **28**, 1095–1104 (1998).
139. Kreidberg, J. A. et al. Alpha 3 beta 1 integrin has a crucial role in kidney and lung organogenesis. *Development* **122**, 3537–3547 (1996).
140. Kim, Y. Y. et al. Cellular localization of alpha3beta1 integrin isoforms in association with myofibrillogenesis during cardiac myocyte development in culture. *Cell Adhes. Commun.* **7**, 85–97 (1999).
141. DiPersio, C. M. et al. alpha3beta1 Integrin is required for normal development of the epidermal basement membrane. *J. Cell Biol.* **137**, 729–742 (1997).
142. Anton, E. S., Kreidberg, J. A. & Rakic, P. Distinct functions of alpha3 and alpha(v) integrin receptors in neuronal migration and laminar organization of the cerebral cortex. *Neuron* **22**, 277–289 (1999).
143. Delwel, G. O. et al. Distinct and overlapping ligand specificities of the alpha 3 A beta 1 and alpha 6 A beta 1 integrins: recognition of laminin isoforms. *Mol. Biol. Cell* **5**, 203–215 (1994).
144. Georges-Labouesse, E., Mark, M., Messaddeq, N. & Gansmuller, A. Essential role of alpha 6 integrins in cortical and retinal lamination. *Curr. Biol.* **8**, 983–986 (1998).
145. Fujiwara, H. et al. Physiological roles of integrin alpha 6 beta 1 in ovarian functions. *Horm. Res.* **50**, 25–29 (1998).

146. Reynolds, L. E. et al. Dual role of pericyte alpha6beta1-integrin in tumour blood vessels. *J. Cell Sci.* **130**, 1583–1595 (2017).
147. van der Neut, R. et al. Epithelial detachment due to absence of hemidesmosomes in integrin beta 4 null mice. *Nat. Genet.* **13**, 366–369 (1996).
148. Welsler-Alves, J. V. et al. Endothelial beta4 integrin is predominantly expressed in arterioles, where it promotes vascular remodeling in the hypoxic brain. *Arterioscler. Thromb. Vasc. Biol.* **33**, 943–953 (2013).
149. Dowling, J., Yu, Q. C. & Fuchs, E. Beta4 integrin is required for hemidesmosome formation, cell adhesion and cell survival. *J. Cell Biol.* **134**, 559–572 (1996).
150. Margadant, C., Frijns, E., Wilhelmson, K. & Sonnenberg, A. Regulation of hemidesmosome disassembly by growth factor receptors. *Curr. Opin. Cell Biol.* **20**, 589–596 (2008).
151. Giancotti, F. G. Targeting integrin beta4 for cancer and anti-angiogenic therapy. *Trends Pharmacol. Sci.* **28**, 506–511 (2007).
152. Georges-Labouesse, E. et al. Absence of integrin alpha 6 leads to epidermolysis bullosa and neonatal death in mice. *Nat. Genet.* **13**, 370–373 (1996).
153. Soung, Y. H., Clifford, J. L. & Chung, J. Crosstalk between integrin and receptor tyrosine kinase signaling in breast carcinoma progression. *BMB Rep.* **43**, 311–318 (2010).
154. Wang, L., Dong, Z., Zhang, Y. & Miao, J. The roles of integrin beta4 in vascular endothelial cells. *J. Cell. Physiol.* **227**, 474–478 (2012).
155. Hayashi, Y. K. et al. Mutations in the integrin alpha7 gene cause congenital myopathy. *Nat. Genet.* **19**, 94–97 (1998).
156. Mayer, U. et al. Absence of integrin alpha 7 causes a novel form of muscular dystrophy. *Nat. Genet.* **17**, 318–323 (1997).
157. Flintoff-Dye, N. L. et al. Role for the alpha7beta1 integrin in vascular development and integrity. *Dev. Dyn.* **234**, 11–21 (2005).
158. Calderwood, D. A., Campbell, I. D. & Critchley, D. R. Talins and kindlins: partners in integrin-mediated adhesion. *Nat. Rev. Mol. Cell Biol.* **14**, 503–517 (2013).
159. Zhu, J., Zhu, J. & Springer, T. A. Complete integrin headpiece opening in eight steps. *J. Cell Biol.* **201**, 1053–1068 (2013).
160. Nevo, J. et al. Mammary-derived growth inhibitor (MDGI) interacts with integrin α -subunits and suppresses integrin activity and invasion. *Oncogene* **29**, 6452–6463 (2010).
161. Kasirer-Friede, A., Tjahjono, W., Eto, K. & Shattil, S. J. SHARPIN at the nexus of integrin, immune, and inflammatory signaling in human platelets. *Proc. Natl Acad. Sci. USA* **116**, 4983–4988 (2019).
162. Gao, J. et al. Sharpin suppresses β 1-integrin activation by complexing with the β 1 tail and kindlin-1. *Cell Commun. Signal.* **17**, 101 (2019).
163. Liu, W. et al. Mechanism for KRIT1 release of ICAP1-mediated suppression of integrin activation. *Mol. Cell* **49**, 719–729 (2013).
164. Liu, J. et al. Structural mechanism of integrin inactivation by filamin. *Nat. Struct. Mol. Biol.* **22**, 383–389 (2015).
165. Vinogradova, O. et al. A structural mechanism of integrin α (IIb) β (3) “inside-out” activation as regulated by its cytoplasmic face. *Cell* **110**, 587–597 (2002).
166. Legate, K. R., Wickstrom, S. A. & Fassler, R. Genetic and cell biological analysis of integrin outside-in signaling. *Genes Dev.* **23**, 397–418 (2009).
167. Kim, C. et al. Basic amino-acid side chains regulate transmembrane integrin signalling. *Nature* **481**, 209–213 (2011).
168. Kanchanawong, P. & Calderwood, D. A. Organization, dynamics and mechanoregulation of integrin-mediated cell-ECM adhesions. *Nat. Rev. Mol. Cell Biol.* <https://doi.org/10.1038/s41580-022-00531-5> (2022).
169. Lau, T. L., Kim, C., Ginsberg, M. H. & Ulmer, T. S. The structure of the integrin α IIb β 3 transmembrane complex explains integrin transmembrane signalling. *EMBO J.* **28**, 1351–1361 (2009).
170. Kim, C., Ye, F., Hu, X. & Ginsberg, M. H. Talin activates integrins by altering the topology of the beta transmembrane domain. *J. Cell Biol.* **197**, 605–611 (2012).
171. Sun, H. et al. Transmission of integrin beta7 transmembrane domain topology enables gut lymphoid tissue development. *J. Cell Biol.* **217**, 1453–1465 (2018).
172. Sun, H. et al. Frontline Science: A flexible kink in the transmembrane domain impairs beta2 integrin extension and cell arrest from rolling. *J. Leukoc. Biol.* **107**, 175–183 (2020).
173. Bu, W., Levitskaya, Z., Tan, S. M. & Gao, Y. G. Emerging evidence for kindlin oligomerization and its role in regulating kindlin function. *J. Cell Sci.* **134**, jcs256115 (2021).
174. Shams, H. & Mofrad, M. R. K. alpha-actinin induces a kink in the transmembrane domain of beta3-integrin and impairs activation via talin. *Biophys. J.* **113**, 948–956 (2017).
175. Case, L. B. et al. Molecular mechanism of vinculin activation and nanoscale spatial organization in focal adhesions. *Nat. Cell Biol.* **17**, 880–892 (2015).
176. Bays, J. L. & DeMali, K. A. Vinculin in cell-cell and cell-matrix adhesions. *Cell. Mol. Life Sci.* **74**, 2999–3009 (2017).
177. Lopez-Colome, A. M., Lee-Rivera, I., Benavides-Hidalgo, R. & Lopez, E. Paxillin: a crossroad in pathological cell migration. *J. Hematol. Oncol.* **10**, 50 (2017).
178. Zhao, X. & Guan, J. L. Focal adhesion kinase and its signaling pathways in cell migration and angiogenesis. *Adv. Drug Deliv. Rev.* **63**, 610–615 (2011).
179. Wen, L., Moser, M. & Ley, K. Molecular mechanisms of leukocyte beta2 integrin activation. *Blood* **139**, 3480–3492 (2022).
180. Bouti, P. et al. beta2 integrin signaling cascade in neutrophils: more than a single function. *Front. Immunol.* **11**, 619925 (2020).
181. Sari-Ak, D. et al. Structural, biochemical, and functional properties of the Rap1-interacting adaptor molecule (RIAM). *Biomed. J.* **45**, 289–298 (2022).
182. Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **144**, 646–674 (2011).
183. Worbs, T., Hammerschmidt, S. I. & Forster, R. Dendritic cell migration in health and disease. *Nat. Rev. Immunol.* **17**, 30–48 (2017).
184. Xiao, Y. et al. Collective cell migration in 3D epithelial wound healing. *ACS Nano* **13**, 1204–1212 (2019).
185. Scarpa, E. & Mayor, R. Collective cell migration in development. *J. Cell Biol.* **212**, 143–155 (2016).
186. Changede, R. & Sheetz, M. Integrin and cadherin clusters: a robust way to organize adhesions for cell mechanics. *Bioessays* **39**, 1–12 (2017).
187. Mishra, Y. G. & Manavathi, B. Focal adhesion dynamics in cellular function and disease. *Cell Signal* **85**, 110046 (2021).
188. Byron, A. et al. A proteomic approach reveals integrin activation state-dependent control of microtubule cortical targeting. *Nat. Commun.* **6**, 6135 (2015).
189. Manninen, A. & Varjosalo, M. A proteomics view on integrin-mediated adhesions. *Proteomics* **17**, 1600022 (2017).
190. Horton, E. R. et al. Definition of a consensus integrin adhesome and its dynamics during adhesion complex assembly and disassembly. *Nat. Cell Biol.* **17**, 1577–1587 (2015).
191. Horton, E. R. et al. The integrin adhesome network at a glance. *J. Cell Sci.* **129**, 4159–4163 (2016).
192. Bouchet, B. P. et al. Talin-KANK1 interaction controls the recruitment of cortical microtubule stabilizing complexes to focal adhesions. *eLife* **5**, e18124 (2016).
193. Sun, Z. et al. Kank2 activates talin, reduces force transduction across integrins and induces central adhesion formation. *Nat. Cell Biol.* **18**, 941–953 (2016).
194. Zaidel-Bar, R., Ballestrem, C., Kam, Z. & Geiger, B. Early molecular events in the assembly of matrix adhesions at the leading edge of migrating cells. *J. Cell Sci.* **116**, 4605–4613 (2003).
195. Zaidel-Bar, R., Cohen, M., Addadi, L. & Geiger, B. Hierarchical assembly of cell-matrix adhesion complexes. *Biochem. Soc. Trans.* **32**, 416–420 (2004).
196. Jacquemet, G. et al. Filopodium mapping identifies p130Cas as a mechanosensitive regulator of filopodia stability. *Curr. Biol.* **29**, 202–216.e207 (2019).
197. Bachir, A. I. et al. Integrin-associated complexes form hierarchically with variable stoichiometry in nascent adhesions. *Curr. Biol.* **24**, 1845–1853 (2014).
198. Geiger, B. & Yamada, K. M. Molecular architecture and function of matrix adhesions. *Cold Spring Harb. Perspect. Biol.* **3**, a005033 (2011).
199. Hu, K. et al. Differential transmission of actin motion within focal adhesions. *Science* **315**, 111–115 (2007).
200. Giannone, G. et al. Lamellipodial actin mechanically links myosin activity with adhesion-site formation. *Cell* **128**, 561–575 (2007).
201. Elosegui-Artola, A., Trepast, X. & Roca-Cusachs, P. Control of mechanotransduction by molecular clutch dynamics. *Trends Cell Biol.* **28**, 356–367 (2018).
202. Choi, C. K. et al. Actin and alpha-actinin orchestrate the assembly and maturation of nascent adhesions in a myosin II motor-independent manner. *Nat. Cell Biol.* **10**, 1039–1050 (2008).
203. Diaz, C. et al. Recruitment of α IIb β 3 integrin to α 5 β 1 integrin-induced clusters enables focal adhesion maturation and cell spreading. *J. Cell Sci.* **133**, jcs232702 (2020).
204. Chinthalapudi, K., Rangarajan, E. S. & Izard, T. The interaction of talin with the cell membrane is essential for integrin activation and focal adhesion formation. *Proc. Natl Acad. Sci. USA* **115**, 10339–10344 (2018).
205. Nader, G. P., Ezratty, E. J. & Gundersen, G. G. FAK, talin and PIPK γ regulate endocytosed integrin activation to polarize focal adhesion assembly. *Nat. Cell Biol.* **18**, 491–503 (2016).
206. Legerstee, K., Geverts, B., Slotman, J. A. & Houtsmuller, A. B. Dynamics and distribution of paxillin, vinculin, zyxin and VASP depend on focal adhesion location and orientation. *Sci. Rep.* **9**, 10460 (2019).
207. Tang, K., Boudreau, C. G., Brown, C. M. & Khadra, A. Paxillin phosphorylation at serine 273 and its effects on Rac, Rho and adhesion dynamics. *PLoS Comput. Biol.* **14**, e1006303 (2018).
208. Zamir, E. & Geiger, B. Molecular complexity and dynamics of cell-matrix adhesions. *J. Cell Sci.* **114**, 3583–3590 (2001).
209. Goult, B. T., Yan, J. & Schwartz, M. A. Talin as a mechanosensitive signaling hub. *J. Cell Biol.* **217**, 3776–3784 (2018).
210. Schiller, H. B. & Fassler, R. Mechanosensitivity and compositional dynamics of cell-matrix adhesions. *EMBO Rep.* **14**, 509–519 (2013).

211. Hynes, R. O. Integrins: bidirectional, allosteric signaling machines. *Cell* **110**, 673–687 (2002).
212. Iskratsch, T., Wolfenson, H. & Sheetz, M. P. Appreciating force and shape—the rise of mechanotransduction in cell biology. *Nat. Rev. Mol. Cell Biol.* **15**, 825–833 (2014).
213. Case, L. B. & Waterman, C. M. Integration of actin dynamics and cell adhesion by a three-dimensional, mechanosensitive molecular clutch. *Nat. Cell Biol.* **17**, 955–963 (2015).
214. Isomursu, A. et al. Integrin signaling and mechanotransduction in regulation of somatic stem cells. *Exp. Cell Res.* **378**, 217–225 (2019).
215. Atherton, P., Stutchbury, B., Jethwa, D. & Ballestrem, C. Mechanosensitive components of integrin adhesions: role of vinculin. *Exp. Cell Res.* **343**, 21–27 (2016).
216. Yao, M. et al. The mechanical response of talin. *Nat. Commun.* **7**, 11966 (2016).
217. Chen, H., Choudhury, D. M. & Craig, S. W. Coincidence of actin filaments and talin is required to activate vinculin. *J. Biol. Chem.* **281**, 40389–40398 (2006).
218. Yao, M. et al. Mechanical activation of vinculin binding to talin locks talin in an unfolded conformation. *Sci. Rep.* **4**, 4610 (2014).
219. Zhu, L. et al. Structure of Rap1b bound to talin reveals a pathway for triggering integrin activation. *Nat. Commun.* **8**, 1744 (2017).
220. Goult, B. T. et al. RIAM and vinculin binding to talin are mutually exclusive and regulate adhesion assembly and turnover. *J. Biol. Chem.* **288**, 8238–8249 (2013).
221. Totaro, A., Panciera, T. & Piccolo, S. YAP/TAZ upstream signals and downstream responses. *Nat. Cell Biol.* **20**, 888–899 (2018).
222. Nishida, N. et al. Activation of leukocyte beta2 integrins by conversion from bent to extended conformations. *Immunity* **25**, 583–594 (2006).
223. Shattil, S. J., Kim, C. & Ginsberg, M. H. The final steps of integrin activation: the end game. *Nat. Rev. Mol. Cell Biol.* **11**, 288–300 (2010).
224. Ye, F., Kim, C. & Ginsberg, M. H. Reconstruction of integrin activation. *Blood* **119**, 26–33 (2012).
225. Schuerpf, T. & Springer, T. A. Regulation of integrin affinity on cell surfaces. *EMBO J.* **30**, 4712–4727 (2011).
226. Hamidi, H. & Ivaska, J. Every step of the way: integrins in cancer progression and metastasis. *Nat. Rev. Cancer* **18**, 532–547 (2018).
227. Chen, W. et al. Molecular dynamics simulations of forced unbending of integrin $\alpha(v)\beta_3$. *PLoS Comput. Biol.* **7**, e1001086 (2011).
228. Puklin-Faucher, E., Gao, M., Schulten, K. & Vogel, V. How the headpiece hinge angle is opened: New insights into the dynamics of integrin activation. *J. Cell Biol.* **175**, 349–360 (2006).
229. Saltel, F. et al. New PI(4,5)P2- and membrane proximal integrin-binding motifs in the talin head control beta3-integrin clustering. *J. Cell Biol.* **187**, 715–731 (2009).
230. Chen, Y. et al. Force regulated conformational change of integrin $\alpha v \beta 3$. *Matrix Biol.* **60–61**, 70–85 (2017).
231. Uhm, J. H. et al. Vitronectin, a glioma-derived extracellular matrix protein, protects tumor cells from apoptotic death. *Clin. Cancer Res.* **5**, 1587–1594 (1999).
232. Scatena, M. et al. NF-kappaB mediates alphavbeta3 integrin-induced endothelial cell survival. *J. Cell Biol.* **141**, 1083–1093 (1998).
233. Courter, D. L., Lomas, L., Scatena, M. & Giachelli, C. M. Src kinase activity is required for integrin alphaVbeta3-mediated activation of nuclear factor-kappaB. *J. Biol. Chem.* **280**, 12145–12151 (2005).
234. Bao, W. & Stromblad, S. Integrin alphav-mediated inactivation of p53 controls a MEK1-dependent melanoma cell survival pathway in three-dimensional collagen. *J. Cell Biol.* **167**, 745–756 (2004).
235. Stupack, D. G. et al. Apoptosis of adherent cells by recruitment of caspase-8 to unligated integrins. *J. Cell Biol.* **155**, 459–470 (2001).
236. Miranti, C. K. & Brugge, J. S. Sensing the environment: a historical perspective on integrin signal transduction. *Nat. Cell Biol.* **4**, E83–E90 (2002).
237. Lawson, C. et al. FAK promotes recruitment of talin to nascent adhesions to control cell motility. *J. Cell Biol.* **196**, 223–232 (2012).
238. Palazzo, A. F. et al. Localized stabilization of microtubules by integrin- and FAK-facilitated Rho signaling. *Science* **303**, 836–839 (2004).
239. Alanko, J. et al. Integrin endosomal signalling suppresses anoikis. *Nat. Cell Biol.* **17**, 1412–1421 (2015).
240. Bugide, S. et al. Hematopoietic PBX-interacting protein (HPIP) is over expressed in breast infiltrative ductal carcinoma and regulates cell adhesion and migration through modulation of focal adhesion dynamics. *Oncogene* **34**, 4601–4612 (2015).
241. Huvneers, S. & Danen, E. H. Adhesion signaling—crosstalk between integrins, Src and Rho. *J. Cell Sci.* **122**, 1059–1069 (2009).
242. Colo, G. P. et al. Focal adhesion disassembly is regulated by a RIAM to MEK-1 pathway. *J. Cell Sci.* **125**, 5338–5352 (2012).
243. Mitra, S. K. & Schlaepfer, D. D. Integrin-regulated FAK-Src signaling in normal and cancer cells. *Curr. Opin. Cell Biol.* **18**, 516–523 (2006).
244. Paoli, P., Giannoni, E. & Chiarugi, P. Anokis molecular pathways and its role in cancer progression. *Biochim. Biophys. Acta* **1833**, 3481–3498 (2013).
245. Zhang, Y., Reif, G. & Wallace, D. P. Extracellular matrix, integrins, and focal adhesion signaling in polycystic kidney disease. *Cell Signal.* **72**, 109646 (2020).
246. Torres-Gomez, A., Cabanas, C. & Lafuente, E. M. Phagocytic integrins: activation and signaling. *Front. Immunol.* **11**, 738 (2020).
247. Goel, H. L. et al. Neuropilin-2 regulates alpha6beta1 integrin in the formation of focal adhesions and signaling. *J. Cell Sci.* **125**, 497–506 (2012).
248. Dower, C. M., Wills, C. A., Frisch, S. M. & Wang, H. G. Mechanisms and context underlying the role of autophagy in cancer metastasis. *Autophagy* **14**, 1110–1128 (2018).
249. Torres-Gomez, A. et al. RIAM-VASP Module relays integrin complement receptors in outside-in signaling driving particle engulfment. *Cells* **9**, 1166 (2020).
250. Hehlhans, S., Eke, I. & Cordes, N. Targeting FAK radiosensitizes 3-dimensional grown human HNSCC cells through reduced Akt1 and MEK1/2 signaling. *Int. J. Radiat. Oncol. Biol. Phys.* **83**, e669–e676 (2012).
251. Eke, I. et al. beta(1)Integrin/FAK/cortactin signaling is essential for human head and neck cancer resistance to radiotherapy. *J. Clin. Invest.* **122**, 1529–1540 (2012).
252. Dupont, S. et al. Role of YAP/TAZ in mechanotransduction. *Nature* **474**, 179–183 (2011).
253. Elbediwy, A. et al. Integrin signalling regulates YAP and TAZ to control skin homeostasis. *Development* **143**, 1674–1687 (2016).
254. Vartiainen, M. K., Guettler, S., Larjani, B. & Treisman, R. Nuclear actin regulates dynamic subcellular localization and activity of the SRF cofactor MAL. *Science* **316**, 1749–1752 (2007).
255. Dong, X. et al. Force interacts with macromolecular structure in activation of TGF-beta. *Nature* **542**, 55–59 (2017).
256. Campbell, M. G. et al. Cryo-EM reveals integrin-mediated TGF-beta activation without release from latent TGF-beta. *Cell* **180**, 490–501.e416 (2020).
257. Hamidi, H. & Ivaska, J. Every step of the way: integrins in cancer progression and metastasis. *Nat. Rev. Cancer* **18**, 533–548 (2018).
258. Desgrosellier, J. S. & Cheresch, D. A. Integrins in cancer: biological implications and therapeutic opportunities. *Nat. Rev. Cancer* **10**, 9–22 (2010).
259. Cagnet, S. et al. Signaling events mediated by $\alpha 3 \beta 1$ integrin are essential for mammary tumorigenesis. *Oncogene* **33**, 4286–4295 (2014).
260. White, D. E. et al. Targeted disruption of beta1-integrin in a transgenic mouse model of human breast cancer reveals an essential role in mammary tumor induction. *Cancer Cell* **6**, 159–170 (2004).
261. Barkan, D. & Chambers, A. F. $\beta 1$ -integrin: a potential therapeutic target in the battle against cancer recurrence. *Clin. Cancer Res.* **17**, 7219–7223 (2011).
262. Uchihara, T. et al. Extracellular vesicles from cancer-associated fibroblasts containing annexin A6 induces FAK-YAP activation by stabilizing $\beta 1$ integrin, enhancing drug resistance. *Cancer Res.* **80**, 3222–3235 (2020).
263. Lau, M. T., So, W. K. & Leung, P. C. Integrin $\beta 1$ mediates epithelial growth factor-induced invasion in human ovarian cancer cells. *Cancer Lett.* **320**, 198–204 (2012).
264. Zhao, G. et al. Cullin5 deficiency promotes small-cell lung cancer metastasis by stabilizing integrin $\beta 1$. *J. Clin. Invest.* **129**, 972–987 (2019).
265. Govaere, O. et al. The PDGFR α -laminin B1-keratin 19 cascade drives tumor progression at the invasive front of human hepatocellular carcinoma. *Oncogene* **36**, 6605–6616 (2017).
266. Ludlow, A. et al. Characterization of integrin beta6 and thrombospondin-1 double-null mice. *J. Cell. Mol. Med.* **9**, 421–437 (2005).
267. Moore, K. M. et al. Therapeutic targeting of integrin $\alpha v \beta 6$ in breast cancer. *J. Natl Cancer Inst.* **106**, dju169 (2014).
268. Onodera, Y., Nam, J. M. & Bissell, M. J. Increased sugar uptake promotes oncogenesis via EPAC/RAP1 and O-GlcNAc pathways. *J. Clin. Invest.* **124**, 367–384 (2014).
269. Yang, P. et al. Pyruvate kinase M2 facilitates colon cancer cell migration via the modulation of STAT3 signalling. *Cell Signal* **26**, 1853–1862 (2014).
270. Nolte, M. & Margadant, C. Controlling Immunity and Inflammation through Integrin-Dependent Regulation of TGF-beta. *Trends Cell Biol.* **30**, 49–59 (2020).
271. Zhang, Y. et al. Integrin beta7 inhibits colorectal cancer pathogenesis via maintaining antitumor immunity. *Cancer Immunol. Res.* **9**, 967–980 (2021).
272. Cooper, J. & Giancotti, F. G. Integrin signaling in cancer: mechanotransduction, stemness, epithelial plasticity, and therapeutic resistance. *Cancer cell* **35**, 347–367 (2019).
273. Visvader, J. E. & Stingl, J. Mammary stem cells and the differentiation hierarchy: current status and perspectives. *Genes Dev.* **28**, 1143–1158 (2014).
274. Lawson, D. A. & Witte, O. N. Stem cells in prostate cancer initiation and progression. *J. Clin. Invest.* **117**, 2044–2050 (2007).
275. Yoshioka, T. et al. $\beta 4$ Integrin signalling induces expansion of prostate tumor progenitors. *J. Clin. Invest.* **123**, 682–699 (2013).
276. Plow, E. F. et al. Ligand binding to integrins. *J. Biol. Chem.* **275**, 21785–21788 (2000).
277. Puloss, F. E. et al. Talin-dependent integrin activation is required for endothelial proliferation and postnatal angiogenesis. *Angiogenesis* **24**, 177–190 (2021).

278. Brooks, P. C. et al. Integrin alpha v beta 3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels. *Cell* **79**, 1157–1164 (1994).
279. Somanath, P. R., Malinin, N. L. & Byzova, T. V. Cooperation between integrin alphavbeta3 and VEGFR2 in angiogenesis. *Angiogenesis* **12**, 177–185 (2009).
280. Mahabeleshwar, G. H. et al. Integrin affinity modulation in angiogenesis. *Cell Cycle* **7**, 335–347 (2008).
281. Mahabeleshwar, G. H. et al. Mechanisms of integrin-vascular endothelial growth factor receptor cross-activation in angiogenesis. *Circ. Res.* **101**, 570–580 (2007).
282. Damiano, J. S. Integrins as novel drug targets for overcoming innate drug resistance. *Curr. Cancer Drug Targets* **2**, 37–43 (2002).
283. Kwakwa, K. A. & Sterling, J. A. Integrin $\alpha v \beta 3$ signaling in tumor-induced bone disease. *Cancers* **9**, 84 (2017).
284. Liapis, H., Flath, A. & Kitazawa, S. Integrin alpha V beta 3 expression by bone-residing breast cancer metastases. *Diagn. Mol. Pathol.* **5**, 127–135 (1996).
285. Sloan, E. K. et al. Tumor-specific expression of alphavbeta3 integrin promotes spontaneous metastasis of breast cancer to bone. *Breast Cancer Res.* **8**, R20 (2006).
286. McCabe, N. P. et al. Prostate cancer specific integrin alphavbeta3 modulates bone metastatic growth and tissue remodeling. *Oncogene* **26**, 6238–6243 (2007).
287. Harms, J. F. et al. A small molecule antagonist of the alpha(v)beta3 integrin suppresses MDA-MB-435 skeletal metastasis. *Clin. Exp. Metastasis* **21**, 119–128 (2004).
288. Fontana, F. et al. VLA4-targeted nanoparticles hijack cell adhesion-mediated drug resistance to target refractory myeloma cells and prolong survival. *Clin. Cancer Res.* **27**, 1974–1986 (2021).
289. Haeger, A. et al. Collective cancer invasion forms an integrin-dependent radioresistant niche. *J. Exp. Med.* **217**, e20181184 (2020).
290. Schwartz, M. A. et al. Integrin agonists as adjuvants in chemotherapy for melanoma. *Clin. Cancer Res.* **14**, 6193–6197 (2008).
291. Duro-Castano, A., Gallon, E., Decker, C. & Vicent, M. J. Modulating angiogenesis with integrin-targeted nanomedicines. *Adv. Drug Deliv. Rev.* **119**, 101–119 (2017).
292. Philippe, C. L. Therapeutic value of an integrin antagonist in prostate cancer. *Curr. Drug Targets* **17**, 321–327 (2016).
293. Lainé, A. et al. Regulatory T cells promote cancer immune-escape through integrin $\alpha v \beta 8$ -mediated TGF- β activation. *Nat. Commun.* **12**, 6228 (2021).
294. Ahmed, K. M. et al. $\beta 1$ -integrin impacts Rad51 stability and DNA double-strand break repair by homologous recombination. *Mol. Cell. Biol.* **38**, e00672–17 (2018).
295. Dickreuter, E. et al. Targeting of $\beta 1$ integrins impairs DNA repair for radiosensitization of head and neck cancer cells. *Oncogene* **35**, 1353–1362 (2016).
296. Eke, I. et al. $\beta 1$ Integrin/FAK/cortactin signaling is essential for human head and neck cancer resistance to radiotherapy. *J. Clin. Invest.* **122**, 1529–1540 (2012).
297. Jung, S. H. et al. Integrin $\alpha 6 \beta 4$ -Src-AKT signaling induces cellular senescence by counteracting apoptosis in irradiated tumor cells and tissues. *Cell Death Differ.* **26**, 245–259 (2019).
298. Baltes, F. et al. $\beta(1)$ -Integrin binding to collagen type 1 transmits breast cancer cells into chemoresistance by activating ABC efflux transporters. *Biochim. Biophys. Acta-Mol. Cell Res.* **1867**, 118663 (2020).
299. Ravindranath, A. K. et al. CD44 promotes multi-drug resistance by protecting P-glycoprotein from FBXO21-mediated ubiquitination. *Oncotarget* **6**, 26308–26321 (2015).
300. Jahangiri, A. et al. Cross-activating c-Met/ $\beta 1$ integrin complex drives metastasis and invasive resistance in cancer. *Proc. Natl Acad. Sci. USA* **114**, E8685–e8694 (2017).
301. Fu, Y. et al. Abnormally activated OPN/integrin $\alpha v \beta 3$ /FAK signalling is responsible for EGFR-TKI resistance in EGFR mutant non-small-cell lung cancer. *J. Hematol. Oncol.* **13**, 169 (2020).
302. Pang, X. et al. SPP1 promotes enzalutamide resistance and epithelial-mesenchymal-transition activation in castration-resistant prostate cancer via PI3K/AKT and ERK1/2 pathways. *Oxid. Med. Cell. Longev.* **2021**, 5806602 (2021).
303. Lu, H. et al. $\alpha v \beta 6$ integrin promotes castrate-resistant prostate cancer through JNK1-mediated activation of androgen receptor. *Cancer Res.* **76**, 5163–5174 (2016).
304. Bagati, A. et al. Integrin $\alpha v \beta 6$ -TGF β -SOX4 pathway drives immune evasion in triple-negative breast cancer. *Cancer Cell* **39**, 54–67.e59 (2021).
305. Henderson, N. C., Rieder, F. & Wynn, T. A. Fibrosis: from mechanisms to medicines. *Nature* **587**, 555–566 (2020).
306. Henderson, N. C. & Sheppard, D. Integrin-mediated regulation of TGFbeta in fibrosis. *Biochim. Biophys. Acta* **1832**, 891–896 (2013).
307. Khalil, N. TGF-beta: from latent to active. *Microbes Infect.* **1**, 1255–1263 (1999).
308. Meng, X. M., Nikolic-Paterson, D. J. & Lan, H. Y. TGF-beta: the master regulator of fibrosis. *Nat. Rev. Nephrol.* **12**, 325–338 (2016).
309. Stewart, A. G., Thomas, B. & Koff, J. TGF-beta: master regulator of inflammation and fibrosis. *Respiology* **23**, 1096–1097 (2018).
310. Batlle, E. & Massague, J. Transforming growth factor-beta signaling in immunity and cancer. *Immunity* **50**, 924–940 (2019).
311. Lodyga, M. & Hinz, B. TGF-beta1—a truly transforming growth factor in fibrosis and immunity. *Semin. Cell Dev. Biol.* **101**, 123–139 (2020).
312. Kim, K. K., Sheppard, D. & Chapman, H. A. TGF-beta1 signaling and tissue fibrosis. *Cold Spring Harb. Perspect. Biol.* **10**, a022293 (2018).
313. Horan, G. S. et al. Partial inhibition of integrin alpha(v)beta6 prevents pulmonary fibrosis without exacerbating inflammation. *Am. J. Respir. Crit. Care Med.* **177**, 56–65 (2008).
314. Puthawala, K. et al. Inhibition of integrin alpha(v)beta6, an activator of latent transforming growth factor-beta, prevents radiation-induced lung fibrosis. *Am. J. Respir. Crit. Care Med.* **177**, 82–90 (2008).
315. Ong, C. H. et al. TGF-beta-induced fibrosis: a review on the underlying mechanism and potential therapeutic strategies. *Eur. J. Pharmacol.* **911**, 174510 (2021).
316. Bhalra, N. et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. *Hepatology* **54**, 1208–1216 (2011).
317. Powell, E. E., Wong, V. W. & Rinella, M. Non-alcoholic fatty liver disease. *Lancet* **397**, 2212–2224 (2021).
318. Angulo, P. Nonalcoholic fatty liver disease. *N. Engl. J. Med.* **346**, 1221–1231 (2002).
319. Angulo, P. et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* **149**, 389–397.e310 (2015).
320. Younossi, Z. M. et al. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* **64**, 73–84 (2016).
321. Estes, C. et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* **67**, 123–133 (2018).
322. Marcellin, P. & Kutala, B. K. Liver diseases: a major, neglected global public health problem requiring urgent actions and large-scale screening. *Liver Int* **38**, 2–6 (2018).
323. Chen, W. et al. Lysyl oxidase (LOX) family members: rationale and their potential as therapeutic targets for liver fibrosis. *Hepatology* **72**, 729–741 (2020).
324. Younossi, Z. M. et al. Improvement of hepatic fibrosis and patient-reported outcomes in non-alcoholic steatohepatitis treated with selonsertib. *Liver Int* **38**, 1849–1859 (2018).
325. Hiroshima, S. et al. Quantitative evaluation of hepatic integrin alphavbeta3 expression by positron emission tomography imaging using (18)F-FPP-RGD2 in rats with non-alcoholic steatohepatitis. *EJNMMI Res.* **10**, 118 (2020).
326. Puche, J. E., Saiman, Y. & Friedman, S. L. Hepatic stellate cells and liver fibrosis. *Compr. Physiol.* **3**, 1473–1492 (2013).
327. Henderson, N. C. et al. Targeting of alpha v integrin identifies a core molecular pathway that regulates fibrosis in several organs. *Nat. Med.* **19**, 1617–1624 (2013).
328. Hartimath, S. V. et al. Imaging fibrogenesis in a diet-induced model of non-alcoholic steatohepatitis (NASH). *Contrast Media Mol. Imaging* **2019**, 6298128 (2019).
329. Tang, M. et al. Osteopontin acts as a negative regulator of autophagy accelerating lipid accumulation during the development of nonalcoholic fatty liver disease. *Artif. Cell. Nanomed. Biotechnol.* **48**, 159–168 (2020).
330. Liu, J. et al. High glucose regulates LN expression in human liver sinusoidal endothelial cells through ROS/integrin alphavbeta3 pathway. *Environ. Toxicol. Pharmacol.* **42**, 231–236 (2016).
331. Rokugawa, T. et al. Evaluation of hepatic integrin alphavbeta3 expression in non-alcoholic steatohepatitis (NASH) model mouse by (18)F-FPP-RGD2 PET. *EJNMMI Res.* **8**, 40 (2018).
332. Drescher, H. K. et al. beta7-Integrin and MAdCAM-1 play opposing roles during the development of non-alcoholic steatohepatitis. *J. Hepatol.* **66**, 1251–1264 (2017).
333. Ester, C. et al. The role of beta-7 integrin and carbonic anhydrase IX in predicting the occurrence of de novo nonalcoholic fatty liver disease in liver transplant recipients. *Chirurgia* **113**, 534–541 (2018).
334. Rai, R. P. et al. Blocking integrin alpha4beta7-mediated CD4 T cell recruitment to the intestine and liver protects mice from western diet-induced non-alcoholic steatohepatitis. *J. Hepatol.* **73**, 1013–1022 (2020).
335. Guo, Q. et al. Integrin beta1-enriched extracellular vesicles mediate monocyte adhesion and promote liver inflammation in murine NASH. *J. Hepatol.* **71**, 1193–1205 (2019).
336. Honda, M., Kimura, C., Uede, T. & Kon, S. Neutralizing antibody against osteopontin attenuates non-alcoholic steatohepatitis in mice. *J. Cell Commun. Signal.* **14**, 223–232 (2020).

337. Levine, D. et al. Expression of the integrin alpha8beta1 during pulmonary and hepatic fibrosis. *Am. J. Pathol.* **156**, 1927–1935 (2000).
338. Cai, Q. et al. Epigenetic silencing of microRNA-125b-5p promotes liver fibrosis in nonalcoholic fatty liver disease via integrin alpha8-mediated activation of RhoA signaling pathway. *Metabolism* **104**, 154140 (2020).
339. Rahman, S. R. et al. Integrins as a drug target in liver fibrosis. *Liver Int* **42**, 507–521 (2022).
340. Rajagopal, K. et al. Idiopathic pulmonary fibrosis and pulmonary hypertension: Heracles meets the Hydra. *Br. J. Pharmacol.* **178**, 172–186 (2021).
341. Humbert, M. et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J. Am. Coll. Cardiol.* **43**, 135–245 (2004).
342. Schermuly, R. T., Ghofrani, H. A., Wilkins, M. R. & Grimminger, F. Mechanisms of disease: pulmonary arterial hypertension. *Nat. Rev. Cardiol.* **8**, 443–455 (2011).
343. Rabinovitch, M. Pathobiology of pulmonary hypertension. *Annu. Rev. Pathol. Mech. Dis.* **2**, 369–399 (2007).
344. Botney, M. D. et al. Extracellular matrix protein gene expression in atherosclerotic hypertensive pulmonary arteries. *Am. J. Pathol.* **140**, 357–364 (1992).
345. Crouch, E. C. et al. Regulation of collagen production by medial smooth muscle cells in hypoxic pulmonary hypertension. *Am. Rev. Respir. Dis.* **140**, 1045–1051 (1989).
346. Durmowicz, A. G. & Stenmark, K. R. Mechanisms of structural remodeling in chronic pulmonary hypertension. *Pediatr. Res.* **20**, e91–e102 (1999).
347. Umesh, A. et al. Alteration of pulmonary artery integrin levels in chronic hypoxia and monocrotaline-induced pulmonary hypertension. *J. Vasc. Res.* **48**, 525–537 (2011).
348. Martinez-Lemus, L. A. et al. Integrins as unique receptors for vascular control. *J. Vasc. Res.* **40**, 211–233 (2003).
349. Umesh, A. et al. Integrin ligands mobilize Ca²⁺ from ryanodine receptor-gated stores and lysosome-related acidic organelles in pulmonary arterial smooth muscle cells. *J. Biol. Chem.* **281**, 34312–34323 (2006).
350. Liu, A. et al. Role of miR-223-3p in pulmonary arterial hypertension via targeting ITGB3 in the ECM pathway. *Cell Prolif.* **52**, e12550 (2019).
351. Lafyatis, R. Transforming growth factor beta—at the centre of systemic sclerosis. *Nat. Rev. Rheumatol.* **10**, 706–719 (2014).
352. Berg, D. T. et al. Negative regulation of inducible nitric-oxide synthase expression mediated through transforming growth factor-beta-dependent modulation of transcription factor TCF11. *J. Biol. Chem.* **282**, 36837–36844 (2007).
353. Hummers, L. K., Hall, A., Wigley, F. M. & Simons, M. Abnormalities in the regulators of angiogenesis in patients with scleroderma. *J. Rheumatol.* **36**, 576–582 (2009).
354. McDonald, P. C., Fielding, A. B. & Dedhar, S. Integrin-linked kinase—essential roles in physiology and cancer biology. *J. Cell Sci.* **121**, 3121–3132 (2008).
355. Kudryashova, T. V. et al. HIPPO-integrin-linked kinase cross-talk controls self-sustaining proliferation and survival in pulmonary hypertension. *Am. J. Respir. Crit. Care Med.* **194**, 866–877 (2016).
356. Serrano, I. et al. Inactivation of the Hippo tumour suppressor pathway by integrin-linked kinase. *Nat. Commun.* **4**, 2976 (2013).
357. Meng, L. et al. Osteopontin plays important roles in pulmonary arterial hypertension induced by systemic-to-pulmonary shunt. *FASEB J.* **33**, 7236–7251 (2019).
358. Jia, D. et al. Osteopontin disruption attenuates hyalu-induced pulmonary hypertension through integrin alphavbeta3/FAK/AKT pathway suppression. *Circ. Cardiovasc. Genet.* **10**, e001591 (2017).
359. Corne-Le Gall, E., Alam, A. & Perrone, R. D. Autosomal dominant polycystic kidney disease. *Lancet* **393**, 919–935 (2019).
360. Arroyo, J. et al. The genetic background significantly impacts the severity of kidney cystic disease in the Pkd1(RC/RC) mouse model of autosomal dominant polycystic kidney disease. *Kidney Int.* **99**, 1392–1407 (2021).
361. Bergmann, C. et al. Polycystic kidney disease. *Nat. Rev. Dis. Prim.* **4**, 50 (2018).
362. Qiu, Z. et al. Obacunone retards renal cyst development in autosomal dominant polycystic kidney disease by activating NRF2. *Antioxidants* **11**, 38 (2021).
363. Subramanian, B. et al. The regulation of cystogenesis in a tissue engineered kidney disease system by abnormal matrix interactions. *Biomaterials* **33**, 8383–8394 (2012).
364. Wallace, D. P. et al. Periostin induces proliferation of human autosomal dominant polycystic kidney cells through alphaV-integrin receptor. *Am. J. Physiol. Ren. Physiol.* **295**, F1463–F1471 (2008).
365. Wallace, D. P. et al. Periostin promotes renal cyst growth and interstitial fibrosis in polycystic kidney disease. *Kidney Int.* **85**, 845–854 (2014).
366. Raman, A. et al. Periostin overexpression in collecting ducts accelerates renal cyst growth and fibrosis in polycystic kidney disease. *Am. J. Physiol. Ren. Physiol.* **315**, F1695–F1707 (2018).
367. Kim, H. et al. Identification of osteopontin as a urinary biomarker for autosomal dominant polycystic kidney disease progression. *Kidney Res. Clin. Pract.* <https://doi.org/10.23876/j.krcp.21.303> (2022).
368. Kreidberg, J. A. & Symons, J. M. Integrins in kidney development, function, and disease. *Am. J. Physiol. Ren. Physiol.* **279**, F233–F242 (2000).
369. Shi, M. et al. Enhancing integrin alpha1 inserted (I) domain affinity to ligand potentiates integrin alpha1beta1-mediated down-regulation of collagen synthesis. *J. Biol. Chem.* **287**, 35139–35152 (2012).
370. Rubel, D. et al. Collagen receptors integrin alpha2beta1 and discoidin domain receptor 1 regulate maturation of the glomerular basement membrane and loss of integrin alpha2beta1 delays kidney fibrosis in COL4A3 knockout mice. *Matrix Biol.* **34**, 13–21 (2014).
371. Wagrowska-Danilewicz, M. & Danilewicz, M. Expression of alpha5beta1 and alpha6beta1 integrins in IgA nephropathy (IgAN) with mild and severe proteinuria. An immunohistochemical study. *Int. Urol. Nephrol.* **36**, 81–87 (2004).
372. Chang, Y. et al. Pharmacologic blockade of alphavbeta1 integrin ameliorates renal failure and fibrosis in vivo. *J. Am. Soc. Nephrol.* **28**, 1998–2005 (2017).
373. Bagnato, G. L. et al. Dual alphavbeta3 and alphavbeta5 blockade attenuates fibrotic and vascular alterations in a murine model of systemic sclerosis. *Clin. Sci.* **132**, 231–242 (2018).
374. Hahm, K. et al. Alphav beta6 integrin regulates renal fibrosis and inflammation in Alport mouse. *Am. J. Pathol.* **170**, 110–125 (2007).
375. Has, C. et al. Integrin alpha3 mutations with kidney, lung, and skin disease. *N. Engl. J. Med.* **366**, 1508–1514 (2012).
376. Finney, A. C., Stokes, K. Y., Pattillo, C. B. & Orr, A. W. Integrin signaling in atherosclerosis. *Cell. Mol. Life Sci.* **74**, 2263–2282 (2017).
377. Yurdagul, A. Jr et al. Oxidized LDL induces FAK-dependent RSK signaling to drive NF-κB activation and VCAM-1 expression. *J. Cell Sci.* **129**, 1580–1591 (2016).
378. Chen, J. et al. αvβ3 integrins mediate flow-induced NF-κB activation, proinflammatory gene expression, and early atherogenic inflammation. *Am. J. Pathol.* **185**, 2575–2589 (2015).
379. Bhullar, I. S. et al. Fluid shear stress activation of IκappaB kinase is integrin-dependent. *J. Biol. Chem.* **273**, 30544–30549 (1998).
380. Sun, X. et al. Activation of integrin α5 mediated by flow requires its translocation to membrane lipid rafts in vascular endothelial cells. *Proc. Natl Acad. Sci. USA* **113**, 769–774 (2016).
381. Arnaout, M. A. Biology and structure of leukocyte β (2) integrins and their role in inflammation. *F1000Res.* **5**, F1000 Faculty Rev–F1000 Faculty2433 (2016).
382. Sadhu, C. et al. CD11c/CD18: novel ligands and a role in delayed-type hypersensitivity. *J. Leukoc. Biol.* **81**, 1395–1403 (2007).
383. Wu, H. et al. Functional role of CD11c + monocytes in atherogenesis associated with hypercholesterolemia. *Circulation* **119**, 2708–2717 (2009).
384. Lund, S. A. et al. Osteopontin mediates macrophage chemotaxis via α4 and α9 integrins and survival via the α4 integrin. *J. Cell. Biochem.* **114**, 1194–1202 (2013).
385. Yakubenko, V. P., Yadav, S. P. & Ugarova, T. P. Integrin alphaDbeta2, an adhesion receptor up-regulated on macrophage foam cells, exhibits multiligand-binding properties. *Blood* **107**, 1643–1650 (2006).
386. Antonov, A. S., Kolodgie, F. D., Munn, D. H. & Gerrity, R. G. Regulation of macrophage foam cell formation by alphaVbeta3 integrin: potential role in human atherosclerosis. *Am. J. Pathol.* **165**, 247–258 (2004).
387. Yakubenko, V. P., Bhattacharjee, A., Pluskota, E. & Cathcart, M. K. αMβ2 integrin activation prevents alternative activation of human and murine macrophages and impedes foam cell formation. *Circ. Res.* **108**, 544–554 (2011).
388. Gray, J. L. & Shankar, R. Downregulation of CD11b and CD18 expression in atherosclerotic lesion-derived macrophages. *Am. Surg.* **61**, 674–679 (1995).
389. Savill, J., Dransfield, I., Hogg, N. & Haslett, C. Vitronectin receptor-mediated phagocytosis of cells undergoing apoptosis. *Nature* **343**, 170–173 (1990).
390. Hanayama, R. et al. Autoimmune disease and impaired uptake of apoptotic cells in MFG-E8-deficient mice. *Science* **304**, 1147–1150 (2004).
391. Antonov, A. S. et al. αVβ3 integrin regulates macrophage inflammatory responses via PI3 kinase/Akt-dependent NF-κB activation. *J. Cell. Physiol.* **226**, 469–476 (2011).
392. Liu, W. et al. Nexinhib20 inhibits neutrophil adhesion and beta2 integrin activation by antagonizing Rac-1-guanosine 5'-triphosphate interaction. *J. Immunol.* **209**, 1574–1585 (2022).
393. Yurdagul, A. Jr et al. α5β1 integrin signaling mediates oxidized low-density lipoprotein-induced inflammation and early atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **34**, 1362–1373 (2014).
394. Li, G. et al. Periostin mediates vascular smooth muscle cell migration through the integrins alphavbeta3 and alphavbeta5 and focal adhesion kinase (FAK) pathway. *Atherosclerosis* **208**, 358–365 (2010).
395. Schaller, M. D. Biochemical signals and biological responses elicited by the focal adhesion kinase. *Biochim. Biophys. Acta* **1540**, 1–21 (2001).
396. Moiseeva, E. P., Williams, B., Goodall, A. H. & Samani, N. J. Galectin-1 interacts with beta-1 subunit of integrin. *Biochem. Biophys. Res. Commun.* **310**, 1010–1016 (2003).

397. Lee, B. H. et al. betaig-h3 triggers signaling pathways mediating adhesion and migration of vascular smooth muscle cells through alphavbeta5 integrin. *Exp. Mol. Med.* **38**, 153–161 (2006).
398. Estevez, B., Shen, B. & Du, X. Targeting integrin and integrin signaling in treating thrombosis. *Arterioscler. Thromb. Vasc. Biol.* **35**, 24–29 (2015).
399. Bernardi, B. et al. The small GTPase Rap1b regulates the cross talk between platelet integrin alpha2beta1 and integrin alphallbeta3. *Blood* **107**, 2728–2735 (2006).
400. Mackman, N. Triggers, targets and treatments for thrombosis. *Nature* **451**, 914–918 (2008).
401. Wagner, C. L. et al. Analysis of GPIIb/IIIa receptor number by quantification of 7E3 binding to human platelets. *Blood* **88**, 907–914 (1996).
402. Jamasbi, J. et al. Platelet receptors as therapeutic targets: past, present and future. *Thromb. Haemost.* **117**, 1249–1257 (2017).
403. Tadokoro, S. et al. Talin binding to integrin beta tails: a final common step in integrin activation. *Science* **302**, 103–106 (2003).
404. Shattil, S. J. & Newman, P. J. Integrins: dynamic scaffolds for adhesion and signaling in platelets. *Blood* **104**, 1606–1615 (2004).
405. Law, D. A., Nannizzi-Alaimo, L. & Phillips, D. R. Outside-in integrin signal transduction. Alpha IIb beta 3-(GP IIb IIIa) tyrosine phosphorylation induced by platelet aggregation. *J. Biol. Chem.* **271**, 10811–10815 (1996).
406. Flevaris, P. et al. Two distinct roles of mitogen-activated protein kinases in platelets and a novel Rac1-MAPK-dependent integrin outside-in retractile signaling pathway. *Blood* **113**, 893–901 (2009).
407. Ley, K., Rivera-Nieves, J., Sandborn, W. J. & Shattil, S. Integrin-based therapeutics: biological basis, clinical use and new drugs. *Nat. Rev. Drug Discov.* **15**, 173–183 (2016).
408. Lim, E. H., Danthi, N., Bednarski, M. & Li, K. C. A review: integrin alphavbeta3-targeted molecular imaging and therapy in angiogenesis. *Nanomedicine* **1**, 110–114 (2005).
409. Hodivala-Dilke, K. alphavbeta3 integrin and angiogenesis: a moody integrin in a changing environment. *Curr. Opin. Cell Biol.* **20**, 514–519 (2008).
410. Somanath, P. R., Ciocea, A. & Byzova, T. V. Integrin and growth factor receptor alliance in angiogenesis. *Cell Biochem. Biophys.* **53**, 53–64 (2009).
411. Bennett, J. S. et al. Agonist-activated alphavbeta3 on platelets and lymphocytes binds to the matrix protein osteopontin. *J. Biol. Chem.* **272**, 8137–8140 (1997).
412. Sahni, A., Sahni, S. K. & Francis, C. W. Endothelial cell activation by IL-1beta in the presence of fibrinogen requires alphavbeta3. *Arterioscler. Thromb. Vasc. Biol.* **25**, 2222–2227 (2005).
413. van Gils, J. M., Zwaginga, J. J. & Hordijk, P. L. Molecular and functional interactions among monocytes, platelets, and endothelial cells and their relevance for cardiovascular diseases. *J. Leukoc. Biol.* **85**, 195–204 (2009).
414. Sakuma, T. et al. Simultaneous integrin alphavbeta3 and glycoprotein IIb/IIIa inhibition causes reduction in infarct size in a model of acute coronary thrombosis and primary angioplasty. *Cardiovasc. Res.* **66**, 552–561 (2005).
415. Chico, T. J. et al. Effect of selective or combined inhibition of integrins alpha(IIb) beta(3) and alpha(v)beta(3) on thrombosis and neointima after oversized porcine coronary angioplasty. *Circulation* **103**, 1135–1141 (2001).
416. Bianconi, D. et al. Integrin beta-3 genetic variants and risk of venous thromboembolism in colorectal cancer patients. *Thromb. Res.* **136**, 865–869 (2015).
417. Kapoor, S., Opneja, A. & Nayak, L. The role of neutrophils in thrombosis. *Thromb. Res.* **170**, 87–96 (2018).
418. Noubououssie, D. F., Reeves, B. N., Strahl, B. D. & Key, N. S. Neutrophils: back in the thrombosis spotlight. *Blood* **133**, 2186–2197 (2019).
419. Iba, T. & Levy, J. H. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. *J. Thromb. Haemost.* **16**, 231–241 (2018).
420. Yang, Y. et al. Cell adhesion mediated by VCAM-ITGa9 interactions enables lymphatic development. *Arterioscler. Thromb. Vasc. Biol.* **35**, 1179–1189 (2015).
421. Nishimichi, N. et al. Polymeric osteopontin employs integrin alpha9beta1 as a receptor and attracts neutrophils by presenting a de novo binding site. *J. Biol. Chem.* **284**, 14769–14776 (2009).
422. Saldanha-Gama, R. F. et al. alpha(9)beta(1) integrin engagement inhibits neutrophil spontaneous apoptosis: involvement of Bcl-2 family members. *Biochim. Biophys. Acta* **1803**, 848–857 (2010).
423. Dhanesha, N. et al. Targeting myeloid-cell specific integrin alpha9beta1 inhibits arterial thrombosis in mice. *Blood* **135**, 857–861 (2020).
424. Brill, A. et al. Neutrophil extracellular traps promote deep vein thrombosis in mice. *J. Thromb. Haemost.* **10**, 136–144 (2012).
425. Campos, J. et al. Neutrophil extracellular traps and inflammasomes cooperatively promote venous thrombosis in mice. *Blood Adv.* **5**, 2319–2324 (2021).
426. Sharma, S. et al. Neutrophil extracellular traps promote fibrous vascular occlusions in chronic thrombosis. *Blood* **137**, 1104–1116 (2021).
427. Nakamura, M. & Sadoshima, J. Mechanisms of physiological and pathological cardiac hypertrophy. *Nat. Rev. Cardiol.* **15**, 387–407 (2018).
428. Pham, C. G. et al. Striated muscle-specific beta(1D)-integrin and FAK are involved in cardiac myocyte hypertrophic response pathway. *Am. J. Physiol. Heart Circ. Physiol.* **279**, H2916–H2926 (2000).
429. Li, R. et al. beta1 integrin gene excision in the adult murine cardiac myocyte causes defective mechanical and signaling responses. *Am. J. Pathol.* **180**, 952–962 (2012).
430. Keller, R. S. et al. Disruption of integrin function in the murine myocardium leads to perinatal lethality, fibrosis, and abnormal cardiac performance. *Am. J. Pathol.* **158**, 1079–1090 (2001).
431. Krishnamurthy, P., Subramanian, V., Singh, M. & Singh, K. Deficiency of beta1 integrins results in increased myocardial dysfunction after myocardial infarction. *Heart* **92**, 1309–1315 (2006).
432. Jia, N. et al. A newly developed angiotensin II type 1 receptor antagonist, CS866, promotes regression of cardiac hypertrophy by reducing integrin beta1 expression. *Hypertens. Res.* **26**, 737–742 (2003).
433. Johnston, R. K. et al. Beta3 integrin-mediated ubiquitination activates survival signaling during myocardial hypertrophy. *FASEB J.* **23**, 2759–2771 (2009).
434. Valiente-Alandi, I., Schafer, A. E. & Blaxall, B. C. Extracellular matrix-mediated cellular communication in the heart. *J. Mol. Cell. Cardiol.* **91**, 228–237 (2016).
435. Graham, Z. A., Gallagher, P. M. & Cardozo, C. P. Focal adhesion kinase and its role in skeletal muscle. *J. Muscle Res. Cell Motil.* **36**, 305–315 (2015).
436. Brancaccio, M. et al. Melusin, a muscle-specific integrin beta1-interacting protein, is required to prevent cardiac failure in response to chronic pressure overload. *Nat. Med.* **9**, 68–75 (2003).
437. De Acetis, M. et al. Cardiac overexpression of melusin protects from dilated cardiomyopathy due to long-standing pressure overload. *Circ. Res.* **96**, 1087–1094 (2005).
438. White, D. E. et al. Targeted ablation of ILK from the murine heart results in dilated cardiomyopathy and spontaneous heart failure. *Genes Dev.* **20**, 2355–2360 (2006).
439. Lu, H. et al. Integrin-linked kinase expression is elevated in human cardiac hypertrophy and induces hypertrophy in transgenic mice. *Circulation* **114**, 2271–2279 (2006).
440. Liu, L. et al. Myocardin-related transcription factor A regulates integrin beta 2 transcription to promote macrophage infiltration and cardiac hypertrophy in mice. *Cardiovasc. Res.* **118**, 844–858 (2022).
441. Meagher, P. B. et al. Cardiac fibrosis: key role of integrins in cardiac homeostasis and remodeling. *Cells* **10**, 770 (2021).
442. Gulati, A. et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *J. Am. Med. Assoc.* **309**, 896–908 (2013).
443. Yokota, T. et al. Type V collagen in scar tissue regulates the size of scar after heart injury. *Cell* **182**, 545–562.e523 (2020).
444. Turner, C. J. et al. alpha5 and alphaV integrins cooperate to regulate vascular smooth muscle and neural crest functions in vivo. *Development* **142**, 797–808 (2015).
445. Pan, L. et al. Legumain is an endogenous modulator of integrin alphaVbeta3 triggering vascular degeneration, dissection, and rupture. *Circulation* **145**, 659–674 (2022).
446. Lu, R. et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* **395**, 565–574 (2020).
447. Bugatti, K. alpha(V) beta(6) integrin: an intriguing target for COVID-19 and related diseases. *ChemBioChem* **22**, 2516–2520 (2021).
448. Aguirre, C. et al. Covid-19 in a patient with multiple sclerosis treated with natalizumab: may the blockade of integrins have a protective role? *Mult. Scler. Relat. Disord.* **44**, 102250 (2020).
449. Sigrist, C. J., Bridge, A. & Le Mercier, P. A potential role for integrins in host cell entry by SARS-CoV-2. *Antivir. Res.* **177**, 104759 (2020).
450. Tresoldi, I., Sangiuolo, C. F., Manzari, V. & Modesti, A. SARS-CoV-2 and infectivity: possible increase in infectivity associated to integrin motif expression. *J. Med. Virol.* **92**, 1741–1742 (2020).
451. Beaudoin, C. A. et al. Can the SARS-CoV-2 spike protein bind integrins independent of the RGD sequence? *Front. Cell. Infect. Microbiol.* **11**, 765300 (2021).
452. Park, E. J. et al. The spike glycoprotein of SARS-CoV-2 binds to beta1 integrins expressed on the surface of lung epithelial cells. *Viruses* **13**, 645 (2021).
453. Beddingfield, B. J. et al. The integrin binding peptide, ATN-161, as a novel therapy for SARS-CoV-2 infection. *JACC-Basic Transl. Sci.* **6**, 1–8 (2021).
454. Nader, D., Fletcher, N., Curley, G. F. & Kerrigan, S. W. SARS-CoV-2 uses major endothelial integrin alphaVbeta3 to cause vascular dysregulation in-vitro during COVID-19. *PLoS ONE* **16**, e0253347 (2021).
455. Kliche, J., Kuss, H., Ali, M. & Ivarsson, Y. Cytoplasmic short linear motifs in ACE2 and integrin beta(3) link SARS-CoV-2 host cell receptors to mediators of endocytosis and autophagy. *Sci. Signal.* **14**, eabf1117 (2021).
456. Simons, P. et al. Integrin activation is an essential component of SARS-CoV-2 infection. *Sci. Rep.* **11**, 20398 (2021).

457. Ballana, E. et al. Cell adhesion through alphaV-containing integrins is required for efficient HIV-1 infection in macrophages. *Blood* **113**, 1278–1286 (2009).
458. Ballana, E. et al. $\beta 5$ integrin is the major contributor to the α V integrin-mediated blockade of HIV-1 replication. *J. Immunol.* **186**, 464–470 (2011).
459. Urbinati, C. et al. Integrin α v β 3 as a target for blocking HIV-1 Tat-induced endothelial cell activation in vitro and angiogenesis in vivo. *Arterioscler. Thromb. Vasc. Biol.* **25**, 2315–2320 (2005).
460. Arthos, J. et al. The role of integrin $\alpha(4)\beta(7)$ in HIV pathogenesis and treatment. *Curr. HIV/AIDS Rep.* **15**, 127–135 (2018).
461. Liu, Q. & Lusso, P. Integrin $\alpha 4\beta 7$ in HIV-1 infection: a critical review. *J. Leukoc. Biol.* **108**, 627–632 (2020).
462. Schmidt, K. et al. Integrins modulate the infection efficiency of West Nile virus into cells. *J. Gen. Virol.* **94**, 1723–1733 (2013).
463. Chu, J. J. & Ng, M. L. Interaction of West Nile virus with alpha v beta 3 integrin mediates virus entry into cells. *J. Biol. Chem.* **279**, 54533–54541 (2004).
464. Schornberg, K. L. et al. Alpha5beta1-integrin controls ebolavirus entry by regulating endosomal cathepsins. *Proc. Natl Acad. Sci. USA* **106**, 8003–8008 (2009).
465. Tomassi, S. et al. Halting the spread of herpes simplex virus-1: the discovery of an effective dual α v β 6/ α v β 8 integrin ligand. *J. Med. Chem.* **64**, 6972–6984 (2021).
466. Akter, S. et al. The frequency of circulating integrin $\alpha 4\beta 7(+)$ cells correlates with protection against *Helicobacter pylori* infection in immunized mice. *Helicobacter* **24**, e12658 (2019).
467. Altorki, T., Muller, W., Brass, A. & Cruickshank, S. The role of $\beta(2)$ integrin in dendritic cell migration during infection. *BMC Immunol.* **22**, 2 (2021).
468. An, J. S. et al. Integrin alpha 6 as a stemness driver is a novel promising target for HPV (+) head and neck squamous cell carcinoma. *Exp. Cell Res.* **407**, 112815 (2021).
469. Basin, S. et al. Severe anti-PD1-related meningoencephalomyelitis successfully treated with anti-integrin alpha4 therapy. *Eur. J. Cancer* **145**, 230–233 (2021).
470. Bieri, M. et al. The RGD-binding integrins α v β 6 and α v β 8 are receptors for mouse adenovirus-1 and -3 infection. *PLoS Pathog.* **17**, e1010083 (2021).
471. Baker, K. F. & Isaacs, J. D. Novel therapies for immune-mediated inflammatory diseases: What can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? *Ann. Rheum. Dis.* **77**, 175–187 (2018).
472. Rieder, F. & Fiocchi, C. Intestinal fibrosis in IBD—a dynamic, multifactorial process. *Nat. Rev. Gastroenterol. Hepatol.* **6**, 228–235 (2009).
473. Atreya, R. & Neurath, M. F. IBD pathogenesis in 2014: molecular pathways controlling barrier function in IBD. *Nat. Rev. Gastroenterol. Hepatol.* **12**, 67–68 (2015).
474. Cammarota, G. et al. The involvement of gut microbiota in inflammatory bowel disease pathogenesis: potential for therapy. *Pharmacol. Ther.* **149**, 191–212 (2015).
475. de Souza, H. S. & Fiocchi, C. Immunopathogenesis of IBD: current state of the art. *Nat. Rev. Gastroenterol. Hepatol.* **13**, 13–27 (2016).
476. Otte, J. M., Rosenberg, I. M. & Podolsky, D. K. Intestinal myofibroblasts in innate immune responses of the intestine. *Gastroenterology* **124**, 1866–1878 (2003).
477. Yoo, J. H., Holubar, S. & Rieder, F. Fibrostenotic strictures in Crohn's disease. *Intest. Res.* **18**, 379–401 (2020).
478. Dotan, I. et al. The role of integrins in the pathogenesis of inflammatory bowel disease: approved and investigational anti-integrin therapies. *Med. Res. Rev.* **40**, 245–262 (2020).
479. Goodman, S. L. & Picard, M. Integrins as therapeutic targets. *Trends Pharmacol. Sci.* **33**, 405–412 (2012).
480. Fischer, A. et al. Differential effects of alpha4beta7 and GPR15 on homing of effector and regulatory T cells from patients with UC to the inflamed gut in vivo. *Gut* **65**, 1642–1664 (2016).
481. Yu, Y. et al. Structural specializations of alpha(4)beta(7), an integrin that mediates rolling adhesion. *J. Cell Biol.* **196**, 131–146 (2012).
482. Berlin, C. et al. alpha 4 integrins mediate lymphocyte attachment and rolling under physiologic flow. *Cell* **80**, 413–422 (1995).
483. Denucci, C. C., Mitchell, J. S. & Shimizu, Y. Integrin function in T-cell homing to lymphoid and nonlymphoid sites: getting there and staying there. *Crit. Rev. Immunol.* **29**, 87–109 (2009).
484. Berlin, C. et al. Alpha 4 beta 7 integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. *Cell* **74**, 185–195 (1993).
485. Erle, D. J. et al. Expression and function of the MAdCAM-1 receptor, integrin alpha 4 beta 7, on human leukocytes. *J. Immunol.* **153**, 517–528 (1994).
486. Arihiro, S. et al. Differential expression of mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in ulcerative colitis and Crohn's disease. *Pathol. Int.* **52**, 367–374 (2002).
487. Minagawa, S. et al. Selective targeting of TGF-beta activation to treat fibroinflammatory airway disease. *Sci. Transl. Med.* **6**, 241ra279 (2014).
488. Elices, M. J. et al. VCAM-1 on activated endothelium interacts with the leukocyte integrin VLA-4 at a site distinct from the VLA-4/fibronectin binding site. *Cell* **60**, 577–584 (1990).
489. Lamb, C. A. et al. alphaEbeta7 integrin identifies subsets of pro-inflammatory colonic CD4 + T lymphocytes in ulcerative colitis. *J. Crohns Colitis* **11**, 610–620 (2017).
490. Kurmaeva, E. et al. T cell-associated alpha4beta7 but not alpha4beta1 integrin is required for the induction and perpetuation of chronic colitis. *Mucosal Immunol.* **7**, 1354–1365 (2014).
491. Makker, J. & Hommes, D. W. Etrolizumab for ulcerative colitis: the new kid on the block? *Expert Opin. Biol. Ther.* **16**, 567–572 (2016).
492. Briskin, M. et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am. J. Pathol.* **151**, 97–110 (1997).
493. Schon, M. P. et al. Mucosal T lymphocyte numbers are selectively reduced in integrin alpha E (CD103)-deficient mice. *J. Immunol.* **162**, 6641–6649 (1999).
494. Wagner, N. et al. Critical role for beta 7 integrins in formation of the gut-associated lymphoid tissue. *Nature* **382**, 366–370 (1996).
495. Zundler, S. et al. Hobit- and Blimp-1-driven CD4(+) tissue-resident memory T cells control chronic intestinal inflammation. *Nat. Immunol.* **20**, 288–300 (2019).
496. Zundler, S. et al. Blockade of alphaEbeta7 integrin suppresses accumulation of CD8(+) and Th9 lymphocytes from patients with IBD in the inflamed gut in vivo. *Gut* **66**, 1936–1948 (2017).
497. del Rio, M. L., Rodriguez-Barbosa, J. I., Kremmer, E. & Forster, R. CD103- and CD103 + bronchial lymph node dendritic cells are specialized in presenting and cross-presenting innocuous antigen to CD4 + and CD8 + T cells. *J. Immunol.* **178**, 6861–6866 (2007).
498. El-Asady, R. et al. TGF- β -dependent CD103 expression by CD8(+) T cells promotes selective destruction of the host intestinal epithelium during graft-versus-host disease. *J. Exp. Med.* **201**, 1647–1657 (2005).
499. Cepek, K. L. et al. Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the alpha E beta 7 integrin. *Nature* **372**, 190–193 (1994).
500. Zhang, N. & Bevan, M. J. Transforming growth factor-beta signaling controls the formation and maintenance of gut-resident memory T cells by regulating migration and retention. *Immunity* **39**, 687–696 (2013).
501. Allez, M. et al. CD4 + NKG2D + T cells in Crohn's disease mediate inflammatory and cytotoxic responses through MICA interactions. *Gastroenterology* **132**, 2346–2358 (2007).
502. Mann, E. R. et al. Human gut dendritic cells drive aberrant gut-specific t-cell responses in ulcerative colitis, characterized by increased IL-4 production and loss of IL-22 and IFN γ . *Inflamm. Bowel Dis.* **20**, 2299–2307 (2014).
503. Nguyen, D. T., Nagarajan, N. & Zorlutuna, P. Effect of substrate stiffness on mechanical coupling and force propagation at the infarct boundary. *Biophys. J.* **115**, 1966–1980 (2018).
504. Roberts, A. I. et al. Spontaneous cytotoxicity of intestinal intraepithelial lymphocytes: clues to the mechanism. *Clin. Exp. Immunol.* **94**, 527–532 (1993).
505. Gofu, G. et al. Beta7 integrin deficiency suppresses B cell homing and attenuates chronic ileitis in SAMP1/YitFc mice. *J. Immunol.* **185**, 5561–5568 (2010).
506. Agace, W. W. T-cell recruitment to the intestinal mucosa. *Trends Immunol.* **29**, 514–522 (2008).
507. Picarella, D. et al. Monoclonal antibodies specific for beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) reduce inflammation in the colon of scid mice reconstituted with CD45RBhigh CD4 + T cells. *J. Immunol.* **158**, 2099–2106 (1997).
508. Chen, H. et al. Transgenic overexpression of ITGB6 in intestinal epithelial cells exacerbates dextran sulfate sodium-induced colitis in mice. *J. Cell. Mol. Med.* **25**, 2679–2690 (2021).
509. Xie, H. et al. Integrin α v β 6 contributes to the development of intestinal fibrosis via the FAK/AKT signaling pathway. *Exp. Cell Res.* **411**, 113003 (2022).
510. Wight, T. N. & Potter-Perigo, S. The extracellular matrix: an active or passive player in fibrosis? *Am. J. Physiol. Gastroint. Liver Physiol.* **301**, G950–G955 (2011).
511. Bonnans, C., Chou, J. & Werb, Z. Remodelling the extracellular matrix in development and disease. *Nat. Rev. Mol. Cell Biol.* **15**, 786–801 (2014).
512. Bosman, F. T. & Stamenkovic, I. Functional structure and composition of the extracellular matrix. *J. Pathol.* **200**, 423–428 (2003).
513. Johnson, L. A. et al. Matrix stiffness corresponding to strictured bowel induces a fibrogenic response in human colonic fibroblasts. *Inflamm. Bowel Dis.* **19**, 891–903 (2013).
514. Garlatti, V., Lovisa, S., Danese, S. & Vetrano, S. The multiple faces of integrin-ECM interactions in inflammatory bowel disease. *Int. J. Mol. Sci.* **22**, 10439 (2021).
515. Eslami, A. et al. Expression of integrin α v β 6 and TGF- β in scarless vs scar-forming wound healing. *J. Histochem. Cytochem.* **57**, 543–557 (2009).
516. Li, Z. B. et al. (64)Cu-labeled tetrameric and octameric RGD peptides for small-animal PET of tumor α (v) β (3) integrin expression. *J. Nucl. Med.* **48**, 1162–1171 (2007).
517. Rozario, T. & DeSimone, D. W. The extracellular matrix in development and morphogenesis: a dynamic view. *Dev. Biol.* **341**, 126–140 (2010).

518. Missan, D. S., Mitchell, K., Subbaram, S. & DiPersio, C. M. Integrin alpha3beta1 signaling through MEK/ERK determines alternative polyadenylation of the MMP-9 mRNA transcript in immortalized mouse keratinocytes. *PLoS ONE* **10**, e0119539 (2015).
519. Feagan, B. G. et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. *N. Engl. J. Med.* **352**, 2499–2507 (2005).
520. Vermeire, S. et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet* **384**, 309–318 (2014).
521. Ko, H. H. & Bressler, B. Natalizumab: pharmacology, clinical efficacy and safety in the treatment of patients with Crohn's disease. *Expert Rev. Gastroenterol. Hepatol.* **1**, 29–39 (2007).
522. Traynor, K. FDA advisers endorse natalizumab for Crohn's disease. *Am. J. Health-Syst. Pharm.* **64**, 1886 (2007). 1888, 1890.
523. Jovani, M. & Danese, S. Vedolizumab for the treatment of IBD: a selective therapeutic approach targeting pathogenic a4b7 cells. *Curr. Drug Targets* **14**, 1433–1443 (2013).
524. Feagan, B. G. et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. *Clin. Gastroenterol. Hepatol.* **15**, 229–239.e225 (2017).
525. Sandborn, W. J. et al. Efficacy and safety of abrilumab in a randomized, placebo-controlled trial for moderate-to-severe ulcerative colitis. *Gastroenterology* **156**, 946–957.e918 (2019).
526. Hibi, T. et al. Efficacy and safety of abrilumab, an alpha4beta7 integrin inhibitor, in Japanese patients with moderate-to-severe ulcerative colitis: a phase II study. *Intest. Res.* **17**, 375–386 (2019).
527. Yoshimura, N. et al. Safety and efficacy of AJM300, an oral antagonist of alpha4 integrin, in induction therapy for patients with active ulcerative colitis. *Gastroenterology* **149**, 1775–1783.e1772 (2015).
528. Fukase, H. et al. AJM300, a novel oral antagonist of alpha4-integrin, sustains an increase in circulating lymphocytes: a randomised controlled trial in healthy male subjects. *Br. J. Clin. Pharmacol.* **86**, 591–600 (2020).
529. Kawamoto, E. et al. Anti-integrin therapy for multiple sclerosis. *Autoimmun. Dis.* **2012**, 357101 (2012).
530. Gharekhani Digehsara, S. et al. Effects of *Lactobacillus casei* Strain T2 (IBRC-M10783) on the modulation of Th17/Treg and evaluation of miR-155, miR-25, and IDO-1 expression in a cuprizone-induced C57BL/6 mouse model of demyelination. *Inflammation* **44**, 334–343 (2021).
531. Goverman, J. Autoimmune T cell responses in the central nervous system. *Nat. Rev. Immunol.* **9**, 393–407 (2009).
532. Yednock, T. A. et al. Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha 4 beta 1 integrin. *Nature* **356**, 63–66 (1992).
533. Lefevre, S. et al. Synovial fibroblasts spread rheumatoid arthritis to unaffected joints. *Nat. Med.* **15**, 1414–1420 (2009).
534. Lowin, T. & Straub, R. H. Integrins and their ligands in rheumatoid arthritis. *Arthritis Res. Ther.* **13**, 244 (2011).
535. Attur, M. G. et al. Functional genomic analysis in arthritis-affected cartilage: yin-yang regulation of inflammatory mediators by alpha 5 beta 1 and alpha V beta 3 integrins. *J. Immunol.* **164**, 2684–2691 (2000).
536. Monti, M. et al. Integrin-dependent cell adhesion to neutrophil extracellular traps through engagement of fibronectin in neutrophil-like cells. *PLoS ONE* **12**, e0171362 (2017).
537. Nakamura, I., Duong, L. T., Rodan, S. B. & Rodan, G. A. Involvement of alpha(v) beta3 integrins in osteoclast function. *J. Bone Miner. Metab.* **25**, 337–344 (2007).
538. van Hamburg, J. P. & Tas, S. W. Molecular mechanisms underpinning T helper 17 cell heterogeneity and functions in rheumatoid arthritis. *J. Autoimmun.* **87**, 69–81 (2018).
539. Emori, T. et al. Constitutive activation of integrin alpha9 augments self-directed hyperplastic and proinflammatory properties of fibroblast-like synoviocytes of rheumatoid arthritis. *J. Immunol.* **199**, 3427–3436 (2017).
540. Wang, L. et al. Tissue and cellular rigidity and mechanosensitive signaling activation in Alexander disease. *Nat. Commun.* **9**, 1899 (2018).
541. Millard, M., Odde, S. & Neamati, N. Integrin targeted therapeutics. *Theranostics* **1**, 154–188 (2011).
542. Paleolog, E. M. Angiogenesis in rheumatoid arthritis. *Arthritis Res.* **4**, S81–S90 (2002).
543. Avraamides, C. J., Garmy-Susini, B. & Varnier, J. A. Integrins in angiogenesis and lymphangiogenesis. *Nat. Rev. Cancer* **8**, 604–617 (2008).
544. Sugahara, S., Hanaoka, K. & Yamamoto, N. Integrin, alpha9 subunit blockade suppresses collagen-induced arthritis with minimal systemic immunomodulation. *Eur. J. Pharmacol.* **833**, 320–327 (2018).
545. Kanwar, J. R. et al. Beta7 integrins contribute to demyelinating disease of the central nervous system. *J. Neuroimmunol.* **103**, 146–152 (2000).
546. Khawaja, A. A. et al. Autoimmune rheumatic disease IgG has differential effects upon neutrophil integrin activation that is modulated by the endothelium. *Clin. Rep.* **9**, 1283 (2019).
547. Conrad, C. et al. Alpha1beta1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. *Nat. Med.* **13**, 836–842 (2007).
548. Gal, B. et al. Increased circulating anti-alpha6-integrin autoantibodies in psoriasis and psoriatic arthritis but not in rheumatoid arthritis. *J. Dermatol.* **44**, 370–374 (2017).
549. Mrugacz, M., Bryl, A., Falkowski, M. & Zorena, K. Integrins: an important link between angiogenesis, inflammation and eye diseases. *Cells* **10**, 1703 (2021).
550. Xiong, S. et al. 5β1 integrin promotes anchoring and integration of transplanted stem cells to the trabecular meshwork in the eye for regeneration. *Stem Cells Dev.* **29**, 290–300 (2020).
551. Ho, T. C., Yeh, S. I., Chen, S. L. & Tsao, Y. P. Integrin av and vitronectin prime macrophage-related inflammation and contribute the development of dry eye disease. *Int. J. Mol. Sci.* **22**, 8410 (2021).
552. Perez, V. L. et al. Lifitegrast, a novel integrin antagonist for treatment of dry eye disease. *Ocul. Surf.* **14**, 207–215 (2016).
553. Van Hove, I. et al. Targeting RGD-binding integrins as an integrative therapy for diabetic retinopathy and neovascular age-related macular degeneration. *Prog. Retin. Eye Res.* **85**, 100966 (2021).
554. Teitelbaum, S. L. Osteoporosis and integrins. *J. Clin. Endocrinol. Metab.* **90**, 2466–2468 (2005).
555. Hu, H. et al. Osteoactivin inhibits dexamethasone-induced osteoporosis through up-regulating integrin β1 and activate ERK pathway. *Biomed. Pharmacother.* **105**, 66–72 (2018).
556. Lin, T. H. et al. Inhibition of osteoporosis by the avβ3 integrin antagonist of rhodostomin variants. *Eur. J. Pharmacol.* **804**, 94–101 (2017).
557. Murphy, M. G. et al. Effect of L-000845704, an alphaVbeta3 integrin antagonist, on markers of bone turnover and bone mineral density in postmenopausal osteoporotic women. *J. Clin. Endocrinol. Metab.* **90**, 2022–2028 (2005).
558. Wyssenbach, A. et al. Amyloid β-induced astrogliosis is mediated by β1-integrin via NADPH oxidase 2 in Alzheimer's disease. *Aging Cell* **15**, 1140–1152 (2016).
559. Zenaro, E. et al. Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 integrin. *Nat. Med.* **21**, 880–886 (2015).
560. Pietronigro, E. et al. Blockade of α4 integrins reduces leukocyte-endothelial interactions in cerebral vessels and improves memory in a mouse model of Alzheimer's disease. *Sci. Rep.* **9**, 12055 (2019).
561. Manocha, G., Ghatak, A., Puig, K. & Combs, C. Anti-α4β1 integrin antibodies attenuated brain inflammatory changes in a mouse model of Alzheimer's disease. *Curr. Alzheimer Res.* **15**, 1123–1135 (2018).
562. Matsuoka, K. et al. AJM300 (carotegrast methyl), an oral antagonist of α4-integrin, as induction therapy for patients with moderately active ulcerative colitis: a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Gastroenterol. Hepatol.* **7**, 648–657 (2022).
563. Blue, R. et al. Application of high-throughput screening to identify a novel alphaIIb-specific small-molecule inhibitor of alphaIIb beta3-mediated platelet interaction with fibrinogen. *Blood* **111**, 1248–1256 (2008).
564. Zhu, J. et al. Structure-guided design of a high-affinity platelet integrin alphaIIb beta3 receptor antagonist that disrupts Mg²⁺ binding to the MIDAS. *Sci. Transl. Med.* **4**, 125ra132 (2012).
565. Kereiakes, D. J. et al. First human use of RUC-4: a nonactivating second-generation small-molecule platelet glycoprotein iib/iiia (integrin alphaIIb beta3) inhibitor designed for subcutaneous point-of-care treatment of ST-segment-elevation myocardial infarction. *J. Am. Heart Assoc.* **9**, e016552 (2020).
566. Li, J. et al. Novel pure alphaV beta3 integrin antagonists that do not induce receptor extension, prime the receptor, or enhance angiogenesis at low concentrations. *ACS Pharmacol. Transl. Sci.* **2**, 387–401 (2019).
567. Yu, Y., Schürpf, T. & Springer, T. A. How natalizumab binds and antagonizes α4 integrins. *J. Biol. Chem.* **288**, 32314–32325 (2013).
568. Decaris, M. L. et al. Dual inhibition of α(v)β(6) and α(v)β(1) reduces fibrogenesis in lung tissue explants from patients with IPF. *Respir. Res.* **22**, 265 (2021).
569. Sandborn, W. J. et al. PTG-100, an oral α4β7 antagonist peptide: preclinical development and phase 1 and 2a studies in ulcerative colitis. *Gastroenterology* **161**, 1853–1864.e1810 (2021).
570. Byron, A. et al. Anti-integrin monoclonal antibodies. *J. Cell Sci.* **122**, 4009–4011 (2009).
571. Tam, S. H., Sassoli, P. M., Jordan, R. E. & Nakada, M. T. Abciximab (ReoPro, chimeric 7E3 Fab) demonstrates equivalent affinity and functional blockade of glycoprotein IIb/IIIa and alpha(v)beta3 integrins. *Circulation* **98**, 1085–1091 (1998).
572. Hatley, R. J. D. et al. An av-RGD integrin inhibitor toolbox: drug discovery insight, challenges and opportunities. *Angew. Chem. Int. Ed.* **57**, 3298–3321 (2018).
573. Duong, L. T. & Coleman, P. J. Ligands to the integrin receptor avβ3. *Expert Opin. Ther. Pat.* **12**, 1009–1021 (2002).
574. Gubatan, J. et al. Anti-integrins for the treatment of inflammatory bowel disease: current evidence and perspectives. *Clin. Exp. Gastroenterol.* **14**, 333–342 (2021).

575. Danese, S. et al. Etrolizumab versus infliximab for the treatment of moderately to severely active ulcerative colitis (GARDENIA): a randomised, double-blind, double-dummy, phase 3 study. *Lancet Gastroenterol. Hepatol.* **7**, 118–127 (2022).
576. Ahmad, K. et al. Targeting integrins for cancer management using nanotherapeutic approaches: recent advances and challenges. *Semin. Cancer Biol.* **69**, 325–336 (2021).
577. Ragelle, H. et al. Intracellular siRNA delivery dynamics of integrin-targeted, PEGylated chitosan-poly(ethylene imine) hybrid nanoparticles: a mechanistic insight. *J. Control. Release* **211**, 1–9 (2015).
578. Cheng, Y. & Ji, Y. RGD-modified polymer and liposome nanovehicles: recent research progress for drug delivery in cancer therapeutics. *Eur. J. Pharm. Sci.* **128**, 8–17 (2019).
579. Hölftke, C. isoDGR-peptides for integrin targeting: is the time up for RGD? *J. Med. Chem.* **61**, 7471–7473 (2018).
580. Ghitti, M. et al. Molecular dynamics reveal that isoDGR-containing cyclopeptides are true $\alpha v\beta 3$ antagonists unable to promote integrin allostery and activation. *Angew. Chem. -Int. Ed.* **51**, 7702–7705 (2012).
581. Wallstabe, L. et al. CAR T cells targeting $\alpha(v)\beta(3)$ integrin are effective against advanced cancer in preclinical models. *Adv. Cell Gene Ther.* **1**, e11 (2018).
582. Phanthaphol, N. et al. Chimeric antigen receptor T cells targeting integrin $\alpha v\beta 6$ expressed on cholangiocarcinoma cells. *Front. Oncol.* **11**, 657868 (2021).
583. Zhu, Z. et al. ^{99m}Tc -3PRGD2 for integrin receptor imaging of lung cancer: a multicenter study. *J. Nucl. Med.* **53**, 716–722 (2012).
584. Nakamoto, R. et al. Pilot-phase PET/CT study targeting integrin $\alpha(v)\beta(6)$ in pancreatic cancer patients using the cystine-knot peptide-based (18)F-FP-R(0)1-MG-F2. *Eur. J. Nucl. Med. Mol. Imaging* <https://doi.org/10.1007/s00259-021-05595-7> (2021).
585. Shen, B. et al. A directional switch of integrin signalling and a new anti-thrombotic strategy. *Nature* **503**, 131–135 (2013).
586. Shen, C. et al. The 14-3-3zeta-c-Src-integrin-beta3 complex is vital for platelet activation. *Blood* **136**, 974–988 (2020).
587. Cierniewski, C. S. et al. Peptide ligands can bind to distinct sites in integrin $\alpha\text{IIb}\beta 3$ and elicit different functional responses. *J. Biol. Chem.* **274**, 16923–16932 (1999).
588. Peter, K. et al. Induction of fibrinogen binding and platelet aggregation as a potential intrinsic property of various glycoprotein IIb/IIIa ($\alpha\text{IIb}\beta 3$) inhibitors. *Blood* **92**, 3240–3249 (1998).
589. Holmes, M. B., Sobel, B. E., Cannon, C. P. & Schneider, D. J. Increased platelet reactivity in patients given orbofiban after an acute coronary syndrome: an OPUS-TIMI 16 substudy. Orbofiban in patients with unstable coronary syndromes. Thrombolysis in myocardial infarction. *Am. J. Cardiol.* **85**, 491–493 (2000).
590. Bloomgren, G. et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N. Engl. J. Med.* **366**, 1870–1880 (2012).
591. Lebwohl, M. et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N. Engl. J. Med.* **349**, 2004–2013 (2003).
592. Gordon, K. B. et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* **290**, 3073–3080 (2003).
593. Major, E. O. Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies. *Annu. Rev. Med.* **61**, 35–47 (2010).
594. Kappos, L. et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. *Lancet Neurol.* **10**, 745–758 (2011).



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