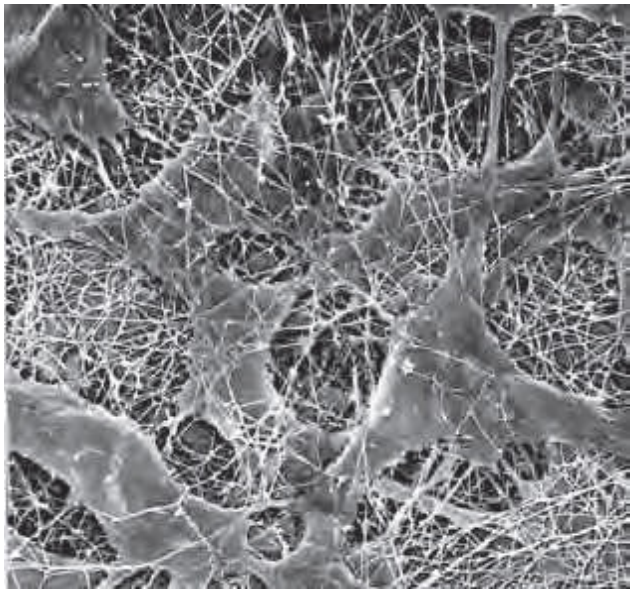
Physics of cancer

Cancer: role of microenvironment

Historically, cancer has been considered a **disease of the cell**, caused by **mutations in genes** that control proliferation, differentiation, and death.

Recently, the **microenvironment surrounding the cancer cell** has gained notoriety as a co-conspirator in tumor initiation, progression, immune evasion, and treatment response.

The extracellular matrix (ECM) is composed of many different **proteins and polysaccharides** that are **secreted locally** and **assembled into an organized meshwork** in close association with the surfaces of the cells that produce them.

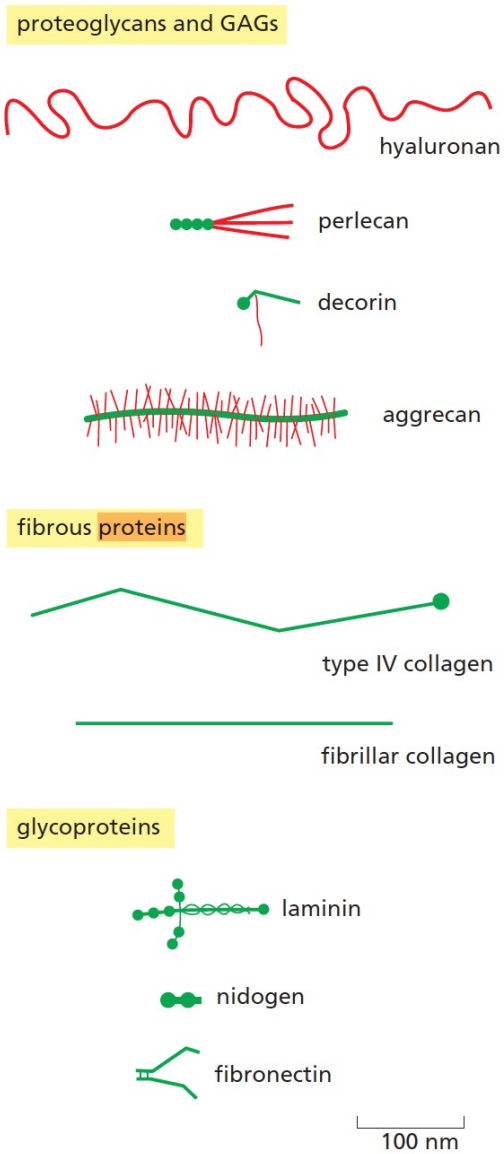


Macromolecules constituting ECM in different animal tissues are broadly similar, but variations in the relative amounts of different classes of molecules and in the ways in which they are organized give rise to an amazing diversity of materials: calcified as the rock-hard structures of bone or teeth; transparent in the cornea; ropelike organization for tendons tensile strength.

Extracellular Matrix

The extracellular matrix is more than a passive scaffold to provide physical support. It has an active and complex role in **regulating the behavior of the cells that touch it**, inhabit it, or crawl through its meshes, influencing their survival, development, migration, proliferation, shape, and function.

The **macromolecules of the matrix are mainly produced locally by cells in the matrix**. These cells also help to organize the matrix: the orientation of the cytoskeleton inside the cell can control the orientation of the matrix produced outside.

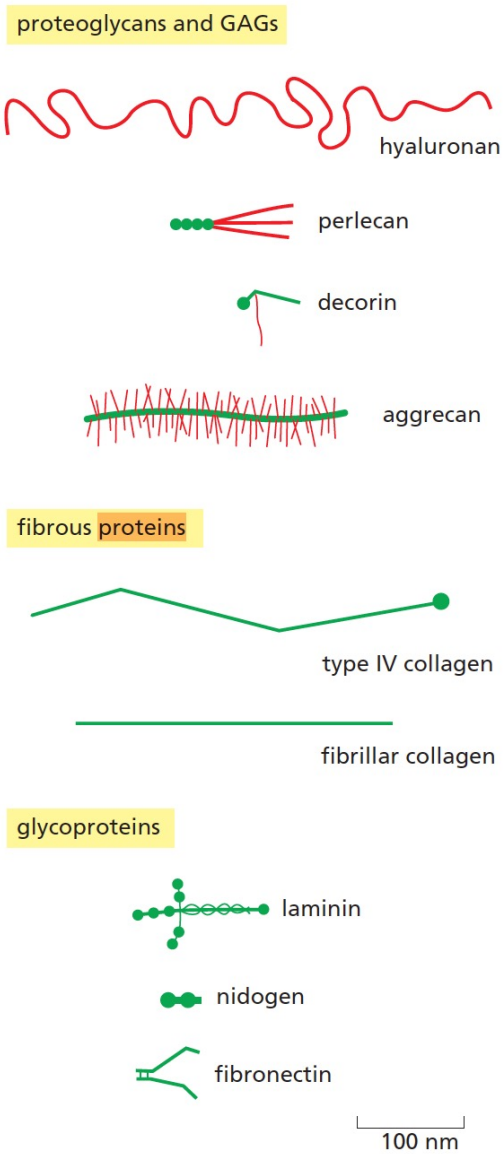


Extracellular Matrix

ECM macromolecular composition:

(1) **glycosaminoglycans (GAGs)**, which are large and highly charged polysaccharides that are usually covalently linked to protein in the form of proteoglycans;
(2) **fibrous proteins**, which are primarily members of the **collagen** family;
(3) a large class of **noncollagen glycoproteins**, which carry conventional asparagine-linked oligosaccharides.

Mammals have almost 300 matrix proteins: 36 proteoglycans, about 40 collagens, and over 200 glycoproteins, which usually contain multiple subdomains and self-associate to form multimers.
Add to this the large number of matrix-associated proteins and enzymes that can modify matrix behavior by cross-linking, degradation, or other mechanisms:
the matrix is an almost infinitely variable material. Each tissue contains its own unique blend of matrix components, resulting in an ECM that is specialized for the needs of that tissue.



Extracellular Matrix

The **proteoglycan** molecules in connective tissue typically form a **highly hydrated, gel-like** "ground substance" in which collagens and glycoproteins are embedded.
The polysaccharide gel **resists compressive forces on the matrix** while **permitting the rapid diffusion of nutrients**, metabolites, and hormones between the blood and the tissue cells.

The **collagen fibers** strengthen and **help organize the matrix**, while **other fibrous proteins**, such as the rubberlike elastin, give it **resilience**.

Finally, the many **matrix glycoproteins** help cells migrate, settle, and differentiate in the appropriate locations.

Cells interact with the extracellular matrix **mechanically** as well as **chemically.**
Studies in culture suggest that the mechanical interaction can have dramatic effects on the architecture of connective tissue.

Thus, when fibroblasts are mixed with a meshwork of randomly oriented collagen fibrils that form a gel in a culture dish, the fibroblasts tug on the meshwork, drawing in collagen from their surroundings and thereby causing the gel to contract to a small fraction of its initial volume.

Fibroblasts may have a similar role in organizing the extracellular matrix inside the body.
First they **synthesize the collagen fibrils** and deposit them **in the correct orientation**.
Then they **work on the matrix they have secreted**, crawling over it and tugging on it so as to create tendons and ligaments and the tough, dense layers of connective tissue that surround and bind together most organs.

The tumour microenvironment provides:

chemical gradients, for example of oxygen and nutrients;

a physical environment as **unique mechanical forces.**

The mechanical microenvironment may cause malignant transformation, possibly through:

- activation of oncogenic pathways
- inhibition of tumour suppressor genes
- influencing processes such as epithelial-to-mesenchymal transition
- enhancing cell survival through autophagy
- affecting sensitivity of tumour cells to therapeutics.

It appears the **increased stiffness in tumours** is:

- not be caused by increased stiffness of the tumour cells
- related to a higher cell density, making them more rigid
- related to increased matrix deposition in the tumour
- related to increased interstitial fluid pressure

Tumour mechanics are significantly different from normal tissue. It should be further explored for use in cancer prevention, detection and treatment.

Cell-ECM organization and cancer

Unlike free-living cells such as bacteria, which compete to survive, **the cells of a multicellular organism are committed to collaboration:** the cells send, receive, and interpret an elaborate set of extracellular signals that serve as social controls, directing cells how to act.
As a result, **each cell behaves in a socially responsible manner**—resting, growing, dividing, differentiating, or dying—as needed for the good of the organism.

In a human body with more than 10^{14} cells, billions of cells experience **mutations** every day, potentially disrupting the social controls. Most dangerously, a mutation may give one cell a selective advantage, allowing it to grow and divide slightly more vigorously and survive more readily than its neighbors and in this way to become a founder of a growing mutant clone.

Over time, **repeated rounds of mutation**, **competition, and natural selection** operating within the population of somatic cells can cause matters to go from bad to worse.

These are the basic ingredients of cancer: it is a disease in which an individual mutant clone of cells begins by prospering at the expense of its neighbors. In the end—as the clone grows, evolves, and spreads—it can destroy the entire cellular society.

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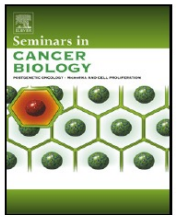

Review

The mechanical microenvironment in cancer: How physics affects tumours

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Cancer's hallmarks

Uncontrollable and infinite proliferation of cells
cancer cells have obtained self-sufficiency in growth signals; insensitive to growth-inhibitory signals; continuously escape death (apoptosis).
Supporting this constant growth requires increased supply of oxygen and nutrients. Therefore, cancer cells require continuous formation of new blood vessels (angiogenesis).

Ability of tumour cells to spread through their host, invading surrounding tissue and forming metastases at distant sites.

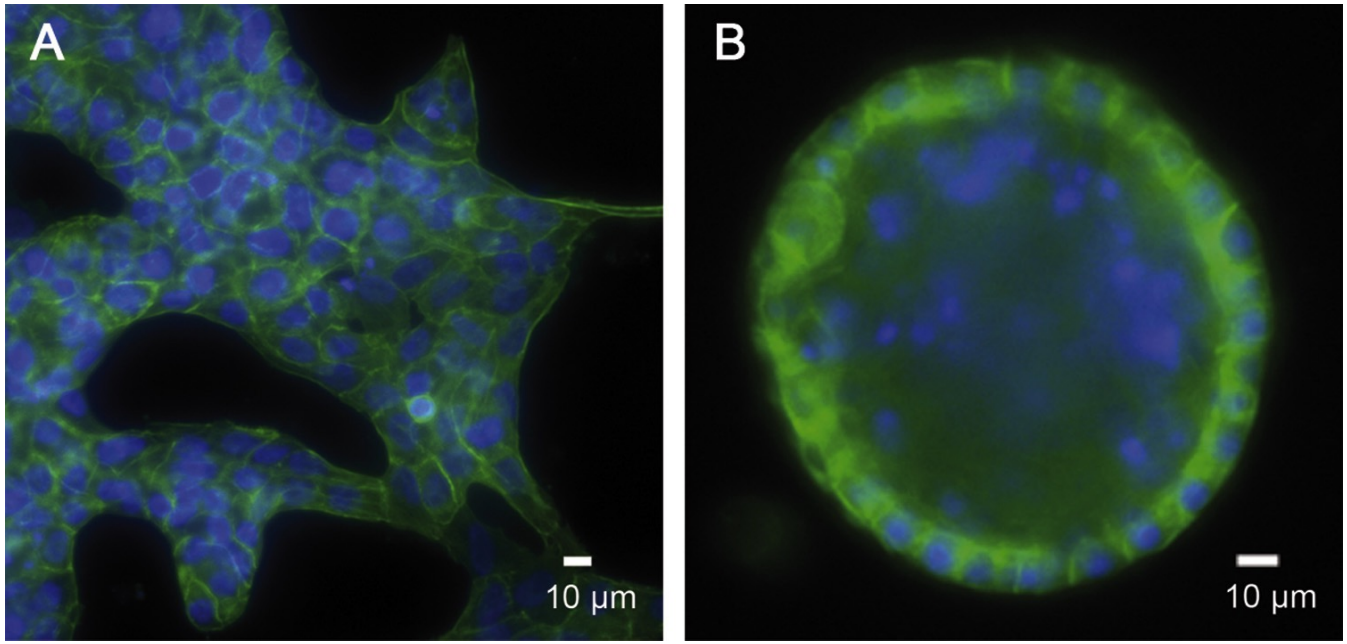
Cancerous cells **acquire features** that are primarily focussed on **cell survival**.
Cancer cells are capable of reprogramming their energy metabolism allowing them to survive the often harsh conditions of the tumour microenvironment.

Evade the host's immune system, which may destruct cancer cells.
For example by alterations in the glycocalyx.

Promote inflammation in the host, which support tumour growth.

Genomic instability, characterized by increased mutation rates chromosomal rearrangements and aberrant chromosome numbers.

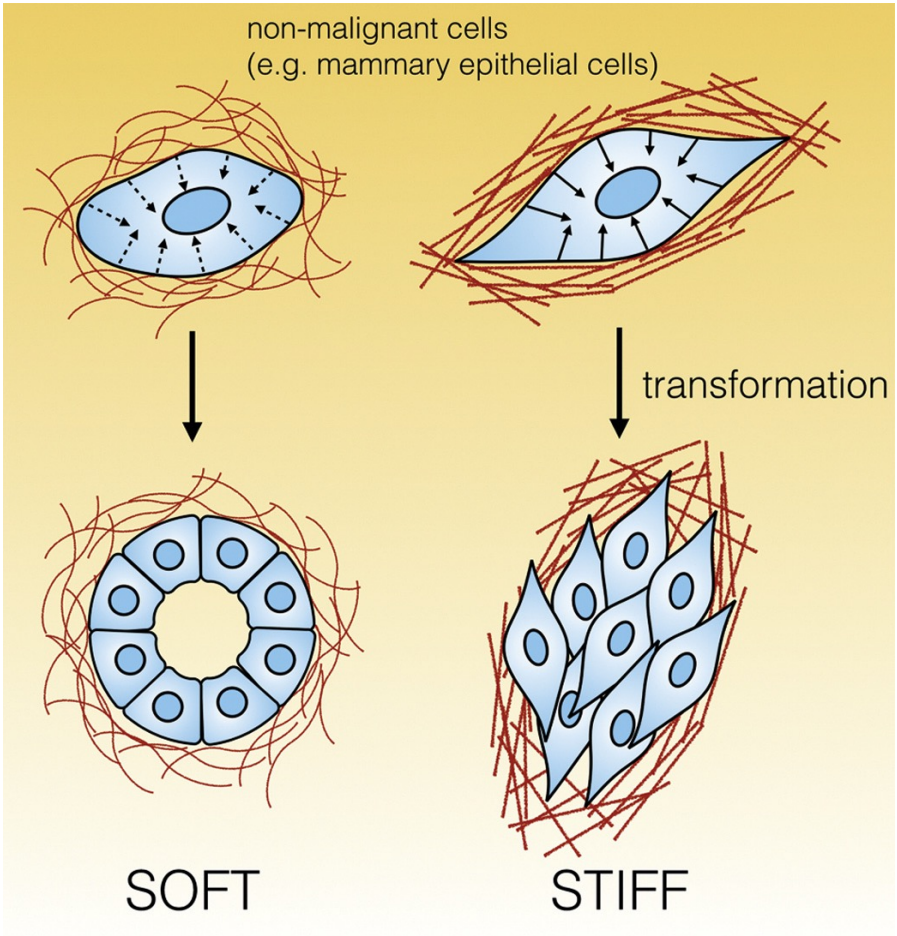
Role of substrate stiffness



Morphology of normal mammary epithelial cells is controlled by the underlying substrate. On tissue culture plastic (A) MCF10A cells form a monolayer, whereas on a thin layer of basement membrane matrix, (B) MCF10A cells form growth arrested hollow acini within two weeks. Nuclei are stained in blue, filamentous actin in green.

A. Nagelkerke et al. / Seminars in Cancer Biology 35 (2015) 62–70

Role of substrate stiffness



Model for the effect of substrate stiffness on normal mammary epithelial cell behaviour. When cells are placed in soft matrices, they differentiate into characteristic acini. When cells are placed in stiff matrices however, programmes are activated within the cells that cause dedifferentiation and transformation.

A. Nagelkerke et al. / Seminars in Cancer Biology 35 (2015) 62–70

Epithelial-mesenchimal transition

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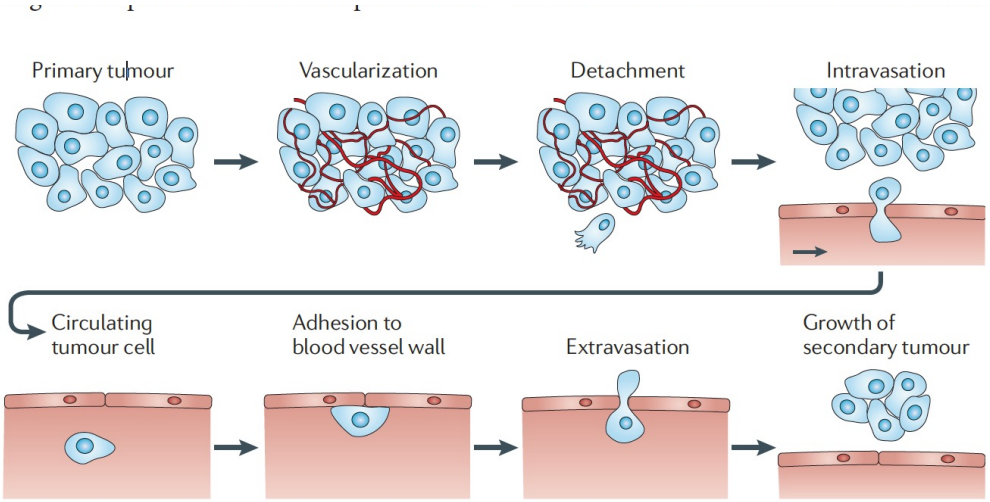

Figure 1 | **The metastatic process.** In this complex process, cells detach from a primary, vascularized tumour, penetrate the surrounding tissue, enter nearby blood vessels (intravasation) and circulate in the vascular system. Some of these cells eventually adhere to blood vessel walls and are able to extravasate and migrate into the local tissue, where they can form a secondary tumour.

The detachment of carcinoma cells from the epithelium and the subsequent invasion of the underlying stroma resembles, at both the cellular and molecular levels, the well-characterized **epithelial-to-mesenchymal transition (EMT) in embryogenesis.**

Critical to EMT is the loss of E-cadherin (an intercellular adhesion molecule) and cytokeratins, which leads to dramatic changes in the physical and mechanical properties of cells: specifically, reduced intercellular adhesion and a morphological change from cuboidal epithelial to mesenchyma, with acquisition of a motile phenotype.

Epithelial-mesenchimal transition

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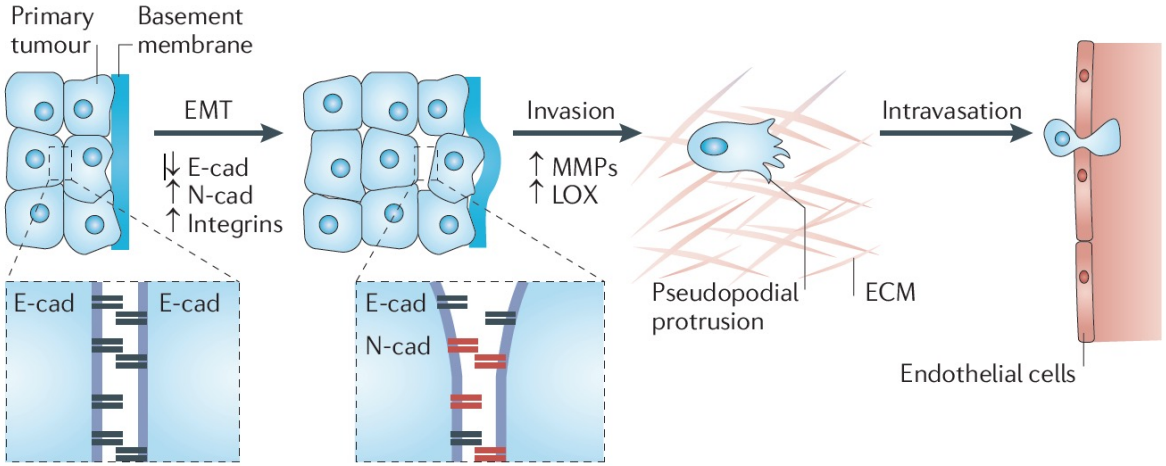

Figure 2 | **The physics of invasion and intravasation.** The epithelial-to-mesenchymal transition (EMT) is associated with a loss of adhesion through downregulation of E-cadherin (E-cad) and a change in morphology. Invasion by tumour cells of the surrounding tissue and subsequent motion is dictated by the physicochemical properties of the extracellular matrix (ECM). By squeezing between blood vessel endothelial cells, tumour cells can enter the vascular system. All of these steps involve physico-chemical processes, such as adhesion and deformation, that are dependent on the local environment. LOX, lysyl oxidase; MMPs, matrix metalloproteinases; N-cad, N-cadherin.

Cells **Epithelial-to-mesenchymal transition** or EMT is then a transdifferentiation process in which epithelial cells, growing in epithelial sheets, detach from their neighbouring cells and acquire mesenchymal features. This switch enhances cell motility and invasive properties, and is associated with induction and repression of mesenchymal (e.g. vimentin) and epithelial markers (e.g. E-cadherin), respectively.

Transitions between the phenotypic state of cells turn out to be **highly dynamic**, allowing cells to fully or partially adopt epithelial and mesenchymal phenotypes, but also switch between them. This gives cells a high level of **plasticity** and may lead to a range of phenotypes.

Epithelial-mesenchimal transition

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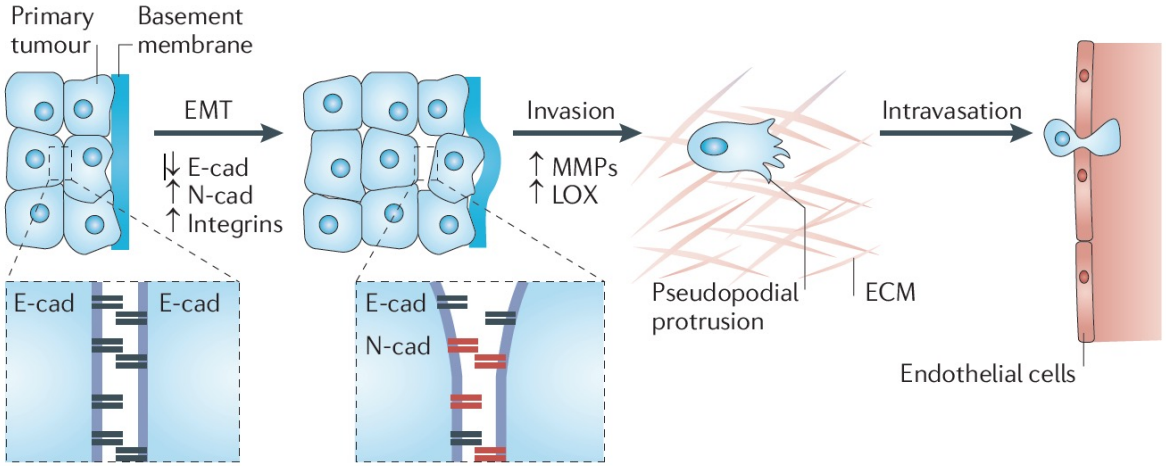

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Also, they express **Matrix Metalloproteinase (MMP)** which promote the digestion of the laminin- and collagen IV-rich basement membrane.

It has been shown that soft substrates inhibit transition to the mesenchymal phenotype in several cell types, importantly all with epithelial characteristics.

Epithelial-mesenchimal transition

Cancer is an extraordinarily complex disease.

Methods that are commonly used in physics can reduce the complexity of cancer to a manageable set of underlying principles and phenomena.

In particular, Transport OncoPhysics views cancer as a disease of multiscale mass transport deregulation involving the biological barriers that separate different body compartments.

Probes that can be used to investigate the mass transport properties of tissues can be used as directed vectors for the localized, preferential release of therapeutics into tumours.

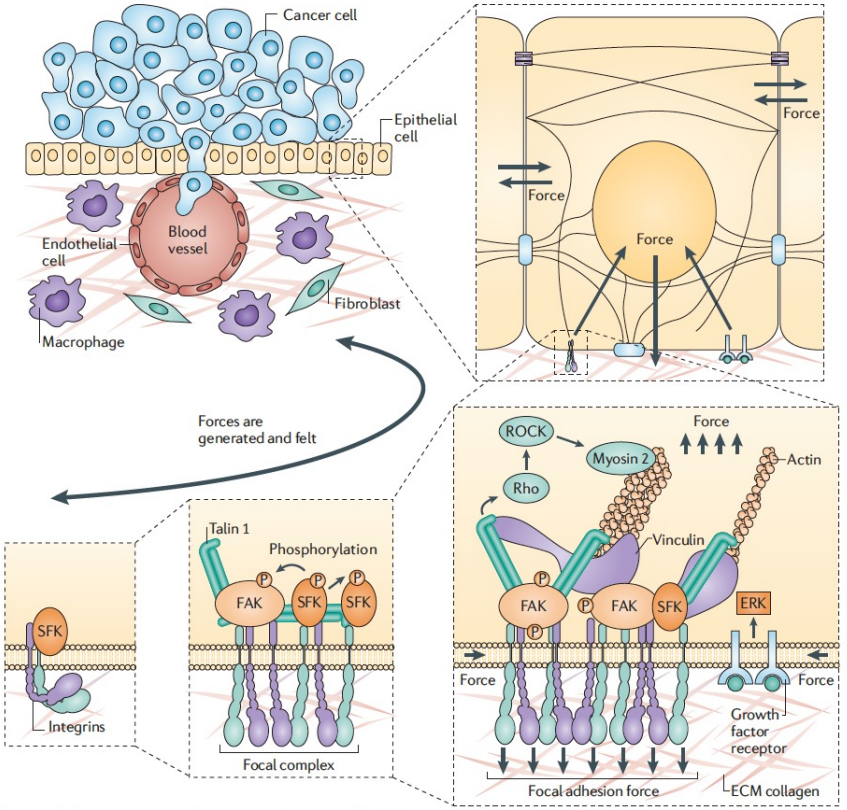
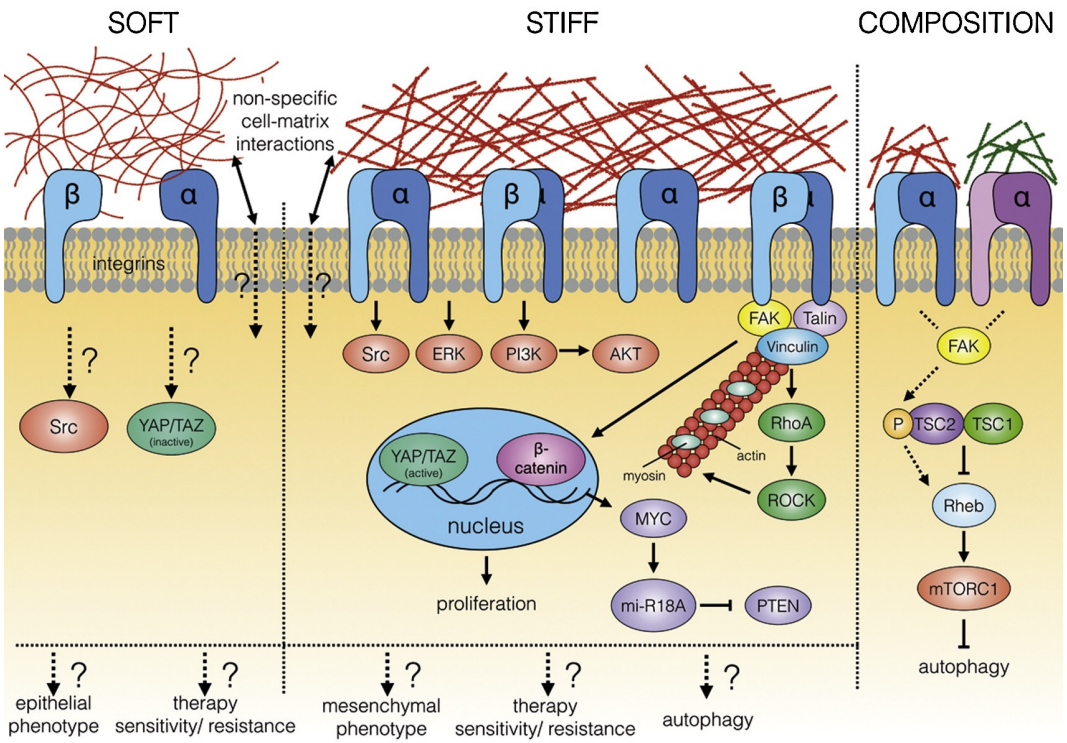


Figure 2 | **Tissues are complex dynamic systems that feature multiscale mechanochemical coupling.** Progress has been made particularly in delineating the molecular mechanisms of force generation by the cytoskeleton, the details of cell–cell adhesion and force sensing by proteins such as talin 1 and vinculin. However, mechanical effects in biology are inherently multiscale, in the sense that single cells can generate stresses and strains that contribute to the mechanics and the organization of entire tissues, and in turn, millimetre-scale tension fields within tissues can provide signals that are sensed by potentially millions of cells within that tissue. Understanding this interplay will require new types of experiments that can interrogate all relevant scales simultaneously, and broad conceptual and theoretical advances. ECM, extracellular matrix; FAK, focal adhesion kinase; P, phosphorylation; ROCK, Rho-associated, coiled-coil containing protein kinase; SFK, SRC family kinase.

Mechanotransduction



After leaving the tumour microenvironment, motile tumour cells encounter the architecturally complex **extracellular matrix (ECM), which is rich in collagen I and fibronectin**.

In the vicinity of a tumour (mammary), the **matrix is often stiffer** than in normal **tissue owing to enhanced collagen deposition and lysyl-oxidase-mediated crosslinking of the collagen fibres** by tumour-associated fibroblasts. **Collagen crosslinking enhances integrin signalling** as well as the bundling of individual fibres. Such changes in the physicochemical properties of the matrix can enhance cell proliferation and invasion in a **positive feedback loop**.

Remarkably little is known about the molecular and physical mechanisms that drive motile cancer cells away from primary tumour and into the stromal space, especially at the subcellular level.

Cells are able to perceive the mechanics of their substrate and translate this information into signals inside, a process known as outside-in signalling or mechanotransduction.

Cancer cell motility

What we know on CELL MOTILITY is coming from 2D cell cultures.

Many features that are thought to be crucial for 2D motility, such as focal adhesions, stress fibres, wide lamellipodia and lamella, multiple filopodial protrusions at the leading edge and apical polarization, **are either drastically reduced in size or entirely missing from motile carcinoma or sarcoma cells in a 3D matrix**.

Similarly, several cellular features that are important in 3D cell motility have little or no role in 2D cell motility, including nuclear deformation, MMP production and major reorganization of the ECM.

When in 2D culture a cell is in contact with a contiguous substrate (FA can have 1 micron dia). A cell in a 3D matrix has confined local contact with quasi-1D fibres (collagen, 100 nm dia).

Collagen fibres in a 3D matrix could support the formation of **small and highly dynamic integrin clusters**, with sizes on the order of **tens of nanometres and lifetimes shorter than a few seconds**, which may still be crucial to 3D cell motility.

Cancer cell motility

Cells *in vivo* could promote the **bundling of collagen fibres** through the generation of contractile forces produced by cellular protrusions. Such collagen bundles would enhance the surface area available and potentially promote the formation of larger adhesions.

Inhibition of actomyosin contractility is often substantially less effective in blocking 3D cell motility than in blocking 2D cell motility, suggesting that the role of stress fibres is dependent on dimensionality.

Hence, eliminating the apical polarization of cells in 2D culture reduces the number of focal adhesions and stress fibres, and therefore fundamentally changes the role of components such as focal adhesion proteins and proteins highly enriched in stress fibres, such as the F-actin binding proteins α-actinin, myosin II and tropomyosins.

Cancer cell motility: circulating TC

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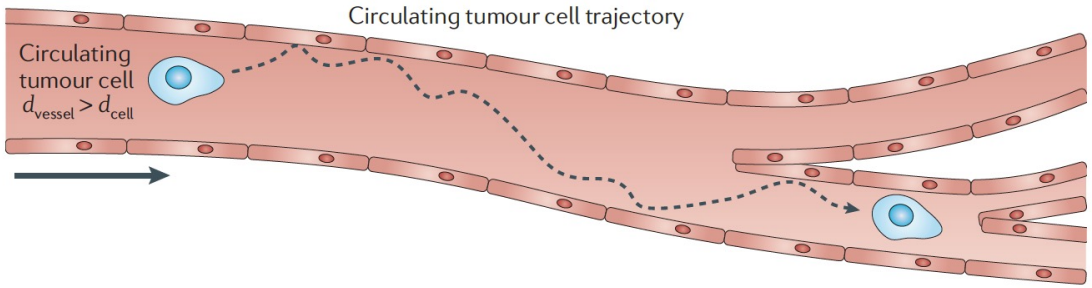
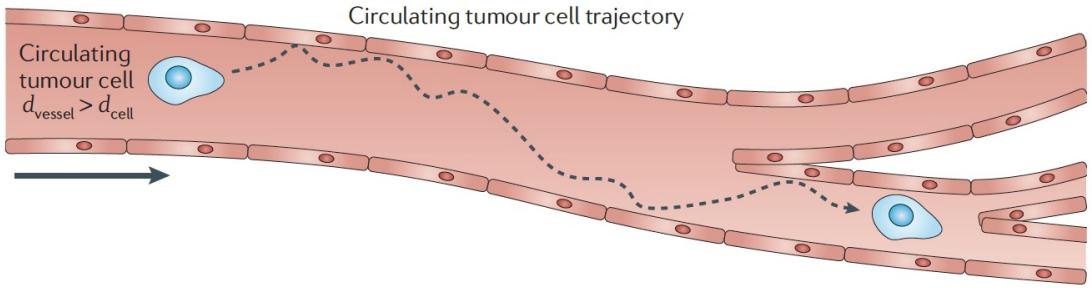


Figure 3 | **Arrest of circulating tumour cells.** Tumour cells with a diameter (d_{cell}) less than the diameter of the blood vessel wall (d_{vessel}) will follow a trajectory that is determined by the local flow pattern and by collisions with host cells and blood vessel walls. Collisions with a blood vessel wall may lead to arrest. Tumour cells with diameter greater than the diameter of a blood vessel will be arrested owing to mechanical trapping (physical occlusion).

The trajectory or path of a CTC is influenced by a number of physical and mechanical parameters:
the pattern of blood flow; the diameter of the blood vessels and the complex interplay between **shear flow and intercellular adhesion** that leads to the arrest of cell movement in larger vessels.

During their transit through the circulatory system, tumour cells are subjected to haemodynamic forces, immunological stress and collisions with host cells, such as blood cells and the endothelial cells lining the vessel wall. All of these stresses could affect cell survival and the ability to establish metastatic foci.
Only circulating tumour cells (CTCs) that overcome or even exploit the effects of fluid shear and immunosurveillance will adhere to the vascular endothelium of distant organs, exit the circulation and successfully enter these tissues. A tiny fraction of CTCs survive to generate metastases; most CTCs die or remain dormant.

Shear stress



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Shear stress (τ) arises between adjacent layers of fluid (in this case blood) of viscosity (μ) moving at different velocities.

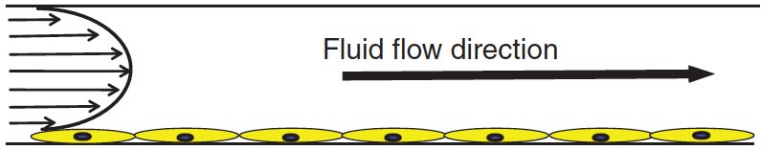
V is maximum at the centre and zero at the cylinder walls, and the relative velocities of parallel adjacent layers of fluid in laminar flow define the **shear rate**

$$d\gamma/dt \equiv \gamma$$

where γ is the amplitude of deformation and t is the time elapsed.

Shear stress is defined by the product of fluid viscosity and shear rate.

Effect of shear stress on cells



$$\tau_w = \frac{6\mu Q}{bh^2}$$

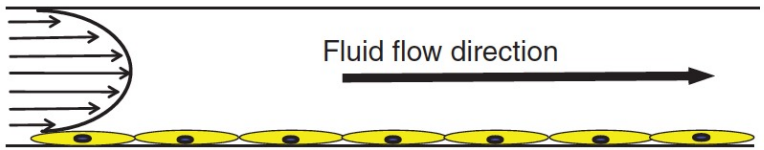
τ_w = shear stress (dyn cm^{-2})
μ = viscosity (kg m^{-1} s^{-1})
Q = volumetric flow rate (ml s^{-1})
b = width (mm)
h = height (mm)

Figure 1 Shear stress at the wall of a parallel plate bioreactor. The most common bioreactor design for calculating shear stress of cells *in vitro* is a parallel plate system. Poiseuille's law for flow through a tube is modified here for the alternate geometry in order to calculate the shear stress, τ_w, at the wall of a parallel plate system. Another common bioreactor design for imparting steady laminar shear stress to cells (not discussed here) include the modified cone-and-plate viscometer for sterile cell cultures.

Shear stress is the tangential stress derived from the **friction of fluid flowing along a solid surface**.
In the blood vessel, shear stress is generated from the blood flow across the surface of the endothelial cells (ECs) lining the inner lumen of the blood vessel and is felt by the ECs through various potential mechanosensing mechanisms. The value of shear stress is expressed in units of force per unit area (Nm^{-2} or Pascal or dyne cm^{-2}). This stress is proportional to the fluid (or blood) viscosity, μ, and the spatial gradient of the fluid velocity at the wall.

Effects of Shear Stress on Cells , KE McCloskey, University of California, Merced, CA, USA

Effect of shear stress on cells



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Laminar Re < 2100
Turbolent Re > 4000
2100<Re<4000 transitional flow

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The nature of fluid flow is also important and dependent on the geometry of the tube through which the fluid flows. The **fluid flow may be 'laminar'–**relatively smooth, streamlined flow with little separation or recirculation **–or more stochastic**, called **'turbulent' flow**. For each specific flow geometry, the Reynold's number (Re) is the dimensionless parameter defining whether the flow is laminar or turbulent.

$$Re = \rho DV/\mu$$

ρ = density of the fluid; V = velocity of the fluid flow; D = diameter of the tube; μ = viscosity of the fluid

Effects of Shear Stress on Cells , KE McCloskey, University of California, Merced, CA, USA

The **viscosity of blood** is about 4 centipoise (cP), which is **considerably greater than the viscosity of water** (0.7 cP at 37 °C), primarily owing to the presence of red blood cells.

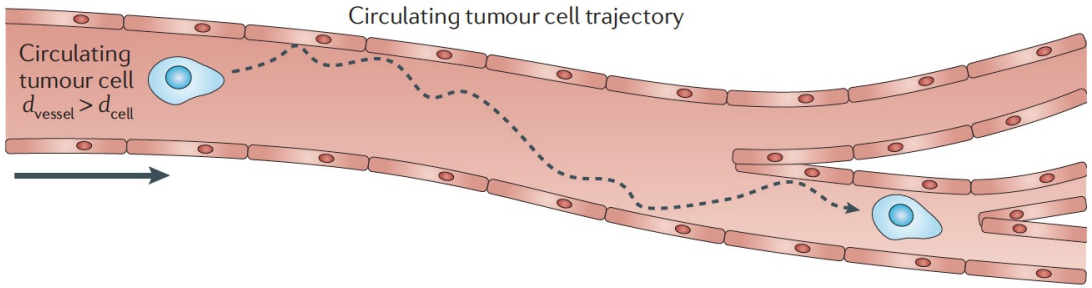
At shear rates greater than 100 s^{-1}, **blood is considered a Newtonian fluid, implying that the shear stress increases linearly with shear rate**.

The normal time-averaged levels of shear stress vary between 1–4 dyn cm^{-2} in the venous circulation and 4–30 dyn cm^{-2} in the arterial circulation.

The maximum shear stress is experienced at the vessel wall. The mean blood velocity (v_{av}) in arteries for a vessel of diameter d = 4 mm is 0.45 m s^{-1}, whereas v_{av} = 0.1 m s^{-1} in a 5 mm vein. The corresponding shear rates ($d\gamma/dt = 8v_{av}/d$) are 900 s^{-1} in arteries and 160 s^{-1} in veins.

The interstitial fluid velocity in other tissues, such as cartilage and bone subjected to mechanical loading during daily activity, induces varying levels of fluid shear stress up to 30 dyn cm^{-2}

Shear stress and extravasation



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Extravasation of a tumour cell from a large blood vessel (*d*cell < *d*vessel) requires the adhesion of the cell to the vessel wall through the formation of specific bonds.

The probability (P) of arrest at a large vessel can be written as $P \propto ft$, where f is the collision frequency between membrane-bound receptors and endothelial ligands and t is the residence time.

The residence time is dependent on the shear force exerted on the cell and the adhesive forces associated with ligand–receptor pairs between the circulating tumour cell and the endothelial cells of the blood vessel wall. Increasing fluid shear is expected to increase the collision frequency with the endothelium but decrease the residence time of receptor–ligand pairs.

Translational and tangential velocity

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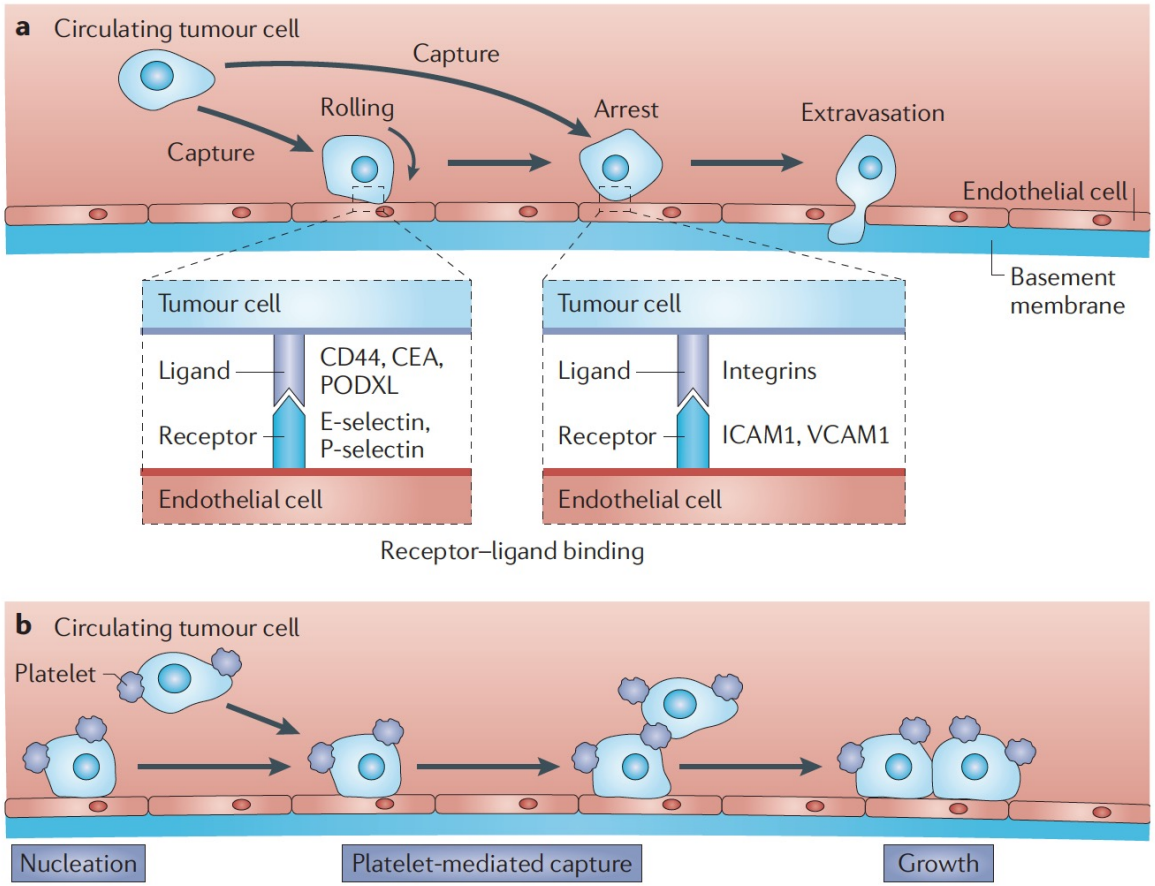
A cell moving along a vessel wall has both translational and tangential (angular) velocity

Box 2 | **Fluid shear stress and slipping velocity**

For a moving spherical object with translational velocity (v_{cell}), the angular velocity (ω) describes the rate of spinning about its rotational axis, and the surface tangential velocity (v_{tg}) describes the velocity at the surface. For example, the translational velocity of the earth (about 30 km s^{-1}) results in one rotation around the sun in one year. The angular velocity results in one rotation around the polar axis in one day (about 2π radians per day) and is independent of longitude. The surface tangential velocity is highest at the equator and is about 465 m s^{-1}. For a spherical object in contact with a surface in a low viscosity fluid, such as air, the translational velocity is synchronized with the angular velocity. This situation can be envisioned as a ball rolling along the floor where $v_{tg}/v_{cell} = 1$. Numerical solutions of v_{tg}/v_{cell} (REF. 119) show that for a spherical cell touching the surface in a viscous fluid, $v_{tg}/v_{cell} = 0.57$. Therefore, both translational motion and rotation along a vessel wall contribute to receptor–ligand interactions. In the absence of a slipping motion, each cell receptor can only interact with a limited number of immobilized counter-receptors located within its reactive zone. Binding occurs only when the separation distance between a receptor and a ligand is sufficiently small, within the reactive radius around a receptor. Thus, when a free ligand is brought inside this reactive zone, the complex will react. By contrast, when a cell moves with a finite slipping velocity, each cell receptor can potentially bind to any counter receptor present within its reactive zone. Thus, the slipping velocity has been reported to enhance the receptor–ligand encounter rate[75].



The probability of arrest, leading to extravasation, is expected to be maximum at intermediate values of shear stress. The kinetic (ON and OFF rates) and micro-mechanical (tensile strength) properties of a single receptor–ligand bond dictate whether a bond will form at a prescribed shear stress level as well as the macroscopic pattern of cell adhesion

Physics of the metastatic process

The physical interactions of cancer cells with the diverse microenvironments encountered during the metastatic process have a key role in the spread of cancer.

Mechanical forces modulate cell motility in the architecturally complex extracellular matrix during invasion and in the vascular system during intravasation and extravasation. Shear flow in the vascular system dictates the trajectory of circulating tumour cells and has a role in regulating adhesion at blood vessel walls, a key step in extravasation.

The emerging insight into the role of physical and mechanical processes in metastasis should contribute to the development of new approaches for cancer diagnosis and treatment.

For instance, it is noteworthy that several drug candidates show potential when examined *in vitro* but fail in clinical trials. This failure may stem at least in part from the use of conventional *in vitro* systems that fail to replicate the physiological microenvironment in humans as well as the lack of cell-phenotypic measurements.

Physics of the metastatic process

The effect of key microenvironmental physical properties on cancer and stromal cell responses to drug candidates have yet to be explored in a systematic fashion.

These physical properties include mechanical forces, ECM stiffness and the ECM pore size and tortuosity.

Moreover, **current cutting-edge '-omic' measurements conducted on patient specimens need to be complemented with state-of-the-art physical measurements of, for example, cell and tissue microrheology, cell and nuclear shape and cell–cell and cell–matrix adhesion**.

Such a holistic approach could drastically reduce the divergent effects of potential drug candidates on cell responses in animal models and in patients, and could help us to identify the appropriate and efficacious targets for treatment.

Physical traits of cancer

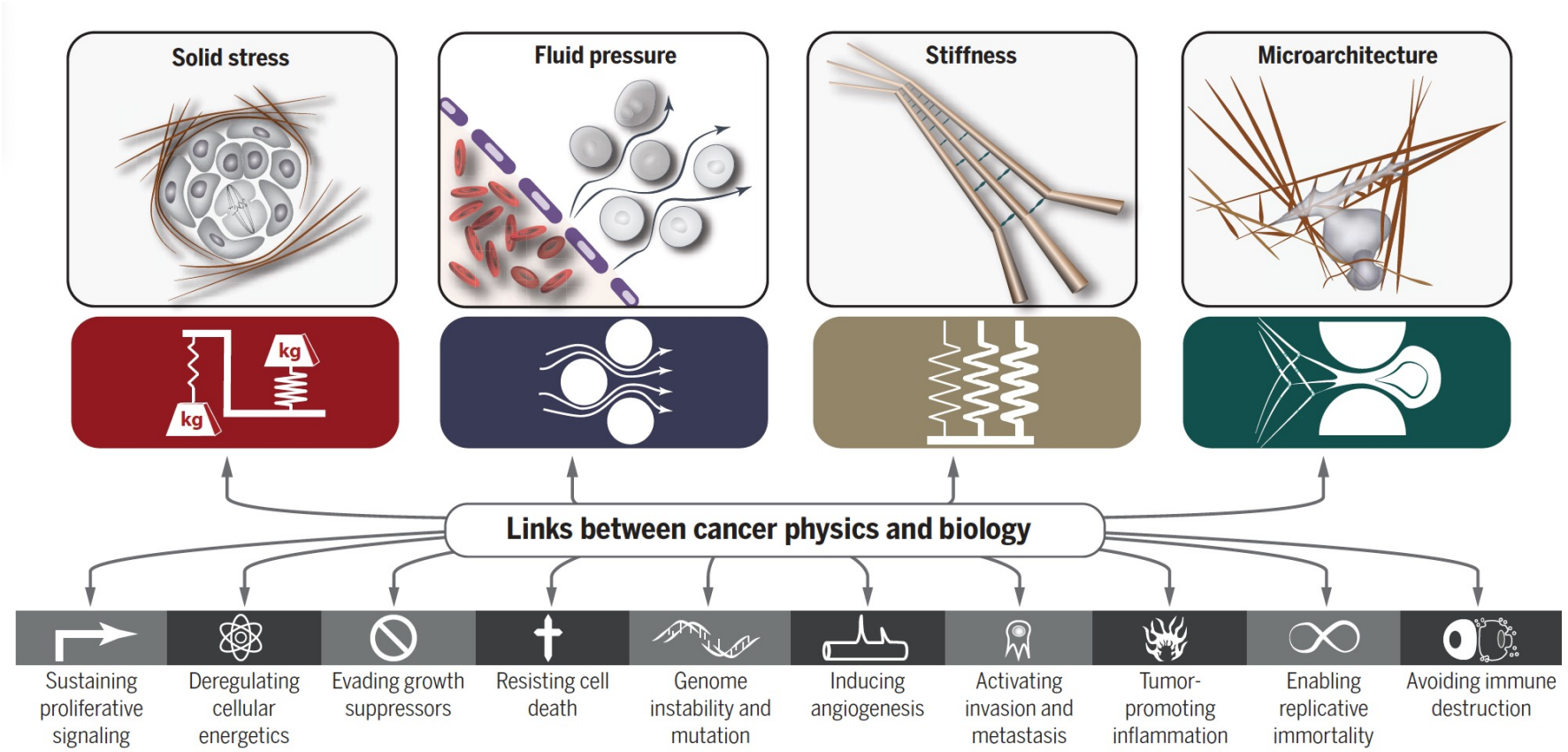


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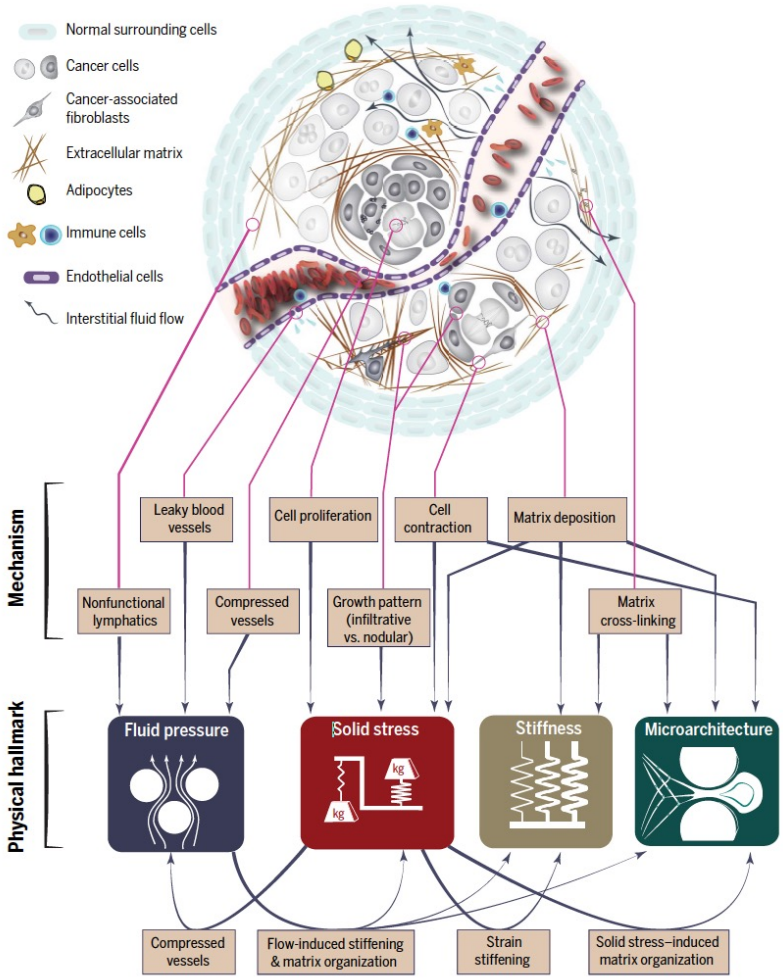
Fig. 2. Origins of the physical traits of cancer. Physical interactions of cancer cells with stroma give rise to physical traits of tumors through distinct and interconnected mechanisms. Leaky and compressed blood vessels and nonfunctional lymphatics lead to increased interstitial fluid pressure within the tumor and interstitial fluid flow in the tumor margin. Cellular proliferation, matrix deposition, cell contraction, and abnormal growth patterns lead to compressive and tensile solid stresses. Matrix deposition and cross-linking cause increased stiffness in tumors. Cell contraction, matrix deposition, and cross-linking also alter the architecture of the tissue. The physical traits also interact with each other; solid stresses compress blood and lymphatic vessels and contribute to increased fluid pressure in tumors. Tensile solid stresses result in stretched and aligned matrix, and through strain-stiffening, solid stresses also increase tumor stiffness. Fluid flow activates fibroblasts, which then contribute to increased solid stresses and stiffness values and alter ECM architecture.



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REVIEW

CANCER

Physical traits of cancer

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The role of the physical microenvironment in tumor development, progression, metastasis, and treatment is gaining appreciation. The emerging multidisciplinary field of the physical sciences of cancer is now embraced by engineers, physicists, cell biologists, developmental biologists, tumor biologists, and oncologists attempting to understand how physical parameters and processes affect cancer progression and treatment. Discoveries in this field are starting to be translated into new therapeutic strategies for cancer. In this Review, we propose four physical traits of tumors that contribute to tumor progression and treatment resistance: (i) elevated solid stresses (compression and tension), (ii) elevated interstitial fluid pressure, (iii) altered material properties (for example, increased tissue stiffness, which historically has been used to detect cancer by palpation), and (iv) altered physical microarchitecture. After defining these physical traits, we discuss their causes, consequences, and how they complement the biological hallmarks of cancer.

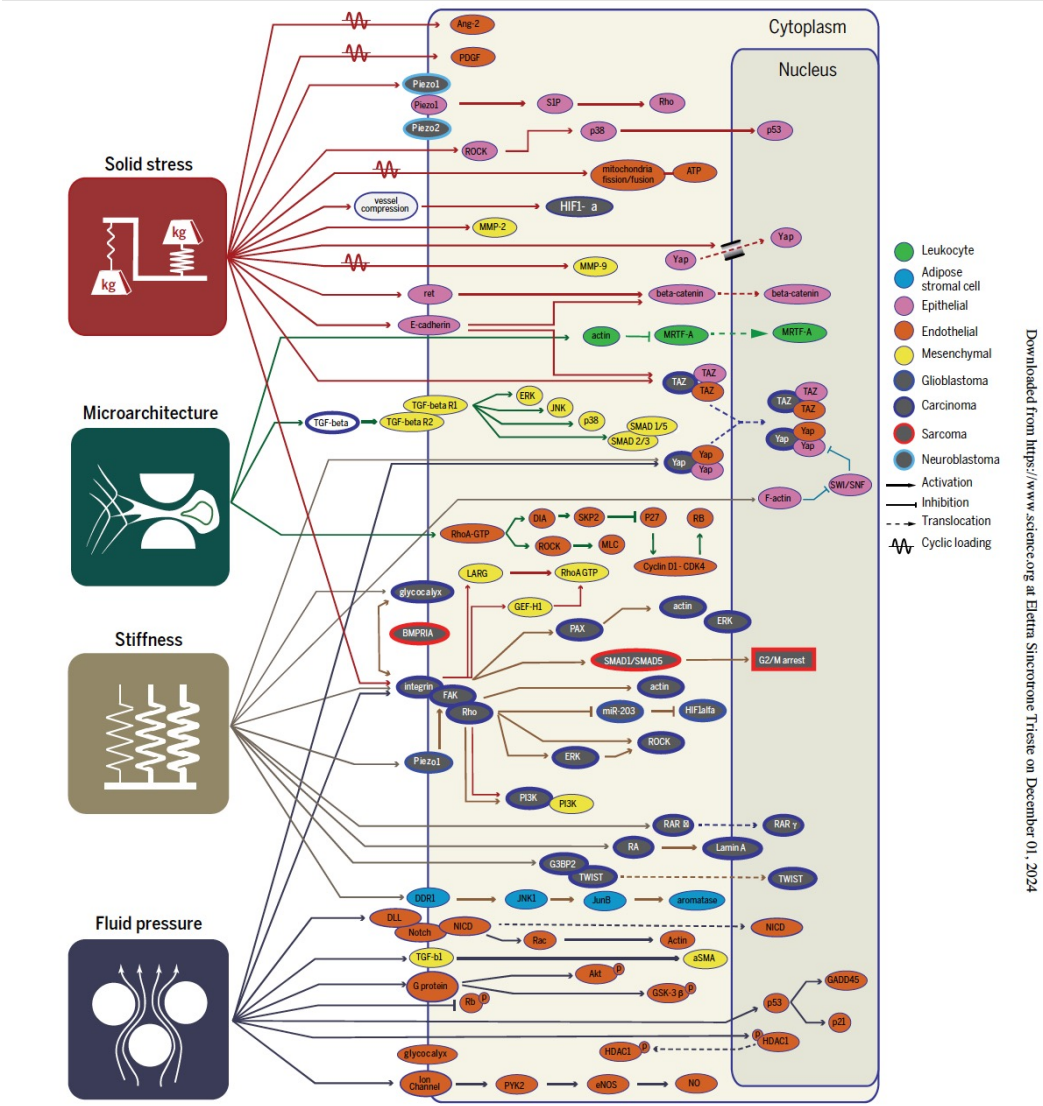

Fig. 3. Pathways associated with the physical traits of cancer. Physical traits of cancer activate a large cascade of mechanoresponsive pathways in cancer cells and stromal cells, including endothelial, epithelial, mesenchymal, and immune cells. Pathways such as integrin and YAP/TAZ are responsive to all four physical traits, whereas many other pathways appear to be more specific.

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