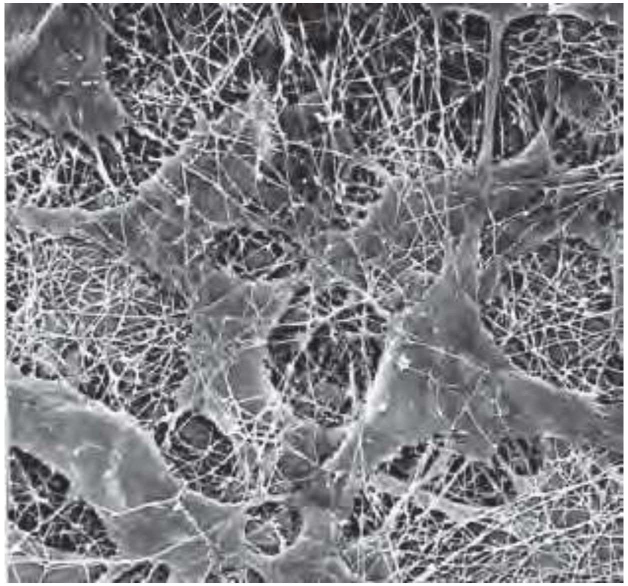
Physics of cancer

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.

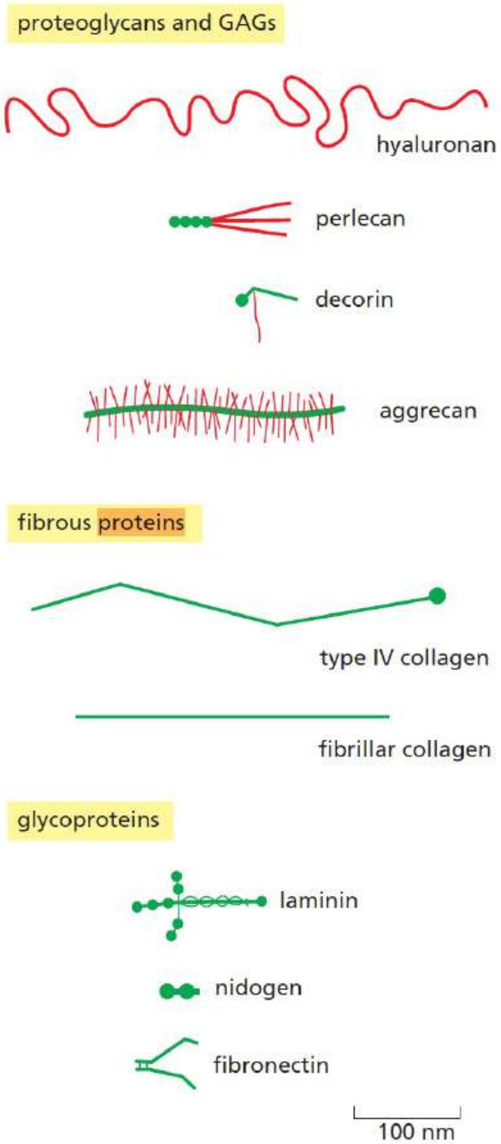


Macromolecules constituting ECM in different animal tissues are broadly similar, but variations in the relative amounts of different classes of molecules and in the ways in which they are organized give rise to an amazing diversity of materials: calcified as the rock-hard structures of bone or teeth;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

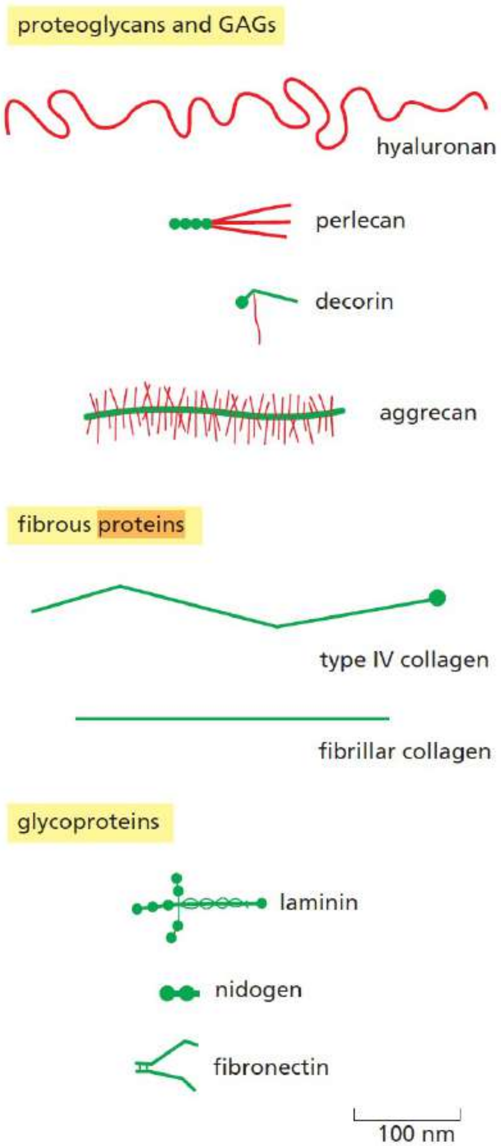


Extracellular Matrix

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.

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

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.

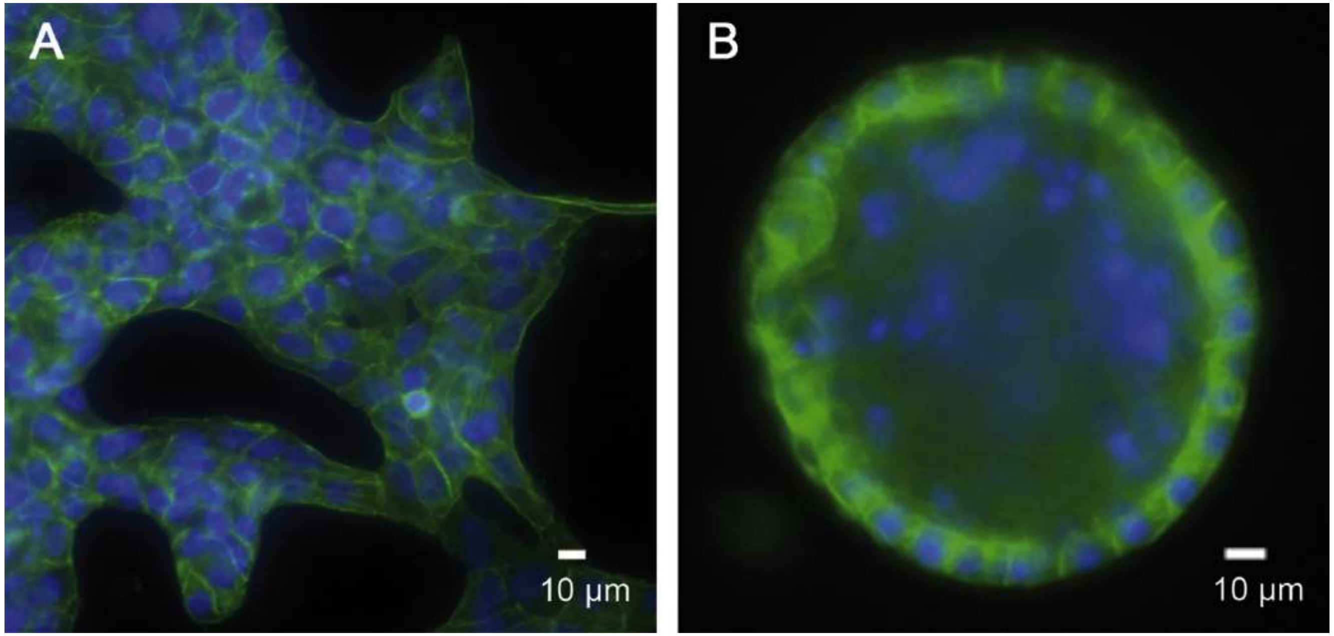
Cancerous cells **acquire features** that are primarily focussed on **cell survival**.
Cancer cells are capable of reprogramming their energy metabolism allowing them to survive the often harsh conditions of the tumour microenvironment.

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.

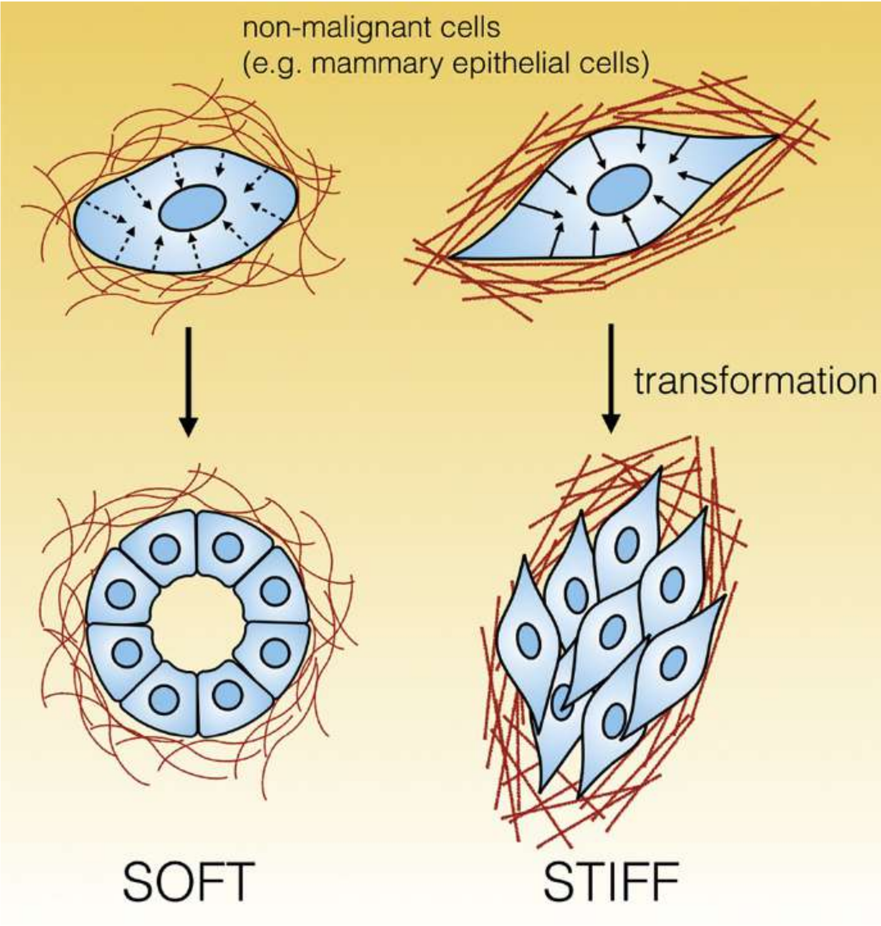
Role of substrate stiffness



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.

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Cell mechanics

All materials deform in response to stress and cells are no exception (Kollmannsberger and Fabry, 2011; Lange and Fabry, 2013).

In general, the stiffness of materials is quantified by measuring the Young modulus E, defined as the ratio between the applied stress, the force per unit area,

$\sigma = F/A$,

and the relative elongation or strain

$\varepsilon = dL/L$

in the direction of the force (both tensorial quantities):

$\boldsymbol{\sigma = E\, \varepsilon}$

an equation valid for Hookean solids in the limit of small deformations.

Cell mechanics

For completeness, we should recall the basic elements of the theory of linear elasticity (Landau and Lifishitz,1970).

Given the local displacement field, $\mathbf{u}(\mathbf{r})$, it is useful to define the symmetric *strain tensor* as

$$\epsilon_{ik} \equiv \frac{1}{2}\left(\frac{\partial u_i}{\partial x_k} + \frac{\partial u_k}{\partial x_i}\right). \tag{6.2}$$

When a solid deforms, interactions at the molecular scale provide restoring forces that tend to bring the solid back to static equilibrium. Due to the action-reaction principle, the resulting force acting on the volume element V, $\int_V dV\mathbf{F}$ is only given by surface terms. Thus each component of $\mathbf{F}$ is the divergence of a vector field (i.e $F_i = \sum_k \frac{\partial \sigma_{ik}}{\partial x_k}$) so that

$$\int_V dV F_i = \int_S dS \sum_k n_k \sigma_{ik}, \tag{6.3}$$

where S is the surface of the volume V, n_k is a unit vector normal to S and σ_{ik} is the *stress tensor*. The equilibrium condition for the body implies $F_i = 0$, which in terms of the stress tensor can be written as

$$\sum_j \frac{\partial \sigma_{ij}}{\partial x_j} = 0. \tag{6.4}$$

Cell mechanics

For completeness, we should recall the basic elements of the theory of linear elasticity (Landau and Lifishitz,1970).

In the limit of small deformations, there is a linear relation between stess and strain

$$\sigma_{ij} = \sum_{i,j,k,l} C_{ijkl}\epsilon_{kl}, \tag{6.5}$$

where C_{ijkl} is the elastic moduli tensor. The Hooke law, reported in its most general form in Eq. 6.5, usually takes a simpler form since symmetry considerations can be used to reduce the number of independent component of C_{ijkl}. In particular, for isotropic solids, we have only two independent components and the Hooke law can be written as

$$\sigma_{ij} = \frac{E}{(1+\nu)}\left(\epsilon_{ij} + \frac{\nu}{1-2\nu}\delta_{ij}\sum_k \epsilon_{kk}\right), \tag{6.6}$$

where E is the Young modulus and ν is the Poisson ratio. For a uniaxial deformation along the direction z, Eq. 6.6 reduces to $\sigma_{zz} = E\epsilon_{zz}$, which is in the form of Eq. 6.1.

Cell mechanics

In some cases it is convenient to rewrite the strain tensor as the sum of a compressive part, involving a volume change, and a shear part, which does not. The Hooke law becomes then:

$$\sigma_{ij} = K\delta_{ij}\sum_k \epsilon_{kk} + 2G(\epsilon_{ij} - \frac{1}{3}\delta_{ij}\sum_k \epsilon_{kk}), \tag{6.7}$$

where K is the bulk modulus and G is the shear modulus. These coefficients are related to the Young modulus $E \equiv \frac{9KG}{G+3K}$ and the Poisson ratio $\nu \equiv \frac{1}{2}\left(\frac{3K-2G}{3K+G}\right)$. Finally, the equation for stress equilibrium for an isotropic elastic medium can be written in terms of the displacement field $\mathbf{u}$, combining Eq. 6.6 with Eq. 6.4

$$\frac{E}{2(1+\nu)}\nabla^2\mathbf{u} + \frac{\nu E}{2(1+\nu)(1-2\nu)}\vec{\nabla}(\vec{\nabla}\mathbf{u}) = 0. \tag{6.8}$$

with appropriate boundary conditions.

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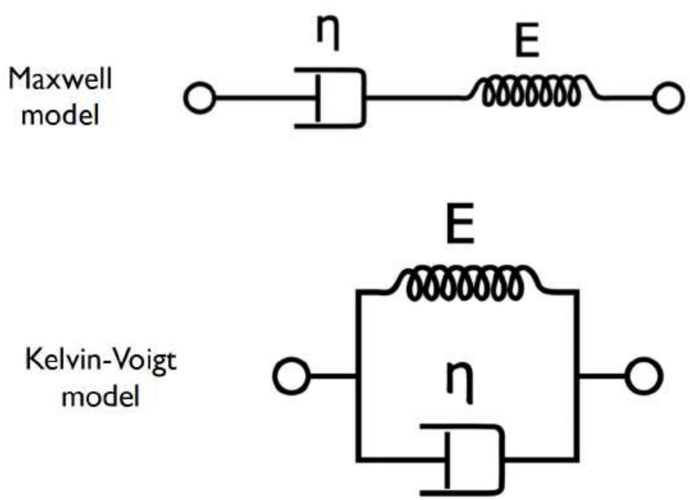
Cell mechanics

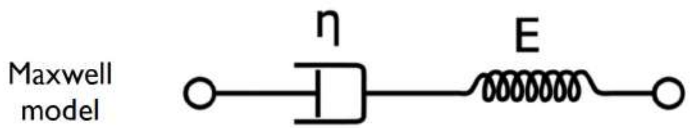


Cells are extremely soft materials, with a Young modulus around E =1kPA, which can be measured by different means as for example atomic force microscopy.

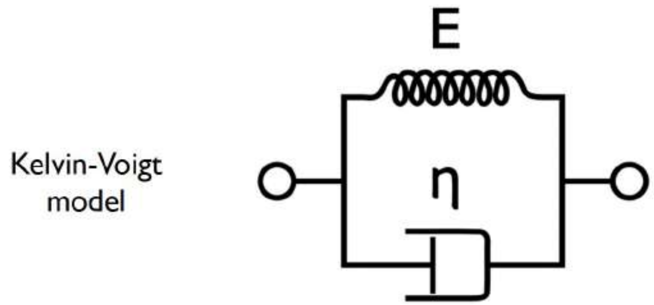
Cells, however, are not simple Hookean solids since their mechanical response is time dependent and include a viscous component typical of fluids.

The simplest description of viscoelasticity is in terms of springs (E) and dashpots (η) that can be combined in series, leading to the Maxwell model, or in parallel, leading to the Kelvin-Voigt model.

Cell mechanics



$$\frac{d\epsilon}{dt} = \frac{\sigma}{\eta} + \frac{1}{E}\frac{d\sigma}{dt}$$ Eq. (6.9)



$$\sigma = E\epsilon + \eta\frac{d\epsilon}{dt}$$ Eq. (6.10)

Cell mechanics

The Maxwell and Kelvin-Voigt model predict exponential relaxations of strain and stress, respectively, with a characteristic time $\tau = E/\eta$. Relaxation in cells is not exponential as predicted by this models, but decays as a power law (Fabry et al., 2001; Moeendarbary et al., 2013). In particular the time-dependent response to a constant applied stress σ, or creep, follows

$$\epsilon(t) = \sigma \left(\frac{t}{t_0}\right)^{\beta}, \qquad (6.11)$$

with $\beta \simeq 0.1 - 0.5$ Fabry et al. (2001). Similarly, the stress relaxation in response to a fixed deformation decays as a power law at long time scales

$$\sigma(t) \simeq t^{-\alpha} \qquad (6.12)$$

while at short time scales there one observed deviations (Moeendarbary et al., 2013) attributed to the poroelastic behavior of the cell (Mitchison et al., 2008).

Cell respond to stress actively

Viscoelastic behavior is common to many polymeric materials but cells are different because its response to stress is not only passive but contains an active component due to acto-myosin driven contraction of the cytoskeleton. This behavior can be described theoretically by models of active fluids and gels (Liverpool and Marchetti, 2003; Voituriez et al., 2006; Salbreux et al., 2009; Joanny and Prost, 2009; Marchetti et al., 2013; Prost et al., 2015). In the active gel theory, the stress tensor obeys a viscoelastic constitutive equation similar to Eq. 6.9 or Eq. 6.10 but it is decomposed in the sum of a passive and and an active component: $\sigma_{ij} = \sigma_{ij}^{(p)} + \sigma_{ij}^{(a)}$. Here the active stress is written as

$$\sigma_{ij}^{(a)} = \tilde{\zeta}\delta_{ij} + \zeta(\pi_i\pi_j - \delta_{ij}/3) \tag{6.13}$$

where the first term is the "volumetric" stress and the second "deviatoric" term (i.e. not involving volume changes) is coupled to the local orientation π_i of the actin fibers composing the cytoskeleton (Prost et al., 2015). The coefficients $\tilde{\zeta}$ and ζ are proportional to the density of actin fibers and myosin motors.

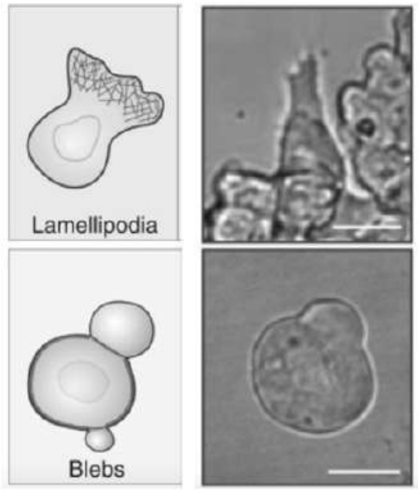
Cell mechanics

There is a wide literature on the role of mechanical stresses on tumor growth, as reviewed by Taloni et al. (2015a). The mechanical properties of cancer cells appear to be correlated with their malignancy, in such a way that cells become softer during cancer progression (Fritsch et al., 2010). This has been shown for cell lines (Lekka et al., 1999; Guck et al., 2005) and tumor tissues (Cross et al., 2007; Remmerbach et al., 2009). The distribution of optical deformability of breast tumors shows a distinct shift towards softer cells with respect to normal mammary tissue obtained from surgical breast reductions (Fritsch et al., 2010). The shift is attributed to the change in actin structure from fibrous to diffuse (Sanger, 1975). At large strains cytoskeletal filaments inherently strain-harden, compensating for the weak linear elastic strength of the actin cortex (Janmey et al., 1991). It has been argued that intermediate filaments such as vimentin could be the right candidate to support the pressure generated by division and dynamics against the surrounding stroma (Chen et al., 2008). It is usually assumed that cell softening is needed by malignant cells by more easily overcome barriers posed by the ECM. The reality is likely more complex since cell migration has been shown to be correlated also with nuclear size, cell adhesion and contractility (Lautscham et al., 2015).

Individual cell motion

Cell migration plays a key role in many physiological processes such as embryogenesis and morphogenesis, immune response, wound healing and tissue repair, but it is also a crucial determinant for cancer invasion and metastasis.

Broadly speaking, we can identify two main migration modes for individual cells (Ruprecht et al., 2015): i) Lamellipodia-driven mobility which relies on the formation of a single lamellipodium at the cell leading edge and ii) amoeboid cell migration which is based on the formation of blebs in the plasma membrane (Fackler and Grosse, 2008; Paluch and Raz, 2013) due to its detachment from a contracting acto-myosin cortex. Crucial role in blebs formation is played by water transfer through the membrane, thanks to the the aquaporin water channel (Taloni et al., 2015b). In confined environments, cell are able to migrate relying exclusively on water transport even when actin polymerization and myosin driven contraction are inhibited.

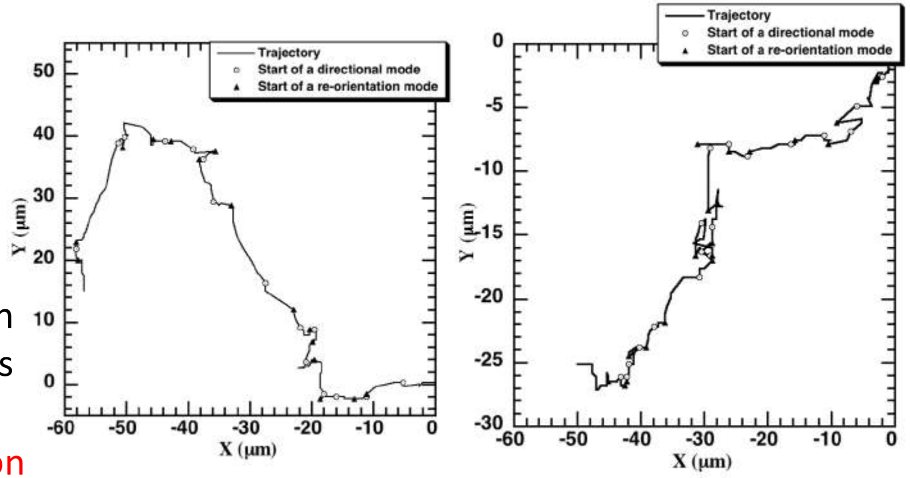


Individual cell motion

The simplest method to investigate individual cell migration is to observe cell trajectories *in vitro*(Potdar et al.,2010).

The trajectories display an erratic behavior typical of Brownian motion (Codling et al., 2008), but a closer quantitative analysis shows that cells do not perform a simple random walk. In particular, the figs show period of persistent directional motion in one direction followed by re-orientation events when the direction changes completely.

The simplest stochastic process that reproduces this behavior is the persistent random walk (PRW) described by the Langevin equation.



Mammary epithelial cells moving in two dimensions for two hours.

Individual cell motion

$$\frac{d\mathbf{v}}{dt} = -\frac{\mathbf{v}}{\tau} + \sqrt{\frac{D}{\tau}}\eta(t),$$

where v is the cell velocity, τ is the persistence time, η(t) is an uncorrelated Gaussian noise with zero mean and unit variance, and the noise strength is tuned by D. This linear stochastic model can be easily solved and yields a
mean-square displacement

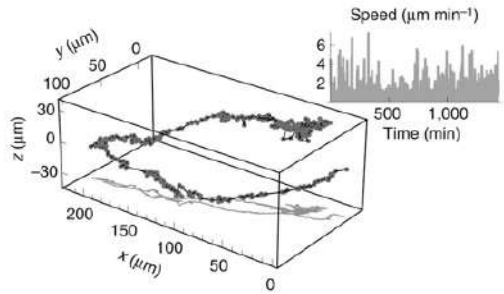
$$\langle(\mathbf{r}(t+t_0) - \mathbf{r}(t_0))^2\rangle = 2D\tau\left(\exp(-t/\tau) - \frac{t}{\tau} - 1\right)$$

Which interpolates from an exponential increase at short times to a linear diffusive behavior at large times which agrees with experimental data for two dimensional motion (Wu et al., 2014). An alternative model to explain the deviation from pure Brownian motion invoking anomalous diffusion (e.g. a mean square displacement scaling as $t^2\alpha$, with $\alpha > 1/2$) instead of persistence (Dieterich et al., 2008).

Individual cell motion

$$\langle(\mathbf{r}(t+t_0)-\mathbf{r}(t_0))^2\rangle = 2D\tau\left(\exp(-t/\tau)-\frac{t}{\tau}-1\right)$$

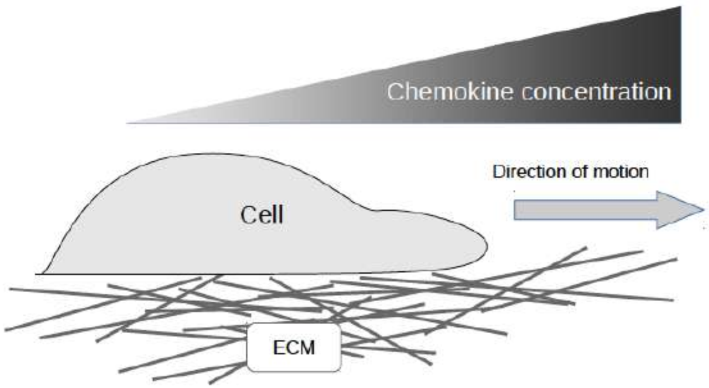
Recent experiments tracked cell motion on three dimensional collagen matrices revealing clear deviation from the simple PRW model (Wu et al., 2014; Metzner et al., 2015).



In particular, experiments show that the distribution of velocities is not Gaussian as predicted by the PRW. The correct distribution can be obtained by modeling cell heterogeneity and substrate anisotropies and more recently by introducing a superstatistical framework (Metzner et al., 2015) where the motion is modeled by a persistent random walk with parameters (e.g. τ and D) that are themselves evolving stochastically.

The superstatistical framework allows to obtain excellent results for cell motion in two and three dimensions (Metzner et al., 2015).

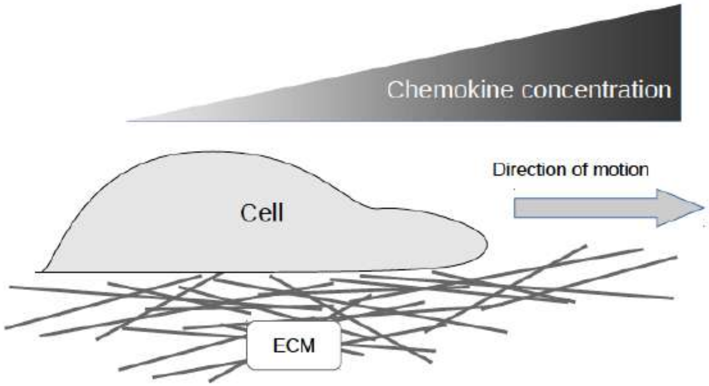
Chemotaxis



Cells move in response to external stimuli and in particular to changes in the chemical environment, a process known as chemotaxis.
Contrary to bacteria, eukaryotic cells are large enough to be able to sense chemical gradients and respond to them by polarizing their cytoskeleton, moving towards the higher concentration. This is a accomplished through a uniform array of receptor molecules sitting on the cell surface that bind specific chemoattractant molecules, such as chemokines.

Receptor binding leads to a signal transduction inside the cell through the activation of complex pathways.
The cell must then be able to detect differences in signaling resulting from differences in occupied receptors on the surface, a process referred to as ”gradient sensing”. As a result of this,
cells polarize changing their cytoskeleton by actin polymerization, forming pseudopodia in the front of the cell and finally moving in the direction of the higher gradient.
N.B.: gradient sensing does not necessarily imply movement!!! Sensitivity in conc. differences < 1%

Chemotaxis



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The kinetic reactions are:

$$\frac{d[L_f]}{dt} = k_+[L_f][R_f] - k_-[LR_f] \quad (7.3)$$

$$\frac{d[L_b]}{dt} = k_+[L_b][R_b] - k_-[LR_b], \quad (7.4)$$

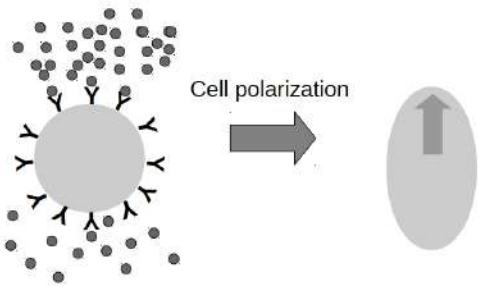
which in the steady state ($t \to \infty$) yields signals S as the fraction of occupied receptors (Rappel and Levine, 2008a)

$$S_f = \frac{[LR_f]}{[LR_f] + [R_f]} = \frac{c(1+p)}{c(1+p) + K_d} \quad (7.5)$$

$$S_b = \frac{[LR_b]}{[LR_b] + [R_b]} = \frac{c(1-p)}{c(1-p) + K_d}, \quad (7.6)$$

where $K_d = k_+/k_-$ is the dissociation constant. These equations are fully deterministic and predict a signal difference between front at back $S_f - S_b$

proportional to p at small gradient:



Cell mechanics

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Cell mechanics

Tumors grow at the expense of normal tissues. Hence, space limitations give rise to non-fluid related pressure, i.e. solid stress.
This stress depends on tumor size and local mechanical properties, which are influenced by tumor associated ECM modifications (degradation, crosslinking, overproduction), altered tissue tensional homeostasis, increased compression force due to the solid state pressure exerted by the expanding tumour mass and matrix stiffening due to the desmoplastic response.

Solid-phase stresses are prominent in elastically stiff regions such as cranium and bones.
Stresses can be divided into two categories: the externally applied stress, which is developed through mechanical interactions between the solid components of the growing tumor and the surrounding tissue, and the growth-induced stress, which is stored within the tumor as the proliferating cancer and stromal cells modify the structural components of the tumor microenvironment. The growth-induced stress is a residual stress since it persists even after the tumor is excised and external confining stresses from surrounding tissues have been removed.

Cell mechanics

Observations of tumor spheroid growth in environments of different stiffness have raised the interesting possibility that a stiffer matrix can be viewed as a host barrier to tumor invasion, and increasing tissue stiffening could actually impede cancer progression---stress hinder tumor growth.
However, other past studies have suggested that changes in ECM structure or mechanics, such as whether the matrix is stiff enough to resist cell traction forces, might actively contribute to tumor formation.

The reasons for this apparent discrepancy may include the dynamic nature of stress, deficient instrumentation for measuring it in vivo, and challenges in evaluating its individual biological role.

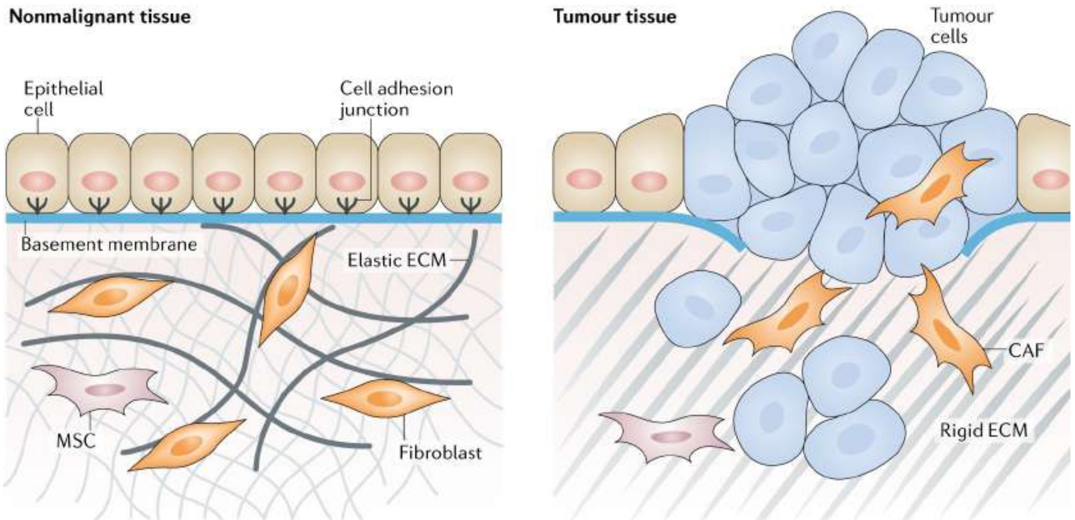
Another possible reason is that mechanical stresses displace the homeostasis threshold by inhibiting simultaneously proliferation and apoptosis rates, also inducing phenotypic changes.

Cell mechanics

The tumor-associated stroma is composed of several cell types including **adipocytes, fibroblasts, and immune cells**, as well as a variety of ECM proteins, such as collagen and fibronectin.

The onset and progression of cancer leads to distinct changes in the stiffness of the ECM surrounding tissue. Indeed, tumors are often detected as a palpable stiffening of the tissue and approaches such as magnetic resonance imaging elastography and sono-elastography have been developed to exploit this observation to enhance cancer detection.

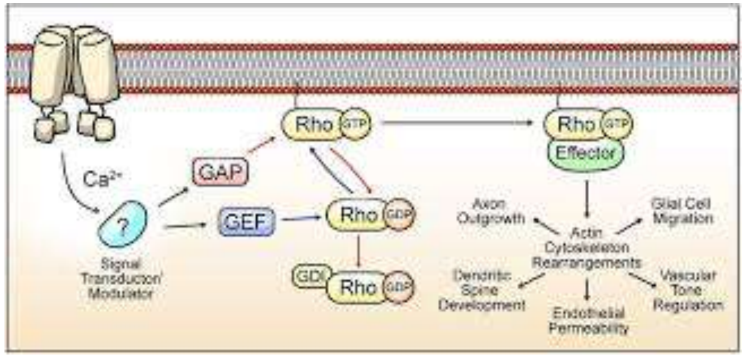
Furthermore, altered stromal-epithelial interactions precede and could even contribute to the malignant transformation (Levental et al., 2009). In fact, the desmoplastic stroma that is present in many solid tumors is typically significantly stiffer than normal (Paszek et al., 2005). The cause of the increase in tumor stromal stiffness and its relation with cancer progression are still open questions in a mechanical view of tumorigenesis.



Cell mechanics

Mechanical stresses are perceived and integrated by the cell at the molecular level through mechanically responsive sensors triggering biochemical signaling cascades which yield a specific cellular response, a process known as **mechanotransduction**. Once mechanical cues have been detected indeed, cells must propagate, amplify the physical cue creating in each of them and translate the signal into either a transient response or a sustained cellular behavior.

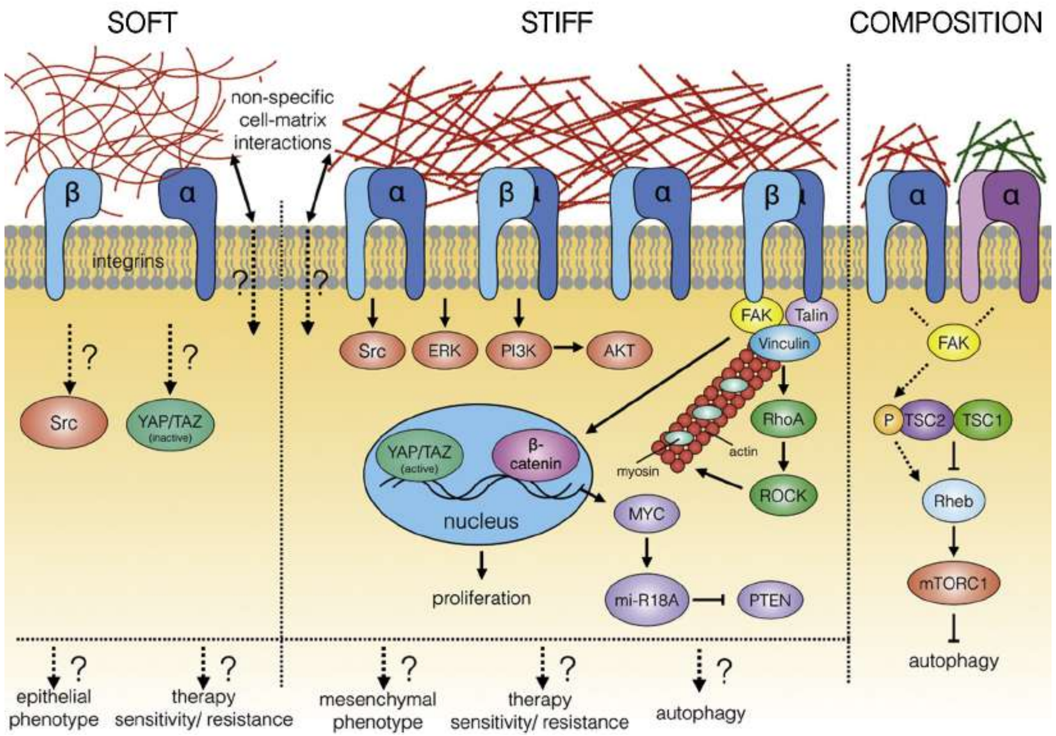
For instance, force and growth factor receptors can each influence cell growth, survival, differentiation, shape and gene expression by regulating the activity of RhoGTPases that, in turn, modulate actomyosin contractility and actin dynamics.



Another example of mechanotransducer are integrins which interact with the ECM. They regulate integrin dependent extracellular-signal regulated kinase (Erk) that is involved in cell motility affecting the capability of the cells to interact with the environment through the assembly of focal adhesion.

All these evidences show how the cells respond actively to solid stresses altering biochemical pathways and finally remodeling the cytoskeleton.

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.

Cell mechanics

High mechanical forces could compromise cell differentiation and alter mechano-responsiveness, thus promoting the malignant transformation.
This is not, however, a one-way process. Cell traction forces generated in the actin cytoskeleton are exerted on these same sites so that integrins and focal adhesions are maintained in a state of isometric tension. A rise of cell tension further increases ECM stiffness by tensing or realigning ECM components, thereby creating a deadly, self-sustaining positive feedback loop: **cells generate more force, disrupt cell-cell junctions, spread, increase proliferation, and loose acinar organization.**

Paszek et al. (2005) explored the role of bidirectional force transfer across integrins in the context of differentiation and tumor formation. Using an electromechanical indentor they showed that explanted mouse mammary tumors are stiffer than healthy mammary gland. Moreover, culturing normal mammary epithelial cells on ECM gels with varying mechanical compliance, they observed that stiff (force-resisting) ECM gels promote expression of the undifferentiated malignant phenotype, and Rho activity was also higher in these cells.

Provenzano et al. (2006) detected local alterations in collagen density around tumors. Local cell invasion was found predominantly to be oriented along certain aligned collagen fibers, suggesting that radial alignment of collagen fibers relative to tumors facilitates invasion.
Regions of high breast density were associated with increased stromal collagen (Provenzano et al., 2008). Indeed, an increase in ECM protein concentration, i.e. an increased matrix crosslinking or parallel reorientation of matrix fibrils within a stromal matrix, can stiffen a tissue locally to alter cell growth or direct cell migration, albeit to differing degrees.

Basics of cell migration

Cell migration plays a fundamental role in cancer being at the basis of the metastatic process, where cancer cells detach from the primary tumor, invade neighboring tissues and finally spread to distant organs.

The main biological and physical aspects of migration, include the motion of individual cells and the statistical characterization of their trajectories in terms of stochastic processes.

Cells respond to chemical signals, in a process known as chemotaxis, and then polarize and move in the direction of the chemical gradient. In order to move, cells make use of a vast class of cell adhesion molecules.

Motion results from the application of traction forces to the ECM which can be quantified experimentally. Cell adhesion molecules play also an important role in the interaction between cells, leading to collective effects.

Epithelial-mesenchimal transition

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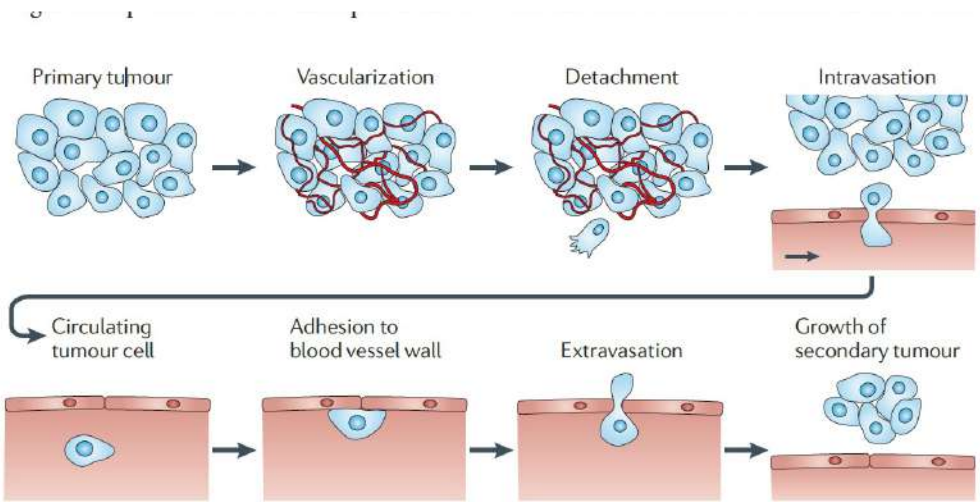

Figure 1 | **The metastatic process.** In this complex process, cells detach from a primary, vascularized tumour, penetrate the surrounding tissue, enter nearby blood vessels (intravasation) and circulate in the vascular system. Some of these cells eventually adhere to blood vessel walls and are able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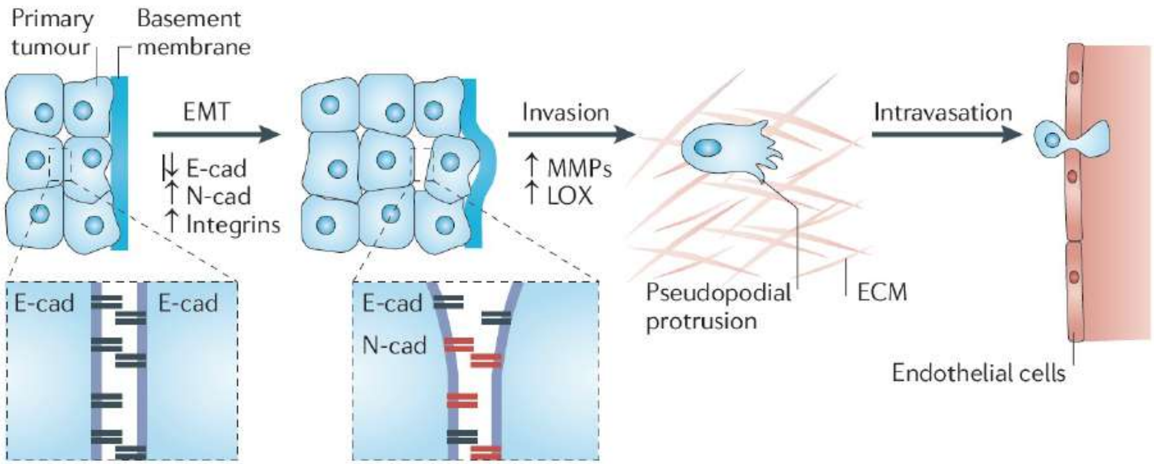

Figure 2 | **The physics of invasion and intravasation.** The epithelial-to-mesenchymal transition (EMT) is associated with a loss of adhesion through downregulation of E-cadherin (E-cad) and a change in morphology. Invasion by tumour cells of the surrounding tissue and subsequent motion is dictated 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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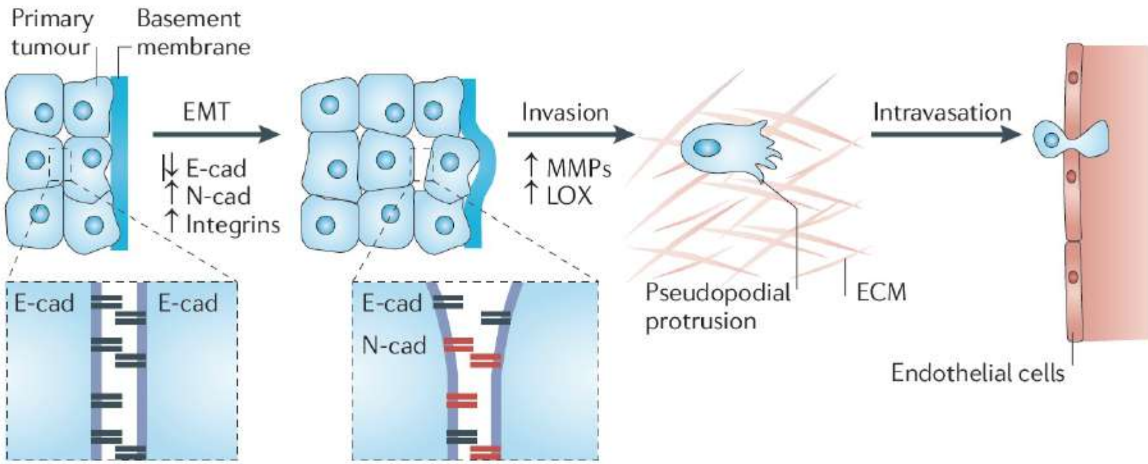

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Also, they express **Matrix Metalloproteinase (MMP)** which promote the digestion of the laminin- and collagen IV-rich basement membrane.

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

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** , an interdisciplinary field based on math and phys description of transport, 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.

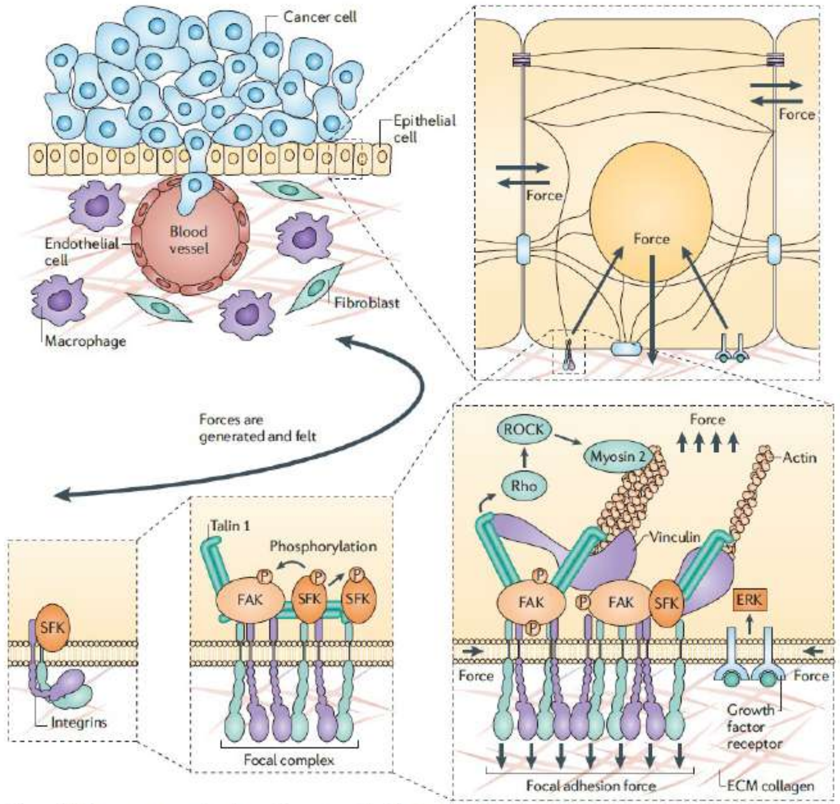
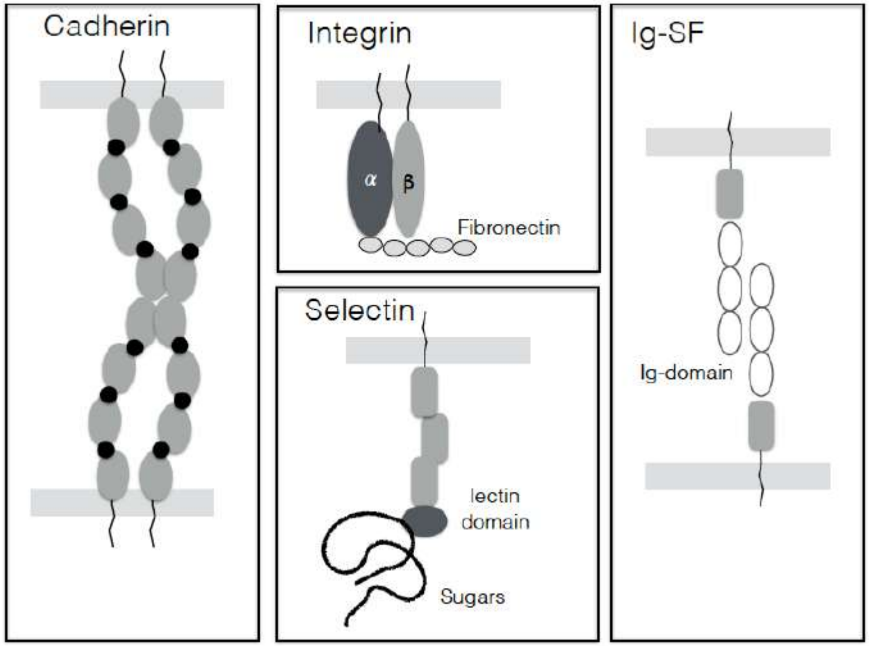


Figure 2 | **Tissues are complex dynamic systems that feature multiscale mechanochemical coupling.** Progress has been made particularly in delineating the molecular mechanisms of force generation by the cytoskeleton, the details of cell–cell adhesion and force sensing by proteins such as talin 1 and 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.

Cell adhesion



Migration requires that individual cells attach to the surrounding ECM, while collective cell migration also involves attachments to neighboring cells.
At the microscopic level, cell-cell and cell-ECM attachments are possible thanks to cell adhesion molecules (CAM), which provide structure to cells and tissues, allow cell signalling, tissue repair and wound healing (Makrilia et al., 2009).

The most important classes of CAM are cadherins, integrins, selectins and members of immunoglobulin superfamily (IgSF).

Cadherins insure cell-cell adhesion (EMT)
Integrins, (see molecular clutch) are involved both in cell-cell and cell-ECM interactions and they play crucial role in cell proliferation, differentiation and migration due to their ability to transfer signals from the ECM into the cell
Selectins and IgSF family members are mainly involved in wound healing and in the immune response

Traction forces during cancer cell migration

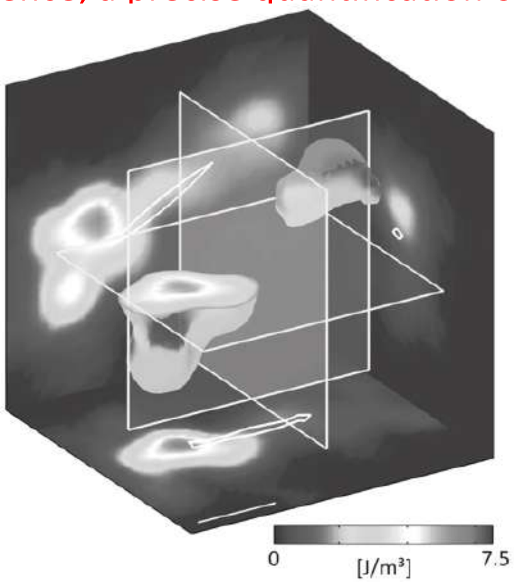
In order to migrate and invade neighboring tissues, cancer cells have to exert mechanical forces on the surrounding ECM.

Experiments revealed significant differences between traction forces between metastatic and non-metastatic cells (Kraning-Rush et al., 2012).

Cellular traction forces are, however, not only involved in cancer metastasis and angiogenesis but also in physiological processes such as as contraction, cell migration, wound healing. Hence, a precise quantification of traction forces is becoming an extremely important challenge.

In 2D, cellular traction forces are typically measured by placing cells on planar flexible gel substrate on which beads are embedded. The strain field on the substrate is reconstructed by observing the displacements of the beads after the cells are removed.

But cancer needs 3D: dispersing beads in 3D cell cultures (computing the elastic strain energy stored in the matrix due to traction-induced deformations)



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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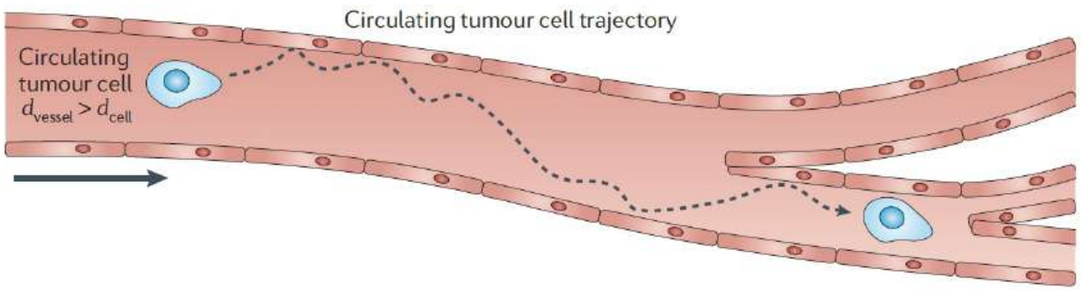
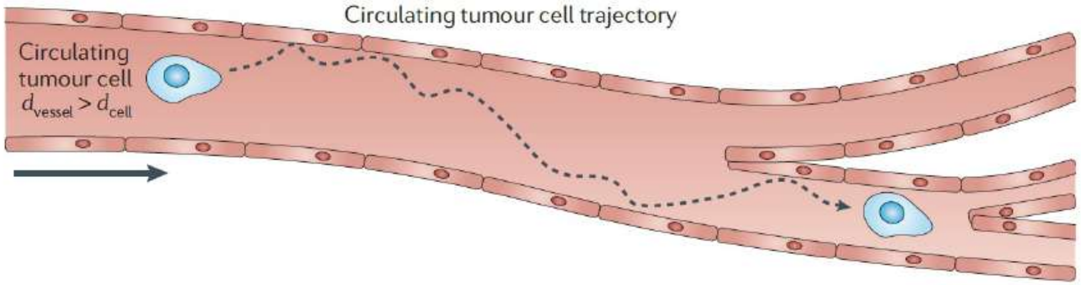


Figure 3 | **Arrest of circulating tumour cells.** Tumour cells with a diameter (d_{cell}) less than the diameter of the blood vessel wall (d_{vessel}) will follow a trajectory that is determined by the local flow pattern and by collisions with host cells and blood vessel walls. Collisions with a blood 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.

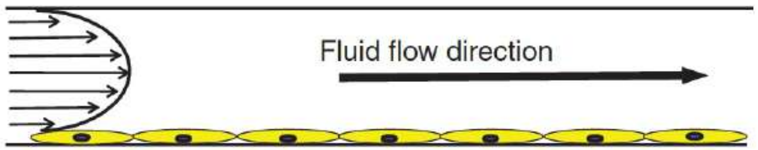
V is maximum at the centre and zero at the cylinder walls, and the relative velocities of parallel adjacent layers of fluid in laminar flow define the **shear rate**

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

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



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

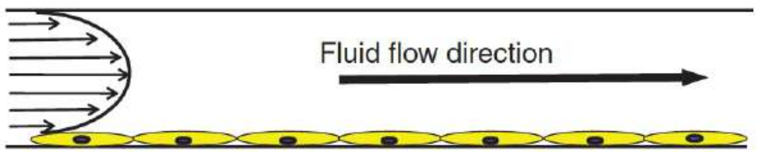
τ_w = shear stress (dyn cm^{-2})
μ = viscosity (kg m^{-1} s^{-1})
Q = volumetric flow rate (ml s^{-1})
b = width (mm)
h = height (mm)

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



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

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

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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.

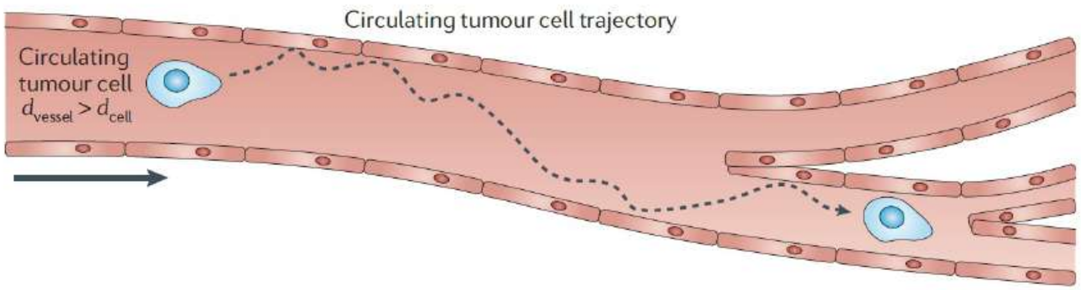
At shear rates greater than 100 s^{-1}, **blood is considered a Newtonian fluid, implying that the shear stress increases linearly with shear rate**.

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].

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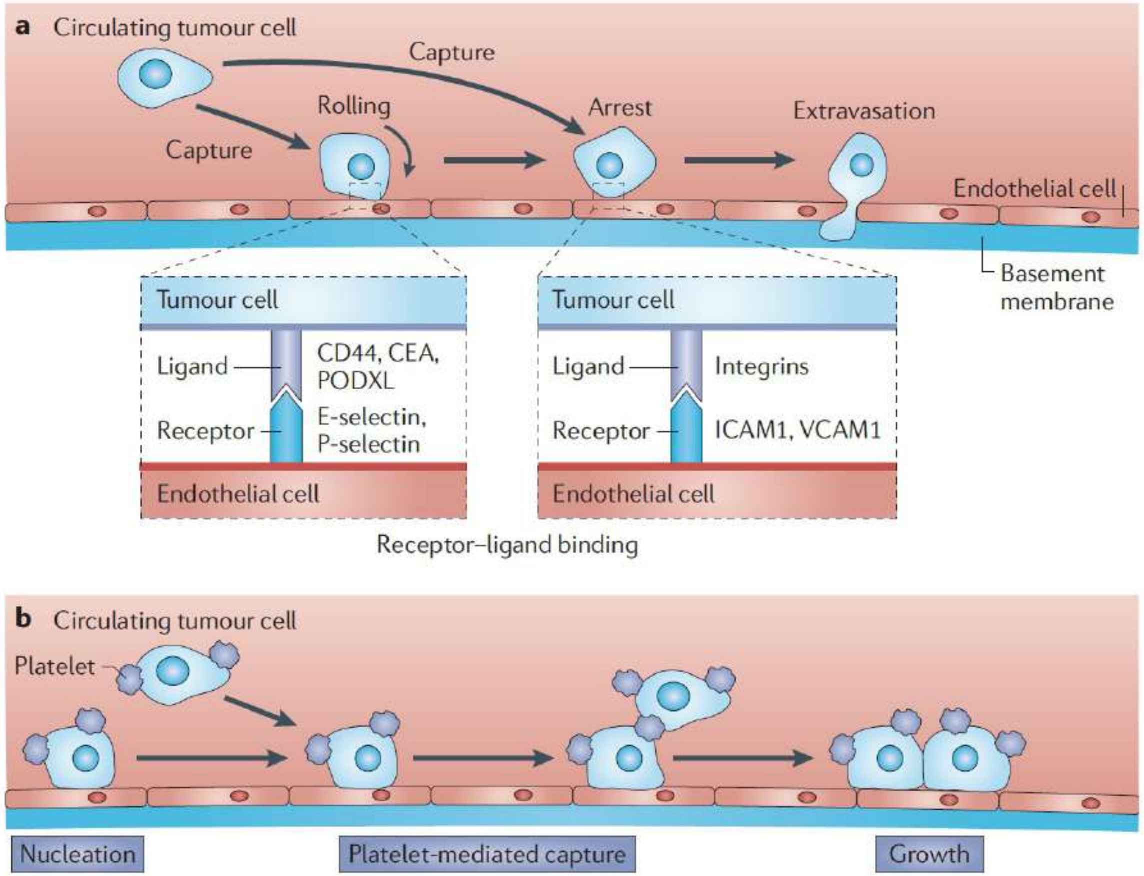

The probability of arrest, leading to extravasation, is expected to be maximum at intermediate values of shear stress. The kinetic (ON and OFF rates) and micro-mechanical (tensile strength) properties of a single receptor–ligand bond dictate whether a bond will form at a prescribed shear stress level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

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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

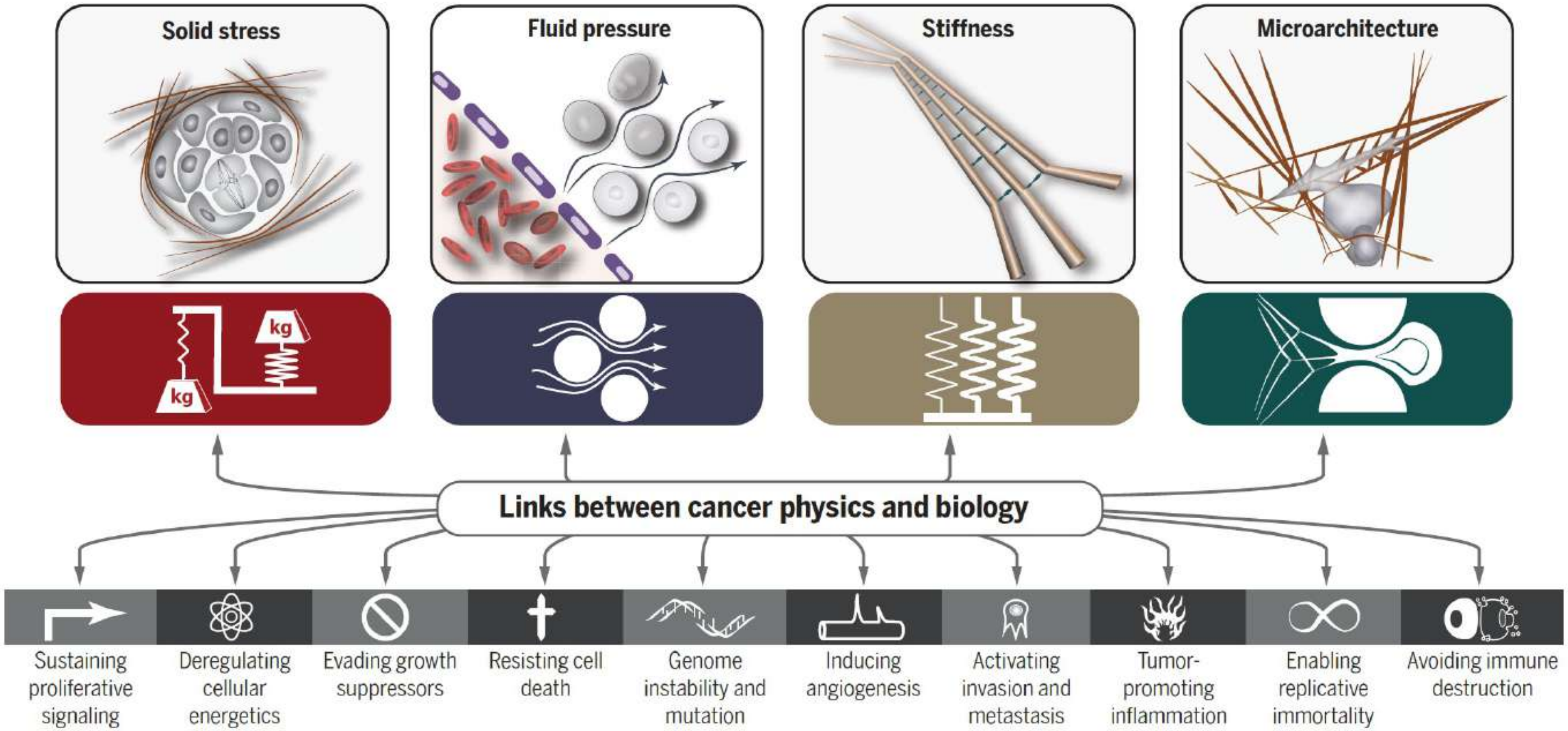

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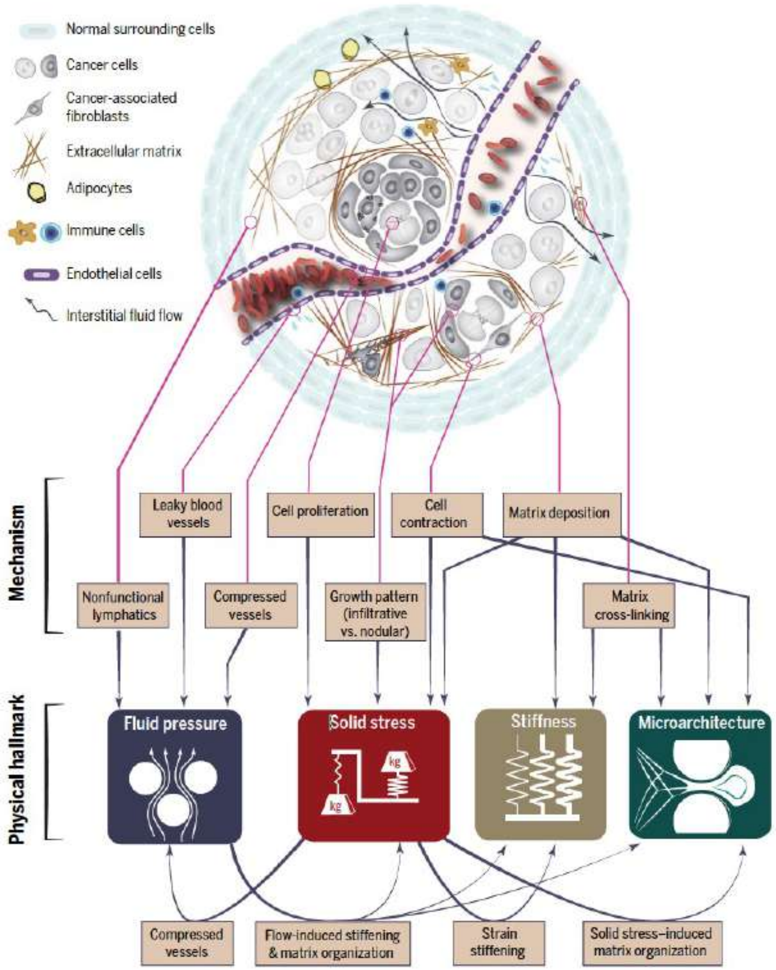
Fig. 2. Origins of the physical traits of cancer. Physical interactions of cancer cells with stroma give rise to physical traits of tumors through distinct and interconnected mechanisms. Leaky and compressed blood vessels and nonfunctional lymphatics lead to increased interstitial fluid pressure within 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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RESEARCH

REVIEW

CANCER

Physical traits of cancer

Hadi T. Nia[1,2], Lance L. Munn[1], Rakesh K. Jain[1,3]*

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.

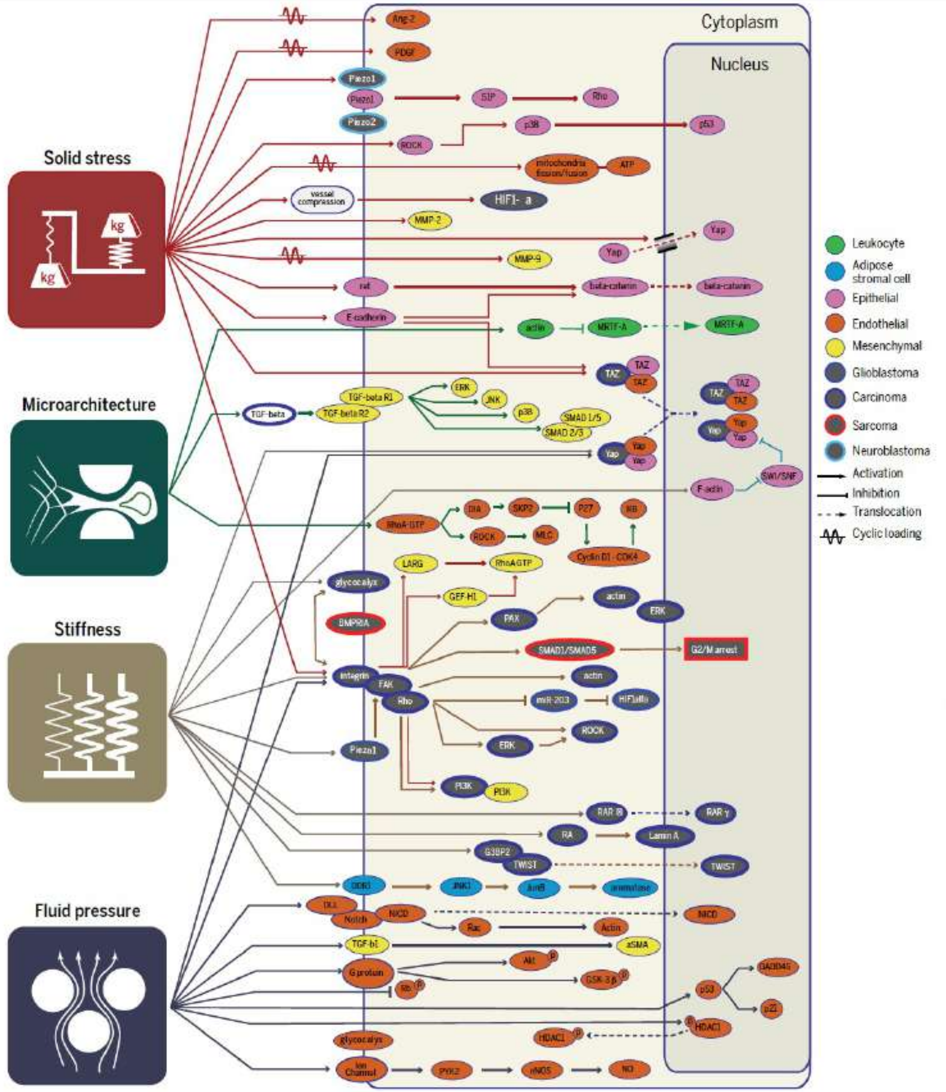

Fig. 3. Pathways associated with the physical traits of cancer. Physical traits of cancer activate a large cascade of mechanoresponsive pathways in cancer cells and stromal cells, including endothelial, epithelial, mesenchymal, and immune cells. Pathways such as integrin and YAP/TAZ are responsive to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

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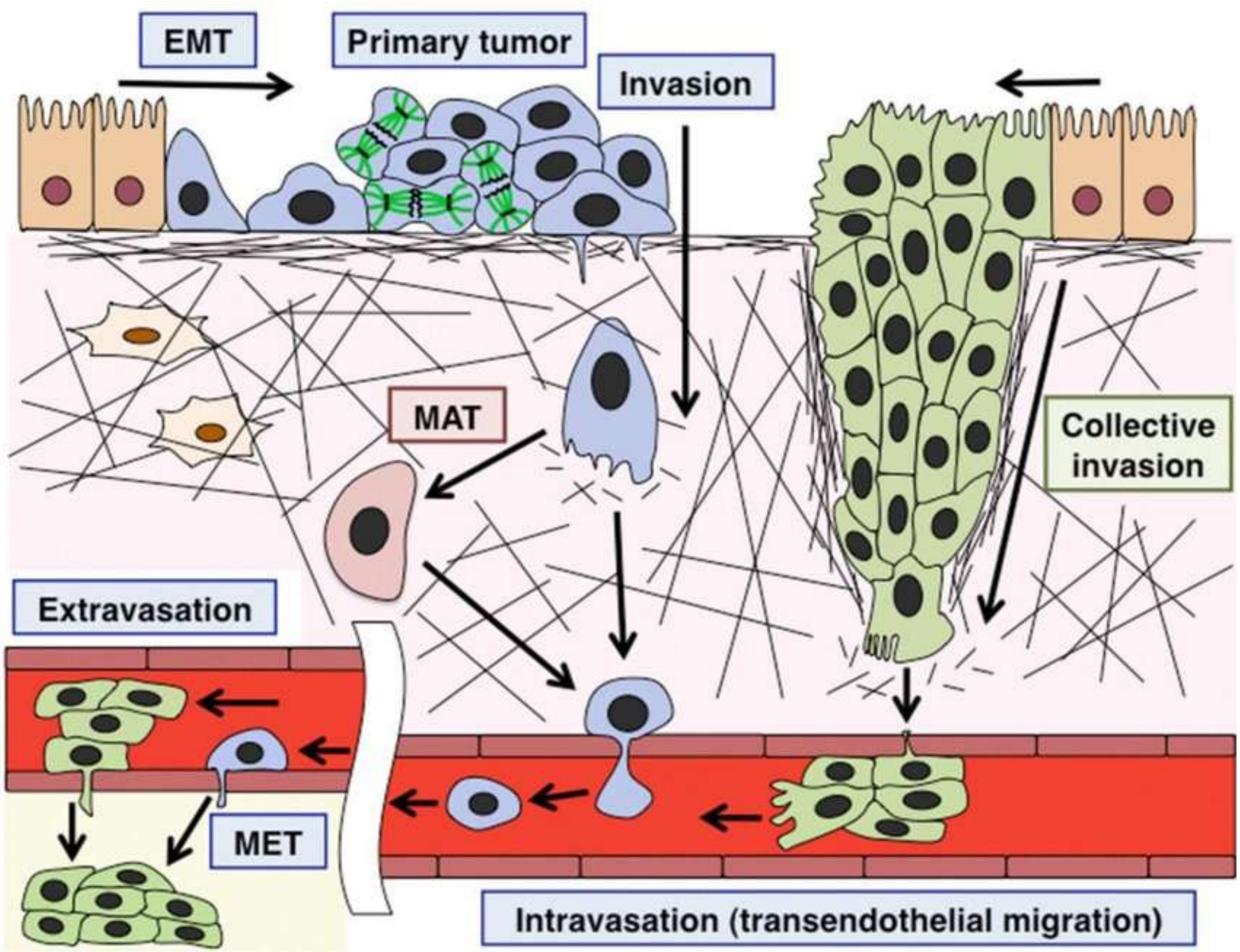
Collective phenomena

Collective cell migration is a key feature of epithelial tissue but it is often encountered in cancer metastasis . This observation is at odd with the conventional idea according to which cancer cell first undergo an epithelial-to-mesenchymal transition and then migrate individually. While in individual cell migration chemotaxis, mechaotransductions and the resulting signaling cascades all occur within a single cells, in collective cell migration all these functions are coherently shared by a group of cell that can behave as a multicellular unit in which internal communication takes place via cell-cell junctions.

wound-healing assay: a confluent cell monolayer is scratched and the motion of the ensuing cell front is observed by time lapse microscopy as it invades the empty space.

Traction force microscopy during wound healing reveals that collective motion arises from mechanical stresses transmitted between neighboring cells (Tambe et al., 2011) giving rise to long-ranged stress waves in the monolayer.
Experiments performed on plates with different coating such as gels, micro-patterned or deformable substrates show that cell migration is guided by the substrate structure and stiffness.
P-cadherin is related to the strength of the adhesion force, while E-cadherin controls the rate of its buildup.


EMT
Primary tumor
Invasion
MAT
Collective invasion
Extravasation
MET
Intravasation (transendothelial migration)

Theoretical models:

-cells are a set of self-propelled interacting particles and analyzes their collective motion.
-Interactions typically include: attraction, due to adhesion, between neighboring particles and hard core repulsion at short distances.
-Another important ingredient is the tendency of active particle to align their velocities.
- Finally, the dynamics is affected by noise.

Jumming/unjumming transition

•**A solid-like (jammed) epithelium** has cells packed so tightly they cannot rearrange. Migration is suppressed.

•**An unjammed tissue** behaves like a viscous or viscoelastic fluid: cells slip past each other, align, stream, and flow.

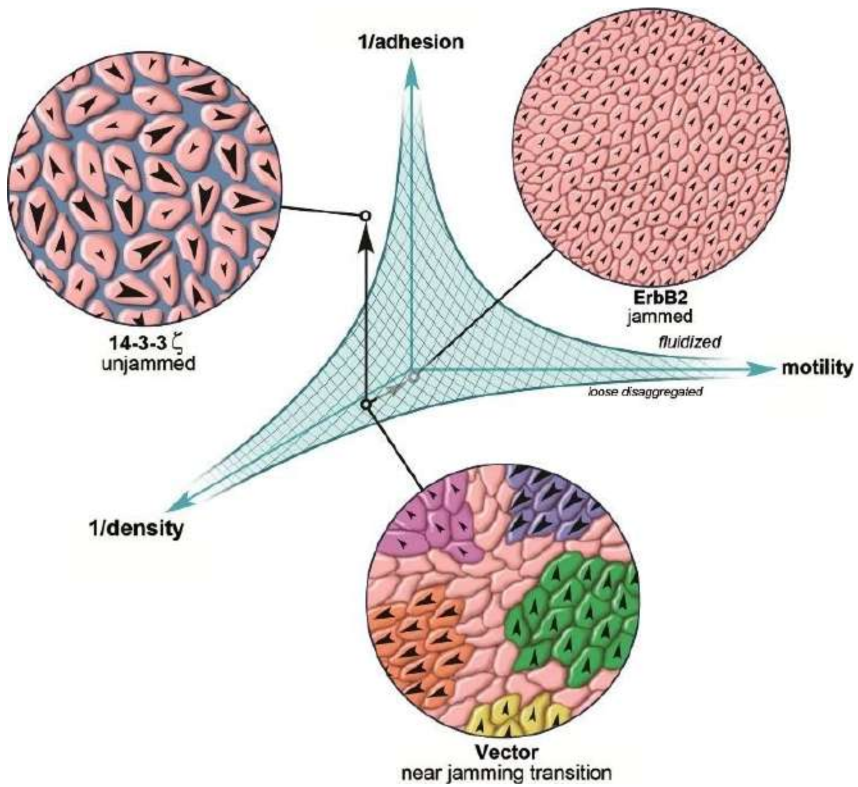
•Tumors often create **unstable regions of high activity** at their periphery, where cells gain protrusive forces and elongate into finger-like structures.

•These peripheral cells **unjam**, breaking the mechanical constraints of the primary tumor and forming **invasive streams**, a hallmark of metastatic potential.

This unjamming is **mechanically driven**, distinct from purely biochemical EMT pathways.

Jumming/unjumming transition

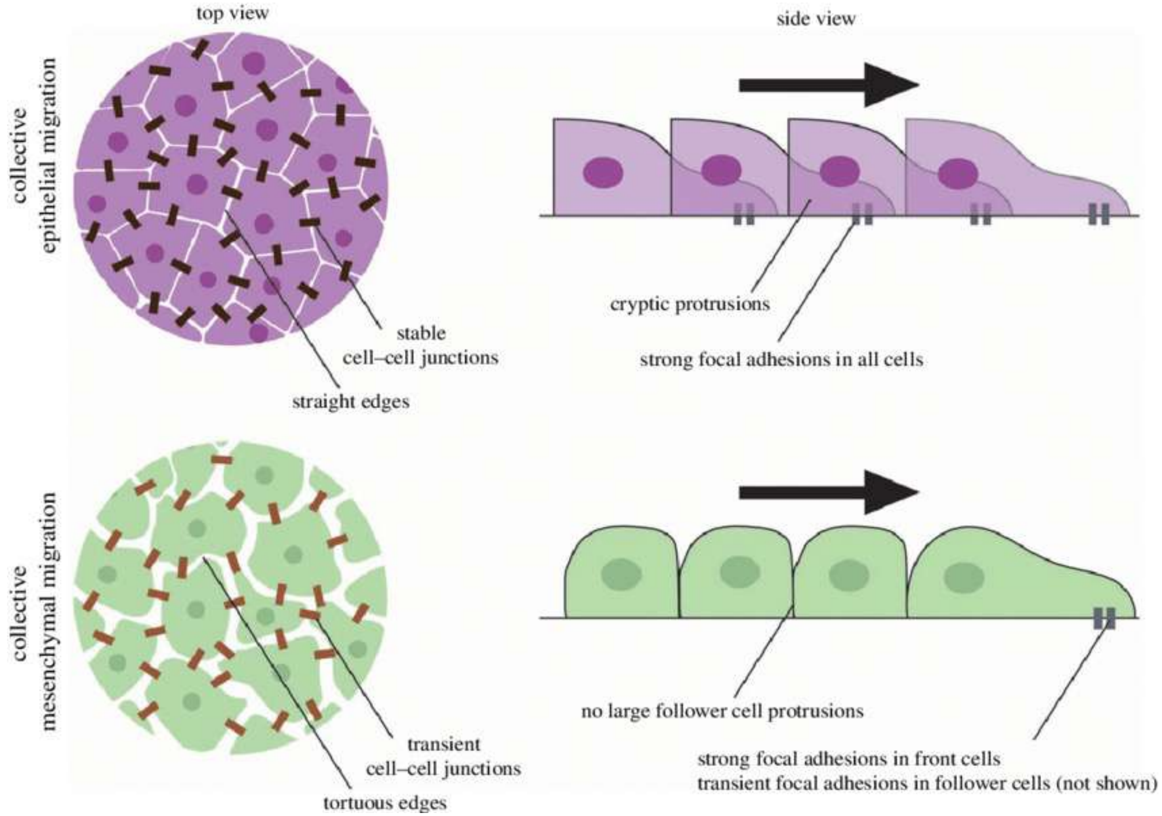
Hypothetical phase diagram of the jamming/unjamming transition. The shaded area represents the jammed state, which is influenced by the density of cells, the motility of cells in the monolayer and the cell-cell adhesion strength.



Jumming/unjumming transition

Collective migration of epithelial cells and mesenchymal cells.

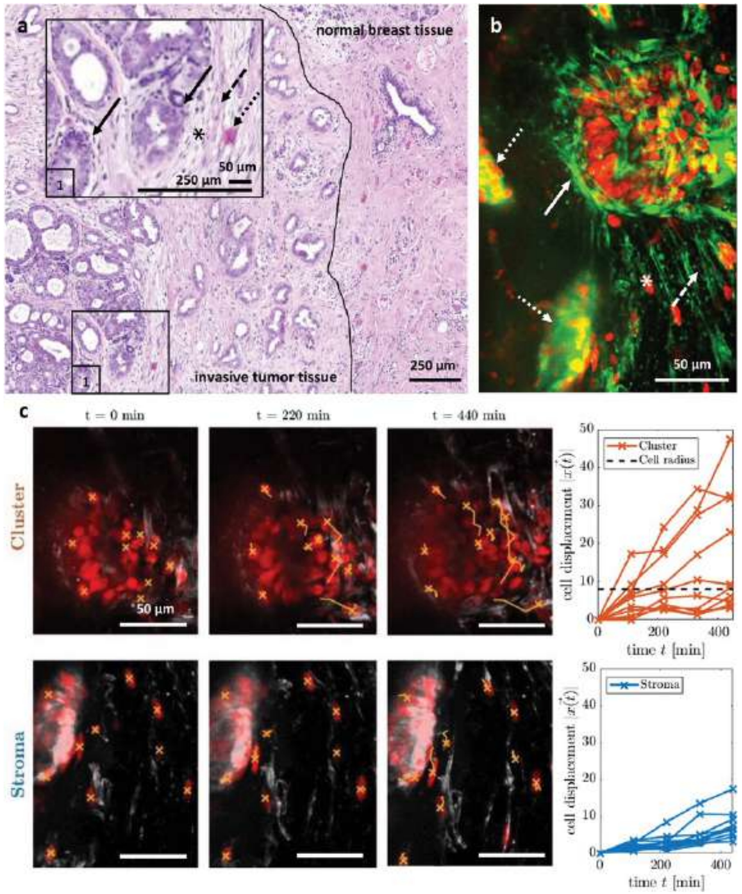
Epithelial migration can arise from an unjamming transition of quiescent epithelial sheets, with packs of collectively migrating cells (purple cells), while maintaining strong intercellular junctions (dark brown rectangles) and epithelial markers, such as E-cadherin. Epithelial migration is also evident in wound healing. Leader cells tend to form large forward-facing protrusions, with follower cells also contributing significant traction forces to move the sheet forward (teal rectangles).



Mesenchymal migration can arise from an epithelial-to-mesenchymal transition, in which cells (green cells) lose apicobasal polarity in favour of front-rear polarity.
Intercellular adhesions become weaker and more transient (light brown rectangles), which is associated with a change in gene expression, such as E-cadherin being replaced by N-cadherin. Whereas leader cells form strong focal adhesions, follower cells do not. The black arrow indicates the direction of migration.

Jumming/unjumming transition

Fluid-like and solid-like behavior in a primary human breast carcinoma. a) representative H&E-stained histological slice showing invasive tumor tissue on the left and normal breast tissue on the right. The insert (1) gives a more detailed view on an area with high cell density, identifying cell clusters (black solid arrows), surrounding stromal tissue (dashed black arrows) with single cells (*), presumably cancer associated fibroblasts (CAFs). The brighter pink color further indicates small blood vessel (dotted black arrow). b) Snapshot (maximum intensity projection) of vital tissue from a different tissue explant from the same tumor shows a cluster of cancer cells (bold white arrow) that is connected via elongated cells (asterisks) to a low-cellular, most likely stromal area (dashed arrows) indicated by fiber-like orientation of the cells green actin signal. Several vessel-like structures are visible in the background of the image volume (white dotted arrow). Manually dissected pieces of the tumor were stained with a vital DNA stain (red SPY650-DNA) and a vital F-actin stain (green, SPY555-Actin). Z-projection of 180 µm (20 image slices) recorded after an experimental runtime of 36 h. c) Vital nucleus tracking showed cells with high motility in the cluster-like region (top row) in contrast to slower single cells in the stroma-like region (bottom row). Tracking of 10 representative cells was done manually in Matlab. Scale bars: 50 µm.



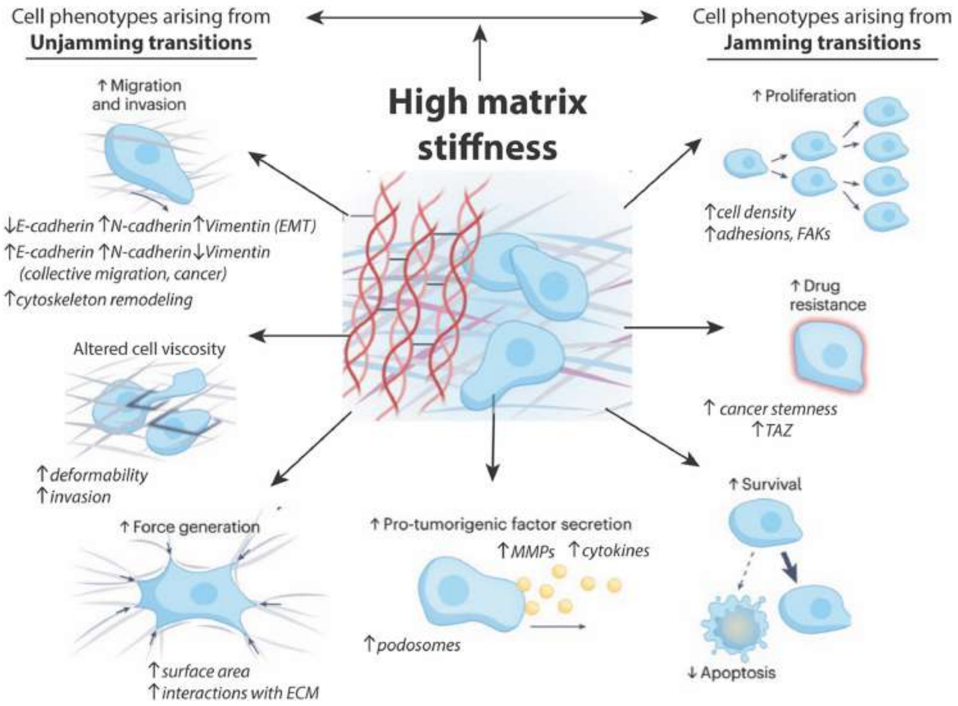
A **jamming transition** is the change from a **fluid-like state**, where cells can easily rearrange, to a **solid-like state** where rearrangements are suppressed.
This concept originates from soft matter physics (foams, grains, emulsions) and has been applied to **epithelial tissues**.

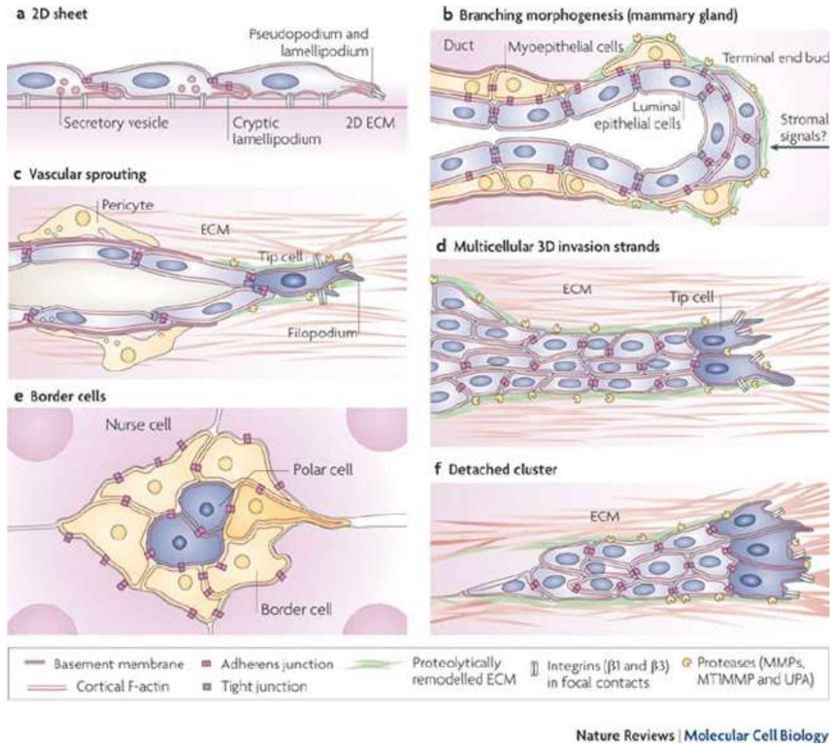
In epithelia:

State	Physical Behavior	Biological Interpretation
Unjammed (fluid-like)	Cells move, rearrange, migrate collectively	Seen in wound healing, development, *and often in invasive tumor fronts*
Jammed (solid-like)	Cells caged by neighbors, minimal motion	Seen in homeostatic epithelia, non-migratory tumors

Tumoral or pre-metastatic tissues often show a shift toward **unjammed, fluid-like dynamics**, associated with:

- elongated cell shapes
- decreased intercellular adhesion or increased traction forces
- higher effective temperature / fluctuations
- collective invasion streams





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A 2D epithelial sheet can be approximated by a **vertex model**, where each cell is a polygon with area A and perimeter P.
Define the **shape index:**
$p = P/\sqrt{A}$

There is a critical value:
$p_c \approx 3.81$

-$p<p_c$ **Jammed / Solid-like**
-$p>p_c$ **Unjammed / Fluid-like**

Tumor regions often show **elongated and anisotropic** cells (higher P), pushing p above the critical line. This index provides a direct geometric–mechanical bridge between **cytoskeletal tension**, **adhesion**, and **collective migratory ability**.

Although biological tissues are active matter (not at thermal equilibrium), one can define an *effective temperature* T_{eff} from velocity fluctuations:

$$T_{\mathrm{eff}} \propto \langle v^2 \rangle$$

Higher T_{eff} → more rearrangements → **unjammed**.

Metastatic fronts often show elevated fluctuations due to:
•actomyosin contractility
•leader cell protrusive forces
•local unjamming waves traveling through the tissue
Cerbino’s work uses light scattering and microrheology to quantify such fluctuations.

Cells treated as **active Brownian particles** with self-propulsion speed v_0 time τ.

A dimensionless activity parameter:
$\alpha = v_0 \tau$

When α exceeds a threshold, the system becomes fluid-like even at high densities.

Metastatic potential correlates with increased α due to enhanced cytoskeletal drive, Rac1 (receptor) activation, or lamellipodial protrusion (themes familiar from Scita’s work).

Mechanical Stress & Yielding Criteria

Stress tensor:
$\sigma ij = \sigma ij_{passive} + \sigma ij_{active}$

Active stress often modeled as:
$\sigma ij_{active} = -\zeta c\ ninj$
where
•c = actomyosin concentration
•n = polarity vector
•ζ= activity coefficient

When active stress exceeds a yield criterion, the tissue unjams:
$|\sigma| > \sigma_{yield}$
Tumor cells often modulate ζ\zetaζ through Rho/ROCK pathways → increased contractility → unjamming fronts.

“Unjamming Waves” and Collective Modes
Mean cell velocity field v(x,t) can show:
•**soliton-like waves**,
•**vortices**,
•**coherent migration**,
•**density waves** near jams.

A simplified continuum equation for active tissues:

$$\partial_t \mathbf{v} = -\frac{1}{\tau_v}\mathbf{v} - \nabla P + \mu \nabla^2 \mathbf{v} + \mathbf{f}_{\text{active}}$$

$$|\mathbf{f}_{\text{active}}| > \frac{1}{\tau_v}|\mathbf{v}|$$

Unjamming condition.

Giavazzo’s modeling often uses such viscous active fluid formulations.

Key empirical findings from recent biophysical oncology:

(A) Metastatic tumors often show Unjamming Rather Than EMT

Many invasive tumors do **not** fully undergo EMT (epithelial-mesenchymal transition).

Instead, they switch to a **fluid-like collective migration mode**:

- elongated, anisotropic cells
- reduced packing density
- coordinated leader–follower chains
- long-range traction forces

This is a **collective unjamming** phenomenon.

(B) Mechanical Heterogeneity Creates “Fluid Pockets”

Border regions can have:

- higher p (shape index)
- higher Teff
- reduced adhesion
- increased active stress

These pockets nucleate migratory streams → early metastatic escape.

Key empirical findings from recent biophysical oncology:

(C) Jamming Protects Inner Tumor Regions

Interior cells often remain:

•round

•tightly packed

•highly constrained

This **jammed core** is mechanically stable and resistant to rearrangements.

Some models treat tumors as **jammed cores with unjammed invasive shells** (an onion-like architecture).

(D) Physical–mathematical picture of metastasis onset

A conceptual inequality summarizing many models:

Invasion occurs when:

$$\alpha + T_{\mathrm{eff}} + \frac{\sigma_{\mathrm{active}}}{\sigma_{\mathrm{yield}}} + (p - p_c) \ > \ \Theta$$

where Θ is an effective *invasion threshold* depending on microenvironmental resistance (ECM, confinement, stroma).

This is not a literal clinical formula—just a compact physical abstraction capturing the essence of **jamming-mediated metastatic transitions**.