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Mechanisms and impact of altered tumour mechanics

Hamid Mohammadi and Erik Sahai*

The physical characteristics of tumours are intricately linked to the tumour phenotype and difficulties during treatment. Many factors contribute to the increased stiffness of tumours; from increased matrix deposition, matrix remodelling by forces from cancer cells and stromal fibroblasts, matrix crosslinking, increased cellularity, and the build-up of both solid and interstitial pressure. Increased stiffness then feeds back to increase tumour invasiveness and reduce therapy efficacy. Increased understanding of this interplay is offering new therapeutic avenues.

The mechanical properties of tissues can vary widely[1]. Brain and adipose tissue are soft with elastic moduli around 100 Pa and, at the other end of the spectrum, bone is very stiff with a modulus of over 100 kPa[2–4]. These mechanical features can enable tissue function, as is the case in bones, and can also more subtly modulate tissue function through their effects on cell behaviour[5]. In conditions of tissue homeostasis, the mechanical properties of a tissue are mostly invariant, but this can change in pathological contexts. Tumours are typically stiffer than the surrounding healthy tissues[6,7], a property that is used for clinical diagnosis; most simply by tissue palpation[8], but also using X-ray and ultrasound techniques[9,10]. Many factors can promote the development of a stiff, fibrotic microenvironment in tumours, including changes in the constituents of the cellular and extra-cellular matrix (ECM) of the tumour and disrupted interstitial fluid balance. These changes can, in turn, promote numerous cellular functions that promote tumour progression and metastasis. Accordingly, targeting tumour stiffening is an emerging approach for therapeutic intervention. Here, we first discuss the causes of the altered tumour stiffness and subsequently the effects of these alterations on tumour and stromal cell functions. Lastly, we discuss tumour mechanics as a therapeutic target.

Why are tumours stiffer than healthy tissues?

Changes in tissue mechanics have been intensively studied in breast cancer, because altered tissue stiffness and matrix density are key to its detection, either by palpation or mammographic density screening. Furthermore, increased breast density is a risk factor for the development of the disease. Normal breast tissue has an elastic modulus in the range 500–1,000 Pa, but this increases to more than 1,000 Pa in most breast tumours. Similar increases are common in other solid tumours, including pancreatic ductal adenocarcinoma (PDAC) and colorectal carcinoma[11]. ECM stiffening typically occurs over a period of months to years and involves a complex interplay of several different processes. One major cause of stiffening is the disrupted balance between the deposition of ECM and its degradation leading towards an increased quantity of matrix proteins in the tumour microenvironment[12] (Fig. 1). Many factors within the tumour environment, including hypoxia and TGF-β, promote the overproduction of ECM components, including fibrillar collagens, fibronectin isoforms, TNC, OPN, SPARC and POSTN in tumours[13,14]. Matrix metalloproteinases (MMPs), which degrade ECM, are also upregulated, however, the overall balance of synthesis and degradation typically remains in favour of a net increase in ECM.

The mechanical properties of the ECM are complex. Although there are relationships between the level of certain ECM components and matrix stiffness[15], the mechanical properties of the ECM are not simply determined by the abundance of ECM components (Figs 2 and 3). In particular, ECM fibre crosslinking can modulate whether it behaves in an elastic or plastic manner (Box 1); that is, whether it returns to its original form once the applied force is relaxed (elastic) or remains deformed (plastic). The balance between elastic and plastic deformation also depends on the amount of force that is applied. Crosslinks have a profound effect on the mechanical properties of the ECM. Covalent inter-fibre bonds prevent monomers and fibres from sliding relative to one another when the ECM is subjected to external load, leading to markedly reduced plastic behaviour of the ECM (Fig. 2b). Furthermore, crosslinking increases the resistance of the ECM to applied force, which is manifested as an increased elastic modulus of the ECM (Box 1 and Fig. 2b). Both TGF-β and hypoxia upregulate the lysyl oxidase (LOX) family of enzymes that mediate crosslinking of the ECM, in particular of fibrillar collagens[16–18]. Increased crosslinking can also be driven by increased transglutaminase 2 levels[19,20].

An additional complexity is that the resistance of crosslinked ECM increases with increasing matrix deformation, a process called strain stiffening[21]. This is particularly relevant when the ECM undergoes cell-induced deformation (Box 1) as a result of forces exerted by both cancer and stromal cells (Figs 1 and 2). Cancer-associated fibroblasts (CAFs) can exert considerable ROCK-dependent actomyosin-generated force on the ECM through integrin-mediated adhesions[22]. The strain stiffening of collagen means that the tensile forces that are generated by actomyosin contractility in the tumour microenvironment contribute to increase ECM stiffness[23,24]. Pancreatic cancer cells can also stiffen their surrounding ECM through FAK- and ROCK-dependent contractility[25–27]. Similarly, cell-induced compression of the matrix can lead to increased matrix stiffness[28]. In contrast to the production of LOX enzymes, the contractility of CAFs is reduced under hypoxic conditions[29].

Non-crosslinked collagen and many other biological polymers exhibit both elastic and plastic behaviours when subjected to cell-induced deformation forces. The amount of plastic deformation is determined by the rate and magnitude of the matrix deformation[30]. Slow rates of force-mediated collagen remodelling can lead to permanent alignment of collagen fibres, which is linked to worse cancer outcomes, particularly if fibres are oriented perpendicular to the tumour margin[31]. Proteolytic cleavage, for example by MMP14 (MT1-MMP), can reduce matrix stiffness and indirectly counteract the effect of crosslinking[32]. Over long time scales, it is probable that cycles of proteolytic degradation, new synthesis and crosslinking enable the permanent remodelling of matrices that have mostly elastic properties when they are subjected to short-lived forces.

Francis Crick Institute, London, UK. *e-mail: erik.sahai@crick.ac.uk

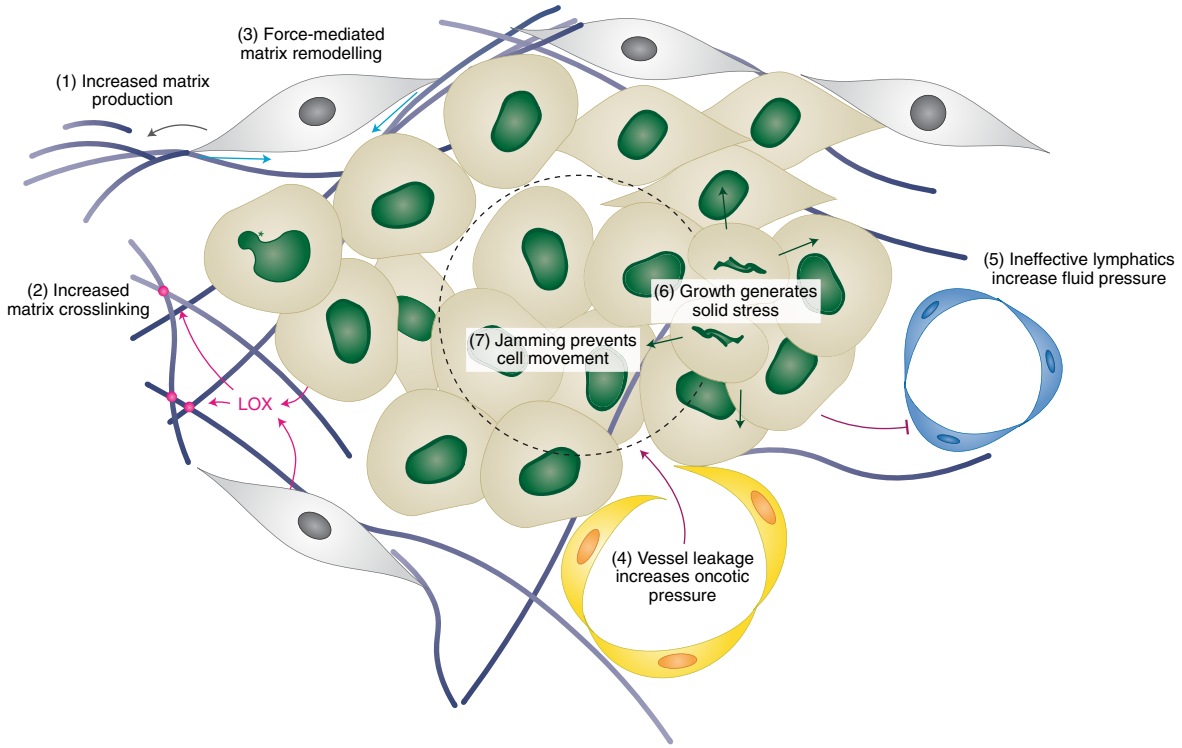

Fig. 1 | Schematic view of mechanobiology in tumours. Cancer cells are in light green with green nuclei, stromal fibroblasts in grey, endothelial cells in yellow (blood) and blue (lymphatic), and ECM in dark blue. The diverse sources of altered tissue mechanics in tumours are shown: (1) increased matrix deposition; (2) increased matrix crosslinking (indicated by pink dots); (3) contractile force driving local compaction and distant ECM stretching (light blue arrows); (4) leakage from blood vessels increasing both oncotic and fluid pressure (purple arrow); (5) defective lymphatic drainage; (6) cell growth generating solid pressure (green arrows); (7) high cell densities leading to cell jamming.

Deregulated growth and the resulting increased cell density can contribute to tumour stiffening (Fig. 1). If the cells have a higher elastic modulus than the surrounding matrix, then the simple process of increasing cellularity will lead to an overall gain in tissue stiffness. The elastic modulus of cancer cells ranges from a few hundred Pa to several kPa, which is above that of some normal tissues and in a similar range to many tumour tissues[33]. Cell stiffness can be modulated through cell-intrinsic mechanisms. Actomyosin contractility can modulate cell stiffness in at least two ways—by pulling on the plasma membrane and thus increasing hydrostatic pressure (discussed in more detail below) or by generating tensile stress on F-actin fibres, which leads to stiffening of the network[34,35]. It should be noted that cells do not only exhibit elastic properties, but also more viscous behaviours over longer time scales, leading to a behaviour called viscoelastic. Numerous studies have shown how the actin cytoskeleton positively influences the viscoelastic properties of cells[36–38]. Notably, cancer cell lines measured in two-dimensional cultures frequently have a lower elastic modulus than their non-transformed counterparts; in these circumstances, increased cellularity may not be an important factor for the increase in tumour stiffness[39,40]. A reduced elastic modulus of cells may even promote invasion in the context of ovarian cancer[41], possibly by enabling cells to squeeze through small gaps.

The bulk mechanical properties of tumour cell aggregates may additionally be determined by cell 'jamming', which is an emergent property of multicellular systems. This phenomenon occurs when objects, such as cells, are densely packed in a way that does not allow their movement relative to one another in response to the application of force[42]. In cell systems, this typically occurs when cells have pentagonal or hexagonal shapes[43]. Changes in the shape of the cells and Rab5 dynamics can promote 'unjamming', that is, the transition to a fluid-like state and the dissipation of applied force[44]. Accordingly, cell jamming may partly explain the apparent paradox of stiff tumours with constituent cells that are softer than their non-transformed counterparts, but this remains to be tested rigorously.

Tumour stiffening may also arise from increased pressure within the tumour. Tumour pressure has two components, solid pressure and interstitial fluid pressure, and both contribute to the tumour stiffening[45]. Solid pressure is a result of an increased quantity of the solid phase of tumours, including tumour cells and ECM. This is mostly driven by the uptake of soluble nutrients by tumour cells and their conversion into insoluble biomass. In addition, it can be enhanced by the absorption of water into extracellular proteins, such as proteoglycans. For example, changes in hyaluronan in particular, have been implicated in the altered mechanical properties of PDAC[46]. The expansion of biomass is resisted by the surrounding tissue leading to increased compressive stress in the interior of the tumour. The stiffening of the surrounding ECM (outlined above) further accentuates the increase in pressure. Notably, the mechanical stress within the tumour is non-uniformly distributed with a pressure rise towards the centre[47,48]. This stored compressive stress is perhaps most clearly demonstrated by the swelling of the tumour interior after cutting through an excised tumour[49].

In addition, the interstitial fluid in tumours has an associated pressure[50]. Blood pressure causes both liquid and solutes to leave small vessels and enter the interstitial space. This is effectively drained by the lymphatic system in normal tissue, whereas in tumours, the lymphatic system is frequently disrupted, leading to a higher hydrostatic interstitial pressure. The solid pressure of the tumour also affects the fluid pressure in the tumour by imposing compressive stress on blood and lymphatic vessels, which leads to perturbation of the balance of fluid entry and exit[51]. There is a second source of fluid pressure: in normal physiology, colloid oncotic pressure (Box 1) arising from serum proteins helps water

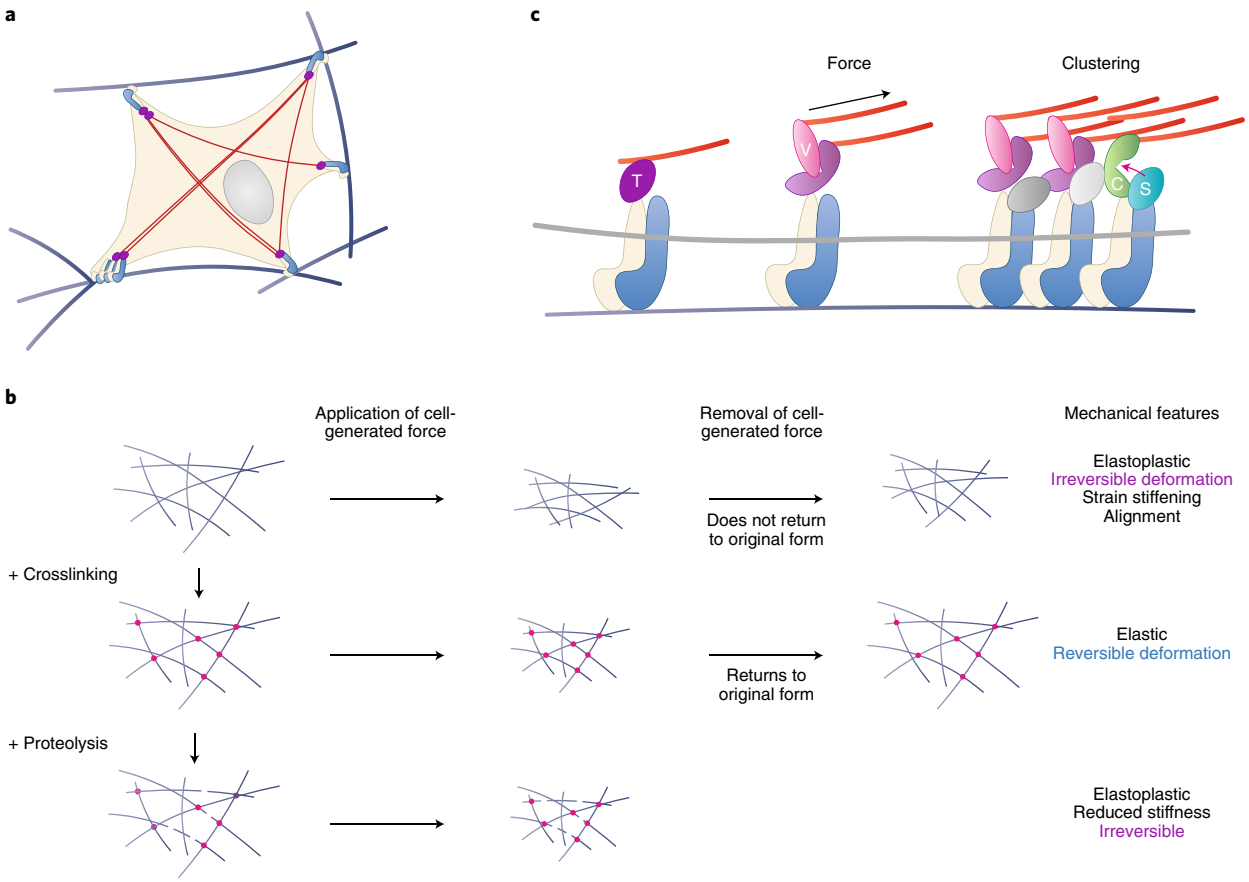

Fig. 2 | Schematic view of cell-mediated matrix remodelling. a, A cell exerts contractile force on matrix fibres (contractile fibres in red and matrix in dark-blue lines). **b**, The interconnectivity of different mechanisms of matrix remodelling and their consequences for the mechanical properties of the ECM is shown (pink dots indicate matrix crosslinking). **c**, Schematic view of a matrix adhesion coupled to F-actin (red) with integrins (blue and light grey) spanning the plasma membrane (grey line) to contact the matrix (dark-blue line). The application of force to nascent adhesions (grey arrow) leads to talin (T; in purple) unfolding and subsequent vinculin (V) binding. This allows linkage to an additional actin filament. Further mechanisms promote clustering of integrin-mediated adhesions and the generation of a 'signalling hub' with further force-mediated unfolding of p130Cas (C; in dark green) and its phosphorylation by Src (S).

to move into capillaries, but the leakage of plasma proteins from disrupted vessels into the tumours reverses this to increased fluid pressure. The imbalance in fluid pressure is perhaps most notably evident when patients with malignant disease in the peritoneal cavity develop ascites. This is particularly common in ovarian cancer. In contrast to solid pressure, fluid pressure exhibits little variation across the tumour interior[52]. Physical remodelling of interstitial ECM mediated by contractile tumour cells and CAFs may lead to fluid extrusion, further illustrating the interconnections between the different drivers of increased tumour stiffness.

What are the consequences of tumour stiffening?

The abnormal mechanical properties of the tumour microenvironment are not simply passive indicators of the development of a tumour, but actively influence the behaviour of both tumour and stromal cells throughout tumour progression[53]. Tumour cells can sense and respond to the mechanical properties of their surrounding microenvironment through specialized ECM receptors, primarily the integrin family of receptors[54]. These membrane-spanning dimers bind to the ECM outside the cell and are coupled to the F-actin cytoskeleton in the cell interior. The interaction between the highly dynamic cytoskeleton and integrins enables differences in the mechanical environment to be transduced into altered cell signalling. The application of tensile forces that result from either actin polymerization dynamics or actomyosin contractility on proteins that link integrins to the actin network, such as talin and vinculin, leads to their partial unfolding if the underlying substrate is stiff[55,56]. If it is soft, the substrate deforms before conformational changes in the proteins that link integrins to F-actin occur (Fig. 2c). The conformational changes on stiff substrates alter either the range of proteins that bind to talin or vinculin or the phosphorylation state of p130Cas by Src-family kinases to modulate signalling networks[57]. The threshold at which the applied force modulates protein conformation can be tuned by the strength and characteristics of integrin–substrate binding[58]. This provides a mechanism for different integrins to sense different ranges of substrate stiffness[58]. The conformation of the actin crosslinking protein filamin is also modified by the application of force, leading to further modulation of RAC1 activity and actin dynamics[59,60]. Such local feedback on the actin cytoskeleton can mediate cell stiffening. On stiff two-dimensional substrates, the end result of these processes is often the increased assembly of micrometre-scale focal adhesions that act as 'signalling hubs' that contain high concentrations of protein kinases and adaptor molecules, such as p130Cas and paxillin (Fig. 2c). Focal adhesions regulate the activation of Src-family kinases, FAK, RHO-family GTPases, ERK (also known as MAP kinase), and inhibition of the tumour suppressor PTEN[61,62]. The situation in complex three-dimensional environments is less well-described, but recent studies have provided evidence of integrin clusters and ample genetic evidence supports their role in

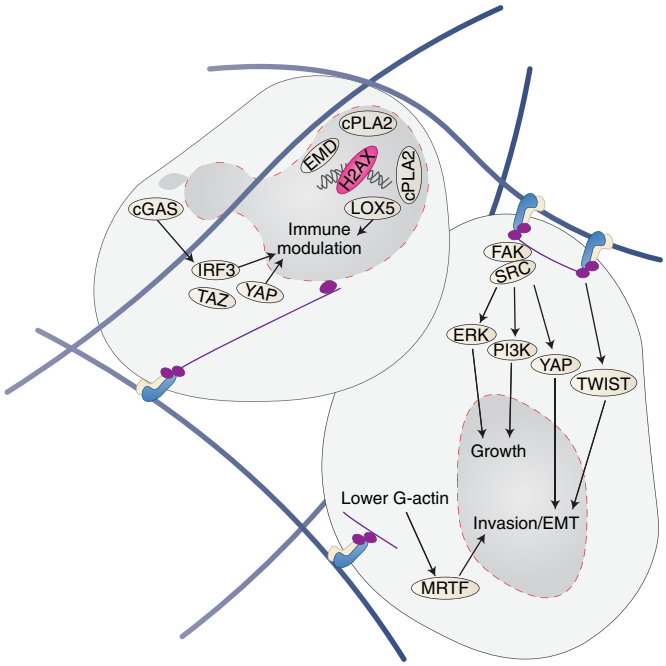

Fig. 3 | Mechanisms of mechanotransduction. The different ways in which the altered mechanical environment in tumours can affect tumour cells. Left, a cell illustrating how mechanical forces, both compressive and tensile, can affect the nucleus causing DNA damage, leakage of DNA into the cytoplasm, and altered nuclear import. Darker grey represents DNA, lighter grey represents cytoplasm, dotted red line represents the nuclear envelope, actin cables shown in purple, matrix fibres shown as dark blue lines, and integrins illustrated as in Fig. 2. Right, illustration of a cell to show integrins link to changes in cell signalling, transcription, cell growth and invasion.

transducing mechanical cues[63]. As might be expected, these changes alter a multitude of cellular proteins and processes, including transcription regulators and factors. Of particular note, stiff underlying substrates promote integrin- and F-actin-dependent activation of the transcription regulators YAP1 and TAZ (also knwon as WWTR1)[64]. This, in turn, promotes the expression of pro-proliferative and pro-migratory genes[65]. Furthermore. stiff substrates reduce the association of TWIST1 with G3BP2, promoting the activation of an epithelial to mesenchymal transition (EMT)[66]. Adhesion to stiff substrates also alters the relative levels of F-actin to G-actin. The reduced levels of G-actin releases MKL family transcriptional regulators (also known as MRTFs) MKL1 from sequestration, enabling it to increase the SRF-dependent expression of pro-proliferative and migratory genes[67,68]. The activation of YAP1 and MKL proteins is not restricted to tumour cells. Increased matrix stiffness contributes to the YAP1-induced activation and maintenance of CAFs. In this setting, the cytoskeleton does not directly regulate LATS-mediated phosphorylation of YAP1, instead actomyosin contractility suppresses the nuclear export of YAP1 and promotes its Src-dependent phosphorylation[23,69]. Downstream transcriptional targets of YAP1 and SRF include the ECM proteins CTGF and CYR61, and pro-contractile cytoskeleton components[70]. This generates a positive feedback loop that reinforces matrix stiffening and can confer the memory of exposure to stiff substrates[71]. The altered ECM in tumours also affects cell signalling through its retention of various growth factors, including TGFβ. Increased contractile forces in tumours then release the active form of TGF-β from its latent binding peptide, providing yet more positive feedback[72].

In addition to changes in ECM stiffness, tumours can experience considerable compressive stress, the net result of which is usually cell-cycle arrest. Accordingly, the smooth transition from compressive stress at the tumour interior to tensile stress at the tumour periphery leads to heterogeneous proliferation rates across the tumour[73]. The molecular mechanisms for responding to compressive stress are less well-understood than those involved in tension sensing. Changes in membrane topology that are associated with compression can regulate ion channels. Indeed, the stretch-activated ion channel PIEZO is active in MCF7 breast cancer cells[74] and is likely to trigger downstream calcium signalling[75]. TRP-family ion channels are also extensively implicated in cancer biology[76]; however, more work is needed to determine their level of involvement in responding to mechanical stresses on the plasma membrane.

Box 1 | Mechanobiology concepts

Colloid oncotic pressure is generated by proteins in the blood, notably albumin, and interstitial fluids generate a form of osmotic pressure that regulates the water balance.

Cell-induced ECM deformation is reorganization of the ECM network by application of cell-generated forces. This can lead to tensile forces pulling on the ECM and promoting the alignment of ECM fibres. It can also lead to compaction: the pushing force generated by the cells that compact the ECM proximal to the cell[28].

Elastic materials return to their original shape after the external load is removed.

Jamming transition is a material phase transition in a confluent cell population that is induced by increased cell density in a confined microenvironment, leading to dynamical arrest of the cells.

Plastic materials undergo irreversible deformation and only partially recover after removal of external load. This precludes substantial resistance of the material to deformation force. Elastoplasticity describes materials that exhibit both elastic and plastic characteristics when they are subjected to external load.

Stiffness is the extent of resistance of the tumour to deformation by applied forces and is measured as various moduli including Young's, shear and bulk, which apply to different types of deformation.

Strain is the extent of deformation, usually the change in length divided by the original length.

Tensile means related to stretching, this contrasts with **compressive**.

Strain stiffening is an example of **nonlinear elasticity** in which the resistance of the material to applied force increases with the amplitude of deformation.

Stress is the force applied per unit area.

Tumour fluid pressure is the pressure that results from the liquid phase of the tumour, mainly the interstitial fluid that surrounds cells. Fluid pressure has both hydrostatic and osmotic components.

Tumour solid pressure is the pressure that results from the solid state of the tumour, including ECM, cancer and stroma cells.

Viscoelasticity describes materials for which the resistance depends on time and rate of the application of deformation force. Unlike elastic materials that recover their original shape immediately after the external load is removed, the viscoelastic materials may exhibit a delayed response until they fully recover.

Several lines of evidence are also pointing to the nucleus as a sensor of mechanical forces. Deformation of the nucleus that is triggered by either tensile or compressive stress has been reported to alter nuclear pore complexes[77]. This leads to a reduction in the energy requirement to unfold certain protein domains as they move into the nucleus. In particular, the barrier to the movement of YAP1 through the nuclear pore is reduced by the transmission of forces exerted on stiff substrates to the nuclear envelope through the actin cytoskeleton and LINC complex[77,78]. Furthermore, application of force through LINC proteins can stiffen isolated nuclei; this depends on Src-mediated phosphorylation of the nuclear envelope-associated protein EMD (also known as emerin)[79]. Finally, compressive stress can lead to cell stiffening in normal brain tissue and glioma models, and this may involve the nucleus as a mechanoresponsive organelle[80]. Expansion of the nucleus after osmotic perturbation leads to the recruitment of the enzyme cPLA2 to the inner nuclear membrane. This, in turn, promotes LOX5-dependent generation of pro-inflammatory eicanosoids[81]. Severe nuclear deformation can result in local breakdown of envelope function and DNA entering the cytoplasm, which can trigger innate damage-sensing pathways, such as cGAS–STING, and promote the expression of immune-modulating genes including interferons[82]. Together with recent findings that YAP1 regulates T-cell responses[83], it appears that the altered expression of inflammatory and immune modulators is an emerging theme in the response of cells to the physical deformation of the nucleus.

As described above, the prevailing view is that stiffer substrates always promote more aggressive tumour phenotypes. However, there are some examples that show that this may not hold. In ovarian cancer, it has been shown that cells are more invasive and chemotherapy resistant on 2.8 kPa substrates compared to 35 kPa substrates[84]. An inversion between phenotype and substrate stiffness has also been observed if cells are completely surrounded by engineered matrix[85]. If the high stiffness of the surrounding environment prevents cells from generating a space to extend protrusions, then mechanosignalling, and invasion are likely to be reduced. These studies highlight that although two-dimensional substrates are widely used because of their convenience, they may not accurately reproduce cell behaviour in three-dimensional contexts[86]. Furthermore, it is important not to view stiffness as a simple variable, but to consider differences between uniform hydrogels and fibrillar networks that may contain very stiff fibres but have a relatively low bulk modulus.

The migratory behaviour of tumour cells is a key determinant of metastasis, which is closely linked to patient mortality. The mechanical properties of the tumour microenvironment can also have a marked influence on the state of tumour cells, and therefore the migratory potential of these cells. Tumour stiffening that arises from ECM crosslinking and excessive deposition of the ECM can promote the activity of TWIST1, which in turn induces EMT[66]. The transition to a mesenchymal state is characterized by increased migratory behaviour of individual cells that results from decreased intercellular adhesions, particularly downregulation of E-cadherin expression[87,88].However, given the multitude

The structural properties of the matrix, such as alignment and porosity have a strong effect on the propensity for and patterns of cancer invasion as well as angiogenesis[89–91]. The alignment of the matrix fibres perpendicular to the tumour periphery facilitates the persistent and rapid migration of the cells away from the tumour[92]. Force-mediated matrix remodelling can locally increase the pore size of the ECM by concentrating smaller fibres into larger bundles. This promotes the generation of permissive routes through the ECM for cancer cell invasion[22]. Cell invasion can then proceed independently of matrix degradation and remodelling in regions in which the pore size of the matrix is larger than the dimensions of the nucleus[90]. This mode of migration is termed amoeboid and has a low dependency on integrins, but a high dependency on actomyosin contractility. It has been proposed that traction stress is mediated by friction during amoeboid migration[93]. Alternatively, the inter-digitation of lateral protrusions into gaps in the matrix may also enable traction[94]. When cells migrate through narrow pores, they can use the nucleus as a piston to generate increased hydrostatic pressure at the front of the cell and promote its forward motion[95]. This form of migration, termed lobopodial, requires integrins and is preferred by ECM with elastic properties[96] (the various modes of cell migration in three-dimensional environments have been reviewed previously[89]).

The collective migratory behaviour of tumour cells is also influenced by biophysical interactions with stromal cells and the ECM. Mechanical coupling of epithelial cancer cells to stromal fibroblasts through heterotypic adherens junctions promotes collective invasion[97]. Furthermore, stiffness heterogeneity and anisotropy in the tumour microenvironment as a result of abnormal ECM crosslinking and deposition may guide the directional migration of the tumour cells[31]. Stiffness gradients in the ECM can direct the collective migration of the tumour cells from softer to stiffer regions, a process called durotaxis[98]. Whereas the in vitro evidence for durotaxis is indisputable, in vivo analysis remains hampered by a lack of methods that enable the simultaneously determination of tissue stiffness and monitoring of cell migration in living tissue. Collective migration also requires that densely packed cells transition from a jammed to an unjammed state, and it is interesting to note that the more-elongated cell shapes associated with EMT have a lower theoretical likelihood of jamming[99].

Increased genomic instability is likely to promote the emergence of more aggressive cancer cell genotypes. As outlined above, the spread of invasive tumour cells involves cell migration into constricted spaces within the tumour microenvironment, which is under compressive pressure. The mechanical constraints imposed by the surrounding microenvironment on the cell body are transmitted to the nuclear envelope either through the cytoskeleton network or simply by compressive stress. In both cases, this can lead to nuclear envelope rupture and permit unrestricted mixture of content between the cytoplasm and the nucleus[100]. The shear stress on DNA that result from extrusion out of the nucleus contributes to increased γH2AX foci, which indicate DNA damage, in particular double-strand breaks that are capable of leading to large-scale genomic alterations[101]. This damage is exacerbated by the depletion of DNA-repair factors, such as Ku70/80, as a result of damage to the nuclear envelope. Genomic analysis of cancer cells following repeated cycles of migration through small rigid pores reveals frequently chromosomal copy-number changes[102,103]. Accordingly, the mechanical properties of the nuclear envelope have an important role in maintaining nucleus integrity under external load. Even in the absence of migration through pores, increased actomyosin contractility can lead to nuclear envelope rupture, γH2AX foci, and chromosomal alterations on rigid substrates[104,105]. Furthermore, tumour cells with lower expression of lamin A/C, key components of the nuclear lamina, have relatively soft nuclei and are more prone to nuclear envelope rupture and DNA damage[106–108]. Following physical rupture, the nuclear envelope can be repaired by the ESCRT III complex and this limits the extent of DNA damage and cell death[82].

Exploiting altered tumour mechanics in cancer therapy

The dense ECM network of solid tumours with high internal pressure may impede the transport of therapeutic agents within the tumour tissue. Delivery of therapeutic agents into the tumour is mainly mediated by the tumour vasculature network. Both the aberrant blood flow in tumour vasculature and the high interstitial pressure hinder the effective distribution of drugs within tumours[109]. Further, elevation of interstitial fluid pressure within the tumour may decrease or even invert the pressure gradient from blood vessels to the interstitium, which is essential for convective delivery of the drugs. This problem is thought to be particularly pronounced in PDAC, which typically has high levels of dense ECM and low vascularization[46]. In preclinical models, targeting highly contractile

Table 1 | Summary of clinical trial activity targeting tumour 'mechanobiology'

Target	Name	Drug/biological agent	Mechanism	Current status
Integrin $\alpha_V\beta_3$	Cilengitide	Ligand mimetic	Integrin binding	Clinical trials stopped due to lack of efficacy
Integrin $\alpha_V\beta_6$	GSK2634673F and BG00011	Ligand mimetic	Integrin binding	Preclinical and fibrosis trials
FAK	Defactinib (VS-6063, PF-04554878)	Small molecule	Downstream of integrin signalling	Clinical trials ongoing
Abl and Src kinases	Dasatinib	Small molecule	Downstream of integrin signalling	Clinical trials ongoing, some reported lack of efficacy
Hedgehog	IPI-926 (saridegib) and vismodegib	Small molecule	Reduces CAF activation	Clinical trials ongoing, some reported lack of efficacy
ROCK	AT13148	Small molecule	Contractility	Phase I clinical trial completed
LOXL2	Simtuzumab (GS 6624)	Blocking antibody	Anti-crosslinking	Preclinical and fibrosis trials
CTGF	FG-3019	Blocking antibody	Blocks receptor binding[a]	Early phase clinical trials ongoing
Hyaluronidase	PEGPH20	PEGylated enzyme	ECM degradation	Clinical trials ongoing

List of agents in the process of clinical testing that interfere with either the mechanical properties of tissue or signalling responsive to changes in tissue mechanics. [a]CTGF has many binding partners and it is unclear which are most critical for its pro-tumorigenic role. Information obtained from https://clinicaltrials.gov/.

CAFs through blockade of hedgehog signalling promoted the intratumoral concentration of gemcitabine[110]. Similarly, targeting contractility directly using a ROCK inhibitor leads to better tumour control[111]. In some cases, ECM density may be increased by cancer therapies. For example, BRAF inhibitors used in the treatment of melanoma can activate stromal fibroblasts and promote their matrix remodelling capabilities. This has the undesirable consequence of promoting integrin-dependent prosurvival and growth signals in the melanoma cells thus undermining the efficacy of the treatment[112]. Notably, the chemotherapeutic drug cisplatin binds directly to collagen-rich ECM[113], but it is not clear whether this might diminish the efficacy of the drug.

Given that the stiffening of the tumour microenvironment contributes to tumour growth and metastasis, preventing or reversing tumour stiffening is a possible approach for therapeutic intervention (Table 1). However, the complex and multifactorial changes in tumour mechanobiology make it difficult to predict whether targeting a single protein or process will be sufficient to revert a complex pathological system. Targeting matrix crosslinking, a major contributor to tumour stiffening, through inhibition of LOX or related LOXL family members has been investigated in some depth. In preclinical breast cancer models, inhibition of LOX family enzymes using β-aminopropionitrile (often abbreviated to BAPN) or blocking antibodies, has been shown to reduce tumour growth and metastasis[16]. Blockade of LOX, LOXL2 and LOXL4 in mouse models of pancreatic, breast and gastric tumours, respectively, has been associated with improved pathological outcomes[114–116]. However, LOX enzymes may also suppress tumour growth, for example, by inhibition of EGFR signalling as a result of association with the HTRA protease or modulation of HRAS signalling[117,118]. Despite promise in preclinical models, clinical trials testing LOXL2 inhibition have so far been disappointing[119]. This may reflect an inability to achieve doses that are high enough to sufficiently reduce ECM stiffness in patients, difficulties in measuring suitable metastatic endpoints, or the fact that other factors besides crosslinking, such as actomyosin contractility, might need to be blocked concurrently with crosslinking.

As documented above, contractile force can lead to matrix stiffening and also increase tumour pressure. Reversing these changes is therefore an appealing target; however, actomyosin contractility has a key role in many physiological processes besides ECM stiffening, including control of blood pressure. Indeed, ROCK inhibitors trigger vasodilation and are clinically used to control vasospasm[120] and can improve the control of PDAC in preclinical models[111]; however, they have not been found to have a role in oncology as yet[121].

More specific strategies have been developed that either target CAFs, which are major contributors to actomyosin force generation in tumours, or ECM molecules linked to contractility phenotypes. An early hope for targeting CAFs in PDAC centred on preventing their activation by hedgehog signalling[110]. In preclinical models, saridegib, which blocks hedgehog signalling, enhanced the efficacy of conventional chemotherapy, but sadly the subsequent clinical trials did not show positive results[48]. This may be because CAFs also have tumour-suppressing activities[122,123], but the molecular details of CAF-mediated tumour suppression remain unclear. A potentially more specific approach involves targeting of the ECM component CTGF, which is upregulated as a result of increased mechanical tension. A monoclonal antibody that targets CTGF is effective in preclinical PDAC models and is currently in phase II clinical trials[124]. It is also probable that many broad or 'dirty' RTK inhibitors that block PDGFR and FGFR function will modulate CAF biology, but they have not yet been linked to altered mechanobiology in vivo.

Targeting the mechanosensing mechanisms by which cancer and stroma cells sense the stiffening of the tumour microenvironment may also serve as an alternative approach for anti-tumorigenic therapies. Targeting of integrins has been explored in two main ways: the use of ligand mimetic peptides and function-blocking antibodies. Given that integrins have key roles in normal physiology, the challenge is identifying strategies with a sufficient 'therapeutic window'. Most attention has focussed on targeting either integrin $\alpha_V\beta_3$ or $\alpha_V\beta_6$ heterodimers as these show clear upregulation in tumours[125]. A cyclic peptide that targets α_V integrins, cilengitide, is well-tolerated but has not shown clear efficacy in phase III clinical trials[126], and $\alpha_V\beta_6$-targeting antibodies are at an earlier stage of development[127]. Inhibition of signalling pathways that are downstream of integrin complexes, such as Src-family kinases and FAK, is also being actively pursued[128]. However, it is difficult to determine whether these compounds are blocking 'mechanosignalling', or growth-factor signalling, which they also participate in.

High internal solid and fluid pressures of the tumour microenvironment mostly contribute to restricted drug delivery to the tumour cells[129]. Accordingly, therapeutic strategies that target the sources of either high solid or high fluid pressure on the tumour vasculature, the major route for drug access, may profoundly improve the drug delivery at the tumour site[45]. For example, the use of the hormone relaxin reduced ECM density, as assessed by second harmonic generation imaging of fibrillar collagen, and increased drug delivery[130,131]. Similar results were also achieved with bacterial collagenase and MMP1 and MMP8 activation[132]. Targeting of hyaluronan

using a PEGylated enzyme reduces pressure and increasing lifespan in murine pancreatic cancer models, although it remains controversial whether this reduces solid or interstitial fluid pressure[46,133]. Many of the strategies that target contractility and/or CAFs may also modulate tumour pressure; for example, ROCK inhibition promotes the efficacy of chemotherapy in pancreatic cancer models[111]. This is consistent with the efficacy of saridegib in preclinical PDAC models being attributed to increased drug delivery. It has also been proposed that appropriate use of anti-angiogenic therapies to 'normalize' the vascular network and function in tumours will enhance drug delivery and provide therapeutic benefit[134,135]. This can be achieved in preclinical models by genetically modulating the levels of PHD2, but achieving this clinically is difficult[136]. Anti-angiogenic therapies only provide modest benefits in relatively few cancer types and there is a risk that excessive vascular targeting promotes more aggressive disease[137]. Conversely, enhancing tumour vascularization by promoting the recycling of integrins on endothelial cells can improve the efficacy of conventional chemotherapy[138]. In addition, vascular organization may also be modulated by strategies that target matrix crosslinking[91].

Future perspectives

Research into the mechanobiology of tumours is at a crucial stage. It is clear that the mechanical features of tumours are markedly different from normal tissue and that this has consequences for the behaviour of cancer cells. However, the development of clinical strategies that exploit this knowledge remains challenging. The complex interconnectivity of events that determine the mechanical properties of tumours could make targeting any single regulatory event ineffective. Numerous clinical trials are underway targeting ECM crosslinking and mechanosignalling (Table 1 and reviewed in ref. [139]) and interpretation of these studies and the planning of future trials will depend critically on determining whether agents are having the intended effect in vivo. Mechanobiology 'biomarkers' are less well-developed than more conventional cell proliferation and cell death readouts, and it will be important to utilize techniques to monitor tissue mechanics in vivo, such as magnetic resonance elastography and ultrasound methods[140–142]. Patient stratification will also need to be considered; this could be based on expression levels of the target or high levels of fibrillar ECM[111]. However, given the multitude of factors that determine tumour mechanobiology, more complex stratification strategies might be needed. Improvements in measuring mechanobiology in vivo, both in preclinical and clinical settings, and greater sophistication in engineering complex experimental system will shed light on how best to target the altered mechanical properties of tumours for patient benefit.

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Competing interests

The authors declare no competing interests.

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