Mechanotransduction gone awry

Diana E. Jaalouk and Jan Lammerding

Abstract | Cells sense their physical surroundings through mechanotransduction — that is, by translating mechanical forces and deformations into biochemical signals such as changes in intracellular calcium concentration or by activating diverse signalling pathways. In turn, these signals can adjust cellular and extracellular structure. This mechanosensitive feedback modulates cellular functions as diverse as migration, proliferation, differentiation and apoptosis, and is crucial for organ development and homeostasis. Consequently, defects in mechanotransduction — often caused by mutations or misregulation of proteins that disturb cellular or extracellular mechanics — are implicated in the development of various diseases, ranging from muscular dystrophies and cardiomyopathies to cancer progression and metastasis.

Sensory cells
Cells involved in the sensory reception of touch or hearing, often using specialized cellular structures such as hair bundles or proteins (for example, stretch-activated ion channels) to detect applied forces and deformations.

Vascular smooth muscle cells
Non-striated muscle cells found in the medial layer of arteries and arterioles. These cells are involved in regulating blood pressure and vessel tone.

Brigham and Women's Hospital, Harvard Medical School, Department of Medicine, Cardiovascular Division, 65 Landsdowne Street, Room 283, Cambridge, Massachusetts 02139, USA.
Correspondence to J.L.
e-mail:
jlammerding@rics.bwh.harvard.edu
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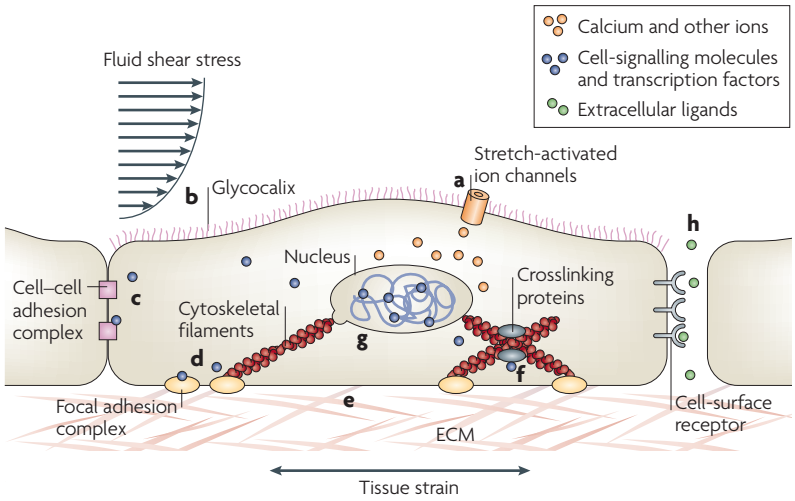
Mechanotransduction describes the cellular processes that translate mechanical stimuli into biochemical signals, thus enabling cells to adapt to their physical surroundings. Extensive research over the past decades has identified several molecular players that are involved in cellular mechanotransduction (BOX 1). However, many components, and especially the identity of the primary mechanosensor(s), remain incompletely defined.

Research in mechanotransduction has often focused on sensory cells, such as hair cells in the inner ear. These specialized cells often have evolved specific cellular structures (FIG. 1) that are tailored to transduce mechanical inputs into biochemical signals (for example, by opening ion channels in response to applied forces) and thus provide a good model to study cellular mechanosensing. With these models, it has become apparent that mechanotransduction signalling has a crucial role in the maintenance of many mechanically stressed tissues, such as muscle, bone, cartilage and blood vessels. Consequently, research has expanded to diverse cell types such as myocytes, endothelial cells and vascular smooth muscle cells, which show that mechanotransduction is involved in a broad range of cellular functions, not just in a subset of specialized cells and tissues. For example, stem cells can be steered towards specific fates during differentiation on the basis of the geometry and stiffness of the substrate on which the cells are grown[1], and intercellular physical interactions such as tension and adhesion might be as important in embryonic development as concentration gradients of morphogenic factors (see the Review by Wozniak and Chen[88] in this issue).

In this Review, we discuss how mutations and modifications that interfere with normal mechanotransduction and cellular sensitivity to mechanical stress could be implicated in a wide spectrum of diseases that range from loss of hearing to muscular dystrophies and cancer (TABLE 1). Many of these diseases share few similarities at first sight. How could muscular dystrophies be related to atherosclerosis or kidney failure? We will highlight some of these disorders and discuss how they could be traced back, at least in part, to defects in mechanotransduction, revealing some unexpected similarities. A common denominator of many mechanobiology diseases is a disruption in the intricate force transmission between the extracellular matrix (ECM), the cytoskeleton and the interior of the nucleus (FIG. 2). Cellular mechanosensing is based on force-induced conformational changes in mechanosensitive proteins that are subject to molecular forces that result in opening of membrane channels or altered affinities to binding partners, thereby activating signalling pathways. Hence, any changes in normal intracellular force transmission through changes in cellular (or extracellular) structure and organization can lead to altered molecular forces acting on these proteins, resulting in attenuated or increased mechanosensitive signals. In addition to the defects that affect cellular structure and organization, and thus cellular mechanosensing, mutations in proteins that are involved in the downstream signalling pathways can also cause impaired mechanotransduction. Examples include mutations in proteins that are involved in intracellular calcium signalling or members of the Rho or mitogen-activated protein kinase (MAPK) pathways[2]. Generally, any changes in cellular or extracellular structure, the cellular mechanosensing

Box 1 | **Cellular mechanotransduction**



Several biological components, not mutually exclusive, have been proposed to act as cellular mechanosensors and are schematically depicted in a representative cell (see figure). Note that most of these features can be found in many cell types, although some (for example, changes in intercellular space) might only be relevant in a subset of cells. **a** | Stretch-activated ion channels in the plasma membrane open in response to membrane strain and allow the influx of calcium and other ions. **b** | In endothelial cells, the glycocalix, a layer of carbohydrate-rich proteins on the cell surface, can mediate mechanotransduction signalling in response to fluid shear stress. **c**,**d** | Cell–cell junctional receptors or extracellular matrix (ECM)–cell focal adhesions allow cells to probe their environments. **e** | Force-induced unfolding of ECM proteins, such as fibronectin, can initiate mechanotransduction signalling outside the cell. **f** | Intracellular strain can induce conformational changes in cytoskeletal elements such as filaments, crosslinkers or motor proteins, thereby changing binding affinities to specific molecules and activating signalling pathways. **g** | The nucleus itself has been proposed to act as a mechanosensor. Intracellular deformations can alter chromatin conformation and modulate access to transcription factors or transcriptional machinery. However, direct evidence for this mechanism is still lacking. **h** | Compression of the intercellular space can alter the effective concentration of autocrine and paracrine signalling molecules. Additionally, changes in G-protein-coupled receptors, lipid fluidity and even mitochondrial activity have been proposed as mechanosensors. Generally, almost all cells respond to mechanical stimulation with adaptive changes in cell function. These changes include short-term responses (such as increases (or decreases) in intracellular tension, adhesion, spreading or migration) as well as changes in long-term effects (such as in protein synthesis and secretion, structural reorganization, proliferation and viability). These effects are often mediated through multiple, overlapping and crosstalking signalling pathways.

process itself or the subsequent downstream signalling pathways can result in altered and abnormal mechanotransduction and lead to disease (FIG. 3). Identifying the molecular details that are involved in normal and defective mechanotransduction will lead to a better understanding of the underlying disease mechanisms and normal cellular function and may provide us with new avenues of therapeutic approaches for these diseases.

Mechanosensitive proteins
Proteins that are directly involved in sensing forces or deformations. Microscopic forces result in conformational changes in these proteins, thereby altering their affinity to binding partners or ion conductivity and initiating downstream signalling pathways.

Cells need to feel the force

All cells and organisms across the evolutionary spectrum, from the most primitive to the most complex, are mechanosensitive[3,4]. This 'universal' property allows cells to relay mechanical stimuli from their physical surroundings or from within the organism to electrochemical or biochemical signals, which then regulate a wide repertoire of physiological responses. As such, mechanotransduction — be it involved in sensing externally applied forces (for example, in touch sensation) or in regulating forces and tension in the body (for example, in muscle tension or regulation of blood pressure) — is essential to developmental pathways and to normal tissue homeostasis, primarily in the maintenance of tissues in which cellular adaptive responses are crucial to counteract substantial variations from normal conditions[4,5]. For example, muscle tissue responds to exercise with hypertrophic growth — that is, there is an increase in cell size. The vascular system can maintain a constant blood pressure despite changes in cardiac output by vasoconstriction and vasodilation (the contraction or relaxation of the smooth muscle cells that surround blood vessels).

One often cited example of mechanotransduction is its role in hearing and balance, which results from electrochemical responses to sound waves, pressure and gravity (see Review by Chalfie[89] in this issue). These mechanical forces cause small displacements in the stereocilia of hair cells in the inner ear. The deflection of the stereocilia causes tension in the tip links, small extracellular filaments that connect the tips of stereocilia with adjacent stereocilia, thereby pulling open mechanically-gated ion channels (FIG. 1). The rapid influx of calcium and other ions can then initiate further downstream signalling. Motor proteins that are located at the distal ends of the tip links can relax or contract to restore resting tension, thus providing a mechanism to allow the system to adjust to dynamic stimulation[6]. Similarly, mechanotransduction is pivotal to touch sensation and proprioception (the internal sensing of the relative position of one's body parts), which have similar underlying mechanisms for mechanotransduction signalling as hearing[7,8].

Mechanotransduction also has a fundamental role in regulating physiological phenomena in other specialized tissues that are not directly involved in sensory functions. For example, skeletal and cardiac muscles can respond to increased load such as intensive resistance exercise, with hypertrophic growth, whereas immobilized muscles will atrophy over time[9]. The role of regulatory mechanotransduction in the cardiovascular system is particularly fascinating. It is now well established that the morphology and physiology of the heart and vasculature are influenced by pressure and shear stress that are generated from flowing blood[10–13], and low interstitial flow rates are sufficient to stimulate lymphangiogenesis[14]. Sophisticated *in vivo* studies in zebrafish embryos have revealed that distinct high-shear flow patterns are present during crucial stages in the developing heart: artificially perturbing the shear forces by occlusion results in abnormally formed hearts (for example, abnormal third chamber, reduced looping or defective valves), with defects that are similar to those that are observed in some congenital heart diseases[15]. In the mature cardiovascular system, it is thought that laminar shear stress and circumferential vessel stretch exert an atheroprotective effect on endothelial cells. Consistent with this idea, atherosclerotic lesions are often found at specific sites of disturbed (that is, turbulent) flow patterns, characterized by low and oscillatory shear stress at the endothelium (see the Review by Hahn and Schwartz[90] in this issue).

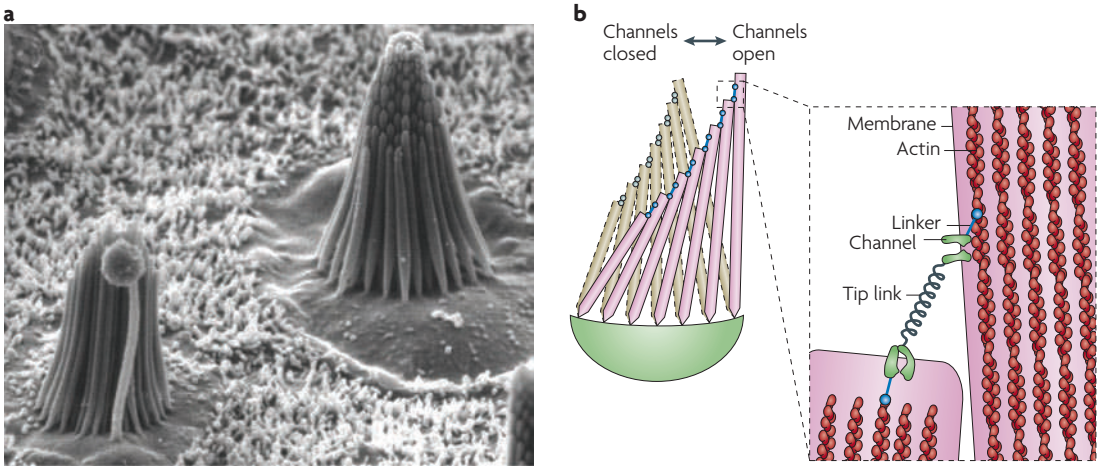


Figure 1 | **Mechanotransduction in hair cells. a** | A scanning electron micrograph of two hair bundles in the sensory macula of the bull frog saccule, showing the stereocilia arranged in bundles with centrally increasing heights. These bundles are ~8 μm tall and contain 50–60 stereocilia. **b** | Schematic drawing of a hair bundle in resting (green) and deflected (pink) configuration. Deflection, that is shearing of the stereocilia relative to each other, causes the ~150–200 nm long tip links to pull directly on K^+ channels in the stereocilia, causing the channels to open. Myosin motors that link the channels to the actin core of the stereocilia can adjust the position to restore resting tension in the tip link, allowing adaptation to persistent stimulation. Mutations in the K^+ channel, the linker proteins or in the unconventional myosins, which keep the tip links under tension, can result in deafness. Figure is modified with permission from REF. 83 © (2000) the National Academy of Sciences.

Stereocilia
Finger-like cytoplasmic extensions that project from the apical end of the inner ear's hair cells into the cochlear fluid. Stereocilia respond to fluid movement and changes in fluid pressure to mediate various sensory functions, including hearing.

Motor proteins
Proteins that generate the intracellular forces that are required for molecular transport or cell tension and contractility. Include dynein and kinesin.

Cilia
Hair-like projections on the outer surface of some cell types and unicellular organisms. Beating in unison in wave-like motion, cilia serve multiple functions including mechanosensing, motility and feeding.

Deafness genes
A set of genes, including the cadherin-23 gene, that encode tip link proteins, which are found in the hair cells in the inner ear and play a central role in the conversion of physical stimuli into electrochemical signals. Mutations in these genes can cause deafness.

Another example for the role of mechanotransduction in tissue maintenance is bone. Compact bone is comprised of concentric layers of bone matrix, in which small cavities known as lacunae are interspersed at regular intervals. These lacunae harbour osteocytes and are connected through canaliculi, a network of interconnecting canals. Gravity and compressive forces that are generated by muscle contractions during locomotion result in small deformations of the poro-elastic bone, resulting in pressure gradients that drive interstitial fluid flow through the lacunae–canalicular network. This load-induced fluid flow is thought to stimulate localized bone remodelling and optimize the physical performance of the bone through mechanotransduction signalling[16]. Likewise, chondrocytes (the main cells that comprise cartilage) adapt to widely varying stresses by secreting a glycosaminoglycan-rich ECM that gives cartilage its dynamic mechanical properties. Moreover, lung physiology from development through maturation is influenced by the continuously changing mechanical stress and strain that is caused by the cyclic distension and contraction of the lungs[17]. Similarly, urine flow inside the kidney tubules has a central role in regulating kidney morphogenesis, as these cells sense fluid shear stress by the bending of primary cilia[18].

Mechanotransduction and disease

The ability of cells to respond to changes in their physical environments is crucial in the development and maintenance of tissues that are exposed to varying mechanical stress (for example, muscle and bone), but also in physiological processes that affect the entire organism (for example, control of blood pressure and blood flow). On the cellular level, mechanotransduction can modulate diverse functions such as protein synthesis, secretion, adhesion, migration, proliferation, viability and apoptosis. Consequently, defects in cellular mechanotransduction — often through inherited or acquired mutations — can result in, or can at least contribute to, various human diseases (TABLE 1). Alternatively, changes in the cellular physical environment can elicit pathological consequences, even when the cellular mechanotransduction processes function properly. Examples for this scenario include disturbed fluid shear stress at bifurcations that trigger vascular remodelling, which can result in the development of atherosclerosis[19], or the loss of bone mass in conditions of microgravity[20]. In these cases, it is the abnormal mechanical stress at the cellular level that — through (normal) mechanotransduction signalling — modulates cellular processes that can result in the breakdown of normal tissue function.

So what diseases can arise from defects in mechanotransduction? As almost all cells rely on mechanotransduction signalling for normal function, many tissues can be affected by impaired biomechanics or mechanosensing. An obvious example is loss of hearing that is caused by mutations in the deafness genes that encode mechanosensitive proteins[6] (FIG. 1). Other examples of affected tissues include bone[16,20], cartilage, the lung[21–23], the immune system[24–26] and the central nervous system[27,28]. Below, we focus on mechanotransduction defects in skeletal and cardiac muscle that result in muscular dystrophy or cardiomyopathies[29–31], and also briefly discuss defects in the eye.

Cardiac mechanosensing and hypertrophy. More than 400 different mutations have been identified in patients with cardiomyopathy, affecting 9 separate sarcomeric genes, including actin, α-tropomyosin, troponin, titin and, most commonly, β-myosin heavy chain[32]. To understand how mutations in these structural proteins can result in pathological hypertrophy, it is helpful to view these proteins in the context of cardiac mechanotransduction.

Table 1 | **Diseases associated with defects in mechanotransduction**

Disease	Primary cells/tissues affected	Selected references
Deafness	Hair cells in the inner ear	6
Arteriosclerosis	Endothelial and smooth muscle cells	10–13, 19
Muscular dystrophies and cardiomyopathies	Myocytes, endothelial cells and fibroblasts	35, 36, 41, 85
Osteoporosis	Osteoblasts	20
Axial myopia and glaucoma	Optic neurons and fibroblasts	43–45
Polycystic kidney disease	Epithelial cells	51, 52
Asthma and lung dysfunction	Endothelial cells and alveolar tissue	15, 21–23
Premature ageing (HGPS)	Multiple cell types and tissues	55, 57
Developmental disorders	Multiple cell types and tissues	46–50, 86
Cancer	Multiple cell types and tissues	2, 58–60, 68, 71, 73, 87
Potential immune system disorders	Leukocytes	24–26
Potential central nervous system disorders	Neurons	27, 28

HGPS, Hutchinson–Gilford progeria syndrome.

Cardiac myocytes can respond directly to mechanical deformation or stretch through several internal mechanosensors, although the precise mechanosensing mechanisms often remain incompletely understood. The presumptive mechanosensors include stretch-sensitive ion channels at the cell membrane, integrins and integrin-associated proteins (such as melusin or integrin-linked kinase (ILK)) sarcomeric proteins (such as titin, myosin or the small LIM-domain protein MLP) and cell-surface receptors (such as G-protein-coupled receptors (GPCRs) and angiotensin II type 1 receptors) that can be activated by stretch even in the absence of ligands. These mechanosensors activate multiple and overlapping cellular signalling pathways that include Ras/Rho and MAPK signalling, phospholipase C activation, calcium/calcineurin-mediated signalling and microRNAs[32] (FIG. 4). These pathways trigger the expression of hypertrophic genes and cause an increase in myocyte length and/or width (reviewed in REFS 32,33). These mechanotransduction pathways, along with often overlapping neurohormonal mechanisms (for example, GPCR signalling that is activated by angiotensin or catecholamines) allow the heart to adapt to prolonged changes in the mechanical workload with an increase in cardiac myocyte size (hypertrophy) and modification of the surrounding ECM, referred to as cardiac remodelling.

The cardiac hypertrophic response is often categorized into physiological or pathological hypertrophy. Physiological hypertrophy, which arises as a consequence of aerobic exercise or pregnancy, is characterized by the addition of sarcomeres in series (to lengthen the cells) and in parallel (to increase cell width), resulting in increased cardiac wall thickness and chamber dimensions to adapt to the elevated haemodynamic load. By contrast, pathological hypertrophy is caused by abnormal changes in the cardiac workload, for example through hypertension, aortic stenosis, myocardial infarction or by congenital defects that are due to mutations in genes that encode sarcomeric proteins. As in physiological hypertrophy, cardiac myocytes sense the increased ventricular wall stress and respond with an increase in cell size. However, in pathological hypertrophy, myocytes often show a disproportional increase in either width, resulting in increased ventricular wall thickness, or length, leading to a dilated ventricle. The hypertrophic response is initially beneficial as it normalizes ventricular wall stress and is thus often referred to as compensatory hypertrophy[9,34]. However, elevated stress levels that persist over extended time periods often lead to maladaptive remodelling of the myocytes and ECM, which is accompanied by myocyte apoptosis and necrosis and eventually results in cardiac failure[32].

The precise molecular mechanisms that govern the transition from compensatory hypertrophy to pathological remodelling remain incompletely understood. Several lines of evidence suggest that hypertrophy can further destabilize cardiac mechanics, as hypertrophic tissue is often characterized by impaired contractility and relaxation dynamics. In addition, the cellular programme that is responsible for pathological hypertrophy results in the re-expression of genes that are normally associated with the embryonic myocardium. This causes disorganized cellular structure, impaired calcium dynamics and increased interstitial fibrosis, worsening the mechanical imbalance between cardiac function and haemodynamic load[35]. The maladaptive remodelling of the ECM can also result in slippage of cardiac myocytes, further exacerbating the mechanical imbalance in the myocardium. Encouraging findings in animal models of cardiac hypertrophy suggest that pathological hypertrophy can be prevented or even reversed by modulating signalling pathways that are involved in the hypertrophic response, motivating the search for specific pharmacological modulators[32,33]. The challenge in developing these therapeutic approaches lies in unravelling the dichotomy of physiological and compensatory hypertrophy on one hand and pathological hypertrophy on the other, as significant overlap exists between the signalling pathways that are involved in these processes.

Mechanotransduction and muscular dystrophies. In skeletal muscle cells, forces that are generated in the sarcomeres are transmitted to the ECM through a specialized protein complex that consists of dystrophin and the dystrophin-associated protein complex in the plasma membrane (FIG. 2), thereby shielding the cell membrane from excessive stress. In Duchenne muscular dystrophy, mutations in the dystrophin gene disrupt the force transmission between the cytoskeleton and the ECM, resulting in progressive muscle degeneration[36]. Importantly, the disruption of cytoskeletal–ECM coupling not only renders cells more susceptible to membrane damage, but also causes aberrant activation of MAPK extracellular signal-regulated kinase 1 (ERK1)

Stretch-sensitive ion channels
Ion channels that can change their conformation from closed to open in response to mechanical strain in the membrane.

Sarcomeres
Basic functional units in striated muscle cells, consisting mostly of thick myosin filaments and thin actin filaments to generate forces.

Aortic stenosis
A condition that is characterized by abnormal narrowing of the valve opening between the left ventricle and the aorta in the heart, restricting blood flow and impeding the ability of the heart to pump blood to the body.

Ventricular wall stress
The mechanical stress, that is force per unit area, in the myocardium. Decrease in wall thickness, following loss of myocytes after infarction can result in increased left ventricular stress and can damage the remaining myocytes.

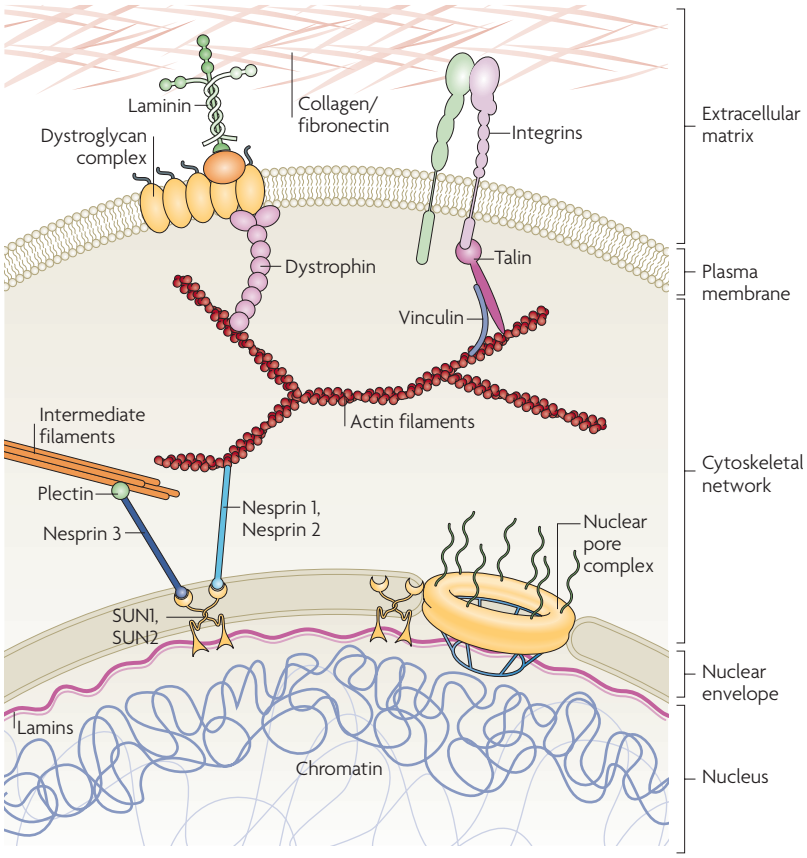


Figure 2 | **Force transmission between the extracellular matrix and the nucleus.** Extracellular forces are transmitted through the extracellular matrix (ECM), which consists of tissue-specific proteins such as collagen, laminin and fibronectin. Adhesion complexes at the cell surface physically link the ECM to the cytoskeleton. For example, focal adhesions, comprised of integrins, talin, vinculin and other proteins, connect the ECM to actin filaments. In skeletal muscle, the dystrophin-associated protein complex links the ECM to actin filaments. The configuration and binding affinity of these complexes can be modulated through intra- and extracellular signalling. Intracellular forces are then transmitted through the cytoskeletal network (that is, actin filaments, microtubules and intermediate filaments). The cytoskeleton is coupled to the nucleus through nesprins and possibly through other proteins on the outer nuclear membrane. The giant isoforms of nesprin 1 and nesprin 2 bind to actin filaments, whereas nesprin 3 can associate with intermediate filaments through plectin. Nesprins interact across the luminal space with inner nuclear membrane proteins (for example, SUN1 and SUN2) that are retained there by interaction with other nuclear envelope proteins such as lamins and emerin[84]. Nuclear lamins and SUN proteins also bind to nuclear pore complexes, which could contribute to nuclear cytoskeletal coupling. Finally, lamins form stable nuclear structures and can bind to DNA, thus completing the force transmission between the ECM and the nuclear interior. Mutations in any of these components, as well as changes in cellular structure and organization or changes in the cellular environment, could disturb mechanotransduction signalling and result in altered cellular function. However, this has only been conclusively demonstrated for a subset of these molecules, motivating further research.

Interstitial fibrosis
A progressive condition that is characterized by fibrous connective tissue replacing normal tissue, such as muscle, that is lost by injury or by infection and infiltration of inflammatory cells into the small spaces between tissues.

and ERK2 signalling in response to stretch[37]. This abnormal mechanotransduction signalling could further impact cell function and viability. Recent experiments indicate that in dystrophin-deficient muscle fibres, stress-induced rupture of the more fragile plasma membrane allows influx of extracellular calcium. This causes abnormal muscle contraction and, combined with the defective coupling between the cytoskeleton and the ECM, leads to physical damage of the cytoskeleton, which subsequently results in the loss of muscle cells[38]. Interestingly, dystrophin is also involved in the endothelial cell response that is necessary for the fluid-shear-stress-mediated dilation of arteries. Consequently, endothelial cells from dystrophin-deficient mice have impaired mechanotransduction signalling in response to fluid shear stress, resulting in attenuated dilation of arteries and a decreased vascular density in cardiac muscle, which could further contribute to the progressive loss of muscle[39].

Similarly, mutations in the cytoskeletal proteins desmin, titin and myosin, which are important sarcomere components, result in disorganized sarcomeres and disturbed cellular mechanics, including impaired force generation and altered (passive) cytoskeletal stiffness, which can impair relaxation dynamics of myocytes. The deleterious effects of these mutations can result from direct changes in intracellular force distribution and/or generation due to ultrastructural disorganization, but can also arise from downstream effects of altered cellular mechanosensing, as myosin and titin can function as mechanosensors[40]. Investigating the relative contributions of these mechanisms to muscular dysfunction may provide important clinical insights, as defects in mechanotransduction pathways could potentially be attenuated with pharmacological reagents. This research is hampered, however, by the fact that mechanotransduction can directly influence cellular structure and function, making it difficult to discern cause and effect.

The recent findings that muscular dystrophies can arise from mutations in nuclear envelope proteins (namely lamins A and C, emerin or nesprins) further highlight the concept that disturbed intracellular structure and force transmission can contribute to muscular disease. Although these proteins are expressed in most differentiated cells, the resulting phenotypes are often muscle specific and suggest that cells of affected patients have an increased sensitivity to mechanical stress. New insights have come from a mouse model of Emery–Dreifuss muscular dystrophy that lacks lamins A and C. Cells from these animals are characterized by decreased nuclear stiffness, increased nuclear fragility and impaired activation of mechanosensitive genes, causing decreased viability in cells subjected to repetitive strain[41]. The increased nuclear fragility could result in nuclear rupture and cell death in mechanically stressed tissues. However, nuclear rupture can only explain a fraction of the cell death that is observed during repetitive strain application, especially in cells from emerin-null mice, which have normal nuclear mechanics and increased strain-induced apoptosis[42]. Therefore, it is likely that the attenuated expression of mechanosensitive, anti-apoptotic genes, such as *Iex1*, contributes to the increased cellular sensitivity to mechanical stress[41,42]. Currently, it remains unknown what causes the mechanotransduction defects in these cells. Although the nucleus has often been proposed as a cellular mechanosensor — for example, by altering chromatin accessibility in response to deformations — direct evidence for this function is still elusive,

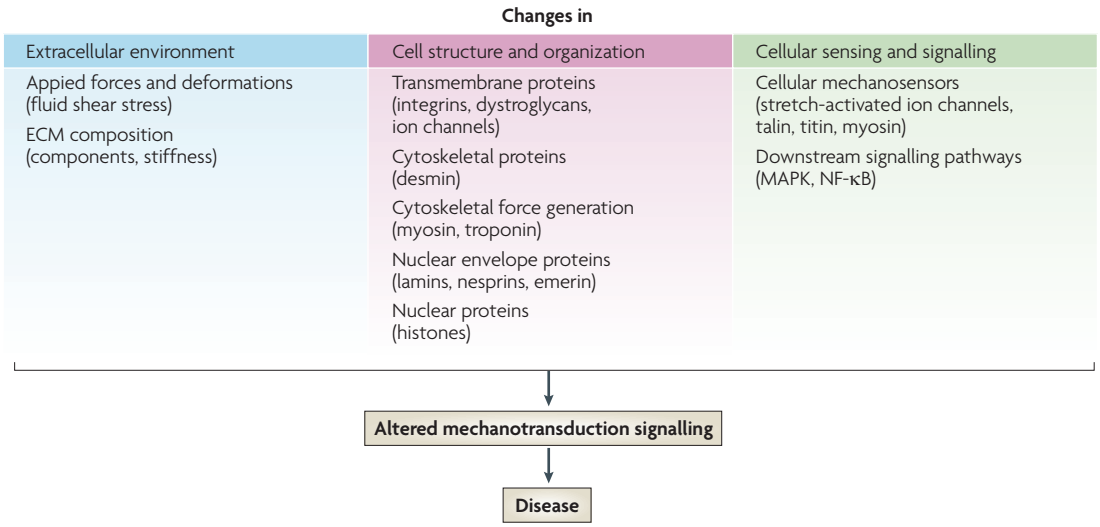


Figure 3 | **Unifying characteristics of mechanotransduction disorders.** Altered cellular mechanotransduction signalling can be caused by changes in the extracellular environment (for example, variations in the mechanical forces or deformations that are experienced by the tissue, or changes in extracellular matrix (ECM) composition that affect its stiffness and biochemical properties), the structure and organization of a cell, or the elements of the mechanotransduction process itself. Changes in cellular structure and organization often result from inherited or *de novo* mutations in proteins that are part of the force-generating machinery, the cytoskeletal network or the nuclear envelope and interior. This category also includes transmembrane proteins that are involved in cell–cell or ECM–cell adhesion. Abnormal function of these proteins can alter the intracellular force distribution and thus mechanotransduction signalling. By contrast, defects in the cellular mechanosensors can disturb mechanotransduction signalling even in the case of normal force distribution. Many proteins can fall into more than one category, as structural proteins can also have mechanosensing capabilities and mechanotransduction signalling can in turn cause changes in cellular structure and organization as well as in the extracellular environment. Importantly, mechanical activation often initiates multiple signalling pathways at once, and these can have significant overlap and crosstalk, making it difficult to study specific pathways. Several of the signalling pathways are often shared with 'classical' receptor-mediated pathways. For example, the mitogen-activated protein kinase (MAPK) pathway can be turned on by mechanical strain as well as by receptor-linked tyrosine kinases (for example, by the epidermal growth-factor receptor). Ultimately, excessive and prolonged disturbances in normal mechanotransduction signalling can result in disease conditions. NF-κB, nuclear factor-κB.

and future research has to address whether defects in mechanotransduction signalling arise as a direct consequence of altered nuclear stiffness or whether they mainly reflect broader defects in specific signalling pathways (for example, in nuclear factor-κB signalling) that are modulated by nuclear lamins.

Trouble in the eye. Another unexpected organ that is affected by disturbed mechanotransduction is the eye. Several recent findings suggest that modulated mechanotransduction signalling due to increased mechanical stress could significantly contribute to the pathogenesis of glaucoma and axial myopia[43]. In glaucoma, elevated hydrostatic pressure and altered biomechanics of the optic nerve head could initiate mechanisms that result in loss of vision. Recent experimental evidence suggests that human (and monkey) eye tissues deform in response to even minute changes in intraocular pressure[44]. In addition, ambient hydrostatic pressure elevations resembling intraocular conditions in glaucoma can induce apoptosis of retinal ganglion cells *in vitro*, consistent with *in vivo* findings[44]. Moreover, human scleral fibroblasts (the primary cells that are implicated in the scleral remodelling that accompanies axial elongation during the development of myopia) express many genes that are modulated by mechanical strain application. These include genes that encode ECM proteins (such as tenascin C), protein kinases (such as human lymphocyte-specific protein tyrosine kinase (LCK)), cell receptors (such as parathyroid hormone (PTH)/PTH-related peptide (PTHrP) receptor), cell growth and differentiation factors (such as fibroblast growth factors and bone morphogenetic proteins) and transcription factors (such as Jun B)[45]. Although the role of some of these proteins in ocular development and axial elongation is obscure and rather speculative, the contribution of others is more obvious. For example, activation of the PTH/PTHrP receptor by calcium-regulating hormones triggers several intracellular signalling events including the activation of protein kinase C, which is directly involved in scleral remodelling. Moreover, tenascin C, which has been implicated in tissue remodelling during development, can act as a mediator of the scleral response to stretching by increasing the synthesis of proteolytic enzymes that affect ECM remodelling. These findings suggest that increased intraocular pressure — mediated by normal mechanotransduction signalling in scleral fibroblasts — can contribute to the abnormal remodelling that occurs in axial myopia.

Haemodynamic load
The forces that are generated from cardiac output and physical resistances due to the flow of blood in circulation.

Glaucoma
A disease in which the optic nerve is permanently damaged due to abnormally high fluid pressure in the eye. Results in impaired or complete loss of vision.

Axial myopia
Near- or short-sightedness associated with an increase in the eye's axial length.

Intraocular pressure
The pressure inside the eyeball that is generated by resistance to the outward fluid flow of aqueous humour. This pressure helps maintain the shape of the eye, but can result in glaucoma if it is too high.

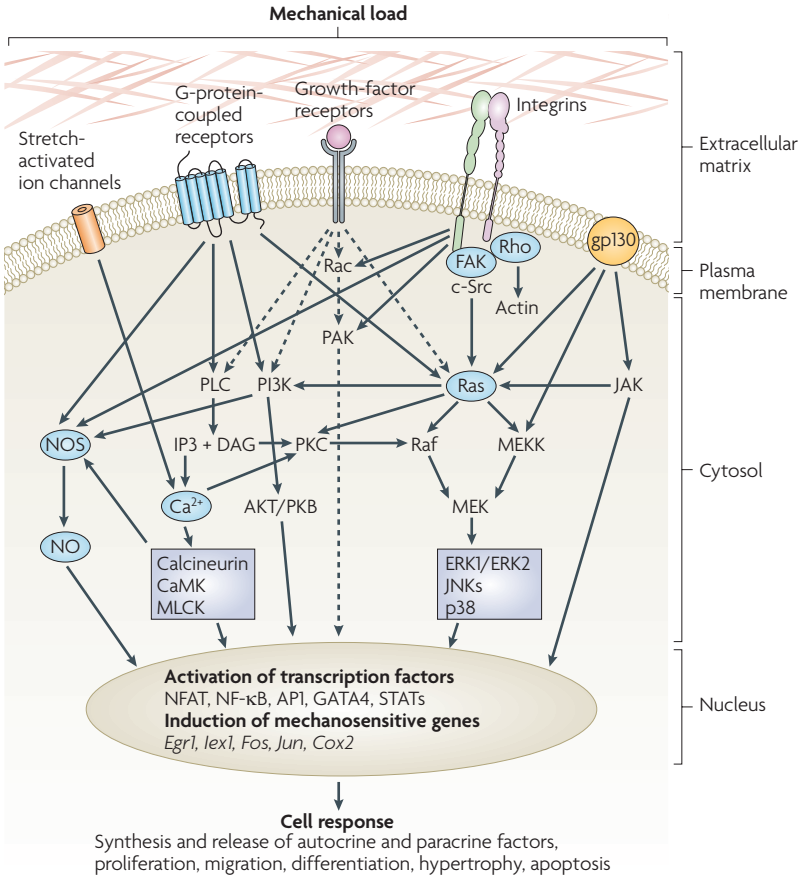


Figure 4 | **Cardiac mechanotransduction signalling.** Cardiac myocytes respond to altered haemodynamics by activating multiple intracellular signalling pathways that are implicated in the maintenance and regulation of cardiac myocyte function. Mechanical loading can be sensed by cardiomyocytes through a diverse group of membrane-anchored mechanosensors including stretch-activated ion channels, cell-membrane-spanning G-protein-coupled receptors, growth-factor receptors and integrins. This mechanical sensation is then converted to biochemical signals by triggering the multi-step activation of downstream partners in an array of signalling cascades in the cytoplasm. The highlights of such cascades include the three modules of the mitogen-activated protein kinase (MAPK) family underscored by the activation of Ras, the Janus-activated kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, Rac activation, calcium (Ca^{2+}) and nitric oxide (NO) signalling. The convergence of these pathways results in the activation of select transcription factors including nuclear factor-κB (NF-κB) and nuclear factor of activated T cells (NFAT), which then translocate to the nucleus and modulate the expression of a panel of mechanosensitive genes including *Egr1* and *Iex1*. Ultimately, the net sum of gene-expression reprogramming in cardiomyocytes dictates the functional response of a cell to mechanical stress.

Development and premature ageing

Mounting evidence suggests that mechanotransduction also has a crucial role in development[46–49]. Thus, any disturbances to normal mechanotransduction mechanisms or to a cell's physical environment can result in broad developmental defects[50]. A classical example to illustrate this is Kartagener's syndrome, which is characterized by a left–right reversal of the primary visceral organs. Left–right patterning in early mammalian embryos is dictated by cilia-driven leftward fluid flow during gestation, which — through mechanotransduction signalling — differentially induces expression of nodal, a transforming growth factor (TGF)-family molecule, and a signalling cascade of other factors in the left side of the embryo. Mutations in the dynein motor proteins that are primarily responsible for Kartagener's syndrome block cilia motion in the epithelium of a midline node in the embryo and thus prevent the leftward fluid flow; in the absence of flow, the left–right patterning becomes random.

Similarly, mutations in the genes that encode the ciliary proteins polycystin 1 or the transient receptor potential channel family protein polycystin 2 (TRPP2) provide direct evidence for defects in mechanotransduction that result in kidney disease[51]. Polycystins form mechanosensitive ion channels in the cilia of renal epithelial cells and allow influx of calcium in response to flow-induced bending of the cilia, thus acting as a cellular flow-sensor in the kidney[51]. Polycystin mutations that are associated with loss of function leave cells unable to sense the fluid flow that normally regulates kidney morphogenesis, resulting in several types of polycystic kidney disease (PKD) that include autosomal dominant PKD, a disease characterized by progressive cyst formation that culminates in kidney destruction[51,52].

Disturbed mechanotransduction can also underlie several other diseases that are not traditionally approached from a biophysical perspective. One such example is Hutchinson–Gilford progeria syndrome (HGPS), a progeroid disorder that is caused by mutations in the *LMNA* gene, which encodes lamin A. Patients with HGPS appear normal at birth, but fail to thrive shortly thereafter and die in their early teens. Arteriosclerosis is the leading cause of death in patients with HGPS[53], and post-mortem analysis of vascular tissue from patients with HGPS and from a mouse model of HGPS have revealed extensive loss of vascular smooth muscle cells and an unusual susceptibility to haemodynamic stress[54,55]. Mechanotransduction in vascular cells in response to fluid shear stress and strain from vessel expansion is a crucial protective mechanism against arteriosclerosis and can mediate apoptosis, proliferation and ECM secretion in healthy vascular smooth muscle cells[56]. Recent experiments from our laboratory revealed that fibroblasts from patients with HGPS have decreased viability when subjected to repetitive mechanical strain, and that cells from patients with HGPS lack the strain-induced proliferation response that is seen in cells from healthy controls[57]. These findings suggest that increased cellular sensitivity of vascular cells subjected to normal fluid shear stress and vessel expansion could be a possible mechanism for the progressive loss of smooth muscle cells and severe arteriosclerosis in patients with HGPS. Although increased cellular sensitivity to mechanical strain is certainly not the only factor in HGPS, our experiments suggest that it could have an important role in the development of severe arteriosclerosis that leads to lethal stroke or myocardial infarction in human patients[55]. Furthermore, it could contribute to defects in other mechanically loaded tissues, perhaps causing the bone abnormalities and skeletal muscle dystrophy that are characteristic of HGPS.

Cancer cells have lost their touch

Perhaps the most intriguing of all of the mechanotransduction diseases is cancer. In the past decade, sudden changes in ECM mechanics, ECM remodelling and the resultant disturbance in cytoskeletal tension and mechanotransduction signalling have emerged as important factors that can promote malignant transformation, tumorigenesis and metastasis[58–60]. In addition to a combination of genetic mutations and increased oncogene activity, cytoskeletal reorganizations — particularly those that are manifested by alterations in the tensional force that is generated by the actin–myosin apparatus in the cell — play a pivotal role in the morphological changes that are adopted by tumour cells as they develop invasive phenotypes. One of the main regulators of cytoskeletal tension is the Rho family of GTPases. Among its many targets, Rho functions via Rho kinase (ROCK) to regulate myosin light chain phosphorylation through inhibitory phosphorylation of myosin phosphatase. Although studies on Rho activity in tumours have yielded contradictory results (some reports provided substantial evidence supporting the notion that tumours have increased Rho activity and exhibit more cytoskeletal tension whereas others reported decreased Rho activity in solid tumours[61–66]) it has become apparent that cytoskeletal tension significantly impacts signalling pathways that are implicated in cancer progression. Discrepancy in these studies may be partly attributable to the multivariant experimental conditions that were used and to the limitations that are associated with two dimensional (2D) monolayer cell cultures.

Furthermore, several studies have shown that cytoskeletal tension in tumours is influenced by ECM stiffness[2,58,67]. Tumours are generally much stiffer than the surrounding normal tissue. Concurrent changes in tissue stiffness, tumour growth due to proliferating cells and/or elevated interstitial fluid pressure all combine to affect the physical environment of cancerous cells inside the tumour and the adjacent normal cells[68]. This altered physical environment can modulate the fate of these cells through mechanotransduction (FIG. 5). For example, higher ECM stiffness can result in disruption of normal epithelial cell polarity, inducing mammary epithelial cells to fill the cystic lumens in breast cancer[2]. Paszek and co-workers investigated whether the increased tissue stiffness that is observed in mammary tumours in 3D matrices promotes the malignant phenotype by influencing integrins, cell-surface receptors that connect specific ECM molecules to the cytoskeleton[2] (FIG. 2). They found that matrix stiffness (exogenous force) and cytoskeletal tension (endogenous force) functionally cooperate in a 'mechano-circuit' that modulates phenotypic transformations in tumours by coupling the mechanosensing role of integrins in relaying external physical cues to Rho and ERK signalling pathways. As such, the stiffer matrix disturbs epithelial morphogenesis by causing force-dependent aggregation and clustering of integrins, thus resulting in elevated Rho–ROCK-dependent cytoskeletal tension, which amplifies the formation and stabilization of focal adhesion assembly. This increase in cell-generated force and in focal adhesion assembly was accompanied by focal adhesion kinase signalling, ROCK-mediated

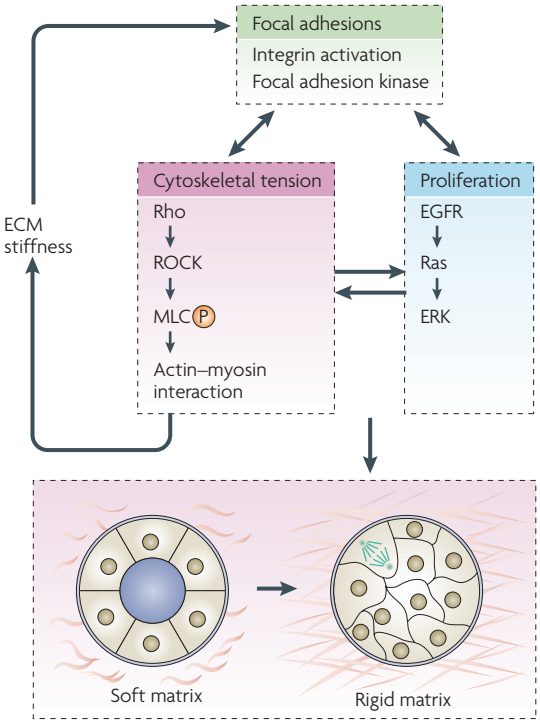


Figure 5 | **Mechanotransduction in cancer cells.** Schematic representation of how increased extracellular matrix (ECM) stiffness and altered cytoskeletal tension can contribute to tumour formation. Increased ECM stiffness can arise from fibrosis or in response to increased cytoskeletal tension, caused, for examples, by oncogene (Ras)-driven extracellular-signal-regulated kinase (ERK) activation. The increased ECM stiffness is sensed by focal adhesions and activates integrins and focal adhesion kinase, thereby promoting focal adhesion assembly and stimulating the Rho–ROCK (Rho kinase) pathway. ROCK activation increases cytoskeletal tension by increasing myosin light chain (MLC) phosphorylation, which can result in further increases in ECM stiffness due to cellular mechanotransduction signalling, completing a self-enforcing (positive) feedback loop. Crosstalk between the Rho–ROCK pathway and the epidermal growth-factor receptor (EGFR)–Ras–ERK pathway, as well as modulation of growth-factor-dependent ERK activation by integrins, results in increased proliferation. ERK activation can also increase cytoskeletal tension through ROCK, further complementing the crosstalk between cytoskeletal tension and proliferative pathways. In breast cancer cells, the combined action of increased contractility and proliferation, triggered by increased ECM stiffness, may drive the undifferentiated and proliferative phenotype of mammary epithelial cancer cells and result in tumour formation. Decreasing Rho-mediated cytoskeletal contractility or ERK activity is sufficient to revert EGFR-transformed cells that form disorganized and invasive colonies into phenotypically normal cells that form polarized and growth-arrested acini in three-dimensional culture[2]. Figure is modified with permission from REF. 58 © (2005) Elsevier.

Focal adhesions
Dynamic protein complexes at the plasma membrane that connect the extracellular matrix to the actin cytoskeleton. Focal adhesions consist of integrins, talin, paxillin and signalling molecules such as focal adhesion kinase. Several of these proteins are thought to act as mechanosensors and to participate in mechanotransduction signalling.

disruption of adherens junctions, enhanced growth-factor-dependent ERK activation driving tumour cell proliferation and disruption of basal polarity, hence abrogating lumen formation and remodelling mammary tissue architecture. Disrupting Rho or ERK signalling to reduce cytoskeletal tension to normal levels resulted in significant reduction in tumour cell proliferation and in repression of the malignant phenotype. Recent experiments also demonstrated that both integrins and Rho-mediated regulation of intracellular tension are needed to promote the invasive behaviour of fibroblasts and cancer cells in co-cultures[69,70].

All cells, with the exception of haematopoietic cells, need to adhere to a solid substrate for normal cell-cycle progression and survival. Notably, cancer cells lose this dependency on anchorage and cell-surface tension as they become able to invade other tissues[71,72]. This hallmark of metastatic cells, that is, their ability to break through the basal lamina, infiltrate blood vessels, exit the blood vessels and form new tumours, requires finely regulated biomechanical interactions between the cancer cell and its physical milieu. For example, adhesion of melanoma cells to the endothelial cells that line blood vessels (a crucial step to extravasation and metastasis) is in part regulated by the hydrodynamic shear rate, which mediates melanoma–leukocyte aggregation thereby enhancing adhesion of tumour cells to the endothelium[73]. Moreover, although tumours are stiffer, metastatic cells can be distinguished from non-invasive cancer cells and from normal cells by reduced cytoskeletal stiffness and increased deformability[60,74,75]. Recent evidence suggests that cell deformability strongly correlates with passage time through narrow pores and with enhanced metastatic potential in mouse melanoma cells[76]. Thus, increased cellular and nuclear deformability can enable the passage of metastatic cancer cells through size-limiting pores and blood vessels, resulting in enhanced metastatic spreading. Although some of these studies to measure the stiffness of cancer cells had technical limitations (for example, measurements of normally adherent cells were performed in suspension, or only a small number of cells were tested), the experiments illustrate that many cancer cells are characterized by altered physical properties and that biomechanical measurements of cells isolated from pleural effusions may have significant diagnostic and prognostic value.

Clearly, cancer is not exclusively caused by defective mechanotransduction signalling, as deregulation of cell-cycle control, defects in DNA-damage repair, suppression of apoptosis and altered adhesion and/or migration all contribute to this multifaceted disease. However, many of the cellular functions that are involved in tumorigenesis and metastasis are modulated by mechanotransduction. Hence, altered mechanotransduction signalling may be an important component in tumour formation and metastatic progression. Improved cell culture modalities that would permit the study of tumour progression in a 3D context would greatly enhance our ability to decipher the effects of mechanotransduction aberrations in cancer progression.

Pleural effusions
Fluids that collect in the space between the lungs and the chest wall.

Conclusions and future perspectives

The above examples demonstrate that the mechanotransduction feedback loops that couple cellular structure and function, and that modulate cellular structure and the extracellular environment, play an important role in the maintenance of normal tissue function. Moreover, events that disrupt these feedback loops, either by affecting cellular mechanosensing, intracellular mechanotransduction signalling or intracellular or extracellular force distribution, can result in various clinical phenotypes.

One challenge that remains is to determine the effects of defective structural or motor proteins on mechanotransduction. Often, structure, function and mechanotransduction are tightly linked, as the examples of myosin, titin (both recently identified as potential cellular mechanosensors), talin and lamins illustrate. Talin and vinculin are structural components of the focal adhesion complex, linking integrins to actin filaments (FIG. 2). Molecular dynamic models suggest that force-induced conformational changes in talin can activate a cryptic vinculin binding site, enabling subsequent recruitment of vinculin to reinforce focal adhesion sites[77]. Similarly, lamins were first identified as nuclear intermediate filaments, but were subsequently shown to have an important role in transcriptional regulation as well as in DNA and RNA synthesis[78]. These examples highlight our still limited understanding of the cellular structure–function relationships — that is, we still do not fully understand how the 3D organization of the cytoskeleton and the nucleus affect cellular functions such as DNA and RNA transcription. Future research should focus on how changes in intracellular structure, through induced deformations or remodelling for example, can modulate these cellular functions and processes.

Understanding these processes may also provide us with new clues in the search for the elusive cellular mechanosensors and the question of how cells manage to sense their physical surroundings. The many reports of putative mechanosensing proteins suggest that multiple mechanisms exist, even in single cell types, so that the interplay of redundant or complementary mechanotransduction pathways has to be viewed in a 'systems biology' context[3]. This will be especially important when designing treatment approaches for mechanotransduction diseases. Although mutations in structural proteins may require the replacement of affected genes or cells by targeted gene or stem-cell therapy — currently a challenging and daunting task — an alternative approach for at least some of these diseases could be to correct downstream signalling pathways that are disturbed by altered mechanotransduction signalling. For some dominant-negative mutations, another strategy could be based on the possible redundancy of related proteins; it might be possible to reduce levels of the mutant protein using RNA interference. Such an approach has been proposed for a lamin A mutation that is associated with HGPS, as studies in a lamin A-deficient mouse model suggest that lamin C might be sufficient to maintain cellular function without an increase in cellular sensitivity[79]. Alternatively, some

cellular mechanical defects can potentially be directly addressed using small molecules approaches. For example, the membrane sealant poloxamer 188 has been successfully used to reduce damage to the plasma membrane in a mouse model of Duchenne muscular dystrophy, resulting in significant improvement in cellular function in cardiac and skeletal muscle[80,81].

The past years have provided increasing evidence that the finely tuned feedback between cells and their physical surroundings is crucial for many important cellular functions, ranging from differentiation to proliferation and viability. Events that interfere with these cellular mechanotransduction processes may thus result in diseases that affect various tissues and organs. Studying the mechanisms that underlie these diseases may lead us to new treatment strategies, improved tissue-engineering design and enhanced biomaterials, and will also provide us with an opportunity to learn more about mechanotransduction and mechanobiology in normal cells and physiology.

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DATABASES

Entrez Gene: *http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene*
lex1
OMIM: *http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM*
Duchenne muscular dystrophy | *Emery–Dreifuss muscular dystrophy* | *Hutchinson–Gilford progeria syndrome* | *Kartagener's syndrome*
UniProtKB: *http://ca.expasy.org/sprot*
Emerin | *ERK1* | *ERK2* | *tenascin C*

FURTHER INFORMATION

Jan Lammerding's homepage: http://vascular.bwh.harvard.edu/Lammerding

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