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Decoding mechanical cues by molecular mechanotransduction

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Abstract

Cells are exposed to a variety of mechanical cues, including forces from their local environment and physical properties of the tissue. These mechanical cues regulate a vast number of cellular processes, relying on a repertoire of mechanosensors that transduce forces into biochemical pathways through mechanotransduction. Forces can act on different parts of the cell, carry information regarding magnitude and direction, and have distinct temporal profiles. Thus, the specific cellular response to mechanical forces is dependent on the ability of cells to sense and transduce these physical parameters. In this review, we will highlight recent findings that provide insights into the mechanisms by which different mechanosensors decode mechanical cues and how their coordinated response determines the cellular outcomes.

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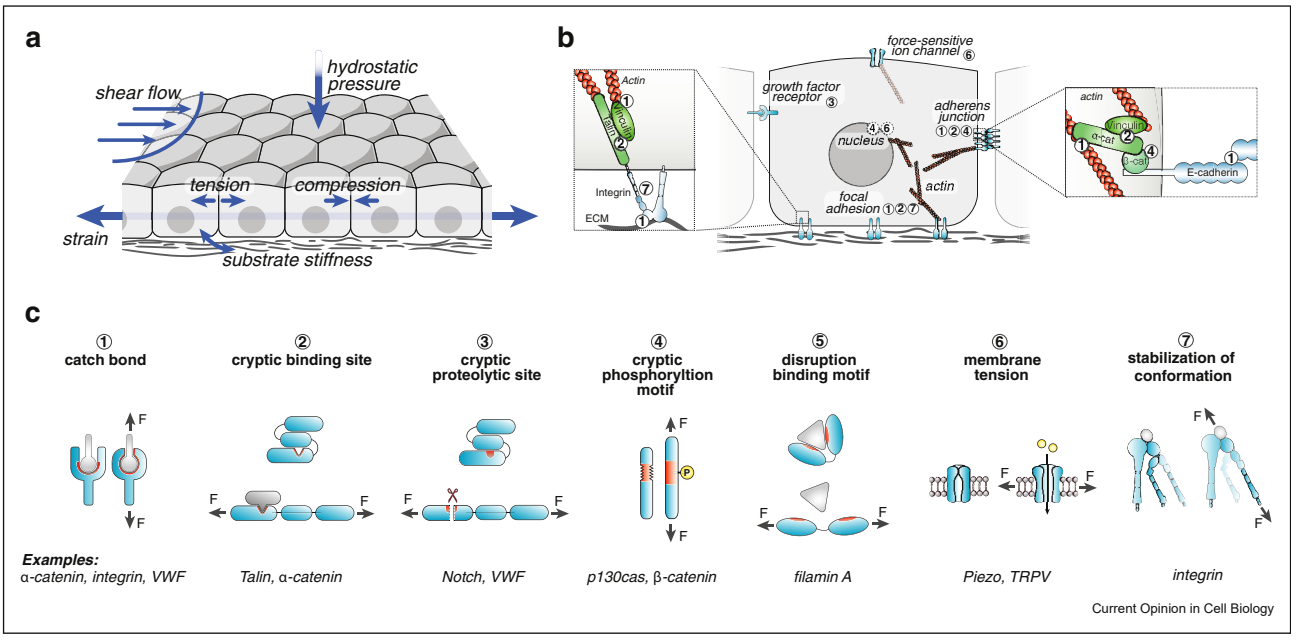
Introduction

Every aspect of physiology has a component that directly relies on the ability of cells to sense and respond to mechanical cues. These cues include forces experienced by cells from their surroundings such as neighboring cells, blood flow or pressure generated in confined interstitial spaces (Figure 1a). In addition, cells use their own force-generating apparatus to probe the mechanical properties of the local tissue. Any of these forces can elicit a diversity of cellular responses, relying on common principles of 'mechanotransduction' in which cells convert mechanical information to distinct intracellular biochemical pathways. While the list of cellular and tissue-scale processes regulated through mechanotransduction has continued to expand, it is also becoming clear that forces can induce specific responses dependent on the cell type, on cellular context, or on how they are sensed by the cell. To achieve both diversity and specificity in responses, mechanical cues must function similar to biochemical signals, where variations in ligand identity and concentrations recognized by a repertoire of receptors regulate the vast number of cellular functions. Complexity of the cellular response thus arises from the depth of information embedded in the physical parameters of mechanical forces, such as their magnitude, direction and temporal dynamics, and the ability of cells to extract that information. In this review, we will discuss recent findings that show how force-transducing molecules are able to sense and respond distinctly to these different physical parameters and how these molecular responses are integrated to determine the cellular outcome.

General principles of molecular mechanotransduction

Forces exerted on cells, and applied by cells on the extracellular environment, result in stresses and deformations that are sensed by a group of specialized molecules called mechanosensors. These mechanosensors undergo a force-dependent conformational change, which alters the biochemical function of the protein. Forces from the cellular surroundings are typically first experienced at the cell surface, where the force-generating cytoskeleton also exerts stresses when encountering different mechanical environments. The adhesion complexes at which cells are anchored to the surrounding tissue (through focal adhesions [FAs]) and to other cells (through adherens junctions, [AJs]) have therefore emerged as central nodes in transducing forces [1,2] (Figure 1b). However, cells possess a much broader ensemble of mechanosensors, including several structurally distinct families of force-sensitive ion channels [3] and receptors for biochemical ligands that directly respond to force (e.g. notch [4] and plexin [5]). Moreover, forces at the cell periphery are transmitted by the cytoskeleton to other cellular sites such as the nucleus

Figure 1



Principles of mechanotransduction. a. Different types of mechanical forces to which cells are exposed and forces exerted by cells on their substrate that can have different mechanical properties. **b.** The repertoire of mechanosensor proteins and protein assemblies in cells, for which the types of mechanotransduction mechanisms (see Figure 1c) that have thus far been demonstrated, is indicated (and putative mechanotransduction mechanisms in dotted lines). Focal adhesions and adherens junctions both consist of multiple mechanosensor proteins with distinct mechanotransduction mechanisms (indicated in the insets). Although only adherens junctions are shown, other cell–cell adhesions complexes (desmosomes, tight junctions) may similarly transduce forces. The nuclear envelope contains several proteins and protein assemblies that respond to membrane tension (i.e. nuclear pore complex) or which are phosphorylated in a force-dependent manner (i.e. emerin, lamin), although it remains to be determined whether these are mechanosensors themselves. Although the gating function of force-sensitive ion channels is regulated by force-induced changes in membrane tension, several ion channels are also directly regulated by forces transmitted through the associated actin cytoskeleton [14]. **c.** Distinct mechanisms of mechanotransduction used by different mechanosensors, with examples of each indicated below.

[6], which also contain mechanosensitive components and contribute to the cellular response to external and intrinsic forces (Figure 1b).

Mechanosensors act through a set of shared mechanisms by which the force-induced conformational changes affect either molecular interactions or protein activity (see Figure 1c). Forces can directly strengthen protein–protein interaction of mechanosensors by increasing the bond life time (catch bond), as opposed to most protein–protein interactions, where the lifetime decreases with force (slip bond) [7]. Moreover, forces can modulate interactions through protein unfolding or unmasking that can either reveal cryptic binding sites (CBSs) [8,9] or disrupt binding motifs [10]. The nature of the cryptic site varies in different mechanosensors, and forces can also expose proteolytic sites [11,12] or motifs for post-translational modifications [13]. Several membrane-associated mechanosensors are regulated by force-induced changes in membrane tension, for instance controlling the gating function of mechanosensitive ion channels [14]. Finally, forces from the cytoskeleton can also stabilize specific structural conformations of mechanosensors such as integrins [15]. Mechanosensors often form larger multimolecular clusters with combinations of mechanosensors regulated through different mechanisms, of which FAs and AJs are prototypical examples (Figure 1b).

Mechanosensors do not act as simple on-off switches, but their response depends on various properties of the forces. Forces can act on different parts of the cell, but can also have different range of magnitudes, directions, and temporal profiles, all of which can result in a unique response and distinct biological outcomes. The specific mechanisms of force transduction in individual mechanosensors, as well as their organization within the cell, will determine the ability to discriminate between these different parameters, as outlined in the next sections.

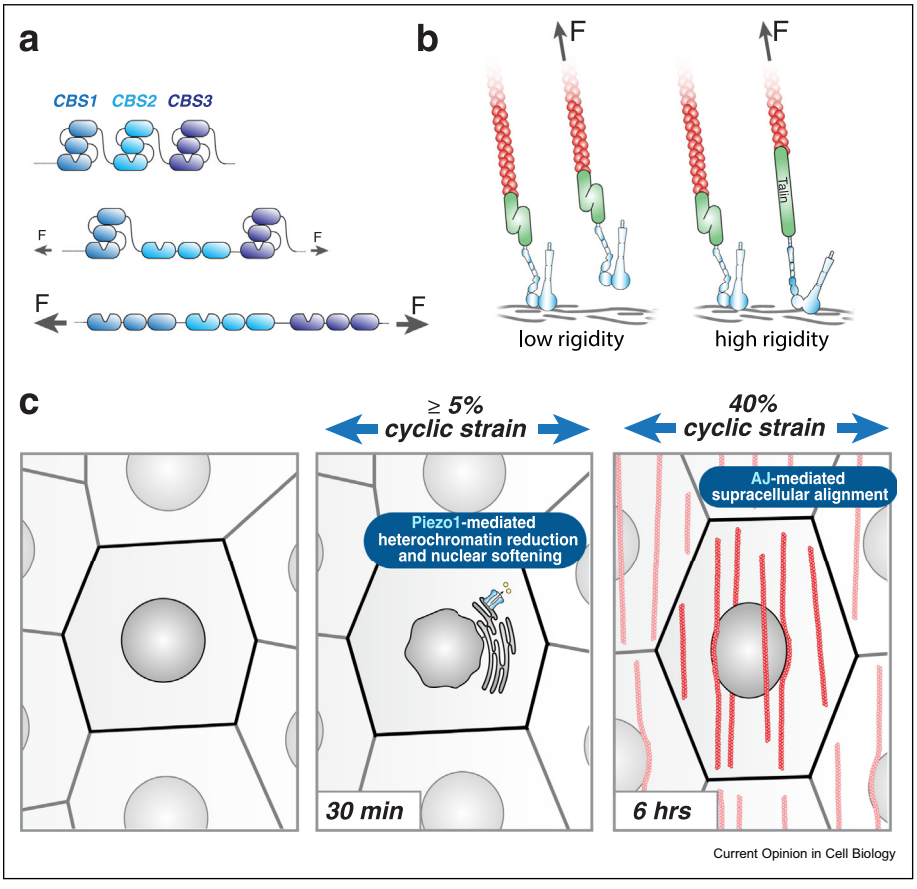
Decoding magnitude of forces

Cellular responses to mechanical cues such as flow, extracellular matrix (ECM) rigidity, and tissue strain are dependent on the magnitude of forces associated with these cues. The range of force magnitudes that cells

sense, and the sensitivities of different mechanosensors over that range, determines how cells respond to the mechanical cue. Although the molecular mechanisms of sensitivity to force magnitude are still not completely understood, several mechanisms by which cells are able to extract this information have been uncovered.

One molecular explanation of sensitivity to force magnitudes is mechanosensors having a threshold force of activation, for instance the force required for CBS exposure or the force range where catch bonds are formed. This sensitivity may be further fine-tuned by the presence of stable intermediate states of the force-dependent conformations of mechanosensors. Single-molecule force spectroscopy of catch bonds has shown at least 3 states (weak, intermediate, and strongly bound) at a range of force magnitudes for integrin–fibronectin [16], vinculin–F-actin [17], and VWF–GPIb [18]. However, it remains to be determined if these states exist in cells and if they are associated with distinct levels of biochemical output. Intermediate states can similarly be present in mechanosensors containing multiple force-sensitive domains that unfold at different force magnitude (Figure 2a). This has been demonstrated for the CBSs in the different rod domains of talin, with the R3 domain unfolding at 5 pN force and the remaining domains at 10–25 pN [19]. As these rod domains have distinct binding partners, this can

Figure 2



Mechanisms for decoding different force magnitudes. a. Molecular scale: A single mechanosensor with multiple mechanosensory domains (e.g. multiple cryptic binding sites [CBSs] as shown) can lead to magnitude sensitivity. Low forces (middle panel) may result in unfolding of a single CBS, whereas a higher magnitude (bottom panel) results in unfolding of all the CBSs. Differences in the number and/or type of unfolded CBS can lead to an amplified or an altered downstream response. Talin is an example of such a mechanosensor. **b.** Multimolecular scale: Magnitude sensing can occur because of serial linkage between different mechanosensors such as in focal adhesions. At low ECM stiffness (left panel), on initial integrin–ECM binding, slow loading rate results in dissociation of the integrin–ECM catch bond before force transmission and unfolding of the talin molecule. At higher ECM rigidity (right panel), optimal loading rate results in stabilized integrin–ECM linkage and transmission of forces to talin and its unfolding leading to a subsequent downstream cellular response. **c.** Cell and tissue scale: Magnitude sensing can arise on a cellular scale by distinct mechanosensors responding to different magnitudes of force, as shown for the amplitude-dependent response of cells to uniaxial stretch. Epidermal cells exposed to 5% cyclic stretch show deformation of the nucleus, which induces Piezo1-mediated calcium release from the endoplasmic reticulum and changes in heterochromatin resulting in nuclear softening. Forty percent cyclic stretch results in a similar initial Piezo1-mediated response and leads to the subsequent cadherin-dependent supracellular alignment of the epithelial layer and the actin cytoskeleton, both contributing to nuclear protection to mechanical stresses.

potentiate diversity in mechanotransduction pathways dependent on the level of forces.

In addition to the force magnitude–dependent regulation of individual mechanosensors, magnitude sensitivity originates from molecular assemblies containing multiple mechanosensors with different thresholds of activation. This has been shown for ECM stiffness–dependent mechanotransduction by FAs, which requires simultaneous engagement of the integrin–fibronectin catch bond and the unfolding of talin (Figure 2b). As both events only occur within a selective force range, this confers sensitivity to the level of stiffness [20,21]. Magnitude sensing may not only rely on cooperativity between mechanosensors within these molecular assemblies but could also involve their mutually exclusive function. For instance, tensile forces can strengthen the link between actin and β-catenin/α-catenin at cadherin adhesions [22], but also induce the release of β-catenin from cadherin to allow its transcriptional function [23], which potentially can be explained by distinct force thresholds. Magnitude sensing can similarly arise on a cellular scale, from distinct types of mechanosensors localized distal from each other becoming activated at different force magnitudes. This is, for instance, implicated in the different mechanisms of nuclear stress protection dependent on strain magnitude, with low strain levels inducing Piezo-mediated nuclear softening and high strain levels also resulting in alignment of cells and their actin cytoskeleton in a cadherin-dependent manner (Figure 2c) [24].

Specific sensitivities of different mechanosensors allow for assembly of circuits in which the cellular sensitivity to mechanical cues can be modulated. For instance, different integrin subtype and ligands [25], different members of the same mechanosensor family (e.g. talin-1 and talin-2 [26]), or splice variants of the same mechanosensor (e.g. of Piezo-1 [27]) can respond to different levels of force. Moreover, the mechanical state of the cell itself (i.e. actomyosin contractility and cellular stiffness) will impact how cells respond to external mechanical cues, by affecting membrane deformability or applying pre-stress on mechanosensors that lowers their threshold for ectopic forces. These mechanisms further contribute to the complexity in regulation of the dynamic range and sensitivity of cells and the diversity in cellular responses to changes in force magnitudes.

Decoding directions of forces

As forces are vector quantities that not only have a magnitude but also have a direction, they intrinsically provide directional information unlike biochemical signals that require a gradient. Directionality, which for instance originates from direction of blood flow or tissue strain, can result in anisotropic cellular responses and thereby establish polarized cellular outcomes. As such, directional tension in epithelia results in the alignment of cell divisions and collective migration along the tension axis through mechanotransduction at AJs [28,29]. Similarly, most cell types orient themselves perpendicular to the direction of uniaxial stretch, relying on the anisotropic mechanoresponse and disassembly of FAs [30]. The regulation of AJ dynamics may also depend on the force direction, as forces distributed perpendicular to cell–cell contacts stabilize AJs, whereas parallel shear forces have been shown to result in their disassembly [31].

In addition to establishing polarized cell behaviors upon directional forces, individual mechanosensors can elicit different responses dependent on the orientation of forces applied on it. Piezo1 senses both tensile and compressive forces in epithelia that can induce cell division and extrusion, respectively [32]. Interestingly, Piezo1 shows different sensitivities to these opposing forces [33], although distinct responses may also involve different cellular pools of Piezo1 and/or the effect of calcium influx in compressed versus stretched cells [32]. Several mechanotransduction pathways have further been shown to be selectively activated only when forces are exerted in a specific orientation. For instance, signaling through the mechanosensitive TCR/MHC complex in T-cells occurs efficiently only when forces are applied parallel to the binding interface [34]. Along the same lines, only unidirectional shear forces on endothelial cells activate integrins and force-sensitive calcium channels to trigger an athero-protective response [35–37].

The mechanisms by which mechanosensors convert directional information into direction-specific cellular responses still remain poorly understood. This may rely on the organization of mechanosensors in the cell being anisotropic and/or their mechanical activation (e.g. catch bond or CBS unfolding) occurring most efficiently when forces are applied in a particular geometry. Indeed, stabilization of the connection between actin filaments and adhesion complexes was recently proposed to be dependent on the direction of actomyosin-generated forces. The catch bond interaction between vinculin and actin preferentially occurs when forces are directed to the minus end of actin [17], and similar directional asymmetry may underlie α-catenin/actin binding [38]. Furthermore, the interaction between vinculin and its CBS in talin, and other force-dependent interactions, is more stable when tensile forces are applied parallel instead of perpendicular to the binding interface [39]. This geometry dependence of the force-mediated stabilization of actin interactions with cell adhesions biases the organization of the actin filaments. Similarly, the activation of mechanosensors by external forces may rely on their own geometry and orientation relative to the force vector. This organization of mechanosensors is

likely anisotropic, and therefore, only a fraction of molecules may sufficiently align with the direction of force to become activated, whereas unaligned mechanosensors may be irresponsive or respond less (Figure 3). Importantly, anisotropic forces can also become isotropically redistributed across the cell via transmission to the cytoskeletal network [40], and as such, the anisotropy of the cytoskeleton will likely aid in the polarized cellular response to directional cues.

Decoding dynamics of forces

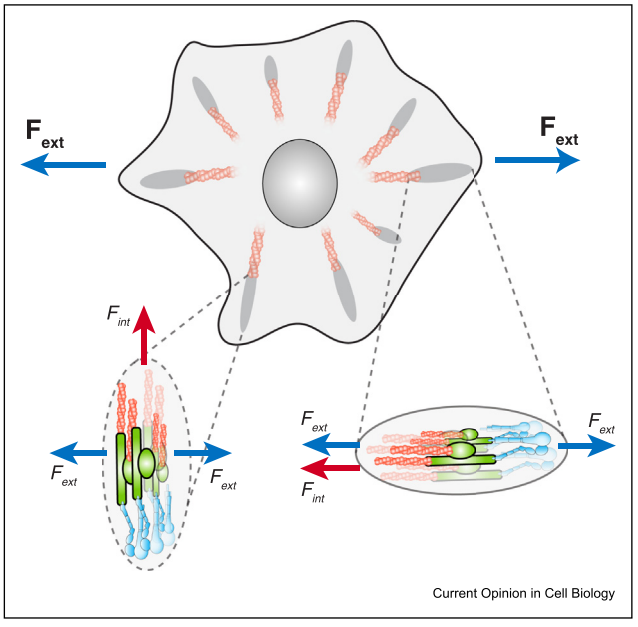
Forces acting on cells can be short-lived, lasting on the order of seconds, such as acute strain, or hours and days, such as morphogenetic movements or a remodeled ECM. Similarly, the cellular mechanoresponse to these cues occurs at various time scales, as reviewed in [41]. In addition to variable durations, forces can oscillate over time, for instance due to pulsatile stretching of arterial walls or 'tugging' cell–ECM interactions [42]. These oscillatory forces result in distinct cellular outcomes compared with static forces, such as selective activation of signaling pathways and cellular reorganization by cyclical stretch or hydrostatic pressure [40,43–45]. Moreover, cells can respond distinctly to different frequencies of force oscillations, which has for instance been shown to affect the level of cellular alignment to axial strain [46].

Oscillation-dependent responses can be explained by the activation of mechanosensors being dependent on the temporal dynamics of the force. For instance, cyclical forces can increase the bond lifetime of catch bonds compared to static forces by favoring the transition to a strongly bound state, as has been experimentally demonstrated for the α5β1-FN catch bond [47]. Recent findings further demonstrate that mechanosensors can act as bandpass filters, as their transduction efficiencies vary with stimulus frequency. This has been demonstrated for Piezo, which is rapidly inactivated after its force-dependent opening. As a result, the amplitude of Piezo activity can be altered by repetitive forces, which has been shown to be dependent on the stimulation frequency [48]. Recently, the unfolding–refolding events of talin were shown to synchronize with oscillatory forces, but this only occurs at specific frequencies [49]. Although the functional significance and underlying structural explanation of these mechanisms remain to be elucidated, these studies indicate that different mechanosensors can interpret and selectively transduce frequency-dependent mechanical information.

The loading rate, or the speed at which forces are applied, is also a critical determinant of the cellular response. Strain rates, for instance, vary between different tissues, being high in rapidly extending tissues such as the lung during air inhalation and low during morphogenetic movements. The rate of forces exerted by cells themselves depends on the viscoelastic properties of the ECM, which can lead to distinct levels of adhesion strengthening and cell spreading [21,50]. Similarly, the ability of cell–cell adhesions to withstand mechanical stress through induction of actin remodeling occurs in a strain rate–dependent manner [51]. These differences in loading rate may directly impact transduction efficiencies of mechanosensors, as unfolding of cryptic sites and binding kinetics of formed interactions of several mechanosensors are dependent on loading rate [52].

Finally, sensing of temporal dynamics of forces depends on the timescale at which the forces change, relative to the timescale of activation and inactivation of mechanosensors as well as their turnover rate. A mismatch in

Figure 3



Anisotropic mechanical cues acting differentially on mechanosensitive complexes across a cell. Cells are exposed to anisotropic forces such as uniaxial strain (F_{ext}). In this example, focal adhesions in a cell span a range of orientations across the cell, and thus, the angle between different adhesions and external strain also varies. Within a single focal adhesion, forces generated from the acto-myosin contractility and resistance from the ECM result in anisotropic internal tension or force (F_{int}), which also results in anisotropic organization of different molecular components. The net resulting force acting across a focal adhesion and all of its components is thus dependent on its orientation with respect to the external force and the magnitudes of internal and external forces. In the two example focal adhesions shown, an adhesion perpendicular to the direction of strain (bottom, left) will have a different resultant force acting across all its molecular components (integrin–ECM, talin–vinculin, vinculin–actin) compared with a focal adhesion parallel to the direction of strain (bottom, right). These differences across a cell or even tissues can result in differences in activation of the different mechanosensory components and have downstream effects on adhesion fate (assembly versus disassembly), signaling, and cell and tissue scale outcomes.

these timescales would result in cells losing the temporal information of forces acting on it, thus leading to a different response.

Interplay between different mechanosensors and with biochemical signals

Although different mechanosensors can elicit diverse responses, they frequently impinge on the same cellular processes and can coordinate the response. For instance, mechanotransduction through integrins, cadherin adhesions, and Piezo control progression through multiple phases of the cell cycle [32,53–56]. Similarly, Piezo-mediated nuclear softening and E-cadherin–dependent cellular realignment together coordinate nuclear protection against mechanical stresses [24]. Multiple mechanosensors also act on the same signaling pathway, as extensively shown for the regulation of the Hippo pathway (reviewed in [57]). Analogously, β-catenin–mediated transcription is mechanically activated by its phosphorylation at cadherin adhesions [23], as well as by integrin-mediated inhibition of the destruction complex [58]. Through these interconnectivities, mechanical cues acting on distinct mechanosensors may not only elicit similar biological responses but also enable different mechanosensors to act together and ensure robustness (or diversification) of the response.

Coordination not only arises through interplay at the level of downstream mechanotransduction pathways, but mechanosensors also influence how forces are distributed on and transduced by one another. This has been extensively studied for FAs and AJs, between which force distribution is balanced by their connection through the actin cytoskeleton (reviewed in [59]). As such, increased matrix stiffness sensed by integrins also results in elevated tensile forces at AJs [60], and vice versa, AJs modulate traction forces exerted by integrins [61–64]. More recently, Piezo was shown to associate with FAs and to be activated at sites of traction forces [65,66]. Conversely, Piezo contributes to the generation of traction forces by FAs and their sensitivity to substrate stiffness [66,67]. Many other examples of interplay by which individual mechanosensors, both locally (at the same complex) or distally (across complexes, e.g. adhesions and nucleus), impact each other's regulation and function have been uncovered [5,68–71], which constitute the complexity of the cellular response to mechanical cues.

Besides cross talk between different mechanotransduction machineries, the cellular response to mechanical forces relies on their interplay with biochemical cues (e.g. growth factors). As mechanotransduction entails conversion of forces into an intracellular biochemical response, forces will impinge on similar pathways and cellular processes regulated by these growth factor signals. Moreover, forces can regulate the very same receptors activated by biochemical ligands, in which they control receptor activity either at the level of binding of the receptor ligand itself (e.g. for EGFR [72], and TGFβ-R [73], in a ligand-independent manner [plexin D1 [5]]) or potentially both (e.g. notch [68,69]). Mechanical and biochemical cues may hereby synergistically trigger downstream signaling pathways. In contrast, some receptors show selective downstream signaling in response to mechanical activation [68] or trigger distinct signaling pathways when activated either by mechanical cues or its biochemical ligand [5].

Importantly, the biochemical response induced by mechanosensors can modulate the original mechanical cue. This biochemical feedback can be established by attenuating the level of force on individual mechanosensor molecules (e.g. by inducing FA growth) or by triggering a cellular response that dissipates the original forces (e.g. by inducing proliferation and consequently reducing tensile forces). Adding to this complexity, biochemical pathways can impinge on the cellular force-generating machinery. This can attenuate cellular sensitivity to mechanical cues [74], and also propagate mechanical forces across the tissue as recently shown via the reciprocal regulation of ERK activity and tensile forces between neighboring cells [75].

Conclusions and future perspectives

Cells are exposed to a variety of mechanical forces that they sense and transduce through their repertoire of mechanosensors. The cellular responses to these forces depend on the magnitude, direction, and temporal dynamics of the acting forces. We are beginning to understand how cells extract this spatiotemporal information, through distinct sensitivities of the mechanosensors and their underlying transduction mechanisms to these different force parameters. Although these mechanisms are better established for some mechanosensors, they remain to be elucidated for many of the recently discovered ones. To transmit mechanical information, mechanosensors do not function in isolation, and it is now emerging that different mechanosensors across the cell are integrated and form molecular circuits that coordinate the cellular responses to mechanical cues. The cytoskeleton not only serves as a key integrator of these molecular circuits but also serves as a mesoscale mechanosensor with its own layer of regulation and dynamics. These interconnectivities underscore the need for system-level approaches to investigate mechanotransduction both at the cellular and tissue level, including the cross talks between mechanotransduction pathways and the interplay with biochemical signals. These approaches together with recent advances in technologies, which allow for precise control over different force parameters and visualization

of forces and their responses in complex tissues, will lead to a better understanding of mechanotransduction across different scales and tissues.

Conflict of interest statement

Nothing declared.

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