Revision

Tensile forces and mechanotransduction at cell-cell junctions.

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Abstract

Cell-cell junctions are specializations of the plasma membrane responsible for physically integrating cells into tissues. We are now beginning to appreciate the diverse impacts that mechanical forces exert upon the integrity and function of these junctions. Currently, this is best understood for cadherin-based adherens junctions in epithelia and endothelia, where cell-cell adhesion couples the contractile cytoskeletons of cells together to generate tissue-scale tension. Junctional tension participates in morphogenesis and tissue homeostasis. Changes in tension can also be detected by mechanotransduction pathways that allow cells to communicate with each other. In this review, we discuss progress in characterising the forces present at junctions in physiological conditions; the cellular mechanisms that generate intrinsic tension and detect changes in tension; and, finally, we consider how tissue integrity is maintained in the face of junctional stresses.

Introduction

Cell-cell junctions are specialized regions of the plasma membrane that couple cell surfaces together: they make tissues out of what would otherwise be disconnected populations of cells [1]. Intercellular contacts can be transient interactions that regulate collective migration of mesenchymal cells [2] or stable junctions that allow epithelia and endothelia to form tissue barriers in the body [3]. Central elements that define the type of intercellular junction are specific transmembrane receptors whose extracellular domains mediate cell-cell engagement and whose cytoplasmic tails interact with signaling and cytoskeletal networks. These membrane-embedded receptors are also regulated by membrane trafficking [4] and the local lipid composition of the membrane [5]. On the other hand, junctions can also influence features of the membrane such as local curvature and cytoskeletal organisation in the submembranous actomyosin cortex. However, less is known about how mechanical forces arising in physiological functions or in development interplay with junctions.

In this review, we focus on intercellular adhesion junctions and our emerging understanding of how their biology is adapted to their mechanical function. Cell adhesion systems resist forces that would tend to tear the tissue apart (or tensile forces). Thus, almost by definition, their biology has evolved to fulfil the mechanical nature of their function. It is often assumed that cell-cell adhesions resist tensile forces that are *extrinsic* to their tissues, such as are applied to the skin and

pulmonary epithelium. More recently, however, two major developments have revolutionized the way we think about forces at junctions.

First, we have come to appreciate that many of the forces that act on junctions are generated by the cells of the tissue themselves; i.e. they are *intrinsic* forces. These are generally tensile forces that arise when adhesion is coupled to the contractile actomyosin cytoskeleton. They were first identified, during morphogenesis in the embryo [6, 7] however, they are also evident in more quiescent adult tissues, especially epithelial and endothelial monolayers [8-10], where they may participate in barrier maintenance [9] and proliferative control [11]. Second, it is increasingly apparent that changes in mechanical force can be sensed at cell-cell junctions [12-14]. This implies that, as well as contributing to morphogenesis and tissue integrity, mechanical forces at junctions may provide a mode of cell-cell communication that can complement better-understood biochemical modes of communication via gap junctions or secreted factors. Indeed, potential advantages of mechanical signals are that they can propagate very fast and, when there is little ECM, they can propagate very far [15].

Accordingly, in this review we will consider the characterization of mechanical force at cell-cell junctions; the cellular mechanisms responsible for generating force and sensing changes in force at junctions; and, finally, some of the biological implications of force-generation and force-sensing. We principally focus on adherens junctions (AJ) in epithelia and endothelia, where the classical cadherin adhesion complex interacts with the actomyosin cytoskeleton. However, it is likely that the same principles will apply to other types of cell-cell junctions, such as tight junctions and synapses, which are connected to the actomyosin cytoskeleton.

Characterizing forces at junctions.

Recent efforts to understand the mechanobiology of intercellular adhesion have characterised the forces involved on three scales: at the level of molecular adhesion complexes, cell-cell junctions, and tissues (Fig 1). These also correspond to the scales studied in biochemistry and single molecule studies, cell biology, and developmental biology. Definitions of the mechanical terminology used in the following can be found in Text box 1 and a brief overview of the forces acting at junctions can be found in Text box 2.

Tissue-level forces. Forces acting at the tissue level have been best characterized in epithelia (Fig 1a). Stresses *in vivo* have primarily been studied using laser ablation techniques where tensile stresses were revealed by the rapid opening of wound edges following cutting [16-20]. More recently, analyses of the spatial pattern of junctional morphology using Bayesian inference techniques have also reported predominantly tensile stresses within epithelial tissues [21-23]. *In vitro*, stress distributions in epithelial monolayers can be inferred from traction force microscopy measurements [24, 25] and here, again, stresses are generally tensile.

As noted above, tensile stresses on tissues may arise from intrinsic or extrinsic sources. In early embryonic epithelia where little or no ECM is present, stresses generated by actomyosin contraction of the cells in one tissue are transmitted over long ranges via intercellular adhesions to other tissues. Thus, intrinsic tension generated in some embryonic tissues acts as extrinsic stresses on other tissues. For example, in the Drosophila wing disk, contraction of the wing hinge applies tension on the wing blade [26, 27]. During dorsal extension, stresses exerted by the invaginating dorsal midgut play a role in orienting junction elongation after intercalation [28]. During epiboly in zebrafish, an actin belt in the yolk cell applies tension on the enveloping layer [29]. When a stiff ECM is present, however, spatial stress distributions vary more rapidly [24, 30, 31] indicating that stress transmission operates over shorter ranges (~5-10 cell diameters) [31-33]. Interestingly, recent

work examining tissues on ECM revealed that they can transmit long range stresses on hour-long time-scales [31, 33]. The origin of such long range transmission is not fully understood and it likely involves complex cycles operating on second to minute time scales. These may involve multiple cellular-scale phenomena such as cellular contraction, mechanotransductory responses, and contact inhibition. Later in life, extrinsic loads arise from systemic functions (such as respiration, digestion, or pulsatile fluid flow) and from loads due to interaction with the outside world, in addition to contractions intrinsic to the tissue.

It is important to note that the rate at which tissues are deformed (known as the strain rate – see box 1) influences the peak stresses to which cells are subjected. In embryonic epithelia, strain rates are low (~0.4%/s during Drosophila germ band extension, [34]), whereas in adult tissues, strain rates can be very high (>10%/s; [35-37]). On second to minute time-scales, most biological tissues behave as viscoelastic solids, which signifies that they are elastic like solids at minute time-scales but also display viscous properties at short time-scales (see box 1). When strain rates are low, loading is quasi-static, signifying that only the tissue's elastic properties are solicited. In contrast, when strain rates are high, the tissue's viscous properties are solicited in addition to its elastic properties leading to additional stress. As a result, tissues are subjected to transiently higher peak stresses when deformed at high strain rate and adhesions must be able to withstand this. The duration of such peak stresses is complex to evaluate *in vivo* but *in vitro* measurements on cell monolayers show that they last on the order of a minute [38, 39]. Adding further complexity, the duration of the applied load plays a role in the final steady state. Indeed, on minute to hour time-scales, tissues behave as viscoelastic fluids, which can bear stresses at minute time scales but completely dissipate stress at hour-long time scales (box 1). When subjected to short pulses of contractility, tissues behave as elastic solids but, in response to longer pulses of contractility, they behave as viscous fluids and adopt the imposed shape as their rest shape [40]. Thus, when discussing adhesions, it is important to consider the physiological loading conditions to understand mechanotransduction and rupture. Interested readers are referred to recent reviews [39, 41].

In contrast to these tensile patterns in epithelia, few measurements of stress distribution have been carried out in other highly cellularised tissues, likely because of experimental and analytical challenges. However novel techniques relying on calibrated fluorocarbon vesicles functionalised with cadherins have revealed that, anisotropic compressive stresses appear to dominate in organoids or the tooth bud [42, 43]. In addition, forces in epithelia can transiently and locally become compressive. It is unclear how mechanical information stemming from compression of junctions is integrated, although shear stresses might stimulate cadherin-catenin complexes [43, 44]. In support of this hypothesis, cells in monolayers try to minimise the magnitude of shear stresses to which they are subjected [24]. However, more generally, relatively little is known about shear stresses within tissues. In cultured epithelia, compressive stresses give rise to cell extrusion or delamination [45] and appear associated with local mismatches in the alignment of cellular long axes [46]. In these experiments, loss of α-catenin leads to an increase in the number of mismatches and extrusions within the epithelium, again suggesting a role for signalling downstream of junctions in optimising epithelial organisation. Thus, although it is unclear how cadherin-catenin complexes sense shear and compressive stresses, they appear to play a role in mediating cellular reactions to these stimuli.

Stresses on junctions. *In vivo*, little is known about the forces that exist across whole intercellular junctions. Recent work where intercellular junctions were trapped with optical tweezers has revealed junctional tensions of ~50-300pN in the AJ of early *Drosophila* embryos [47]. *In vitro*, quantitative measurements have revealed the presence of tensile forces of ~50-100nN across lateral intercellular junctions in

cultured mammalian epithelia [48, 49]. Although the range of forces appears very different, the height of the junctions and the density of adhesive complexes must be taken into account when we compare them. If the density of adhesive complexes is similar, the smaller height of the AJ in Drosophila tissue compared to cuboidal cultured cells (100-500nm vs 10μm [50]) might suggest that the stress at AJs are similar *in vitro* and *in vivo*, on the order of ~100Pa, a value consistent with stresses measured in monolayers [24] (Fig 1a,b). However, in response to high deformation or rapid loading, stresses at junctions can reach several kPa, several fold higher than at rest [38, 51].

Molecular-level forces. To determine the force acting on each adhesion complex, we must know the density of cadherins engaged in intercellular adhesion at cell-cell junctions. In cultured epithelia and Drosophila embryonic tissues, superresolution microscopy techniques have revealed cadherin densities of ~2000 molecules/μm^2 in adherens junctions [52-54]. Based on this, we can estimate that each cadherin-catenin complex is subjected to a tension of ~5pN under resting conditions rising to ~50pN in stressed conditions. Biochemical studies and superresolution imaging [53] show that E-cadherin, β-catenin, and α-catenin are arranged in series, signifying that each protein within this complex is subjected to the same tension (Fig 1C). In cultured epithelial cells, FRET reporters that measure tension based on the unfolding of soft unstructured domains have revealed that individual cadherin-catenin complexes are subjected to tension on the order of 2pN under resting conditions [9, 10, 55, 56] [57], consistent with our estimate.

Building intrinsic tension at adherens junctions

Intrinsic tension at cell-cell junctions arises when adhesion receptors are coupled to the contractile cytoskeleton. One such structure is the submembranous cell cortex, which is a ubiquitous contractile structure composed of actomyosin [58]. Minimally, tension could be exerted on cadherin-catenin complexes if they were to couple the cortices of two adjacent cells. However, adhesion may not be essential for cadherins to interact with the cytoskeleton, as cadherin expressed on the surface of single isolated cells is subject to cortical actomyosin flows [59]. This adhesion-independent interaction might reflect uncomplexed cadherins that are trapped in mobile corrals of F-actin or weak binding of cadherin-catenin complexes to the cortex [60] [61, 62]. Evidence for the latter comes from the observation that molecular tension across E-cadherin was evident even in surfaces of epithelial cells not engaged in adhesion [55], although this appears cell-type specific [10]. In any case, tension across cadherin-catenin complexes increases when cadherins engage in intercellular adhesion. One possibility to explain this increase is that the initiation of intercellular adhesion stabilises the physical association between the cadherin molecular complex and the actomyosin cytoskeleton. This phenomenon may be due to specific properties of the cadherin-catenin complex. Indeed, when subjected to increasing load, the bond between the cadherin-catenin complex and F-actin acts as a catch bond [63, 64], signifying that its dissociation time increases. Conversely, bonds for which the dissociation life decreases with increases in load are known as slip bonds. Thanks to these catch bond properties, loading of the cadherin molecular complex by initiation of adhesion should stabilise its engagement with the cortical cytoskeleton.

Such force-sensitive coupling of cadherins to the cortical actomyosin network may represent a mechanism for junctional tension to be generated when cells first engage one another (Fig 2a). However, intercellular adhesions strengthen over time [65] and with the application of force [66, 67]. This may be due to multiple signalling mechanisms that allow prolonged adhesive engagement to remodel the contractile cortex (Fig 2b). First, cadherin adhesion promotes local actin assembly through Arp2/3 [68, 69] and formin nucleator activity [9, 70-72], which both contribute to

junctional tension [9, 73]. Interestingly, however, the earliest phases of cadherin-based actin assembly appear dominated by Arp2/3 [69, 74]. Arp2/3 generates branched actin networks that contrast with the prominent bundled structures seen at the zonulae adherentes of mature polarized epithelia. As bundled F-actin organization is likely more efficient in producing contractility, this suggests that reorganization of branched networks into bundles may help increase junctional and tissue tension [75]. Consistent with this concept, proteins participating in the disassembly of branched F-actin networks (such as Coronin 1B, [76]) and the assembly of linear contractile structures (such as the formin mDia1 [72, 77]) promote junctional tension [9, 74].

Second, cadherin adhesion promotes the activation and junctional recruitment of non-muscle myosin II (NMII) [78]. This occurs through the combination of cadherin-based cell signaling and the generation of linear F-actin networks favourable to NMII binding. Thus, although it is down-regulated when cells first contact one another [79, 80], RhoA becomes active as AJ mature [81, 82] and, indeed, is established in a prominent zone when cells develop contractile zonulae adherentes [83]. This reflects regulatory pathways that are elicited by adhesive engagement of the cadherin/catenin complex, such as recruitment of centralspindlin/Ect2 to junctions by α-catenin [83]. Cortical proteins, such as synaptopodin [84] and F-actin [85] itself also contribute to stabilizing NMII at junctions. Together, these pathways for actin regulation and NMII activation constitute mechanisms that can allow cadherins engaged in intercellular adhesion to enhance the intrinsic contractile capacity of the cell cortex, and thereby increase junctional tension.

By contrast, it is less clear whether regulated changes in cadherin adhesion contribute to modulating junctional tension. Here it is important to note that at cell-cell junctions, the resistive element in tension is active, arising from the actively remodelling cytoskeleton of neighbouring cells, whose mechanical force is transmitted through adhesions. This contrasts with cell-matrix adhesion where the resistive element (the ECM) is essentially passive. Therefore, increasing cadherin adhesion could potentially increase tension by promoting greater mechanical coupling between cells. Developmentally-regulated association of cadherin adhesion to cytoskeletal contractility has been reported [86, 87], but whether cadherin adhesion is altered to modulate tension is less clear.

Mechanosensors and transducers at cell-cell junctions.

The ability of AJ to transmit tension, taken with their location at the cell periphery, makes them ideal sites for cells to detect changes in tension. Mechanotransduction entails the conversion of mechanical information into biochemical signals that alter cellular behaviour [88, 89]. Indeed, recent studies have demonstrated that the application of force to E-cadherin induces its association with signaling molecules, including many protein kinases, and their activation [66, 67, 90]. These signals must represent the outcome of molecular cascades beginning with molecules that sense changes in junctional tension (mechanosensors) and that couple to downstream signaling pathways. There are several ways in which this can occur.

Force-sensing through the cadherin molecular complex. Efforts to identify mechanosensors at AJ have principally focused on elements of the cadherin molecular complex (Fig 3a). Here it is noteworthy that although classical cadherins are under tension at junctions [10, 55, 56, 91] and necessary to transfer contractile signals between cells [74, 92], there is no evidence yet that their molecular function is altered by tension. If so, cadherins may principally serve to passively transmit changes in contractile forces between cells. The minimal cadherin-β-α-catenin complex can then be regarded as protein springs organized in series where each

element bears the same tension, but the extent to which each protein deforms depends on its stiffness. The softest element will be the mechanosensor. Here, the most-intensively studied candidate is α–catenin, which is well-placed to sense changes in force as it directly bridges between the cadherin/β-catenin complex and F-actin. Indeed, FRET-based molecular tension sensors have revealed that junctional α–catenin is under tension generated by actomyosin contractility [9].

This has led to the engaging hypothesis that force-induced changes in its molecular conformation allow α–catenin to serve as a mechanotransducer. This notion was prompted by early evidence that α–catenin can be autoinhibited by intramolecular interactions that mask binding sites for associated proteins [13, 93] . The concept was reinforced by FRET-based conformational sensors and super-resolution imaging that indicated that α–catenin was present in an open configuration at cadherin adhesions [53, 94]. However, it should be noted that all proteins can be conformationally altered by mechanical force; what is important to determine is if those responses occur for physiologically-relevant forces and affect signal transduction. In vitro work has estimated that tensions of ~5pN are sufficient to unfold α-catenin [95], in the same range as estimates of basal forces that adhesive complexes may experience in epithelia. Furthermore, stimulation of contractility in cells exposes cryptic epitopes near the vinculin-binding region of α-catenin [13] and promotes the recruitment of vinculin [14]. These observations support the general hypothesis that α-catenin may be a mechanosensor that transduces force into biochemical signals via conformational change. Furthermore, α-catenin has diverse potential binding partners, such as p115 RhoGEF [96] that can promote RhoA signalling.

Force-sensing by the junctional cytoskeleton. Although it has been studied extensively, α-catenin is not the only potential force sensor at adherens junctions. Tension exerted on cadherins is transmitted to the cytoskeleton and many mechanosensitive cortical proteins, such as formins and filamin B are found at AJ [9, 70, 97, 98] [99-101]. Especially interesting are Myosin motors (Fig 3b), several of which (I, II, VI, VII and IXa) have been reported at AJ. The mechanochemical cycle that governs interaction of their motor head domains with actin filaments is intrinsically mechanosensitive [102]. In particular, resistive forces that act against the direction of movement of the myosin head delay the detachment of the motor from the actin filament and thereby stabilize its subcellular localization. An increase in the tension transmitted through the AJ can increase resistive loading on myosins found in the junctional cortex, thereby promoting their junctional localization. Once localized in response to force, myosins also possess a diverse capacity to influence cell signaling. Non-muscle Myosin IIA can regulate the availability of Rho-family GEFs [103, 104] and scaffold bistable feedback networks that reinforce RhoA signaling [82, 105]; while Myosin IXA bears a RhoGAP domain that limits RhoA signaling when cells first contact one another [106]. As motors such as Myosin II have been identified as cortical mechanosensors in single cells [100], their role in junctional mechanotransduction may then represent another instance where fundamental mechanical elements of the cell cortex become co-opted in the specialized case of an adhesive junction.

Of note, the extent to which transmitted forces result in load upon myosin will depend on the degree to which the junctional actin network is free to slide relative to the membrane and on how crosslinked it is. Therefore, the prevalence of the mechanosensitive response of junctional myosins will also depend on the properties of their associated actin filament networks. Simplistically, resistive forces can convert filament-sliding motors into localized, dynamic anchors acting as additional crosslinks. As the elastic modulus of gels depends on the density of crosslinks, extra crosslinking via myosins induced by mechanical stress will naturally lead to stiffening

of the cytoskeleton. The crosslinking role of myosins has been well-documented for Myosin II [107] and VI [108], so is likely a general feature of many myosins.

Force sensing by the junctional membrane. A third force-sensitive element at AJ is the plasma membrane itself, whose curvature can be affected by local cortical forces (Fig 3c). This is observed when cells make so-called focal adherens junctions, finger-like projections that are oriented transverse to the cell-cell interface. These are commonly seen in migratory endothelial cells [109-111], where they reflect differences in contractile forces across the junction, but are also found in other cell types [109]. Such structures would be expected to be associated with deformations of the plasma membrane that could potentially be sensed by BAR domain proteins [112]. Indeed, the F-BAR protein, Pacsin 2, was recruited selectively to the trailing (concave inwards) surfaces of these adhesions, a phenomenon that required its curvature-sensing F-BAR domain [109] The capacity for BAR proteins to interact with signalling and cytoskeletal proteins then provides an additional pathway for signal transduction.

Functional consequences: the need to preserve tissue integrity against stress.

Coupling contractility to AJ contributes to a wide range of biological phenomena, from morphogenetic movements to the regulation of cell proliferation (reviewed in [113]). Although these phenomenona operate over a wide range of time- and length-scales, a fundamental challenge in all cases is for tissue integrity to be maintained despite the application of force. Quantitative measurement of stress at rupture indicates that intercellular junctions in epithelial monolayers can withstand stresses of several kPa before fracturing [38, 51]. This suggests that forces of >50pN will rupture individual cadherin-catenin complexes, an estimate consistent with single protein experiments which indicate that rupture occurs for forces of >30pN [95] and within the realistic range to be expected from either intrinsic or extrinsic stresses. As each protein within the cadherin-catenin complex is subjected to the same tension, the point of rupture will be determined by the weakest bond in the series. This could be the adhesive bond that couples cadherins together, one of the cytoplasmic bonds that couple the proteins within the cadherin-catenin complex [114], or one of the bonds that couple them to the cytoskeleton. Furthermore, when an adhesive bond dissociates, the load on the remaining bonds increases because the overall force becomes distributed over fewer adhesive complexes. This in turn increases the probability of further bonds rupturing, potentially initiating a catastrophic rupture of the cell-cell adhesion. We are only just starting to understand the diverse mechanisms that tissues use to preserve their integrity in response to stress. For the purposes of our current discussion, it is useful to consider two classes of response: mechanisms that reinforce junctions against stress and mechanisms that can dissipate stresses. As we shall discuss, some of the functional consequences of junctional mechanotransduction may be interpreted as solutions to the challenge of maintaining epithelial integrity.

Reinforcement of junctions in response to stress. One way to reinforce junctions against stress is to make detachment less likely. Catch bonds, whose probability of unbinding decreases when stress is applied, are an elegant solution. To date, the extracellular domain of E-Cadherin, the cadherin-actin interaction mediated by α–catenin, and the vinculin-actin interaction have all been shown to possess catch-bond properties [115, 116]. In particular, E-Cadherin-E-cadherin bonds show a maximum in their lifetime when subjected to forces in the range of those predicted to induce rupture (~35pN [116]). However, such a solution can only be temporary because it impedes the normal function of proteins and it must therefore be complemented by another type of reinforcement to prevent junctional rupture.

Reinforcement against stress can also be achieved by increasing the number of adhesive complexes in a junction. This seems to occur in simple epithelia, where E-cadherin is stabilized and concentrated into zonulae adherentes at the regions of greatest tension within junctions [85, 117]. Such coordination may reflect several mechanisms that couple the distribution of cadherins to cortical actomyosin (Fig 4a). These include movement of cadherin linked to the cytoskeleton [118], which are predicted to flow towards sites of higher contractile stress [105, 119, 120]; clustering of cadherin by F-actin [54] and myosin [121]; and cortical actin regulation [9, 54, 73]. Some of the recently-identified stress-responsive mechanotransductory pathways can reinforce junctions by these means. For example, when pacsin-2 is recruited to regions of high membrane curvature, it strengthens adhesion by inhibiting endocytic removal of E-cadherin from the membrane [109] (Fig 4b). Concomitantly, tension-sensitive recruitment of vinculin by α-catenin can promote junctional actin assembly through Ena/VASP proteins that also enhances E-cadherin accumulation [14] and clustering [122]. Indeed, mechanosensitive signaling pathways can have diverse downstream effects that collaborate to reinforce adhesion. This is exemplified by the activation of LKB-AMPK signaling when force is applied to E-cadherin [66]. This can promote the activation of vinculin at junctions via Abelson protein kinase signaling [53, 67] and also stimulate glucose uptake and ATP production to sustain the metabolic demands of enhanced actin assembly [66].

Protecting junctions by stress dissipation. The reinforcement mechanisms described above can also be complemented by strategies to dissipate stresses (Fig 5). One way is through the fluid-like behaviour of the actin cytoskeleton at minute-long time-scales [123]. These allow extrinsic stresses to be dissipated by molecular turnover of cytoskeletal components, thereby reducing the load on each adhesion complex [39-41] (Fig 5C). Molecular turnover is evident in the contractile actin networks that apply force to AJ [85, 124] and, conversely, AJ ruptured during Drosophila gastrulation when actin turnover by cofilin was blocked [124]. The time-scale over which these dissipative mechanisms act is likely commensurate with the molecular turnover time of the F-actin cytoskeleton and junctions, i.e. a few minutes [125, 126].

Over longer time scales, stress on intercellular junctions can be reduced by rearranging tissue organization through cellular intercalations or oriented cell divisions [18, 26, 27, 127, 128]. Both of these cellular mechanisms act along the same principle, redistributing cell mass such that mass is added along the principal stress axis (Fig 5B). During intercalation, cells rearrange their junctions such that the resulting length of the aggregate is increased. During a division, the combined long axis of the daughter cells is larger than that of the mother cell whereas their short axis is smaller, signifying that each division results in a lengthening in the direction of division and a shortening in the direction perpendicular to it, similar to the intercalations [127]. When most divisions or intercalations within a tissue are oriented, this results in a global lengthening of the tissue in the direction of stress. To understand how lengthening decreases the stress resulting from application of a constant deformation, we can grossly approximate the whole tissue to a spring. The force in a spring is proportional to how much it is deformed from its rest length. If the deformation is kept constant and the rest length increases, then the force will decrease. Rest length change can occur either at the cellular scale, as in oriented divisions and intercalations, or at the molecular-scale through remodelling of the cytoskeleton.

One interesting implication of this discussion is that several functional consequences of junctional mechanotransduction can be understood as higher-order consequences of mechanisms whose first function may be to preserve tissue integrity against stress. For example, cell intercalation during convergent-extension is driven by the application of pulsed contractions against AJ that induce cell shape

changes that must also be sustained when contraction is released after each pulse [129]. This can be achieved by the viscous dissipation of stress through actin turnover [40] that we discussed above as a mechanism to protect junctional integrity. Another interesting example is cell proliferation [11], which can be stimulated when stress is applied to epithelia, either by artificially stretching them [130] or by stimulating cellular contractility [131]. In the latter case, proliferation was mediated by Yap/Taz signaling that was disinhibited when elements of the Hippo pathway were sequestered at AJ in response to force [131]. Cell proliferation also represents a mechanism to reduce junctional isotropic stress, and can thus be considered a longer-term adaptation stemming from the need to preserve tissue integrity.

Future directions.

It is timely that the work that we have discussed comes at the centenary anniversary of D'Arcy Wentworth Thompson's "On Growth and Form". We are well-placed now to integrate the constraints that geometry and physical forces exert on biological systems with the rich mechanistic insights of the molecular revolution. It seems probable that the principles that operate at adherens junctions will apply to other cell-cell junctions. There are many interesting challenges for the future. We will mention just four. First, although we have focused on classical cadherins and adherens junctions, many other junctions mechanically couple cells, including desmosomes and tight junctions. How these bear force and whether they may regulate force is beginning to be studied. The function of the zonula occludens proteins of tight junctions is regulated by tension [132] and desmosomes influence tissue mechanics [133]. Moreover, many cells bear multiple cadherins and, while they often show degrees of redundancy, functional differences between them are emerging. An interesting example was reported for monolayer tension development in MCF10A cells, where P-cadherin was critical for the steady-state level of tension, while E-cadherin influenced the rate of stress development [8]. Second, we need to understand how mechanical integration within the cell affects junctions. Regions of the cortex that are physically separate from cell-cell contacts, such as the medial-apical domain, can be regulated separately from the junctional cytoskeleton. Yet, they will exert forces on junctions through cytoskeletal connections. Third, is to eludicated how mechanical properties at different physical scales relate to one another, and particularly how complex behaviours of larger scale structures emerge naturally from the interactions of their microscopic components. Finally, it should be noted that most attention has focused on circumstances where increases in junctional tension may elicit mechanotransductory responses. But, tension can also be reduced, as occurs across VE-cadherin when endothelial monolayers were exposed to fluid flow [10] and when epithelial monolayers were treated with hepatocyte growth factor (HGF) [134]. How junctional forces may be down-regulated, how they may be sensed, and what their functional consequences may be, remain to be elucidated. Clearly, much remains to be done.

Text box 1:

Mechanical terminology:

Tensile force: A force that would tend to tear a tissue apart.
Compressive force: A force that would tend to make a tissue more compacted.
Strain: Strain is a measure of a material's deformation from a reference shape. For example, in **diagram *A (left and middle)***, the epithelium originally has a length L_0 and it is stretched to a length L by an external force acting perpendicular to its surfaces. The strain in the direction of extension is defined as $\varepsilon = (L-L_0)/L_0$. It is known as the normal strain because the forces are acting normal to the boundaries of the material.
Stress: Stress is a measure of the tension exerted within a material. It is defined as a force per unit area. For example, the stress σ at a junction is the total force F exerted over the junction divided by its area A: $\sigma = F/A$.
Shear stress: When forces are applied tangential to the material's boundaries, they give rise to a shear stress (**diagram A, right**). The shear strain is defined as the deformation in the direction of the shear force divided by the original length perpendicular to it: $\gamma = {}^{\Delta L}/_{L}$.
Compressive/Tensile stress: when forces are exerted normal to the material's boundaries, they give rise to normal stresses (**diagram A, middle**). Stress is positive by convention if the force would tend to stretch the material. Thus, tensile stresses are positive and compressive stresses negative in this convention.
Strain rate: the rate at which a given strain ε is applied onto a material is called the strain rate and it is defined as $\varepsilon / \Delta t$ with Δt the duration of the deformation.
Elastic material: elastic materials are characterised by a reversible relationship between stress and strain regardless of the rate at which strain is applied. Rubbers provide good examples of elastic materials. In linear elastic materials, stress is proportional to strain with the Young's modulus or elasticity E being the proportionality constant: $\sigma = E\varepsilon$. The stress-strain relationship of an elastic material is represented in **diagram B**. E is the slope of the line.
Viscoelastic material: In viscoelastic materials, the stress depends on the strain rate of the deformation. When deformations are applied fast, stress reaches higher values than when they are applied slowly.
Viscoelastic solid: A viscoelastic solid presents viscous behaviours at short time scales but behaves as a solid at long time-scales, meaning that it bears load. When subjected to a step strain (**left, diagram C**), stress will be maximum immediately after loading (**right, diagram C**). Stress will be dissipated during a transitory period and the equilibrium stress will be non-zero. The transition between the two behaviours occurs for a characteristic time τ. If strain is applied sufficiently slowly, viscoelastic solids behave as elastic solids.
Viscoelastic fluid: A viscoelastic fluid presents solid behaviours at short time scales but behaves as a fluid at long time-scales, meaning that it will flow in response to stress. When subjected to a step strain (**left, diagram C**), stress will be maximum immediately after loading (**right, diagram C**). Stress will be dissipated during a transitory period and the equilibrium stress will be zero. The transition between the two behaviours occurs for a characteristic time τ. If strain is applied sufficiently slowly, viscoelastic fluids behave as viscous fluids.

Text box 2:
Forces acting at intercellular junctions.
A number of different forces act at junctions and together give rise to the net junctional tension (γ)These are described in detail in [135-138] and here we will only provide the briefest of summaries of these studies. Adhesion stemming for example

from the cadherins of one cell binding those of an adjacent cell will tend to make intercellular junctions longer because energy is released as more cadherins bind to one another. After the adhesion has formed, the cadherins interface to the actomyosin and hence the cytoskeleton also contributes to junctional tension. As actomyosin is contractile, it tends to shrink the junction. Thus, adhesion and contractility antagonise one another in junctions. To add further complexity to this picture, signalling signifies that functions are often interwined when sufficiently long time-scales are considered. For example, it is well-established cadherins can contribute to both adhesion and contractility. The net junctional tension can be written in the general form:

$$\gamma = F_{cytoskeleton} - F_{adhesion} + F_{other}$$

With $F_{cytoskeleton}$ the force exerted at the junction by the cytoskeleton, $F_{adhesion}$ the force exerted by adhesion at the junction, and F_{other} resulting from other forces acting on the junction of interest. Current experimental techniques allow measurement of the net junctional tension, which is always positive.

Acknowledgements
The authors wish to thank A Kabla (Cambridge), N Khalilgharibi and J Duque (UCL) for insightful comments on the manuscript; and apologise to colleagues whose work we have been unable to cite for reasons of space. GC is funded by a consolidator grant from the European Research Council (MolCellTissMech, agreement 647186). ASY was supported by the National Health and Medical Research Council of Australia (1037320, 1067405, 1044041, 1136692) and Australian Research Council (DP150101367).

Declaration of Interests.

The authors declare no competing interests.

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Figure captions

Figure 1: Hierarchical loading of tissues, cell junctions, and adhesion complexes. **A**) At the tissue level, a force F_{tissue} applied onto a tissue of width l_{tissue} and height h will lead to the emergence of a stress $\sigma=F_{tissue}/(h.l_{tissue})$. This stress can also be computed from the strain ε in the tissue and its elastic modulus E: $\sigma=E.\varepsilon$, if these parameters are known.
B) As experimental work suggests that stress and strain are homogenous within tissues [38, 127], the stress on a junction should be the same as the stress in the tissue. Therefore, we can compute the force applied onto this junction as $f_{cell}=\sigma.(h.l_{cell})$.
C) If the number of adhesive complexes N_{AJ} in an intercellular junction is known, then the force on a single adhesive complex is $f_{molecular}=f_{cell}/N_{AJ}$. E-cadherin is shown in light green, α- and β-catenin in dark green, the membrane is in purple.

Figure 2: Building intrinsic tension at adherens junctions.
(a) Coupling of cadherin complexes to the actomyosin membrane cortex may generate tension when cells first make adhesive contacts with one another.
(b) Prolonged cadherin adhesion elicits active cellular mechanisms that reinforce intrinsic tension, including signaling pathways that activate Myosin II (e.g. RhoA) and actin assembly (nucleated by Arp2/3 and formins) that reinforces the junctional actin cytoskeleton.

Figure 3: Mechanisms for sensing tensile stress at cadherin junctions.
(a) Tension-sensing by components of the cadherin-catenin complex. Tension induces unfolding of α-catenin, leading to the association of proteins such as vinculin.
(b) Tension-sensing by the cadherin-associated cytoskeleton. Tensile forces transmitted to the cytoskeleton can alter the dynamics of proteins such as myosins (here illustrated for Myosin II, although similar effects may be experienced by other junctional myosins).
(c) Tension sensing by curvature sensing proteins. Membrane curvature at sites of junctional tension can recruit BAR-domain proteins, such as Pacsin-2.

Figure 4: Reinforcing junctions against stress.
(a) Tension-activated actin assembly mediated by mechanisms such as recruitment of vinculin can reinforce adhesion by promoting cadherin clustering and stabilization.
(b) Recruitment of the BAR-protein Pacsin-2 to membranes that are curved by local stresses inhibits cadherin internalization to reinforce adhesion.

Figure 5: Cellular and molecular mechanisms of stress dissipation. In this thought experiment, a tissue is subjected to a step deformation at time t_1 and is maintained stretched until t_2 at what point the tissue is returned to its initial length (**A**). This strain regimen (grey line) results in a stress that peaks immediately after the deformation step [38, 127] before decaying over time (orange line). **B**) Potential mechanisms of stress dissipation at the cellular scale. These mechanisms tend to occur over time-scales of minutes to hours. A cell quadruplet within the tissue has an initial length L_0 and its stress is low. Immediately after application of the deformation, its length is $L=L_0.(1+\varepsilon)$ and its stress is high. Oriented cell division [127] and intercalation [28] both reduce the stress in the quadruplet by redistributing cell mass: removing it from the direction perpendicular to the stretch and adding it in the direction of stretch. Even though stress is dissipated, the length L of the quadruplet

remains the same as long as deformation is maintained. When the tissue is returned to its initial length, the length of the quadruplet L_f is larger than the initial length L_0. However, the quadruplet's width has decreased in the direction perpendicular to stretch. **C**) Potential mechanism of stress dissipation at the molecular scale. These mechanisms tends to take place at second to minute time-scales. At the molecular level, the cytoskeleton in the junction is a membrane associated network of F-actin (orange lines), myosins (light grey circles), and crosslinkers (light grey circles). Following extension, the actomyosin network is under-stress and its length is $L=L_0.(1+\varepsilon)$. Over time, turnover of the proteins composing the cytoskeletal network dissipates stress by remodelling the junctional network (new actin filaments are shown in brown and newly bound crosslinkers/myosins in dark grey) such that it adopts the length imposed by the deformation. Even though remodelling dissipates stress, the length L of the quadruplet remains constant. When the tissue is returned to its initial length, the length of the quadruplet L_f is larger than the initial length L_0 and the organisation of the network has changed substantially compared to its initial configuration.