E-cadherin junctions as active mechanical integrators in tissue dynamics

Thomas Lecuit and Alpha S. Yap

During epithelial morphogenesis, E-cadherin adhesive junctions play an important part in mechanically coupling the contractile cortices of cells together, thereby distributing the stresses that drive cell rearrangements at both local and tissue levels. Here we discuss the concept that cellular contractility and E-cadherin-based adhesion are functionally integrated by biomechanical feedback pathways that operate on molecular, cellular and tissue scales.

Cellular contractility is a cardinal determinant of cell and tissue morphogenesis. Indeed, our understanding of morphogenesis has evolved from the classical view that tissue remodelling is driven by differential adhesion between groups of cells[1,2], to the current appreciation that actomyosin contractility contributes to morphogenesis by critically influencing cell contact dynamics and cell movements[3,4]. As an illustration of this shift in focus, the seminal ideas of Steinberg on cell sorting were first interpreted from the standpoint of differential adhesion strength associated with cadherin binding energies[1]. However, cell sorting and tissue arrangements in embryos are also influenced by actomyosin-dependent cortical tension[5,6]. These different views can be reconciled by the realization that actomyosin tension and cadherin-based adhesion both contribute to the interfacial energy in epithelial tissues[7,8]. Furthermore, cadherin adhesion mechanically couples the contractile cortices of neighbouring cells together[6,9,10] and allows cell-level forces to yield supracellular, tissue-level forces[10–12]. Thus, cortical tension and cell–cell adhesion are intimately linked[6].

In this Review, we examine recent evidence from a range of cell and model systems that define how cadherin-based junctions and contractility are integrated. We focus on epithelia, where E-cadherin forms homophilic adhesive complexes[10,13] to stabilize the surfaces of contacting cells. Epithelial cells exhibit complex and rich dynamics during development and regeneration, but must also preserve tissue integrity and barrier function. For instance, epithelial cells divide while maintaining contacts with their neighbours, and thereby produce new cell–cell interfaces[14–17]. Cell extrusion, in response to apoptosis[18,19], oncogenes[20,21] or external pressure[22,23], is accompanied by the loss of several cell contacts. Finally, epithelial cells remodel their contacts by a process of neighbour exchange called intercalation[24], which may occur in a random orientation to allow cell movement in an epithelial tissue, or may be planar-polarized to drive directed tissue extension[25–28]. Cell division[14–17], cell extrusion[20,22,23] and cell intercalation[26,27,29] are basic cellular processes that add, remove, or exchange cell junctions and thereby fluidize epithelial tissues on time scales of tens of minutes to hours[12,30]. All these cases involve the application of contractile forces at E-cadherin junctions, which can both resist deformation and transmit subcellular stresses[11,31]. This implies that epithelial dynamics hinge on how the mechanical properties of their E-cadherin-based cell–cell junctions are regulated during these different processes.

We suggest that elucidating the biomechanical complexity of these processes can be guided by two themes. First, junctions serve not only to couple adhesion and contractility, but also influence the biogenesis of the contractile apparatus itself. Cadherin junctions (often called adherens junctions) can then be regarded as active agents in the morphogenetic process, rather than solely as passive resistance elements. Second, adhesion and the actomyosin cytoskeleton are integrated at junctions by a combination of biochemical pathways and biomechanical feedback: biochemistry determines mechanics and mechanics regulates biochemistry. Here, we focus on actomyosin, although it is important to note that microtubules and intermediate filaments also interact with junctional adhesion systems[32,33].

Integrating adhesion and contractility at E-cadherin junctions

Adherens junctions are enriched in cortical actomyosin[34–37] and are also physically linked to the actomyosin networks found in the apical (or medial–apical) epithelial cell cortex[37,38] (Fig. 1a). These actomyosin networks display pulsatile behaviour when myosin II contractility drives the aggregation of its associated actin networks[39,40]. Such pulses occur with similar periodicity (~100 s) in the medial–apical network of morphogenetically active embryonic cells[37,41–45] and at the lateral junctions in cultured epithelia[20]. These actomyosin pulses deform cell-cell junctions in embryonic cells and generate oscillatory planar movements of cadherin clusters in cultured epithelia[20]. In embryonic epithelial cells, anisotropic flows of pulsating actomyosin also feedback

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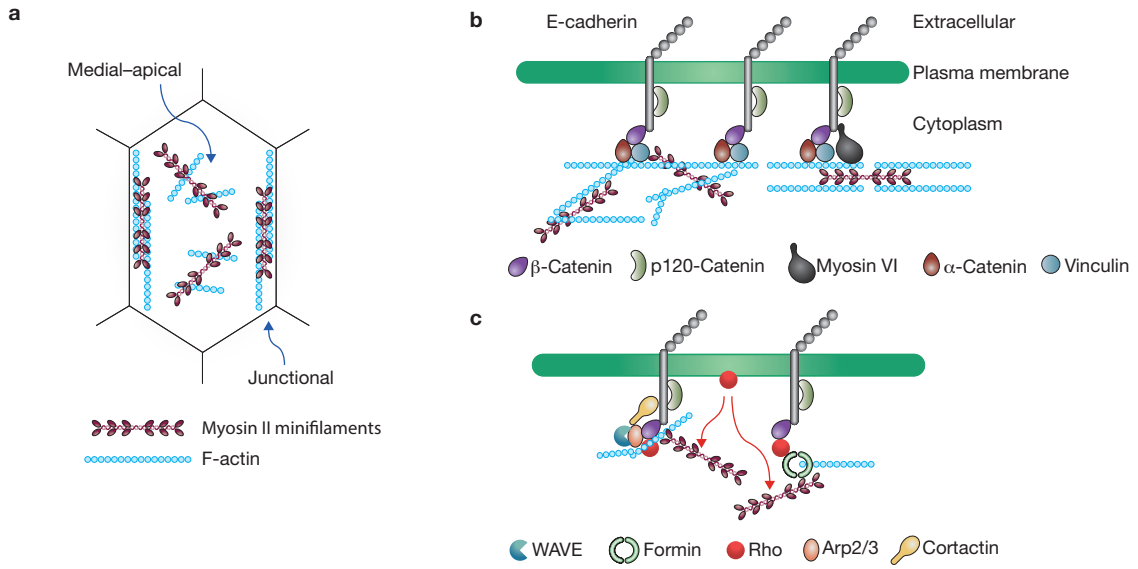

Figure 1 Actomyosin at epithelial junctions. (**a**) Schematic of actomyosin organization in simple epithelial cells. Cells in a monolayer are depicted as hexagons when viewed in the apical plane. Myosin minifilaments interact with F-actin networks both at the cortices of cell–cell junctions and in the medial–apical pole of the cells. (**b**) Mechanisms for the E-cadherin molecular complex to associate with F-actin of the actomyosin apparatus. Actin filaments may bind directly to α-catenin, interact with α-catenin-associated proteins, such as vinculin or EPLIN, or bind to proteins such as myosin VI, which can associate with E-cadherin independently of α-catenin. (**c**) Cadherin adhesions support biogenesis of the junctional actomyosin apparatus by promoting actin assembly (for example, through nucleation by engaging Arp2/3, formins and associated proteins such as cortactin) and Rho-dependent activation of myosin II.

on the asymmetric distribution of clustered E-cadherin at junctions[46]. These coupled patterns of movement therefore indicate that E-cadherin adhesion and actomyosin are physically linked to one another, allowing actomyosin to transmit forces to the adhesion system.

The physical connection between cadherin complexes and the contractile apparatus is principally mediated by association with the F-actin component of actomyosin. Multiple mechanisms link E-cadherin to F-actin (Fig. 1b). A key role is played by α-catenin[47,48], which can directly bind actin filaments[49] and also supports less direct interactions through proteins such as vinculin[48,50,51] and EPLIN (also known as LIMA1)[52]. Other molecular mechanisms also participate, such as the unconventional motor myosin VI, which can associate directly with E-cadherin[53] and is recruited to apical cadherin junctions (zonulae adherente) in polarized epithelia[54]. Although we do not yet understand why such a wide range of proteins are able to link cadherins to cortical F-actin, one interesting possibility is that they may be making distinct contributions to the mechanical properties of the junctions. For example, although myosin VI is a processive motor that moves towards the minus-ends of actin filaments, under resistive load — such as it might experience at adherens junctions — it can potentially convert to an actin-binding anchor[55] that might serve to reinforce cadherin–actin associations under stress. Alternatively, they may reinforce mechanical coupling with forces that have different orientations to the junctions (for instance, perpendicular (or normal) versus tangential to junctions)[51]. More generally, this emphasizes the notion that multiple actin pools exist which interact with, and organize, subsets of cadherins within the junctions[56–58].

However, E-cadherin adhesions also contribute to the biogenesis of the junctional actomyosin cortex itself (Fig. 1c). E-cadherin adhesions are sites of Rho signalling[59,60], which activates myosin II, and the cadherin–catenin complex participates in coordinating the balance of Rho activators (guanine nucleotide exchange factors (GEFs)) and inactivators (GTPase-activating proteins (GAPs)) at adherens junctions[60]. Rho signalling is mediated by the ROCK protein kinase, which also associates with E-cadherin at cell–cell junctions[61,62]. Other proteins that can interact with ROCK to promote its junctional accumulation, such as the actin-binding protein Shroom, also have important roles in controlling junctional tension and morphogenesis[61,63]. Additionally, E-cadherin adhesions promote actin assembly at the junctional cortex by recruiting actin regulators (for example, Arp2/3 (ref. 64), formins (ref. 65), CD2AP (ref. 66) and cortactin (ref. 67)) and the signalling pathways that activate them. These associations between signalling molecules and actin regulators at E-cadherin-based junctions help generate the actin networks that are necessary for actomyosin contractility. Thus, the integration of adhesion and contractility that is seen at adherens junctions[6] involves a contribution from E-cadherin to building the contractile apparatus itself, an effect that is most evident for junctional actomyosin. Although it is not known whether cadherin-based actin assembly also affects the medial–apical networks, it can extend outwards from junctions[68].

This capacity for cadherin adhesion actively to build, as well as passively bind to, actomyosin complicates the analysis of junctional mechanics. In parsing this problem, it is important to appreciate that the timescale of analysis influences the apparent mechanical properties of cell–cell interactions. The total mechanical stresses (force/surface area) in the plane of the junctions between cells consist of elastic, viscous and active stresses[69–71]. Elastic stresses depend on the extent of deformations, whereas viscous stresses depend on the rate of deformations and active stresses depend on myosin II motor activity, actin dynamics and crosslinking. On short timescales (seconds), elastic behaviour dominates and allows long-range propagation of tension within and between cells in a tissue[72]. The junctional[73–75] and medial–apical actomyosin networks[12,37,76] make contributions to such elastic stresses, as do passive connections between the actin network and E-cadherin complexes[38,57]. On longer timescales

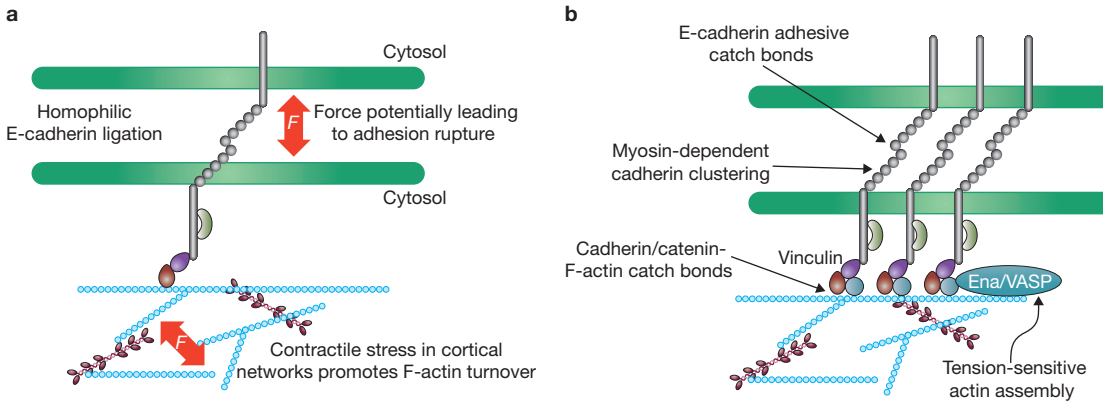

Figure 2 Forces and mechanosensitivity at E-cadherin junctions. (**a**) The E-cadherin–actomyosin system encounters multiple patterns of force (*F*), including forces acting on the ectodomains that would tend to rupture the adhesion bonds, and stresses that tend to cause turnover of F-actin in the junctional actomyosin network. Elements of the cadherin–catenin complex are depicted as in Fig. 1b. (**b**) Mechanosensitive response mechanisms include passive and active processes. Adhesion can be strengthened to resist detachment forces by catch bonds in the ectodomain adhesive interaction and actomyosin-dependent clustering of cadherin receptors. The junctional cytoskeleton can be reinforced against stress by catch bonds between the cadherin–catenin complex, and F-actin and tension-sensitive actin assembly mediated by vinculin and Ena/VASP.

(minutes and longer), however, viscous stresses become more apparent as the turnover of components (E-cadherin, actin filaments, myosin II and crosslinkers) allows stress dissipation, fluid behaviour of subcellular networks[70] and cell interfaces, as well as large-scale deformations in the tissues, with cells sliding past one another as in a viscous fluid[3]. On these longer timescales, cadherin adhesion may also contribute to active stresses by regulating the actomyosin apparatus[60].

Mechanosensitivity and the impact of force

Force can affect the behaviour of the cadherin–actomyosin system at many levels and through different mechanisms, both passive and active. It should be noted that the distinction between passive and active processes can sometimes cause confusion between biologists and physicists. For physicists, active processes consume energy and therefore exist out of thermodynamic equilibrium[72], whereas passive processes do not consume energy. The biological use of these terms is less precise, but active processes are commonly taken to involve complex cellular responses (for example, signalling) that are elicited by instructive stimuli. As we shall see, mechanosensitivity in the cadherin–actomyosin system involves mechanisms that are passive or active in both the physical and biological senses of these terms.

With regard to tension-sensitive adhesion, the coupling of E-cadherin to actomyosin contractile networks carries a potential paradox. Although the generation of contractile stress contributes to morphogenesis by remodelling cell junctions, it would tend to disrupt the cell–cell adhesions that transmit those stresses (Fig. 2a). This implies that mechanisms must exist to strengthen adhesion in proportion to contractility and which themselves may be regulated to achieve either junction remodelling or reinforcement. Indeed, one mechanism for force-dependent adhesive strengthening is an intrinsic property of the cadherin adhesive bond itself. The strength of interaction between associated molecules can respond to force in three theoretically distinct ways: they may become more short-lived (slip bonds); longer-lived (catch bonds); or become insensitive to stress (ideal bonds)[77,78]. Crystallographic analyses indicate that isolated cadherin ectodomains can form two distinct *trans*-conformations: a strand-swap dimer in which opposing cadherins insert a conserved tryptophan residue into a hydrophobic pocket on their binding partner, and an X-dimer formed by extensive interactions between the amino-termini of the ectodomains[79]. The X-dimer is thought to be an intermediate state to the adhesive strand-swap dimer[79]. Interestingly, measurement of bond lifetimes of single molecules under force using atomic force microscopy revealed that cadherin mutants favoured to form X-dimers display catch bonds[80,81]. Effectively, the tendency of catch bonds to strengthen under stress would allow transitional X-dimers to resist tensile forces, and thereby stabilize cell–cell interactions (Fig. 2b). However, this may not be sufficient to reinforce adhesion against stress. Strand-swap dimers of E-cadherin ectodomains — the putative mature form of adhesion — showed slip-bond behaviour[80], implying that they could weaken under stress.

At the cellular level, however, cadherin-based adhesion is not solely determined by the intrinsic binding activity of the ectodomains, but is also promoted by the lateral organization of cadherins into finite-sized clusters[82], a process that requires cytoplasmic contributions[83–85]. E-cadherin clusters are evident at epithelial cell–cell junctions, and their number, size, lateral mobility and compositional turnover depend to a large extent on associations with actin filaments[20,57,85,86]. As the strength of adhesion depends on these properties of clusters, it might be predicted to be influenced by the junctional cytoskeleton. Indeed, cortical actomyosin stabilizes E-cadherin at the zonula adherens[87], promotes cadherin clustering and strengthens adhesion[35,36]. Cadherin clustering in response to cortical actomyosin would then provide an additional mechanism for adhesion to be strengthened at sites where stress is being applied (Fig. 2b). On the basis of our earlier discussion, adhesive strengthening of catch bonds represents a passive process, whereas strengthening via cadherin clustering is an active process, as it entails Rho–ROCK signalling and myosin activity[35,36], which consume energy.

At another level, the junctional actomyosin system is itself sensitive to force. Cells undergo stiffening when mechanical forces are applied to adhesions formed by cadherin-coated beads[88], a response that is accompanied by the accumulation of F-actin at the adhesions[89]. This implies that the cytoskeleton can be altered by the application of force to cadherin adhesions. At native cell–cell junctions such mechanosensitivity would be

predicted to respond to the stresses that are transmitted across junctions through cadherin adhesions. Consistent with this, the amount of F-actin at the zonulae adherente of epithelial cells depends on myosin[36,90], whereas stimulation of contractility can also increase the amount of myosin at the junctions[74]. Thus, force on the cadherin–actomyosin system is able to regulate the actomyosin system as well as strengthen adhesion.

As occurs with adhesive strengthening, tension sensitivity in the junctional cytoskeleton is likely to reflect both passive and active molecular processes. These include the associations between cadherin and F-actin itself (Fig. 2b). As noted earlier, one mechanism to link the cadherin molecular complex to F-actin is via α-catenin, which is capable of binding directly to actin filaments[49]. Nevertheless, efforts to reconstitute interactions between a minimal cadherin–catenin complex and F-actin were unsuccessful when performed in solution using purified proteins[91]. It now transpires that a more stable interaction occurs when these elements are engaged under force, a tension-sensitive process that is attributable to the formation of catch bonds between the cadherin–catenin complex and actin filaments[92]. In its simplest form, this would represent a passive mechanism to promote the cadherin–actin interaction under stress. Similarly, myosins are liable to remain attached when load is applied to the actin filaments[93], thereby tending to convert motors into actin-based anchors. This intrinsic mechanosensitivity occurs through force-sensitive modulation of the kinetics of the myosin mechanochemical cycle[93–95]. This affects myosin II (ref. 96), as well as myosin VI, and may account for the observed ability of tension to stabilize myosin II at junctions[74]. The forces that load myosins could derive from contractility itself, and could also be generated from the growth of actin filaments that are crosslinked into networks by myosin[94].

Tensile stress can also affect the junctional cytoskeleton by active processes such as actin assembly (Fig. 2b). Stimulation of contractility increased actin assembly at the zonulae adherente of cultured epithelial cells, whereas inhibiting contractility reduced assembly[90]. The mechanism involved the tension-sensitive recruitment of vinculin to the zonulae adherente, where it serves to localize members of the Ena/VASP family that promote the growth of actin filaments at their barbed ends[97,98]. α-Catenin is a dominant mechanism to recruit vinculin to junctions, and the tension sensitivity of vinculin recruitment may reflect force-induced changes in the conformation of α-catenin itself, leading to the appearance of previously cryptic interaction sites[89,95,99].

It is worth noting that the impact of force on the cadherin–actomyosin system can be negative, as well as positive. For example, contractile stresses can induce turnover of the actin filaments on which myosin acts, a process that will ultimately limit contractility[20]. Indeed, myosin-induced F-actin turnover occurs at the lateral junctions of epithelial cells, located below the zonula adherens[20] (Fig. 2a). At the zonula adherens, however, F-actin content appears to be protected from stress-induced turnover by the actions of proteins such as N-WASP[20], which stabilizes actin filaments[56], and vinculin–Ena/VASP, which promote actin assembly[90]. These differences in the local response to stress would be predicted to have mechanical consequences: the ability of cortical actin to resist turnover and deformation promotes elasticity, whereas filament turnover facilitates fluidization, dissipates stress and favours viscous behaviour[70]. Consistent with this, junctional tension was higher at the zonula adherens than at the lateral junctions, due to local stabilization of cortical F-actin[20].

Finally, cadherins might respond to the force that they experience[100,101] by modulating cortical signalling. One example of cadherin-based mechanotransduction occurs in vascular endothelial cells, where VE-cadherin functions as an adaptor that couples PECAM-1, an immunoglobulin family adhesion protein, to the VEGF receptor 2 signalling pathway, thereby conferring cellular sensitivity to sheer flow[102]. Ligation of E-cadherin itself can also activate a range of cellular signalling pathways, including Rho family[60,64,103] and Rap GTPases[104], Src-family kinases[105] and phosphatidylinositol-3-OH kinase (PI(3)K)[106]. However, whether such cadherin-activated signalling pathways are responsive to force exerted on cadherin adhesions during morphogenesis remains to be characterized.

From dynamic cells to tissue dynamics

To illustrate how spatial control over junction remodelling dictates different tissue outcomes, in particular with respect to the interplay between E-cadherin and actomyosin networks, we present a few typical examples of tissue morphogenesis in more detail.

Epithelial tissues exhibit astonishing plasticity during embryonic development, notably during gastrulation — the process associated with the formation of the different tissue layers — and organogenesis. Studies in both vertebrate and invertebrate model organisms have recently shed light on the cellular and molecular mechanisms of tissue morphogenesis, revealing their conservation across species and the central role of junction dynamics in epithelia. Two general classes of morphogenetic processes exist in animals, namely tissue invagination and tissue extension[107]. Invagination is usually initiated by apical cell constriction, whereas extension is driven by cell intercalation and convergence–extension movements[24].

Apical constriction is associated with geometric cell shape changes, whereby cells maintain contact with their neighbours but shrink the length of all junctions through the apical accumulation of myosin II and contractile stresses (Fig. 3a). Isotropic apical contractile actomyosin networks exert traction forces against all junctions and reduce the apical cell perimeter. This often requires apical Rho activation, phosphorylation of the myosin II regulatory light chain[38,76,108,109] and recruitment of Shroom[110–112]. The connection between E-cadherin-associated proteins, in particular α-catenin, and pulsatile actomyosin networks is required for the mechanical coupling between apical tensile forces and cell junctions, as shown in *Caenorhabditis elegans*[38] and *Drosophila*[108]. Individual contractions within the apical zones of cells are coupled across several cell diameters, which reveals the E-cadherin-dependent build-up of elastic tissue stresses[12]. Such elastic tissue-scale stresses are proposed to cause tissue buckling and tissue invagination. In the vertebrate neural tube, invagination of the neuroectoderm requires planar-polarized supracellular actomyosin cables that connect many cells together and produce incomplete cell intercalation[29,61]. Cells shrink some junctions but do not intercalate. As a result, tissue-level elastic stresses build up and cause tissue buckling. In this system actomyosin tension requires Rho1 pathway activation by the planar cell polarity pathway and Shroom[29,61], emphasizing the conserved role for actomyosin regulation. The role of cadherins in this process has not been described, but N-cadherin could be the cadherin involved in connecting the actomyosin network to junctions.

Tissue-level stresses can be dissipated by cell intercalation (Fig. 3b), a process that drives tissue extension in the *Drosophila* germband[26,27], the chick epiblast[113], the mouse endoderm[114] and in *Xenopus* gastrulation[115]. Planar cell intercalation first requires junction shrinkage and the formation of a four-way or higher-order vertex, and then requires new junction

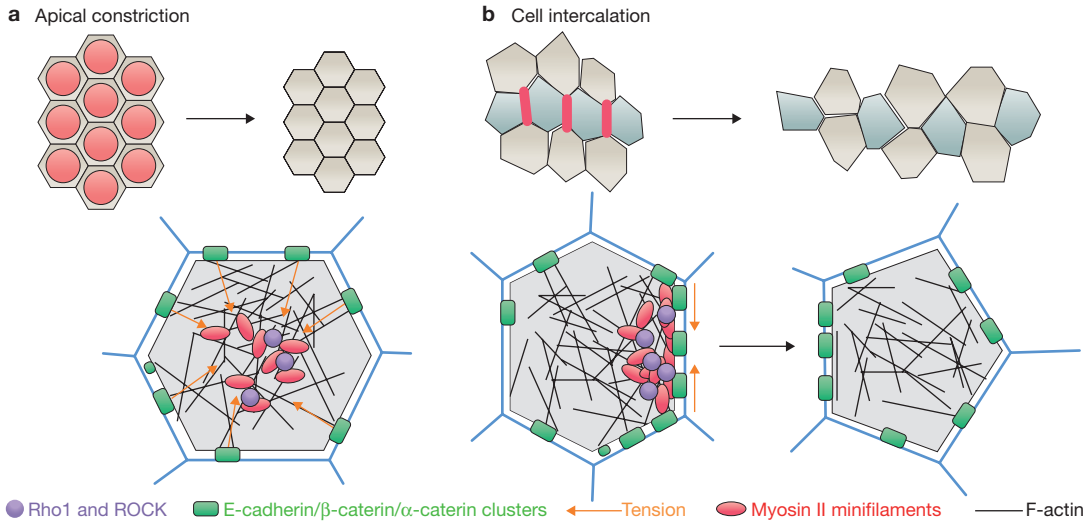

Figure 3 Spatial patterns of contraction underlying apical constriction and cell intercalation. (**a**) During apical constriction, cells reduce their apical surface area. Individual cells within a monolayer are depicted by hexagons. Pulsatile contraction in medial–apical actomyosin networks exerts traction forces against E-cadherin complexes at cell–cell contacts, leading to constriction of the apical poles of the cells. Myosin II contraction requires Rho1- and ROCK-dependent phosphorylation of the myosin II regulatory light chain. (**b**) During cell intercalation, cells exchange neighbours by polarized junction remodelling. 'Vertical' junctions' (marked in red) shrink owing to anisotropic tension exerted by medial–apical actomyosin flows that deform junctions and polarized junction myosin II accumulation that stabilizes them. Tension transmission requires E-cadherin complexes. Shrinkage of vertical junctions results in the intercalation of cells (marked in mid-blue) between other cells (marked in light blue).

growth in a perpendicular orientation, thereby effectively allowing neighbour exchange and stress dissipation in the tissue[8,25]. The mechanisms of junction shrinkage have been mostly deciphered in *Drosophila*, in which planar-polarized flows of actomyosin pulses produce stepwise junction shrinkage[37] followed by stabilization of junction length by junctional actomyosin[37,74]. Planar-polarized actomyosin also requires the Rho1–ROCK pathway[26,63,116] and a contribution from Shroom[63]. Actomyosin flows are oriented towards junctions by asymmetric coupling to E-cadherin complexes through α-catenin[46]. Planar junction remodelling is also associated with planar-polarized regulation of E-cadherin: E-cadherin endocytosis is upregulated in a Rho1-dependent manner when junctions are under stress[117] and E-cadherin clusters are also downregulated via inhibition of Par3 by the kinase ROCK[116]. Thus, concerted downregulation of adhesion and activation of actomyosin stresses may drive intercalation.

Concluding remarks

We propose that cell–cell junctions can be understood as mechanical agents, which contribute to morphogenesis by functionally integrating cell adhesion and actomyosin-based contractility. We suggest that the complex biochemical pathways that support junctional mechanics and contractility will ultimately prove to be themselves regulated by mechanical feedback. Mechanosensitivity, both passive and active, is evident in many of the mechanisms that integrate E-cadherin adhesion and contractility at junctions. So far, however, this has been largely explored at the molecular and cellular level. An important challenge will be to test whether these mechanisms operate within the more complex environments of intact tissues and embryos. An exciting development has been the implementation of tension biosensors in model systems. A recent example revealed polarized patterns of molecular tension across E-cadherin during the morphogenetic process of border cell migration, which reflected feedback between E-cadherin adhesion and chemotactic Rac signalling[118]. This may be just a first glimpse of much more complex systems of biomechanical regulation. Furthermore, it is interesting to note that adhesion and the cytoskeleton are also integrated at integrin-based adhesions. Indeed, many of the issues that we have highlighted in discussing cell–cell junctions also apply to integrin adhesions. The notion of cross-talk between cadherins and integrins has been a persistent, if elusive, theme in the biology of cell adhesion. As actomyosin contributes to the mechanical coherence of the cytoplasm[119], it is enticing to speculate that cadherin and integrin adhesions may ultimately be found to be mechanically coupled to one another. Mechanical integration may then provide an avenue for adhesive cross-talk, one where the biochemistry of either cadherin or integrin junctions may be affected by the mechanical influence of the other adhesive system.

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ADDITIONAL INFORMATION

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

1. Foty, R. A. & Steinberg, M. S. The differential adhesion hypothesis: a direct evaluation. *Dev. Biol.* **278,** 255–263 (2005).
2. Takeichi, M. Cadherin cell adhesion receptors as a morphogenetic regulator. *Science* **251,** 1451–1455 (1991).
3. Guillot, C. & Lecuit, T. Mechanics of epithelial tissue homeostasis and morphogenesis. *Science* **340,** 1185–1189 (2013).
4. Heisenberg, C. P. & Bellaiche, Y. Forces in tissue morphogenesis and patterning. *Cell* **153,** 948–962 (2013).
5. Krieg, M. *et al.* Tensile forces govern germ-layer organization in zebrafish. *Nat. Cell Biol.* **10,** 429–436 (2008).
6. Maitre, J. L. *et al.* Adhesion functions in cell sorting by mechanically coupling the cortices of adhering cells. *Science* **338,** 253–256 (2012).

7. Lecuit, T. & Lenne, P. F. Cell surface mechanics and the control of cell shape, tissue patterns and morphogenesis. *Nat. Rev. Mol. Cell Biol.* **8,** 633–644 (2007).
8. Farhadifar, R., Roper, J. C., Aigouy, B., Eaton, S. & Julicher, F. The influence of cell mechanics, cell-cell interactions, and proliferation on epithelial packing. *Curr. Biol.* **17,** 2095–2104 (2007).
9. Brieher, W. M. & Yap, A. S. Cadherin junctions and their cytoskeleton(s). *Curr. Opin. Cell Biol.* **25,** 39–46 (2013).
10. Takeichi, M. Dynamic contacts: rearranging adherens junctions to drive epithelial remodelling. *Nat. Rev. Mol. Cell Biol.* **15,** 397–410 (2014).
11. Lecuit, T., Lenne, P. F. & Munro, E. Force generation, transmission, and integration during cell and tissue morphogenesis. *Annu. Rev. Cell Dev. Biol.* **27,** 157–184 (2011).
12. Martin, A. C., Gelbart, M., Fernandez-Gonzalez, R., Kaschube, M. & Wieschaus, E. F. Integration of contractile forces during tissue invagination. *J. Cell Biol.* **188,** 735–749 (2010).
13. Yonemura, S. Cadherin-actin interactions at adherens junctions. *Curr. Opin. Cell Biol.* **23,** 515–522 (2011).
14. Founounou, N., Loyer, N. & Le Borgne, R. Septins regulate the contractility of the actomyosin ring to enable adherens junction remodeling during cytokinesis of epithelial cells. *Dev. Cell* **24,** 242–255 (2013).
15. Guillot, C. & Lecuit, T. Adhesion disengagement uncouples intrinsic and extrinsic forces to drive cytokinesis in epithelial tissues. *Dev. Cell* **24,** 227–241 (2013).
16. Herszterg, S., Leibfried, A., Bosveld, F., Martin, C. & Bellaiche, Y. Interplay between the dividing cell and its neighbors regulates adherens junction formation during cytokinesis in epithelial tissue. *Dev. Cell* **24,** 256–270 (2013).
17. Morais-de-Sa, E. & Sunkel, C. Adherens junctions determine the apical position of the midbody during follicular epithelial cell division. *EMBO Rep.* **14,** 696–703 (2013).
18. Toyama, Y., Peralta, X. G., Wells, A. R., Kiehart, D. P. & Edwards, G. S. Apoptotic force and tissue dynamics during *Drosophila* embryogenesis. *Science* **321,** 1683–1686 (2008).
19. Muliyil, S., Krishnakumar, P. & Narasimha, M. Spatial, temporal and molecular hierarchies in the link between death, delamination and dorsal closure. *Development* **138,** 3043–3054 (2011).
20. Wu, S. K. *et al.* Cortical F-actin stabilization generates apical–lateral patterns of junctional contractility that integrate cells into epithelia. *Nat. Cell Biol.* **16,** 167–178 (2014).
21. Hogan, C. *et al.* Characterization of the interface between normal and transformed epithelial cells. *Nat. Cell Biol.* **11,** 460–467 (2009).
22. Eisenhoffer, G. T. *et al.* Crowding induces live cell extrusion to maintain homeostatic cell numbers in epithelia. *Nature* **484,** 546–549 (2012).
23. Marinari, E. *et al.* Live-cell delamination counterbalances epithelial growth to limit tissue overcrowding. *Nature* **484,** 542–545 (2012).
24. Walck-Shannon, E. & Hardin, J. Cell intercalation from top to bottom. *Nat. Rev. Mol. Cell Biol.* **15,** 34–48 (2014).
25. Aigouy, B. *et al.* Cell flow reorients the axis of planar polarity in the wing epithelium of *Drosophila*. *Cell* **142,** 773–786 (2010).
26. Bertet, C., Sulak, L. & Lecuit, T. Myosin-dependent junction remodelling controls planar cell intercalation and axis elongation. *Nature* **429,** 667–671 (2004).
27. Blankenship, J. T., Backovic, S. T., Sanny, J. S., Weitz, O. & Zallen, J. A. Multicellular rosette formation links planar cell polarity to tissue morphogenesis. *Dev. Cell* **11,** 459–470 (2006).
28. Bosveld, F. *et al.* Mechanical control of morphogenesis by Fat/Dachsous/Four-jointed planar cell polarity pathway. *Science* **336,** 724–727 (2012).
29. Nishimura, T., Honda, H. & Takeichi, M. Planar cell polarity links axes of spatial dynamics in neural-tube closure. *Cell* **149,** 1084–1097 (2012).
30. Campinho, P. *et al.* Tension-oriented cell divisions limit anisotropic tissue tension in epithelial spreading during zebrafish epiboly. *Nat. Cell Biol.* **15,** 1405–1414 (2013).
31. Gomez, G. A., McLachlan, R. W. & Yap, A. S. Productive tension: force-sensing and homeostasis of cell–cell junctions. *Trends Cell Biol.* **21,** 499–505 (2011).
32. Delva, E., Tucker, D. K. & Kowalczyk, A. P. The desmosome. *Cold Spring Harb. Perspect. Biol.* **1,** a002543 (2009).
33. Akhmanova, A., Stehbens, S. J. & Yap, A. S. Touch, grasp, deliver and control: functional cross-talk between microtubules and cell adhesions. *Traffic* **10,** 268–274 (2009).
34. Miyake, Y. *et al.* Actomyosin tension is required for correct recruitment of adherens junction components and zonula occludens formation. *Exp. Cell Res.* **312,** 1637–1650 (2006).
35. Shewan, A. M. *et al.* Myosin 2 is a key Rho kinase target necessary for the local concentration of E-cadherin at cell–cell contacts. *Mol. Biol. Cell* **16,** 4531–4532 (2005).
36. Smutny, M. *et al.* Myosin II isoforms identify distinct functional modules that support integrity of the epithelial zonula adherens. *Nat. Cell Biol.* **12,** 696–702 (2010).
37. Rauzi, M., Lenne, P. F. & Lecuit, T. Planar polarized actomyosin contractile flows control epithelial junction remodelling. *Nature* **468,** 1110–1114 (2010).
38. Roh-Johnson, M. *et al.* Triggering a cell shape change by exploiting preexisting actomyosin contractions. *Science* **335,** 1232–1235 (2012).
39. Soares e Silva, M. *et al.* Active multistage coarsening of actin networks driven by myosin motors. *Proc. Natl Acad. Sci. USA* **108,** 9408–9413 (2011).
40. Murrell, M. P. & Gardel, M. L. F-actin buckling coordinates contractility and severing in a biomimetic actomyosin cortex. *Proc. Natl Acad. Sci. USA* **109,** 20820–20825 (2012).
41. Behrndt, M. *et al.* Forces driving epithelial spreading in zebrafish gastrulation. *Science* **338,** 257–260 (2012).
42. Blanchard, G. B., Murugesu, S., Adams, R. J., Martinez-Arias, A. & Gorfinkiel, N. Cytoskeletal dynamics and supracellular organisation of cell shape fluctuations during dorsal closure. *Development* **137,** 2743–2752 (2010).
43. Martin, A. C., Kaschube, M. & Wieschaus, E. F. Pulsed contractions of an actin–myosin network drive apical constriction. *Nature* **457,** 495–499 (2009).
44. Mayer, M., Depken, M., Bois, J. S., Julicher, F. & Grill, S. W. Anisotropies in cortical tension reveal the physical basis of polarizing cortical flows. *Nature* **467,** 617–621 (2010).
45. Solon, J., Kaya-Copur, A., Colombelli, J. & Brunner, D. Pulsed forces timed by a ratchet-like mechanism drive directed tissue movement during dorsal closure. *Cell* **137,** 1331–1342 (2009).
46. Levayer, R. & Lecuit, T. Oscillation and polarity of E-cadherin asymmetries control actomyosin flow patterns during morphogenesis. *Dev. Cell* **26,** 162–175 (2013).
47. Desai, R. *et al.* Monomeric α-catenin links cadherin to the actin cytoskeleton. *Nat. Cell Biol.* **15,** 261–273 (2013).
48. Yonemura, S., Wada, Y., Watanabe, T., Nagafuchi, A. & Shibata, M. α-Catenin as a tension transducer that induces adherens junction development. *Nat. Cell Biol.* **12,** 533–542 (2010).
49. Rimm, D. L., Koslov, E. R., Kebriaei, P., Cianci, C. D. & Morrow, J. S. α_1(E)-Catenin is an actin-binding and -bundling protein mediating the attachment of F-actin to the membrane adhesion complex. *Proc. Natl Acad. Sci. USA* **92,** 8813–8817 (1995).
50. Watabe-Uchida, M. *et al.* α-Catenin–vinculin interaction functions to organize the apical junctional complex in epithelial cells. *J. Cell Biol.* **142,** 847–857 (1998).
51. Huveneers, S. *et al.* Vinculin associates with endothelial VE-cadherin junctions to control force-dependent remodeling. *J. Cell Biol.* **196,** 641–652 (2012).
52. Abe, K. & Takeichi, M. EPLIN mediates linkage of the cadherin catenin complex to F-actin and stabilizes the circumferential actin belt. *Proc. Natl Acad. Sci. USA* **105,** 13–19 (2008).
53. Mangold, S., Norwood, S. J., Yap, A. S. & Collins, B. M. The juxtamembrane domain of the E-cadherin cytoplasmic tail contributes to its interaction with myosin VI. *BioArchitecture* **2,** 185–188 (2012).
54. Maddugoda, M. P., Crampton, M. S., Shewan, A. M. & Yap, A. S. Myosin VI and vinculin cooperate during the morphogenesis of cadherin cell–cell contacts in mammalian epithelial cells. *J. Cell Biol.* **178,** 529–540 (2007).
55. Chuan, P., Spudich, J. A. & Dunn, A. R. Robust mechanosensing and tension generation by myosin VI. *J. Mol. Biol.* **405,** 105–112 (2011).
56. Kovacs, E. M. *et al.* N-WASP regulates the epithelial junctional actin cytoskeleton through a non-canonical post-nucleation pathway. *Nat. Cell Biol.* **13,** 934–943 (2011).
57. Cavey, M., Rauzi, M., Lenne, P. F. & Lecuit, T. A two-tiered mechanism for stabilization and immobilization of E-cadherin. *Nature* **453,** 751–756 (2008).
58. Zhang, J. *et al.* Actin at cell–cell junctions is composed of two dynamic and functional populations. *J. Cell Sci.* **118,** 5549–5562 (2005).
59. Yonemura, S., Hirao-Minakuchi, K. & Nishimura, Y. Rho localization in cells and tissues. *Exp. Cell Res.* **295,** 300–314 (2004).
60. Ratheesh, A. *et al.* Centralspindlin and α-catenin regulate Rho signalling at the epithelial zonula adherens. *Nat. Cell Biol.* **14,** 818–828 (2012).
61. Nishimura, T. & Takeichi, M. Shroom3-mediated recruitment of Rho kinases to the apical cell junctions regulates epithelial and neuroepithelial planar remodeling. *Development* **135,** 1493–1502 (2008).
62. Smith, A. L., Dohn, M. R., Brown, M. V. & Reynolds, A. B. Association of Rho-associated protein kinase 1 with E-cadherin complexes is mediated by p120-catenin. *Mol. Biol. Cell* **23,** 99–110 (2012).
63. Simoes Sde, M., Mainieri, A. & Zallen, J. A. Rho GTPase and Shroom direct planar polarized actomyosin contractility during convergent extension. *J. Cell Biol.* **204,** 575–589 (2014).
64. Kovacs, E. M., Ali, R. G., McCormack, A. J. & Yap, A. S. E-cadherin homophilic ligation directly signals through Rac and PI3-kinase to regulate adhesive contacts. *J. Biol. Chem.* **277,** 6708–6718 (2002).
65. Carramusa, L., Ballestrem, C., Zilberman, Y. & Bershadsky, A. D. Mammalian diaphanous-related formin Dia1 controls the organization of E-cadherin-mediated cell–cell junctions. *J. Cell Sci.* **120,** 3870–3882 (2007).
66. Tang, V. W. & Brieher, W. M. FSGS3/CD2AP is a barbed-end capping protein that stabilizes actin and strengthens adherens junctions. *J. Cell Biol.* **203,** 815–833 (2013).
67. Han, S. P. *et al.* Cortactin scaffolds Arp2/3 and WAVE2 at the epithelial zonula adherens. *J. Biol. Chem.* **289,** 7764–7775 (2014).
68. Nandadasa, S., Tao, Q., Menon, N. R., Heasman, J. & Wylie, C. N- and E-cadherins in *Xenopus* are specifically required in the neural and non-neural ectoderm, respectively, for F-actin assembly and morphogenetic movements. *Development* **136,** 1327–1338 (2009).
69. Koenderink, G. H. *et al.* An active biopolymer network controlled by molecular motors. *Proc. Natl Acad. Sci. USA* **106,** 15192–15197 (2009).
70. Kim, T., Gardel, M. L. & Munro, E. Determinants of fluidlike behavior and effective viscosity in cross-linked actin networks. *Biophys. J.* **106,** 526–534 (2014).
71. Marchetti, M. C. *et al.* Hydrodynamics of soft active matter. *Rev. Mod. Phys.* **85,** 1143 (2013).
72. Joanny, J. F. & Prost, J. Active gels as a description of the actin–myosin cytoskeleton. *HFSP J.* **3,** 94–104 (2009).
73. Rauzi, M., Verant, P., Lecuit, T. & Lenne, P. F. Nature and anisotropy of cortical forces orienting *Drosophila* tissue morphogenesis. *Nat. Cell Biol.* **10,** 1401–1410 (2008).
74. Fernandez-Gonzalez, R., Simoes Sde, M., Roper, J. C., Eaton, S. & Zallen, J. A. Myosin II dynamics are regulated by tension in intercalating cells. *Dev. Cell* **17,** 736–743 (2009).
75. Bambardekar, K., Clement, R., Blanc, O., Chardes, C. & Lenne, P. F. Direct laser manipulation reveals the mechanics of cell contacts *in vivo*. *Proc. Natl Acad. Sci. USA* **112,** 1416–1421 (2015).

76. Sherrard, K., Robin, F., Lemaire, P. & Munro, E. Sequential activation of apical and basolateral contractility drives ascidian endoderm invagination. *Curr. Biol.* **20,** 1499–1510 (2010).
77. Dembo, M., Torney, D. C., Saxman, K. & Hammer, D. The reaction-limited kinetics of membrane-to-surface adhesion and detachment. *Proc. R. Soc. Lond. B Biol. Sci.* **234,** 55–83 (1988).
78. Rakshit, S. & Sivasankar, S. Biomechanics of cell adhesion: how force regulates the lifetime of adhesive bonds at the single molecule level. *Phys. Chem. Chem. Phys.* **16,** 2211–2223 (2014).
79. Harrison, O. J. *et al.* Two-step adhesive binding by classical cadherins. *Nat. Struct. Mol. Biol.* **17,** 348–357 (2010).
80. Rakshit, S., Zhang, Y., Manibog, K., Shafraz, O. & Sivasankar, S. Ideal, catch, and slip bonds in cadherin adhesion. *Proc. Natl Acad. Sci. USA* **109,** 18815–18820 (2012).
81. Manibog, K., Li, H., Rakshit, S. & Sivasankar, S. Resolving the molecular mechanism of cadherin catch bond formation. *Nat. Commun.* **5,** 3941 (2014).
82. Wu, Y., Kanchanawong, P. & Zaidel-Bar, R. Actin-delimited adhesion-independent clustering of E-cadherin forms the nanoscale building blocks of adherens junctions. *Dev. Cell* **32,** 139–154 (2015).
83. Yap, A. S., Brieher, W. M., Pruschy, M. & Gumbiner, B. M. Lateral clustering of the adhesive ectodomain: a fundamental determinant of cadherin function. *Curr. Biol.* **7,** 308–315 (1997).
84. Angres, B., Barth, A. & Nelson, W. J. Mechanism for transition from initial to stable cell–cell adhesion: kinetic analysis of E-cadherin-mediated adhesion using a quantitative adhesion assay. *J. Cell Biol.* **134,** 549–557 (1996).
85. Truong Quang, B. A., Mani, M., Markova, O., Lecuit, T. & Lenne, P. F. Principles of E-cadherin supramolecular organization *in vivo*. *Curr. Biol.* **23,** 2197–2207 (2013).
86. Engl, W., Arasi, B., Yap, L. L., Thiery, J. P. & Viasnoff, V. Actin dynamics modulate mechanosensitive immobilization of E-cadherin at adherens junctions. *Nat. Cell Biol.* **16,** 587–594 (2014).
87. Priya, R., Yap, A. S. & Gomez, G. A. E-cadherin supports steady-state Rho signaling at the epithelial zonula adherens. *Differentiation* **86,** 133–140 (2013).
88. le Duc, Q. *et al.* Vinculin potentiates E-cadherin mechanosensing and is recruited to actin-anchored sites within adherens junctions in a myosin II-dependent manner. *J. Cell Biol.* **189,** 1107–1115 (2010).
89. Barry, A. K. *et al.* α-Catenin cytomechanics—role in cadherin-dependent adhesion and mechanotransduction. *J. Cell Sci.* **127,** 1779–1791 (2014).
90. Leerberg, J. M. *et al.* Tension-sensitive actin assembly supports contractility at the epithelial zonula adherens. *Curr. Biol.* **24,** 1689–1699 (2014).
91. Drees, F., Pokutta, S., Yamada, S., Nelson, W. J. & Weis, W. I. α-Catenin is a molecular switch that binds E-cadherin-β-catenin and regulates actin-filament assembly. *Cell* **123,** 903–915 (2005).
92. Buckley, C. D. *et al.* The minimal cadherin-catenin complex binds to actin filaments under force. *Science* **346**, 1254211 (2014).
93. De la Cruz, E. M. & Ostap, E. M. Relating biochemistry and function in the myosin superfamily. *Curr. Op. Cell Biol.* **16,** 61–67 (2004).
94. West-Foyle, H. & Robinson, D. N. Cytokinesis mechanics and mechanosensing. *Cytoskeleton (Hoboken)* **69,** 700–709 (2012).
95. Yonemura, S., Wada, Y., Watanabe, T., Nagafuchi, A. & Shibata, M. α-Catenin as a tension transducer that induces adherens junction development. *Nat. Cell Biol.* **12,** 533–542 (2010).
96. Norstrom, M. F., Smithback, P. A. & Rock, R. S. Unconventional processive mechanics of non-muscle myosin IIB. *J. Biol. Chem.* **285,** 26326–26334 (2010).
97. Hansen, S. D. & Mullins, R. D. VASP is a processive actin polymerase that requires monomeric actin for barbed end association. *J. Cell Biol.* **191,** 571–584 (2010).
98. Bear, J. E. *et al.* Antagonism between Ena/VASP proteins and actin filament capping regulates fibroblast motility. *Cell* **109,** 509–521 (2002).
99. Yao, M. *et al.* Force-dependent conformational switch of α-catenin controls vinculin binding. *Nat. Commun.* **5,** 4525 (2014).
100. Borghi, N. *et al.* E-cadherin is under constitutive actomyosin-generated tension that is increased at cell–cell contacts upon externally applied stretch. *Proc. Natl Acad. Sci. USA* **109,** 12568–12573 (2012).
101. Conway, D. E. *et al.* Fluid shear stress on endothelial cells modulates mechanical tension across VE-cadherin and PECAM-1. *Curr. Biol.* **23,** 1024–1030 (2013).
102. Tzima, E. *et al.* A mechanosensory complex that mediates the endothelial cell response to fluid shear stress. *Nature* **437,** 426–431 (2005).
103. Noren, N. K., Niessen, C. M., Gumbiner, B. M. & Burridge, K. Cadherin engagement regulates Rho family GTPases. *J. Biol. Chem.* **276,** 33305–33308 (2001).
104. Hogan, C. *et al.* Rap1 regulates the formation of E-cadherin-based cell–cell contacts. *Mol. Cell Biol.* **24,** 6690–6700 (2004).
105. McLachlan, R. W., Kraemer, A., Helwani, F. M., Kovacs, E. M. & Yap, A. S. E-cadherin adhesion activates c-Src signaling at cell–cell contacts. *Mol. Biol. Cell* **18,** 3214–3223 (2007).
106. Pece, S., Chiariello, M., Murga, C. & Gutkind, J. S. Activation of the protein kinase Akt/PKB by the formation of E-cadherin-mediated cell–cell junctions. *J. Biol. Chem.* **274,** 19347–19351 (1999).
107. Martin, A. C. & Goldstein, B. Apical constriction: themes and variations on a cellular mechanism driving morphogenesis. *Development* **141,** 1987–1998 (2014).
108. Dawes-Hoang, R. E. *et al.* Folded gastrulation, cell shape change and the control of myosin localization. *Development* **132,** 4165–4178 (2005).
109. Mason, F. M., Tworoger, M. & Martin, A. C. Apical domain polarization localizes actin–myosin activity to drive ratchet-like apical constriction. *Nat. Cell Biol.* **15,** 926–936 (2013).
110. Bolinger, C., Zasadil, L., Rizaldy, R. & Hildebrand, J. D. Specific isoforms of *Drosophila* shroom define spatial requirements for the induction of apical constriction. *Dev. Dyn.* **239,** 2078–2093 (2010).
111. Haigo, S. L., Hildebrand, J. D., Harland, R. M. & Wallingford, J. B. Shroom induces apical constriction and is required for hingepoint formation during neural tube closure. *Curr. Biol.* **13,** 2125–2137 (2003).
112. Hildebrand, J. D. Shroom regulates epithelial cell shape via the apical positioning of an actomyosin network. *J. Cell Sci.* **118,** 5191–5203 (2005).
113. Voiculescu, O., Bertocchini, F., Wolpert, L., Keller, R. E. & Stern, C. D. The amniote primitive streak is defined by epithelial cell intercalation before gastrulation. *Nature* **449,** 1049–1052 (2007).
114. Trichas, G. *et al.* Multi-cellular rosettes in the mouse visceral endoderm facilitate the ordered migration of anterior visceral endoderm cells. *PLoS Biol.* **10,** e1001256 (2012).
115. Shindo, A. & Wallingford, J. B. PCP and septins compartmentalize cortical actomyosin to direct collective cell movement. *Science* **343,** 649–652 (2014).
116. Simoes Sde, M. *et al.* Rho-kinase directs Bazooka/Par-3 planar polarity during *Drosophila* axis elongation. *Dev. Cell* **19,** 377–388 (2010).
117. Levayer, R., Pelissier-Monier, A. & Lecuit, T. Spatial regulation of Dia and Myosin-II by RhoGEF2 controls initiation of E-cadherin endocytosis during epithelial morphogenesis. *Nat. Cell Biol.* **13,** 529–540 (2011).
118. Cai, D. & Montell, D. J. Diverse and dynamic sources and sinks in gradient formation and directed migration. *Curr. Opin. Cell Biol.* **30C,** 91–98 (2014).
119. Cai, Y. *et al.* Cytoskeletal coherence requires myosin-IIA contractility. *J. Cell Sci.* **123,** 413–423 (2010).