REVIEW

Mechanics of Epithelial Tissue Homeostasis and Morphogenesis

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Epithelia are robust tissues that support the structure of embryos and organs and serve as effective barriers against pathogens. Epithelia also chemically separate different physiological environments. These vital functions require tight association between cells through the assembly of junctions that mechanically stabilize the tissue. Remarkably, epithelia are also dynamic and can display a fluid behavior. Cells continuously die or divide, thereby allowing functional tissue homeostasis. Epithelial cells can change shape or intercalate as tissues deform during morphogenesis. We review the mechanical basis of tissue robustness and fluidity, with an emphasis on the pivotal role of junction dynamics. Tissue fluidity emerges from local active stresses acting at cell interfaces and allows the maintenance of epithelial organization during morphogenesis and tissue renewal.

Epithelia form sheets of cells organized in a monolayer, as in developing embryos and the gut, or multilayered, as in the skin. Epithelial cohesion requires the formation of adhesive contacts supported mainly by E-cadherin molecules. E-cadherin forms cis and trans homophilic clusters that are stabilized by actin filaments via catenin molecules such as β-catenin and α-catenin, vinculin, and other proteins (*1*, *2*) (Fig. 1A). E-cadherin clusters concentrate in the adherens junctions and form an adhesive belt that stitches cells together. From a mechanical point of view, the extent of cell contacts depends on adhesion forces that stabilize cell-cell interfaces, balanced against cortical tension exerted by the actomyosin network that tends to reduce cell contacts [reviewed in (*3*)]. At the molecular level, adhesion reflects both the ligation of E-cadherin ectodomains (*4*, *5*) and the mechanical coupling to the cortical actomyosin network via α-catenin and vinculin (*6*–*10*), which stabilizes E-cadherin complexes. As a consequence, adhesion complexes are under tension and transmit subcellular forces exerted by actomyosin networks to the cortex (Fig. 1A) (*6*, *7*). By virtue of their symmetrical organization at cell contacts, E-cadherin clusters mechanically couple cells in a tissue. The interplay between E-cadherin complexes and actomyosin networks controls two key features of junction mechanics and dynamics: the ability to deform and remodel cell contacts by transmitting cell tension, and the resistance to cell deformation by cell adhesion. Thus, the balance between tension transmission and adhesion controls local junction dynamics.

Epithelial cell packing is responsible for characteristic polygonal cell geometries, in which edges are junctions between two cells, and vertices mark points of contact among three or more cells (Fig. 1A′). One can describe the organization of an epithelium according to the number and distribution of edges and vertices. A brief (less than a minute) external stress will elastically deform (elongate by stretching) this cellular array by cell shape changes where edges lengthen or shorten, while preserving the integrity of the epithelium (Fig. 1B, upper right). These deformations are geometrical and reversible, and they reflect the amplitude of intercellular adhesion forces together with the active response of the contractile cell cortex. When the stress is applied on longer time scales (tens of minutes), the tissue exhibits a fluid behavior where cells move much like particles that diffuse in a liquid. This requires topological changes by remodeling of cell contacts (elongation by rearrangement): Some edges disappear and others form (Fig. 1B, lower right). Epithelial cells not only respond actively

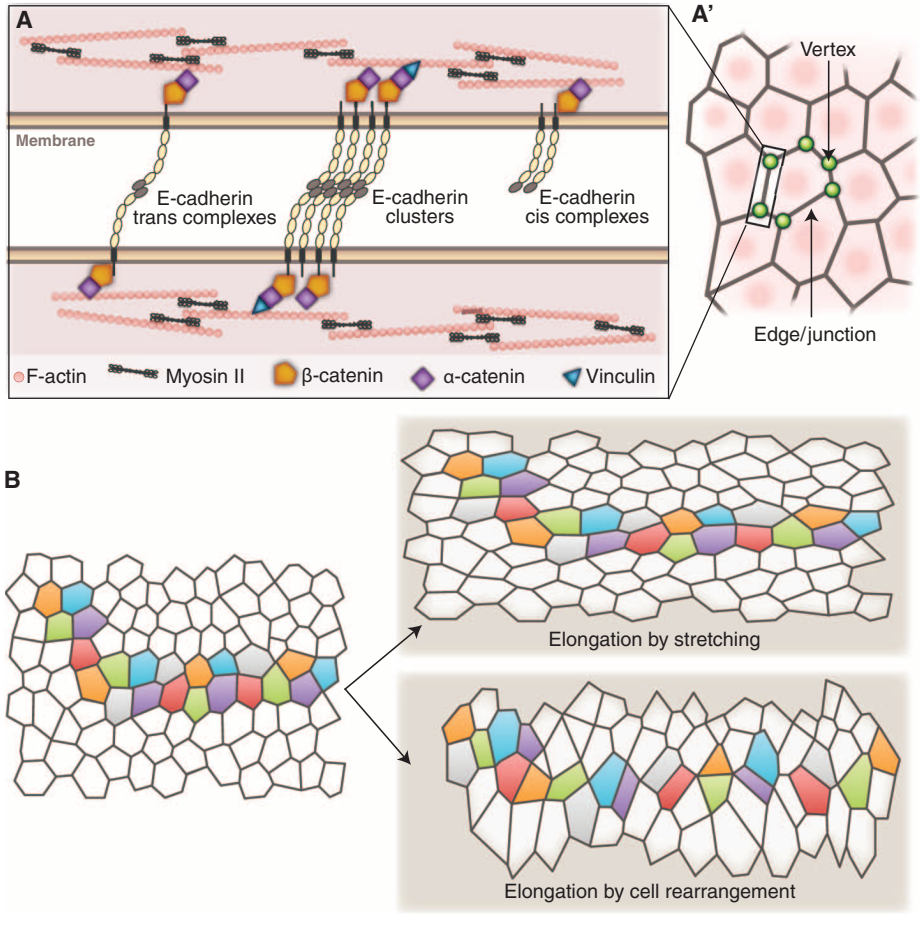

Fig. 1. Structure and plasticity of epithelial junctions during tissue stretching and remodeling. (**A**) E-cadherin forms cis and trans clusters stabilized by interaction between extracellular domains and actin filaments (F-actin, pink) via β-catenin, α-catenin, and vinculin (gold, purple, and light blue elements, respectively). (**A′**) These complexes control adhesion and tension transmission at cell junctions. Epithelial junctions form a polygonal network of edges (black) and vertices (green). (**B**) A tissue deforms elastically if it is stretched on short time scales (less than a few minutes); cells change their geometry (upper right). On longer time scales (tens of minutes), cells change their position by remodeling the topology of cell contacts and thereby dissipate the stress like a viscous fluid (lower right).

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to externally applied stress (e.g., coming from another tissue), but also generate their own internal stress through the regulation of subcellular actomyosin networks.

The source of epithelial plasticity and fluid behavior thus resides in the ability to actively remodel cell junctions. We review three main types of remodeling and extract general principles underlying these diverse processes (Fig. 2). First, cell division produces new cell junctions (*11*). Second, live cell extrusion and cell death remove cell junctions (*12*). Last, cell movement by intercalation changes the position of junctions (*13*, *14*). Remarkably, in all cases, junction dynamics is an active and multicellular process.

Formation of New Contacts During Division

Cell division profoundly affects the organization of epithelial tissues (Fig. 3A). Cell division is responsible for the rapid emergence of a robust equilibrium pattern of cell topologies (*11*). This results from simple empirical rules of cell division, shared among animals and plants, in particular, the fact that a division produces a new edge and two new vertices with minimal cell rearrangement. In turn, the cell topology affects the shape of its neighbors and thereby affects the orientation of cell division in this cell. If all cells are hexagonal, then cell shapes are similar and isotropic and cell divisions are randomly oriented. However, a hexagonal cell that contacts a four-sided cell will elongate parallel to the contact between the two cells. In turn, the cleavage plane of this elongated cell will be biased perpendicular to the contact between the two cells (*15*). The interplay among cell topology, cell shape, and cell division orientation is a striking manifestation of how cell proliferation participates in the steady-state organization of an epithelium by controlling how cell contacts are distributed locally and globally.

It has remained unclear how cell division occurs in an epithelium—in particular, what enables a new adhesive interface to form during division (Fig. 3B). This is a fundamental problem because division must preserve the integrity of an epithelium, in particular its barrier function. Do cells lose their adhesive contacts with neighbors as they divide? What is the link between junction formation and cell cleavage during cytokinesis? Cytokinesis requires the formation of a contractile actomyosin ring that deforms the dividing cells (*16*). If cells remain adhesive during division, such deformations will be resisted by cell adhesion with neighbors and the effective tension exerted by neighbors via cell junctions on the dividing cell. Madin-Darby canine kidney (MDCK) epithelial cells have been reported to maintain adhesion and apico-basal polarity as they divide (*17*). This is also observed in *Drosophila* epithelial cells at different stages of development and in the mouse neuroepithelium, so it is likely to be a general mechanism (*18*–*20*). Partitioning of the polarized cell progresses from basal to apical, and requires apical anchoring of the cytokinetic ring to cell junctions (Fig. 2B).

In most cases reported so far, dividing cells remain in contact during and immediately after division, although one cell may later exchange neighbors (see below). As a consequence, the clonal descendants of an epithelial cell are not scattered and tend to form a cohesive clone, as seen in early zebrafish (*21*) and *Drosophila* tissues (*22*). Further investigations in other systems will be useful in determining whether this is always the case, especially when cell polarity and a columnar epithelial organization are not evident.

Recent studies in *Drosophila* provide a simple model for understanding how formation of the new junction is coupled to cleavage in the plane of junctions (Fig. 3C) (*18*–*20*). Contraction of the ring deforms the cell junctions during cleavage up to a point where local disengagement of E-cadherin complexes in the cleavage furrow causes the separation of the membranes of the dividing cell and its neighbors (Fig. 3C and movie S1). A new membrane interface forms between the two daughter cells, which restores E-cadherin clusters, thereby maintaining adhesion. The length of the membrane interface requires nonautonomous actomyosin tension in the *Drosophila* pupa, which forces annealing between the surfaces of the two daughter cells (*18*, *20*). Local adhesion disengagement is also an active process. It requires tension exerted by the ring (which depends on septin and anillin) together with the tension exerted by neighboring cells pulling orthogonally to the junction (*18*, *19*). However, it is possible that adhesion disengagement is also the result of local biochemical regulation. E-cadherin clusters transmit and integrate intrinsic and extrinsic tension. In pupal epithelia, another remarkable active process is involved: Arp2/3-dependent actin polymerization causes maintenance of the newly formed interface (*20*), although the exact mechanism is still unclear. When these active processes are perturbed, either new junction formation is strongly delayed and ultimately fails, or the new junction is short and not stabilized, sometimes causing intercalation with neighbors.

During epithelial cell division, the addition of new junctions and the control of junction length is thus an active and multicellular process that preserves the tissue barrier function. It will be interesting to investigate these mechanisms in other organisms and see whether cells can escape this mechanism during tumor progression, and if so, how this is accomplished.

Removal of Junctions and Cells by Extrusion

Cell division increases the number of cells and cell contacts in a tissue. When division is associated with cell growth, the tissue expands, such as in developing embryos and organs or during regeneration. Once the tissue has attained its final adult size, however, the epithelium reaches a steady state (homeostasis) where cell divisions are balanced by cell death or live cell extrusion. A striking example is the mammalian gut. Cell divisions are concentrated in the crypt where stem cells produce progenitors (*23*). Cells then migrate along the side of microvilli and reach their tip (Fig. 4A). Remarkably, at the tips of microvilli, the majority of cells that extrude from the epithelium are nonapoptotic. Live cell extrusion was observed in other systems, such as in MDCK cell monolayers, developing fins in the zebrafish (*24*), or the midline of the developing dorsal adult *Drosophila* epithelium, called the notum (Fig. 4B) (*25*). In all but the *Drosophila* notum, extrusion is apical (*24*, *25*). Recent studies have shed light on the mecha-

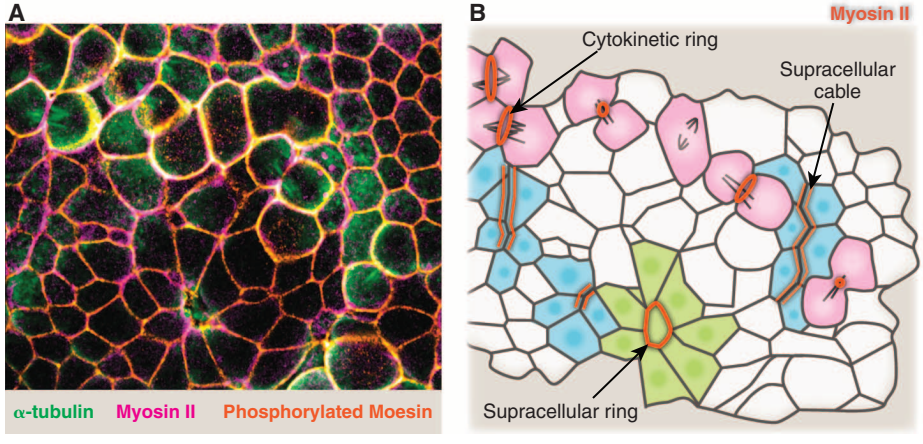

Fig. 2. Plasticity of epithelia is due to cell division, extrusion, and intercalation. (**A**) Immunostaining shows microtubule (green), myosin II (pink), and phosphorylated moesin marking the cell cortex (orange) of a *Drosophila* embryo. (**B**) Schematic of (A) showing cell division (pink), cell extrusion (green), and intercalation (blue) events in the tissue. Cell boundaries are in gray; myosin II is in orange.

nisms of cell junction removal during live cell extrusion. They reveal interesting differences with apoptotic extrusion but also show evidence of conserved pathways.

The trigger for nonapoptotic cell extrusion appears to be a buildup of tissue compression due to tissue growth and/or active cell movements. Although tissue pressure is difficult to measure directly, a series of observations supports this view. Reducing or increasing proliferation respectively inhibits or induces cell extrusion in the *Drosophila* notum (*25*). Cell extrusion also happens in regions where cells converge, such as in zebrafish fins (*24*). In addition, as MDCK cells are grown on a stretched elastic matrix, when the substratum is released and relaxes back, cell density increases within the first 30 min; after a few hours, cells extrude and restore the original cell density (*24*).

Because a whole cell disappears during extrusion, an average of six junctions must be removed. Cell extrusion proceeds in two main steps. First, two to three junctions disappear as neighbors are pushed away from the extruding cell by local cell intercalation events called T1 swaps (Fig. 4C). This step is most likely dependent on tissue compression and resultant differential junction tension: In *Drosophila*, cell-cell junctions relaxed more slowly after focal laser ablation in the dorsal midline than away from it (*25*). Once cells have about three junctions, an actomyosin supracellular ring is assembled in surrounding cells (Fig. 2B) and its contraction completes cell extrusion by a so-called T2 process, as reported in apoptotic cell extrusion or during wound closure (*26*). In zebrafish, cell extrusion requires stress-activated ion channels (called Piezo) and sphingosine-1-phosphate signaling, which could control the final step of the process through regulation of the Rho1–myosin II pathway (*24*).

Junction removal thus allows cell extrusion when tissue compression is too high. This contributes to maintaining a steady state in the epithelium. The inhibition of growth by contact inhibition is also a major component of homeostasis (*27*). Junction removal is an active and collective process that requires nonlocal forces emerging from a buildup in tissue pressure, as well as local forces produced by immediate neighbors.

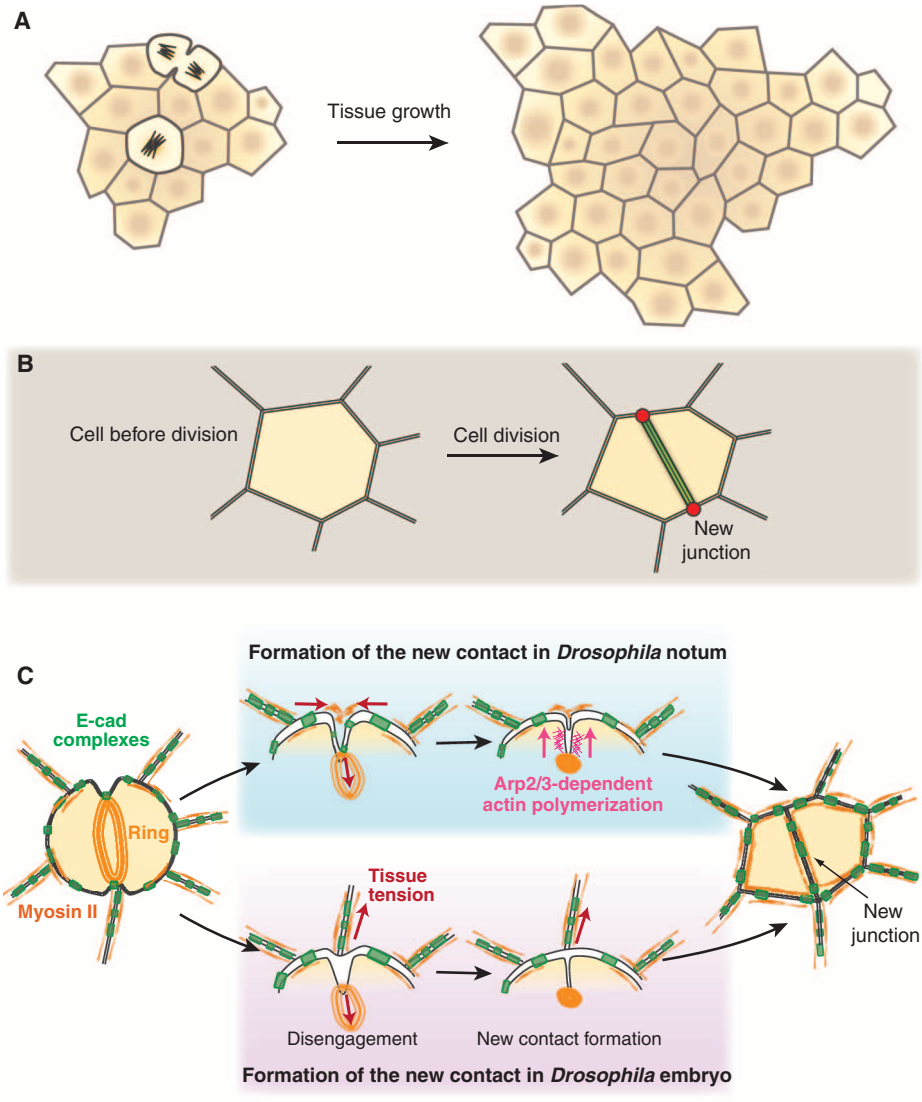

Fig. 3. Cell division in an epithelial layer. (**A**) Expansion of an epithelium by cell division. (**B**) Cell division produces a new cell junction (green) and two new vertices (red). (**C**) Successive stages of cell division in the *Drosophila* notum (top) and embryo (bottom), showing how intrinsic tension (due to ring contraction, red arrow) and extrinsic tension (red arrows) control disengagement of E-cadherin (E-cad) complexes and annealing of cell surfaces (top). Arp2/3-dependent polymerization controls new contact formation and/or stability (purple arrow, top).

Moving Cells by Intercalation and Junction Exchange

Local neighbor exchange, or cell intercalation, is a driving force during convergent extension movements in different organisms (*1*, *28*–*32*) and enables stress dissipation in a growing tissue (Fig. 1). During morphogenesis, it also participates in the extensive tissue remodeling as epithelia acquire their complex three-dimensional (3D) shapes. As imaging methods become more powerful to track cells in complex 3D environments (*33*), the cellular bases of tissue morphogenesis are gradually emerging in a variety of systems. A striking example of tissue morphogenesis is the elongation of an epithelium (Fig. 5, A and B). Cell intercalation allows cells to rearrange their positions, such as in the mouse visceral endoderm (*34*), in the *Xenopus* (*30*) and chick neural tube (*35*), and in the *Drosophila* germ band (*36*, *37*) (Fig. 5C and movie S2).

In essence, cell intercalation enables cell movement by changing the position of cell junctions in the tissue (Fig. 5C). In a first step, cell junctions are removed. This brings four or more cells together, producing a high-order vertex in a tetrad (*36*) or a rosette (*37*). Tetrads and rosettes have been described in a variety of systems (*34*–*37*). They are transient (and possibly unstable) structures that resolve through the formation of new junctions orthogonal to those that were removed. Intercalation is an irreversible process that is also planar-polarized when it drives tissue extension: The set of junctions that is removed is dependent on its orientation with respect to the tissue. For instance, in the *Drosophila* germ band, contacts between anteroposterior neighbors disappear selectively. The new junctions are formed at the interface between dorsal-ventral neighbors. As a result, the tissue elongates along the anteroposterior axis (*36*, *37*). In the chick neural tube, similar cell rearrangements have been described (*35*).

In principle, cell junction remodeling and intercalation could be controlled by external constraints acting on the tissue. In the *Drosophila* pupal wing, this is likely to be the case, as hinge contraction drives cell rearrangements (*38*). However, in several systems, cells locally produce the energy used to remodel contacts by forming planar-polarized actomyosin cables connecting two or more vertices together (Fig. 5, A and B). This process is both active and to a certain degree collective, as it involves a minimum of four cells, and as many as seven or eight cells, connected by supracellular contractile cables (Fig. 2B).

Studies in *Drosophila* and chicken delineate a similar pathway for polarized regulation of actomyosin contractility by the Rho1 pathway (Fig. 5D). RhoGEFs (*35*, *39*), ROCK (*40*, *41*), and myosin II regulatory light chain (*35*–*37*) are recruited and activated in a planar-polarized manner by surface receptors. Although these remain unknown in *Drosophila*, in the chick, PDZ-RhoGEF is activated by the planar cell polarity pathway, namely Celsr2, the ortholog of *Drosophila* Fmi (*35*). The increased bond tension at cell interfaces (*42*, *43*) could explain cell contact remodeling as shown using computational methods (*35*, *43*). Adhesion is also likely lower in anteroposterior contacts of the *Drosophila* germ band, because there are fewer and smaller E-cadherin adhesion clusters in these contacts (*37*, *39*). Cell intercalation was recently shown to depend on interfacial tension controlled by another myosin called Dachs, which is involved in planar cell polarization (*44*).

Cell intercalation drives tissue extension when the process is planar-polarized. The polarity is imposed by the orientation of interfacial stresses controlled by actomyosin networks. It is unclear how extension of the new junction occurs and whether this is an active or a passive process.

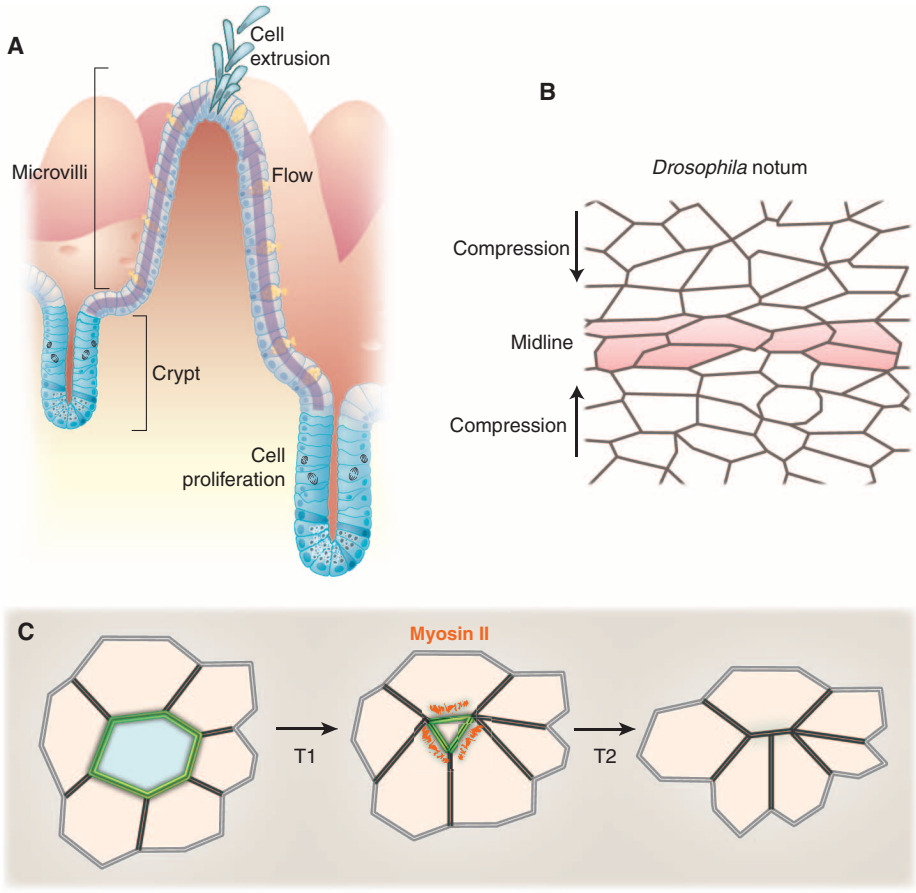

Fig. 4. Cell extrusion in epithelia can be mechanically induced. (**A**) In the mammalian gut, cells divide in the crypt and move to the top of microvilli, where they die or extrude while alive. (**B**) In *Drosophila*, cell compression due to tissue growth changes cell shape (red) and causes live cell extrusion. (**C**) Live cell extrusion requires displacement of two or three cell neighbors by junction removal using T1 swaps (see Fig. 5C). This is followed by accumulation of myosin II in a ring in neighboring cells (orange), producing T2 events and complete cell extrusion.

Toward a Multiscale Model of Tissue Dynamics

General principles of tissue homeostasis and morphogenesis emerge from the comparison of how junctions are formed, removed, or exchanged in epithelia. Junction dynamics is not a passive response to external and internal forces; it is an active process at cell contacts, whereby cells act collectively to remodel the junctions. On long time scales, junction dynamics confer fluid behavior through the dissipation of active stresses propagating in the tissue from its boundaries or internally controlled. This fluid behavior may explain how large-scale deformations, such as morphogenesis, arise. In some cases, junction remodeling is prevented and cells are stretched by multicellular actomyosin cables. This is the case at compartment boundaries, which prevent miscibility between two large groups of cells (*45*, *46*). In the chick neural tube, similar large-scale supracellular cables may allow tissue buckling by accumulating stress in the tissue as it closes (*35*). It will be important to investigate the cellular mechanisms controlling whether a cell can or cannot remodel cell contacts in response to internal stresses and the compressive forces acting from the tissue boundaries into the whole tissue. The adaptive response of E-cadherin adhesive complexes to actomyosin stresses, namely their ability to remodel or to reinforce, is likely an important area of future study. Cell junction dynamics requires dynamics of vertices where interplay occurs between actomyosin tension and adhesive clusters. Whether vertices are subject to a specific regulation relative to junctions will be an important consideration in determining how cell mechanics drives tissue dynamics.

Cell division, cell death, and cell intercalation modify the distribution of cell stresses in an epithelium. It is unclear how these local phenomena affect the global properties of the tissue (such as its global stress pattern), or how changes in global properties may in turn affect these local processes (*47*, *48*). For instance, polarized cell division would result in an effective polarized growth and stress that could potentially affect tissue organization. Whether cells can dissipate this stress by live cell extrusion or intercalation will have a profound impact on tissue organization and morphogenesis. Likewise, an overgrowth could affect the accumulation of stress in a tissue depending on whether cells can extrude. We are just beginning to see what sort of mechanical interplay exists between local and tissue scales in epithelia, and this will be an important avenue of investigation.

As we have seen, cell and tissue behaviors are also controlled by biochemical signals that control, for instance, actomyosin network dynamics and contractility. Biomechanical feedbacks operate on two different scales. At the cellular scale, cell deformation and actomyosin flows in cells transport polarity proteins and regulators of actomyosin contractility, thereby explaining to some extent how cell deformations and polarization are self-organized (*49*). At the tissue level, signals that are produced and exchanged at cell interfaces, and that coordinate cell contractility, may be influenced by the very cell deformation they control. Changes in the orientation or number

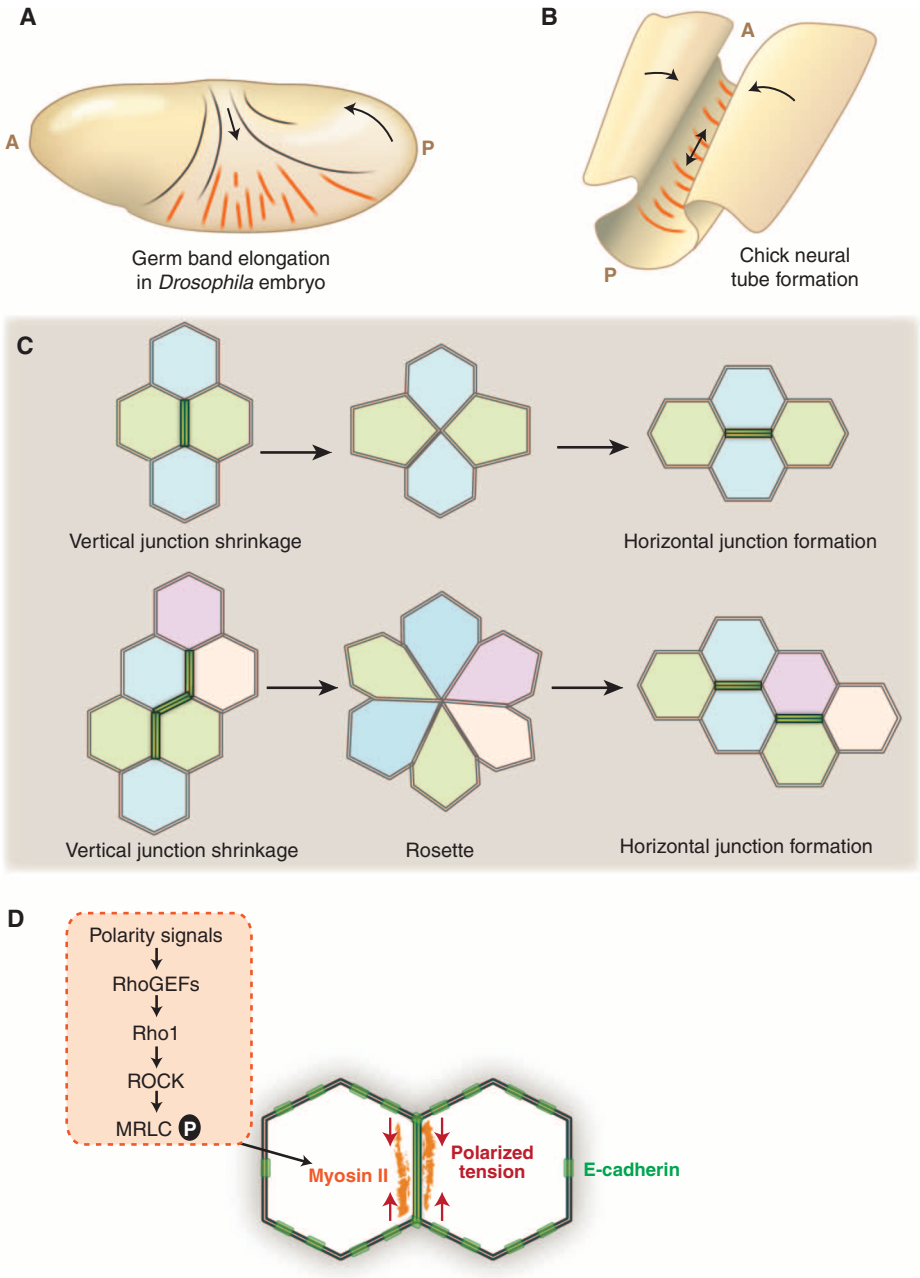

Fig. 5. Epithelial remodeling by cell intercalation. (**A** and **B**) *Drosophila* germ band extension (A) and chick neural tube closure (B) require cell intercalation (T1 swap) driven by polarized myosin II accumulation at cell contacts. (**C**) Planar junction remodeling consists of two steps: junction shrinkage to produce tetrads (top) or rosettes (bottom), and junction growth at a perpendicular. This process is planar-polarized in elongating tissues. (**D**) Junction shrinkage requires polarized phosphorylation of myosin II regulatory light chain (MRLCp), enrichment of myosin minifilaments, and polarized interfacial tension.

of cell junctions may affect the flow of information through the tissue; whether this information is in the form of polarity complexes that interact locally and propagate by proxy (*38*, *50*) and/or whether it is in the form of long-range morphogens (*51*) remains to be elucidated.

We are entering an exciting time when interdisciplinary research enables us to understand the fundamental properties of tissue functional homeostasis and morphogenesis by considering the interplay between biochemical and mechanical signals across different scales of organization.

References and Notes

1. G. A. Gomez, R. W. McLachlan, A. S. Yap, *Trends Cell Biol.* **21**, 499 (2011).
2. S. Yonemura, *Curr. Opin. Cell Biol.* **23**, 515 (2011).
3. T. Lecuit, P. F. Lenne, *Nat. Rev. Mol. Cell Biol.* **8**, 633 (2007).
4. J. Brasch, O. J. Harrison, B. Honig, L. Shapiro, *Trends Cell Biol.* **22**, 299 (2012).
5. P. Katsamba *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 11594 (2009).
6. N. Borghi *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **109**, 12568 (2012).
7. M. Cavey, M. Rauzi, P. F. Lenne, T. Lecuit, *Nature* **453**, 751 (2008).
8. R. Desai *et al.*, *Nat. Cell Biol.* **15**, 261 (2013).
9. S. Huveneers *et al.*, *J. Cell Biol.* **196**, 641 (2012).
10. J. L. Maître *et al.*, *Science* **338**, 253 (2012).
11. M. C. Gibson, A. B. Patel, R. Nagpal, N. Perrimon, *Nature* **442**, 1038 (2006).
12. Y. Gu, J. Rosenblatt, *Curr. Opin. Cell Biol.* **24**, 865 (2012).
13. T. Nishimura, M. Takeichi, *Curr. Top. Dev. Biol.* **89**, 33 (2009).
14. A. Vichas, J. A. Zallen, *Semin. Cell Dev. Biol.* **22**, 858 (2011).
15. W. T. Gibson *et al.*, *Cell* **144**, 427 (2011).
16. M. Glotzer, *Science* **307**, 1735 (2005).
17. S. Reinsch, E. Karsenti, *J. Cell Biol.* **126**, 1509 (1994).
18. N. Founounou, N. Loyer, R. Le Borgne, *Dev. Cell* **24**, 242 (2013).
19. C. Guillot, T. Lecuit, *Dev. Cell* **24**, 227 (2013).
20. S. Herszterg, A. Leibfried, F. Bosveld, C. Martin, Y. Bellaiche, *Dev. Cell* **24**, 256 (2013).
21. N. Olivier *et al.*, *Science* **329**, 967 (2010).
22. A. L. Knox, N. H. Brown, *Science* **295**, 1285 (2002).
23. B. D. Simons, H. Clevers, *Exp. Cell Res.* **317**, 2719 (2011).
24. G. T. Eisenhoffer *et al.*, *Nature* **484**, 546 (2012).
25. E. Marinari *et al.*, *Nature* **484**, 542 (2012).
26. K. J. Sonnemann, W. M. Bement, *Annu. Rev. Cell Dev. Biol.* **27**, 237 (2011).
27. A. Puliafito *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **109**, 739 (2012).
28. J. P. Trinkaus, M. Trinkaus, R. D. Fink, *J. Exp. Zool.* **261**, 40 (1992).
29. K. D. Irvine, E. Wieschaus, *Development* **120**, 827 (1994).
30. L. A. Davidson, R. E. Keller, *Development* **126**, 4547 (1999).
31. R. Keller *et al.*, *Philos. Trans. R. Soc. London Ser. B* **355**, 897 (2000).
32. E. M. Munro, G. M. Odell, *Development* **129**, 13 (2002).
33. P. J. Keller, *Science* **340**, 1184 (2013).
34. G. Trichas *et al.*, *PLoS Biol.* **10**, e1001256 (2012).
35. T. Nishimura, H. Honda, M. Takeichi, *Cell* **149**, 1084 (2012).
36. C. Bertet, L. Sulak, T. Lecuit, *Nature* **429**, 667 (2004).
37. J. T. Blankenship, S. T. Backovic, J. S. Sanny, O. Weitz, J. A. Zallen, *Dev. Cell* **11**, 459 (2006).
38. B. Aigouy *et al.*, *Cell* **142**, 773 (2010).
39. R. Levayer, A. Pelissier-Monier, T. Lecuit, *Nat. Cell Biol.* **13**, 529 (2011).
40. T. Nishimura, M. Takeichi, *Development* **135**, 1493 (2008).
41. S. M. Simões *et al.*, *Dev. Cell* **19**, 377 (2010).
42. R. Fernandez-Gonzalez, S. M. Simoes, J. C. Röper, S. Eaton, J. A. Zallen, *Dev. Cell* **17**, 736 (2009).
43. M. Rauzi, P. Verant, T. Lecuit, P. F. Lenne, *Nat. Cell Biol.* **10**, 1401 (2008).
44. F. Bosveld *et al.*, *Science* **336**, 724 (2012).
45. K. P. Landsberg *et al.*, *Curr. Biol.* **19**, 1950 (2009).
46. B. Monier, A. Pélissier-Monier, A. H. Brand, B. Sanson, *Nat. Cell Biol.* **12**, 60 (2010).
47. B. I. Shraiman, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 3318 (2005).
48. T. Aegerter-Wilmsen *et al.*, *Development* **137**, 499 (2010).
49. N. W. Goehring *et al.*, *Science* **334**, 1137 (2011).
50. D. Ma *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 18800 (2008).
51. O. Wartlick, A. Kicheva, M. González-Gaitán, *Cold Spring Harb. Perspect. Biol.* **1**, a001255 (2009).

Acknowledgments: We thank members of our group, as well as R. Le Borgne and B. Shraiman, for useful comments, and C. Collinet for contributing movie S2. Supported by CNRS, ANR (Programme Blanc, Archiplast, and Labex INFORM, ANR-11-LABX-0054 under the A*MIDEX program ANR-11-IDEX-0001-02), ERC (grant 323027-Biomecamorph), and ARC (grant SL220120605305).

10.1126/science.1235249