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Shaping Organs: Shared Structural Principles Across Kingdoms

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Abstract

Development encapsulates the morphogenesis of an organism from a single fertilized cell to a functional adult. A critical part of development is the specification of organ forms. Beyond the molecular control of morphogenesis, shape in essence entails structural constraints and thus mechanics. Revisiting recent results in biophysics and development, and comparing animal and plant model systems, we derive key overarching principles behind the formation of organs across kingdoms. In particular, we highlight how growing organs are active rather than passive systems and how such behavior plays a role in shaping the organ. We discuss the importance of considering different scales in understanding how organs form. Such an integrative view of organ development generates new questions while calling for more cross-fertilization between scientific fields and model system communities.

Contents

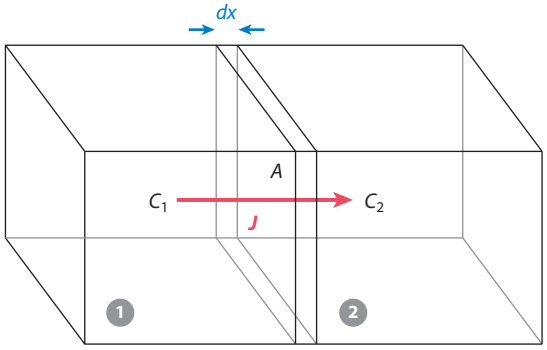
INTRODUCTION

Organ shapes can be simple; for example, in plants, many berries exhibit spherical shapes. As with a pressurized vessel, storage does not require directional reinforcements of the fruit envelope (Evert et al. 2013). Scaling up, many alpine shrubs are dome shaped. As an adaptation to higher wind, lower temperature, and dehydration, this minimizes their exposed surface, traps the sun's warmth, and acts as a hygrometry trap (Evert et al. 2013). Similarly, animals in colder climates generally display more spherical body shapes. The biophysical benefits associated with certain geometries are usually observed across multiple scales and can constitute the basis for evolutionary convergence.

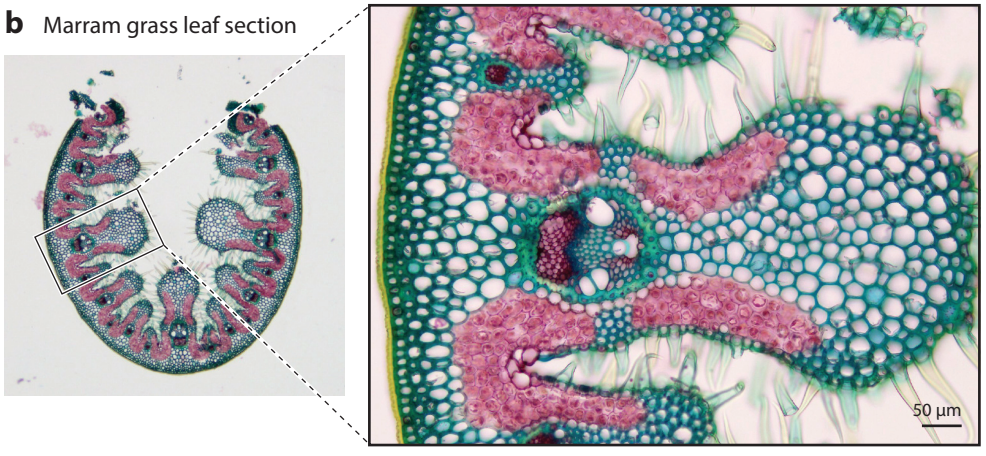
Fick's law of diffusion explains how organ shapes help to manage exchanges with the environment: The exchange of material (flux) increases if the surface area and the gradient of concentrations increase, while thicker interfaces decrease flux (Berg 1993) (**Figure 1*a***). For example, the gut is a long, twisted tube, which maximizes its surface area (Helander & Fändriks 2014); similarly, lungs have considerable branching networks (Hannezo et al. 2017). In both tissues, cell interfaces are thin and concentration gradients are large. In contrast, adaptation to dry environments in plants usually results in morphologies that reduce water exchange, such as in the Marram grass (**Figure 1*b***). Though an important area of research, we do not consider the contribution of external cues to organ shapes further, as our aim here is to concentrate on the intrinsic mechanisms behind shape emergence.

What is the minimal number of deformations sufficient to recapitulate all organ shapes? Starting from an isotropic sphere, elongating one axis generates an anisotropic ovoid or, in the most extreme case, a rod. Shortening one axis of a sphere generates flat shapes. From flat shapes, folding

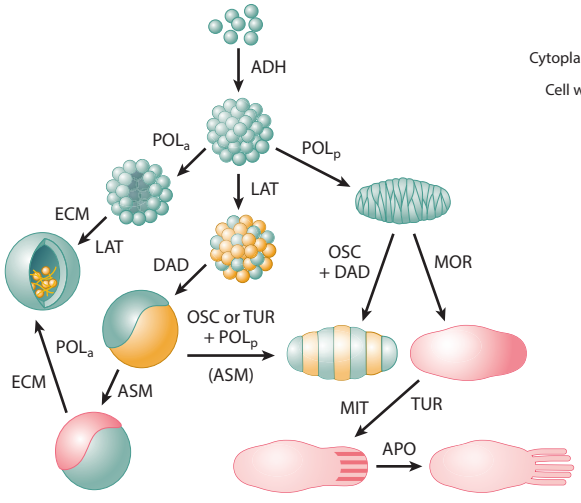
a Fick's law: $J = -DA dC/dx$



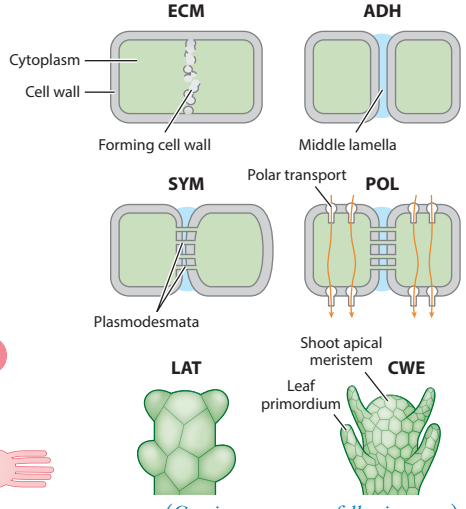
b Marram grass leaf section



c Dynamical patterning modules in metazoans



d Dynamical patterning modules in plants



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Elemental approaches to organ shape. (*a*) Fick's law defines the movement of particles (flux, $\vec{J}$) by diffusion between two compartments at different concentrations C_1 and C_2. The membrane thickness (dx), surface area (A), and diffusion constant (D) determine the flux. (*b*) Marram grass leaves exhibit a cylindrical shape (low A) and a thick, lignified cortex (high dx) to resist water stress (in their dune environment), whereas gas exchange is allowed by the convoluted shapes inside (high A) and the reduced thickness of the interface at the bottom of the crypt (low dx). Photos in panel *b* provided by M. Maillart. (*c*) Dynamical patterning modules correspond to a limited set of biophysical principles that recapitulate organ shaping in metazoans. Panel *c* adapted from Newman & Bhat (2009) under CC-BY-4.0. (*d*) Dynamical patterning modules may also be defined for plant tissues. Panel *d* adapted from Hernández-Hernández et al. (2012) under CC-BY-4.0. Abbreviations: ADH, cell–cell adhesion; APO, apoptosis; ASM, asymmetry; CWE, cell wall extension; DAD, differential cell adhesion; ECM, extracellular matrix secretion; LAT, lateral inhibition; MIT, mitosis; MOR, morphogen diffusion; OSC, oscillation; POL, polarity; POL_a, apical-basal polarity; POL_p, planar polarity; SYM, symplastic diffusion (through plasmodesmata); TUR, Turing-type reaction diffusion.

can generate, for example, tubes. The combination of these elemental shapes and deformations, along with growth, is sufficient to describe most plant and animal organ shapes (Coen & Rebocho 2016, Coen et al. 2004). Typically, two axes of polarity are sufficient to generate flat shapes, while a third axis is required for folded shapes (Whitewoods et al. 2020). Variants of this approach have been used to identify conserved features of tooth morphogenesis during evolution (Salazar-Ciudad & Jernvall 2010). Alternatively, morphological deformations can be decomposed into key physical processes, such as diffusion, adhesion, or polarity (so-called dynamical patterning modules), that occur at the cell level (Newman & Bhat 2009) (**Figure 1*c***). Initially developed for animal systems, such dynamical patterning modules can also be extended to plant systems (Hernández-Hernández et al. 2012) (**Figure 1*d***).

Does this decomposition into elemental geometries and physical deformation reflect an absence of biological control behind organ morphogenesis? In the footsteps of D'Arcy Thompson (1917), the sphere could be considered the default shape in nature due to its simple surface energy minimization. However, rounding can also be the result of active mechanisms. Animal cells typically round before division (Sauer 1935), and such rounding is required for the proper processing of the mitotic spindle (Lancaster et al. 2013) and the control of cell division plane orientation (Bosveld et al. 2016); it has even been associated with larger-scale tissue deformation such as folding (Kondo & Hayashi 2013). The decomposition of complex organ forms into elementary shapes and deformation is thus rather an incentive to decipher the cellular mechanisms and physical constraints behind organ shape emergence, maintenance, and robustness. Fundamentally, biological systems are active systems responding to physical inputs and constraints.

In the following discussion, we use plant and animal systems to outline general principles for shaping organs. We summarize the current knowledge regarding the interplay between biochemical and biomechanical signals that underlies the formation of complex organ shapes.

Growth: irreversible increase in volume; cell contraction, migration, and death can account for neutral (shape changes with no increase in volume) or negative (reduction in volume) growth

FROM SUPRACELLULAR BIOCHEMICAL CUES TO ORGAN SHAPE THROUGH MECHANICS

To control organ morphogenesis, the initiation, maintenance, and combination of elemental deformations require coordinated mechanisms. Supracellular biochemical signals known as morphogens are spatially heterogeneous across a tissue and can impart spatial information to the cells within the tissue (Rogers & Schier 2011) (**Figure 2*a***). A classic example is the transcription factor Bicoid, which imparts anteroposterior positional information to the developing *Drosophila* embryo (Driever & Nüsslein-Volhard 1988, Huang & Saunders 2020). This information is interpreted into specific domains that form the future body plan (Petkova et al. 2019). Generally,

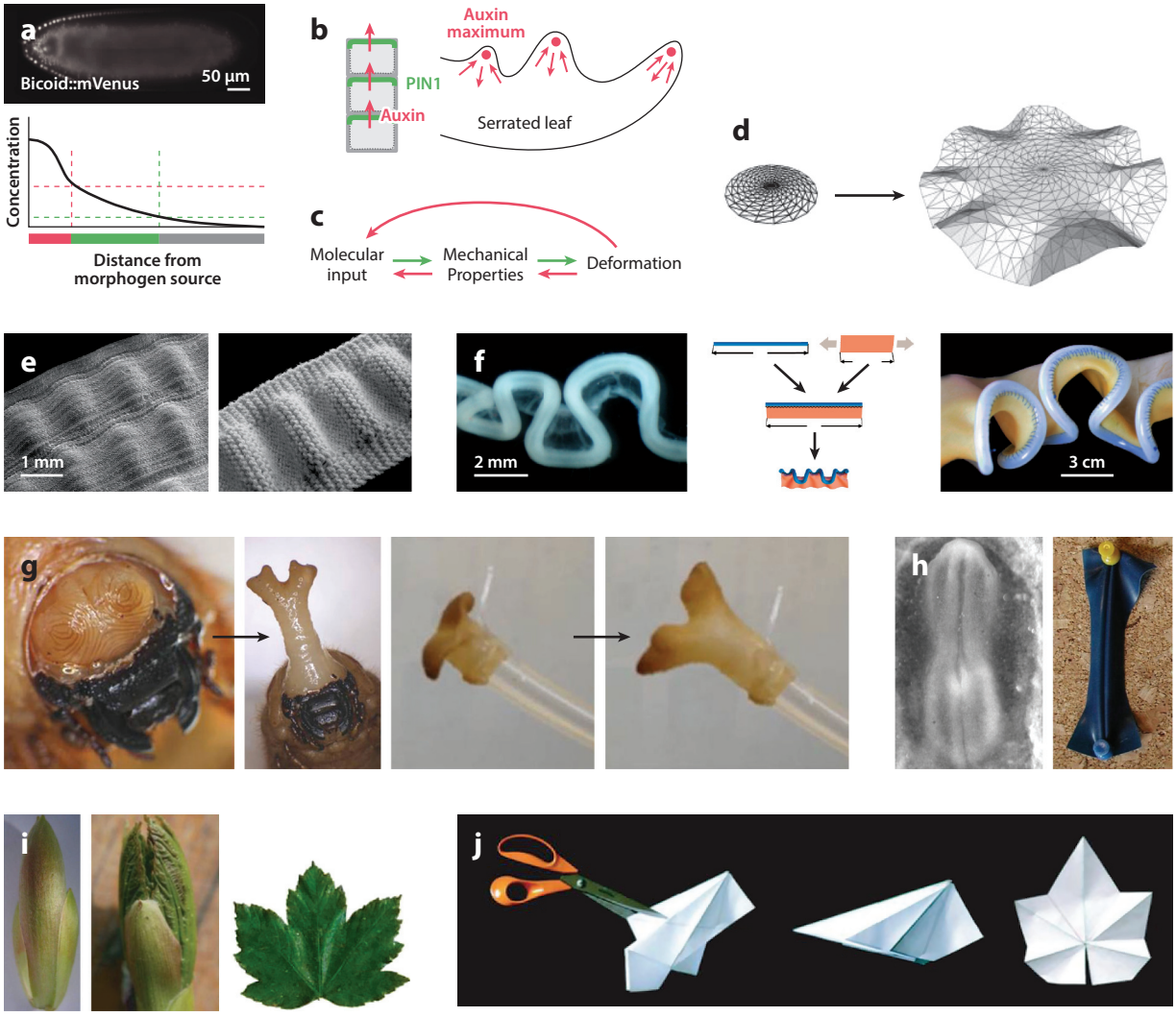


Figure 2

From biochemical cues to organ shape changes. (*a*) Morphogen gradients provide positional information. (*Top*) Nuclear cycle 14 *Drosophila* embryo expressing Bicoid::mVenus. (*Bottom*) Gene expression boundaries (*colored rectangles*) are formed at specific concentrations of the morphogen (*dashed colored lines*). (*b*) Intercellular communication allows long-range coordination. For instance, PIN-FORMED1-dependent auxin transport generates auxin maxima leading to serrated or lobed leaves. (*c*) A schematic pathway linking molecular factors, including feedback mechanisms, to deformation. (*d*) Passive buckling emerging from mechanical conflicts in a disc-shaped computational model in which the margins are growing faster than the center. Panel *d* adapted with permission from Coen et al. (2004); copyright 2004 National Academy of Sciences, USA. (*e*, *Left*) Rippling pattern in maize leaves due to mechanical conflicts between lamina and vein, and (*right*) an analog model in the form of a knitted band with different numbers of stitches. Panel *e* adapted with permission from Dumais (2007). (*f*) Chick gut shape (*left*) can be mimicked by gluing two rubber bands together, with one being tensed beforehand (*middle*): upon relaxation, buckling occurs (*right*). Panel *f* adapted with permission from Savin et al. (2011). (*g*, *Left*) The mechanical prepattern behind the branching structure in insect horns (without the head cuticle) that is revealed upon manual abdominal compression. (*Right*) Similarly, fixed horn primordia can extend when attached to a tube and then inflated. Panel *g* adapted with permission from Matsuda et al. (2017) under CC-BY-4.0. (*h*) An analog model for (*left*) neural tube morphogenesis in the form of (*right*) a rubber band pinned down on a board. Panel *h* adapted with permission from Fleury (2013). (*i*) Lobes in leaves from deciduous trees can emerge from the way they arrest their growth within buds. (*j*) Kirigami can explain the formation of lobed leaves in buds, with the restricting bud walls playing the role of developmental scissors. Panels *i* and *j* adapted with permission from Couturier et al. (2011).

morphogens in animals are extracellular proteins (Bejsovec 2018, Ingham 2001). They define specific cellular domains within a tissue that can have subsequent spatial effects on tissue mechanics (Gilmour et al. 2017, Nelson 2009, Recho et al. 2019, Wartlick et al. 2011).

Buckling: sudden change in material shape under compression or shear forces

Interestingly, plants appear to utilize a broader range of morphogen-like factors, such as transcription factors (Yadav et al. 2011), microRNAs (Skopelitis et al. 2012), peptides (Hirakawa & Sawa 2019), hormones (Chickarmane et al. 2012), and other chemical components such as oxygen gradients (Kelliher & Walbot 2012). Arguably, this could reflect plants' stronger dependence on environmental factors, given their sessile status and associated plastic and indeterminate postembryonic development. The morphogenetic signals can be very small molecules: For example, the hormone auxin is the size of the amino acid tryptophan. Such molecules can thus cross multiple cells through either plasmodesmata (Faulkner 2018) or cell walls (Tepfer & Taylor 1981). Note that plasmodesmata allow diffusion and transport of molecules as large as viruses. Such long-range cell–cell communication echoes gap junctions (Hervé & Derangeon 2013) or directed intercellular communication via the filopodia-like protrusions called cytonemes (Ramírez-Weber & Kornberg 1999) in animal cells.

In addition to passive diffusion, morphogens can be actively transported at the plasma membrane in plant cells, resulting in large-scale polar transport and thus polarity-dependent positional information in tissues. For instance, PIN-FORMED1-dependent auxin transport controls the formation of leaf serrations (Bilsborough et al. 2011) (**Figure 2*b***). Although plants and animals use different dynamic processes to generate morphogen gradients, the use of such gradients to impart spatial information to developing tissues is common across multicellular organisms.

Ultimately, morphogen gradients spatially modify the behavior of cells, including their mechanical properties (**Figure 2*c***). The boundary between domains with different cell mechanical properties can be the site of mechanical conflicts within tissues. During *Drosophila* wing growth, morphogens define specific cellular domains with distinct mechanical properties (Umetsu et al. 2014). These differences ensure that cells do not mix and boundaries stay straight during growth. Such tension also impacts the actomyosin cytoskeleton within cells, further preventing cell mixing (Landsberg et al. 2009).

Spatially defined mechanical conflicts can generate anisotropic deformations, which can lead to tissue buckling and folding. For instance, if marginal cells of a disc-shaped organ are growing faster than central cells, buckling occurs at the margins, leading to ruffling (Coen et al. 2004) (**Figure 2*d***). This hypothesis has been verified experimentally: Ruffled leaves in the snapdragon (*Antirrhinum majus*) mutant *cincinnata* are consistent with mechanical conflicts arising at the leaf margin (Nath et al. 2003). This also implies that the wild-type leaf is not flat by default: It requires tight control of its growth pattern to stay flat (**Figure 2*e***). Similarly, buckling can be achieved by stitching stretched and unstretched elastic materials together and then releasing the tension; formation of the vertebrate gut is highly analogous (Savin et al. 2011) (**Figure 2*f***). A striking example of predefining mechanical properties prior to growth is horn formation in the Japanese rhinoceros beetle. The horns derive from multifolded tissues consisting of dense furrows, akin to origami. When hydrostatic pressure is applied, they expand into distinctive horns (Matsuda et al. 2017) (**Figure 2*g***).

The exact contribution of mechanical conflicts to the resulting buckling into folded shapes is a major developmental question. Mechanical conflicts may aid in triggering gastrulation in early embryogenesis, as shown in *Drosophila* and zebrafish, for instance (Martin et al. 2009, Sherrard et al. 2010), and may contribute to the formation of the vertebrate neural tube (Fleury 2013) (**Figure 2*h***) and the *Drosophila* wing disc (Tozluoğlu et al. 2019). In plants, tissue folding during organ initiation at the shoot apical meristem (SAM) occurs as a result of differential growth and the associated mechanical conflict (Hamant et al. 2008, Kwiatkowska & Dumais 2003).

Mechanical conflicts can generate more complex plant shapes, such as snapdragon petals (Coen & Rebocho 2016) or modified leaves from the carnivorous plant *Utricularia* (Whitewoods & Coen 2017). Deciduous tree leaves form inside closed buds. As the leaves grow in the bud, they completely fill the available space through folding events, and the growth of leaf edges is geometrically constrained by the stiff bud envelope. When the bud opens, the leaves unfold, showing the distinctive lobed shape that is due to the mechanical constraints imposed during growth (**Figure 2*i***). This echoes the art of kirigami, in which folded paper sheets are cut and then unfolded to exhibit lobes (**Figure 2*j***) (Couturier et al. 2011).

Mechanical conflicts can be controlled by tuning adhesion between tissues. In the developing zebrafish myotome, differential coupling between the myotome and surrounding tissues results in the breaking of morphological symmetry and initiates the formation of a distinctive chevron shape (**Figure 3*a***) (Tlili et al. 2019). Earlier in zebrafish development, the adhesion molecule E-cadherin mediates the positioning of the neural anlage between the prechordal plate and the neuroectoderm (Smutny et al. 2017). Similar coupling between the embryo and extraembryonic tissues is also important in shaping the postimplantation mouse embryo (Christodoulou et al. 2019). In *Arabidopsis*, the waxy cuticle at the surface of the growing embryo prevents friction with the neighboring endosperm in the developing seed, thereby ensuring the proper development of cotyledons (Moussu et al. 2017). Similarly, reducing cell–cell adhesion in mutants with twisted cell growth can relax stem torsion (Verger et al. 2019). Spatially varying adhesion—and consequently mechanically heterogeneous regions—is critical in driving complex morphogenesis.

Friction: the resistance to movement between two surfaces; the level of friction can be tuned by controlling the expression of appropriate adhesion molecules

Endocycle: duplication of the genome during a cell cycle without mitosis; also known as endoreduplication

CELLULAR PROCESSES GUIDING TISSUE DEFORMATION

To go beyond these global deformations and understand how such shape changes are controlled, one needs to consider the deformation of individual cells and the biological and physical mechanisms at that scale. Recent years have seen substantial advances in our understanding of how behavior at the cellular scale translates to effects at the tissue scale. In this section, we cover a number of examples demonstrating how both tightly and spatiotemporally regulated cellular processes can drive complex tissue morphogenesis.

Cell Number: Proliferation and Death

The shape of each organ appears to strongly depend on events early in its development. A meta-analysis across plant species has revealed that the final size of aerial plant organs primarily depends on cell number, a parameter that is determined by meristem size at the onset of organogenesis (Gázquez & Beemster 2017). Control of cell number and hence organ size shares some commonality between plants and animals, in particular through the target of rapamycin (TOR) pathway (Rexin et al. 2015). Translationally controlled tumor protein (TCTP) is highly conserved, with evidence that the gene can be swapped between *Arabidopsis* and *Drosophila*. However, only the role of TCTP as a positive regulator of mitotic growth is conserved between plants and animals, with its role in postmitotic growth apparently being specific to animals (Brioudes et al. 2010).

Most cell cycle regulators, such as cyclins, are conserved in plants and animals (Harashima et al. 2013). However, the relationship between proliferation and tissue growth can diverge significantly between plants and animals. Growth generally correlates well with proliferation rate in animals (Barresi & Gilbert 2020). In plants, though, after an initial phase of proliferation, growth strongly correlates with cell expansion (Czesnick & Lenhard 2015); the number of endocycles—rather than the number of divisions—usually scales with cell size, although this is debated (Tsukaya 2019).

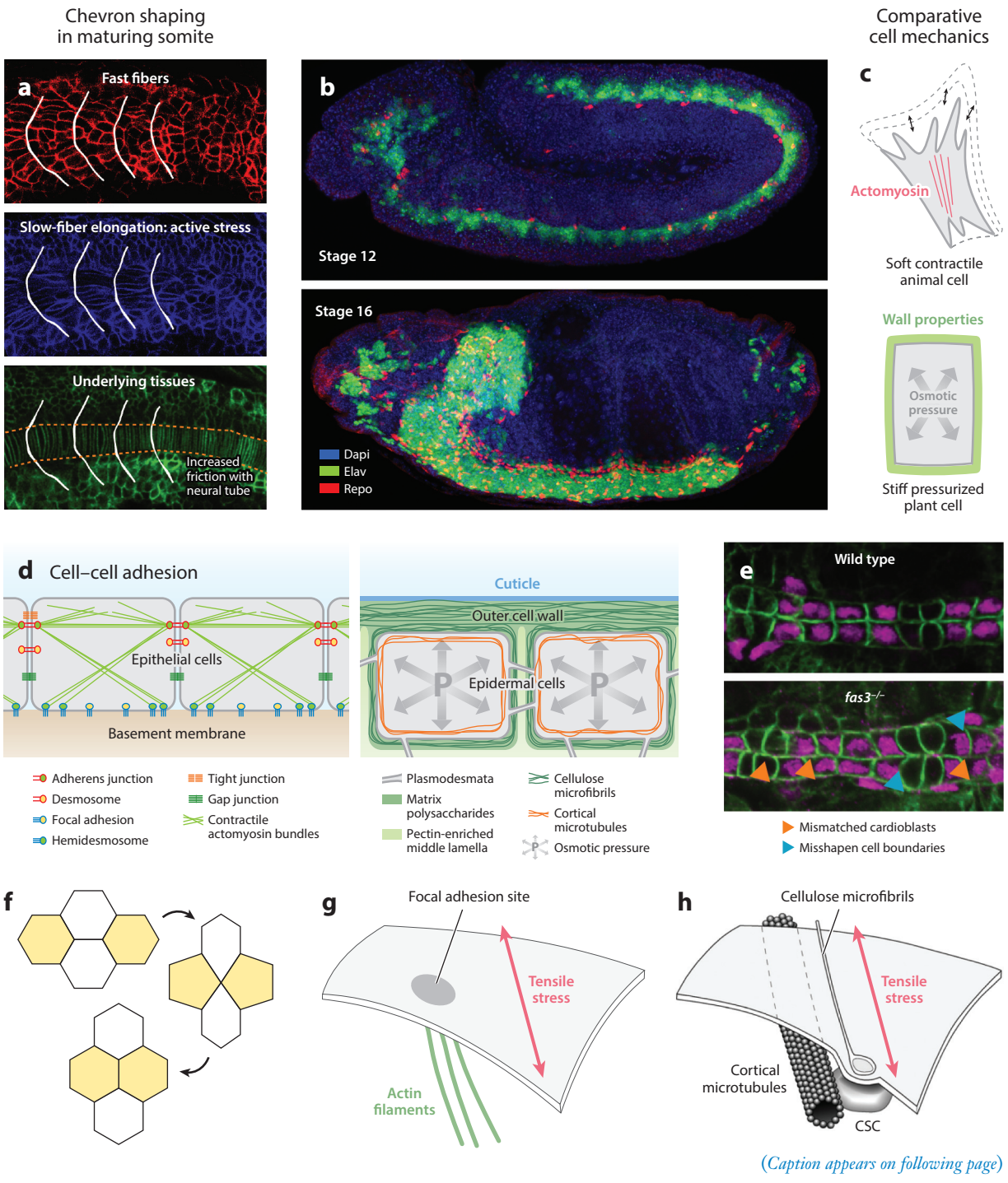


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Figure 3 (*Figure appears on preceding page*)

Cell behavior behind organ shape changes. (*a*) Upon slow muscle elongation (active stress), friction between adjacent tissues (increased friction in the neural tube but reduced friction in the notochord) generates the chevron shape in zebrafish somites. Images of embryos expressing Lyn-tdTomato are acquired as described in Tlili et al. (2019). (*Top*) Plane showing fast fibers prior to their elongation. (*Middle*) Plane showing the slow muscle fibers. (*Bottom*) Plane showing tissues underlying the developing myotome. (*b*) Central nervous system contraction upon large-scale apoptosis. Images taken on a confocal microscope after immunostaining embryos for Dapi (DNA, *blue*), Elav (cells in the central nervous system, *green*), and Repo (glial cells, *red*) at stages 12 and 16. (*c*) Comparative cell mechanics in plants and animals. (*d*) Cell–cell adhesion in (*left*) animal and (*right*) plant epithelia. Panel *d* adapted with permission from Galletti et al. (2016). (*e*) *fas3* loss-of-function mutants exhibiting misshapen cardioblasts because of reduced cell–cell adhesion. Images acquired as described in Zhang et al. (2018). (*f*) Tissue topology changes through cell–cell adhesion modulation and contractile behavior (T1 transition). (*g*) Actin filaments align with maximal tension and control cell shape and contractility in animal cells. (*h*) Cortical microtubules align with maximal tensile stress and guide the trajectory of the cellulose synthase complex (CSC), thereby channeling the mechanical anisotropy of plant cell walls. Panel *h* adapted with permission from Burget & Fratzl (2009).

In contrast, endocycles are rare in animal cells; a counterexample is provided by liver damage response, in which increased cell size compensates for cell loss (Lee et al. 2009).

Programmed cell death, or apoptosis, plays an important role in shaping a range of organs (Fuchs & Steller 2011). Organs can prune cells to generate specific morphologies. During mammalian digit specification (Chen & Zhao 1998), apoptosis occurs in distinct regions defined by a Turing-like reaction–diffusion network (Sheth et al. 2012). In *Drosophila*, the embryonic nerve cord retracts from a maximum length of over 500 μm (prior to germ-band retraction) to around 200 μm at hatching (**Figure 3*b***). This process of condensation requires apoptosis at precise spatial and temporal locations (Pinto-Teixeira et al. 2016). In contrast, cell death is rare in young plant tissues (Daneva et al. 2016). It follows that cell growth provides a good proxy for final organ shape in plants. However, there are counterexamples: aerenchyma in aquatic species, endosperm in the immature seed, and xylem formation. Furthermore, lateral roots emerge from inner tissues, and programmed cell death of more cortical root cells facilitates this process (Escamez et al. 2020). In general, understanding how mechanical interactions are regulated and directed within condensing and shrinking tissues during development remains an open challenge.

Cell Contractility: Tissue Shaping with Fluid Mechanics

Animal cells are typically soft (in the kilopascal range) in comparison to plants (in the megapascal range) (**Figure 3*c***). Consequently, animal cells can be considered more amenable to shape changes, such as contraction, which are critical in altering tissue morphology (Martin et al. 2009). Apical contractility induces buckling and hence internalization of the mesoderm during gastrulation (Garcia De Las Bayonas et al. 2019). Within a single cell, there are often distinct mechanical domains driven by localization of mechanical elements, such as Myosin II, cell junctions, and microtubules (Lecuit et al. 2011).

Because of stiff walls, cell contractility is typically absent in young plant tissues (Evert et al. 2013), though there are exceptions. The *Arabidopsis* zygote undergoes a transient contraction before the first asymmetric division (Kimata et al. 2019), and cells at the boundary between the emerging organ and the SAM are compressed by the growing organ, leading to radial contraction of the outer wall of these boundary cells (Kwiatkowska & Dumais 2003). Cell contraction can even occur in dead tissues, notably through desiccation-dependent wall deformation; such processes are involved in the formation of several seed dispersal catapult systems (e.g., see Noblin et al. 2012).

Apoptosis: controlled and normal cell death as part of an organism's life cycle

Cell Shaping Through Balancing Cell Stiffness and Hydraulic Forces

Plants, algae, fungi, bacteria, and archaea all have stiff walls. In addition, their cell shape is mainly determined by a balance between osmotic pressure and turgor pressure, which is hydrostatic

pressure that the cell wall exerts on the cell contents (**Figure 3*c***). Cell deformation occurs primarily through modulation of both wall stiffness and, to a lesser extent, turgor pressure. In the plant shoot, auxin triggers the acidification of cell walls, which activates enzymes and wall remodelers, leading to softening and an increased growth rate (Rayle & Cleland 1970). In contrast, in the root, auxin can trigger the alkalinization of cell walls and thus a reduced growth rate (Barbez et al. 2017).

Hydraulic pressure: force per unit area on a region due to a fluid

Vertex modeling: a statistical mechanics approach used to model cell behavior, particularly in 2D epithelial sheets

Hydrostatic pressure plays a critical yet distinct role in animal morphogenesis. During early *Drosophila* development, the hydrostatic properties of the cytoplasm propagate apical forces within the epithelial tissue, resulting in cell elongation (He et al. 2014). In the early mouse blastocyst, hydraulic pressure plays a critical role in regulating the embryo size (Chan et al. 2019). The more fluid-like behavior of animal cells can result in hydrostatic forces shaping particular cellular and tissue architectures.

From an evolutionary point of view, organisms with walled and nonwalled cells represent two very different strategies to survive in a hypoosmotic environment: (*a*) Walled-cell organisms allow osmotic pressure to build up inside their cells, while (*b*) nonwalled-cell organisms use osmoregulation to create close to isoosmotic local environments inside the body. This key divide between plant and animal mechanics translates into different deformation strategies at the cell, and ultimately also the tissue, level.

Cell–Cell Adhesion: Transitioning Between Fluid and Solid Behavior

Plant cells are glued to one another through a pectin-rich middle lamella in their contiguous cell walls (Daher & Braybrook 2015) (**Figures 1*d*** and **3*d***). The only known exceptions to this rule are pollen tubes and fiber cells, both of which exhibit invasive behavior (Gorshkova et al. 2012, Marsollier & Ingram 2018). In contrast, animal cells usually adhere through direct protein–protein interactions. Modulating the level of adhesion allows rearrangement, contraction, and delamination (Baum & Georgiou 2011). Some animal epithelia do exhibit tight adhesion, as in plants, and packing can thus play instructive roles (Bosveld et al. 2016, Gibson et al. 2011).

Cell-adhesion molecules play a critical role in determining cell shape and tissue morphogenesis. For example, fasciclins, members of the immunoglobin superfamily, aid in shaping the brain (Chiba et al. 1995), gut (Wells et al. 2013), and heart (Zhang et al. 2018). Loss of Fasciclin III during *Drosophila* cardiogenesis results in deformed cardioblasts with less rigid cell boundaries (Zhang et al. 2018) (**Figure 3*e***). Similar results have recently been reported for neural cell interactions in the developing zebrafish (Tsai et al. 2019), in which cadherins and protocadherins act to mechanically couple specific cells. The positioning of adherens junctions is also important in tissue morphogenesis. During the formation of the dorsal folds in the early *Drosophila* embryo, cells within the fold shift the position of the adherens junctions more basally, with neighboring cells maintaining their adherens junctions near the apical surface (Collinet & Lecuit 2013, Wang et al. 2012). Such movement is under the regulation of Par proteins, a highly conserved polarity network (Lang & Munro 2017), which can interact with the cell cytoskeleton and hence regulate cell shape (Nance & Zallen 2011). The ability of tissues to spatially and temporally tune the expression and position of adhesion molecules and cellular junctions appears to be critical in tissue morphogenesis. However, there remain open questions: How is such mechanical information integrated by the forming tissues, and how are these processes genetically regulated, particularly regarding control of the timing of events?

Cell groups—i.e., tissues—can display either solid-like or fluid-like behavior. Vertex modeling of epithelial tissues has shown how tuning cell–cell adhesion and cortical tension can switch tissues between these two states (Bi et al. 2015). Tissue fluidization enables rapid cell rearrangements, such

as T1 transitions (**Figure 3*f***). Evidence for such behavior has been found in tissue repair (Tetley et al. 2019) and convergent extension (Wang et al. 2019). Conversely, in the developing zebrafish presomitic mesoderm, there is a fluid-like to solid-like jamming transition (Mongera et al. 2018). This process is regulated at least partially by stresses determined by N-cadherin. Animal cells are able to modulate their effective external state through regulation of their mechanical state. This provides flexibility in both forming organs during development and responding to injuries.

Stress: force per unit area upon which the force is acting (measured in pascals)

Dynamics: The Role of the Cytoskeleton in Tissue Shaping

The cytoskeleton plays a major role in cell deformation in both plants and animals, but the relevant players exhibit specific behaviors. In animals, the cell cortex is rich in actin filaments, whereas in plants, it is rich in cortical microtubules. In fact, microtubules were first observed in plants for this reason (Ledbetter & Porter 1963). This difference may again relate to cell mechanics. Plant cells synthesize stiff walls that contain cellulose microfibrils as the main load-bearing components. With cortical microtubules being three orders of magnitude stiffer in vitro than actin (Gittes et al. 1993), natural selection in the plant lineage may have favored stiff cytoskeletal tracks to guide the trajectory of cellulose synthase complexes at the plasma membrane (**Figure 3*g***). In contrast, in animal cells an actomyosin-rich cortex coupled with a generally soft extracellular matrix allows contractility and cell deformation (Jacinto et al. 2000) (**Figure 3*h***). In *Drosophila*, pulses of actomyosin contractility drive gastrulation in the early embryo (Martin et al. 2009), whereas sustained Myosin II localization at the leading edge of the ectoderm zips up the dorsal side of the embryo during dorsal closure (Hayes & Solon 2017). Similarly, during mouse blastocyst formation, coupling of actin rings at cell junctions triggers Myosin II accumulation and hence zippering of the blastocyst (Zenker et al. 2018).

Needless to say, there are many exceptions to these different actions of actin and microtubules. As animal cells differentiate and lose their centrosomes, microtubules self-organize and usually populate the cell cortex (Muroyama & Lechler 2017), as in plant cells. Similarly, at very early stages, mouse embryos do not have centrosomes, yet their microtubules are also cortical (Zenker et al. 2017). These homologous behaviors suggest that the cortical localization of microtubules in cells emerges from their intrinsic stiffness and ability to self-organize against the cytosolic cell surface, independent of the kingdom of the organism in which they are present (Mirabet et al. 2018). Plant cells also accumulate actin in their cortex, though the filaments are less distinct than in animals. The role of these filaments has mainly been associated with vesicle transport and cytoplasmic streaming (Nebenführ & Dixit 2018). Interestingly, in pollen tubes, which exhibit the most animal-like growth behavior of plant tissues, even mimicking axonal tip growth, microtubules play a minor role, and actin filaments drive growth direction through the polar exocytosis of wall components at the pollen tip (Fu 2015).

Mechanical Polarities: Triggering Anisotropic Shapes

Knowing the magnitude of a deformation is insufficient to explain shape changes: Creating specific shapes requires spatially oriented deformations. These changes can be triggered through cell polarity that is mediated, for example, by the Par polarity network. A classic example of spatial symmetry breaking is the positioning of daughter cell formation in budding yeast. This location is determined through a stochastic biochemical reaction that incorporates positive feedback to generate a unique site of enrichment at the cell periphery (Altschuler et al. 2008). In epithelial tissues, heterogeneous stress can generate a polarization of the actomyosin network (Duda et al. 2019). This network reorganization helps to buffer mechanical stress and preserve tissue shape.

Plant cells also exhibit molecular polarities leading to mechanical polarities in their walls and localized wall deformation. These wall changes have been proposed to drive the initial directional growth of hypocotyl cells (Peaucelle et al. 2015) and the formation of wavy walls in jigsaw-puzzle-shaped cells in leaf epidermis (Altartouri et al. 2019, Majda et al. 2017).

Biased cell division orientation can also lead to anisotropic shapes. This is particularly relevant in animals, in which growth relies mainly on cell division. A key pathway is the planar cell polarity network (Segalen & Bellaïche 2009). This network defines specific axes for division and subsequently tissue deformation (Li et al. 2017) as well as buffers mechanical variability (Martin et al. 2020). In plants, oblique cell divisions are associated with the switch from filamentous growth to branching structures in the moss *Physcomitrealla patens* (Coudert et al. 2019), and such divisions also play a role in defining the embryo apical-basal axis (Ueda & Berger 2019).

Material Properties: Maintaining Anisotropic Shapes

Growth anisotropy provides only a dominant axis of deformation, yet this may be sufficient to determine the 3D architecture of an organism. In plants, growth anisotropy is actively maintained by the mechanical anisotropy of the cell walls; the presence of coaligned cellulose microfibrils generally prevents wall extension in a given orientation (Baskin 2005). Upon microfibril disorganization, organs become spherical, and, geometrically, cells behave like soap bubbles (Corson et al. 2009). Interestingly, the elongated shape of the *Drosophila* follicle also involves the deposition of aligned fibers: The mechanical anisotropy of the extracellular matrix channels the follicle elongation. Disruption of this mechanical anisotropy results in a deformed egg shape (Horne-Badovinac 2014). Although collagen is not deposited like cellulose microfibrils in plants, the follicle rotation may prescribe such anisotropic patterns. In the end, collagen and microtubules are perpendicular to the maximal axis of organ elongation, as in plants (Viktorinová & Dahmann 2013). However, egg elongation can be uncoupled from egg rotation, so the exact mechanism behind the deposition of aligned collagen remains to be explored (Aurich & Dahmann 2016).

A local increase in growth rate has been classically associated with organ formation in both plants (Reinhardt et al. 2003) and animals (Ede & Law 1969). However, a quantitative analysis of mouse limb initiation has revealed that organ outgrowth primarily depends on anisotropic deformation (filopodia extension and cell division plane orientations) instead of increased cell proliferation (Boehm et al. 2010). Similarly, organ outgrowth in the plant meristem is thought to typically depend on auxin-dependent wall loosening. However, a local switch from mechanical anisotropy to mechanical isotropy in the wall can promote an outgrowth in the early steps of organogenesis in *Arabidopsis* (Sassi et al. 2014).

Many open questions remain about how cellular behaviors are integrated to shape tissues. Computational modeling and quantitative imaging are essential tools to address the relative contributions of these cell processes in organ shapes. This extends to the formalization of feedback from multicellular shape onto individual cell behavior, as we discuss next.

ACTIVE FEEDBACK: CELLS AND ORGANS MONITOR THEIR GEOMETRY

Cells and tissues are able to sense their own shape, deformation, and chemical and mechanical status and to modulate their growth and gene expression patterns (Farge 2011, Hamant & Moulia 2016). In other words, the morphological status of the cell and tissue may in turn act as an instructive cue to shape organs. This corresponds to an active feedback mechanism. As we outline in this section, such feedback can be essential for robust organ morphogenesis.

Living Tissues as Active Materials

Living systems are active materials (Fletcher & Geissler 2009) that can do work to reshape structures rather than simply passively respond to external stresses. The field of active matter has advanced significantly in recent years, including both new experimental (Needleman & Dogic 2017, Pérez-González et al. 2019) and theoretical developments (Chen et al. 2020, Marchetti et al. 2013, Prost et al. 2015). Epithelial tissues can display fluid-like behavior on short timescales but behave more like solids on larger timescales (Noll et al. 2017). Such viscoelastic properties can emerge due to turnover of mechanosensitive proteins (e.g., E-cadherin) (Iyer et al. 2019). Spontaneous, self-organized patterns can also emerge due to the interplay between biochemical and biomechanical processes, such as in the polarization of the *Caenorhaditis elegans* embryo (Gross et al. 2019). Topological defects generated in active tissues can even play a role in cell death and extrusion (Kawaguchi et al. 2017, Saw et al. 2017). Active processes appear to be advantageous in compensating for cellular heterogeneities in animal tissues. But how do such active forces and stresses help organs form specific shapes?

Active materials: materials that do work on their environment, which requires continual energy input such as from ATP

Mechanosensitive molecules: molecules that change configuration or state in response to mechanical force

Active pumping and the role of the resulting hydrostatic pressure in driving morphogenesis has long been appreciated in plants, but it is increasingly apparent that it also plays a key role in animal morphogenesis. In the early mouse embryo (Dumortier et al. 2019) and the growing zebrafish inner ear (Mosaliganti et al. 2019), hydrostatic pressure drives the formation of lumina. Such pressure generates mechanical heterogeneities in tissues, leading to complex 3D morphologies.

Recent work in the developing zebrafish myotome has shown how the active stress generated by elongating muscle fibers can deform the developing myotome into a chevron-like shape (Tlili et al. 2019). Combined with differential tissue coupling (see the previous section titled Cell–Cell Adhesion: Transitioning Between Fluid and Solid Behavior) between the future myotome and the surrounding tissues, the process of muscle formation generates active stresses along the anteroposterior axis of the embryo, sharpening the tissue into its final chevron shape (see **Figure 3*a***). Therefore, active stress at the cellular scale can deform tissues into specific shapes.

Monitoring Size with Biochemical Cues

Cells respond to size-related inputs during progression through the cell cycle. Such inputs can be related to volume, total mass (Kafri et al. 2013), surface area, or even length (Ginzberg et al. 2015). For example, fission yeast cells appear to measure their surface area (Pan et al. 2014) to ensure division at predictable sizes. Cells can also assess their length. In the antenna model, elongated cells have longer microtubules, which then bind more motor proteins, leading to protein accumulation that scales to cell length (Varga et al. 2006). Cells may take advantage of the combinatorial distribution of multiple chemical factors to assess their size and shape.

Using biochemical signals to infer organ size is challenging, as organs are generally larger than typical ranges for spatial signaling molecules. Instead of spatial information, cells may utilize temporal information from local changes in morphogen gradients during growth (Wartlick et al. 2011). By measuring the rate of change of morphogen signals, cells can infer information about growth and position within the tissue (Aguilar-Hidalgo et al. 2018). However, alternative models suggest that such a mechanism is not essential for regulating wing patterning and size in *Drosophila* (Alexandre et al. 2014). Self-organizing, long-range patterns can occur through reaction–diffusion mechanisms (Müller et al. 2012). In this case, patterns can be robustly defined across long length scales (Diego et al. 2018, Sheth et al. 2012). However, how such mechanisms reliably position boundaries in the presence of biological noise in vivo remains an open question.

Monitoring Local Deformation with Mechanosensors

Mechanotransduction: the conversion of mechanical inputs into cellular responses (such as altering gene regulation)

Cells can monitor their deformation more directly through proteins that trigger a signaling cascade upon cell deformation. Mechanotransduction plays a critical role in animal tissue integrity (Charras & Yap 2018, DuFort et al. 2011). Arguably the best-described mechanosensors are mechanosensitive channels: When membranes become thinner upon being pulled, the reduced lipid interactions with the channel lead to conformation changes (Haswell et al. 2011). The Piezo mechanosensitive channel is involved in many cell and physiological pathways in animals (Bagriantsev et al. 2014, He et al. 2018). Although plant genomes contain Piezo homologs, no altered phenotype has been reported in the corresponding mutants. The calpain protease, a downstream target of Piezo channels in animals, is involved in remodeling focal adhesions (Zhong et al. 2018). Mutants of the plant-specific phytocalpain gene *DEK1* hinder epidermis specification and lead to embryo lethality. Interestingly, the plant calpain homolog contains a large transmembrane domain that is required for calcium mechanosensitive channel activity, suggesting evolutionary convergence for this mechanoperception pathway (Tran et al. 2017).

The Hippo/YAP pathway can also regulate tissue growth through mechanical feedback (Totaro et al. 2018). This pathway is sensitive to mechanical stress (Dupont et al. 2011); its mechanosensitivity is related to changes in nuclear pore permissiveness under stress (Elosegui-Artola et al. 2017). During tissue inflammation, this pathway can be aberrantly activated and affect tissue repair (Nowell et al. 2016). In plants, the Hippo/YAP pathway is not conserved, except for the ARABIDILLO protein, which exhibits some homology with β-catenin (Coates et al. 2006). Its role in lateral root development, which involves invasive growth through several cell layers, may relate to the perception of mechanical signals, although this remains to be tested.

Integrins have long been known to contribute to mechanosensing and mechanotransduction in animals (Kechagia et al. 2019). Integrin-mediated adhesion of tissues to the overlying vitelline membrane plays a critical role in controlling tissue deformation by generating local asymmetric forces that regulate where and when the embryonic tissue detaches from the membrane (Bailles et al. 2019, Münster et al. 2019). In plants, certain wall receptors exhibit an RGD binding motif and in theory may have integrin-like activities (Canut et al. 1998). Although some impact on growth has been reported, the role of this motif in development remains largely unknown. Note that the downstream factors in focal adhesions—e.g., vinculin or talin—do not appear to be conserved in plants. This may relate to the differing roles of the cortical cytoskeleton in plants and animals.

Monitoring Cell and Tissue Integrity Through Mechanotransduction

Plant cell walls must be able to resist their own turgor pressure, or else their walls would break and the cells would die (**Figure 3*c***). Consistently, the presence of wall breaks is a hallmark of mutants impaired in cellulose synthases (Fagard et al. 2000). The magnitude of wall stress also depends on geometric parameters. In particular, assuming uniform properties, the tensile stress in the wall depends on wall thickness. During cell expansion, the wall can become thinner. This thinning triggers wall synthesis to resist stress and reach wall homeostasis (Cosgrove 2005). Further, upon wall loosening (through wall remodeling), turgor pressure decreases, which induces a net movement of water into the cell that restores the high hydrostatic pressure and induces cell expansion. However, wall thickness may not always be a good predictor of wall properties. In particular, upon pharmacological inhibition of cellulose deposition, walls become thicker as the cell attempts to compensate for the loss of cellulose with extra layers of pectin-rich material (Manfield et al. 2004). Similarly, defects in wall-integrity sensing often lead to increased wall lignification

(Hématy et al. 2007). The stress levels in the wall may indirectly act as a proxy for cell size by negatively regulating growth. Cells also respond to high-stress-induced wall building by modulating their geometry. In particular, plant cells can keep the stress magnitude low in their walls through frequent division, thereby keeping their small size as well as arguably having lower stress (Sapala et al. 2018) in, e.g., plant meristematic regions.

Wall-integrity pathways have been uncovered in plants and may represent other functional homologs of integrins. The receptors THESEUS and FERONIA (FER) bind pectins in the wall (Feng et al. 2018) and trigger a signaling cascade through their intracellular kinase domain, leading to shape changes. Through mechanical tests, calcium and pH signatures, and touch-induced gene expression, FER is the closest bona fide transmembrane mechanosensor known so far in plants (Shih et al. 2014).

When cells are not dividing, they can still increase their volume through anisotropic growth, thereby reducing stress when compared to a similar increase in volume through isotropic growth. In fact, when tissue growth is isotropic, epidermal cells often form jigsaw-puzzle shapes, which allows cell volume to increase while keeping tensile stress low (Sapala et al. 2018) (**Figure 4*a***). Here, we have focused on the analogy between integrin action in animal cells and cell wall behavior in plants; again, we see commonality in function and response, although distinct differences in the molecular components.

Restricting Organ Size Through Mechanotransduction

Mechanical feedback has been proposed as a mechanism for inhibiting cell proliferation and thereby controlling tissue size (Hufnagel et al. 2007, LeGoff & Lecuit 2016, Shraiman 2005). For example, stress in the *Drosophila* wing imaginal disc increases as it grows, which eventually inhibits proliferation. Anchoring between the developing wing disc and the surrounding cuticle is essential in shaping the tissue (Ray et al. 2015), along with reduced growth induced by the Hippo signaling pathway (Pan et al. 2016) (**Figure 4*b***). In the *Arabidopsis* sepal, growth conflicts trigger the alignment of microtubules, resulting in wall stiffening prior to growth arrest (Hervieux et al. 2016) (**Figure 4*c***). Note that other targets of mechanical signals, such as reactive oxygen species, are likely involved in the final stages of growth arrest in sepals (Hong et al. 2016). A key concept here is that the boundary—with either neighboring cells or tissues—imparts essential information to the growing system; in other words, the attainment of a specific organ shape and size is not an intrinsic property of the tissue but relies on interactions with external tissues, compartments, and boundaries.

Because cells can sense their own shape and size, it follows that they have the ability—through coordinated action—to compensate for growth or deformation defects. When systems exhibit reduced cell division rates, they usually generate larger cells to compensate and in the end produce organs of regular size (Potter 2001). This has been notably studied in both leaves (Horiguchi & Tsukaya 2011) and *Drosophila* wing formation (Day & Lawrence 2000).

Monitoring Organ Shape Through Mechanotransduction

What are the mechanical forces restricting and regulating cell and tissue behavior? The actin cytoskeleton plays a critical role in shaping animal cells and tissues, yet its mode of action varies significantly between cells. The formation of actin filaments can be initiated and maintained by a positive feedback loop whereby Myosin II is recruited to regions of high tension (Bertet et al. 2004, Duda et al. 2019, Fernandez-Gonzalez et al. 2009). Actin filaments often form in the direction of maximal tensile stress (Bertet et al. 2004, Riveline et al. 2001) (**Figure 3*g***). Similarly, in plants,

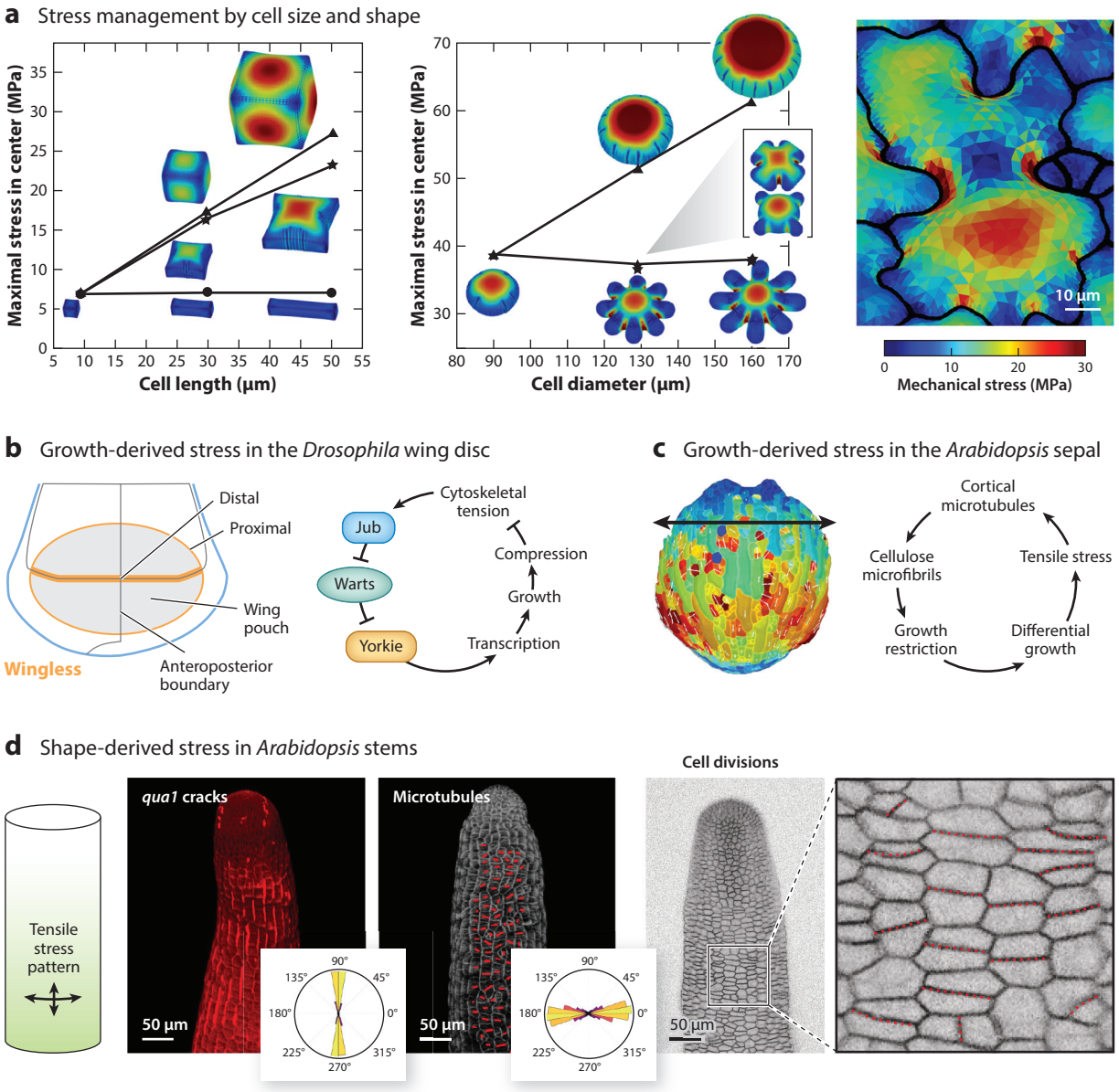

Figure 4

Monitoring mechanical stress levels when shaping organs. (*a*) Cell size and shape prescribe mechanical stress levels in plant cells. Panel *a* adapted from Sapala et al. (2018) under CC-BY-4.0 (*b*) Differential growth generates mechanical conflicts that may induce growth arrest and control final organ size and shape in the *Drosophila* wing. Panel *b* adapted with permission from Pan et al. (2016). (*c*) Differential growth generates mechanical conflicts that may induce growth arrest and control final organ size and shape in the *Arabidopsis* sepal. Panel *c* adapted with permission from Hervieux et al. (2016). (*d*) Shape-derived stress as calculated from a pressure-vessel model analogy: Tensile stress is twice as high in the circumferential direction, which is validated in mutants with cell–cell adhesion defects and also matches cortical microtubules and cell division plane orientations. Panel *d* adapted from Verger et al. (2018) under CC-BY-4.0 and Louveaux et al. (2016).

cortical microtubules align with the direction of maximal tensile stress (Green & King 1966, Hamant et al. 2008) (**Figure 3*b***). Both of these responses reflect the differences in cytoskeleton-dependent growth regulation while providing the cell with mechanical resistance either directly (actin filaments) or indirectly (microtubules guiding cellulose deposition).

Curvature plays a role in cell packing within highly curved epithelia (Gómez-Gálvez et al. 2018, Rupprecht et al. 2017). Due to such curvature, the stresses present on the apical and basal sides of the cell are different, resulting in cellular rearrangements along the apical-basal axis of the cell. Active mechanisms at the basal surface of epithelial sheets can also drive tissue rearrangement (Sun et al. 2017) and folding (Sui et al. 2018); this implies that an understanding of tissue morphogenesis requires a clear picture of the full 3D topology of the cell.

Beyond mechanical conflicts, organ shape in the steady state condition can also bias the mechanical stress pattern and serve as a morphogenetic cue. For instance, assuming that the epidermis is under tension, a continuous model of tensile stress using a pressure-vessel analogy predicts that plant stems exhibit a bias of tensile stress in the circumferential direction (Williamson 1990). This prediction has been validated by measuring whether the gap opens or closes following a cut (Kutschera & Niklas 2007). Mutants with cell–cell adhesion defects have also been used to map the tensile stress pattern in tissues (Verger et al. 2018) (**Figure 4*d***). Such large-scale, shape-derived stress patterns channel supracellular microtubule behavior (Hamant et al. 2008, Verger et al. 2018) and cell division plane orientations (Louveaux et al. 2016) (**Figure 4*d***). Assessing similar mechanical responses in animals has been challenging. However, recent advances using mechanically characterized oil droplets have enabled the forces within the developing zebrafish tail to be measured. These measurements have revealed a jamming transition along the embryo anteroposterior axis (Mongera et al. 2018).

CONCLUSION

We have focused on mechanisms that shape organs in both animals and plants. Although animal and plant cells can use molecular components quite differently, there are important similarities in how these cells utilize mechanical force to shape organs. Organs can both self-organize into specific shapes and be instructed through external signals. Indeed, systems appear to use a combination of both mechanisms to drive tissue formation and shaping (Green & Sharpe 2015). Relatedly, feedback—both biochemical and biomechanical—is essential in shaping organs (Hannezo & Heisenberg 2019). Negative feedback is important for regulating and arresting growth. Positive feedback can play a key role in symmetry breaking and ensuring rapid system response to stimuli. These concepts are applicable to both plant and animal cells despite significant structural differences.

Biomechanical forces can play multiple roles in shaping organs. Such forces can be long-range, providing a mechanism for size control across large distances. Mechanosensory and mechanotransduction pathways are essential for translating the information embedded within the mechanical forces across the tissue into appropriate genetic and cellular responses. Such responses play a critical role in organ scaling and growth compensation as well as injury response (Tetley et al. 2019). Indeed, the response to injury may utilize many elements underlying the initial growth of the tissue or organ.

Biological systems are active materials. Our understanding of passive systems (e.g., soap bubbles) cannot be straightforwardly applied to biological tissues despite some remarkable similarities (Hayashi & Carthew 2004). For example, cell proliferation alters cellular packing and tissue organization (Gibson et al. 2006). However, a number of systems, perhaps most strikingly the emergence of beetle horns, generate a pattern of prestress that is then translated through a

passive response to pressure into complex shapes. Therefore, biological systems use both active and passive mechanisms—often in the same tissue—to generate a plethora of tissue shapes and sizes.

The overarching aims of this review have been twofold: (*a*) to highlight essential biophysical mechanisms that drive tissue shaping, and (*b*) to discuss the similarities of and differences between organ shaping in plants and animals. We have omitted discussion of the temporal coordination of events during tissue shaping (Colombani et al. 2012). Environmental factors, perhaps most strikingly temperature, also play an important role in growth and size (Debat et al. 2003). For example, fruit flies grow larger at lower temperatures, yet how such temperature adaptation is precisely regulated remains an open question (Ghosh et al. 2013). Forming specific tissue shapes goes hand in hand with tissue scaling, which we have only briefly mentioned; organs must grow to the correct size (Umulis & Othmer 2013). Finally, we have predominantly focused on results from model organisms. However, important insights can be made about growth and shape using other species, including dragonflies (Hoffmann et al. 2018), bivalves (Moulton et al. 2020), and characean green algae (Foissner & Wasteneys 2014).

Despite the many studies highlighted in this review, with a few notable exceptions, our understanding of how organs obtain their shapes remains limited. With improvements in microscopy [e.g., light sheet (Krzic et al. 2012)], biophysical tools [e.g., liquid droplets (Mongera et al. 2018)], and biological systems [e.g., organoid systems (Brassard & Lutolf 2019, Serra et al. 2019)], together with insights from computational modeling (e.g., explorations into robustness, self-organization, and biophysical and biochemical integration), we envisage there will be rapid advances in understanding how complex shapes emerge during development.

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