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Review

Geometric control of tissue morphogenesis

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ABSTRACT

Morphogenesis is the dynamic and regulated change in tissue form that leads to creation of the body plan and development of mature organs. Research over the past several decades has uncovered a multitude of genetic factors required for morphogenesis in animals. The behaviors of individual cells within a developing tissue are determined by combining these genetic signals with information from the surrounding microenvironment. At any point in time, the local microenvironment is influenced by macroscale tissue geometry, which sculpts long range signals by affecting gradients of morphogens and mechanical stresses. The geometry of a tissue thus acts as both a template and instructive cue for further morphogenesis.

1. Introduction

Morphogenesis is the process by which a population of cells rearranges into the distinctive shape and form of a tissue. The development of functional organ architectures from simpler ones has captivated biologists and physical scientists for hundreds of years [1]. Recent progress in the sequencing of a wide variety of animal genomes, coupled with systematic examination of tissue-specific and time-varying gene expression patterns, has enabled identification of the genes required for different morphogenetic processes. With the advent of systems biology, we can now attempt to explain complex developmental processes using gene regulatory networks [2,3]. Each specific biological task can be ascribed to a subcircuit of genes, and combining the subcircuits is thought to yield a network diagram that can explain how development is choreographed in space and time [4].

Whereas it is a significant advancement over reductionist approaches, this explanation is incomplete. In the lab we tend to identify and describe cells based on the genes they express, but gene expression – in and of itself – does not define the cell or the tissue. Morphogenesis (and likewise, differentiation and homeostasis) depends on what cells do, which is ultimately a function of environmental inputs as much as it is a function of gene expression. Indeed, a small number of genes is used repeatedly throughout development in the morphogenesis of a wide variety of structures. For example, the Notch pathway is required for development of insect wings and bristles [5,6], bird feathers [7], and mammalian inner ear hair cells and mammary glands [8,9]. Across the animal kingdom there is no one-to-one correspondence between homologous genes and morphological structures [10]. The behavior of a cell expressing a given gene or subset of genes depends entirely on where that particular cell is in the body, and at what point in development. The phenotypic output of a gene is therefore best described as context-dependent [11].

What is the context during morphogenesis? Virchow's principle, "omnis cellula e cellula" (all cells come from cells), can easily be scaled from single cells to tissues: all tissues develop from other tissues. Morphogenetic processes mold simple tissue primordia (sheets or clusters of cells) into more complex forms (tubes, branches, bends, folds). Any action imposed by gene expression must work in the context of the pre-existing rudimentary tissue in order for morphogenesis to succeed. Tissue geometry can therefore be considered as an additional signal that changes in time. Here, I describe how the developmental history of a tissue and its geometric structure provide contextual information for developmental genes. I discuss how geometry controls the behavior of individual cells, how the collective action of cells underlies morphogenetic movements, and how tissue geometry sculpts the signals that direct morphogenesis.

2. Geometric control at the single cell level

The earliest classification of cells was based on their appearance. There are more than 100 kinds of cells that can be visibly distinguished in a vertebrate animal. They organize into a variety of tissues, including epithelium (squamous, columnar, and cuboidal), muscle, nerves, and bone. Cells from these tissues can also be distinguished from one another when isolated and plated individually in culture. For example,

Abbreviations: AP, anterior–posterior; Bcd, Bicoid; Dpp, Decapentaplegic; DV, dorsal–ventral; ECM, extracellular matrix; FGF, fibroblast growth factor; GDNF, glial cell-derived neurotrophic factor; Hh, hedgehog; TGFβ, transforming growth factor-β; 2D, two-dimensional; 3D, three-dimensional

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epithelial cells resemble individual tiles in a cobblestone path, whereas fibroblasts have a more stellate morphology with numerous protrusions. Although we now understand that there are tissue- and organ-specific differences between cells, simple classification based on appearance was remarkably prescient. Early cell culture studies noted a correlation between cell geometry and cell function. Indeed, numerous cellular behaviors in culture, including proliferation [12–16], apoptosis [15,17], lamellipodial extension [18], migration [19], glucose metabolism [20], RNA processing [21–25], differentiation [26–29], epithelial–mesenchymal transition [30], and stem cell fate [31] have been found to be determined by cellular geometry. Although we must be cautious about translating these findings to the regulation of cell function in vivo, they serve as a useful guidebook, as much of tissue morphogenesis depends on the change in shape of individual cells.

3. Cellular rearrangements in tissue morphogenesis

Alterations in shape lead individual cells to rearrange with respect to each other, a driving force for tissue morphogenesis. There are a number of different evolutionarily conserved rearrangements classically described during embryonic development (Fig. 1). The movements highlighted below share many features, including regulation by cell adhesion and contractility.

3.1. Epiboly

Morphogenesis results from repacking of cells. One of the first major morphogenetic movements during zebrafish and *Xenopus* gastrulation is epiboly. During epiboly, a superficial cellular sheet spreads as a unit across underlying layers of cells, causing the tissue to both expand in area and decrease in thickness, and thereby enclose deeper layers of the embryo. Whereas the details differ between species, the principal mechanisms driving epiboly are an increase in the number of cells comprising the sheet, both by cell division and by radial intercalation of cells from several underlying layers [32]. Epibolic movements in zebrafish gastrulation require concerted cadherin-mediated interactions between cells, as antisense morpholino oligonucleotides [33] or mutations in the *E-cadherin (cdh1)* gene [34,35] disrupt the process. Studies in *Xenopus* embryos have also revealed a major role for the extracellular matrix (ECM) molecule fibronectin in the cellular rearrangements that drive later stages of epiboly, as treatment with antibodies that disrupt fibronectin/integrin interactions or expression of dominant-negative β1-integrin constructs prevented radial intercalations [36]. Aside from gastrulation, movements similar to epiboly have been reported to occur in development of tissue engineered dermis [37]. Thus, epiboly-related mechanisms likely regulate the morphogenesis of many tissues.

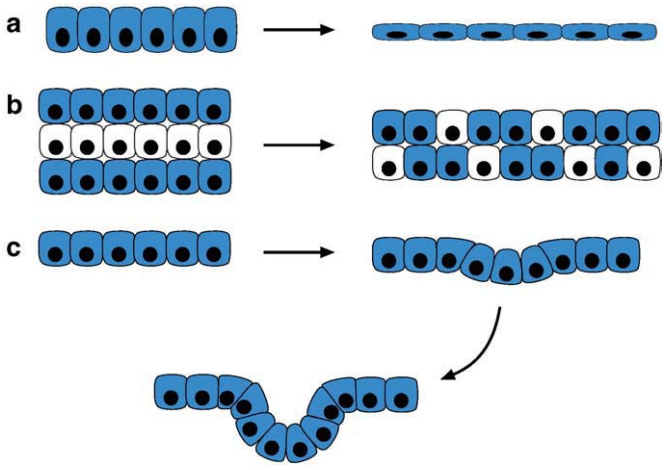

Fig. 1. Cellular rearrangements in tissue morphogenesis. (a) Epiboly, (b) convergence and extension, and (c) invagination.

3.2. Convergence and extension

Perhaps the most well studied morphogenetic movement is convergence and extension. 'Convergence and extension' refers to the narrowing and lengthening of a population of cells, a process ubiquitous during embryonic development [38,39]. Convergence and extension events can occur via a number of mechanisms, including cell growth and cell shape changes, but mediolateral cellular intercalation, in which cells squeeze in between their neighbors and thereby lengthen the sheet perpendicular to the direction of migration, appears to drive most examples [40]. Contraction of individual cells must generate sufficient traction forces against the underlying ECM to change the shape of the sheet, which in turn leads to a stiffening of the embryo [41]. Similar to epiboly, integrin- and cadherin-mediated adhesive dynamics control the patterned migrations of convergence and extension [36]. Convergence and extension movements are responsible for a wide variety of developmental distortions, including elongation of the dorsal axis and development of the notochord (reviewed in [40]).

3.3. Invagination and cleft formation

Simple epithelial sheets are converted into complex, multi-layered, folded, and branched structures by the processes of invagination and cleft formation. Preceding invagination, apical constriction within a region of cells in the monolayer causes the cells to become wedge-shaped and thereby induces the sheet to buckle and protrude [42]. Apical constriction requires myosin-mediated contraction of the actin microfilaments that are prominently localized at the apical plasma membrane and associated with adherens junctions [43], leading to a reduction in the apical perimeter relative to the basal perimeter. Analysis of ventral furrow development in *Drosophila* gastrulation has revealed that these polarized constrictions are controlled in part by recruitment of myosin motors and regulators of Rho family GTPases from basal to apical regions via specific target genes of the transcription factor Twist [44], which leads to pulsed contractions of the cortical actin–myosin network [45]. The protrusion that forms due to apical constriction then expands by either differential adhesion between the invaginating cells and the surrounding tissue (akin to the spreading of liquids with different surface tensions) [46,47], or by active extension of cellular processes such as filopodia [48]. Invagination is thus driven by the active coordination of cell shape changes amongst a population of cells.

The tree-like architectures of epithelial organs, including the lung, kidney, and salivary gland, are generated by the process of branching morphogenesis. Branching can be initiated in part by invagination and the formation of nascent clefts between cells within the epithelial monolayer [49], which likely involve different mechanisms. Cleft formation requires the synthesis of ECM proteins, such as fibronectin and collagens, which accumulate focally at specific sites and induce clefting [50,51]. Epithelial cells adjacent to the emerging cleft adhere to the ECM fibrils via integrins, and subsequent downstream signaling is thought to downmodulate cadherin-mediated cell–cell adhesion, leading to separation of neighboring cells and lengthening of the cleft [50]. Conversely, regions adjacent to buds show a decrease in ECM proteins, specifically a thinning of the basement membrane [52]. The directional translocation of the ECM fibrils is balanced by the dynamics of cell adhesion and cell motility to build clefts during branching morphogenesis of the salivary gland [53]. Recent studies have reported that clefting events are reconstituted by suspensions of isolated submandibular gland epithelial cells sufficiently well to form a rudimentary salivary gland ex vivo, suggesting that the patterning of

branching in this organ may be stochastic rather than genetically pre-specified, an exciting possibility for eventual creation of a tissue engineered replacement [54,55]. Fibronectin-induced clefting plays a minor role during branching morphogenesis of the lung, kidney, and mammary epithelial cells [50,56], suggesting distinct mechanisms for control of branching of different mammalian organs. Invagination and clefting thus help to build complex branching structures from simple epithelial anlagen.

4. Morphogen gradients

Morphogenetic movements in and of themselves are not sufficient to build a functional tissue architecture — they must occur at the correct location and time. One mechanism by which cell behaviors are organized spatially is via gradients of diffusing molecules, known as morphogens [57–60]. The morphogen theory posits that a signal produced at a defined location forms a concentration gradient as it spreads through the surrounding tissue (reviewed in [61]). Cells located at different positions within the tissue are presented with different concentrations of the signal and respond according to these thresholds. Morphogen gradients therefore turn uniform fields of cells into discrete domains, and the behavior of a developing cell is determined by its location and the geometry of the tissue. Proper morphogenesis is thereby controlled by the shape of the concentration gradient, which depends in part on two parameters: the geometry of the population of cells that secretes the morphogen (the source), and the geometry of the surrounding tissue (the sink). Manipulating the source or the sink can alter the concentration profile of the morphogen (Fig. 2), in the absence of changes to other biochemical or biophysical parameters. Candidate morphogens include members of the hedgehog (Hh), Wnt, and transforming growth factor (TGF)-β families [62]. Work from several groups has yielded insight into the mechanisms by which morphogen gradients are formed in a number of different developmental systems [62–64]. Recent studies have also revealed how tissue geometry regulates the formation of morphogen gradients.

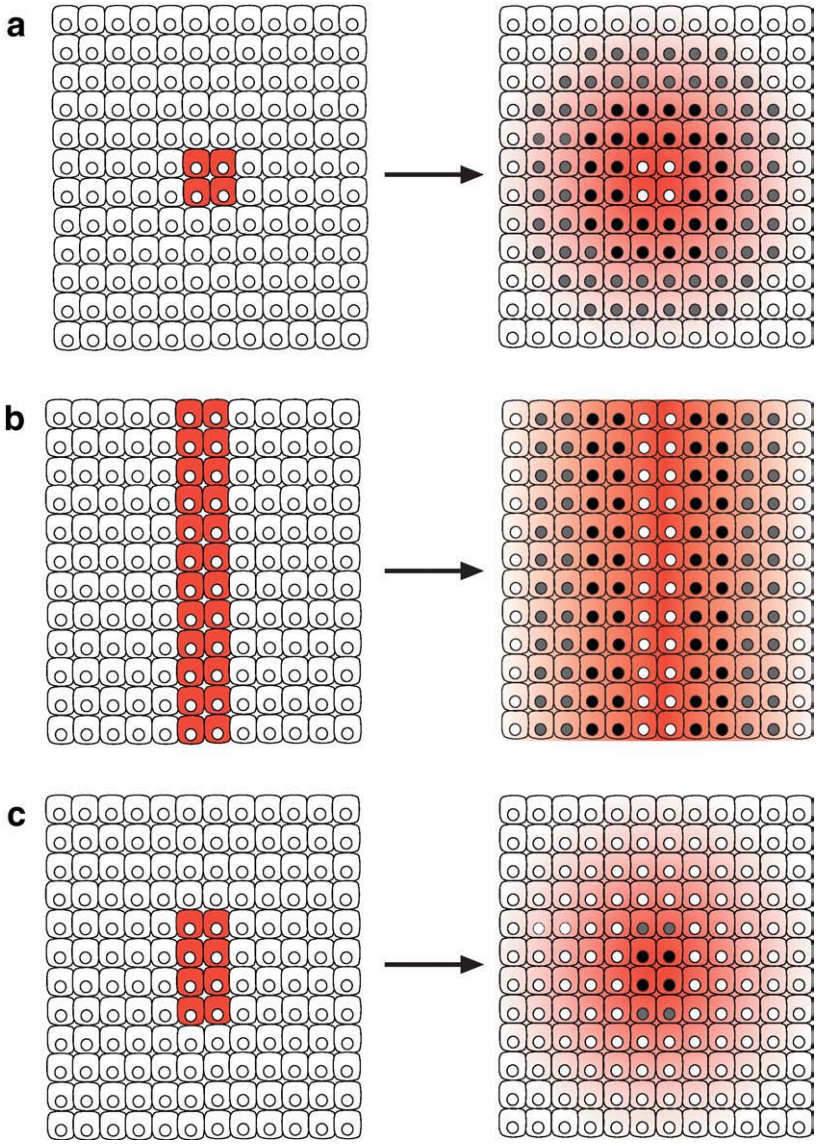

Fig. 2. Geometric control of morphogen gradients. On the left are depicted a population of cells that express morphogen (red) amongst a population of cells that do not. The concentration of morphogen that results is depicted on the right. (a) Cells that express receptors for the morphogen respond differently to high concentrations of the morphogen (black nuclei), medium concentrations of the morphogen (gray nuclei), or not at all to low concentrations of the morphogen. (b) Changing the relative geometry of the source (morphogen-producing cells) to the sink (the surrounding population) changes the pattern of response. (c) In autocrine systems, the same population of cells produces and responds to the morphogen. The geometry of this population affects the shape of the gradient.

4.1. Morphogens in organogenesis: geometric control of the source

Morphogen gradients are instructive during organogenesis, particularly in the branching morphogenesis process responsible for sculpting the ramified architectures of organs such as the lung, kidney, and mammary gland. During branching morphogenesis of the mammalian lung and *Drosophila* trachea, positional information is encoded by stimulatory morphogens secreted by adjacent mesenchymal tissues, including members of the fibroblast growth factor (FGF) family, which act as chemoattractants for growing epithelial branches [65,66]. This mechanism requires an initial pre-pattern of FGF signal within the mesenchyme, and is thought to account for the highly stereotyped branching patterns of the airways. The morphogenesis of these organs thereby depends on the geometry (size and position) of the inducing population of cells — exogenous expression of FGF induces ectopic branching [67–69]. What determines the initial expression pattern of FGFs? The answer to this question remains unclear, but in the case of *Drosophila* trachea, the pattern of FGF expression appears to be controlled in part by earlier patterning cues that establish the anterior–posterior (AP) and dorsal–ventral (DV) axes of the embryo [65]. Chemoattractive mechanisms likely direct the outgrowth of branches in a number of other stereotyped organs, such as via glial cell-derived neurotrophic factor (GDNF) in the ureteric bud [70].

In contrast, there is no evidence that morphogen chemoattraction plays a role in directing the morphogenesis of non-stereotyped organs such as the mammary gland [71], which develops during puberty apparently in the absence of embryonic patterning cues. Instead, it was proposed in the late 1980s that the branching pattern of the mammary gland is determined by chemorepulsion [72], where the spacing between adjacent branches depends on gradients of inhibitory morphogens generated by the ductal epithelium itself [73]. Such a mechanism would require that the epithelium express both the inhibitory morphogen as well as its receptor, and would ensure that the ducts are relatively isolated from one another, thus producing the 'open' architecture of the mammary gland observed at the end of puberty. The concentration profile of inhibitors and subsequent morphogenesis would therefore be controlled by the initial geometry of the epithelium. One principal negative regulator of mammary gland development is TGFβ1. Mice that overexpress TGFβ1 under control of the MMTV promoter have a hypoplastic mammary tree [74]. Conversely, mice heterozygous for a null allele of TGFβ (TGFβ+/−) show 90% reduction in TGFβ protein and increased branching morphogenesis [75]. A gradient of TGFβ1 surrounds mammary epithelial ducts in vivo [75–77] and ducts reconstituted in culture [78]. As predicted, altering the shape and spacing of ducts engineered in culture alters the shape of the gradient, resulting in branch formation in locations where the proximity to other cells – and hence the concentration of TGFβ – is lowest [78]. TGFβ1 globally inhibits branching in most other branched organs (reviewed in [49]), raising the possibility that tissue geometry regulates patterning via autocrine inhibitory gradients in other systems.

4.2. Morphogens in the embryo: geometric control of the sink

The relative shape of a morphogen gradient is also sensitive to the geometry of the tissue(s) that surround the morphogen-synthesizing cells. One well-studied morphogen system responsible for patterning the fruit fly is the Bicoid (Bcd) gradient. Early in embryogenesis, before cellularization, Bcd is synthesized at the anterior end of the embryo and disperses within the syncitium, forming a concentration gradient along the AP axis that is highest at the anterior pole [79,80]. The Bcd transcription factor is interpreted by cells into precise regions of gene transcription along the length of the embryo [81,82], and is critical for later development of the head [83]. Similar to Bcd, an inverse pattern of the transcription factor Nanos forms by localized synthesis and dispersion from the posterior pole of the embryo [84]. Examination of the Bcd profile in related species with different sized embryos demonstrated that the Bcd concentration gradient scales with the size of the embryo [85]. Importantly, even though the size of dipteran embryos can vary 5-fold, the aspect ratio of different sized embryos appears to be constant [86]. This observation may be significant, as altering the aspect ratio of the embryo would be expected to change the shape of the gradient.

4.3. Coupling morphogenesis and growth: a moving boundary problem

One of the first morphogen systems to be described experimentally was the Decapentaplegic (Dpp) gradient that defines the AP axis during development of the wing primordium (known as the imaginal disk) in *Drosophila* larvae (reviewed in [87]). Dpp, the fly homolog of TGFβ family members Bmp2/4, is expressed in a group of cells that forms a stripe along the AP compartment boundary of the larval imaginal disk, and determines the positioning of the wing veins along the AP axis. The mechanism of patterning downstream of Dpp is well defined: The extracellular gradient of Dpp leads to cytoplasmic and nuclear gradients in Mad phosphorylation [88], which leads to production of an inverse Brk repression gradient [89]; Brk levels then determine the gene expression thresholds for patterning [90]. Spatially restricted ectopic expression of Dpp in mosaic clones changes the geometry of the Dpp concentration gradient, and alters the long-range pattern of induction [91,92]. Proper morphogenesis of the wing therefore depends on the geometry of the Dpp-producing tissue.

Developing tissues are usually sculpted into their final functional architectures at the same time as their resident cells are undergoing proliferation. Morphogenesis (change in shape) therefore usually occurs concomitantly with growth (change in mass). The larval wing disk is a striking example — the wing primordium grows from approximately 50 cells in the first instar larva to 50,000 cells in the adult, an ~1000-fold expansion in mass during the time the tissue is being patterned. This leads to an interesting unsolved problem: How do cells and tissues couple changes in form (a time-scale issue) with changes in size (a length-scale issue)? As the tissue grows, the geometries of both the morphogen source and sink change. Increasing evidence suggests that morphogens themselves can couple patterning and growth by communicating information about the size of an organ to individual cells [93]. In addition to directing morphogenesis, the Dpp gradient is thought to play a role in specifying appendage size by controlling cell proliferation. Ectopic overexpression of Dpp leads to enhanced cell proliferation resulting in large wings [91,92], whereas loss of Dpp in the wing primordium leads to production of a stump [94,95]. These observations have led to the proposal that cells in the wing disk proliferate depending on the local slope of the Dpp morphogen gradient [93]. As the size of the tissue increases, the steepness of the gradient decreases, leading to a cessation of proliferation upon reaching a specific threshold. However, the situation is probably more complicated than simple sensing of gradient, as recent detailed studies have shown that manipulating Dpp expression alters the microtubule-based apical cytoskeleton and affects cell shape [96,97]. These results suggest that Dpp affects the growth rate of the tissue in part by altering cell morphology, which can control tissue geometry by affecting mechanical stresses [98]. Tissue morphogenesis and growth are thus likely coupled by a combination of signaling from gradients of morphogens and mechanical stresses.

5. Mechanical gradients

In addition to gradients of chemical cues, it is clear that tissue development and homeostasis are fundamentally influenced by mechanical forces. Compressive and tensile stresses are well

appreciated in the development of muscle and bone tissues [99,100]. Bone is actively deposited in response to mechanical strain. Conversely, long-term exposure to microgravity, such as that experienced by astronauts during space flight, leads to bone resorption [101]. Mechanical stresses also influence the behaviors of cells in soft tissues, and tension-dependent signaling has been widely investigated in single cells in culture [102,103]. Substrate stiffness [104] and stress gradients [105] have recently been found to direct lineage commitment of human mesenchymal stem cells, suggesting a role for mechanical stresses during developmental differentiation. Tissue pattern formation is determined by the interplay between cell-generated forces and the mechanical properties of the local microenvironment. In particular, the mechanical properties of cells and their surrounding microenvironment determine how tissues resist deformation and how forces are transmitted across the tissue.

5.1. Mechanical control of proliferation

Tissue forms often result from spatial differentials in cell proliferation. For example, during epithelial branching morphogenesis and vascular sprouting, cells located at the tips of branching buds proliferate more rapidly than neighboring cells located in the subtending ducts [106,107]. However, bud outgrowth has been found to precede localized proliferation [108,109], suggesting that increased proliferation is a response to tissue deformation. Indeed, the size and geometry of populations of cells determines the distribution and magnitude of traction forces within the tissue in 2D and 3D [110]. Cells located within a protruding bud would be expected to experience greater stress than those located in a resting duct [111]. The positions of highest mechanical stress have been found to correspond to sites of most rapid growth; disrupting the transmission of mechanical tension completely abolishes the patterning of proliferation [110]. Importantly, the gradient of stress is precisely determined by the geometry and size of the tissue, suggesting that the higher ordered architectures of mature organs arise from mechanical feedback mechanisms that encourage the evolution of ever more complex structures from simpler ones.

Mechanical stresses do not act in isolation — cells are constantly receiving biochemical signals from their surrounding environment and integrating these chemical cues with physical cues. Such integration has been proposed to account for the uniform proliferation of cells in the *Drosophila* wing imaginal disk [112,113]. As described above, Dpp regulates growth of the disk, causing uniform proliferation even while presenting cells with a graded signal. In addition to responding to the Dpp signal, cells in the disk are also confronted by altered mechanical cues — tangential stretching, which is known to increase proliferation in cultured cells [114], and compression, which would cause cell rounding and inhibit proliferation [12,15]. Any non-uniformity in proliferation caused by a graded Dpp stimulus would lead to accumulation of these mechanical stresses and thereby provide cells with a feedback signal to regulate growth of the tissue [115]. As the disk grows in size, compression – and, hence, inhibition – would tend to dominate, providing one possible mechanism to control the final size of the appendage [87].

5.2. Mechanical control of tissue bending

The bending of epithelial sheets also requires patterning of mechanical stresses and strains within the tissue. During gastrulation in the frog *Xenopus laevis*, a band of tissue at the equator of the embryo known as the marginal zone moves to the inside of the embryo through an opening at the surface called the blastopore. These movements are critical for forming and organizing the three primary germ layers (endoderm, mesoderm, and ectoderm) in their proper locations. Gastrulation begins when a small population of cells (called bottle cells), sandwiched between the marginal zone and the vegetal endoderm, invaginates to form the dorsal lip of the future blastopore. At the onset of gastrulation, prospective bottle cells actively constrict their apical surfaces. The movements this constriction generates depend on the mechanical properties of the surrounding tissues. Notably, the marginal zone is thinner and more deformable than the vegetal endoderm. Therefore, even though apical constriction generates force isotropically, it leads to inward bending of the epithelial sheet and a net vegetal lengthening of the tissue because the surrounding microenvironment is anisotropic [116,117]. Altering the geometry of the surrounding tissue by removing the vegetal endoderm alters the mechanical gradient, leads to isotropic contraction of the bottle cells and failure of involution [116]. Later in gastrulation, the involuting marginal zone lengthens and narrows, stiffening anisotropically even further as it bends around the blastopore lip [41]. Convergence and extension movements then squeeze the blastopore shut and elongate the embryo along the AP axis. Changes in cell shape thereby lead to the mechanical alterations that help drive gastrulation.

5.3. Mechanical control of organogenesis

Organogenesis is also a physical process, during which tissues are pushed, pulled, and bent. Mechanical forces – both transmitted and received by tissues – are essential for development of organs including the heart and lungs. The vertebrate heart begins as a simple linear tube, from which cardiac chambers expand via torsion and looping. Importantly, the heart is beating and blood is flowing during cardiac morphogenesis, generating significant shear forces and transmural pressures that appear to be required for proper heart development [118]. Decreasing shear by blocking cardiac flow prevents formation of valves and looping in zebrafish embryos [118]. The magnitude and orientation of these shear stresses depends on the size and geometry of the vessel through which fluid flows. As the primitive tube bulges into defined chambers, each chamber acquires a bean-like shape comprised of two curved surfaces, an outer convex curvature and an inner concave curvature. Curvature is initiated by changes in the shapes of cells at these two surfaces, with cells flattening and increasing in area at the outer curvature, and cells remaining rounded at the inner curvature [119,120]. The change in shape and the location at which it is initiated appear to be determined by blood flow. Importantly, the inner curvature has been found to be significantly stiffer (2–3 times) than the outer curvature [121], suggesting that gradients in mechanical force (possibly via pressure differentials) are responsible for the differences in cell shape changes that drive bending of the tube. Spatial differences in the mechanical properties of a tissue can thus induce morphogenesis by leading to spatial differences in cell shape.

Mechanical force is also a major determinant of fetal lung development [122], affecting patterning, growth, and differentiation. Tension gradients direct the pattern of budding during branching morphogenesis, as determined by mouse embryonic lung organ culture experiments [111,123]. As morphogenesis proceeds, the tissue distorts, causing a change in the magnitude and direction of force felt by any individual cell within that tissue. Mechanical forces are thus a function of the geometry of the tissue and are constantly changing during its development. Repetitive stretching of the lung, as occurs during third trimester fetal breathing movements, is required for cell proliferation and organ growth [124]. Reduced distention leads to pulmonary hypoplasia [125], one of the most common anomalies amongst dying neonates [126]. Conversely, increased distention accelerates fetal lung growth and development [127,128]. Mechanical forces are also required for differentiation of lung epithelium, as reduced distention inhibits production of surfactant protein [129] and correlates with a reduction in the number of cells expressing smooth muscle α-actin [130]. Mechanical stresses can thus influence differentiation by patterning changes in the shapes of individual cells in the tissue.

6. Conclusions and perspectives

Tissue geometry thus acts as both a signal for future morphogenesis, as well as an indicator of past events. From flies to frogs, fish, and humans, the geometric control of morphogenesis via chemical and mechanical gradients is ubiquitous. It is important to note that other gradients are also present in developing tissue. Because many molecules carry a net charge, chemical gradients of morphogens likely also create electrical gradients, which have been shown to be especially important for regenerative morphogenesis [131] and stem cell differentiation [132], and may also play roles during embryonic development [133]. Since manipulating geometry changes many aspects of the tissue, one challenge for the future is to separate the effects of biochemical, mechanical, and electrical gradients.

Finally, these contextual changes in tissue geometry need to be combined with knowledge of gene regulatory networks to provide a spatially accurate description of development. This quantitative understanding will require an ability to specify patterns of gene expression as well as how those patterns lead to morphogenetic movements such as changes in cell shape. The topology of gene regulatory networks predicts the temporal dependence of gene expression during development, but alone cannot describe changes in tissue morphology. Tissue geometry must therefore be incorporated as a separate boundary condition. Recent efforts using Boolean logic to describe spatial changes in gene expression patterns during development of the *Drosophila* eggshell represent a promising start in this endeavor [134]. Future efforts will need to focus on translating how the expression of specific genes, combined with geometric context, leads to the physical sculpting of tissue form.

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