Curvature Feedback for Repetitive Tissue Morphogenesis – Bridging Algorithmic Principles and Self-Regulatory Systems

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Short title:
Curvature Feedback for Morphogenesis

Keywords (max 6):
Curvature sensing; Mechanobiology; Morphogenetic motifs; Pattern formation; Tissue curvature

Abstract

Tissue patterning during organ development consists of intricate morphogenetic processes, driven by the interplay of physical and genetic cues among constituent cells. Despite its complexity, these processes can be decomposed into fundamental morphogenetic motifs that appear repeatedly in a spatiotemporally organized manner, giving rise to diverse organ architectures. Recent studies have highlighted tissue-scale curvature as critical information for constitutive cells, which enables it to bridge mechanical and biochemical signals. In this review, we discuss the regulatory principles underlying the roles of tissue curvature in morphogenesis along with recent insights from earlier studies. Here, we focus on the dual role of tissue curvature as an instructive signal that directs collective cell behavior and as a dynamic property modulated by cellular activities. First, we introduce the concept of morphogenetic motifs and provide examples from developmental processes in various organ systems. Next, we discuss how cells collectively respond to two distinct curvature types, lateral and topographical, and examine the mechanisms by which cells sense these curvatures from a mechanobiological perspective. Finally, we highlight the repetitive terminal bifurcation in developing murine lung epithelium, illustrating how curvature-driven feedback loops, mediated through mechano-chemical multicellular couplings, ensure robust morphogenetic cycles. By integrating geometric, mechanical, and chemical cues, curvature feedback emerges as a framework for self-organized morphogenesis, providing fresh perspectives on the recurrent properties and robustness of development.

1. Introduction

A remarkable aspect of tissue morphogenesis in organ development is the emergence of highly organized multicellular patterns. During these developmental processes, cells give rise to complex architectures, such as branching networks of lungs and intricately folded structures of the brain cortex. Recent advances in developmental biology have shed light on how these tissue patternings are governed by a combination of chemical (e.g., gene regulatory networks, protein signaling pathways) and mechanical (e.g., stress and strain within tissues) factors acting among cells, as well as through interactions with the extracellular matrix (ECM) and fluid (ECF) [1–4]. These multicellular interactions are provided not only by structural support but also by critical chemical and mechanical cues, thereby driving the spatial and temporal progression of tissue morphogenesis across diverse organ systems.

Building on these mechanisms, a key principle in the tissue patterning at the organ level is the repeated use of relatively simple morphogenetic processes. At the heart of many developmental systems lies the idea that a finite set of fundamental deformation modes, when applied repeatedly in different contexts, can generate a remarkable diversity of forms. These recurring motifs, employed in self-organizing processes, can be observed in a wide range of natural systems, where local interactions collectively yield large-scale structures without a predetermined blueprint [5–7]. In many ways, the iterative nature of these morphogenetic processes parallels certain algorithmic operations, in which minimal sets of instructions are orchestrated in a precise spatio-temporal manner. For instance, a simple deformation of the epithelial sheet can serve as an essential motif in the morphogenetic processes that ultimately interconnect to form organ-specific morphology. By modulating the timing, location, and magnitude of these recurring morphogenetic events, organisms can initiate robust developmental programs (**Figure 1A**).

The recurring motifs of tissue morphogenesis exhibit a resemblance to the principles underlying L-systems, an algorithmic formalism developed by Aristid Lindenmayer [8]. In L-systems, simple rewriting rules are applied iteratively, enabling local interactions to yield highly complex structures. Similarly, tissue morphogenesis leverages foundational deformation processes to generate diverse organ architectures. Just as L-systems employ self-similar rules to model branching and recursive patterns, tissue morphogenetic events can be seen as biological analogs of these algorithmic operations [9–13]. Recent advances have revealed how collective cell behaviors organize a variety of simple morphogenetic events and how each motif can be regulated through mechanical and chemical couplings in multicellular systems.

In this review, we explore the regulatory principles underlying how tissue patterns at the organ level emerge through the spatiotemporal integration of simple tissue deformations with recent literature. Specifically, we emphasize tissue bending as a recurring morphogenetic motif that plays a pivotal role in tissue patterning. While earlier reviews discuss the cooperative cellular mechanisms driving tissue bending and curvature development [14], the focus here is on the emergent role of tissue curvature as an informational cue. We highlight how cell sense tissue curvature as a result of tissue bending and how its downstream signaling can feedback into tissue bending. Using lung branching morphogenesis as an example, we illustrate a fundamental

framework for self-organizing systems in tissue patterning, connecting algorithmic rules with self-regulatory processes mediated through the cellular mechano-chemical couplings.

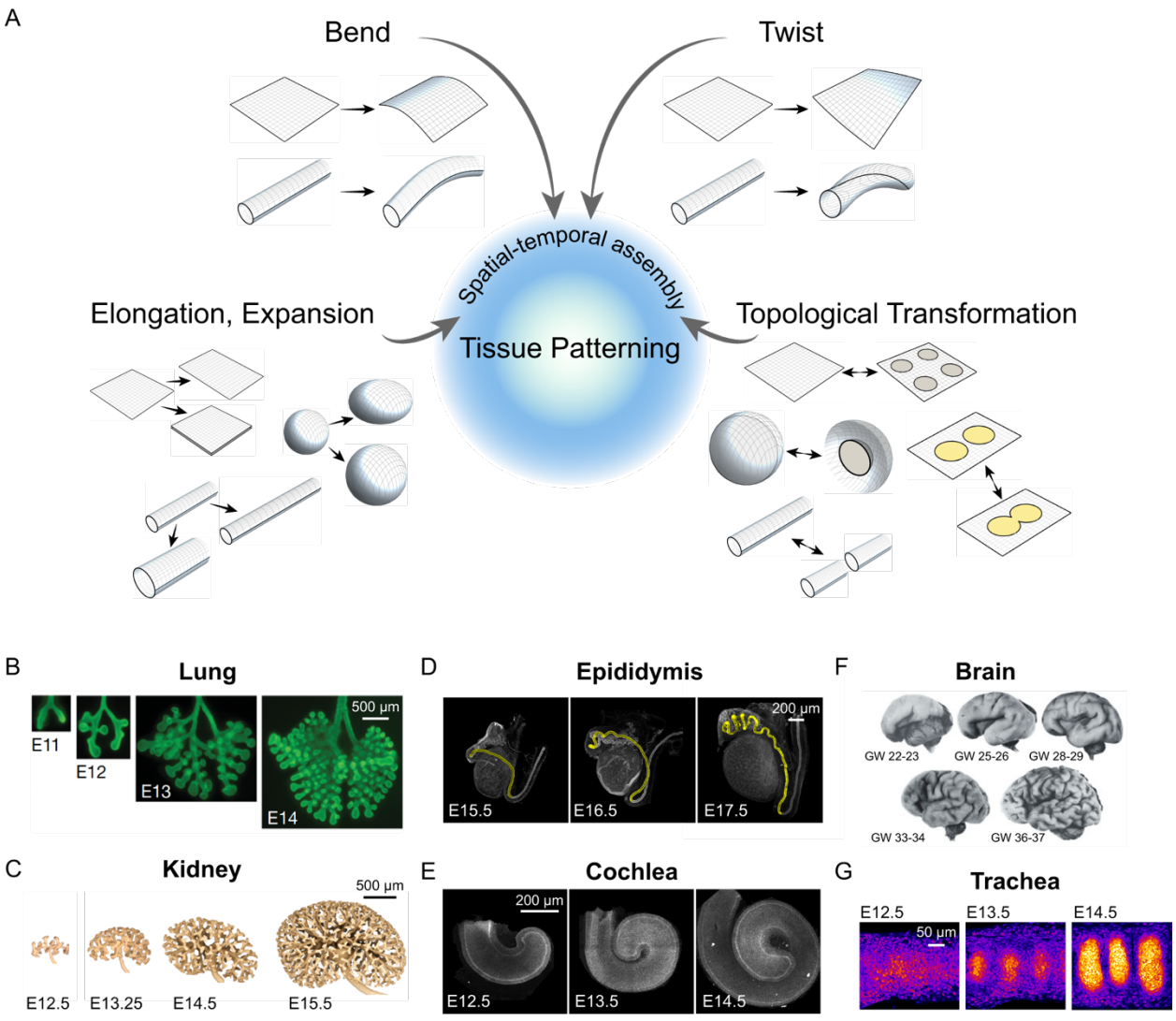

Figure 1 Morphogenetic motifs for tissue patterning in organ development.

(A) Fundamental morphogenetic motifs include bending, twisting, growth (elongation and expansion), and topological transformation. The proper spatiotemporal assembly of these motifs generates intricate tissue patterning.

(B) Branching morphogenesis in murine lung epithelium at E11–E14. Reproduced from [11] with modifications. Scale bar, 500 μm.

(C) Branching morphogenesis in murine kidney epithelium at E12.5–E15.5. Reproduced from [15] with modifications. Scale bar, 500 μm.

(D) Bending and folding morphogenesis of murine epididymal duct, colored in yellow, at E15.5–E17.5. Reproduced from [16] with modifications. Scale bar, 200 μm.

(E) Spiral growth of murine cochlear duct at E12.5–E14.5. Reproduced from [17] with modifications. Scale bar, 200 μm.

(F) Wrinkle formation of the human brain at Gestational week (GW) 22–37. Reproduced from [18] with modifications.
(G) Cartilage ring formation in murine trachea at E12.5 – E14.5. Reproduced from [19] with modifications. Scale bar, 50 μm.
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2. Recurring Morphogenetic Motifs for Tissue Patterning

Many of the intricate shapes observed in developing internal organs arise from a limited set of tissue-scale deformation events (**Figure 1A**). By dissecting these recurring morphological transformations and their underlying cellular and mechanical principles, we gain insight into how local activities culminate in global tissue architectures. In this section, we examine the fundamental modes of tissue morphogenesis, focusing on deformation, growth, and topological change, and highlight their contributions to the spatial and temporal patterning of diverse organs.

2-1. Bend and Twist

Bending of a tissue sheet is the most fundamental and widespread mode of tissue morphogenesis, accomplished through several distinct mechanisms [2]. In most cases, differential growth within a tissue or between adjacent tissues leads, in principle, to the development of tissue curvature [20,21]. For instance, in an epithelial monolayer that bends toward its basal side, cells may undergo apical contraction and/or basal expansion, thereby imposing geometric constraints that produce large-scale tissue bending [22–24]. Another mechanism centers on local cell proliferation, exemplified by pseudostratified epithelia such as the retina or inner ear. In these tissues, cells display interkinetic nuclear migration, shuttling their nuclei apically to divide and returning them basally post-mitosis; when nuclei stall at the apical surface following cell division, this localized accumulation can induce bending [25,26].

Branching morphogenesis in organs such as the murine lung and kidney underscores how repetitive bending events shape complex organ architectures (**Figures 1B and 1C**). Imaging and lineage tracing studies have visualized local deformations during branching processes, including terminal bifurcation and lateral budding [11,15,27]. In each scenario, the repeated bending of epithelial sheets, whether directed basally or apically, facilitates the formation of elaborate branched ductal networks. Bending of an epithelial duct such as in epididymal duct development relies on cooperative sheet bending, where curvature arises in opposite directions across the cross section of the duct (**Figure 1D**). In addition, murine cochlear duct formation also involves active bending of the cell sheet, particularly on the inner side of spiral cochlear duct, which is driven by nuclear stalling during the interkinetic nuclear migration [26] (**Figure 1E**).

Twisting introduces a different dimension of morphological complexity, manifesting as a rotation or helical winding along the longitudinal axis of a duct. While bending involves a change in curvature within a plane without a net rotation, twisting is characterized by an angular displacement of one duct end relative to the other, producing a helical or spiral geometry [28,29]. Discriminating between bending and twisting is crucial for understanding the spectrum of shapes produced during organogenesis. Bending alone can give rise to local curvature, but twisting adds

an additional rotational component. In the developing murine cochlear duct, for example, neuroepithelial cells on the outer side of the duct migrate diagonally across the tissue axes from the proximal-basal to the distal-apex in a helical manner, ultimately forming the spiral cochlea [17]. Together, these processes enable growing tissues to achieve a remarkable diversity of three-dimensional configurations as they develop into functional organs.

2-2. Elongation and Expansion

The elongation and expansion of biological tissues can be realized by two distinct but interconnected aspects: growth and deformation [30]. Tissue growth involves an increase in the number of constituent cells through cell proliferation or cell injection from adjacent regions through changes in cell state, e.g., epithelial–mesenchymal transition. This growth can also occur via cell size enlargement, driven by metabolic and biosynthetic activity. Additionally, ECM can contribute to tissue expansion and complexity [4]. In contrast, tissue deformation, responsible for elongation and expansion without an overall increase in tissue volume, is achieved through shape changes in constituent cells and/or their spatial rearrangement. When tissues elongate along one axis, this is often accompanied by contraction along orthogonal axes, preserving overall volume. Such anisotropic deformation can result from active cellular behaviors or passive responses to external mechanical forces. The extent to which passive deformation induces elongation along one axis while contracting along another depends on the material properties of the tissue.

Elongation and expansion are universal and integral mechanisms in organ development. For instance, branching morphogenesis in the lungs and kidneys relies not only on epithelial sheet bending but also on duct elongation and expansion at their distal tips. In the developing murine epididymis, duct elongation is the predominant mode around embryonic day (E)15.5. This longitudinal elongation creates mechanical instability, leading to duct bending and folding through a process known as buckling [16,31,32]. Similar mechanical principles underlie brain morphogenesis, where in-plane tissue growth drives out-of-plane deformation, resulting in the formation of complex cortical folds [33,34] (**Figure 1F**). Buckling has emerged as a recurring biophysical mechanism to generate regular folding patterns across various systems – all demonstrate folding and wrinkling driven by differential growth and mechanical constraints [35–37].

2-3. Topological Transformation

Beyond the traditional concepts of tissue deformation and growth, morphogenesis also encompasses a diverse array of topological changes—events that fundamentally alter how cells and tissues connect or become compartmentalized. These transformations reshape spatial relationships at the tissue or organ level, creating new structures, lumens, and boundaries vital for proper organ formation. Often acting as a pivotal morphogenetic leap, they can convert relatively simple tissue sheets or clusters into complex, three-dimensional structures.

Topological changes can be broadly categorized into two major types. The first involves the de novo emergence of a region of interest, such as a newly differentiated cell population or a nascent tissue gap [38,39]. An example is the developing tracheal cartilage rings, which arise at regular intervals along the cranial–caudal axis during embryonic development (**Figure 1G**). Starting

around E12.5 in mouse embryos, cartilage differentiation begins within discrete segments, ultimately yielding a series of anatomically distinct and evenly spaced rings [19,40]. These specified cartilage domains form through dynamic cellular behaviors guided by genetic and physical factors, creating the spatial and temporal cues that drive subsequent morphogenetic events and consolidate the characteristic architecture of tracheal duct.

A second major category of topological change involves processes in which two previously separate regions merge into a single continuous domain, or conversely, a single domain subdivides into multiple compartments. For example, vascular remodeling entails the repeated fusion and fission of nascent vessels, forming an interconnected vascular network [41]. Similarly, the formation of a single lumen in a spherical tissue exemplifies the merging of multiple fluid-filled cavities, transforming an epithelial mass into a hollow tubular structure [21,42,43].

3. Curvature as an Information Cue in Tissue Morphogenesis

This section discusses the concept that physiologically derived tissue geometry can serve as a key driver of tissue morphogenesis. Increasing evidence suggests that tissue curvature serves as an instructive signal for cell dynamics, similar to mechanical properties such as ECM elasticity and ECF viscosity that have been extensively studied. Recent reviews have comprehensively summarized how cells detect and respond to curvature at the molecular and cellular levels from a viewpoint of engineering and physics [44,45]. Accordingly, we focus on tissue-scale curvature in the context of cell and developmental biology.

3-1. Collective Cell Responses to Tissue Curvature

Investigating how cells sense and respond to tissue curvature in vivo is challenging because curvature cues often overlap with other biochemical and mechanical signals in developing organs [46]. Recent advancements in engineering techniques have enabled it to mimic well-defined shapes and sizes under in vitro settings, allowing systematic manipulation of curvature while keeping other variables relatively constant. This approach elucidates how cells detect and adapt to curved environments. In general, engineered geometric control addresses two main aspects. One aspect is lateral geometrical confinement, where tissues are placed within precisely shaped and sized boundaries. The other is substrate curvature, a part of topographic features, that modulates balances intracellular and intercellular cytoskeletal forces through cell–substrate adhesion. Such controlled experimental setups not only clarify how curvature directly influences collective cell behavior but also provide a reproducible framework that can be applied to more complex tissue models [47,48]

Growing evidence underscores the crucial role of precise control over tissue-scale curvature and geometry in directing epithelial morphogenesis. For instance, three-dimensional micropatterned assays with mammary epithelial cells have been employed to systematically manipulate the initial shape of epithelial tubules, demonstrating that branching in mammary tissues consistently occurs at curved regions [49]. In studies of intestinal morphogenesis, microfabrication and hydrogel engineering techniques have been employed to guide the self-organization of intestinal stem cells under precisely defined geometric constraints. By tuning these geometric parameters,

reproducible mini-gut tubes or larger-scale intestinal surfaces with robust crypt–villus architectures have been successfully generated [50,51]. Collectively, these approaches indicate that external manipulation of tissue curvature is a potent morphogenetic cue, demonstrating the controllability of tissue patterning.

Tissue-scale curvature can actively influence the behavior of epithelial cells, even in monolayer conditions. Recent experiments using engineered substrates have demonstrated that topographic curvature modulates the fluidity of multicellular monolayers [52–54]. For instance, monolayers of alveolar epithelial tissue derived from human stem cells exhibit more dynamic, fluid-like behavior on highly curved surfaces, whereas flatter surfaces promote larger cell clusters with cohesive, jammed behaviors [53]. These studies propose that the interplay between bending energy and cell packing underpins curvature-driven phenomena. Theoretical analyses further suggest that tissue curvature regulates the balance between solid-like and fluid-like states in epithelial layers: increased curvature reduces the energetic barriers to cell intercalation, thereby promoting unjamming and fluidization in highly curved epithelia [55,56]. These findings highlight how tissue geometry, specifically curvature, governs the transition of cell mobility in epithelial layers through the coupling between tissue mechanics and supracellular geometry.

The mechanism underlying collective cellular responses to tissue curvature involves a complex interplay of cytoskeletal balance, intercellular interactions, and adhesion dynamics. In response to local curvature, cytoskeletal components, including actin fibers and microtubules, tend to align along topographic cues, translating geometric information into cellular organization [57–60]. Local curvature also activates signaling pathways that enhance contractile forces within cells, leading to tissue delamination from the substrate in certain contexts [61–63]. In addition, the recent report shows that the topographic curvature controls cell extrusion from epithelial monolayers as a result of mechanical modulation [64]. In concave regions, where the monolayer tissue protrudes toward the substrate, basal fluid accumulation weakens cell–substrate adhesion and survival signals, resulting in higher rates of cell extrusion. Conversely, in convex regions, inward-directed forces form within the cell sheet, counteracting fluid stress and preserving adhesion, thereby reducing extrusion. Given that epithelial cell extrusion during the tissue homeostasis phase relies on spatial competition at the basal side of cells, governed by the mechanical equilibrium among neighboring cells [65,66], further investigations are warranted to elucidate the relationship between topographic curvature and mechanical competition among cells. These findings highlight how curvature-driven mechanical and biochemical cues collectively regulate tissue morphogenesis and integrity.

3-2. Curvature Sensing and Transduction

How do cell collectives sense the curvature of their tissues and transmit these signals? Recent research has begun to illuminate that cells sense their mechanical states translated from geometrical information and how the molecules and key signaling pathways that underlie curvature-dependent signal transduction.

In monolayer epithelial tissues, changes in tissue curvature directly translate into corresponding alterations in individual cell shape. A simple analogy to a bent elastic beam illustrates this: the

convex side of the beam undergoes stretching, while the concave side experiences compression. Similarly, cells on the apical or basal sides of a curved tissue are subjected to tensile or compressive forces depending on the local curvature, at least on shorter timescales when elastic strain energy is effective. In an epithelial monolayer tissue, if the basement membrane protrudes toward the cell side, defined here as convex, the apical side of the cells is stretched relative to the basal side. Conversely, in concave regions, the basal side is more stretched in a geometrical sense. These deformations can arise from active cellular forces, such as acto-myosin contraction and F-actin–based extension, or from passive processes including buckling or local extracellular matrix accumulation. For further details of the quantitative morphological change of epithelial folds versus cell deformation, refer to the earlier theoretical papers [23,67,68].

Cell stretching is transmitted to the plasma membrane as increased membrane tension, which subsequently activates various mechanosensitive channels and receptors. A prominent example is the mechanosensitive ion channel Piezo1, where elevated plasma membrane tension induces its activation, leading to Ca2+ influx [69,70]. A recent report demonstrates that this influx further promotes endocytosis of epidermal growth factor receptor (EGFR), initiating downstream signaling cascades [71]. Another well-known class of mechanically activated channels that triggers the Ca2+ influx includes the transient receptor potential vanilloid (TRPV) channels [72,73]. Interestingly, during the morphogenesis of Hydra, there is a negative correlation between local Ca2+ levels and fluctuations in tissue curvature [74]. Since multicellular Ca^{2+} dynamics can be regulated by curvature-dependent local tissue stress [75], the precise spatiotemporal control of Ca^{2+} levels plays a pivotal role in morphological transitions exemplified by the Hydra's morphogenesis [76].

At the receptor level, several receptor tyrosine kinases, including EGFR and fibroblast growth factor receptor (FGFR), have been implicated as mechanosensitive receptors. Mechanical stimuli acting on these receptors can trigger downstream signaling cascades that converge on the activation of extracellular signal-regulated kinase (ERK) [77–79]. Studies employing Förster resonance energy transfer (FRET)-based biosensor imaging in epithelial cell lines have demonstrated that ERK activation occurs in response to external cell stretch, reaching a plateau within approximately ten minutes [80–82]. This rapid activation may involve multiple mechanisms, including the inhibition of EGFR activation through direct interaction with E-cadherin [83]. Additionally, stretch-induced ERK activation is observed in murine embryonic lung epithelium [84]. In this context, ERK activation that requires the growth factor FGF distributed outside of the epithelial tissues occurs predominantly localized to the distal tips of the lung epithelium, which exhibit concave curvature. Basal cell stretch in these distal tips is hypothesized to initiate ERK signaling via FGF receptor-mediated endocytosis. However, the detailed mechanisms underlying curvature sensing and the transmission of mechanical signals remain incompletely understood. Interestingly, live imaging studies have also revealed ERK activation in the distal tips of developing embryonic murine kidneys [85]. These findings suggest the potential for a conserved mechanism of curvature-dependent ERK activation across epithelial organs.

Cell compression is another critical factor driving curvature-dependent signal transduction. The interplay between substrate curvature and nuclear responses demonstrates how cells sense and

react to their microenvironment through cytoskeletal forces and nuclear deformation. In epithelial monolayers, substrate curvature strongly influences both cell and nuclear morphology: the convex substrates lead to thinner monolayers in the cellular apico-basal axis with laterally expanded nuclei, whereas the concave substrates result in thicker monolayers and compressed nuclei (Luciano et al., 2021). By way of cytoskeletal linkages spanning the plasma membrane and nuclear envelope, these curvature-dependent morphological changes enhance force transmission to the nucleus, stretching nuclear pores and promoting the translocation of mechanosensitive factors such as Yes-associated protein (YAP) [86–89]. In this case, the nucleus functions as a mechanosensitive organelle, with the resulting mechanotransduction pathway linking nuclear curvature sensing to downstream transcriptional responses and integrating mechanical cues from ECM geometry to regulate subsequent gene expression [90]. Emerging evidence further indicates that this interplay between nuclear mechanics and substrate curvature is essential for orchestrating fundamental cellular processes.

4. Curvature Feedback for Repetitive Tissue Morphogenesis

Building on the concept that cells are capable of sensing tissue curvature, as discussed in preceding sections, this section explores a multicellular feedback system in which tissue curvature acts as a key driving factor for self-organized morphogenesis. We illustrate this by examining lung branching morphogenesis, with a particular focus on the repetitive bifurcation of distal tips in the developing murine lung (**Figure 2A**). To introduce this concept in its most fundamental form, we first focus exclusively on the epithelial system as the minimal element. This foundational framework is then expanded to incorporate additional factors, such as genetic regulation and the contributions of heterotypic cell populations, to provide a more comprehensive understanding of curvature-driven branching morphogenesis.

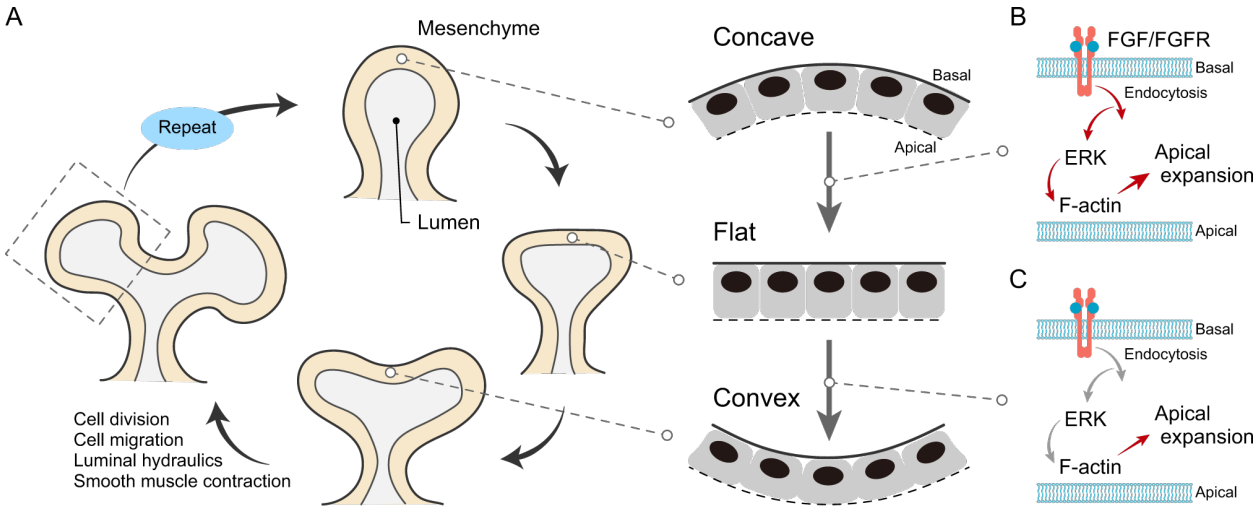

Figure 2 ERK-mediated curvature feedback in monolayer epithelial tissues

(A) Repetitive terminal bifurcation of the murine lung epithelium during embryonic development. Transition from the concave (top) to the convex (bottom) epithelial monolayer involves shape changes in individual epithelial cells. This process is influenced by multiple physicochemical factors and interactions with other

cell types, contributing to the sculpting of enlarged new tips, used for the iterative morphogenetic cycles (from bottom to top).
(B) Curvature-dependent ERK activation promotes apical extension through actin polymerization, driving the transition of the epithelial sheet from the concave to the flat shape.
(C) F-actin-mediated apical expansion continues to drive the transition from a flat to a convex shape, influenced by the residual effects of prior ERK activity but independent of instantaneous ERK activation.

4-1. Tissue Bending from Concave to Convex

A critical mechanism underlying the terminal bifurcation in murine developing lungs is the reversal of tissue curvature, transitioning from a concave shape, where the epithelial monolayer protrudes toward the mesenchyme, to a convex configuration. Several mechanisms have been proposed to explain this shape transition from a mechanical point of view [91,92], but one key factor recently elucidated is ERK-driven apical expansion [84,93]. In the concave region, the basal extension of epithelial cells within the monolayer triggers ERK signaling activation, which in turn promotes actin polymerization at the apical edges of these cells (**Figure 2B**). This process is supported by the fact that ERK interacts directly with actin polymerization regulators to facilitate the polymerization [79,94]. Furthermore, ERK activation has been shown to induce actin polymerization in various epithelial cell types [95,96]. The apical actin polymerization generates mechanical forces that push neighboring cells within the monolayer, leading to lateral cell extension (**Figure 2B**). Consequently, this ERK-mediated reduction in tissue curvature, coupled with curvature-dependent ERK activation, establishes a negative feedback loop between tissue curvature and ERK activity across scales. However, it is important to note that there is no evidence indicating that ERK inactivation induces apical contraction, making this curvature feedback loop asymmetric and conditional.

To switch the tissue curvature from concave to convex, a time lag must exist between changes in tissue curvature and apical expansion. If the apical expansion were perfectly synchronized with curvature, the initially concave tissue would simply flatten, preventing further curvature-dependent deformations. For the concave-to-convex transition to occur, actin polymerization–driven apical expansion must persist even as the tissue bends to form the convex shape (**Figure 2C**). Because ERK activity is sensitive to the local curvature of the monolayer where flatter regions correspond to lower ERK activity, it does not directly drive the transition from a flat to a convex shape. Instead, the transition is governed by the memory effects of F-actin dynamics, as actin polymerization continues to influence tissue shape even after it shifts from concave to flat. The state of F-actin is regulated by processes such as polymerization, depolymerization, and severing, which collectively control apical expansion. The kinetics of these processes establish a time lag that is critical for the repeated terminal bifurcations observed during development [84]. This time lag is maintained through the coordinated action of multiple regulatory factors, ensuring precise control of tissue dynamics. Further research is expected to elucidate the molecular mechanisms underlying this coordination, providing deeper insights into the regulation of tissue curvature.

4-2. Curvature Development in Growing Epithelial Sheet

When the epithelial tissue at its distal tip undergoes localized bending toward the lumen side, the lateral regions of the monolayer passively increase in curvature. As this bending at the distal tip

progresses, the curvature along the lateral sides develops further. This process represents a critical morphogenetic transition from a single bud to bifurcated buds, laying the foundation for terminal bifurcations. Once the newly formed buds emerge with clear concave shapes through this curvature-driven development, the previously distal region transforms into the stem of the newly developed buds. Within the new buds, subsequently, curvature-dependent ERK activation and ERK-driven apical expansion facilitate a transition in tissue bending from concave to convex, thereby sustaining the cycle of curvature-driven morphogenesis [84].

Although ERK-mediated curvature feedback is essential for shaping the early stages of newly formed epithelial buds, additional factors are crucial for achieving their final morphology (**Figure 2A**). One important factor is cell proliferation at the bud tips. Because ERK activity is necessary for cell division, lateral growth within the epithelial monolayer occurs in concave regions, thereby promoting a rounded bud shape. Another key factor is luminal fluid, which can regulate tissue morphology both mechanically and chemically [97,98], as shown in other systems as well [99,100]. Elucidating the roles of luminal hydraulics, including hydrostatic pressure, osmotic pressure, and shear stress, and their interplay with tissue geometry is essential for understanding luminal tissue morphogenesis. In addition, active epithelial cell migration can drive outward expansion of the epithelial monolayer. For instance, in murine lung development, FGFs secreted by the mesenchyme act as chemoattractants for the epithelium [101,102]. Lastly, smooth muscle cells also influence bud formation; in developing lungs, they collectively wrap around the cleft site during terminal bifurcation, deepening the cleft through contraction. Although their necessity remains controversial [103–105], smooth muscle–mediated tissue contraction helps sculpt newly formed stems and tips in a robust manner. Together, these processes alongside ERK-mediated curvature feedback coordinate to shape newly formed buds, ultimately producing the characteristic tissue curvature.

4-3. Integrating Curvature Sensing and Control: A Self-Organizing Framework for Tissue Patterning

A principle of self-organizing systems is that the variable intended to be regulated or the target variable should be directly sensed and controlled by the constituent agents within the feedback loop. In the context of tissue morphogenesis, if the ultimate goal is to achieve a particular morphology characterized by curvature, then the tissue curvature itself should be sensed and modulated by the constituent cells. This direct linkage between sensing and controlling, mediated through mechano-chemical couplings, enables precise corrections that remain robust against inevitable biological noise, as any deviation from the desired target quantity is registered in and acted upon by the cells. By incorporating these key variables into a closed regulatory loop, tissues can orchestrate the relevant cell signaling pathways, mechanical forces, and cellular actions, thereby enabling the maintenance and refinement of emerging morphologies throughout development. Importantly, simple feedback loops not only establish the desired geometric features in dynamic environments but also facilitate the repeated use of morphogenetic motifs as building blocks for more complex structures. Consequently, curvature-based sensing and control within these feedback architectures integrates with higher-level developmental programs, enabling tissues to autonomously replicate, adapt, and stabilize complex geometries.

As an illustrative example of a self-regulatory mechanism in tissue patterning, we here highlight the role of ERK-mediated curvature feedback, coupled with mechanical forces, during murine branching morphogenesis. In this specific context, ERK signaling underpins both the sensing and generation of curvature at the tissue scale. However, the signaling pathways engaged in such feedback loops in general are not limited to the ERK pathway; additional pathways and mechanical ingredients may predominate in different developmental or physiological settings. Moreover, whether these feedback systems require de novo gene expression or instead rely primarily on direct cytoskeletal and mechanical modulation depends on the timescale of the events being regulated. In the future, exploring a broader range of signaling systems, alongside their cellular mechanical regulations and key physical parameters, will be crucial for gaining a more comprehensive understanding of self-organization in tissue morphogenesis.

Acknowledgments

This work was supported by Singapore Ministry of Education (MOE) Academic Research Fund (AcRF) Tier 2 (MOE-T2EP30223-0010) and the National Research Foundation, Singapore (NRF) under its Mid-sized Grant (NRF-MSG-2023-0001). We thank our lab members for their valuable comments on the manuscript.

Competing Interests

The authors declare no competing interests.

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