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Review

Emergence of tissue shape changes from collective cell behaviours

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ABSTRACT

Anyone watching a movie of embryonic development immediately appreciates the importance of morphogenetic movements and cell flows that reshape tissue. Dynamic tissue shape changes are genetically choreographed, but their execution is essentially a mechanical event. How the interplay between genetics and tissue mechanics controls tissue shape is a fundamental question. Key insights into this problem have emerged from studies in different model organisms as well as in cultured epithelia. These studies have revealed how gene expression patterns can generate patterns of planar cell polarity that orient cellular force generation and give rise to anisotropic mechanical properties of cells and tissues. These can autonomously bias the rate and orientation of cellular events such as cell divisions, extrusions, neighbor exchanges and shape changes that drive morphogenesis. However recent studies also highlight how autonomously controlled cell dynamics lead to tissue-wide stress patterns framed by mechanical constraints such as cellular connections to extracellular matrices. These stress patterns themselves can orient the cell behaviours underlying morphogenesis. As a result of this interplay, tissue shape emerges in a mechanical process that tightly couples mechanics and genetics.

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1. Introduction

Understanding epithelial morphogenesis requires an analysis of the full system that integrates genetic regulation with active mechanics and stress-induced cell behaviour at different scales from cells to tissues. Quantitative descriptions of cell dynamics and their response to genetic and mechanical perturbations, analyzed in the context of physical models, are beginning to provide a multiscale explanation of epithelial tissue morphogenesis. Here, we discuss recent work in epithelial cell culture and in different developing epithelial tissues that highlights key emerging principles of epithelial morphogenesis. Epithelial cell cultures reveal the importance of mechanical stresses and stress boundary conditions on cell dynamics. Studies of developing epithelia highlight how gene expression patterns determine tissue-wide patterns of cell mechanical properties and planar polarity that initiate mor-

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phogenetic movements. They show how resulting tissue stresses feed back on cell dynamics to guide tissue flows and generate reproducible tissue sizes and shapes. Finally, they uncover a key function for patterned extracellular matrix attachments in organizing patterns of tissue stresses that guide morphogenesis.

2. Insights into stress-dependent cell dynamics from epithelial cell culture

The accessibility of cultured epithelial cells to mechanical perturbations has made them a good system to study the emergence of long-range epithelial stress patterns and their feedback on cell dynamics. Experiments with Madin-Darby canine kidney Cells (MDCK) grown on micropilllars or patterned substrates have demonstrated how changing boundary constraints exerts effects that reach over long distances into MDCK monolayers. Compared with confluent monolayers, which exert negligible traction forces on the underlying substrate, colonies growing with free edges exert traction forces throughout the colony that are highest at its edges and at the boundaries of cells within the colony [1]. Other studies demonstrate how acutely releasing boundary constraints rapidly induces cell flows that propagate over long distances into the epithelium [2]. These experiments highlight how mechanical conditions at colony boundaries can coordinate cell behaviour over long distances. Over longer times, epithelial stresses that result from changing boundary conditions can control the rate and orientation of cell division, as well as the rate of cell extrusion in epithelia. Planar cell compression correlates with the size at which colonies of MDCK epithelial cells stop growing [3]. In order for a colony to grow at a constant rate, the motility of cells at its edge would have to increase exponentially. This suggests that limits to cell motility reduce the rate of colony area expansion, resulting in smaller apical cross-sectional areas of cells in the colony. Once this cross-sectional area falls below a certain threshold, proliferation decreases and colony growth stops. [3]. Further experiments in which MDCK cells were grown on deformable substrates also suggest that compression reduces MDCK cell proliferation and show that stretch increases it [4,5]. Cell cycle reentry occurs at the G_1-S transition [5] and is controlled by nuclear entry of both beta-catenin and YAP, a transcription factor that can also mediate Hippo signaling [4].

Other studies have emphasized the role of planar compression-induced cell extrusion in maintaining the density of MDCK cell monolayers. Growing these cells to confluence on a pre-stretched membrane, and then releasing the stretch, acutely increases cell packing density. This induces a burst of live cell delamination that returns cell packing density to the initial value after about 6 h. Drug treatments suggest the involvement of stretch-activated ion channels in regulating compression-induced cell extrusion in MDCK cells [6].

Stretching MDCK cell monolayers not only activates proliferation – if it is anisotropic, it also elongates cell shape along the stretch axis. Cell elongation orients cell divisions such that they relax tissue stresses and cell shape. Taken together, these studies in cultured epithelial cells reveal dramatic cellular responses to stretch and compression and set the stage for how tissue stresses could guide epithelial morphogenesis *in vivo.*

3. Epithelial morphogenesis *in vivo*

Morphogenesis of *Drosophila* has provided a powerful model system in which to study the interplay of genetics and mechanics *in vivo*. The advent of fluorescence spinning disc microscopy and selective plane illumination microscopy (SPIM) has allowed faster and less damaging imaging of a variety of different morphogenetic processes in living animals. Furthermore, advances in image processing and analysis have revealed the cell behaviours underlying morphogenesis in quantitative detail. Tissue response to laser ablation provides a powerful tool to study mechanical perturbations and the role of mechanical stresses in morphogenesis. Combining these methods with theoretical approaches and with sophisticated tools for genetic manipulation is deepening our understanding of how tissue shape changes arise from cell dynamics, how patterns of cell dynamics are specified genetically, and how they respond to tissue stresses.

We now discuss the interplay of genetics and mechanics, primarily focusing on three morphogenetic events that take place during *Drosophila* development: pupal wing morphogenesis, embryonic germ band elongation, and the shaping of the pupal thorax. Initially, studies in the embryo and thorax emphasized the role of autonomous planar polarized cell behaviours, while those in the pupal wing highlighted stress- induced remodeling. However deeper analysis of each process is beginning to reveal how autonomous and stress-induced events are intertwined.

3.1. Drosophila *wing development and planar polarity*

The *Drosophila* wing is a roughly ellipsoid structure consisting mainly of two tightly apposed sheets of cuticle. The wing cuticle is covered on its dorsal and ventral surface by a distally-oriented array of wing hairs aligned with the long axis of the wing. The wing surface has a microscopically corrugated texture with microscopic ridges that run in different orientations in the anterior and posterior regions of the wing. The shape of the wing, including its global patterns of ridges and hairs, reflects the shape of the pupal wing epithelium, an epithelial bilayer that secretes the wing cuticle during pupal development and disintegrates after flies eclose. The mechanisms controlling wing size and shape, and how wing shape is coupled to planar polarized patterns of hairs and ridges, have been studied for many years.

Like other appendages, the wing grows during larval stages as an undifferentiated epithelial sac called an imaginal disc. The elongated shape of the wing depends in part on oriented growth during larval stages that is biased along the future PD axis of the wing [7,8]. Once larvae reach an appropriate size, they pupariate and the imaginal discs undergo dramatic morphogenetic movements to assume an approximation of their final shapes, which continue to be refined during pupal development (schematically depicted in Fig. 1C). Our groups have focused on a change in wing shape that occurs between 15 and 32 h after puparium formation, shortly before wing hairs form [9,10]. At this time, the future wing hinge is sculpted by patterned cellular contractions in which cells reduce their apical cross-sectional area, while cells in the wing blade participate in anisotropic flow patterns. These flows elongate the blade in the proximal-distal (PD) axis and narrow it in the anterior-posterior (AP) axis – a process that resembles convergent extension (Figs. 1 C and 2). Shortly afterwards, wing hairs form and the cuticle is secreted.

Planar cell polarity (PCP) in the wing is not only evident in the oriented patterns of hairs and cuticular ridges, but also in the oriented cell dynamics that shape it. Two largely independent but communicating molecular cassettes have important but incompletely understood functions in governing planar cell polarity in many animal tissues: the Fat PCP and Core PCP systems. Each comprises proteins that localize to apical adherens junctions in epithelial tissues, where they form asymmetric cortical domains that are intracellularly polarized and coupled between neighboring cells, forming tissue-wide polarity patterns (Fig. 1). Although their cell biological functions are not completely understood, it is clear that Fat and Core PCP domains can intracellularly polarize