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Current Opinion in Systems Biology

Mechanochemical coupling and developmental pattern formation

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Abstract

Patterning of nascent embryonic structures into their final forms can be influenced by initial geometry, underlying mechanical properties, and distribution of interacting chemical signals. Both mechanical and chemical processes can break the symmetry of an initially uniform state and initiate pattern formation. Here we describe recent work on four developmental systems in which coupling of mechanical and chemical processes are involved in the emerging pattern. These range in spatial scale from polarization of the single-cell *Caenorhabditis elegans* zygote to the looping of the chick gut over millimetres, and include local chemical and mechanical coupling at tissue scale in the vertebrate segmentation clock, the invaginating mesoderm of *Drosophila*, and during villus formation in mouse and chick intestine.

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Current Opinion in Systems Biology 2017, **5**:104–111

This review comes from a themed issue on **Development and differentiation (2017)**

Edited by **Philip Greulich** and **Ben MacArthur**

For a complete overview see the Issue and the Editorial

Available online 1 October 2017

https://doi.org/10.1016/j.coisb.2017.09.007

Keywords

Symmetry breaking, Oscillations, Synchronization, Epithelial mechanics, Cell polarity, Physics of biology.

Introduction

Morphological and chemical patterns that give function to tissues emerge during development. Regardless of the final pattern, the first step involves breaking an initial symmetry. This happens when local instabilities, such as a change in mechanical properties or signalling pathways, trigger non-uniform behaviour in a previously homogeneous domain. A mechanical origin for such instabilities was introduced a century ago by D'Arcy Thompson, writing that for intricate morphological patterns such as folds, tubes and loops, the laws of physics have to be obeyed by the tissue undergoing the transformation [1]. Around mid-twentieth century, an influential model for symmetry breaking in chemical patterns was described by Alan Turing [2], which was complimented by Lewis Wolpert's proposal for the elaboration of pattern in development from an initial asymmetry [3,4]. Subsequently, much attention has focused on how gene expression circuits, biochemical signalling pathways and morphogen gradients drive tissue pattern. More recently, developmental biologists have begun to ask how the interaction of mechanical processes and chemical pathways enable symmetry breaking and subsequent pattern formation. Addressing this complex interplay, referred to as mechanochemical coupling [5], requires a systems-level approach that couples molecular and genetic networks to larger-scale mechanical processes.

Mechanochemical coupling occurs at multiple length scales. At the molecular scale, several transmembrane proteins and associated protein complexes can act as stress sensors converting mechanical forces to chemical and electrical signals [6,7]. At the cellular scale, a local change in curvature of cellular membranes [8] or a change in contractility of cytoskeletal networks can lead to network flows that redistribute associated protein components [9], and thereby result in locally varying biochemical activities. Mechanochemical coupling also occurs at even larger scales in tissues, where directional biochemical gradients can trigger anisotropic mechanical changes in tissues [10], and vice versa, where tissue-scale mechanics can reorganize biochemical polarity fields [11–13]. Interestingly, this coupling is also known to be influenced by changes in external osmotic conditions [14] as well as an increase in internal pressure during embryo growth [15]. In this review, we highlight four biological systems in animal development where there has been recent progress in understanding mechanochemical coupling at cellular and tissue-scales.

Intracellular mechanochemical coupling in anterior-posterior polarization of the *Caenorhabditis elegans* zygote

One of the best-studied examples of intracellular mechanochemical coupling occurs immediately after fertilization in the 1-cell stage embryo of the nematode *C. elegans* when mutually antagonistic PAR (partitioning-defective) polarity proteins [16,17*] are segregated to the anterior and posterior halves of the embryo. Without correct polarization, abnormal cleavage patterns ensue and the embryo fails to segregate germline-specific P

granules accurately. Initially, the system is homogeneous along the long axis of the embryo with the anterior PAR complex (aPARs) enriched in the membrane and the posterior PAR complex (pPARs) in the cytoplasm (Figure 1A). This symmetry is mechanically broken when a sperm-derived factor that locally modulates Rho activity causes the actomyosin cortex to weaken in the posterior [18,19]. The resulting gradient in myosin activity leads to a large-scale cortical flow towards the anterior [20] (Figure 1B). This flow advects membrane-associated aPARs towards the anterior [9], which allows cytoplasmic pPARs to bind to the membrane in the posterior half of the embryo and eventually results in two membrane domains partitioning the long axis of the embryo (Figure 1C). In parallel to the mechanical events at the membrane, symmetry is broken chemically when microtubules emanating from the sperm-donated centrosome protect pPARs from phosphorylation by aPARs [21]. The end-result is a polarized steady state with aPARs enriching the anterior membrane and cytoplasm, and pPARs the posterior [22,23].

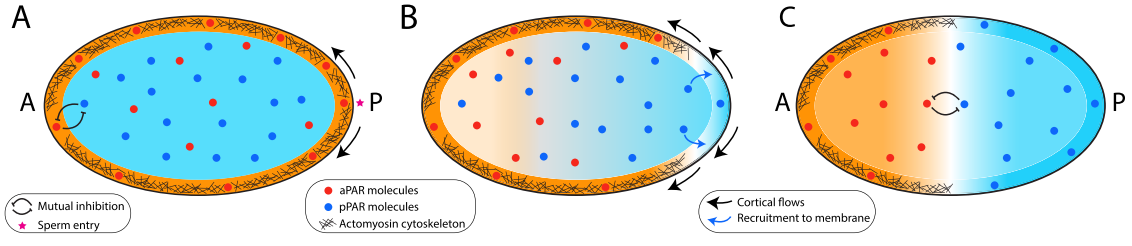
In the absence of external symmetry breaking, the PAR system is a chemical pattern-forming system where mutual antagonism between the PAR complexes results in local self-amplification, i.e. inhibition of pPARs by aPARs allows more aPARs to be recruited and vice versa. To prevent indefinite growth of either domain, long-range inhibition is required. In *C. elegans* 1-cell embryos, this is provided by limited pools of PAR proteins, where expansion of a membrane domain results in depletion of its own components in the cytoplasm restricting further growth [9]. This chemical pattern formation of the PAR proteins appears to be intricately coupled to the mechanical and chemical symmetry breaking events described above, ensuring robust polarization along the long axis of the embryo. However, the full extent of mechanochemical feedback is not well understood and it is likely that it provides robustness and speed to the formation of polarity domains.

Tissue-scale mechanical coupling in the irreversible deformation of epithelia during *Drosophila* gastrulation

Shaping a tissue requires mechanical processes that stretch, compress, fold or rotate groups of cells in a coordinated fashion. Illustrative of this is mechanical coupling during apical constriction of cells in epithelial tissues. Apical constriction functions in diverse physiological contexts [24] and usually involves intracellular pulsatile actomyosin flows, where the pulsatility emerges through self-organization of the actomyosin cytoskeleton [25*,26*]. Since the actomyosin cortex is linked to the membrane and the adherens junctions [27], pulsatile flows and force generation leads to concomitant cell contraction and relaxation (Figure 2A, 1–4). To constrict effectively and prevent the cell from reverting back to its original shape, contracted cell shapes are stabilized through a ratchet mechanism that generates persistent actomyosin network structures in the apical cortex [24] (Figure 2A, 5).

Recent work hints that the ratchet mechanism not only aids in periodic constriction at a cellular level but also enables tissue-scale constriction through mechanical coupling [28]**. Xie *et al.* observed that ventral surface cells in the *Drosophila* embryo transition from an unratcheting to a ratcheting behaviour similar to the transition during dorsal closure [29]. Importantly, increased contractile pulses were observed in cells surrounding a cell undergoing a ratcheted pulse (Figure 2B), implying a feedback mechanism that communicates changes in intracellular dynamics to neighbours. It is likely that an increase in apical myosin during a ratcheted pulse increases tension, which could mechanically activate neighbouring cells. Adherens junctions play a vital role in this coupling [27,30] not only by passively linking actomyosin cortices of neighbouring cells, but also by recruiting several actin regulatory proteins that locally reorganize the cortex [27]. In turn, the cortex feeds back by facilitating clustering of junctional proteins and strengthening adhesion [31,32].

Figure 1



Polarization of the nematode zygote into anterior and posterior domains. (A) Stable homogeneous state of *C. elegans* 1-cell embryo with anterior (A) PAR proteins (aPARs – orange band and circles) enriched in the membrane adjacent to the contractile actomyosin cortex (black sticks) and posterior (P) PAR proteins (pPARs – blue field and circles) in the cytoplasm. Sperm entry (pink star) in the posterior breaks the symmetry and triggers anterior-directed actomyosin flows. The two PAR complexes are mutually antagonistic in nature (shown with inhibitory arrows). **(B)** Cortical flows advect aPARs to the anterior, allowing pPARs to associate with the posterior membrane. **(C)** The end result is a stable, polarized steady-state with two membrane domains maintained by the mutual antagonism of the pPARs and aPARs.