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DEVELOPMENT AT A GLANCE

# Actomyosin networks and tissue morphogenesis

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## ABSTRACT

Tissue morphogenesis is driven by coordinated cellular deformations. Recent studies have shown that these changes in cell shape are powered by intracellular contractile networks comprising actin filaments, actin cross-linkers and myosin motors. The subcellular forces generated by such actomyosin networks are precisely regulated and are transmitted to the cell cortex of adjacent cells and to the extracellular environment by adhesive clusters comprising cadherins or integrins. Here, and in the accompanying poster, we provide an overview of the mechanics, principles and regulation of actomyosin-driven cellular tension driving tissue morphogenesis.


**KEY WORDS: Adhesion, Contractility, Mechanics, Morphogenesis, Myosin**

## Introduction

Tissue morphogenesis drives several developmental processes in plants and animals and is required for the basic organization of embryos and organs. A developing tissue can undergo a diverse set of changes, such as bending, lengthening, narrowing, branching and folding, and during these processes it faces a number of challenges. For example, how do cells in a tissue sort to form embryonic structures containing different cell types? How do forces direct cell movements within a tissue? How does the position of a cell in a tissue affect its fate?

The seminal publication by D'Arcy Thompson, '*On growth and form*' (Thompson, 1917), was a pioneering attempt to explain some of these questions about developmental processes using simple mathematical and physical formulations. Subsequent studies emphasized the fluid properties of tissues. This led to one of the most prevalent hypotheses in the field, the differential adhesion hypothesis (DAH), which explained the sorting behavior of cells by attributing interfacial surface tension to the disparate adhesiveness of cells in the tissue (Steinberg, 1963). This hypothesis was tested in cell culture (Foty et al., 1994) and later on *in vivo* (Hayashi and Carthew, 2004). The DAH has since been a prevailing hypothesis in the field (Takeichi, 1991).

However, around 30 years ago, mechanical models of morphogenesis began to emerge and led to a more general

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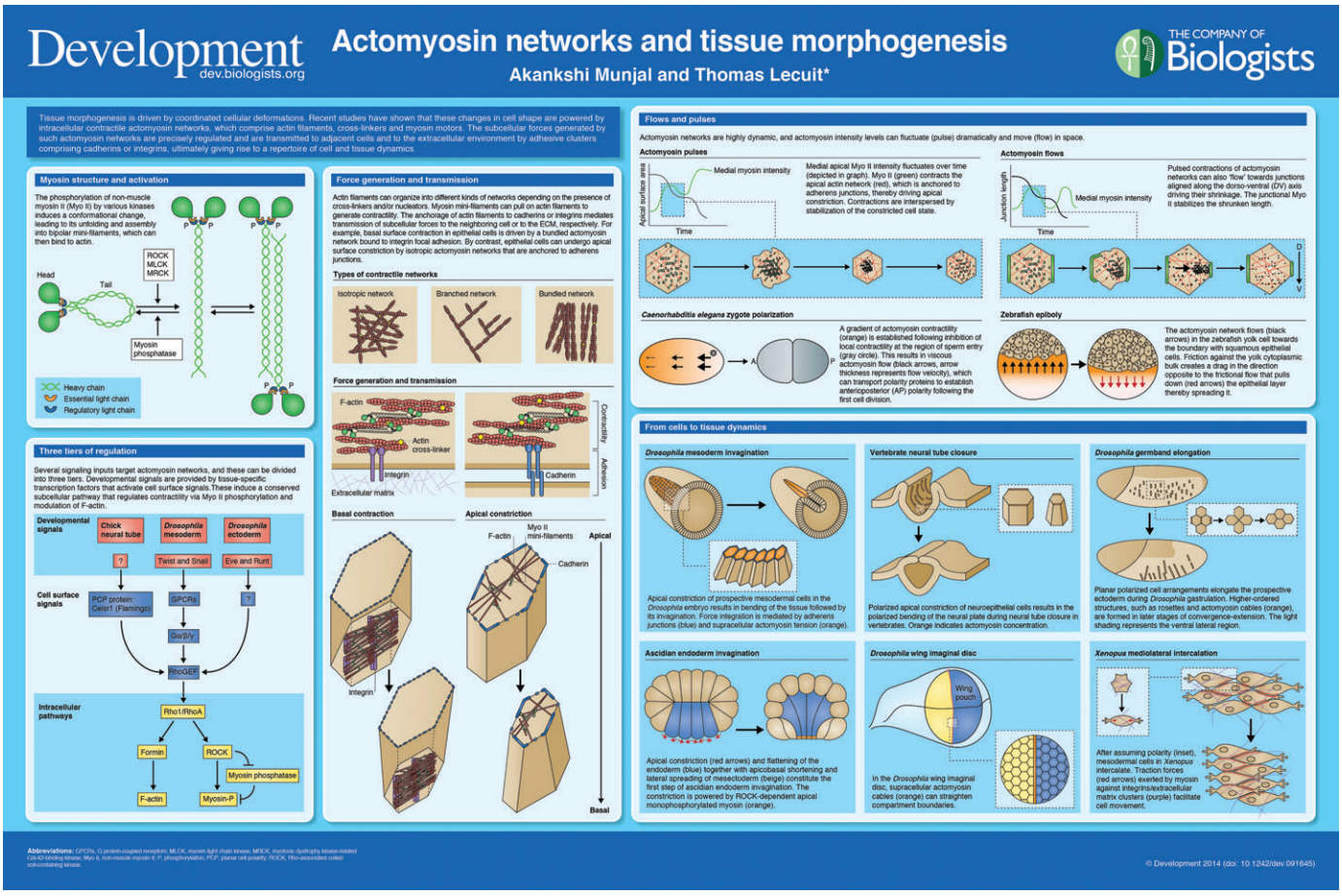

Development (2014) 141, 1789-1793 doi:10.1242/dev.091645

framework for complex tissue deformations based on the existence of active contractile networks and the viscoelastic response of cells to such tensile systems (Odell et al., 1980). Since then, molecular motors were discovered and the complex regulation of actin networks was deciphered, thereby providing a biochemical basis for understanding cell mechanics and morphogenesis. Cells have an inhomogeneous cytoplasm and a dynamic plasma membrane that interacts with the underlying cytoskeleton (Goswami et al., 2008). As a consequence, the cell behaviors that drive morphogenesis cannot simply stem from adhesion alone but must also depend on active cytoskeletal elements, mainly actin filaments and myosin motors (Koenderink et al., 2009). The actin filaments alone can impart rigidity to the plasma membrane, whereas active contractile tension (also called contractility) is generated by myosin motors that use ATP hydrolysis to pull on the actin filaments (reviewed by Wozniak and Chen, 2009).

A number of recent studies have documented that tight control over such actomyosin-based networks can give rise to the interfacial tension that was classically known or hypothesized to reflect differential adhesiveness (reviewed by Lecuit and Lenne, 2007). For example, recent studies have demonstrated the role of cortical tension, in addition to adhesion, in driving progenitor cell sorting in zebrafish embryos (Krieg et al., 2008). Indeed, studies of several organisms over the past 10 years have shown that tissue dynamics require active contributions from actomyosin networks that change cell shape and cell contacts. Furthermore, advances in live-imaging and quantitative analysis have emphasized the role of actomyosin-based cellular contractility in conferring the plasticity needed to remodel all tissues. Here, we provide an overview of the conserved components and principles of actomyosin-driven cellular contractility during tissue morphogenesis.

## The nuts and bolts of cell mechanics: myosin motors, actin networks and adhesion molecules

Myosins are motor proteins that hydrolyze ATP to move along actin filaments. The myosin superfamily is a diverse family of proteins, each containing a conserved head domain and a divergent tail domain harboring properties that are unique to each family member. The features that are important for force production, i.e. the actin-binding sites and the ATP-hydrolysis sites, are conserved in the head domain. Although most myosins are monomeric, members of the myosin II sub-class form hexamers consisting of two heavy chains, two essential light chains (ELCs) and two regulatory light chains (RLCs) (Hartman and Spudich, 2012). The heavy chain folds into an N-terminal globular head that mediates motor activity. The C-terminal part of the heavy chain folds into an alpha helical coiled-coiled tail domain that is required for the formation of tail-to-tail homodimers (Niederman and Pollard, 1975). Monomeric myosin II is poorly processive and exhibits little activity, but once assembled into bipolar filaments made from several homodimers it can act as a processive motor complex that pulls on flexible actin filaments. Although studied extensively in the context of muscle cells, myosin II is also found in non-muscle cells, and recent studies have shown that non-muscle myosin-II performs a number of functions, such as generating cortical tension, mediating cytokinesis and, most importantly, mediating cell shape changes during development. Unlike muscle myosin II, non-muscle myosin II (referred to hereafter simply as Myo II) can undergo dynamic assembly and disassembly, allowing its spatial and temporal regulation (reviewed by Tan et al., 1992).

The assembly and activity of Myo II filaments is regulated by dynamic phosphorylation and dephosphorylation. The phosphorylation of Myo II at highly conserved residues (T18 and S19 in mammals, T20 and S21 in *Drosophila*) within the RLC is the primary mechanism for Myo II activation. *In vitro* experiments suggest that phosphorylation induces changes in the head and tail, resulting in mini-filament assembly via tail-tail interaction, actin-binding via exposure of the head, and an increase in actin-activated ATPase activity (Craig et al., 1983). A large number of kinases, such as ROCK (Rho-associated coiled coil-containing kinase, activated by RhoA), MRCK (myotonic dystrophy kinase-related Cdc42-binding kinase, activated by Cdc42) and MLCK (myosin light chain kinase, activated by $Ca^{2+}$), operate in diverse regulatory pathways to target these residues and modulate Myo II activity (Matsumura, 2005). Recent studies have also highlighted the role of phosphatases in regulating Myo II activity. The activity of phosphatases can be regulated by phosphorylation through kinases, such as ROCK, rendering them inactive (Kimura et al., 1996). For instance, Myo II activity is increased in collective cell migration during *Drosophila* oogenesis by PAR1 kinase-mediated myosin phosphatase inhibition (Majumder et al., 2012).

The mechanical properties of actomyosin networks are also dependent on the organization of actin filaments (e.g. branched versus unbranched filaments, density of filaments). The dynamics of cellular behaviors that drive morphogenesis are crucially dependent on such mechanical properties (reviewed by Levayer and Lecuit, 2012). For instance, in order to resist compression or stretch, a network needs to be stiff. Actin filaments in a loose network, by contrast, can be pulled and reorganized. The forces generated by such networks, however, cannot result in any cellular behaviors, such as migration or cell deformation, unless they are coupled to the plasma membrane or the extracellular matrix (ECM) via adhesion complexes. This anchorage is crucial not only for force transmission but also for force integration between many cells in a tissue. There are two important classes of adhesion molecules. The first comprises cadherins, which mediate intercellular adhesion. In many epithelial tissues, the contractile machinery shrinks the apical surface of the cells and transmits forces through a cadherin-containing adherens junction belt, thereby bending the whole tissue (Sawyer et al., 2010). The second class of adhesion molecules comprises integrins, which mediate anchorage of the cell surface to the ECM. Such coupling with the ECM not only provides a substrate for tissue migration, but can also lead to active remodeling of the ECM during many morphogenetic processes (He et al., 2010; Haigo and Bilder, 2011).

The total mechanical tension in the cellular cortex thus comprises contributions from active stresses (the contractility generated by the actomyosin network), elastic stresses that depend on the organization of the actin network and hence the extent of network deformation, and viscous stresses that are proportional to the rate of network deformation. The emergence of contractility in actomyosin networks requires motor-dependent filament buckling and the presence of actin cross-linkers that dynamically stabilize actomyosin networks under stress (Gardel et al., 2004). Finally, the forces generated by such networks are transmitted to the plasma membrane or the ECM via adhesion complexes, giving rise to a repertoire of cellular morphogenetic outcomes, such as migration, cell shape changes and cell contact remodeling.

## The waves and tides of cellular morphogenesis

Live imaging of actomyosin networks and membrane markers has revealed an unexpectedly high degree of network dynamics during cellular morphogenesis. Although the actomyosin intensity levels are sometimes steady, for example during cytokinesis, there exist other situations in which they fluctuate dramatically over a few tens

Development (2014) 141, 1789-1793 doi:10.1242/dev.091645

of seconds (Martin et al., 2009). These fluctuations are characterized by cycles of recruitment of Myo II and its coalescence to form bigger aggregates, causing spatial deformation, followed by disassembly. These pulsed contractions of actomyosin networks are conserved across species and, depending on the context, can result in completely different outcomes at the cellular level. For instance, the Myo II contractions in the medial apical plane of the *Drosophila* mesoderm correlate with constriction of the apical cell surface (Martin et al., 2009). Similar pulses were reported in the nematode endoderm (Roh-Johnson et al., 2012). Myo II pulses in the *Drosophila* ectoderm control steps of junction shrinkage (Rauzi et al., 2010), which facilitates cell intercalation thereby extending the tissue. Deformations caused by the pulsatile activity of Myo II are often interspersed with stabilization phases to create a step-wise unidirectional process that allows irreversible shape changes, a phenomenon analogous to a mechanical ratchet (reviewed by Mason and Martin, 2011). However, what regulates Myo II spatially and temporally to generate these pulsed contractions during morphogenesis still remains unclear. It is possible that the localization, amplitude and frequency of the pulses are under the control of separate regulatory mechanisms, each controlling the type, range and speed of deformation, respectively.

Another striking behavior displayed by actomyosin networks is their tendency to 'flow' in space. Flows are generated by gradients of contractility (Munro et al., 2004; Mayer et al., 2010) or asymmetric mechanical coupling to E-cadherin clusters (Levayer and Lecuit, 2013). In the *Drosophila* germband, for example, Myo II pulses are preferentially directed towards dorsoventral oriented junctions to selectively shrink them (Rauzi et al., 2010), This is in contrast to pulses in the mesoderm, which do not flow and thereby mediate shrinking of the whole apical surface (Martin et al., 2009). Myo II flows can also be non-pulsatile, as described in the yolk cell of zebrafish embryos during epiboly, a characteristic cell movement that involves the thinning and spreading of an epithelial cell sheet to enclose the embryo during early gastrulation. During this process, the squamous epithelial cell layer at the surface of the embryo is pulled over the underlying yolk cell by a frictional flow generated by the contractile actomyosin ring (Behrndt et al., 2012).

## Spatial control of actomyosin networks by signaling pathways

In a framework in which the local modulation of actomyosin network contraction can emerge into varied cell behaviors and tissue outcomes, spatial and temporal regulation is essential. Contractility is indeed regulated at both cellular and tissue levels by diverse sets of signaling pathways that are conserved across species. We can delineate three tiers in the regulation of actomyosin contractility. First, a conserved subcellular pathway is responsible for regulating Myo II phosphorylation and dephosphorylation. It involves activation by RhoGEFs of the small GTPase Rho1, which in turn activates ROCK as well as formin and formin-related proteins, such as Daam proteins (Nishimura et al., 2012), and inactivates myosin phosphatase (reviewed by Kaibuchi et al., 1999). The actin-binding protein Shroom binds ROCK and is also required for ROCK and Myo II distribution (Nishimura and Takeichi, 2008; Simões Sde et al., 2014). Second, this core subcellular pathway is activated by membrane signaling modules such as those involving the core planar cell polarity protein Celsr1 in the vertebrate neural tube and G protein-coupled receptor (GPCR) signaling in *Drosophila* embryos (Manning et al., 2013). Finally, membrane signaling can be induced by unknown developmental signals downstream of tissue-specific transcription factors. For instance, in the *Drosophila* mesoderm, the apical localization of Myo II activity is regulated by the mesoderm-specific transcription factors Twist and Snail. Twist and Snail activate the expression of an extracellular ligand named Fog that, through an unknown GPCR and a transmembrane protein called T48, leads to the recruitment of RhoGEF2 and activation of Myo II contractility via ROCK (Rok – FlyBase) (Dawes-Hoang et al., 2005).

In some cases, the regulation of Myo II by phosphorylation can be specific such that mono- and bi-phosphorylated Myo II serve distinct functions, as seen in the case of endoderm invagination in ascidians (Sherrard et al., 2010). In this case, the invagination of the endoderm is initiated by apical constriction followed by apicobasal shortening. Whereas apical constriction relies on apical recruitment of ROCK-dependent monophosphorylated Myo II, apicobasal shortening is driven by ROCK-independent basolateral enrichment of monophosphorylated Myo II and ROCK-dependent apical enrichment of bi-phosphorylated Myo II to prevent apical expansion and to mediate deep invagination (Sherrard et al., 2010).

Myo II and its upstream regulators can also be planar polarized in certain developmental processes, such as convergence-extension (CE), which involves first narrowing and then lengthening of the tissue. In the *Drosophila* epithelial ectoderm, for example, the planar polarized distribution of Myo II and its kinase ROCK is under the control of the pair-rule genes *even skipped* and *runt*, which play a primary role in segmenting the *Drosophila* embryo (Bertet et al., 2004; Zallen and Wieschaus, 2004; Simões Sde et al., 2010). The asymmetric enrichment of Myo II at epithelial junctions aligned along the dorsoventral axis and the planar polarized flows of Myo II towards these junctions (Rauzi et al., 2010) result in their shrinkage followed by intercalation and thereby tissue extension. In non-epithelial cells, such as in the *Xenopus* mesoderm, cell intercalation requires planar polarized traction forces exerted by Myo IIB-dependent cortical tension against integrins and ECM clusters (Skoglund et al., 2008) as well as planar polarized interfacial actomyosin tension very similar to that observed in the *Drosophila* germband (Shindo and Wallingford, 2014). The pathway that establishes the planar cell polarity of actomyosin filaments in the neural plate of chicken embryos has also recently been delineated (Nishimura et al., 2012). During neurulation, the neural plate bends, closes and forms a neural tube. This process requires both CE and apical constriction. Nishimura and colleagues showed that planar polarized actomyosin filaments controlled by the polarity protein Celsr1 and its downstream effectors PDZ-RhoGEF and ROCK bring about anisotropic contraction of apical surface to induce the convergence of neuroepithelial cells towards the neural plate midline, resulting in shrinkage and bending of the plate in the mediolateral axis. The planar cell polarity pathway (Frizzled and Dishevelled) is also required for planar actomyosin distribution in *Xenopus* (Shindo and Wallingford, 2014).

Thus, several signaling inputs during morphogenesis target Myo II phosphorylation and actin regulation, which then converts them to a mechanical contractile output.

## Coordinating contractility in a tissue

The existence of subcellular forces generated by actomyosin networks and their transmission at cell contacts by adhesive systems begs the question of whether cells coordinate their local mechanics to yield tissue level deformations. Coordinated cell shape changes require interactions between cells through cell-cell adherens junctions that transmit subcellular tensions (Martin et al., 2010). In addition, supracellular actomyosin cables have

Development (2014) 141, 1789-1793 doi:10.1242/dev.091645

been reported in diverse morphogenetic processes and contexts, such as at compartment boundaries, in tissue wound healing, and during developmental closure events, such as dorsal closure and epiboly (Landsberg et al., 2009; Solon et al., 2009; Behrndt et al., 2012). It is possible that such cables are part of a tissue level network that coordinates contractility across cells. To what extent such tissue level actomyosin networks result from local biochemical control of Myo II by signaling pathways or mechanical coupling between cells is unclear.

Recent studies suggest that the partitioning of tissues into compartments to prevent intermixing of cells does indeed require the formation of large-scale actomyosin networks. As an alternative to the DAH described above, another hypothesis called the 'fence model' attributes compartmentalization to the formation of stiff mechanical barriers that prevent crossing of cells across boundaries (Major and Irvine, 2006). One of the oldest examples of compartment boundaries is in the *Drosophila* wing imaginal disc (the sac of epithelial cells from which the adult wing is formed). Although there is no detectable E-cadherin increase at compartment boundaries, F-actin and Myo II accumulate there, control the local increase in intercellular tension, and prevent cell mixing between compartments (Major and Irvine, 2006). A similar situation was reported in *Drosophila* embryonic segmental boundaries (Monier et al., 2010). Mechanical coupling of cell contractility through formation of supracellular actomyosin cables has also been observed in other developmental contexts. Contractile cables are observed in the intercalating cells of *Drosophila* ectoderm and are suggested to sustain mechanical tension as well as to recruit more Myo II (Fernandez-Gonzalez et al., 2009). Actomyosin cables are also observed at the margins of wounded epithelial sheets or during the pulling of a tissue over another layer. For example, during dorsal closure in *Drosophila*, two sheets of lateral epidermis close over the underlying amnioserosa to form a continuous epidermis. This process is facilitated by actomyosin-driven shape oscillations of amnioserosal cells and supracellular actomyosin cables at the margins of the lateral epidermis (Hutson et al., 2003; Lecuit and Lenne, 2007; Solon et al., 2009).

Myosins have also been implicated in complex morphogenetic processes during organogenesis, such as gut looping (Hozumi et al., 2006) and genitalia rotation (Speder et al., 2006; Petzoldt et al., 2012), both of which require chiral cell behaviors. In the case of *Drosophila*, these processes were shown to depend on type I myosins; however, it remains unclear how tissue-level left-right asymmetric behaviors emerge from the mechanical properties of these motors.

## Conclusion

Although early studies focused on the role of adhesion to explain the repertoire of behaviors observed during morphogenesis, recent advances in light microscopy and quantitative measurements of mechanical perturbations have shed light on the equal importance of the actomyosin force-generating machinery. The elements of this machinery can give rise to fascinating emerging behaviors. This makes the network a highly adaptable biomechanical system that can adjust to external and internal stresses and subtle changes without involving complex genetic circuits. The mechanisms that give rise to the emergent properties of these networks, such as pulsatility and the stabilization of the deformations, however, still remain to be unfurled.

Besides driving changes through force production, actomyosin networks orchestrate intrinsic forces to coordinate tissue movements and shape changes. This coordination is crucial for integrating incoherent or stochastic local deformations into ordered global changes, although the underlying biomechanical signals are still poorly understood. Such fundamental questions can be addressed in the future using a combination of theoretical modeling, measurements from tissue-scale mechanical perturbations, and local modulation of biochemical signals.

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#### Development at a Glance

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Development (2014) 141, 1789-1793 doi:10.1242/dev.091645

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