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Alignment of cytoskeletal structures across cell boundaries generates tissue cohesion during organ formation

Yara E Sánchez-Corrales and Katja Röper

One of the most fascinating aspects of development is the complexity and diversity of tissues and organs that are formed from simple primordia, involving complex coordination between large groups of cells. Lack of coordination leads to developmental defects and failure in organ formation.The simple primordia are often polarised epithelial sheets, with cells connected to neighbours apically via Cadherin-based cell–cell junctions that intracellularly link to the cytoskeleton. Coordination of cells in epithelia during morphogenesis occurs in part at these junctions. Furthermore, in many tissues a striking supracellular order and alignment of cytoskeletal structures can be observed, likely playing an important part in the coordination of cells.Here, we will introduce examples of morphogenetic events where this supracellular order of the cytoskeleton is very apparent and will discuss recent advances in understanding the generation and function of this order.

Address
MRC-Laboratory of Molecular Biology, Cambridge Biomedical Campus, Francis Crick Avenue, Cambridge CB2 0QH, UK

Corresponding author: Röper, Katja (kroeper@mrc-lmb.cam.ac.uk)

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Introduction

A key aspect of morphogenesis is the directed modulation of cell shape. Within an epithelial tissue that maintains its integrity during organ formation coordination of cell shape changes is critical. If coordination fails, an imbalance of mechanical forces can lead to loss of epithelial integrity and tissue rupture or such imbalance can lead to stalling of morphogenesis.

The main factor determining cell shape and changes to shape is the actomyosin cytoskeleton that is both able to exert force [1] as well as respond to forces applied to it [2]. Actomyosin networks within cells tend to be closely associated with the plasma membrane, and in epithelial cells actomyosin is highly concentrated near the apical pole of the cells. A junctional pool is directly connected to adherens junctions, and in many cells a second pool of apical–medial actomyosin can be found just underlying the free apical membrane (Figure 1). A less prominent actomyosin cortex is associated with the plasma membrane, and basally actin also links to cell–matrix junctions [3].

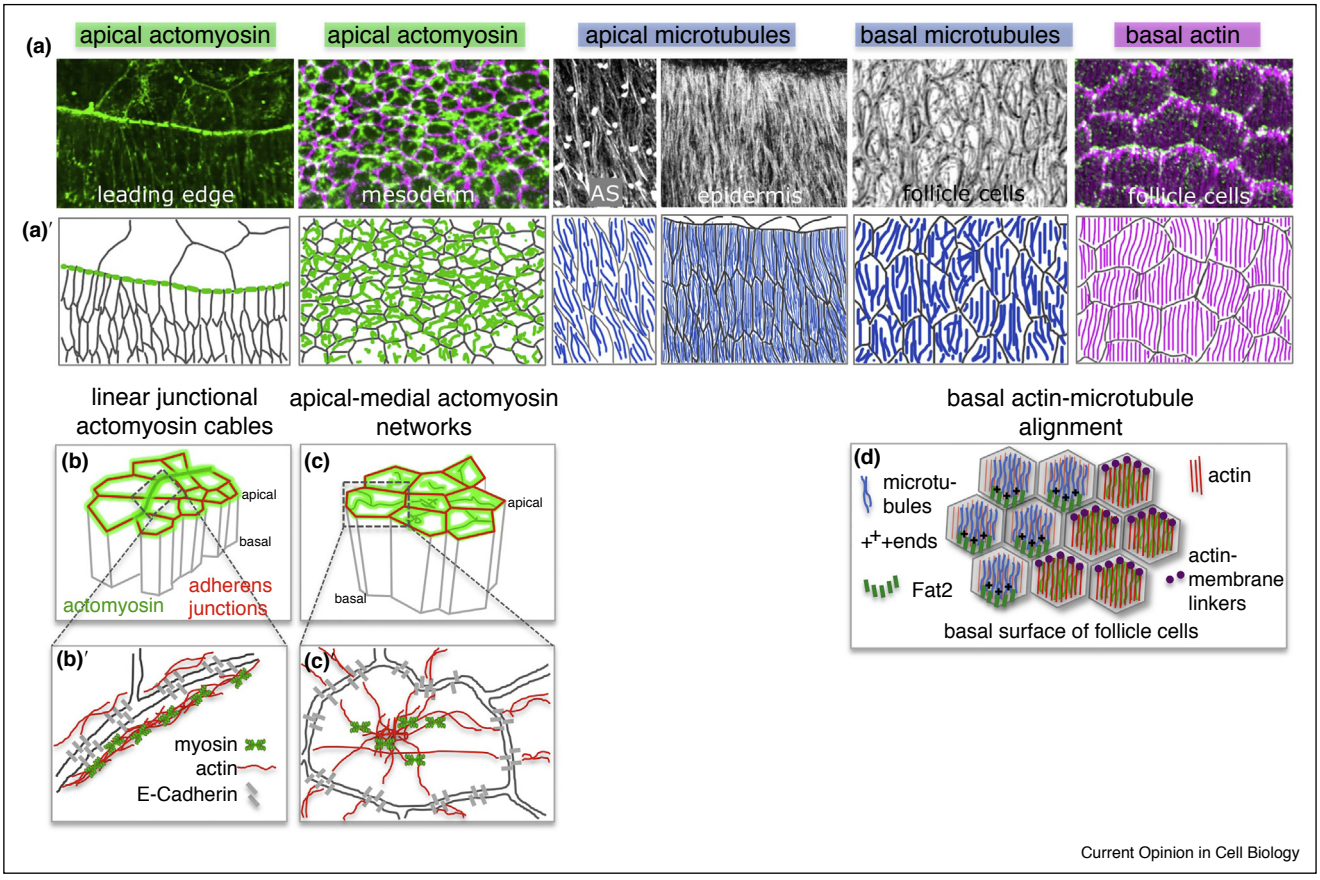
Over the last 15 years it has become apparent that in many cases of morphogenesis and organ formation, actomyosin becomes organised and often polarised in a way that appears to transcend cell boundaries. For instance junctional actomyosin can align between neighbouring cells to form so-called actomyosin cables, and these can stretch across a few, but also up to tens of, cell diameters [4]. Similarly, apical–medial actomyosin in certain tissues can form a complex interlinked network that both visually and functionally appears to cross cell boundaries. In both cases of course, in order to allow coordination of the actomyosin between neighbouring cells, the actomyosin is closely linked to specific cell–cell junctions at which the cell-to-cell communication of activity and forces occurs.

Cytoskeletal coordination across cells is not restricted to actomyosin. In various morphogenetic processes microtubules become aligned between neighbouring epithelial cells, usually within the plane of the epithelium. Again, such coordination requires an upstream signal that is usually associated with cell–cell junctions.

Cytoskeletal regulation and coordination is closely linked to tissue differentiation. In many cases studied, a differentiation cascade often starting from a homeotic transcription factor at the top will lead to specification of a fate for a group of cells. In many cases of epithelial morphogenesis these specified cells will then increase expression of certain cytoskeletal components and regulators to prepare the tissue for events to come [5].

In this review, we will discuss examples of both types of cytoskeletal coordination and alignment, with a focus on recent insights into their generation, maintenance and function and open questions in the field.

Figure 1



Examples of tissue-level cytoskeletal coordination or alignment. **(a,a')** Apical actomyosin can be found in linear actomyosin cables (a,a') such as at the leading edge of the epidermis in dorsal closure, or in interlinked apical–medial actomyosin networks **(b,b')** such as during mesoderm invagination [30]. Highly aligned apical microtubules are present during amnioserosa stretching during axis extension **(c,c')** [48] and also in the epidermal cells at a later stage during dorsal closure **(d,d')** [17]. Follicle cells show striking alignment of both basal microtubules **(e,e')** as well as basal actin fibres **(f,f')** [49,50]. Myosin II is green in (a) and (b), cell junctions are magenta in (b), microtubule labelling is shown in (c)–(e), and actin is shown in magenta in (f) and an actin-membrane linker in green in (f). (b–c') Illustration of the localisation and junctional connectivity of linear actomyosin cables (b,b') as well as apical–medial actomyosin networks (c,c'). (d) Organisation and alignment of actin and microtubules at eh basal surface of the somatic follicle cells in the fly ovary. Microtubules depend on the atypical Cadherin Fat2 for their vectorial and aligned polarisation. Aligned and polarised actin drives the chiral rotation of the edgeless epithelial sheet surrounding each egg chamber (see Figure 2).

Tissue-level cytoskeletal coordination of actomyosin: linear cables

Supracellular alignment of actomyosin was first noticed during embryonic wound healing. Upon wounding, actin and myosin concentrate at the wound margin and retain this localisation dynamically whilst the wound itself is closing, which led to the proposition of a purse-string mechanism of wound closure [6]. This 'purse-string' wound healing is common to both vertebrate and invertebrate embryos [7]. The purse-string could ensure a coordinated closure of the wound by drawing in surrounding epidermal cells in equal measure. Recent studies have revealed that the wound cable is still dynamic but that turn-over decreases with concomitant increase in tension during closure [8]. Also, recent data challenge the notion of a uniformly contractile 'purse-string' driving would closure, as the actomyosin within the cables was found to be heterogeneous and not always continuous. Experimental evidence and modeling suggest that actomyosin-rich segments close faster, in particular when neighboured by segments of the cable with lower levels of actomyosin. The heterogeneity might thus facilitate would closure by reducing local resistance to contraction of individual wound edge cable segments [9••].

But actomyosin cables are not restricted to wound healing, they were soon appreciated as a common feature of developmental processes. All early examples of actomyosin cables functioning during morphogenesis come from studies in *Drosophila*. The first actomyosin cable to be observed in the fly embryo was the prominent cable forming during the process of dorsal closure, where the