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Cell adhesion and mechanics as drivers of tissue organization and differentiation: local cues for large scale organization

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Biological patterns emerge through specialization of genetically identical cells to take up distinct fates according to their position within the organism. How initial symmetry is broken to give rise to these patterns remains an intriguing open question. Several theories of patterning have been proposed, most prominently Turing's reaction–diffusion model of a slowly diffusing activator and a fast diffusing inhibitor generating periodic patterns. Although these reaction–diffusion systems can generate diverse patterns, it is becoming increasingly evident that cell shape and tension anisotropies, mediated via cell–cell and/or cell–matrix contacts, also facilitate symmetry breaking and subsequent self-organized tissue patterning. This review will highlight recent studies that implicate local changes in adhesion and/or tension as key drivers of cell rearrangements. We will also discuss recent studies on the role of cadherin and integrin adhesive receptors in mediating and responding to local tissue tension asymmetries to coordinate cell fate, position and behavior essential for tissue self-organization and maintenance.

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Introduction

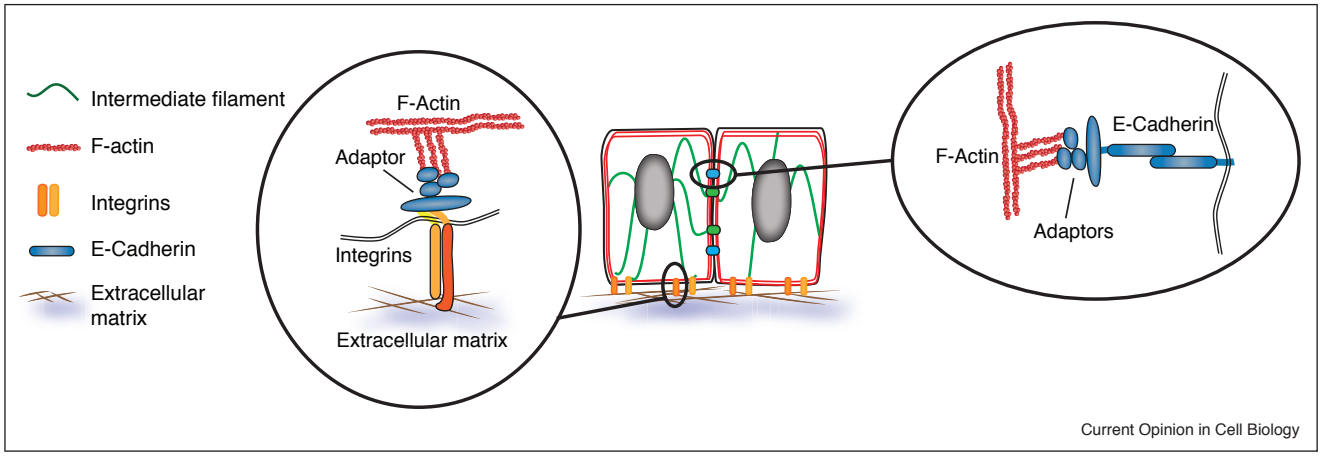
Tissues are formed and maintained in an extremely stereotypic manner. This reproducible patterning necessitates integration of signals that determine cell fate with adhesive and cytoskeletal cues that control cell shape and cellular rearrangements. These shape changes and rearrangements require tightly controlled force generation that occurs through coordinated engagement of the contractile actomyosin cytoskeleton with integrin and cadherin adhesive complexes. Cadherin-dependent intercellular junctions link intercellular adhesion to the organization of the cortical actomyosin cytoskeleton as well as provide landmarks that spatially orchestrate signaling [1,2], thus allowing cells to coordinate their behavior across the tissue [3] (Figure 1). Like cell–cell adhesions, integrin-dependent cell–extracellular matrix (ECM) adhesions link to and regulate actomyosin organization and contractility [4]. What distinguishes integrin adhesions from other adhesive complexes is their ability to bind and dynamically remodel the ECM into a precise configuration (Figure 1). The ECM provides cells with positional and structural information of the surrounding tissues as well as binds and regulates the availability and activation of growth factors, thus acting as a topographical cue and signaling platform [5].

These cell–cell and cell–matrix adhesion receptors can thus recognize and mechanically respond to local changes in their microenvironment. However, how forces generated by adhesion and the cytoskeleton integrate cell fate with the positioning of cells within tissues is less clear. The recent evolution in technology and methods to quantify and experimentally manipulate adhesive and mechanical properties of cells and tissues has revolutionized the field, thus allowing more direct probing of this question. The role of cadherins, integrins and actomyosin in mechanotransduction and tissue morphogenesis has been extensively reviewed, for example in [6–8]. Instead, this review will focus on highlighting recent data on the adhesive and force transduction mechanisms that control cell fate and/or shape to break cellular symmetry within multicellular assemblies, which then drives tissue self-organization.

Triggers of cell shape and force anisotropies

Tissue self-organization and patterning requires the coordinated positioning of cells to couple function with tissue architecture. It is well established that signaling has a key

Figure 1



Cell–cell and cell–matrix adhesions are linked to the contractile actomyosin cytoskeleton. Classical cadherin receptors mediate adhesive binding to cadherins presented on the surfaces of neighboring cells to promote cell–cell adhesion. Integrins bind to extracellular matrix proteins to mediate cell–matrix adhesion. Both adhesive systems mechanically couple to the actomyosin cytoskeleton through cytoplasmic multi-adaptor complexes and regulate its organization and contractility.

instructive role in patterning with several models, especially Turing's reaction-diffusion model [9], explaining how these signaling systems generate periodic patterns. Recent studies have begun to unravel a critical role for cell shape and tension anisotropies in symmetry breaking to generate and shape signaling gradients and promote the self-organization of tissue patterns [10,11].

Adhesion in forming and maintaining boundaries

Cell sorting is a process in which two or more populations of cells self-organize to create fate boundaries and spatially defined structures [12] (Figure 2a). In principle, the outcome of cell sorting can be predicted using models that consider cell-specific differences in interfacial energies, resulting in a configuration that maximizes the most energetically favorable cell interfaces [13]. Historically, this disparity in interfacial energy was considered to be driven by differences in adhesive specificity and/or strength (differential adhesion hypothesis, DAH) with cadherins as best examples [13]. Later work indicated that sorting was primarily driven through differential cortical tension properties of the two populations (differential interfacial tension hypothesis, DITH) [14,15], with adhesive receptors required to couple tensile forces to the cell membrane [16]. In both cases, the action of so-called repulsive signals, for example of Eph–Ephrin receptors, at heterotypic junctions (defined as between two different cell types [12]) was ignored. In contrast, the Fagotto group recently identified a major role for Eph–Ephrin signaling in establishing high heterotypic interface tension (HIT) that drives the separation of Xenopus ectoderm from mesoderm with little to no role for differential adhesion or cortical tension [17••]. These authors then proposed a unifying model in which the rapid and stable formation of sharp tissue boundaries, for example Xenopus ectoderm–mesoderm boundary, is highly dependent on HIT, whereas DAH and/or DITH are likely more important for situations in which cells sort out during active cell rearrangements, for example during convergence extension movements.

Local differences in matrix composition, resulting in a selective ability of different cell populations to adhere to this matrix, can also provide a dominant cell sorting cue. Such a binary interaction signal of presence or absence of cell–matrix contact may robustly buffer the more dynamic rearrangements and spectrum of interaction energies of individual cell–cell interactions. This concept was recently directly explored using the self-organizing capacity of mammary or prostate gland primary epithelial cell aggregates that consist of two different populations. By combining mathematical modelling and knockdown of key adhesion proteins these authors found that only one cell type was able to interact with and spread on the ECM tissue boundary. This binary interaction was essential for cell positioning and gland self-organization, and robustly buffered alterations in key cell–cell adhesion molecules [18]. The principle of a binary instructive cue deriving from basement membrane adhesion triggering self-organization is further beautifully demonstrated in studies of early mammalian development. During the first stages of post-implantation morphogenesis, the pluripotent epiblast that later gives rise to all tissues becomes organized into a rosette-like structure of highly polarized cells and a central lumen is then formed through hollowing of the apical membranes of these polarized cells. This symmetry breaking is orchestrated by polarization cues from the basement membrane and transmitted through β1-integrin receptors [19] in a manner similar to MDCK cyst morphogenesis [20]. Interestingly, studies on