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Connecting polarized cytokinesis to epithelial architecture

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Epithelial cells are organized into polarized sheets that separate distinct compartments of multicellular organisms. Within the epithelial tissue, cells are held together by a set of polarized junctional complexes that regulate adhesion and also separate functionally distinct apical and basolateral membranes. Despite a solid understanding of the establishment of apico–basal polarity and of the remodeling of cell–cell contacts during morphogenesis (reviewed in ref. 1), the interplay between polarized adhesion and epithelial cell division is relatively unexplored. In a recent study, we examined this process using live imaging of the *Drosophila* follicle epithelium. Daughter cells are physically separated by cytokinesis, which is driven by constriction of an actomyosin ring until the formation of the midbody. We found that cleavage ingression proceeds asymmetrically from the basal to the apical side of follicle cells, positioning the midbody apically.[2] Asymmetric cytokinesis has long been described in mammalian epithelial cells,[3,4] but the underlying mechanism and relevance of apical midbody positioning remained unknown. Our work and recent findings in *Drosophila* embryonic[5] and pupal notum[6,7] epithelia provide some answers.

Asymmetric ring constriction has been addressed in the first division of the *C. elegans* zygote, where septins and Anillin exhibit polarized accumulation on the contractile ring, driving asymmetric actomyosin distribution.[8] This mechanism could not explain asymmetric ring constriction in follicle cells for 2 main reasons. First, we found that septins, Anillin, and active myosin display nearly symmetric distribution in the cytokinetic ring. Second, mutants for the septin Peanut maintain apical midbody positioning. We therefore examined the importance of the polarized interactions established within the epithelium. Adherens junctions (AJs) control adhesion and tension at the interface between neighboring cells, being formed by homophilic interactions of the transmembrane protein E-cadherin and linked to the intracellular cytoskeleton by Catenins. While we observed that the apical domain partially depolarizes during mitosis, AJs are maintained at the apical side of the cell, contacting the ring during constriction. Clonal analyses of *armadillo* (β-catenin) mutants revealed that apical midbody positioning is disrupted in AJ-defective cells, and we present evidence that AJs determine the position of the midbody. For instance, if a dividing wild-type cell abuts an *armadillo* mutant cell(s), and thus has an AJ asymmetry, the midbody is invariably positioned at the edge that establishes AJs with wild-type neighboring cells. Polarized assembly of AJ components in otherwise non-polarized *Drosophila* S2 cells also recruits the midbody, indicating that AJs orient midbody position independently of the remaining polarity machinery. We propose that by maintaining adhesion with neighboring cells and anchoring the apical side of the cytokinetic ring, AJs generate asymmetric resistance to ring constriction forces, determining cytokinesis asymmetry and midbody position in follicle cells.

The importance of coordinating the mechanical forces between the dividing and neighboring cells has been further revealed in *Drosophila* embryonic and notum epithelia[5-7] (**Fig. 1**). Asymmetric ring constriction is also linked to AJ-anchoring and independent of septins in these contexts.[5,6] Septins are instead required to generate tension in the cytokinetic ring, which, together with extrinsic pulling forces exerted by the neighboring cells on the junction, triggers disengagement of the ring from AJs.[5,6] Adhesion disengagement enables the formation of new adhesive contacts between daughter cells. However, in the follicle epithelium, the cytokinetic ring remains prevalently connected with AJs formed with one neighboring cell, whereas it disengages from the opposite side. This may result from local asymmetries of adhesion coupled with asymmetric extrinsic forces at the cleavage plane (**Fig. 1**, II). Interestingly, tissue cohesiveness is regulated differently in distinct epithelial tissues. In the embryo, disengagement creates a temporary gap between the neighboring and dividing cell membranes,[5] whereas in the notum, a population of Myosin II that accumulates in neighboring cells generates tension to juxtapose the ingressing membranes, setting the geometry of the interface between daughter cells before the establishment of new AJs.[6,7]

After ring constriction, the midbody seems to participate in the formation of the new adhesive interface. We observed the accumulation of actin around the midbody and extending along the apical interface between daughter cells, which is concomitant with a transient midbody localization of the Arp2/3 complex and precedes the establishment of the new AJs.[2] Although the precise biochemical or mechanical cues connecting midbody position to F-actin polymerization remain

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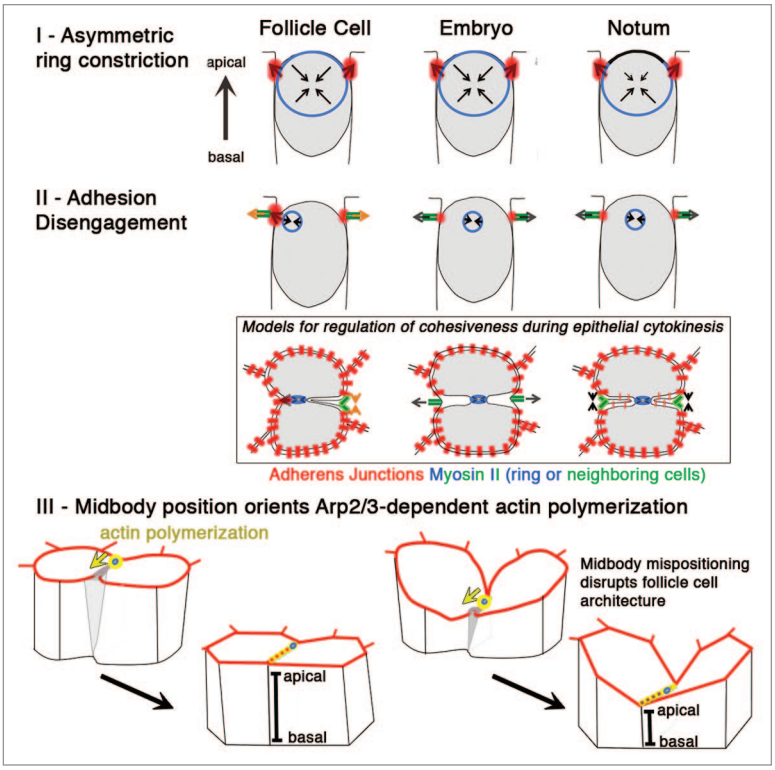

Figure 1. A 3-step model of *Drosophila* epithelial cytokinesis. Step I: AJs anchor the cytokinetic ring at the apical side determining asymmetric constriction of a ring with symmetric intrinsic contractility. In the notum, polarized ring contractility also contributes for asymmetric constriction. Step II: Tension exerted by ring constriction together with extrinsic tension control disengagement of the ring from AJs and the cohesion between dividing and neighboring cell membranes. Orange arrows depict forces that require further characterization. Step III: Actin polymerization is oriented by the midbody and is required for the withdrawal of neighboring membranes to extend/stabilize apical adhesive contacts at the daughter cell interface.

unknown, mispositioning of the midbody and its associated actin polymerization dictates a basal shift of the apical interface between daughter cells, reducing the length of the apico-basal axis relatively to the surrounding cells[2] (**Fig. 1**, III). In the notum, Arp2/3-dependent actin polymerization is also oriented by the midbody and mediates the withdrawal of the neighboring cell membranes to allow the formation of new AJs between daughter cells.[7] Together, these results highlight the importance of placing the midbody apically: it acts to control both the geometry of the new apical interface between daughter cells and the position of this interface relatively to the surrounding tissue. Thus, AJ-dependent midbody positioning transmits epithelial architecture to daughter cells. It is now appealing to study the impact of disrupting this process on the development of pathological features, and examine how the formation of new epithelial junctions is synchronized with cytokinesis in vertebrate epithelial cells, where tight junctions are present above AJs.

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