Cell height: Tao rising

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During oogenesis in Drosophila melanogaster, the cells in the follicular epithelium of the ovary undergo a transition from a cuboidal to a squamous shape. In this issue, Gomez et al. (2012. J. Cell Biol. http://dx.doi.org/10.1083/jcb.201207150) show that the kinase Tao promotes the endocytosis of the cell adhesion molecule Fasciclin 2 from the lateral surface of the cell and is critical for the cuboidal to squamous cell shape transition. Their results indicate that Tao is rising as a regulator of cell height.

As every beginning student of histology learns, epithelial cells can be classified by their shape: columnar cells are tall and narrow, and cuboidal cells are roughly as tall as they are wide, whereas squamous cells are wide and flat. These polarized cells have distinct apical surfaces (facing the outside world or lumen of an internal cavity or tube), lateral surfaces (facing adjacent cells), and basal surfaces (facing the underlying basement membrane). The relative sizes of these surfaces differ in columnar, cuboidal, and squamous cells. For instance, squamous cells have large apical and basal surfaces but small lateral surfaces. Columnar cells are opposite, with large lateral surfaces but small apical and basal surfaces. Though we have learned a great deal about how epithelial cells develop polarity and their three surfaces, we know very little about how these relative surface areas and the corresponding shapes of the cells are determined. In this issue of The Journal of Cell Biology, Gomez et al. have studied the morphogenesis of the follicular epithelium overlying the Drosophila melanogaster ovary. They show that endocytosis of the immunoglobulin superfamily cell–cell adhesion protein Fasciclin 2 from the lateral surface is required for cuboidal to squamous cell shape transition. The serine/threonine kinase Tao promotes the removal of Fasciclin 2 from the lateral surface and thereby causes the shortening of the lateral surface. In short, Tao is rising as a regulator of cell height.

In the lateral surface, there are many cell adhesion molecules, such as Fasciclin 2, which form homophilic interactions. Fasciclin 2 was discovered as a molecule critical for growth cone guidance and neural recognition in insects (Bastiani et al., 1987; Harrelson and Goodman, 1988; Snow et al., 1988), and its clustering, internalization, and integration into the synaptic membrane are crucial for synapse remodeling and plasticity. Later work showed that loss of Fasciclin 2 in Drosophila outer border cells but not inner polar cells, both of which are derived from the ovary follicular epithelium, is critical for timely delamination from the epithelium during development (Szafranski and Goode, 2004). However, how Fasciclin 2 is down-regulated was a mystery until now.

Adherens junctions establish the first connections between two cells in a developing epithelium. In the Drosophila ovary, adherens junctions are found in the apical region of the lateral membrane and rely on DE-Cadherin for cell–cell adhesion. The dynamic nature of adherens junctions is important for epithelial establishment, maintenance, and remodeling. Both the formation and integrity of adherens junctions are regulated. In one case, Notch signaling disassembles the adherens junctions of cells in the follicular epithelium, which are mechanically stretched by the growth of the underlying germine cyst and thereby promotes the flattening of these epithelial cells for proper oogenesis (Grammont, 2007). In another case, Dpp signaling promotes epithelial cell growth in height in the Drosophila wing disc. Dpp’s effect is mediated through remodeling of adherens junctions (Widmann and Dahmann, 2009).

The more basal portion of the lateral surface of the Drosophila ovarian epithelium uses Fasciclin 2 for cell–cell adhesion. Gomez et al. (2012) now show that Fasciclin 2–mediated cell adhesion maintains the height of the cell, and its removal from the lateral surface is critical for cuboidal to squamous cell shape transition. Furthermore, the authors show that Tao is the upstream trigger of this removal. Interestingly, removal of Fasciclin 2 from the lateral surface is mediated by endocytosis, using Rab5-containing vesicles.

Left unresolved are how Tao promotes endocytosis of Fasciclin 2 and whether it is a general regulator of cell height during epithelial morphogenesis in species other than Drosophila. Tao is a member of the Sterile-20 subfamily of serine/threonine kinases, and several seemingly unrelated functions have been ascribed to it (Fig. 1). These include activation of a stress-responsive p38 MAPK, phosphorylation of the kinase Par-1, which regulates microtubule dynamics and cell polarity, and activation of the Salvador–Warts–Hippo pathway involved in proliferation control. Data provided by the authors suggest

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that none of these previously known functions is involved in Fasciclin 2 endocytosis. As Tao’s role in this endocytic process is dependent on its kinase activity, most likely Tao phosphorylates a component of the endocytic machinery, though one or more intermediate steps might also be involved.

Membrane traffic at the lateral surface has previously been shown to affect cell height. Delivery of membrane proteins to the lateral surface utilizes the exocyst, a complex involved in docking exocytic vesicles. Overexpression of the Sec10 exocyst subunit in MDCK cells causes an increase in cell height but not width (Lipschutz et al., 2000). Synthesis of lateral proteins, but not apical proteins, was increased at a posttranscriptional level, suggesting a feedback between delivery of proteins to the lateral surface and their synthesis (Lipschutz et al., 2003). At least in mammalian epithelial cells, the lateral surface is enriched in phosphatidylinositol-3,4,5-trisphosphate. Partial inhibition of the synthesis of this lipid by chemical inhibitors gave a dose-dependent reduction in cell height, suggesting that the abundance of this lipid in the lateral surface is a determinant of the size of that surface and thus of cell shape (Gassama-Diagne et al., 2006).

One surprising observation made by Gomez et al. (2012) is that the Tao mutant causes not only accumulation of Fasciclin 2 at the lateral surface but also concentration of DE-Cadherin, β-Catenin, Crumbs, Par-6, and atypical PKC in the apical surface. Because their data suggest that most likely Tao only promotes endocytosis of laterally localized Fasciclin 2, the authors suggest that the concentration of apical proteins in the Tao mutant is a by-product of failed apical surface expansion. An interesting question raised is why the failure in shortening of the lateral surface causes a failure in expansion of the apical surface. Is there an upstream regulator that couples shortening of one surface with expansion of another surface during plasma membrane remodeling? This might involve a mechanism similar to that used to regulate transcytosis from the lateral to the apical surface. Identifying such a mechanism would deepen our understanding of epithelial morphogenesis in general.

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