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The forces and fates of extruding cells

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Cell extrusion drives most epithelial cell death while maintaining a functional epithelial barrier. To extrude, a cell produces a lipid signal that triggers the neighboring cells to reorganize actin and myosin basally to squeeze the extruding cell out apically from the barrier. More studies continue to reveal other signals and mechanisms controlling apical extrusion. New developmental studies are uncovering mechanisms controlling basal extrusion, or ingression, which occurs when apical extrusion is defective or during de-differentiation in development. Here, we review recent advances in epithelial extrusion, focusing particularly on forces exerted upon extruding cells and their various later fates ranging from cell death, normal development, and cancer.

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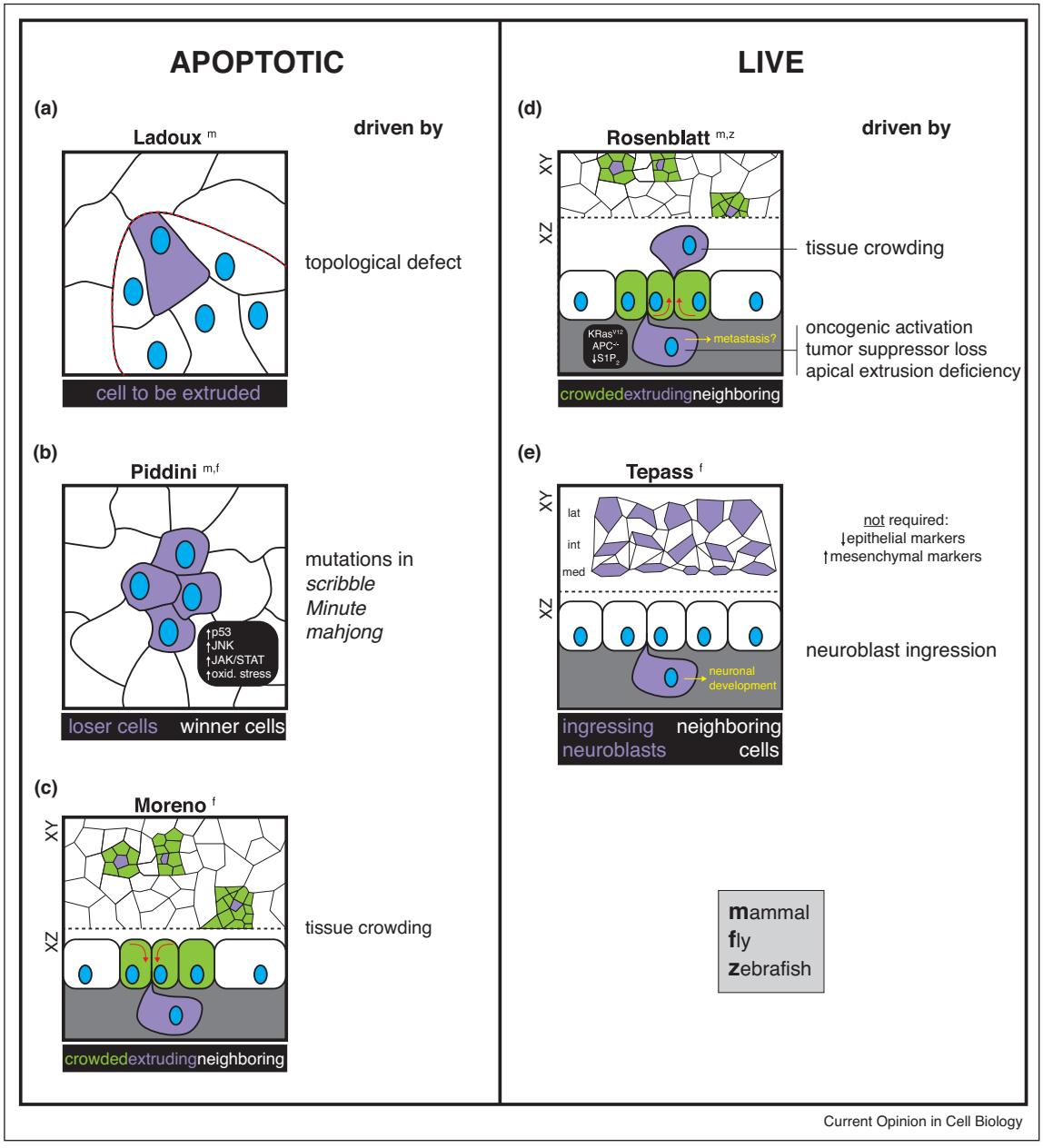
Epithelial cells work together to maintain a tight barrier, yet can turn over rapidly by cell division and death. To help accomplish this feat, epithelia eject cells fated to die by a process called cell extrusion. To extrude, a cell produces and emits the lipid sphingosine-1-phosphate (S1P), which binds to its cognate receptor $S1P_2$ in cells neighboring it to form a intercellular, basolateral, contractile actomyosin ring that squeezes the cell out of the epithelium [1,2]. In this manner, cells triggered to undergo apoptosis [2,3] or, more commonly, supernumerary live cells that later die by anoikis [4], are eliminated without disrupting the barrier [3–7]. Here, we review current cell extrusion literature focusing on its mechanism and signaling, and also highlight emerging new roles for extrusion in driving cell competition and tumor suppression.

One of the most important roles for extrusion is to maintain constant epithelial cell densities by mechanically matching the number of cells that die to those that divide. In vertebrates, mechanical force links cell division with cell death, as crowding triggers apical extrusion of live cells through the stretch-activated channel Piezo1 [4]. Previous work suggested that crowding also drives live cells to basally extrude or delaminate in *Drosophila* notum [8]. However, recent work from Levayer *et al.* shows that crowding causes cells to first undergo apoptosis which, in turn, drives delamination [9••]. Here, inhibition of the apoptotic pathway by *diap1* or p35 overexpression or homozygous loss of *hid*, *grim*, and *reaper* blocks delamination in crowded regions. Additionally, ras^{V12} -overexpressing cells crowd wildtype cells up to three cell diameters away and force their delamination, suggesting that overall tissue crowding causes cell delamination (Figure 1c) [9••]. Differential results in these two systems may be due to differences in the strength of promoters used to overexpress DIAP [8,9••]. In other epithelia at different times during *Drosophila* development, cells activate apoptosis before delaminating, suggesting that flies regulate extrusion of supernumary cells using different signaling pathways to vertebrates [10]. An important reason for this may be due to the fact that extrusion of live cells basally is risky if cells do not later die; for instance, cancer cells or stem cells may use this mechanism to escape their primary epithelial sites and invade or differentiate, respectively. In fact, live neuroblast cells delaminate from the neuroepithelium before becoming neurons [11••]. Thus, activating cell death simultaneously with *basal* extrusion could ensure that supernumerary cells are eliminated.

Although crowding within epithelia drives some cells to extrude, what causes a specific cell within a crowded region to extrude is not well understood. Several recent papers shed light on important signaling and mechanical forces that contribute to one cell extruding. Using Madin-Darby canine kidney (MDCK) epithelial cells grown to confluence on micropatterned, functionalized substrates, Saw *et al.* found that epithelial cells can behave like nematic liquid crystals (liquids comprised of molecules oriented in a crystal-like pattern) that align along their long axes, with cell extrusions occur at sites of patterning defects to relieve cell strain (Figure 1a) [12••]. At these defect sites, extruding cells were not locally crowded but instead the result of perpendicular single-cell collisions. Using elegant experiments where they confined cell growth and movement by plating on matrices of different shapes, they could increase or decrease these defects and collisions, and the extrusion rates, accordingly. Sites of single-cell defects had increased cytoplasmic yes-associated protein (YAP)

Figure 1



The driving forces on and fates of apoptotic and live extruding cells. Depending on species, cell context, and neighboring cell status, cells bound to extrude can have several different fates. **(a,b)** Mammalian cells at the leading edge of a comet-shaped topological defect (a) or harboring 'loser' mutations (b) are destined to die and extrude apically. **(c)** Conversely, cells in the fly notum that are to be eliminated experience crowding forces and delaminate (i.e. extrude basally). In this context, cells necessarily commit to apoptosis, in contrast to a previous report (ref. [4]). **(d)** In mammalian cell cultures, mouse gut epithelia, and the developing zebrafish epidermis, cells that experience crowding forces extrude apically and later die by anoikis. Conversely, cells that harbor oncogenic mutations, lose tumor suppressors, or have deficiencies in apical extrusion machinery extrude basally and may live, revealing a novel path to metastasis. **(e)** Fly neuroblasts ingress (i.e. extrude basally; lateral, intermediate, and medial neuroblasts are shown) in an EMT-independent fashion, and later develop into mature neurons.

and caspase-3 activation [12••], in contrast with live cell extrusions that result from whole epithelial sheet crowding [4,8]. Future work will need to examine if single-cell perpendicular collisions are at the heart of live cell extrusions in crowded regions of tissues, or if this represents another pathway to eliminate cells causing patterning defects in the otherwise regular epithelial fabric that coats organs.