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SPOTLIGHT

Myoepithelial crowd control of cancer cells

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Smooth muscle–like cells can actively remodel epithelia, a mechanism common across developing tissues. In this issue, new work from Sirka et al. (2018. *J. Cell Biol.* https://doi.org/10.1083/jcb.201802144) demonstrates a novel mechanism for tumor suppression by smooth muscle–like myoepithelial cells of the mammary gland.

Dynamic physical interactions between adjacent tissues have long been recognized as essential drivers of morphogenesis. In this issue, Sirka et al. describe a fascinating mechanism by which these interactions can also impede disease progression. Using a powerful combination of inducible mouse models and organoids, the authors probed and directly observed in real-time the relationship between luminal epithelial and myoepithelial cells during Twist1-stimulated mammary epithelial cell dissemination. This approach revealed a novel mechanism for tumor suppression by myoepithelial cells. Individual Twist1-expressing and primary tumor-derived luminal epithelial cells that were in the process of escaping (or had even fully escaped) the organoid were encapsulated and recaptured by Twist1-negative myoepithelial cells (Fig. 1 A). Tumor suppression by myoepithelial cells has historically been thought to be achieved by paracrine signaling (Sternlicht et al., 1997) or by providing a barrier between luminal tumor cells and nearby vasculature, thus preventing angiogenesis required for enhanced tumor growth (Barsky and Karlin, 2005). The dynamic barrier strategy revealed here represents an additional, previously unknown, way in which the myoepithelium might prevent the invasion of ductal carcinoma cells.

Sirka et al. (2018) provide another example of the seemingly universal role for smooth muscle–like tissue in instructing the morphogenesis or movement of epithelia. Smooth muscle–like cells include bona fide smooth muscle, such as that found encircling the viscera and larger blood vessels, myoepithelial cells in the outer layer of mammary ducts, and pericytes that wrap capillaries. Extension of mammary tubes during pubertal development occurs not by invasive or protrusive migration, but instead is accomplished by the collective migration of a multilayered epithelial bud (Ewald et al., 2008). To drive ductal elongation, luminal epithelial cells proliferate and intercalate radially, while spatially patterned myoepithelial cells (around the ducts but absent from the branch tip) provide the constraint necessary for the ensemble to achieve net forward motion (Fig. 1 B; Neumann et al., 2018). There are similarities between the roles of myoepithelial cells in ductal elongation and the epithelial capture described by Sirka et al. (2018). In tumor-model organoids, myoepithelial cells also constrain luminal epithelial expansion, albeit in this case by limiting the invasion of Twist1-expressing cells into the surrounding matrix. Pericytes are smooth muscle–like cells that encircle capillaries (Fig. 1 C). In the retina, pericytes and endothelial cells are present in equal numbers, and the loss of pericytes in diabetic retinopathy leads to leaky blood vessels, immune cell infiltration, a breakdown of the blood–retinal barrier, and eventually blindness (Ferland-McCollough et al., 2017). In the mouse lung, smooth muscle develops concomitantly with the epithelial tree and wraps circumferentially around the airways. Epithelial bifurcation requires spatially patterned smooth muscle differentiation to specify the cleft site and split the growing epithelium into daughter branches (Fig. 1 D; Kim et al., 2015). In each case, the morphogenesis or function of the epithelium requires the presence of smooth muscle or smooth muscle–like cells.

The mechanisms by which smooth muscle–like tissues exert their influence are not yet fully understood. Smooth muscle–like tissues express similar contractile machinery but may have different contractile properties. Unlike smooth muscle that contracts spontaneously, contraction of myoepithelial cells requires stimulation with oxytocin (Gudjonsson et al., 2005). Oxytocin was not provided in the experiments that examined Twist1-induced epithelial dissemination (Sirka et al., 2018) or ductal elongation (Neumann et al., 2018); it therefore remains unclear whether contraction or some other mechanism accounts for the role of myoepithelial cells in these contexts. Expression of smooth muscle contractile machinery could alter the stiffness of myoepithelial cells, but this has not yet been measured, to our knowledge. Alternatively, the energy of differential adhesion could also provide a barrier to luminal epithelial migration past myoepithelial cells; indeed, knockdown of the myoepithelial P-cadherin,

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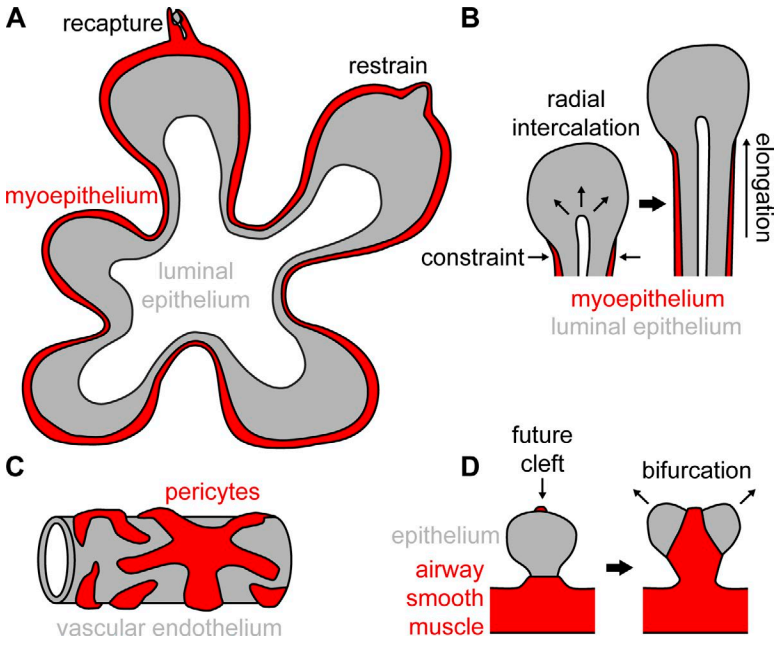

Figure 1. **Smooth muscle–like tissues encircle and instruct their partner epithelia. (A)** Myoepithelial cells restrain and recapture disseminating, Twist1-expressing luminal epithelial cells in organoid models of breast tumors (Sirka et al., 2018). **(B)** Radial intercalation of luminal epithelial cells combined with myoepithelial cell-mediated constraint promotes ductal elongation during mammary branching morphogenesis (Neumann et al., 2018). **(C)** Pericytes wrapped around capillaries support the structural stability and barrier function of the vascular endothelium (Ferland-McCollough et al., 2017). **(D)** Smooth muscle specifies cleft sites and splits growing epithelial buds during airway bifurcation in murine lung development (Kim et al., 2015).

and thus removal of any energetic barrier driven by differential adhesion, led to an increase in the escape of Twist1-expressing luminal epithelial cells (Sirka et al., 2018).

The most common marker of smooth muscle–like cells is smooth muscle actin (Acta2 or αSMA), but its role in smooth muscle and myoepithelial specification, differentiation, and activity is surprisingly complicated. Acta2-null mice form normal mammary glands that only exhibit defects in contraction during lactation (Haaksma et al., 2011); similarly, these mice develop normal cardiovascular systems that exhibit defects only in adult vascular homeostasis and in response to high blood flow (Schildmeyer et al., 2000). Other actin isoforms could compensate for the loss of Acta2 during development of these systems; indeed, skeletal muscle actin is found ectopically in the aortas of Acta2-null mice (Schildmeyer et al., 2000), and myoepithelial cells in the mammary glands of Acta2-null mice still assemble dense stress fibers, likely composed of β- and γ-actin isoforms (Haaksma et al., 2011). In all cases, morphogenesis appears to be intact, suggesting that Acta2 is dispensable for the development of smooth muscle–like tissues and the organs they support. Sirka et al. (2018) find that knockdown of Acta2 impedes the ability of myoepithelial cells to restrain Twist1-expressing luminal epithelial cells. However, it is not clear what knockdown of Acta2 physically accomplishes in these organoids, especially given the surprising results outlined above. Dynamic barrier activity of myoepithelial cells in organoids ex vivo clearly requires Acta2, but the physical and molecular mechanisms by which Acta2 participates in myoepithelial activities remain to be elucidated.

The work highlighted here is an example of how discoveries about morphogenesis and the tools used to uncover them (Ewald et al., 2008; Neumann et al., 2018) can be applied to the understanding of disease (Sirka et al., 2018). Lessons from disease models can also be applied to further our understanding of morphogenesis. For example, during new branch initiation off existing mammary ducts, the luminal epithelium must somehow overcome the myoepithelial barrier. This could occur by breaking through the dynamic barrier, and may involve tuning of the actin cytoskeleton and intercellular adhesion, important regulators of myoepithelial barrier function as demonstrated by Sirka et al. (2018). The restraining role of the myoepithelium will undoubtedly inspire new studies focused on how myoepithelial cells (and other smooth muscle–like tissues) might participate in normal development, tumor progression, and invasion. Future work is required to uncover the molecular and physical mechanisms that regulate the dynamic barrier and how it is related to other known mechanisms of tumor suppression by myoepithelial cells.

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