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Rac and Rho compete to cooperate

Antagonism between RhoA and Rac1 pathways creates cell heterogeneity that aids epidermal morphogenesis.

FOCAL POINT

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(Left to right) Emmanuel Martin, Marie-Hélène Ouellette, and Sarah Jenna describe how the mutual antagonism between Rho and Rac signaling pathways creates cell-to-cell heterogeneity in the epidermis of elongating *C. elegans* embryos. A Rac-like pathway predominates in anterior dorsal epidermal cells (top), controlling the remodeling of apical cell–cell junctions (green) and the formation of lamellipodia that protrude into neighboring lateral cells. In contrast, Rho-like signaling predominates in the lateral cells (bottom), promoting junction remodeling and the formation of amoeboid-like protrusions that extend into neighboring dorsal cells. Cells can switch between the two programs when one of the pathways is compromised, increasing the robustness of embryonic elongation.

Epithelial cells change their shape and remodel their apical cell–cell junctions during tissue morphogenesis. Rho and Rac GTPases control these processes by regulating myosin contractility. Genetic evidence, for example, suggests that RhoA and Rac1 pathways work in parallel to promote the elongation of early *C. elegans* embryos. Yet, within individual cells, these two pathways tend to antagonize each other. Martin et al. resolve this conundrum by analyzing the behavior of individual epidermal cells during embryonic elongation (1).

During development, *C. elegans* embryos elongate along their anterior-posterior axis in a process thought to be driven by the apical constriction of epidermal cells on the lateral sides of the embryo. Early elongation depends on LET-502, a homologue of the Rho effector ROCK, and on the Rac activator PIX-1 and the Rac effector PAK-1 (2–4). These Rho- and Rac-like pathways work synergistically; embryos can partially elongate when one of the pathways is inhibited, but fail to lengthen when both of them are impaired. "But how do these two pathways work in parallel when, in most cells, they function antagonistically?" asks Sarah Jenna, from the Université du Québec à Montréal.

Previous studies have suggested that the Rho- and Rac-like pathways operate in different regions of the embryonic epidermis, and that individual epidermal cells may therefore follow distinct morphogenetic programs during elongation. Intriguingly, the mutual antagonism between Rho and Rac signaling pathways allows tissue culture cells to adopt a variety of different shapes in vitro (5, 6). But whether epithelial tissues in vivo show a similar cell-to-cell heterogeneity is unclear; most studies monitor the behavior of the tissue as a whole, rather than the behavior of individual cells. "We decided to study embryonic elongation at the single cell level," says Jenna.

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Led by graduate student Emmanuel Martin, Jenna and colleagues developed a quantitative imaging method to measure the reorganization of individual epidermal cell junctions in elongating *C. elegans* embryos (1). By comparing embryos lacking either *let-502*, *pix-1*, or *pak-1*, Martin et al. determined that the Rho-like, *let-502*-dependent pathway controls the remodeling of junctions between lateral epidermal cells, whereas Rac-like, *pix-1*– and *pak-1*–dependent signaling regulates junction remodeling in dorsal epidermal cells at the embryo's anterior. Moreover, the researchers discovered that, in the dorsal cells, *pix-1* and *pak-1* promote the formation of basolateral, lamellipodia-like protrusions that extend towards the neighboring lateral cells. The lateral cells, in contrast, formed distinct, amoeboid-like protrusions in a *let-502*–dependent manner. "So individual cells can adopt different morphologies and behaviors within a polarized epithelium," Jenna says.

This heterogeneity is defined by the two GTPase pathways, with lateral cells adopting a Rho-like morphogenetic program, and dorsal cells assuming a Rac-like phenotype. But the mutual antagonism between these two pathways means that the cells can switch programs if one of the pathways is compromised. In embryos lacking *let-502*, PIX-1 and PAK-1 were able to take over and remodel the junctions of lateral epidermal cells, and promote the formation of lamellipodia instead of amoeboid protrusions. Conversely, in the absence of *pix-1* or *pak-1*, LET-502 can partially support the reorganization of dorsal cell–cell junctions.

The heterogeneity created by Rho/Rac antagonism therefore helps the epidermis to elongate in the face of genetic insults, and probably helps the embryo cope with environmental fluctuations, too, thus explaining how, despite their competition at the cellular level, the two pathways work together to promote tissue morphogenesis. Jenna says that it will be important to determine whether heterogeneity plays a similar role in the epithelial tissues of other organisms.

Jenna's group is also interested in the function of the basolateral protrusions in embryonic elongation. "We hypothesize, and we've partially shown in this paper, that the dorsal, lamellipodial protrusions reduce the tension generated at the junctions between dorsal and lateral cells," Jenna says. "This may prevent the embryo from exploding as it undergoes elongation."

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