Setting the spindle’s compass

Two control points determine the orientation of epidermal cell divisions.

The mammalian epidermis is a multi-layered, or stratified, epithelium. Progenitor cells in the basal layer give rise to the outer layers by aligning their mitotic spindles perpendicularly to the basement membrane and dividing asymmetrically to produce one basal and one suprabasal cell. Poulson and Lechler reveal how progenitors decide to orient their spindles for stratification (1).

During his postdoc, Terry Lechler discovered that mouse epidermal cells use the same machinery that fly and worm cells use to divide asymmetrically (2). But in the epidermis, some basal cells orient their spindles parallel to the basement membrane and divide symmetrically to generate more progenitors and expand the skin’s surface area. The balance between asymmetric and symmetric divisions is critical for the development of a functional epidermis. “That’s different from the invertebrate models, in which cells only divide asymmetrically,” says Lechler, now running his own laboratory at Duke University. “We wanted to know whether individual basal cells can divide in both directions.”

Poulson and Lechler labeled small numbers of basal progenitors with GFP and traced their fluorescent progeny. The pattern of labeling suggested that individual basal cells could divide both symmetrically and asymmetrically to produce basal and suprabasal descendants. “The results weren’t consistent with cells being committed to a single division orientation,” Lechler explains. “That doesn’t rule out there being small populations of cells with a committed orientation, but the majority of cells can choose which way to divide.”

When do basal cells make this choice? In asymmetrically dividing Drosophila neuroblasts, centrosomes split and move to opposite ends of the cell during interphase, setting up the spindle’s orientation before it even-assembles (3, 4). Poulson and Lechler didn’t see this interphase centrosome separation in mouse epidermal cells. Instead, the mitotic spindle formed with a random orientation and only adopted a perpendicular or parallel alignment in late metaphase. “That late decision might allow cells to respond quickly to changes in their environment to either increase progenitor number or promote stratification as needed,” says Lechler.

Live imaging of cultured epidermal keratinocytes suggested that fully formed spindles rotate into their desired orientation.

The researchers then turned their attention to how cells choose between asymmetric and symmetric division. In flies, ectopic expression of a protein called Inscuteable reorients the spindle of symmetrically dividing cells (5). Poulson and Lechler therefore generated mice carrying an inducible version of Inscuteable. Brief overexpression of the protein boosted the frequency of perpendicular spindle orientations and asymmetric cell divisions. But this increase wasn’t maintained if Inscuteable was overexpressed for several days— asymmetic cell divisions decreased after prolonged Inscuteable expression, suggesting that an additional mechanism exists to balance the different types of epidermal cell division.

Inscuteable localizes to the apical cortex of asymmetrically dividing cells, forming a complex with another polarized protein called LGN, which captures the mitotic spindle pole protein NuMA to align the mitotic spindle perpendicularly along the apical–basal axis of the cell. Inscuteable and LGN still formed an apical complex after prolonged Inscuteable overexpression, but it was less able to recruit NuMA and guide asymmetric division. Inscuteable expression and NuMA recruitment therefore combine to maintain robust control over spindle orientation and epidermal development. “The epidermis is a barrier to the outside world, and it maintains itself any way that it can,” Lechler says. “This is a nice example of robustness in the epidermis’ function and physiology.”

p63 is considered to be the “master regulator” of stratification because mice lacking this transcription factor fail to form a multi-layered epidermis. But p63 knockout mice still expressed Inscuteable, suggesting that p63 controls spindle orientation in a different way, perhaps by regulating the apical–basal polarity of progenitor cells. Lechler now wants to investigate the external cues that affect spindle orientation. “We’re interested in how tension in the epidermis as well as chemical signals influence Inscuteable expression and NuMA localization,” Lechler says.

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