DEVELOPMENT

Differentiation goes up a Notch

Asymmetric cell division is a highly regulated means for stem and progenitor cells to balance proliferation with differentiation, but the mechanisms and consequences of asymmetric cell division in the context of mammalian tissue architecture are not well understood. However, a new paper from Elaine Fuchs's laboratory has shed some light on these issues; the authors used developing mouse skin epidermis as a model to reveal the importance of mitotic spindle-orienting proteins in mammalian asymmetric divisions, and they also uncovered a link to Notch signalling that is essential for epidermal differentiation.

In mammalian skin epidermis, asymmetric division occurs by switching the orientation of the mitotic spindle in basal keratinocytes to be perpendicular to the tissue plane. This causes the unequal distribution of apically or basally localized proteins into daughter cells and initiates the stratification of mammalian skin epidermis into layers: the more apical (suprabasal) daughter cells terminally differentiate and move upwards, away from the underlying basal lamina.

In *Drosophila* neural progenitor cells, spindle-orienting proteins play an important part in specifying the differential fates of daughter

cells. Do they have a similar function in the context of the mammalian epidermis? Williams *et al.* used *in utero* RNAi to study the role of three spindle-orienting proteins — G-protein-signalling modulator 2 (GPSM2; also known as LGN), nuclear mitotic apparatus protein 1 (NUMA1) and dynactin 1 (DCTN1) — in mouse epidermal differentiation. Although previous work had uncovered apical localization of these proteins during asymmetric keratinocyte division, it was unclear whether they were essential for mammalian asymmetric cell division. Knocking down GPSM2, NUMA1 or DCTN1 using lentiviruses disrupted the spindle orientation and the ability of keratinocytes to divide asymmetrically. As a consequence, epidermal stratification and differentiation was impaired, emphasizing the importance of asymmetric cell divisions for the maintenance of tissue architecture.

In their search for mechanistic consequences of the disruptions to asymmetric cell division, the authors noticed that knocking down these spindle-orienting proteins did not result in abnormalities in apoptosis or proliferation. Instead, they observed an abrogation of Notch signalling, a pathway that is usually a signature of differentiating, suprabasal keratinocytes. Thus, loss of asymmetric cell

division impairs a well-established differentiation pathway. Having previously shown that epidermal ablation of *Rbpj* — the obligate DNA-binding partner of Notch intracellular domains (NICDs) — results in a stratification defect comparable to that seen with the loss of spindle-orienting proteins, the authors demonstrated that Notch signalling lies downstream of asymmetric cell division during epidermal stratification. Spindle alignment still occurred in *Rbpj*-deficient epidermis, and suprabasal expression of an NICD ameliorated the differentiation defects of GPSM2 knockdown.

This work highlights the importance of asymmetric cell division and Notch signalling for balancing stem cell proliferation and differentiation in the developing mammalian epidermis. Given that the consequences of Notch signalling are highly context-dependent, it will be interesting to determine to what extent the links among asymmetric cell division, Notch signalling and differentiation are paralleled in additional tissue types.

Darren J. Burgess

ORIGINAL RESEARCH PAPER Williams, S. E. *et al.* Asymmetric cell divisions promote Notch-dependent epidermal differentiation. *Nature* **470**, 353–358 (2011)