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Creating cellular inequality

Atypical protein kinase C sets the balance between asymmetrical and symmetrical divisions.

Like Peter Pan, some stem cells never grow up. A kinase curbs differentiation of these cells and helps them retain their ability to proliferate, Niessen et al. show (1).

Each time a stem cell or progenitor cell divides, the daughter cells can remain unspecialized or they can differentiate, sometimes losing their capacity for replication. Healthy tissues balance the number of cells choosing each option. Asymmetric cell division is one mechanism for steering the daughter cells toward different fates (2). In the developing skin, for example, the orientation of division sets up the inequality (3). The daughter cell that ends up on the apical side begins to differentiate, whereas the basal daughter remains unspecialized. In organisms such as nematodes and fruit flies, atypical protein kinase C (aPKC) controls whether cells divide asymmetrically and dictates which career choice a daughter cell makes (4). Mammals manufacture two varieties of the protein, aPKCλ and aPKCζ, but researchers weren't sure if the proteins play the same role as in other organisms. Niessen et al. determined the proteins' effects in the epidermis of mice. In this tissue, different types of stem cells and progenitor cells are active in the hair follicles, the skin between the follicles, and the sebaceous glands.

The researchers found that aPKCλ was the predominant form of the kinase in skin. To probe its function, the researchers switched the protein off only in the epidermis. Although mice missing the protein seemed normal at birth, their skin quickly showed signs of abnormal differentiation. Their hair fell out and regrew, and they sprouted misshapen hair follicles. Moreover, hair follicles typically go through a cycle of growth, shrinkage, and rest. Twenty days after birth, all of the hair follicles in control mice were resting, but 60% of the hair follicles in the mice lacking aPKCλ were in the growth stage. Differentiation was also disrupted in the sebaceous glands and in the epidermis between the follicles; mice lacking aPKCλ had swollen sebaceous glands and a thickened epidermis.

> "aPKCλ might [balance] the ratio between asymmetric and symmetric cell divisions."

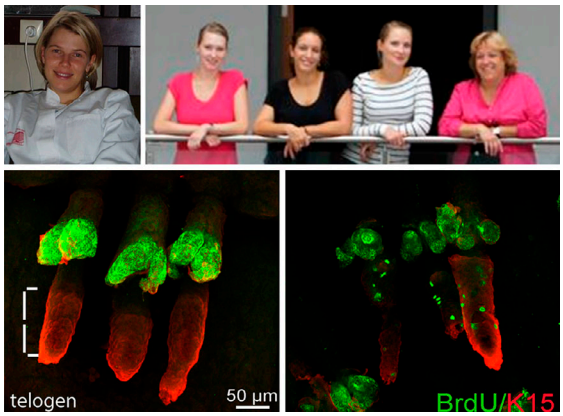
Niessen et al. determined that the loss of aPKCλ increased the ratio between asymmetrical and symmetrical cell divisions in the skin of embryonic mice. The team homed in on a group of cells in the hair follicle, the bulge stem cells. They are normally inert, but, in the mice lacking aPKCλ, they activated and began dividing. The number of bulge stem cells dropped over time, and the number of their more specialized descendants, the junctional zone progenitors, rose transiently.

The researchers performed lineage tracing on a group of bulge stem cells that normally only spawn cells in the lower part of the hair follicle. After Niessen et al. inactivated aPKCλ in the cells, however, their offspring showed up in the upper parts of the hair follicles, in the skin between the follicles, and even in the sebaceous glands.

The team also gauged the long-term effects of aPKCλ loss by culturing keratinocytes from control and mutant mice. Keratinocytes from newborn mice lacking aPKCλ divided more rapidly than did cells from controls. By the time the animals were adults, keratinocytes from control mice were still going strong, but cells from aPKCλ-deficient rodents divided sluggishly and differentiated prematurely. Their loss of proliferative power seemed to accelerate the animals' aging. The mice missing aPKCλ went gray before their time and by the age of one year had lost almost all of their fur.

"aPKCλ might regulate cell fate and differentiation decisions by balancing the ratio between asymmetric and symmetric cell divisions," says senior author Carien Niessen. The protein favors symmetrical division and thus might hinder differentiation and ensure that some stem cells remain undifferentiated and able to divide. Without the protein, stem cells proliferate rapidly and begin to specialize. Eventually animals run low on the cells, resulting in conditions such as baldness. How aPKCλ controls whether division is symmetrical or asymmetrical is unclear. The researchers propose that it may regulate the position of the centrosome during mitosis.

Focal Point



(Top row, left to right) Jeanie Scott, Susanne Vorhagen, Michaela Niessen, Julia Zielinski, Carien Niessen, and colleagues (not pictured) probed how the protein aPKCλ affects stem cell renewal and differentiation in the epidermis of mice. In control hair follicles (bottom left), bulge stem cells (red) are quiescent. But in hair follicles from a mouse lacking aPKCλ (bottom right), the number of dividing bulge cells, indicated by BrdU uptake (green), has surged.

SCOTT PHOTO COURTESY OF CARIEN NIESSEN; GROUP PHOTO COURTESY OF M. RÜBSAM

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