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STEM CELLS

Epidermis — a population in question

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In previous models of epidermal homeostasis, two different cell types are responsible for maintaining the cells that make up the mouse epidermis. Reporting in *Nature*, Clayton *et al.* now challenge this paradigm.

The mammalian epidermis is organized into hair follicles interspersed with interfollicular epidermis (IFE), which comprises layers of keratinocytes. The basal layer consists of proliferating cells that maintain the tissue and post-mitotic basal cells, which migrate out of the basal layer as they differentiate. According to the 'stem/transit-amplifying (TA) cell' hypothesis, the epidermis is maintained by two discrete populations of progenitor cells; long-lived, self-renewing stem cells, which give rise to short-lived progenitors (TA cells). The TA cells in turn generate differentiated cells after a few rounds of cell division.

To overcome previous technical limitations, the authors used genetic labelling and three-dimensional imaging techniques to track the fate of single mouse epidermal progenitor cells over a 1-year timescale *in vivo*. At 2 days post-induction, only single-labelled cells were seen, at a frequency of 1 in 600 cells in the basal layer. This meant that the clusters observed at later time points were clones that were derived from a single progenitor cell. In contrast to the previous notion that TA cells undergo a limited number of cell divisions followed by differentiation, the authors found that clones that consist of three or more cells contained both basal and suprabasal cells — indicative of asynchronous terminal differentiation. A single cell division could generate one cycling and one non-cycling daughter, two cycling daughters or two non-cycling daughters. Asymmetrical cell divisions, as indicated by asymmetrical localization of NUMB protein, also occur in the epidermis.

The most surprising finding was a progressive increase in average clone size throughout the year-long time course. This is in disagreement with the stem/TA model, which suggests that in the long term, the epidermis is organized into epidermal proliferative units that consist of ten basal cells supported by a single self-renewing stem cell. If this model was correct, then clone size would level off at the size of a single epidermal proliferative unit, rather than continuing to expand.

So, on the basis of these findings, Clayton *et al.* developed a model of clonal fate that involves a single type of progenitor cell. The clone size distributions scale with time, which means that they cannot be generated by separate stem and TA cells that divide at different rates. Instead, the epidermis is maintained by a single type of progenitor that divides to give two, one or no cycling daughters in proportions that maintain the epidermis without stem-cell proliferation; stem cells are quiescent unless the epidermis is wounded.

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ORIGINAL RESEARCH PAPER Clayton, E. *et al.* A single type of progenitor cell maintains normal epidermis. *Nature* 28 Feb 2007 (doi:10.1038/nature05574)

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