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STEM CELLS

Hierarchy in the population

The skin is a barrier to the environment, and its maintenance and repair following injury are essential. Here, Blanpain and colleagues show that, in the case of the interfollicular epidermis (IFE), there are two distinct populations that contribute to homeostasis and repair: committed progenitor cells and slow-cycling stem cells.

The IFE comprises a basal layer of proliferative cells and overlying layers of terminally differentiated cells that progressively undergo enucleation to form an external cornified layer. To investigate which cells from the IFE basal layer replenish cells lost during tissue turnover, the authors carried out quantitative analysis of lineage-tracing data. They used transgenic mice carrying the Cre recombinase–oestrogen receptor (Cre–ER) in which the IFE progenitors and their clonal progeny were marked by YFP. Cre–ER was under the control of either the keratin 14 promoter (K14), which drives gene expression in most cells of the basal layer, or the involucrin promoter (Inv), which drives gene expression in suprabasal layers and in some basal cells.

Interestingly, although basal cells marked by these two Cre–ER systems comprised IFE progenitors, the clones that originated from them differed in their survival potential, which was measured by their ability to retain at least one basal cell. Indeed, K14 clones survived up to 1 year post-induction whereas Inv clones were progressively lost. This was the first indication that IFE progenitors are heterogeneous.

To investigate the behaviour of the two pools of basal progenitors, the authors quantified the pattern of growth of individual clones at various time points up to 48 weeks post-induction. They found that the behaviour of the Inv clones was consistent with population asymmetric self-renewal of a single, equipotent, committed progenitor cell population in which the chance of progenitor cell loss through differentiation is compensated for by cell duplication. As a result, the decline in the numbers of surviving Inv clones was compensated for by the expansion of the survivors. These results suggest that Inv–Cre–ER marks the committed progenitor cells that had been identified in previous lineage-tracing studies.

Interestingly, analysis of K14 clones provided evidence of proliferative heterogeneity. In particular, a detailed quantitative analysis of K14 clones revealed a distinct population of slow-cycling cells that, through a similar process of population asymmetric self-renewal, gives rise to committed progenitor cells. These results, which were further supported by differential gene expression-profiling studies, indicate that K14 marks both committed progenitor cells and a second, distinct population of slow-cycling stem cells. These slow-cycling stem cells could give rise to both committed progenitor cells, which proliferate and differentiate, and daughter stem cells, which enter a quiescent phase, leading to clonal persistence.

Importantly, following injury, K14-labelled IFE cells were recruited to the wound area and contributed to the long-term repair of the epidermis, suggesting that they have a role in tissue regeneration. By contrast, only a few smaller and short-lived Inv clones were recruited, which indicates that they make only a limited contribution to wound healing.

This work demonstrates the existence of slow-cycling stem cells that promote tissue repair and of more rapidly cycling progenitors that have a role in skin homeostasis. A similar mechanism of tissue maintenance has been observed in other tissues, for example the blood, muscle and hair follicle, and may thus be well conserved.

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ORIGINAL RESEARCH PAPER Mascré, G. *et al.* Distinct contribution of stem and progenitor cells to epidermal maintenance. *Nature* 2 Sep 2012 (doi:10.1038/nature11393)
FURTHER READING Blanpain, C. & Fuchs, E. Epidermal homeostasis: a balancing act of stem cells in the skin. *Nature Rev. Mol. Cell Biol.* **10**, 207–217 (2009)