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Upward bound: follicular stem cell fate decisions

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Recent data suggest that heterogeneous compartments of the bulge display differential gene expression, and supply cells to different lineages within the pilosebaceous unit (Jaks *et al*, 2008; Jensen *et al*, 2009; Snippert *et al*, 2010). In particular, Lgr6 and Lrig1 are expressed above the CD34+ bulge region and Lgr6 expressing cells contribute primarily to the sebaceous gland (Figure 1). Thus, if and how the multipotent bulge cells give rise to cells to the sebaceous gland is not well understood. In this issue of *The EMBO Journal*, Petersson *et al* (2011) investigate how bulge cells contribute to the sebaceous gland *in vivo* using careful lineage tracing experiments and live bulge cell imaging in intact organ cultures.

Defining the niche for stem cells and the mechanisms that control their activity and lineage pathways is essential for the use of these cells for tissue regeneration and disease prevention. In the skin, the stem cells of the hair follicle have the capacity to generate multiple lineages of the skin including the epidermis, hair follicle and sebaceous gland during grafting and wound healing. Genetic lineage tracing experiments (Morris *et al*, 2004; Zhang *et al*, 2009) have revealed that during skin homoeostasis, the activity of bulge cells is restricted to the lineages of the hair follicle and sebaceous gland, which compose the pilosebaceous unit.

By crossing a mouse line expressing a tamoxifen inducible cre recombinase under the bulge-specific *keratin* 15 (*K15*) promoter (Morris *et al*, 2004) with reporter mouse lines, the authors are able to follow the contribution of bulge cell progeny towards the sebaceous gland. The sebaceous gland requires continual replacement of differentiated sebocytes, which lyse to release their specialized lipids into the hair canal for skin moisturization and protection. Sebaceous gland progenitor cells were identified that can contribute to the gland based on their expression of the transcription factor Blimp1 (Horsley *et al*, 2006), but the precise relationship between the bulge cells and sebaceous gland lineage cells had not been defined. Careful analysis of gene expression and the time course analysis of bulge cell progeny's upwards migration from the quintessential $CD34^+$ region of the bulge allowed the authors to follow the progression of bulge cells through multiple regions of the follicle as they exit the stem cell niche.

To visualize the lineage pathway of bulge cells in real time, the authors pioneered a live cell imaging technique in which labelled bulge cells were followed in real time in epidermal whole-mount preparations of tail skin using confocal microscopy. Cell division of bulge cells and migration of individual labelled progeny towards the upper isthmus were observed. Furthermore, this technique revealed the proliferation and migration of bulge cell progeny within the sebaceous gland. Taken together with the analysis of gene expression of labelled bulge cell progenitors, these data demonstrate that progeny of slow cycling bulge cells migrate above the hair follicle and follow a progression into the $Lrg6^+$, $Lrig1^+$ upper bulge region to the $Blimp1^+$ progenitor population and into the sebaceous gland to repopulate the mature sebocytes.

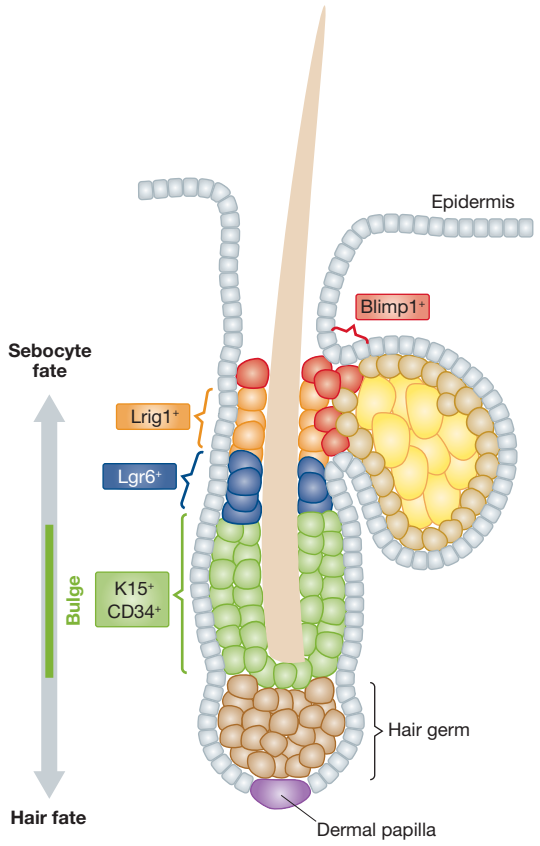

Figure 1 Progression of bulge stem cell fates in pilosebaceous unit. $CD34^+$ and $K15^+$ bulge cells (green) contribute to the hair follicle below the bulge or the sebaceous gland above the bulge. The sebaceous gland fate of bulge cells involves cell migration through the $Lgr6^+$ (blue), $Lrig1^+$ (orange) and $Blimp1^+$ (red) regions of the upper follicle before they differentiate into the oil producing sebocytes.

In addition to defining the lineage progression of bulge cells to the sebaceous gland, the authors provide strong evidence that Wnt signalling is important for directing the activity of bulge cells to the sebaceous gland. Multiple studies have examined the role of Wnt signalling in controlling bulge cell contribution to hair follicle lineages (Fuchs and Horsley, 2008). Interestingly, sebaceous gland tumours develop in mice and humans expressing a dominant-negative form of Lef1 lacking the N terminus (ΔNLef1), which cannot bind to β-catenin, blocking transcription downstream Wnt signalling (Niemann *et al*, 2002; Takeda *et al*, 2006). To determine if expression of the dominant ΔNLef1 transgene results in increased contribution of bulge cell progeny to sebaceous gland formation, the authors follow bulge cell progeny in mice expressing K14-ΔNLef1 or in mice expressing ΔNLef1 in the bulge under the K15 promoter. These experiments revealed that Lef1 activity prohibits bulge cell commitment to the sebaceous gland because tumours from the ΔNLef1 transgenic mice originated from bulge cells. Further analysis of the regulation of Wnt signalling in bulge cells and their progeny may shed light on the mechanisms by which bulge cells contribute to lineages in the skin as well as tumours.

In summary, this manuscript addresses several concepts that are important for the biology of stem cells and the skin, including the relationship of stem cells to their progeny and the regulation of lineage commitment by Wnt signalling. Additional studies revealing how follicular stem cells generate sebocytes could shed light on additional molecular mechanisms that drive bulge cells to the sebaceous gland lineage as well as if bulge cells contribute to acne, a major pathogenesis of the sebaceous gland (Makrantonaki *et al*, 2011).

Conflict of interest

The author declares that she has no conflict of interest.

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