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Hair stem cells born without a home

> early asymmetric divisions of placode cells specify the stem cell population of the mature hair follicle

Adult stem cells reside in specific microenvironments in adult tissues, known as niches, which regulate their function and fate, but how adult stem cells are established during development is poorly understood. Using the hair follicle as a model, Fuchs and colleagues now show that adult stem cells can be specified very early during tissue ontogenesis, in the absence of a pre-established niche. This specification involves asymmetric, perpendicularly oriented divisions of early progenitors, which yield daughters with differential WNT signalling and thus differential responsiveness to sonic hedgehog (SHH) signalling.

Hair follicles arise during development through epidermis thickening to form a plate-like structure known as the placode. The placode expands through cell proliferation and invaginates into the underlying dermis, forming a mature follicle, which includes a population of resident adult stem cells. Using fixed samples, as well as 4D video microscopy of developing mouse hair follicles, the authors found that nearly all cell divisions in the placode were perpendicular to the basement membrane (a layer of extracellular matrix underlying epithelial tissues), thus leading to the generation of basal cells (adjacent to the basement membrane) and suprabasal cells (displaced from the basement membrane). These divisions were asymmetric with regard to WNT signalling: basal cells retained high WNT signalling (WNT^{high}), whereas in the suprabasal cells, WNT signalling was low (WNT^{low}). This asymmetric WNT signalling was further associated with the acquisition of different cell fates, with the basal cells maintaining placode-like characteristics and the suprabasal cells inducing the expression of SOX9, which is a key determinant of hair follicle cell stemness.

Subsequent analysis of cell cycle kinetics revealed that the WNT^{high} (early placode and basal) cells divided rather infrequently, whereas the SOX9-expressing suprabasal cells were highly proliferative. Accordingly, whereas WNT^{high} cell numbers remained constant, the numbers of SOX9-expressing, WNT^{low} cells stably increased during development, indicating their expansion through symmetric cell division. This suggested that the early asymmetric divisions of placode cells specify the stem cell population of the mature hair follicle. Indeed, linage-tracing experiments revealed that the daughters of early placode cells contributed to the stem cell pool in adult hair follicles.

To unravel how differential WNT signalling drives the observed differences in cell fate specification, the authors investigated the role of SHH, which, similarly to WNT, is a known regulator of hair follicle development. They concluded that SHH represses WNT signalling and that basal, WNT^{high} cells are refractive to SHH signalling, whereas in WNT^{low}, SOX9-expressing suprabasal cells, SHH signalling is high. Furthermore, it has been revealed that in SHH mutants, SOX9-expressing cells failed to expand at later developmental stages. These results indicate that SHH promotes stemness and the expansion of the stem cell population, probably by further repressing WNT signalling in WNT^{low} cells.

This study sheds new light on the origin of adult hair follicle stem cells and delineates cellular and molecular events driving this process. It reveals that specification of these adult stem cells occurs in the absence of a predefined stem cell niche and depends on the antagonism between WNT and SHH signalling pathways. It would be interesting to investigate whether similar principles also govern the origins of other adult stem cell compartments.

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ORIGINAL ARTICLE Ouspenskaia, T. *et al.* WNT-SHH antagonism specifies and expands stem cells prior to niche formation. *Cell* **164**, 156–169 (2016)
FURTHER READING Solanas, G. & Aznar-Benitah, S. Regenerating the skin: a task for the heterogeneous stem cell pool and surrounding niche. *Nat. Rev. Mol. Cell Biol.* **14**, 737–748 (2013) | Goodell M. A. *et al.* Somatic stem cell heterogeneity: diversity in the blood, skin and intestinal stem cell compartments. *Nat. Rev. Mol. Cell Biol.* **16**, 299–309 (2015)