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Changing faces: Can a new identity stop balding?

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While the skin epidermis is derived from a single ectodermal origin, the skin dermis arises from three developmental origins; dorsal dermis is from the dermamyotome, ventral dermis is from the lateral plate mesoderm, while craniofacial dermis is derived from neural crest ectoderm (1). These different origins are believed to influence the behaviours and characteristics of hair follicles in each location. For example, frontal scalp follicles are regarded as hormonally sensitive, and in response to elevated dihydrotestosterone (DHT) will undergo miniaturisation leading to androgenetic alopecia. On the other hand, occipital scalp follicles are unresponsive to DHT, meaning balding patterns on the scalp often reflect the developmental origin of the fibroblasts in each location (2). Hair transplantation, when hair follicle units are transferred from the occipital scalp to the frontal scalp to treat androgenetic alopecia, works in principle due to a concept known as donor

dominance (3). Follicles retain the identity of their donor site, and are therefore not susceptible to miniaturising effectors present in the frontal scalp.

If hair transplantation is not a viable option to treat androgenetic alopecia, there are a relatively small number of drugs all detected serendipitously which can postpone, but not reverse hair follicle miniaturisation. As balding becomes more widespread bulge stem cells lose their ability to differentiate into hair germ progenitors (4), while in the mesenchyme there is a reduction in the number of cells in the dermal papilla. It is unknown if this reduction in cell number is due to migration away from the papilla, or apoptosis within the papilla (5). There are a number of research groups currently focusing on identifying ways to reverse the miniaturisation process, by promoting papilla rejuvenation or converting interfollicular fibroblasts to a dermal papilla identity. Given the inherent differences in skin dermis and papillae from different sites on the scalp, the type of papilla rejuvenated, or the origin of the fibroblasts to be reprogrammed into papillae needs to be carefully considered (Figure 1). Surely the most effective strategy for miniturisation is to promote rejuvenation, or regeneration of an occipital scalp papilla in a frontal scalp location?

In this issue of Experimental Dermatology, Kwack et al assess differences in the Wnt receptor SFRP2, in dermal papilla cells isolated from frontal scalp, occipital scalp and beard hair follicles (6). They found highest levels in the beard, and lowest within the frontal scalp. We have previously demonstrated that spheroid culture, or forced condensation of human papilla cells is necessary but not sufficient for the cells to induce hair follicle development in juxtaposed epidermis (7). By incorporating frontal, occipital scalp or beard papilla cells into spheroid cultures to assess inductivity,

Kwack et al demonstrated a positive correlation between SFRP2 expression and inductive potential of papilla cells. Using spheroids established from occipital scalp follicle papillae, substantially more hair induction was observed compared to when spheroids were established from frontal scalp follicle papillae. Next, the authors assessed whether SFRP2 was necessary for spheroid inductivity, and used an siRNA to perturb expression in occipital scalp hair follicles. They found a significant reduction in inductive potential after inhibiting expression of SFRP2, and hence demonstrated its necessity. However, the key experiment with regards to androgenetic alopecia would be to see whether increased SFRP2 expression in a frontal scalp papilla is sufficient to enhance inductivity. This was not assessed in the manuscript discussed, but is it the way to go?

SFRP2 is a member of the frizzled receptor family, and thus has a role in modulating Wnt signalling. While Wnt signalling has been strongly associated with all aspects of hair growth and cycling, the question remains as to where in the signalling hierarchy SRFP2 is involved. In recent years we have seen a multitude of papers where one cell type is reprogrammed into an alternate cell type, with this approach being adopted into the mainstream after somatic cells were reprogrammed to a pluripotent fate by Takahashi and Yamanaka in 2006 (8). Could SFRP2 reprogramme a frontal scalp papilla into an occipital scalp papilla? What many of the reprogramming papers have in common is that they use transcription factors to direct the change in cell identity (9). Systems biologists will tell you that these transcription factors act as master regulators, located at the top of gene regulation hierarchy. Being master regulators, they directly or indirectly control transcription of large numbers of signature genes and signalling pathways, which can subsequently determine a cells

identity. Since SFRP2 is not a transcription factor, it is most likely a pawn in the process of inductivity rather than the queen. However, its expression correlates well with inductivity, and it is a useful marker for hair researchers to use to help characterise dermal papilla cells, and their inductive status. Going forward, research effort will likely focus on identifying master regulators that control the identity of an occipital scalp papilla, as compared to a frontal scalp papilla.

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Conflict of interest

There are no conflicts of interest.

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Figure legend

Figure 1: In hair transplantation follicles are moved from the occipital to the frontal scalp, yet they retain the identity of a follicle on an occipital site. Should research effort be focused on reprogramming frontal follicles to an occipital identity, if we are to successfully reverse miniaturisation?