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Previews

SKPing a Hurdle: Sox2 and Adult Dermal Stem Cells

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In this issue of *Cell Stem Cell*, Biernaskie et al. (2009) demonstrate that a specific subpopulation of dermal papilla fibroblasts, marked by Sox2 expression, displays properties of adult stem cells, including serial hair follicle initiation, dermal cell differentiation, and skin-derived precursor production.

Scientists have long recognized that epithelial-mesenchymal interactions are necessary for the formation and maintenance of hair follicles in mammalian skin. One cell population in particular, fibroblasts residing in the dermal papilla (DP) and dermal sheath (DS) of anagen hair follicles, has been shown to possess inductive properties for hair follicle formation and to contribute to, and accelerate, wound healing (Waters et al., 2007). DP cells have also been found to specifically express Sox2 (Rendl et al., 2005), an established marker of somatic stemness (Takahashi and Yamanaka, 2006), and to exchange cells with the DS (Tobin et al., 2003), raising the possibility that the DP/DS area might represent an adult stem cell niche poised to aid in hair follicle and dermal regeneration and maintenance.

Despite this evidence, the inductive and potential stem cell properties of DP cells remain to be explored. Recently, Driskell et al. (2009) provided evidence that DP cells are a heterogenic population of fibroblasts as defined by their Sox2 expression status. They further showed that distinct types of hair fibers are induced by individual subtypes within this heterogeneous population of DP cells. However, several questions as to the DP cells' ability to function as true adult stem cells were left unanswered. In this issue of *Cell Stem Cell*, Biernaskie et al. (2009) demonstrate the multilineage differentiation potential of $Sox2^+$ DP cells and establish a direct relationship between these cells and skin-derived precursors (SKPs), which can be isolated from dermal papillae and have the ability to differentiate into a broad variety of cell types in vitro, including neurons, smooth muscle cells, and adipocytes (Fernandes et al., 2004).

In their study, Driskell et al. (2009) demonstrated the existence of two distinct cell populations within the DP, each having the ability to induce hair follicles de novo. Both subsets express the DP marker CD133, but they differ in their expression of Sox2. Sox2 is expressed in embryonic skin between embryonic day 14.5 and 16.5, coinciding with the induction of guard, awl, and auchenne types of hair fibers. At embryonic day 18.5, however, when the fourth type of trunk hair—zigzag—is specified, Sox2 expression is conspicuously absent. Consequently, $Sox2^+$ cells isolated from neonatal DPs were shown to induce awl and auchenne hair follicle formation in skin reconstitution assays in vivo, whereas $Sox2^-$ cells exclusively produced zigzag hairs. Interestingly, none of these cell populations was able to induce the formation of guard hairs, even though the DP of all guard hairs scored positive for Sox2 expression. Driskell et al. (2009) also uncovered an interesting divergence of gene expression patterns in the two groups. $Sox2^+$ cells tend to express genes associated with the Wnt, BMP, and FGF signaling pathways, whereas members of the Shh, IGF, Notch, and integrin signaling pathways are preferentially represented in $Sox2^-$ cells. Overall, Driskell et al. (2009) make a convincing case that DPs harbor at least two distinct populations of progenitor cells, characterized by their ability to express Sox2 and by their potential to induce morphologically distinct hair follicles.

Biernaskie et al. (2009) extend the findings of Driskell et al. (2009) by exploring the specific stem cell potential of $Sox2^+$ DP cells. They not only confirm that $Sox2^+$ DP cells can induce hair follicle morphogenesis but also show that these cells tend to home back to the DP and DS upon transplantation into adult mouse skin, strengthening the idea that the DP/DS area represents an adult stem cell niche. However, not all $Sox2^+$ cells follow this migration pattern. Biernaskie et al. (2009) provide evidence that $Sox2^+$ DP cells can terminally differentiate in vivo and contribute to the interfollicular dermis, assuming a gene expression profile appropriate for their new location. In addition, cultured $Sox2^+$ DP cells are able to give rise to neural cells not normally found in the dermis as well as SKPs, which have previously been isolated from DPs of whisker hair follicles (Fernandes et al., 2004). These SKPs mimic the $Sox2^+$ DP cells in their ability to induce hair follicle morphogenesis, home back to the presumptive DP/DS niche, and differentiate into dermal (but not epithelial) cell types. Interestingly, Biernaskie et al. also show that these SKPs have the ability to self-renew as well as serially induce hair follicle formation, up to three times, without losing their multilineage differentiation potential. It will be imperative to test whether $Sox2^+$ DP cells can likewise demonstrate these stem cell-like characteristics. Regardless, the authors' experiments significantly strengthen the case for a $Sox2^+$ stem cell population residing in the DP/DS niche and identify SKPs as immediate progenitor cells that retain stem cell-like properties.

SKPs appear to be derived from the neural crest (Fernandes et al., 2004). $Sox2^+$ DP cells express higher levels of the neural crest markers p75, S100b, and Sox10 (Driskell et al., 2009). The hair follicle bulge, an established reservoir of adult stem cells, also contains neural crest-derived cells (Amoh et al., 2005). It will be interesting to determine the exact lineage of DP stem cells, their potential relationship to bulge stem cells, and when and where the DP/DS niche is first established. In addition, it will be important to assess whether DP stem cells exhibit positional identities similar to

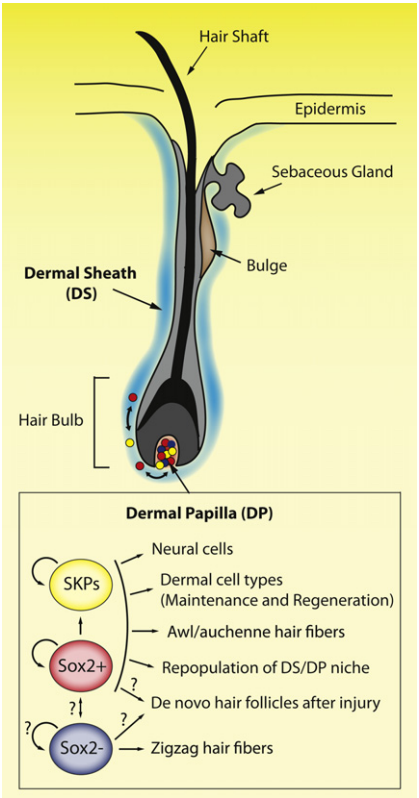

Figure 1. An Adult Dermal Stem Cell Niche
Three defined populations of potential adult stem cells reside in the dermal papilla (DP) of the hair follicle and can migrate to and from the surrounding dermal sheath (DS): Sox2$^+$ (red), Sox2$^-$ (blue), and skin-derived precursors (SKPs, yellow). When isolated from the DP, these cells display a broad array of stem cell-like properties. Sox2$^+$ cells and SKPs can self-renew, repopulate the DP/DS niche, and show a multilineage differentiation and induction potential. Sox2$^-$ cells can induce zigzag hair morphogenesis, but their relationship to Sox2$^+$ cells and SKPs, as well as their ability to self-renew, is still unclear (as indicated by question marks). Dermal stem cells have also been implicated in de novo hair follicle induction following skin injury. However, the roles for each type of stem cell in this process remain to be ascertained.

terminally differentiated dermal fibroblasts (Rinn et al., 2006).

Biernaskie et al. (2009) also provide evidence that both Sox2$^+$ cells and SKPs can leave the DP to migrate toward a site of wounding and contribute to both de novo hair follicle formation and dermal repair. Cells from outside the hair follicle bulge appear to be the main contributors to these new hair follicles in response to Wnt signaling (Ito et al., 2007). Driskell et al. (2009) have shown that Sox2$^+$ DP cells express more genes from the Wnt signaling pathway, strengthening the idea that this DP cell subpopulation establishes hair follicles in wounded skin. However, Driskell et al. (2009) note that the hair follicles induced in the experiments of Ito et al. (2007) all appear to be of the zigzag type, which would arise from a Sox2$^-$ DP cell population. Although it is likely that the DP/DS stem cell population contributes to de novo hair follicle morphogenesis in wounded adult skin (see Ito et al., 2007), a more detailed exploration of this hypothesis is necessary.

The work by Biernaskie et al. (2009) and Driskell et al. (2009) has successfully defined three populations of potential adult stem cells residing in the DP/DS niche: Sox2$^+$, Sox2$^-$, and SKPs (Figure 1). These cells are capable of inducing hair follicle formation, and at least Sox2$^+$ cells and SKPs can leave the niche to contribute to normal or injured dermal tissue (Figure 1). In addition to significantly expanding the field of skin biology, these findings provide exciting avenues for clinical applications. Because dermal stem cells can easily be obtained from and reintroduced into adult human patients, they carry a very low risk of rejection. Furthermore, their multilineage differentiation and induction potential makes dermal stem cells interesting candidates for the treatment of a number of diseases, including Parkinson's disease, type II diabetes, alopecia, and chronic wounds.

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