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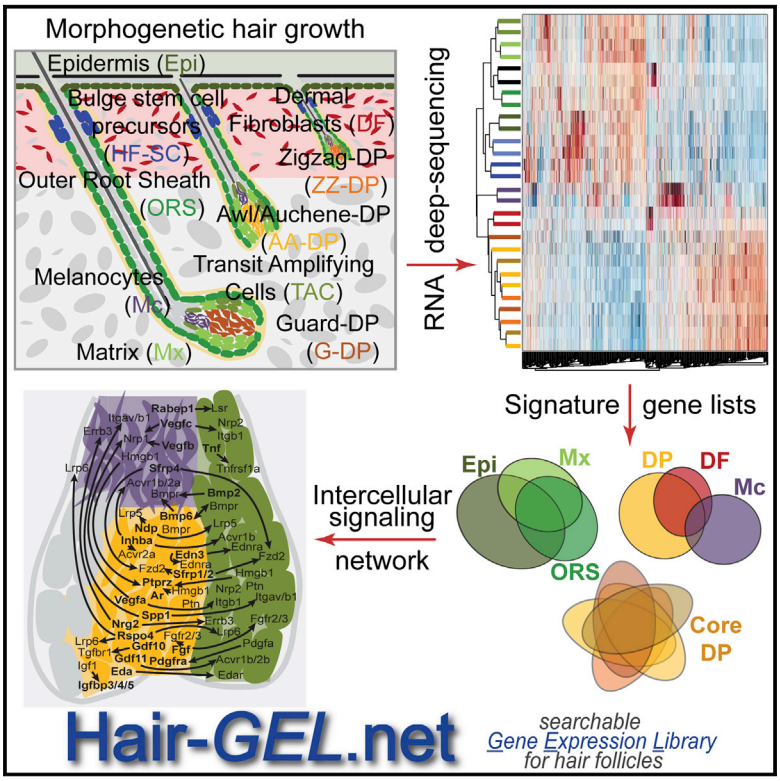
Signaling Networks among Stem Cell Precursors, Transit-Amplifying Progenitors, and their Niche in Developing Hair Follicles

Graphical Abstract



Highlights

- RNA-seq identifies transcriptomes of 14 skin populations during hair growth
- SC precursors, progenitors, and hair-type-specific DP niche signatures are defined
- Comparison with embryonic and adult signatures shows dynamic gene expression
- Signaling interaction network reveals a complex web of intercellular exchanges

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In Brief

Rezza et al. examine signal exchange among bulge stem cell precursors, proliferating progeny, and their niche during morphogenetic hair growth. The authors isolate and characterize 14 specialized skin cell populations, defining signature genes and revealing numerous cell-cell interactions in the hair follicle bulb.

Accession Numbers

GSE77197

Rezza et al., 2016, Cell Reports *14*, 3001–3018
March 29, 2016
http://dx.doi.org/10.1016/j.celrep.2016.02.078

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Signaling Networks among Stem Cell Precursors, Transit-Amplifying Progenitors, and their Niche in Developing Hair Follicles

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http://dx.doi.org/10.1016/j.celrep.2016.02.078

SUMMARY

The hair follicle (HF) is a complex miniorgan that serves as an ideal model system to study stem cell (SC) interactions with the niche during growth and regeneration. Dermal papilla (DP) cells are required for SC activation during the adult hair cycle, but signal exchange between niche and SC precursors/transit-amplifying cell (TAC) progenitors that regulates HF morphogenetic growth is largely unknown. Here we use six transgenic reporters to isolate 14 major skin and HF cell populations. With next-generation RNA sequencing, we characterize their transcriptomes and define unique molecular signatures. SC precursors, TACs, and the DP niche express a plethora of ligands and receptors. Signaling interaction network analysis reveals a bird's-eye view of pathways implicated in epithelial-mesenchymal interactions. Using a systematic tissue-wide approach, this work provides a comprehensive platform, linked to an interactive online database, to identify and further explore the SC/TAC/niche cross-talk regulating HF growth.

INTRODUCTION

Embryonic hair follicle (HF) formation, hair growth after birth, and regulation of the adult hair cycle involve complex signaling interactions among epithelial stem cells (SCs), progenitors, and a dermal specialized niche compartment, the dermal papilla (DP) (Lee and Tumbar, 2012; Rezza et al., 2014; Rompolas and Greco, 2014; Sennett and Rendl, 2012). At the end of the resting phase of the hair cycle, DP cells signal to bulge/germ SCs to activate new HF growth, and recent ligand supplementation experiments and receptor ablation studies in the SCs indicate an important role for DP-derived TGFB2, FGF7, and inhibitory BMP signals (Greco et al., 2009; Kobielak et al., 2003; Oshimori and Fuchs, 2012). Laser-mediated ablation established the absolute requirement of these cells for SC activation during the hair cycle (Rompolas et al., 2012).

Similarly, during hair growth, DP cells are thought to act as a core signaling center for surrounding epithelial progenitors (transit-amplifying cells or TACs) within the wider matrix (Mx) compartment that proliferate, migrate upward, and differentiate into the multiple layers of the hair shaft and the inner root sheath channel (Hsu et al., 2014a). The outer root sheath (ORS) lines the epithelial HF compartment, is contiguous with the Mx and epidermis, and contains the SC precursors of the adult HF bulge during early hair growth (Schlake, 2007). FGF signals from the DP have been implicated in controlling hair growth (Petiot et al., 2003), while BMP and WNT signaling play an important role in hair shaft progenitor differentiation; but, the precise source of BMP and WNT ligands is unclear (DasGupta and Fuchs, 1999; Kobielak et al., 2003). SHH is produced by a subpopulation of TAC progenitors that reside right next to the DP compartment (Gambardella et al., 2000; Hsu et al., 2014b). It is still unclear if a broader requirement for TAC-derived signals interacting with the DP niche exists, as pure TACs of growing HFs have not been isolated and characterized. Finally, the third major cellular component in the HF bulb is melanocytes (Mc) that provide pigment to the epithelial cells and are thought to receive regulatory signals from the DP niche (Enshell-Seijffers et al., 2008, 2010). Whether Mc signal with TAC progenitors and Mx cells is currently unclear.

Previous studies have tried to identify signals involved in driving HF growth using a global transcriptomic approach (Driskell et al., 2009; Rendl et al., 2005). Isolation of HF cell populations during the morphogenetic growth phase and subsequent