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Tic-TACs: Refreshing Hair Growth

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http://dx.doi.org/10.1016/j.cell.2014.04.014

Although stem cells are subject to niche control, evidence is emerging that they also contribute to generating the niche through their offspring. Using the hair follicle as a model, Hsu at al. demonstrate that the transient-amplifying cells, downstream of stem cells and well-known cell producers, signal back to stem cells to maintain long-term regenerative capacity.

Hair follicles (HFs) actively regenerate in adults and contain a heterogeneous mixture of anatomically defined stem, niche, and differentiated cells. They have proven to be particularly fruitful for discoveries in mammalian stem cell (SC) biology. Whether and how the various stem, progenitor, and niche cells communicate during the progression of the HF growth phases, including intricate coordination between many cell types at lengthening anatomical distances, have not been completely elucidated. Hsu et al. (2014) now provide critical insights into these processes.

HFs contain quiescent SCs located in a structure termed the bulge (Bu-SCs) and more activation-prone SCs anatomically located immediately below the Bu-SCs in the hair germ (HG). SCs in the HF have been demonstrated to be regulated by numerous cellular sources, most prominently by mesenchymal cells located below the HG in the dermal papilla (DP). Other potential niche cells for HF SCs include HF terminally differentiated epithelial cells, adipocytes and nerve fibers, among others (Solanas and Benitah, 2013) (Figure 1A).

HFs cycle between production (anagen), destruction (catagen), and resting (telogen) phases. The multistage anagen phase is initiated when "activated" SCs in the HG (Greco et al., 2009) receive proliferative signals, likely from the DP, and differentiate into transit-amplifying cells (TACs). TACs form a structure termed the matrix and eventually give rise to the differentiated cells that compose the HF (Solanas and Benitah, 2013). As anagen progresses, the HF physically expands relative to its resting state leading to increased distances between Bu-SCs, activated SCs, matrix (TACs), and the DP (Figure 1B).

Previously, HG SCs were demonstrated to proliferate first to initiate HF regeneration, with Bu-SCs lagging behind (Greco et al., 2009). Hsu et al. now show that cells of the HG begin to proliferate in anaphase I (AnaI) and lead to matrix formation in AnaII. Bu-SCs proliferate between AnaII and AnaIII and go quiescent at AnaV. By AnaIII, the HF has doubled in size with the bulge now being 200 μm away from the DP. Given that the DP is required for HF regeneration (Rompolas et al., 2012), this begged the question of how Bu-SCs can be activated by cells from such a far-away place.

The answer lies in the TACs. Using multiple in vivo genetic perturbations, the authors demonstrate that coincident with proliferation and long-term HF regeneration, Sonic Hedgehog (SHH) signaling upregulates Bu-SC activity (Figure 1C). A role for SHH in HF biology was well established (Chiang et al., 1999; Morgan et al., 1998; Brownell et al., 2011), but Hsu et al. provide evidence that TACs uniquely secrete SHH and that this is the critical switch for activating the quiescent Bu-SCs necessary for long-term HF regeneration.

They first show that among the many HF cells (including Bu-SCs), only TACs express high levels of SHH during AnaII–III. They then genetically deleted SHH and show that whereas HG cells proliferate, Bu-SCs do not. They subsequently conditionally deleted the receptor for SHH, Smoothened (SMO), or the downstream transcriptional input of SHH signaling, *Gli2*, and this again led to diminished Bu-SC proliferation, confirming that the effects of SHH on Bu-SCs are direct. Of note, conditional *Gli2* knockout in the

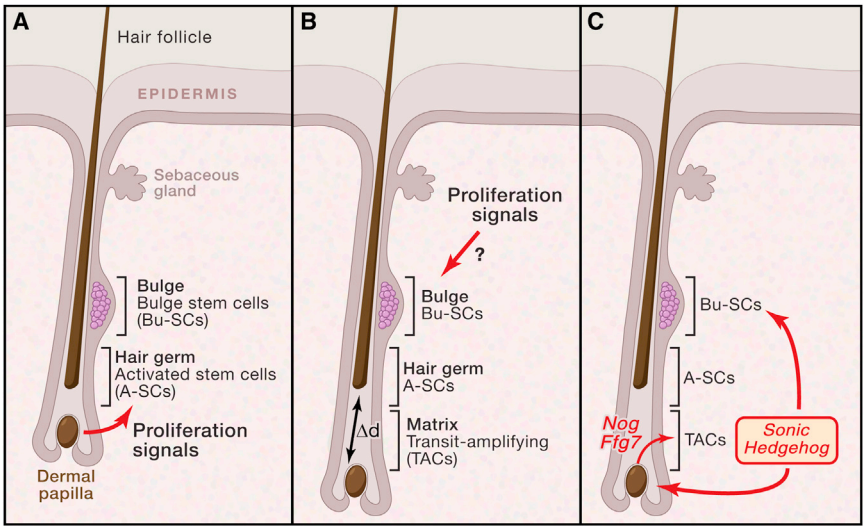

Figure 1. TACs Regulate HF SC Proliferation

(A) During HF regeneration, signals from the DP evoke proliferative responses in activated stem cells (A-SCs) located in the HG below a layer of quiescent Bu-SCs, leading to the initiation of the growth of the HF.

(B) HG proliferation leads to the production of TACs and expansion of the HF area downward, leading to increased distances (Δd) between the DP and the SC populations. After initiation of HF growth, BU-SCs begin to proliferate by unknown mechanisms.

(C) Hsu et al. now show that SHH signals emanating from TACs directly stimulate BU-SC proliferation as well as the DP to secrete *Noggin* (*Nog*) and *Fgf7*, which feed back to TACs, allowing for proper HF regeneration.

HF evoked proliferative defects only in quiescent Bu-SCs and not in activated SCs of the HG. Therefore, SHH directly and selectively alters one set of SCs, revealing a molecular distinction between the two pools of repopulating cells. TAC SHH also appears to directly signal to the DP, controlling its production of *Noggin* and *Fgf7*, factors important for hair-bulb proliferation (Figure 1C). Therefore, TACs provide multiple prompts for HF generation of hair.

The study of Hsu et al. portrays a remarkable choreography in the HF with distinct participants playing interdependent, temporally ordered roles. The primed SCs of the HG respond to DP cues and initiate TAC production. The TACs, once thought mere brute-force cell-production machines, now appear to signal to the quiescent SCs of the bulge, calling them into action while also prompting DP to produce *Noggin* and *Fgf7*.

The simple models of singular niche cells contributing to regulated persistence of a uniform SC population increasingly appear as if they are behind us in mammalian biology. Multiple classes of SCs have been defined in most well-studied systems. These SCs are governed by a complex of cells and signals that, according to the work of Hsu and colleagues, are sequential and involve cells produced from the previous step. SC descendants had been previously noted to be niche participants in the intestine, for example, where Paneth cells play a role (Sato et al., 2011), or hematopoiesis, where macrophages contribute to SC regulation (Winkler et al., 2010; Chow et al., 2011). However, that the descendants are the TACs and that they can feedforward a proliferative signal to a different class of SCs is new ground. How that feedforward process ultimately is quenched, how the system can "read" when to turn on and turn off, and how disorder of the events participates in disease are questions still to be addressed.

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