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The thinning top: why old people have less hair

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Abstract

Changes in the hair cycle underlie age-related alopecia, but the causative mechanisms have remained unclear. Chen and colleagues point to an imbalance between stem cell activating and inhibitory signals as the key determinant of age-related regenerative decline. Further, they identify a secreted protein, follistatin, that may be able to shift the balance toward renewal.

Commentary

An intriguing puzzle in the field of regeneration is why regenerative capacity declines with age. Younger animals have a greater ability to recover from damage and to adjust to physiologic tissue loss than do older ones. In humans, for example, young children can regenerate missing calvarial bone, whereas adults fail to do so (Drake *et al.*, 1993). In rodents, peripheral nerve regeneration is more robust in younger animals than in older rodents (Kang and Lichtman, 2013). Similarly, in the skin the rate of both epidermal renewal and hair follicle cycling declines with age (Keyes *et al.*, 2013). The reasons for age-related loss of regenerative ability are largely unknown. On page ____, Chen and colleagues utilize clever transplantation experiments to characterize changes in hair cycling with age and to provide molecular mechanisms for age-related decline (Chen *et al.*, 2014).

Earlier experiments by Chase in the 1950s demonstrated that hair regeneration in mice proceeds in waves of hair growth emanating from central foci (Chase, 1954). In the current study, Chen and colleagues reexamined this phenomenon by clipping pigmented mouse hairs and observing patterns of hair reemergence with time. By comparing mice at varying ages from 12 to 26 months, they observed that domains of hair growth shrink with increased age, reflecting a decrease in both the rate of hair wave propagation and in the distance a wave will ultimately travel. Further, in mice greater than 12 months of age, they noted an increase in the duration of telogen, the resting phase of the hair cycle, which they termed telogen retention.

Hair follicles are regenerated throughout an organism's lifetime via mobilization of long-lived stem cells in the bulge region. At anagen, the growth phase of the hair cycle, these

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cells divide to self-renew, as well as to give rise to hair germ cells that then reconstitute mature follicles(Alonso and Fuchs, 2006). Given this, one could envision at least two explanations for the observed decrease in follicle regeneration with age: (1) stem cells that repopulate hair follicles decrease in number, and/or (2) stem cell activation is decreased as animals age. Evidence from human studies argues against a decrease in stem cell number, as bulge stem cells are maintained in scalp skin from patients with age-related alopecia(Garza *et al.*, 2011). Consistent with this, the authors find that both young and old mice have similar numbers of stem cells in the bulge as assessed by immunofluorescence for stem cell markers and by FACS. To determine whether reduced regeneration reflects decreased stem cell activation, the authors grafted patches of skin from older animals in telogen onto the backs of young SCID mice. Strikingly, when the experiments were performed with small patches of donor skin, telogen retention was fully reversed, leading to anagen onset and hair follicle regeneration throughout the donor skin. The ensuing wave of hair regeneration even extended into surrounding skin of the recipients. Importantly, hair follicle cycling in grafted skin persisted through multiple cycles, indicating a true reversal of the telogen retention phenotype, rather than a transient stimulation of folliculogenesis by surgical trauma. Larger skin grafts did not respond as completely, however. While initiation of hair cycling was observed at the periphery of larger grafts, the central portions remained in telogen, from the second grafted cycle onward. In both small and large skin grafts, waves of follicle generation initiated at the boundary between donor old skin and recipient younger skin. This suggests that factors elaborated by recipient skin activate previously refractory follicles in the donors.

To characterize mechanisms governing the differing regenerative capacities in young and old mice, the authors examined factors previously known to regulate anagen onset. Activation of the canonical Wnt pathway has been demonstrated to precede anagen in mice(Myung *et al.*, 2013). The authors found that canonical Wnt ligands and the Wnt effector β -catenin were present at similar levels in anagen hair germs of both young and old mice. However, older mice had far higher levels of the Wnt inhibitors Dkk1 and Sfrp4. Similarly, BMP2, which this group had previously identified as a negative regulator of anagen onset, was upregulated in older mice(Plikus *et al.*, 2008). These data suggest that the balance between stem cell activating and inhibitory signals is shifted toward inhibition in older mice. To identify factors that may shift this balance, the authors focused on follistatin, a known positive regulator of anagen onset(McDowall *et al.*, 2008). Follistatin gene expression was higher in the skin of younger mice. Further, follistatin levels were increased in older skin grafts following transplantation onto younger mice. Since follistatin is a secreted molecule, it may be responsible for the reactivation of hair cycling in telogenic donor skin when grafted onto younger recipients. Strikingly, follistatin-releasing beads were sufficient to convert hair follicles in telogen into anagen when placed on the skin of young mice. Whether this effect can be recapitulated in older mice in telogen retention remains to be seen.

These results support an emerging understanding that aging in skin is not fully a cell autonomous phenomenon. However, as intriguing as these findings are, they raise several new questions. The mechanisms by which follistatin or other extrafollicular signals activate

stem cells in the hair bulge are unknown. As follistatin is a known BMP antagonist (McDowall *et al.*, 2008), and since younger mice express higher levels of follistatin, it is tempting to speculate that younger mice are less sensitive to the anagen-inhibitory effects of BMP2. Additionally, whether follistatin is the only molecule in young skin capable of rejuvenating older follicles is not clear. Finally, the reason why waves of hair regeneration dissipate in the center of larger skin grafts remains uncertain. It will be interesting to determine whether this reflects intrinsic hair follicle defects or deficiencies in extrinsic signals. These questions aside, this present study is a compelling demonstration that extrafollicular stimuli govern differences in hair renewal capacities in young and old mice. At least when it comes to hair cycling, you really are as young as your neighbors.

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Clinical relevance

1. Hair follicles in younger mice cycle more frequently than those in older mice.
2. Factors extrinsic to hair follicles can reactivate hair cycling in dormant older skin.
3. The secreted protein follistatin enhances hair follicle cycling, pointing to a potential therapeutic strategy for alopecia.

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