Maintaining Quiescence

In order to sustain cyclic activation of hair follicle (HF) regrowth, quiescent hair follicle stem cells (HFSCs) require transient activation; however, the mechanisms that regulate the behavior of HFSCs remain to be delineated. Ma and colleagues studied the RNA-binding protein Musashi 2 (Msi2) in this process, as this factor has previously been implicated in stem cell regulation in other tissues. Transgenic and knockout mice revealed that Msi2 suppresses hair regeneration and maintains HFSCs in a quiescent state during the telogen-to-anagen transition. Interestingly, Msi2 represses hedgehog (Hh) signaling pathway activity via direct targeting of Shh to regulate hair regrowth. These findings expand our knowledge about the complex signaling pathways involved in cyclic hair growth. See page 1015.

Signature Cytokines

Autoimmunity has been suggested to underlie the pathology of generalized nonsegmental vitiligo. As chemokines are important in inflammatory and autoimmune responses, Rezk and colleagues investigated the role of these molecules in the depigmentation disorder vitiligo and found that expression and secretion of CCL5, CXCL12, CXCL8, and CKLF are upregulated in vitiligo cells. Further studies revealed that dendrocytes and Langerhans cells migrated to sites of CXCL12 administration or transplantation of melanocytes that express CXCL12. In addition, melanocyte-derived CXCL12 and CCL5 are sufficient to recruit T cells and antigen-presenting cells and activate the melanocyte-reactive T cells in vitiliginous skin. Thus, inhibition of these chemotactic players may offer a strategy for vitiligo stabilization. See page 1126.

Combo Approach

Mutational analysis of melanomas has revealed mutations in BRAF, NRAS, and NF1 and spurred development of specific small-molecule inhibitors of BRAF and MEK but not NF1. NF1-mutant melanomas often respond better to inhibitors of ERK than MEK, although combination therapy may further enhance the efficacy for this melanoma subtype. Trousil and colleagues demonstrated that combination treatment with the ERK inhibitor SCH772984 with the AMP-activated kinase activator phenformin synergistically blocked melanoma cell proliferation and enhanced apoptosis in cell lines. Mechanistically, this treatment cooperatively inhibited mTOR, which is a critical signaling factor in NF1 loss-driven tumorigenesis. These findings support further clinical investigation of combined targeted treatment with ERK inhibitors and phenformin for NF1-mutant melanoma. See page 1135.

Topographical Diversity

As with the topographical differences exhibited by the skin microbial communities, immunological distinctions between different skin sites is also likely. Indeed, Dajnoki and colleagues discovered that the epidermal factor thymic stromal lymphopoietin (TSLP), dendritic cells (DCs), and T cells exhibited a similar fine topographical distribution. In healthy sebaceous gland-rich skin, TSLP expression, numbers of inactivated DC, and T cells with an interleukin (IL)-17/IL-10 cytokine milieu were greater than in sebaceous gland-poor skin. Interestingly, in papulopustular rosacea skin, TSLP was absent, DCs were activated, and inflammatory T (Th1 and Th17/23) cells were present, highlighting the apparent preferred localization of inflammatory skin diseases. See page 1114.

Promoting Healing

Skin injury requires immediate reestablishment of the physical skin barrier and antimicrobial response. Yang and colleagues reported that IL-27 is an important regulator of keratinocyte proliferation and differentiation, which are necessary for reestablishment of the barrier following skin injury. Dermal CD301b+ cells produce this cytokine adjacent to the wounded area, and this cell type is critical for optimal wound healing. Treatment of skin wounds with topical IL-27 improved wound repair in defective mice and stimulated the antiviral response, indicating that IL-27 may be a therapeutic target for improving wound healing in the clinic. See page 1166.