Hair Wnt awry

Because the genetic basis of the rare autosomal dominant form of hair miniaturization and loss, hereditary hypotrichosis simplex, is unknown, Shimomura and colleagues performed genetic linkage analysis and identified a mutation (Leu9Arg) in the adenomatosus polyposis downregulated 1 (APCDD1) gene in patients with this disease. The extracellular domain of the APCDD1 protein interacted with WNT3A and LRP5, two Wnt signaling proteins important for hair follicle induction. In addition, APCDD1 appears to be a membrane-tethered Wnt inhibitor that functions in a cell-autonomous manner at the surface of the Wnt-receiving cell. Analysis of the functional ramifications of the Leu9Arg mutation revealed that this mutation probably acts in a dominant-negative manner to destabilize APCDD1 and prevent its localization at the plasma membrane. These results support a requirement for controlled regulation of Wnt signaling during hair follicle morphogenesis and cycling, and, because of the overlap of the location of this gene and identified linkage intervals, this protein may be implicated in additional polygenic hair follicle disorders, such as androgenetic alopecia and alopecia areata. (Nature 464:1043–7, 2010)

Thwarting the vasculogenic potential

Although typically harmless and prone to spontaneous involution, infantile hemangiomas that are deemed dangerous or disfiguring are effectively treated with corticosteroids to stabilize or accelerate regression of the tumor via an incompletely understood mechanism. Because previous work found hemangiona-derived stem cells at the origin of infantile hemangiomas, Greenberger and colleagues investigated the effects of corticosteroids on this cell type. The corticosteroid dexamethasone inhibited vasculogenesis induced by hemangiona-derived stem cells in mice. Dexamethasone also inhibited the secretion of vascular endothelial growth factor A (VEGF-A) by these cells in culture, and this suppression was sufficient to block the vasculogenic potential of the hemangiona-derived stem cells in the mouse model. These exciting findings may offer a foundation for future investigation of the mechanism of corticosteroid activity in hemangioma treatment and may illuminate possibilities for the development of additional therapies targeting VEGF and vasculogenesis. (N Engl J Med 362:1005–13, 2010)

Stop the bleed

Thalidomide, the teratogenic drug once commonly used to treat nausea in pregnant women, is currently used to inhibit bleeding in individuals with gastrointestinal diseases as well as in patients with hereditary hemorrhagic telangiectasia (HHT). HHT is an autosomal dominant disease in which vascular malformations and subsequent bleeding occur because of decreased transforming growth factor-β activation and increased VEGF production. Treatment of HHT has remained challenging because of the dissemination of the vascular anomalies over entire mucosal surfaces. Lebrin and colleagues found that oral administration of thalidomide decreased both the frequency and the duration of epistaxis in HHT patients. Thalidomide exerted these effects by increasing the mural cell coverage of the vasculature, illuminating mural cells as a useful new target for vascular therapy. Thalidomide actually increased the proliferation and ability to form protrusions that embrace the blood vessels in mural cells. In addition, platelet-derived growth factor-β was implicated as a key mediator in this process. (Nat Med 16:420–8, 2010)

Most primitive in the epidermis

The three epidermal compartments—the hair follicle (HF), the sebaceous gland (SG), and the interfollicular epidermis (IFE)—are all capable of self-renewal. Although each of these skin cell populations is maintained by its own discrete stem cells during homeostatic conditions, disruption of these normal conditions can induce any of the three stem cell populations to produce all three structures. Following the identification of leucine-rich repeat-containing G protein (heterotrimeric guanine nucleotide-binding protein)-coupled receptor 5 (Lgr5) on HF stem cells that contribute to all hair lineages, but not to the SG or IFE, Snippert and colleagues found that the related Lgr6 was one of the earliest embryonic placode markers. Lgr6 marks a unique stem cell population that gives rise to all lineages of the skin, and, unlike its relative Lgr5, this protein appears to operate via a Wnt-independent mechanism. Furthermore, Lgr6+ cells functioned in long-term wound repair. Therefore, Lgr6 appears to characterize the most primitive epidermal stem cell. (Science 327:1385–9, 2010)

Stiff skin stuff

Stiff skin syndrome (SSS) is a rare autosomal congenital form of scleroderma characterized by hard, thick skin, usually covering the entire body. Accumulating evidence indicates that fibrillin-1 contributes to the pathogenesis of profibrotic phenotypes via a role in assembly of microfibrils and in regulation of the profibrotic cytokine transforming growth factor-β (TGF-β). Loeys and colleagues identified mutations in the integrin-binding TB4 domain of fibrillin-1 in SSS in humans. These mutations were sufficient to initiate and maintain cutaneous profibrotic phenotypes, and, in accord with previous data regarding fibrillin-1, these mutations altered microfibrillar assembly and microfibril–integrin interactions via dysregulation of TGF-β signaling. Because similar phenotypic characteristics were found in biopsies from patients with the related, and more common, systemic sclerosis, these findings may have much broader clinical relevance. (Sci Transl Med 2:23ra20, 2010)