Education of fibroblasts

Although tumorigenesis has been considered a cell-autonomous process involving genetically transformed cancer cells, cancer-associated fibroblasts (CAFs) promote tumor growth by inducing angiogenesis, recruiting endothelial progenitor cells, and remodeling the extracellular matrix. Recently, Erez and colleagues examined the functions of CAFs in the K14-HPV16 mouse model of multistep squamous skin carcinogenesis. Isolated CAFs expressed a proinflammatory gene signature responsible for tumor promotion. Via expression of these genes, CAFs mediate inflammation and angiogenesis by recruiting macrophages and stimulating angiogenesis. Because this gene signature is induced at the earliest stages of carcinogenesis, these fibroblasts play an important role in creating an inflammatory microenvironment to promote carcinogenesis. In addition, incubation of normal fibroblasts with carcinoma or end-stage orthotopic tumor cells promoted tumor growth or proinflammatory gene expression, respectively, suggesting in vivo education of fibroblasts by the tumor cells. Targeting these fibroblasts might become an important treatment option, given that similar gene profiles were identified in CAFs from multiple cancer types. (Cancer Cell 17:135–47, 2010)

Multifaceted IL-4

The allergic response requires coordination of cytokines to promote effector T-cell development and recruitment of inflammatory cells. In the skin, allergic inflammation results in atopic dermatitis (AD) that is promoted by IL-4, which promotes T helper type 2 (Th2) cell development. Sehra and colleagues recently demonstrated that in the absence of IL-4, expression of epidermal differentiation complex (EDC) genes was upregulated and barrier function was increased; however, in a model of AD mediated by T-cell-specific Stat6 expression, which predisposes the mice to a Th2 response, decreased EDC expression and allergic skin inflammation were observed. Eliminating IL-4 in these Stat6VT mice increased the barrier function and attenuated susceptibility to the development of allergic inflammation. These data specifically implicate IL-4 in skin homeostasis and innate barrier function. (J Immunol 184:3186–90, 2010)

Cell at the center

Stem cells have long been considered the cells at the origin of cancer because their longevity and self-renewal present an increased chance of accumulating oncogenic mutations. To identify the specific cells at the origin of basal cell carcinoma (BCC), Youssef and colleagues employed a murine BCC model that resembles human disease and utilized genetic techniques to conditionally express a Hedgehog signaling pathway molecule (SmoM2 oncogene) in various cellular compartments. Despite the common belief that BCC originates from the bulge stem cells, SmoM2 in bulge stem cells or transit amplifying matrix cells did not invoke BCC development. In contrast, expression of this signaling molecule in resident progenitor cells of the interfollicular epidermis and upper infundibulum resulted in BCC, implicating these cells in BCC origination. In addition, these results highlight the difficulty of identifying cells at the origin of cancer based solely on biochemical and morphological characteristics. (Nat Cell Biol 12:299–305, 2010)

Protease control of barrier function

To maintain the effective barrier function of the epidermis, protease and antiprotease activities must remain carefully balanced, as evidenced by rare genetic skin diseases such as Netherton syndrome (NS), in which this balance is disrupted. NS is caused by mutations in SPINK5, which encodes lymphoepithelial kazal-type-related-inhibitor (LEKTI). A deficiency in LEKTI leads to hyperactivation of kallikrein 5, kallikrein 7, and a third protease. Using tandem mass spectrometry, Bonnart and colleagues identified this unknown protease as elastase 2 (ELA2). This enzyme was shown to degrade (pro-)filaggrin, which is consistent with its hyperactive status in the skin of NS patients. In mice engineered to overexpress ELA2, severe skin barrier dysfunction was observed via the excessive degradation of (pro-)filaggrin and altered lipid metabolism. These findings emphasize the importance of protease activity regulation in maintaining skin barrier function. (J Clin Invest 120:871–82, 2010)

The ins and outs of T-cell circulation

Although T-cell circulation has been studied extensively, the migration of certain T-cell subsets, such as Foxp3+ regulatory T cells (Tregs), in the peripheral organs to the draining lymph nodes (DLNs) is not well understood. Tomura and colleagues labeled resident cells in transgenic mice that express the photoconvertible green fluorescence Kaede protein to assess cell migration from the skin. Memory/effector CD4+Foxp3+ Tregs as well as CD4+Foxp3− non-Tregs migrated from the skin to the DLNs. The number of CD4+ T cells present in the skin and migrating to the DLNs increased during a cutaneous immune response. These migratory Tregs exhibited immunosuppressive activity, and depletion of endogenous Tregs prolonged the contact hypersensitivity response. Taken together, these results indicate that activated Tregs are the major circulating T-cell type that emigrates from the skin during a cutaneous immune response in mice, and that these cells traffic to the DLNs and recirculate back to the skin to contribute to termination of the immune response. (J Clin Invest 120:883–93, 2010)

Journal of Investigative Dermatology (2010) 130, 1483. doi:10.1038/jid.2010.130