Topical treatment to prevent melanoma in congenital giant nevi

Aside from the cosmetic and psychological consequences of congenital giant nevi, these nevi frequently convert to malignant melanoma. Complete removal of these nevi is uncommon, highlighting the need for additional less invasive treatment strategies. Choi et al. (2022) developed murine congenital nevus models with NrasQ61R mutation that recapitulated the genetic and phenotypic characteristics of human giant congenital nevi and found that NrasQ61R drives nevus transformation into invasive melanoma in these mice. Topical treatment of nevi in the murine models with the hapten squaric acid dibutylester (SADBE) resulted in inflammation and destruction of nevus cells through the recruitment of macrophages, including proinflammatory M1-like polarized macrophages. SADBE treatment similarly recruited macrophages and decreased nevus cell numbers in human giant nevus xenografts. Furthermore, topical treatment of mice with congenital giant nevi harboring NrasQ61R mutation with SADBE prevented the formation of melanoma. These findings support further investigation of SADBE and other topical inhibitors, such as signaling inhibitors, for the treatment of congenital giant nevi. (Cell 185:2071-2085, 2022; https://doi.org/10.1016/j.cell.2022.04.025) Selected by I. Brownell

Multipleplex scRNA sequencing characterizes cell-type–specific signatures in lupus

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease that exhibits increased type 1 IFN signaling, dysregulated lymphocyte activation, and failure of apoptotic clearance; however, a comprehensive analysis of circulating immune cells in the context of genetic associations has not been performed. Perez et al. (2022) utilized multiplexed single-cell RNA sequencing (mux-seq) to investigate changes in cell-type composition and cell type-specific gene expression in peripheral blood mononuclear cells from SLE cases and controls. A decrease in naïve CD4+ T cells, an increase in repertoire-restricted GZMH+ CD8+ T cells, and an increase in classical monocyte percentages were noted in SLE cases. The classical monocytes exhibited a pronounced type 1 IFN response with high expression of IFN-stimulated genes, and this expression was inversely correlated with the numbers of naïve CD4+ T cells. Gene expression modules predicted cases and allowed for stratification of patients. mux-seq led to the decomposition of gene expression data into shared and cell-type–specific components and mapping of associated cis-expression quantitative trait loci, underscoring the importance of cellular context for understanding the genetic variants associated with disease risk. (Science. 376:eaabf1970, 2022; https://doi.org/10.1126/science.aabf1970) Selected by M. Udey

Intracellular bacteria drive breast cancer metastasis

Evidence has suggested that host microbiota are an integral component in tumor tissues, but whether these bacteria function in tumor development and progression in various cancers remains unknown. In a spontaneous murine breast tumor model mouse mammary tumor virus-polyoma middle tumor antigen, Fu et al. (2022) reported significant tumor cell–resident microbes in the cytosol. Elimination of these tumor-resident microbes with antibiotics led to reduced lung metastasis but not reduced tumor growth, suggesting that these tumor-resident bacteria promote metastasis in this mouse model. These bacteria were carried along with circulating tumor cells to sites of metastasis and promoted tumor cell survival by enhancing cell resistance to mechanical fluid shear stress through effects on the actin cytoskeleton. Certain bacteria (Staphylococcus and Lactobacillus) increased the colonized metastatic tumor foci, whereas others (Enterococcus and Streptococcus) did not. On the basis of these studies, intracellular microbiota may be a potential target for preventing metastasis in cancer types at an early stage. (Cell 185:1356–72, 2022; https://doi.org/10.1016/j.cell.2022.02.027) Selected by J.T. Elder

Oral baricitinib for treatment of alopecia areata—interim results

Jaks are involved in intracellular cytokine signaling in alopecia areata pathogenesis, and phase 2 studies have shown efficacy for oral Jak inhibitors in these patients. King et al. (2022) conducted two randomized, placebo-controlled phase 3 trials to examine the safety and efficacy of treatment with the selective Jak1 and Jak2 inhibitor baricitinib (at once-daily doses of 4 or 2 mg) in 1,200 adult patients with severe alopecia areata. At 36 weeks, hair regrowth was superior in patients treated with oral baricitinib to the regrowth in patients treated with placebo. Although treatment was well-tolerated by the patients, acne, elevated creatine kinase, and increased high- and low-density lipoprotein cholesterol occurred more frequently in patients treated with baricitinib than in those treated with placebo. These two studies are planned to remain ongoing for 200 weeks to assess the long-term safety and efficacy of this Jak inhibitor in patients with alopecia areata. (N Engl J Med 386:1687-1699, 2022; https://doi.org/10.1056/NEJMoa2110343) Selected by E. Tschachler

ΔNp63 interacts with helicase Senataxin to fine tune keratinocyte differentiation

The transcription factor p63 is a master regulator of keratinocyte (KC) differentiation and skin homeostasis, and the N-terminal truncated form of p63 (ΔNp63) is known to maintain the integrity of stratified epithelial cells. Mechanistically, ΔNp63 regulates the transcription of several genes through the recruitment of epigenetic modulators and chromatin remodeling factors. Gatti et al. (2022) showed that ΔNp63 interacts with the RNA/DNA helicase Senataxin (SETX), which resolves R-loop intermediates over GC-rich termination sites, to coregulate the genes involved in the early differentiation of KCs. These interacting proteins resolve the R-loop structures in the termination region of the early KC differentiation genes ZNF750 and K1, promoting efficient termination and gene expression. Consequently, SETX-depleted KCs were unable to undergo epidermal differentiation. Furthermore, SETX was downmodulated in some squamous cell carcinoma, suggesting a possible tumor suppressor role in this cancer. (Proc Natl Acad Sci 119:2104718119, 2022; https://doi.org/10.1073/pnas.2104718119) Selected by I. Brownell