Hair Shaft Functions as a Niche Component to Affect Stem Cells

Hair shaft miniaturization is correlated with loss of hair follicle stem cells (HFSCs) during aging and androgenic alopecia. On the basis of the observation that changes in the diameters of hair shafts affect the physical size of the niche, which houses HFSCs, Xie et al. (2021) examined the effects of hair shaft miniaturization on HFSCs using molecular, imaging, genetic, and pharmacological techniques. These studies revealed that the hair shaft functions as a niche component and that shrinkage of the physical niche size by hair shaft loss induces hair cycle-dependent ectopic apoptosis of HFSCs through the mechanosensitive calcium channel Piezo1 in collaboration with TNF-α. These molecular mechanisms underlie the hair miniaturization and associated apoptotic loss of HFSCs that are observed during aging in mammals, highlighting not only the self-regulating supply-and-demand regulatory mechanism that involves the hair shaft and HFSCs during tissue regeneration but also the mechanosensitive channel Piezo1 as a target for therapeutic development. (Cell Stem Cell 29:70–85, 2021; https://doi.org/10.1016/j.stem.2021.09.009) Selected by I. Brownell

Dual Checkpoint Inhibition for Advanced Melanoma

Immune checkpoint inhibitor therapy has revolutionized cancer treatment, and combinations of different checkpoint inhibitors have been shown to enhance responses and improve outcomes. Two inhibitory immune checkpoint factors, LAG-3 and PD-1, are often coexpressed on tumor-infiltrating cells, and both contribute to T-cell exhaustion. Subsequent to a phase 1–2 trial that showed that the combination of inhibition of LAG-3 with relatlimab and inhibition of PD-1 with nivolumab resulted in durable objective responses in patients with melanoma who were refractory or resistant to PD-1 inhibition, Tawbi et al. (2021) reported that the combination of relatlimab and nivolumab yielded longer progression-free survival than nivolumab alone and reduced the risk of disease progression or death. However, the combination resulted in a slightly increased number of adverse events. The results of this phase 2–3 global, double-blind, randomized trial of 714 patients with melanoma indicated that blockade of a combination of immune checkpoints is more efficacious than blockade of a single immune checkpoint in patients with previously untreated metastatic or unresectable melanoma. (N Engl J Med 386:24–36, 2021; https://doi.org/10.1056/NEJMoa2109970) Selected by M. Roecken

UVB Radiation Increases Hormonal and Sexual Responses

UVR has been found to increase testosterone levels in men and estradiol and testosterone levels in females, suggesting that the skin may function in hormone-related social, sexual, and reproductive behaviors. Parikh et al. (2021) showed that in mice, UVB treatment increases female attractiveness, testosterone levels in males, sex steroid signaling, and sexual behavior of females. In humans, treatment with UVB radiation resulted in increased romantic passion in both men and women as well as increases in some measures of aggressiveness in men. In addition, UVB resulted in increases in the estrus phase, gonadotropin secretion, follicle growth, and sex steroid synthesis in female mice. Because these changes in attractiveness and behavior were dependent on p53 in the skin in mice, the activity of this protein is implicated in regulating sexual behavior, hormonal release, and physiological ovarian changes through a skin–brain–gonadal axis. This study opens up a new avenue for the development of sex steroid–related dysfunctions. (Cell Rep 36:109579, 2021; https://doi.org/10.1016/j.celrep.2021.109579) Selected by T. Schwarz

CD14+ Dendritic Cell 3 Population Promotes Inflammation in Psoriasis

Dendritic cells (DCs) comprise a heterogeneous cell population that bridges innate and adaptive immune responses. Nakamizo et al. (2021) recently examined the DC population in human skin in the context of the chronic inflammatory skin diseases atopic dermatitis and psoriasis using single-cell flow cytometry in combination with RNA sequencing of index-sorted cells. In psoriatic lesional skin, increased proportions of CD14+ DC3s and macrophages were observed. These CD14+ DC3s highly expressed IL23A and CXCL2, which are related to IL-17 signaling, in psoriatic lesional skin. These factors are central to psoriasis pathogenesis, implicating these cells as inflammation promoters in psoriasis. DCs enriched in immunoregulatory molecules were increased in lesional skin in atopic dermatitis and psoriasis; highly expressed DC3s may be a therapeutic target in skin diseases. (j Exp Med 218:e20202345, 2021; https://doi.org/10.1084/jem.20202345) Selected by M. Udey

Following Fibroblast Fates During Wound Healing

The heterogeneity and functions of fibroblasts during deposition of scar tissue in wound repair have remained enigmatic, in part, owing to challenges in translating results obtained in mice to humans. Foster et al. (2021) employed an integrated, single-cell multimodal -omics approach to investigate fibroblasts during wound repair across time, space, and lineage in a murine wound model that recapitulates human tissue repair. These studies showed that fibroblasts local to the injury are activated along wound edges and proliferate from the outside to the inside in a radial pattern. This clonal proliferation appeared to be dependent on mechanotransduction because focal adhesion kinase inhibitor–treated wounds healed with significantly smaller and thinner scars than untreated wounds. The local tissue mechanics additionally contributed to the transcriptional differences between cells in the outer and inner wound areas. A deeper understanding of the molecular and functional roles of fibroblasts in wound healing will facilitate searches for therapeutic modalities to promote optimal tissue repair. (Proc Natl Acad Sci USA 118:e2110025118, 2021. https://doi.org/10.1073/pnas.2110025118) Selected by M. Tomic-Canic