Higher BMI Increases Risk of Psoriasis

Observational evidence indicates a relationship between increased body mass index (BMI) and psoriasis, but the direction of causality remains unclear. Using mendelian randomization, which randomly allocates individuals to groups based on genotype, of more than 750,000 individuals from large population-based and genome-wide association studies, Budu-Aggrey and colleagues demonstrated that higher BMI causally increases the odds of psoriasis occurrence. This increase is likely to be clinically significant because a 1 kg/m² increase in BMI increases the odds of psoriasis by 9%. Furthermore, these data failed to support a possible causal effect of psoriasis genetic risk on increased BMI. These findings support increased efforts to manage obesity in the general population to perhaps decrease psoriasis risk, since both obesity and psoriasis are increasingly important health issues. (PLoS Med 16:e1002739, 2019; https://doi.org/10.1371/journal.pmed.1002739) Selected by J. Gelfand

Epithelia-Immune Crosstalk for Skin Barrier Regulation

Although innate and adaptive immune cells in the skin have been implicated in infection and inflammation, it remains unclear whether skin-resident immune cells are involved in barrier homeostasis. Relationships between various immune cells and the skin microbiota, which has evolved for protection against pathogens and for host-microbiota symbiosis, are also incompletely defined. In studies in mice, Kobayashi and colleagues found that innate lymphoid cells (ILCs) localize to hair follicles in close proximity to sebaceous glands. In the epidermis and dermis, these ILCs produced tumor necrosis factor and lymphotoxins that negatively regulate sebocyte proliferation via a mechanism involving Notch signaling. Loss of ILCs led to sebaceous hyperplasia and the quantity and quality of sebum was also altered, resulting in enhanced commensalism of Gram-positive bacterial species. These data indicate that skin-resident ILCs regulate the commensal microbiota via crosstalk involving hair follicles and sebaceous glands, demonstrating an alliance of the epithelium and immune system to sustain microbial equilibrium on the skin surface. (Cell 176:1-16, 2019; https://doi.org/10.1016/j.cell.2018.12.031) Selected by I. Brownell and C. Niessen

TFAP2C and p63 Drive Epidermal Lineage Differentiation

Lineage-specific transcription factors program the chromatin landscape and influence tissue development. Li and colleagues utilized stratified epidermal development in which human embryonic stem cells (ESCs) can be differentiated into keratinocytes in culture to investigate associated chromatin dynamic mechanisms. Analysis of the epigenomic landscape during epidermal differentiation revealed two important chromatin networks during ectoderm initiation and keratinocyte maturation. The transcription factor TFAP2C was found to be necessary and sufficient to drive skin differentiation via initiation of the surface ectoderm chromatin landscape and induction of p63. p63 then serves as a maturation factor, modifying the pre-patterned chromatin landscape into that of functional keratinocytes by positive autoregulation of its own locus and inhibition of the immature surface epithelial landscape. This general framework illuminates transcription factor networks that direct chromatin transitions during skin development. (Cell Stem Cell 24: 271-284, 2019; https://doi.org/10.1016/j.stem.2018.12.012) Selected by I. Brownell

NSAIDs Increase Survival for Mutant PIK3CA

A correlation between use of non-steroidal anti-inflammatory drugs (NSAIDs) and survival has been identified in colorectal cancer patients that harbor canonical mutations in PIK3CA, a gene that is also commonly mutated or amplified in head and neck squamous cell carcinoma (HNSCC). In a study of 266 HNSCC patients, Hedberg and colleagues reported increased disease-specific and overall survival with regular NSAID use in patients with canonical or noncanonical PIK3CA mutations or amplifications compared to patients with wild-type PIK3CA. Interestingly, these effects were independent of the presence of human papillomavirus infection, which is a primary risk factor for HNSCC. Signaling via PIK3CA results in production of prostaglandin E₂ (PGE₂) via effects on cyclooxygenase-2 (COX2), which is one of the targets of NSAIDs. In PIK3CA-mutated cell lines and xenograft mouse models, higher levels of PGE₂ were observed. Treatment of these mutated cells and tumors with NSAIDs markedly attenuated the enhanced PGE₂ secretion, suggesting that genomic alteration of PIK3CA upregulates PGE₂ production and cellular proliferation. NSAID use may confer a clinically relevant advantage in survival in patients with PIK3CA-mutated HNSCC by inhibiting COX pathways that are downstream of PIK3CA. (J Exp Med 216: 419-427, 2019; https://doi.org/10.1084/jem.20181936) Selected by I. Brownell

Antimicrobial Protection from Dermal Fat Lessens with Age

As myeloid-derived innate and adaptive immunity is deficient early in life, non-myeloid-resident skin cells may offer critical host defense against invasive pathogens, such as Staphylococcus aureus, during this time. Zhang and colleagues found that neonatal skin has abundant dermal fibroblasts (dFBs) that differentiate locally into adipocytes and produce the antimicrobial peptide cathelicidin through reactive adipogenesis in response to S. aureus infection. During development and aging, the dFB population, immature fat, and adipogenic potential of dFBs are lost with an accompanying increase in fibrotic characteristics, consistent with a drastic pro-adipogenic-to-profibrotic switch. Adult cells with low adipogenic potential were unable to control bacterial growth, suggesting a loss of immune function. Age-dependent activation of the transforming growth factor (TGF)–β pathway led to attenuation of the adipogenic capacity of dFBs and loss of antimicrobial function. Together, these results from mice and human skin suggest that suppression of TGFBR may be a treatment option for combatting skin infections. (Immunity 50:121-136, 2019; https://doi.org/10.1016/j.immuni.2018.11.003) Selected by T. Schwarz