Clinical course and outcome of infections with monkeypox virus

In an analysis of 528 cases, Thornhill et al. (2022) described the presentation, clinical course, and outcomes of confirmed monkeypox infections. The infections were diagnosed between April and June 2022 from 5 continents, 16 countries, and 43 clinical sites. Of these cases, 98% were in gay or bisexual men, and the lesions were primarily in genital, anal, and oral mucosal locations, supporting sexual activity as the most frequently suspected transmission route. Although 95% of cases involved a rash, approximately 10% presented with a single genital lesion. These lesions may lead to misdiagnosis as other sexually transmitted infections because other concomitant laboratory-confirmed sexually transmitted infections were reported in 29% of cases. Another challenge to correct diagnosis is the fact that monkeypox infection was accompanied by a diverse set of dermatologic and systemic manifestations. Cases were largely mild and self-limiting with a 13% rate of hospitalization mainly for pain management and bacterial superinfection, and serious complications of myocarditis and epiglottis were observed in only a small number of cases. Increased understanding of this infection to inform correct diagnosis is necessary to contain the community spread of monkeypox outside areas known for endemic disease. (N Engl J Med 387:679–91, 2022; https://doi.org/10.1056/NEJMoa2207323.606:853) Selected by E. Tschachler

Squalene induces TREM2 macrophages and blocks antimicrobial responses in acne

Foamy macrophages, which express TREM2, are abundant in lesions in patients with acne, a disease characterized by excess lipid production, increased *Cutibacterium acnes* growth, and inflammation. TREM2 macrophages have also been reported at sites of several metabolic diseases characterized by changes in lipid metabolism and chronic inflammation. Do et al. (2022) showed that squalene, which is increased in sebum in acne lesions, hair follicle keratinocytes expressed squalene epoxidase, which converts squalene into squalene epoxide, which scavenges ROS and induces inflammation. Although the squalene-induced TREM2 macrophages phagocytosed *C. acnes*, they were unable to kill the bacteria because squalene blocked the antimicrobial response by inhibiting the generation of ROS and scavenging oxygen free radicals. Together, these findings show that excess squalene production contributes to acne both through the induction of TREM2 macrophages that express proinflammatory genes and through the blockade of antimicrobial responses, shedding light on potential interventions for the treatment of this common and potentially debilitating skin disease. (Sci Immunol 7:eabo2787, 2022; https://doi.org/10.1126/sciimmunol.eabo2787) Selected by A. Dlugosz, T. Schwarz, and E. Tschachler

Obesity induces immune dysregulation in inflammatory disease

Bapat et al. (2022) show that in murine models of atopic dermatitis (AD), obesity caused by a high-fat diet led to increased inflammatory response characterized by severe erythema and scale, expansion of epidermal and dermal layers, increased leukocytic infiltration, and increased disease severity. Although AD is considered a Th2 cytokine-driven disease in lean mice, obesity was found to shift the response to an aberrant Th17 or unfocused inflammatory response. Blockade of the Th2 effector cytokines IL-4 and IL-13 has shown efficacy in managing Th2-driven inflammatory diseases such as AD; however, neutralization of these cytokines in mice with obesity not only failed to improve disease but essentially exacerbated the disease in murine models of AD. These effects were mediated by impairment of peroxisome proliferator—activated receptor-γ (PPARγ) activity. Treatment of mice with obesity with a PPARγ agonist mitigated the Th17-skewed pathology, supporting targeted therapy to facilitate responsiveness to anti-Th2 cytokine therapies in AD and potentially other inflammatory diseases in patients with obesity. (Nature 604:337–42, 2022; https://doi.org/10.1038/s41586-022-04536-0) Selected by T. Schwarz

VEGF-A–induced angiogenesis mediates rejuvenation of aged human skin transplanted onto young mice

Keren et al. (2022) investigated the molecular underpinnings of the rejuvenation of aged human epidermal transplants in a young mouse host environment. Molecularily, human epidermal rejuvenation in this model was accompanied by decreased senescence-associated β-galactosidase activity; expression of p16INK4a, and upregulation of PGC1α, SIRT1, and MT11M that decline in aging human skin. Furthermore, this rejuvenation was associated with upregulated VEGF-A signaling, concomitant enhanced angiogenesis, and reduced inflammation. Injection of antibodies to neutralize VEGF-A abrogated the rejuvenation of aged human skin in the young mouse environment, whereas injection of nanoparticles containing VEGF-A–induced rejuvenation, indicating that VEGF-A is both necessary and sufficient for this rejuvenation. These observations implicate VEGF-A as a master pathway involved in human organ rejuvenation and suggest that angiogenesis-promoting therapies may inhibit or even reverse tissue aging. (Sci Adv 8:eabm6756, 2022; https://doi.org/10.1126/sciadv.abm6756) Selected by M. Tomic-Canic

Embigin regulates interactions of sebaceous gland progenitor cells with their niche and affects sebaceous gland differentiation

Stem cell interactions with the niche regulate their self-renewal and differentiation. Extracellular matrix components and cell–cell interactions are critical features of this stem cell niche. Starting from the analysis of published single-cell RNA-sequencing data and investigating transgenic mouse models, Sipilä et al. (2022) showed that the type 1 transmembrane receptor embigin (EMB) is a key niche-interacting factor in mouse skin and is specifically expressed in sebaceous glands. EMB regulates progenitor cell transition to differentiated sebocytes in the sebaceous gland. Specifically, EMB regulates the expression and function of MCT1 (SLC16A1) in basal sebaceous gland cells and leads to permeabilization of the cells to metabolite flow. In addition, the outer extracellular domain of EMB was found to bind to the N-terminal type I domains of fibronectin, thereby increasing the adhesion of basal sebaceous gland cells to the extracellular matrix. The translational potential of these findings includes improvements in the culture of epidermal stem cells for human skin grafting, the use of soluble factors to support the grafting of bone marrow stem cells, or EMB blockade for the treatment of skin disorders associated with increased lipid production. (Dev Cell 57:1453–1465.e7, 2022; https://doi.org/10.1016/j.devcel.2022.05.011) Selected by E. O’Toole