NETosis Contributes to Severe Cutaneous Adverse Drug Reactions

The pathophysiology of severe cutaneous adverse drug reactions such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is incompletely understood, despite the known contribution of CD8⁺ T cells. Kinoshita et al. (2021) specifically examined the role of neutrophils that are present in SJS/TEN skin and represent early innate immune responders. Neutrophils infiltrated SJS/TEN skin and showed NETosis, a process in which neutrophils actively release neutrophil extracellular traps, in the early phases of SJS/TEN. Further studies of molecular mechanisms revealed that CD8⁺ T cells that were primed by causative drugs and antigen-presenting cells produced LCN-2, which triggered NETosis and the production of the antimicrobial peptide LL-37 by neutrophils. Release of this LL-37 induced the expression of FPP1 by keratinocytes (KC), leading to KC necroptosis and the release of additional LL-37 by KCs. NETosis and concomitant amplification of the necrotic response was specific to SJS/TEN. These findings may inform the development of early diagnostic strategies or therapies to improve patient outcomes in these life-threatening severe adverse drug reactions. (Sci Transl Med 13:eaa2398, 2021; https://doi.org/10.1126/scitranslmed.aax2398) Selected by I. Brownell

Desmoglein 1 Deficiency Results in Th17-skewed Response

KC cytoarchitectural components, such as desmosomes and keratin intermediate filaments, contribute to KC responses to external toxins, pathogens, and mechanical stress. In studies to elucidate the role of the desmosome protein desmoglein 1 (DSG1) in sensing environmental stress, controlling epidermal differentiation, and modulating inflammatory gene expression, Godsel et al. (2022) compared DSG1-deficient mice and biopsies from patients with severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome, which is caused by DSG1 mutation and found that the inflammatory response was skewed toward a Th helper 17 (Th17) response and that IL-36 response genes were upregulated. These gene signatures were more similar to those in a cohort of patients with psoriasis than to those in a cohort of patients with atopic dermatitis. Treatment of two patients with SAM syndrome with ustekinumab, which targets IL-12/IL-23, led to improvement in skin lesions, suppression of the inflammatory response, and restoration of structural adhesive protein expression. In addition to highlighting the potential treatment for DSG1-deficient SAM, these results suggest that DSG1 reduction may be an important biomarker for Th17 skewing in skin disorders. (J Clin Invest 132:e1444363, 2022; https://doi.org/10.1172/JCI1444363) Selected by I. Brownell

IL-36 Antibody May Offer Relief in Generalized Pustular Psoriasis

No treatments are approved for generalized pustular psoriasis (GPP) in the United States or Europe. The recent identification of loss-of-function mutations in the IL36RN prompted a small phase 1 study of the humanized anti–IL-36 receptor mAb spesolimab for the treatment of GPP, and this study showed encouraging results. In a subsequent phase 2 randomized placebo-controlled clinical trial of 53 patients with GPP, Bachelez et al. (2021) found that patients experienced greater clearance of lesions from a flare of GPP 1 week after a single intravenous dose of spesolimab than after placebo treatment. The treatment was well-tolerated by the participants, although infections and drug reactions with eosinophilia and systemic symptoms were associated with spesolimab treatment. Although these results are promising for patients with this life-threatening inflammatory skin disease, longer and larger clinical trials are warranted to fully establish the efficacy of IL-36 inhibition. (N Engl J Med 385:2431–40, 2021; https://doi.org/10.1056/NEJMoa2111563) Selected by J. Gelfand

Loss of Tumor Suppressor Genes Aids Tumor Evasion of the Adaptive Immune System

Tumors must not only acquire cellular alterations that confer growth and survival adaptations to escape tissue homeostasis but must also overcome immune responses that recognize tumor cells as emerging pathogens. Martin et al. (2021) performed CRISPR screens on the basis of a druggable target library in syngeneic mice using multiple tumor cell lines to compare gene alterations with and without the presence of adaptive immune responses. Although many known regulators of antigen presentation and transducers of the IFN response were detected in mice with wild-type immune systems, the screen also identified loss-of-function mutations in genes that function as prototypical tumor suppressor genes. The observation that these were highly enriched in the presence of an adaptive immune response indicated that escape from immune detection is one of the strongest selective forces favoring tumor development. In-depth analysis of one of the identified factors, GNA13, revealed that loss of this protein recruited tumor-associated macrophages that promote tumor growth and that the tumor-suppressive function of this factor involves increased secretion of CCL2. The adaptive immune system serves as a selective driver for the inactivation of tumor suppressor genes. (Science 373:1327–35, 2021; https://doi.org/10.1126/science.abg5784) Selected by M. Udey

Gut Microbiome Modulation to Overcome Immunotherapy Resistance

Immune checkpoint inhibitor therapy has shown efficacy in a subset of patients with melanoma, but most patients either do not respond or progress after a response. Modulation of the gut microbiota has been implicated in altering immune system function, leading Baruch et al. (2021) to conduct a phase 1 trial to evaluate fecal microbiota transplantation (FMT) in immunotherapy-refractory patients with melanoma. FMT from two donors with metastatic melanoma who had achieved complete responses on anti–PD-1 monotherapy was administered to 10 patients with melanoma and confirmed progression on anti–PD-1 therapy. The combination of FMT and reintroduction of anti–PD-1 therapy was safe, with only mild adverse events. Three patients exhibited clinical responses, including one patient with a complete response. This response was associated with changes in the gut microbiome composition, immune cell infiltration, and gene expression profiles. These findings support the feasibility of FMT in patients with melanoma and suggest that modulation of the gut microbiome may overcome resistance to immunotherapy. (Science 371:602–9, 2021; https://doi.org/10.1126/science.abb5920) Selected by T. Schwarz