**EDITORS’ PICKS**

**Relationship between wound bioburden and clinical outcome**

Using shotgun metagenomic sequencing in a longitudinal prospective study, Kalan and colleagues examined the strain-level diversity of the microbiota in neuropathic diabetic foot ulcers, which are chronic wounds that cause considerable morbidity and mortality in the increasing population of patients with diabetes. These investigators identified *Staphylococcus aureus* strains that were present in a majority of the wounds, as well as those that were exclusively associated with unhealed wounds. Strains associated with poor wound healing harbored antibiotic resistance genes and genes encoding enterotoxins. Both biofilm and virulence-related genetic pathways were associated with poor clinical outcomes. Although systemic antibiotic therapy did not alter microbiome diversity, debridement decreased bacterial diversity, especially among anaerobic bacteria, in wounds that achieved complete healing within 12 weeks. These findings from untargeted sequencing of the bulk microbial genomes in clinical specimens of diabetic foot ulcers not only illuminated the strain-specific microbial diversity but also identified targets associated with clinical outcomes to inform development of novel management and treatment strategies. ([Cell Host Microbe](https://doi.org/10.1016/j.chom.2019.03.006) Selected by M. Tomic-Canic)

**Transcriptional network with PITX1 supports SCC**

Tumor propagating progenitor cells (TPCs) are capable of renewal, which sustains squamous cell carcinomas (SCC) and differentiation into supra-basal SCC cells that lack proliferative potential. Transcriptionome analyses revealed expression of transcription factors de novo SRY-box 2 (SOX2) and paired-like homeodomain 1 (PITX1) in TPCs, spurring Sastre-Perona and colleagues to examine transcriptional circuits that govern SCC growth. PITX1 expression in TPCs promoted cell proliferation and repressed squamous cell differentiation, and it was critical for SCC initiation and growth. In cooperation with *Trp63* and *Sox2*, *Pitx1* comprises a tumor-specific feed-forward circuit that enhances the transcription of these genes, represses *Klf4* transcription, and ultimately promotes TPC renewal. Competitive binding with *Klf4* inhibited transcription of the other three transcription factors to prevent TPC renewal and induce differentiation. This bi-stable transcriptional circuit enables TPC self-renewal and differentiation. These results highlight targets for therapies aimed at the stemness properties of SCCs. ([Cell Stem Cell](https://doi.org/10.1016/j.stem.2019.02.016) Selected by M. Tomic-Canic)

**Metabolic changes regulate innate immunity**

Metabolic activities of myeloid cells, especially macrophages and dendritic cells, regulate innate immune responses to pathogens. After activation of these cells via toll-like receptor (TLR) agonists, glycolytic reprogramming, which is required to meet the energy demands for antipathogen defense, results in altered mitochondrial function, reactive oxygen species levels (ROS), and inflammatory cytokine secretion. Additional metabolic signals, such as alterations because of obesity, also affect this innate inflammatory response. Mogilenko and colleagues reported that fatty acids (FA) enhance innate immune activation via TLR. Mechanistically, FAs inhibited hexokinase, leading to metabolic stress, impairment of glycolytic reprogramming, alterations in mitochondrial fitness, and increased ROS. These effects further activated the unfolded protein response (UPR), resulting in increased IL-23 production. Thus, the UPR links the metabolic adaptation of dendritic cells to high-FA environments and resultant inflammation, revealing a new mechanism regulating innate immune responses. ([Cell Host Microbe](https://doi.org/10.1016/j.chom.2019.03.006) Selected by J. Gelfand)

**Targeting of exosomal PD-L1 to induce antitumor immunity**

PD-L1 on cancer cells suppresses antigen-driven T-cell activation by binding to PD-1. Blockade of this interaction results in reactivation of antitumor immune responses, providing the basis for effective immunotherapies for various cancers. These immune checkpoint inhibitors induce variable responses in different cancer types, indicating that a better understanding of the differential therapeutic success of PD-L1 inhibitors may optimize existing therapies. Poggio and colleagues discovered that exosomal PD-L1 promotes cancer cell evasion of antitumor immunity by traveling to lymph nodes and suppressing T cells. Studies in cells and mouse models revealed that genetic blockade of exosome production or deletion of the PD-L1-encoding gene resulted in strong T-cell activation, proliferation, and killing potential, leading to suppression of not only local tumors but also those at distant sites. Anti-PD-L1 antibodies acted synergistically with blockade of exosomal PD-L1 to inhibit tumor growth. Inhibition of T-cell suppression by exosomal PD-L1 inhibition led to durable systemic antitumor immune responses in prostate and colorectal cancer models. ([Cell](https://doi.org/10.1016/j.cell.2019.02.016) Selected by I. Brownell)

**Stratum corneum presents unique endotype for AD with food allergy**

Identification of the various endotypes of atopic dermatitis (AD) is important for clinical management, as patients with AD with multiple allergen sensitizations often progress to food allergy (FA) and respiratory allergy. In a comprehensive prospective study of 100 children, Leung and colleagues uncovered a unique endotype in AD with FA using skin tape stripping samples to specifically assess skin biomarkers. AD with FA was distinguishable from AD without FA by increased transepidermal water loss, decreased filaggrin breakdown products, changes in the stratum corneum lamellar bilayer structure, and altered ceramide ratios at the interface between the stratum corneum and the stratum granulosum in nonlesional skin. Gene expression studies also revealed an increased type 2 immune signature in samples from AD patients with FA. The defective stratum corneum present in nonlesional skin is a key abnormality that distinguishes these endotypes, suggesting the presence of these defects before occurrence of clinical skin lesions and supporting the notion that improving skin barrier function may promote prevention of AD and FA. ([Sci Transl Med.](https://doi.org/10.1126/scitranslmed.aav2685) Selected by T. Schwarz)

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