NEUROIMMUNOLOGY

Responding to sunburn

Nature https://doi.org/10.1038/s41586-021-03563-7 (2021)

Sunburn is a transient form of skin damage leading to an inflammatory response characterized by redness, swelling and a painful sensitivity to touch. How the peripheral nervous system contributes to the ensuing tissue repair process remains unclear. In *Nature*, Hoeffel et al. show that a specific subset of $G\alpha_i$-interacting protein (GINIP)-expressing sensory neurons are necessary to promote tissue repair in a mouse model of UV-induced skin damage. Activated GINIP$^+$ neurons that express C-low-threshold mechanoreceptors elaborate the neuropeptide TAFA4, which acts on TIM4$^+$ dermal-resident macrophages to induce their production of interleukin (IL)-10 and promote skin repair. Conditional ablation of the GINIP$^+$ neurons at the time of UV exposure results in delayed tissue repair and increased skin fibrosis. Similarly, *Tafa4*$^{-/-}$ mice also exhibit delayed healing and higher inflammatory scores upon UV exposure. This loss is accompanied by a reduction of the dermal TIM4$^+$ macrophage population but also increased recruitment of inflammatory Ly6C$^+$ monocytes into the damaged skin. The findings suggest GINIP$^+$ neurons regulate local macrophage populations and tissue repair via a TAFA4–IL-10-dependent axis. *LAD*

https://doi.org/10.1038/s41590-021-00970-w

COVID-19

A STING in the tail for SARS-CoV-2

Sci. Immunol. https://doi.org/10.1126/sciimmunol.abi9007 (2021)
Sci. Immunol. https://doi.org/10.1126/sciimmunol.abi9002 (2021)
Antiviral Res. https://doi.org/10.1016/j.antiviral.2021.105015 (2021)

The ability of SARS-CoV-2 to avoid the immune system is thought to be a result, in part, of inefficient or misdirected antiviral signaling responses. In January, Zhu et al. published in *Antiviral Research* that the potent small molecule STING agonist diABZI can boost interferon signaling to limit the replication of SARS-CoV-2 in primary human airway epithelial air–liquid interface cultures via TBK1–IRF signaling. Two papers now published back-to-back in *Science Immunology* show the same thing but push these findings in vivo, with potential clinical implications. Both Humphries et al. and Li et al. could prevent respiratory disease in SARS-CoV-2-infected ACE2-transgenic mice with a single intranasal dose of diABZI, administered either before or after infection. Additionally, Li et al. showed that diABZI has antiviral activity against the variant of concern B.1.351, commonly referred to as the variant first detected in South Africa, and now as the Beta variant, according to recent WHO nomenclature guidelines. The broad and potent activity of diABZI, along with the efficacy of intranasal delivery, indicate that it is a decent candidate for human trials. *NJB*

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COVID-19

Enhancing antibodies

Cell https://doi.org/10.1016/j.cell.2021.05.032 (2021)

Antibodies against viruses are not always protective. In *Cell*, Arase and colleagues identify Abs against SARS-CoV-2 that bind the N-terminal domain (NTD) of the spike (S) protein and induce an open conformation of the receptor-binding domain (RBD), which results in enhanced binding to the virus receptor ACE2 and enhanced infectivity. In a screen of Abs isolated from patients with COVID-19, some of the Abs to NTD enhance the binding of S protein to ACE2 to a level higher than that of the D614G mutant S protein, which is known to have an open RBD conformation. All enhancing Abs bind the same sites (W64, H66, V213 and R214) in the S protein, dock similarly on the NTD and induce the open RBD state. Enhancing Abs reduce the neutralizing capacity of neutralizing Abs. Patients with COVID-19 have both enhancing and neutralizing Abs, and the difference between enhancing and neutralizing titers is greater in patients with severe as compared to non-severe disease. *IV*

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CANCER IMMUNOLOGY

Mapping the tumor–immune landscape

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Immune checkpoint blockade (ICB), such as anti-PD-1, is beneficial in only a subset of patients with breast cancer. In *Nature Medicine*, Lambrechts and colleagues generate a single-cell atlas of the human breast cancer microenvironment using multiomics to understand how ICB alters the tumor–immune landscape. ICB expands tumor-infiltrating lymphocytes, with the majority of expansion occurring in cells with a classically exhausted PD-1$^+$ and effector phenotype, which the authors refer to as 'experienced cells.' Trajectory analysis shows that among the experienced cells, CD4$^+$ T cells are split into type 1 helper T and follicular helper T cell populations—both in principle beneficial for tumor control. Components of the innate immune system, including PD-L1$^+$ dendritic cells and specific macrophage subsets, also correlate with T cell expansion in response to ICB. Collectively, these data provide a rich resource describing the immunological changes and correlates of T cell expansion in response to ICB in the breast cancer environment. *ZF*

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