Immunometabolism

Dangerous liaisons

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by dysregulated plasmablast generation and the production of autoantibodies. In *Cell Metabolism*, Zeng et al. examined metabolic differences between B cells obtained from individuals with SLE and healthy controls. SLE B cells had higher mitochondrial respiratory activity and increased utilization of fatty acid oxidation as compared to cells from healthy controls. Notably, genes (*CD36*, *FABP4* and *CPT1A*) associated with fatty acid uptake and metabolism were also increased. $CD19^+IgD^-CD27^-CD11c^+$ B cells and $CD19^+IgD^-CD27^+CD38^+$ antibody-secreting cells consistently had the highest uptake of lipids as compared with other B cell subsets. Similar changes were observed in B cells of NZM2328 mice, a mouse model of SLE. In vitro coculture of B cells with splenic fibroblastic reticular cells (FRCs) increased the expression of CD36 and FABP4, as well as lipid uptake and metabolism. Notably, B cell coculture also increased expression of choline acetyltransferase (ChAT) by FRCs. FRCs secrete acetylcholine (ACh), which signals through ACh receptors on B cells to increase lipid utilization via Ca^{2+}-dependent NFAT activation. Injection of wild-type FRCs into NZM2328 mice increased the number of pathogenic antibody-secreting cells that secrete anti-DNA antibodies; however, knockdown of ChAT in FRCs before infusion blunted this response. These findings point to an FRC–B cell axis that enhances B cell activation and plasmablast formation, including potentially pathogenic B cells.

Laurie Dempsey
Nature Immunology

Original reference: *Cell Metab.* https://doi.org/10.1016/j.cmet.2023.03.010 (2023).

Cancer immunology

Probiotics boost immunotherapy

Many patients with melanoma do not respond to immune checkpoint inhibitors (ICIs). One strategy to overcome this limitation is the consumption of probiotics, but evidence to support this is conflicting and how this might work is unclear. New data published in *Cell* show that orally consumed *Lactobacillus reuteri*, a commonly used probiotic, can colonize preclinical melanomas to support ICI therapy. Within the tumor, these bacteria release indole-3-aldehyde (I3A), a tryptophan catabolite that has been linked to aryl hydrocarbon receptor (AhR) activation. The researchers show that I3A promotes anti-tumor $IFN\gamma^+$ $CD8^+$ T cells through AhR activation with induction of important cytotoxic genes; these effects did not occur in mice with CD8-Cre-driven AhR deficiency. Furthermore, a high tryptophan diet could reduce melanoma growth and enhance anti-PD-L1 therapeutic responses in mice via activation of AhR in $CD8^+$ T cells. I3A serum levels were also shown to be high in patients with melanoma who responded well to ICIs, indicating that dietary intervention with probiotics or tryptophan might be a viable adjunctive therapy for patients receiving ICIs.

Nicholas J. Bernard
Nature Immunology

Original reference: *Cell* https://doi.org/10.1016/j.cell.2023.03.011 (2023).

Neuroimmunology

Sensing DCs

Dendritic cells (DCs) in the skin can be found close to nociceptors, and their interactions drive protective or allergic inflammation. In *Science*, Hanč et al. identify several mechanisms by which nociceptors regulate DCs. When mouse bone marrow-derived DCs were cocultured with primary DRG neurons and TLR7, TLR2, TLR4 or TLR5 agonists, the presence of nociceptors enhanced DC production of IL-12p40 and IL-6 in a contact-dependent manner. Nociceptors could secrete CCL2, which attracted DCs to engage in physical interactions, inducing calcium flux and transcriptional changes in DCs. Nociceptors could also induce a contact-independent accumulation of pro-IL-1β in DCs via the release of the neuropeptide CGRP. These interactions were confirmed in vivo, as topical treatment of a TLR7 agonist in mice with nociceptors depleted had reduced levels of IL-12p40 and IL-6. Nociceptor stimulation in mice without a TLR7 agonist resulted in the accumulation of pro-IL-1β in DCs. Finally, when nociceptors did not express CCL2, there were fewer DCs after TLR7 stimulation and the inflammatory response in the skin was reduced. Therefore, there are many ways in which nociceptors control DC function.

Stephanie Houston
Nature Immunology

Original reference: *Science* https://doi.org/10.1126/science.abm5658 (2023).

COVID-19

Primary vaccination imprint

SARS-CoV-2 booster vaccines enhance antibody responses. In *Nature*, Alsoussi et al. analyze lymph nodes (weeks 2 and 8), blood (week 17) and bone marrow (week 26) from vaccinated, COVID-19-naive individuals boosted with an ancestral or a bivalent Beta–Delta mRNA vaccine (dose 3), and show that memory B cells are efficiently re-engaged into germinal center reactions. In three individuals for which data were available on the B cell responses to the primary vaccination (post-dose 2), single-cell RNA sequencing indicated a clonal relationship between the plasma cells induced by the primary vaccine and the lymph node germinal center B cells, circulating memory B cells and bone marrow plasma cells induced by dose 3, with some, but not all clones showing increased somatic hypermutation after dose 3. Of the monoclonal antibodies isolated from individuals boosted with the ancestral, Beta–Delta or an Omicron vaccine (dose 4 after a Beta–Delta dose 3), 61%, 57% or 71% recognized Omicron, respectively. Among the isolated antibodies, none specifically recognized Beta or Delta without cross-reacting to the ancestral strain, whereas the antibodies that bound specifically to Omicron had low somatic hypermutation. This indicates that memory B cells generated in the primary vaccination dominate the recall response, even to variant-based boosters.

Ioana Visan
Nature Immunology

Original reference: *Nature* https://doi.org/10.1038/s41586-023-06025-4 (2023).