IMMUNOMETABOLISM

Itaconate isomers add complexity

Nat. Metab. **4**, 524–533 (2022)
Nat. Metab. **4**, 534–546 (2022)

Itaconate is an important immunomodulatory metabolite that is derived from the tricarboxylic acid (TCA) cycle member aconitate via the enzymatic function of aconitate decarboxylase 1 (ACOD1). Two studies published together in *Nature Metabolism* have identified mesaconate and citraconate as derivative isomers of itaconate that are functional in response to LPS stimulation of macrophages. Although all three metabolites could limit glycolysis, notably neither citraconate nor mesaconate inhibited succinate dehydrogenase, TCA cycling or oxidative phosphorylation as well as itaconate. Nevertheless, like itaconate, both isomers could limit the release of proinflammatory cytokines, resulting in protection from sepsis and reducing influenza replication in mouse models, leading to questions as to how these metabolites are functioning. Further mechanistic work is needed, but mesaconate and citraconate can now be added to the list of potential itaconate-related drug targets for the treatment of inflammatory diseases and might help us to better understand the interplay between metabolism and immunomodulation. *NJB*

https://doi.org/10.1038/s41590-022-01258-3

T CELLS

TCF-1$^+$ progenitors

Immunity https://doi.org/10.1016/j.immuni.2022.05.003 (2022)

After activation, CD4$^+$ T cells differentiate into BCL-6$^+$ follicular helper T (T_{FH}) cells and BCL-6$^-$ effector T (T_{eff}) cells. In *Immunity*, Egawa and colleagues use a model of chronic infection with LCMV clone 13 in mice to characterize a population of PD-1$^+$TCF-1$^+$ BCL-6$^{lo/-}$ CD4$^+$ T cells with memory-like features. Differentiation trajectories based on scRNA-seq, scATAC-seq and TCR-based analysis indicate that the TCF-1$^+$ T progenitor (T_{prog}) cells give rise to both T_{eff} and T_{FH} cells. Chromatin accessibility analysis indicates a two-step process, in which the differentiation of T_{prog} cells is first triggered by TCR signaling, followed by bifurcation to T_{eff} and T_{FH} cells. CD40L-Cre-mediated deletion of BCL-6 in CD4$^+$ T cells results in the loss of T_{prog} and T_{FH} cells, followed by the loss of T_{eff} cells at week 2 after infection, despite their intact expansion at day 8. Thus, after an initial wave of naive T cell-derived T_{eff} and T_{FH} cells, CD4$^+$ T_{eff} and T_{FH} cell responses to persistent antigen are maintained by a pool of TCF-1$^+$ T_{prog} cells. *IV*

https://doi.org/10.1038/s41590-022-01259-2

B CELLS

B cells require exosomes

Sci. Immunol. **7**, eabn2738 (2022)
Sci. Immunol. **7**, eabn2888 (2022)

Patients with trichohepatoenteric syndrome have defects in non-coding RNA (ncRNA) surveillance function, are immunocompromised and exhibit reduced frequencies of circulating lymphocytes. Two reports in *Science Immunology* by Laffleur et al. and Yang et al. show that RNA exosomes, which degrade ncRNAs, are required during antigen receptor V(D)J recombination. The cellular abundance of RNA exosomes increases in B cells during stages when developmental gene recombination occurs (both V(D)J and class-switch recombination). Mice with B cell-specific conditional loss of *Exosc3*, *Exosc10*, *Dis* or *Skiv2l*, which encode components of the RNA exosome machinery, all have a specific block at the pro-B cell stage of development owing to an inability to productively rearrange their *Igh* alleles. Loss of RNA exosome activity results in an accumulation of antisense germline transcripts in the *Igh* locus, but decreased expression of *Igh* coding transcripts. The increased abundance of ncRNAs triggered DNA damage and activation of the p53 pathway, ultimately leading to death of the pro-B cells. *LAD*

https://doi.org/10.1038/s41590-022-01260-9

COVID-19

Inflammatory macrophages

Nature **606**, 585–593 (2022)

High levels of cytokines IL-1β and IL-18 correlate with COVID-19 severity in patients. In *Nature,* Sefik et al. show that SARS-CoV-2 infection of lung-resident macrophages drives disease pathology. When mice with a humanized immune system (MISTRG6-hACE2) were infected with a tagged (mNG) SARS-CoV-2 strain, lung macrophages were mNG$^+$ and viral subgenomic RNA$^+$, indicating that the virus replicates in these cells. Infection is dependent on ACE2 and antibody-mediated Fc-receptor uptake. ASC formation, as a readout of inflammasome activation, is detected in mNG$^+$ lung macrophages and correlates with serum levels of inflammatory cytokines (IL-18 and IL-1RA) and markers of pyroptosis (GSDMD). Blocking viral entry or replication in lung macrophages reduces expression of IL-18, IL-1RA and CXCL10. NLRP3 inhibitors attenuate the production of IL-18, IL-1RA and GSDMD, reverse lung immune pathology and induce higher viral loads in the lung, which suggests that inflammasome activation restricts viral propagation at the cost of hyperinflammation in the lung. *IV*

https://doi.org/10.1038/s41590-022-01261-8

Nicholas J. Bernard, Laurie A. Dempsey and Ioana Visan