ANTIVIRAL DEFENSE

Protecting stem cells

Science **373**, 231–236 (2021)

Most stem cells do not respond well to type I interferons, prompting questions as to how stem cells counter infection by RNA viruses. In *Science*, Poirier et al. identify an isoform of Dicer that can generate antiviral short interfering RNAs (siRNAs) and mediate protection against Sindbis virus, Zika virus and SARS-CoV2. Human induced pluripotent stem cells and several mouse adult stem cells can alternatively splice *Dicer* mRNA, skipping exons 7 and 8 that encode the Hel2i domain of the RNA helicase, to produce antiviral Dicer (aviD). Expression of aviD increases the production of viral-specific siRNAs, thereby reducing viral titers after infection with RNA, but not DNA, viruses. Thus, aviD helps stem cells to counter viral infection. *LAD*

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GUT IMMUNITY

Acetate enhances IgA

Nature **595**, 560–564 (14 July 2021)

Diet has a profound influence on the composition of commensal microbiota. In *Nature*, Takeuchi et al. report that acetate-enriched diets influence host–bacterial commensalism by enhancing the production of secretory immunoglobulin A (SIgA) by gut-resident B cells and altering the fecal SIgA repertoire. Acetate coupled to water-soluble cellulose (WSCA) specifically increases SIgA targeting to Proteobacteria, including *Escherichia coli*, but not to Bacteroidetes. Acetate increases gut epithelial cell production of CCL20, which recruits $CCR6^+CD4^+$ T cells to the gut. These $CD4^+$ T cells respond to Proteobacteria-derived Toll-like receptor agonists and to acetate, increasing their expression of *Bcl6* and *Cxcr5* and differentiation to follicular helper T (T_{FH}) cells. Hence, acetate enhances interactions between T and B cells in the gut and the production of antigen-specific SIgA. *LAD*

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IMMUNOMETABOLISM

Mitochondria control pyroptosis

Cell https://doi.org/10.1016/j.cell.2021.06.028 (2021)

Caspase-mediated cleavage of gasdermin D and its subsequent oligomerization is required for the formation of plasma membrane pores that defines pyroptosis, a form of programmed cell death that is central to many inflammatory processes. Pore formation is regulated upstream of the gasdermin D cleavage event, but research published in *Cell* has now identified a regulatory process that occurs downstream of this cleavage in macrophages. Evavold et al. used a genome-wide screen to identify a requirement for RagA and RagC (members of the Ragulator–Rag complex) and mTORC1 signaling in pyroptosis. The data do not show a direct effect on pore formation, but instead indicate that this pathway drives the production of mitochondrial reactive oxygen species (ROS), which in turn promotes the oligomerization of gasdermin D, although how ROS exert this effect is unclear. Nevertheless, these findings indicate that other effectors of ROS might also exert post-cleavage control over pore formation, thereby linking mitochondrial metabolism to pyroptosis and inflammation. *NJB*

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COVID-19 VACCINES

Intranasal vaccination

Cell Rep. https://doi.org/10.1016/j.celrep.2021.109452 (2021)

Intranasal vaccination can have several advantages over conventional intramuscular vaccines, not least because they can generate strong immune responses at key sites of pathogen exposure such as the lungs. In *Cell Reports*, Diamond and colleagues use a chimpanzee adenoviral-vectorized vaccine that expresses the CoV-2 spike protein (ChAd-SARS-CoV-2-S) and investigate the durability, dose response and cross-protective effects in humanized mice after intranasal administration. A single intranasal dose of vaccine induced humoral responses that were superior to the intramuscular route both in terms of antibody titer and neutralizing efficacy. Intranasal vaccine also generated long-lived plasma cells in the bone marrow that were absent or minimally present with intramuscular dosing. Notably, intranasal vaccination protected against variants of concern such as B.1.351 (Beta) for up to 9 months. *ZF*

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MACROPHAGES

Inflammatory aggregates

Immunity https://doi.org/10.1016/j.immuni.2021.07.002 (2021)

Pro-inflammatory macrophages are key promoters of disease progression in multiple myeloma. In *Immunity*, Hofbauer et al. show that aggregation of phagocytosed β_2-microglobulin (β_2m) protein in the acidic lysosomes of myeloma-associated macrophages (MAMs) results in lysosomal rupture, activation of the NLRP3 inflammasome and production of the pro-inflammatory cytokines IL-1β and IL-18. β_2m, which associates with the heavy chain of the MHCI complex in all nucleated cells, has the propensity to form amyloid aggregates in vivo. Phagocytosis of a low-aggregation form of β_2m or inhibition of lysosomal acidification prevents the formation of β-fibrils, disruption of lysosomes and NLRP3 activation in human monocyte-derived macrophages. Knockdown of β_2m in melanoma cells reduces NLRP3 activation in a transplant mouse model of melanoma. In patients with multiple myeloma, high concentrations of β_2m in the bone marrow correlates with increased production of IL-1β and IL-18, and $amyloid^+$ and active $caspase\text{-}1^+$ MAMs are detected in bone marrow aspirates. *IV*

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