IN BRIEF

COVID-19

SARS-CoV-2 has a sweet tooth

To help understand why uncontrolled diabetes is a risk factor for severe COVID-19, Campos Codo et al. looked at the relationship between glycolysis and SARS-CoV-2 replication in monocytes. Glucose enhanced SARS-CoV-2 viral load and mRNA expression of pro-inflammatory cytokines and type I/III interferons in these cells in a dose-dependent manner. Pretreating human peripheral blood monocytes with metabolic inhibitors showed that these effects of glucose depend on mitochondrial reactive oxygen species (mtROS) and HIF1α. The transition to aerobic glycolysis in SARS-CoV-2-infected monocytes facilitated viral replication and the production of soluble mediators that may contribute to lung damage. Additional studies are needed to investigate the potential for therapeutic targeting of mtROS, HIF1α and glycolysis signalling while maintaining antiviral type I/III interferons.

ORIGINAL ARTICLE Campos Codo, A. et al. Elevated glucose levels favor Sars-Cov-2 infection and monocyte response through a Hif-1α/glycolysis dependent axis. Preprint at *SSRN* https://doi.org/10.2139/ssrn.3606770 (2020)

COVID-19

A versatile mouse model of COVID-19

Israelow et al. report a novel mouse model of COVID-19 using adeno-associated virus (AAV)-mediated expression of human ACE2 (hACE2) in the respiratory tract, which supports productive SARS-CoV-2 infection. Infected mice had acute infiltration of innate and adaptive immune cells to the lungs and developed specific neutralizing antibodies. Transcriptomic analysis showed robust upregulation of cytokines and of interferon-stimulated genes (ISGs), largely overlapping with the signature seen in patient lungs. A key advantage of this model is its application to mice of different genetic backgrounds and age. Infection of AAV–hACE2 mice lacking IFNAR1 or IRF3 and IRF7 showed that type I interferon signalling is required for ISG expression and the recruitment of pro-inflammatory cells to the lungs during infection. Potential future applications of this model include testing therapeutics and vaccines for COVID-19.

ORIGINAL ARTICLE Israelow, B. et al. Mouse model of SARS-CoV-2 reveals inflammatory role of type I interferon signaling. Preprint at *bioRxiv* https://doi.org/10.1101/2020.05.27.118893 (2020)

COVID-19

Neutralizing antibodies in convalescent patients

In a cohort of 149 convalescent patients with variable COVID-19 severity, Robbiani et al. report an overall low neutralizing capacity of plasma serum for SARS-CoV-2. Repertoire analysis of six representative convalescent patients revealed the presence of recurrent and clonally expanded IgG^+ B cells, with specific *IGHV* and *IGLV* gene combinations being shared between different individuals. Potent neutralizing antibodies were found in individuals independently of their overall serum neutralizing capacity. Furthermore, the antibodies targeted distinct neutralizing epitopes on the SARS-CoV-2 glycoprotein spike. These findings indicate that despite low plasma neutralizing capacity, most individuals can generate potent IgG neutralizing antibodies independently of the severity of their symptoms, which has important implications for the design of an effective vaccine.

ORIGINAL ARTICLE Robbiani, D. F. et al. Convergent antibody responses to SARS-CoV-2 infection in convalescent individuals. Preprint at *bioRxiv* https://doi.org/10.1101/2020.05.13.092619 (2020)

Athena Cavounidis, Elizabeth H. Mann, Helene Borrmann, Rachel E. Rigby, Lion F. K. Uhl & Anne Chauveau
OxImmuno Literature Initiative, University of Oxford, Oxford, UK
e-mail: covid19lit@medsci.ox.ac.uk

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MYELOID CELLS

Myeloid memory to non-self

The memory-like adaptation of myeloid cells to previously encountered pathogens, known as trained immunity, has generally been described to be non-specific. Now, a study published in *Science* reports that mouse monocytes and macrophages acquire memory that is specific to non-self MHC class I antigens and shows that this response mediates allograft rejection.

Dai et al. investigated the potential antigen-specific memory-like response of myeloid cells using mice that were devoid of B, T, natural killer and innate lymphoid cells and subjected them to primary and secondary challenges with allogeneic (non-self) or syngeneic (self) grafts. Mice that had received an allogeneic primary challenge showed enhanced rejection when rechallenged with the same allograft compared with mice that received a syngeneic primary challenge. This suggested that myeloid cells appear to acquire specific memory to previously encountered antigens.

By sorting $Ly6C^{hi}$ monocytes raised in the primary alloresponse, the authors showed that, when transferred into naive hosts, these cells could efficiently mount enhanced responses to allografts. Macrophages also acquired specific memory to previously encountered antigens if first challenged with alloantigen in the presence of an agonist antibody to CD40.

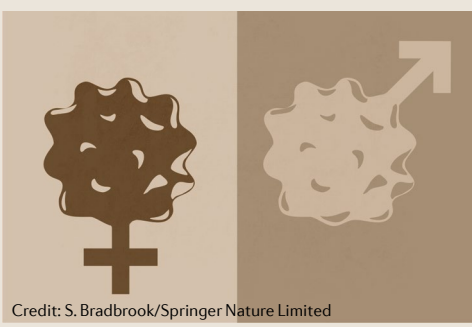
Using mice that differ only at the MHC loci and not at non-MHC loci, Dai et al. confirmed that the myeloid memory response depends on the detection of non-self MHC molecules. Indeed, macrophages bound tetramers of allogeneic but not syngeneic MHC class I molecules. A database search for potential MHC class I-binding molecules revealed

MACROPHAGES

Peritoneal sex differences

Body cavity macrophages have crucial roles in immune surveillance. Of these, peritoneal macrophages have been best studied, with previous results describing differences between the sexes in terms of in vitro function. Bain et al. now show that the sexual dimorphism of peritoneal macrophages is determined by differences in both their rate of turnover and environmental signals.

The major peritoneal macrophage population consists of long-lived $F4/80^{hi}CD102^+$ cells that derive from embryonic progenitors but are later replaced by bone marrow-derived cells. Previous studies have shown that their rate of turnover is higher in male mice than in female mice. Using sex-matched or sex-mismatched, tissue-protected bone marrow chimeric mice, Bain et al. show that this dimorphism is driven by the peritoneal environment rather than cell-intrinsic differences. Furthermore, using a genetic fate-mapping approach, they show that in prepubescent mice the frequency of newly differentiated $F4/80^{hi}CD102^+$ macrophages is the same in male and female mice, whereas by sexual maturity male mice have more newly differentiated macrophages. Bilateral ovariectomy increased the rate of macrophage turnover in female mice, which was not reversed by exogenous oestradiol. Thus, the female reproductive system decreases the turnover of peritoneal $F4/80^{hi}CD102^+$ macrophages in an oestradiol-independent manner.



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