IN BRIEF

COVID-19

NK cells in COVID-19: protectors or opponents?

Natural killer (NK) cells contribute to early antiviral immunity, and in this preprint, Maucourant et al. report reduced NK cell counts in the peripheral blood of 27 patients hospitalized with moderate or severe COVID-19. In early COVID-19, NK cell activation across distinct subsets was elevated in peripheral blood, mirroring the activation signature of NK cells in the bronchoalveolar lavage fluid of patients with COVID-19. Interestingly, severe hyperinflammation was associated with the proliferation and activation of 'adaptive' NK cells, a specialised sub-population with enhanced antibody-dependent cellular cytotoxicity, as well as the arming of CD56^{bright} NK cells with cytotoxic molecules. These results suggest that a distinct NK cell immunophenotype is associated with the severity of COVID-19. Further studies are necessary to define the protective antiviral versus the detrimental pathological roles of NK cells in patients with COVID-19.

ORIGINAL ARTICLE Maucourant, C. et al. Natural killer cell activation related to clinical outcome of COVID-19. Preprint at medRxiv <https://www.medrxiv.org/content/10.1101/2020.07.07.20148478v1> (2020)

COVID-19

Multisystem inflammatory syndrome in children: getting to the heart of the matter

Two preprint studies by Gruber et al. and Consiglio et al. explore the immune landscape underlying the devastating multisystem inflammatory syndrome in children (MIS-C) seen following SARS-CoV-2 infection. Parallels have been drawn between MIS-C and other paediatric vasculitides, such as Kawasaki disease. Consiglio et al. initially compared a small group of patients with MIS-C with healthy controls, paediatric patients with SARS-CoV-2 and patients with Kawasaki disease. Distinct cytokine profiles in MIS-C and Kawasaki disease were demonstrated, with IL-17A levels higher in Kawasaki disease than in MIS-C or in patients with SARS-CoV-2. Gruber et al. compared eight patients with MIS-C to healthy controls, patients with COVID-19 or convalescent individuals, and identified enhanced expression of pro-inflammatory cytokines and chemokines in MIS-C. Patients with MIS-C also had reduced numbers of immune cell types such as monocytes and T cells in peripheral blood, likely due to migration of these cells to inflamed sites. Both studies showed that autoantibodies targeting the heart and blood vessels are prominent in MIS-C. Autoantibody targets in the heart including endoglin and RBPJ were identified by Consiglio et al., whereas Gruber et al. found autoantibodies targeting not only cardiac but also gastrointestinal antigens. These results are consistent with the vasculitis-like symptoms observed in MIS-C. Importantly, a number of treatment strategies were employed in the two studies, including anti-IL-6R, intravenous immunoglobulin therapy, recombinant IL-1RA and corticosteroids. These findings provide significant insight into the disease mechanisms and relevant treatment options for MIS-C.

ORIGINAL ARTICLES Gruber, C. et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Preprint at medRxiv <https://doi.org/10.1101/2020.07.04.20142752> (2020) | Consiglio, C. R. et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Preprint at medRxiv <https://doi.org/10.1101/2020.07.08.20148353> (2020)

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MICROBIOTA

Gut bacteria support antiviral immunity

A healthy gut microbiome is linked to protection from a variety of ills and to a properly functioning immune system. A new study extends its role to supporting antiviral immunity, providing protection from infection and dissemination with Chikungunya virus (CHIKV) — an emerging, mosquito-transmitted alphavirus. The study, published in *Cell*, shows that perturbation of the microbiome dampens antiviral type I interferon (IFN) responses, which could be restored by a single *Clostridium* symbiont and its associated secondary bile acid.

Disruption of the intestinal microbiome of conventionally housed mice by treatment with oral antibiotics for 3 days made the mice more susceptible to systemic infection with CHIKV than vehicle-treated mice. Elevated CHIKV titres, detectable just 1 day post infection, were highest

in the spleen and serum and not at the inoculation site, which was explained by the observation that circulating monocytes showed increased levels of productive viral infection following alteration of the gut microbiome. Indeed, depletion of monocytes normalized viraemia in antibiotic-treated mice, suggesting that the microbiome modulates the permissiveness of monocytes to CHIKV infection.

Single-cell RNA sequencing analysis revealed decreased expression of IFN-stimulated genes in monocytes after CHIKV infection of antibiotic-treated mice. A key role for type I IFN receptor signalling was confirmed using mice with conditional *Stat1* knockout in myeloid cells, which did not show a difference in viraemia following antibiotic treatment compared with controls.

CANCER IMMUNOTHERAPY

CD3ε tunes CAR T cell anticancer activity

Chimeric antigen receptor (CAR) T cells express engineered receptors that allow for the recognition of specific antigens, such as cancer antigens, via their extracellular domain and cellular activation via their intracellular domain. The intracellular domain usually contains a signalling domain derived from the T cell receptor (TCR) subunit CD3ζ. Reporting in *Cell*, Wu et al. now present a new method to examine the signalling patterns of the TCR signalling subunits and show that CD3ε may serve as a useful module in CAR T cell engineering.

The native TCR consists of TCR α- and β-chains as well as CD3 signalling subunits (ζ, δ, γ, ε), which differ with regard to the number of immunoreceptor tyrosine-based activation motifs (ITAMs) and other biochemical

features, such as a unique basic residue-rich sequence (BRS) in CD3ε.

Each ITAM contains two tyrosine phosphorylation sites. Phosphorylation is mainly mediated by the tyrosine kinase LCK and dephosphorylation by the phosphatase CD45. The ITAMs of the different signalling subunits have slightly different sequences, but whether these result in qualitative and/or quantitative differences in TCR signalling is poorly understood.

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