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 CD56dim 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.

The authors declare no competing interests.

There are amendments to 10.1038/s41577-020-0408-0

IN BRIEF

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-transmittedalphavirus. 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.

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 CD3ε. 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.

MICROBIOTA

CANCER IMMUNOTHERAPY

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The authors declare no competing interests.