

IN BRIEF

COVID-19

Does a host restriction factor facilitate entry of SARS-CoV-2?

Interferon-induced transmembrane proteins (IFITMs) are a family of host restriction factors that affect the fusion capacity of many enveloped RNA viruses. A preprint by Prelli Bozzo et al. now reports that SARS-CoV-2 appears to hijack IFITMs, and in particular IFITM2, as cofactors for the infection of lung cells. Whereas overexpression of IFITMs impaired SARS-CoV-2 membrane fusion with HEK293T cells in vitro, knockdown studies in the human lung epithelial cell line Calu-3 showed that endogenous levels of IFITM1, IFITM2 and IFITM3, both in the absence or presence of interferon, boost SARS-CoV-2 infection, with IFITM2 showing the strongest effect.

ORIGINAL ARTICLE Prelli Bozzo, C. et al. IFITM proteins promote SARS-CoV-2 infection of human lung cells. Preprint at bioRxiv <https://doi.org/10.1101/2020.08.18.255935> (2020)

COVID-19

SARS-CoV-2 ORF9c: a mysterious membrane-anchored protein that regulates immune evasion?

In this preprint, Dominguez Andres et al. report that the viral protein ORF9c may be involved in immune evasion. They show that it is highly unstable and is the first human coronavirus ORF9c protein that appears to have acquired a transmembrane domain. When expressed in the human lung epithelial cell line A549, SARS-CoV-2 ORF9c interfered with interferon signalling, antigen presentation and other immune and stress pathways. Interestingly, inhibition of the proteasome or the ATPase VCP counteracted the effects of ORF9c expression. Although mechanistically unclear, the likely membrane localization of ORF9c and its links to the proteasome and VCP suggest it modulates endoplasmic reticulum-associated degradation. Further research is needed to understand the potential role of ORF9c in immune evasion.

ORIGINAL ARTICLE Dominguez Andres, A. et al. SARS-CoV-2 ORF9c is a membrane-associated protein that suppresses antiviral responses in cells. Preprint at bioRxiv <https://doi.org/10.1101/2020.08.18.256776> (2020)

COVID-19

Coordinated and sustained immune memory responses after mild COVID-19

Deciphering the persistence of memory responses to COVID-19 will aid in understanding long-term protection. A preprint by Rodda et al. provides a longitudinal analysis of humoral and cellular memory responses in 15 individuals who recovered from mild COVID-19. Sustained neutralizing IgG antibodies and memory B cells, expressing B cell receptors capable of neutralizing the virus when produced as antibodies, were detectable 3 months after symptom onset. Additionally, SARS-CoV-2-specific memory T cells persisted for more than 3 months. These proliferated and produced T helper 1 (T_H1) and T_H17 cell-associated cytokines upon antigen re-stimulation. Collectively, these data suggest that mild COVID-19 infection induces sustained memory responses that exhibit functional hallmarks associated with potent antiviral immunity. Further studies will be needed to fully dissect immunological memory responses, their durability and their contribution to long-term protection from SARS-CoV-2 re-infection.

ORIGINAL ARTICLE Rodda, L. B. et al. Functional SARS-CoV-2-specific immune memory persists after mild COVID-19. Preprint at medRxiv <https://doi.org/10.1101/2020.08.11.20171843> (2020)

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MACROPHAGES

Macrophages clean up to keep the heart pumping

A recent study by José Enríquez, Andrés Hidalgo and colleagues details a novel way in which cardiac macrophages (cMacs) protect the heart. They show that cardiomyocytes pass subcellular particles containing dysfunctional mitochondria to macrophages; by cleaning up these 'bin bags' of broken mitochondria, macrophages help to maintain cardiac health.

Cardiomyocytes are large muscle cells that are densely packed with mitochondria and myofibrils to support the intense metabolic and mechanical needs of the heart. The authors imaged cardiac tissue in adult mice and found that each cardiomyocyte is surrounded by roughly five cMacs, with each cMac interacting with up to five cardiomyocytes through cellular processes. Depletion of cMacs using a CD169-DTR system increased mitochondrial mass in cardiomyocytes but was associated

with impaired function and ATP production by the mitochondria. In the absence of cMacs, cardiomyocyte mitochondria showed defective oxidative phosphorylation and preferentially switched to glycolysis. Notably, macrophage ablation by this method affected mitochondrial function and mass in the heart but not in the liver, despite macrophages being depleted in both organs. The authors found that cMac depletion led to a loss of left ventricular function in the heart and diastolic dysfunction. Therefore, cMacs are necessary to maintain mitochondrial fitness in cardiac tissue and to support the pumping function of the heart.

Imaging using fluorescent reporter systems showed that cMacs contain large phagolysosome-like vacuoles and actively take up materials from circulating leukocytes, from cardiomyocytes and,

CANCER IMMUNOTHERAPY

Microbial metabolite boosts immunotherapy

Composition of the gut microbiota can determine the response to cancer immunotherapy with immune checkpoint blockade (ICB), but the underlying mechanism is unclear. A new study shows that the microbial metabolite inosine, which leaks out of the gut owing to intestinal barrier defects, enhances antitumour responses when given to tumour-bearing mice together with ICB.

To explore the ICB-promoting effects of the microbiota, the authors searched for bacteria in colorectal tumours following treatment with anti-CTLA4 or anti-PDL1. Twenty-one distinct bacterial isolates could be cultured from homogenized tumours, seven of which were found only in treated tumours.

Tumour-associated bacterial isolates were then used to colonize germ-free (GF) or antibiotic-treated mice. As expected, ICB therapy alone was

much less effective against colorectal tumours in GF and antibiotic-treated mice than in specific-pathogen-free mice. But, colonization of GF mice with the different bacterial species isolated from treated tumours, in particular *Bifidobacterium pseudolongum*, *Lactobacillus johnsonii* or *Olsenella* species, significantly improved antitumour immune responses to subsequent ICB therapy. In the absence of tumours, intestinal *B. pseudolongum*

Credit: Vastram/Alamy

