IN BRIEF

COVID-19

Omicron alone provides limited cross-protection

The COVID-19 pandemic has been characterized by multiple waves of infection with different SARS-CoV-2 variants of concern (VOC). The Omicron variant generally causes milder symptoms than other VOC, especially in vaccinated individuals, and is highly transmissible — leading many to wonder whether immunity induced by Omicron may provide for cross-variant protection and bring us closer to the end of the pandemic. However, a report in *Nature* now shows that Omicron only induces a limited humoral immune response and little cross-variant neutralization in unvaccinated individuals. By contrast, Omicron breakthrough infections in vaccinated individuals induced high titres of neutralizing antibodies against all VOC. This indicates that although Omicron infection acts as a 'booster' in vaccinated individuals, it provides little protection from other VOC in unvaccinated individuals.

ORIGINAL ARTICLE Suryawanshi, R. K. et al. Limited cross-variant immunity from SARS-CoV-2 Omicron without vaccination. *Nature* https://doi.org/10.1038/s41586-022-04865-0 (2022)

COVID-19

Diabetes enhances viral loads in COVID-19

Diabetes is linked to enhanced susceptibility to severe COVID-19, but the underlying reasons are not well understood. Here, Garetta et al. report the development of diabetic-like kidney organoids, induced by an oscillatory glucose regimen. Expression of the cell surface receptor ACE2 was shown to be essential for infection with SARS-CoV-2. Diabetic conditions both enhanced cellular expression of ACE2 and induced a switch from oxidative phosphorylation to aerobic glycolysis, which increased viral loads upon infection of the organoids. Similar observations were made in kidney proximal tubular cells isolated from patients with diabetes, where altered mitochondrial respiration and enhanced glycolysis correlated with higher viral loads after SARS-CoV-2 infection. Conversely, treatment of patient kidney cells with an inhibitor of aerobic glycolysis resulted in reduced viral loads upon viral exposure. This demonstrates that diabetes-associated metabolic reprogramming increases susceptibility of kidney cells to SARS-CoV-2 infection, providing a possible explanation why diabetes can worsen outcome in patients with COVID-19.

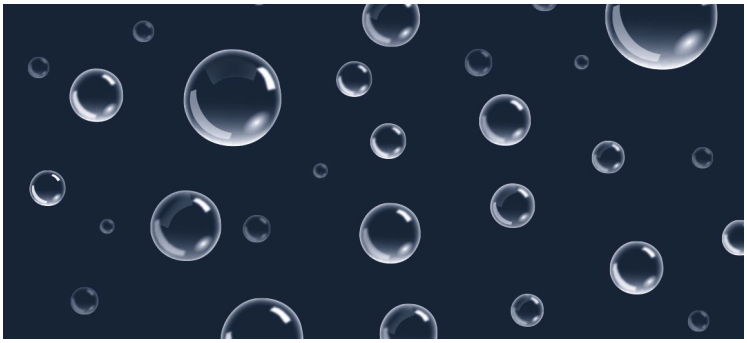
ORIGINAL ARTICLE Garreta, E. et al. A diabetic milieu increases ACE2 expression and cellular susceptibility to SARS-CoV-2 infections in human kidney organoids and patient cells. *Cell Metab.* https://doi.org/10.1016/j.cmet.2022.04.009 (2022)

COVID-19

Vaccines only partially protect against Long COVID

COVID-19 vaccines have proven very successful in protecting against severe disease. However, they only provide partial protection against infection, and an increasing number of individuals suffer breakthrough infections (BTIs) after vaccination. Al-Aly and colleagues investigated the vast US department of Veterans Affairs national health-care database to determine the level of protection vaccines provide against post-acute COVID-19 sequelae ('Long COVID'). They found that individuals with BTIs, compared with unvaccinated individuals, had a lower risk of death and Long COVID between of 1–6 months post-infection, particularly when comparing patients who had been hospitalized with COVID-19. However, the overall protection of the vaccine from Long COVID was only ~15%, which means that the burden of Long COVID is likely to be substantial even in fully vaccinated populations. Therefore, vaccination alone may not be enough to mitigate the long-term health consequences of SARS-CoV-2 infection.

ORIGINAL ARTICLE Al-Aly, Z. et al. Long COVID after breakthrough SARS-CoV-2 infection. *Nat. Med.* https://doi.org/10.1038/s41591-022-01840-0 (2022)



MICROBIOTA

Gut commensals promote antiviral immunity via extracellular vesicles

The role of the microbiota in providing a competitive barrier to bacterial and fungal infections is well known. However, the microbiota can also affect systemic immunity — and a recent study in *Immunity* demonstrates how gut commensals can promote systemic antiviral responses.

Individuals with viral infections are sometimes prescribed antibiotics as a preventive measure, and self-medication of undiagnosed diseases with antibiotics is common. To investigate potential effects of antibiotic use on viral infections, Erttmann et al. treated mice with a cocktail of ampicillin, neomycin and vancomycin and subsequently challenged them with herpes simplex virus type 1 (HSV-1), a DNA virus. The infection was considerably more severe in antibiotic-treated mice. The authors found that antibiotic treatment profoundly reduced gut bacterial abundance and they observed a systemic reduction in the expression of type I interferons (IFNα/β), which are key mediators of antiviral immunity.

The connection between systemic IFNα/β expression and the gut microbiota was further investigated in knockout mice that were deficient in different combinations of components of innate immune pathways. Surprisingly, mice defective in TLR signalling pathways, which are key sensors of extracellular microbes and had previously been assumed to mediate IFNα/β priming by the microbiota, did not show significant impairment in type I interferon expression. Instead, the basal systemic levels of IFNα/β seemed to be induced by commensal bacteria via the intracellular STING pathway, which left the question as to how extracellular bacteria may activate an immune pathway that senses intracellular DNA.

Transwell experiments demonstrated that extracellular bacteria, such as an *Escherichia coli* strain that was modified to prevent activation of TLR4 and was used as a proxy for commensal bacteria (*E. coli* Δ*lpxM*), can activate cGAS, an intracellular sensor of DNA, and thereby the STING pathway, even without direct host cell contact. This pointed to the involvement of bacterial extracellular vesicles (BEVs). These are approximately 20–250 nm in diameter and have many similarities to exosomes secreted from eukaryotic cells — such as the ability to deliver DNA across cell walls.

The authors demonstrated that BEVs containing DNA derived from the gut microbiota can indeed be detected in the systemic circulation of mice. 'Priming' of mice (including mice with defective TLR signalling) with *E. coli* Δ*lpxM*, wild-type *E. coli* or the respective BEVs, increased their resistance to challenge with HSV-1. Similar results were obtained with vesicular stomatitis virus, an RNA virus. In vitro, pre-exposure of bone marrow-derived macrophages to BEVs enhanced the expression of key effectors of the type I interferon response upon HSV-1 infection.

This study highlights the importance of the microbiota in maintaining the immune system in a state of constant preparedness against viruses. It also implies that antibiotics may need to be used with caution in the context of viral infections.

Alexandra Flemming

ORIGINAL ARTICLE Erttmann, S. F. et al. The gut microbiota primes systemic antiviral immunity via the cGAS-STING-IFN-I axis. *Immunity* **55**, 1–15 (2022)