> there is a profound loss of circadian gene expression and immune function in aged macrophages

immune functions seem to be markedly disrupted in macrophages from older mice.

Additional analyses showed that these differences between young and aged macrophages were not caused by alterations in the core clock machinery or differential oscillations in chromatin accessibility. Instead, the authors identified KLF4 as a key transcription factor that undergoes oscillatory expression and drives rhythmic gene transcription in young macrophages, but shows loss of oscillatory expression in aged macrophages. Moreover, knockdown of *Klf4* in young macrophages disrupted diurnal rhythmic phagocytosis in these cells.

To examine the clinical relevance of this pathway, the authors used the UK Biobank to explore whether *KLF4* variants are linked with any age-associated diseases in humans. Of note, carriers of the rs2236599 variant of *KLF4* showed an increased risk of developing *Escherichia coli* infection and also enhanced infection-related mortality overall. However, while non-carriers of this variant older than 65 years showed an elevated risk of contracting *E. coli* compared with younger non-carriers, this age-associated risk was less pronounced in carriers of the rs2236599 variant of *KLF4*.

Overall, these findings indicate that there is a profound loss of circadian gene expression and immune function in aged macrophages that appears to arise from the disruption of rhythmic *Klf4* expression. The authors suggest this pathway could be involved in the increased susceptibility to infection-associated mortality that is seen in older individuals.

Yvonne Bordon

ORIGINAL ARTICLE Blacher, E. et al. Aging disrupts circadian gene regulation and function in macrophages. *Nat. Immunol.* https://doi.org/10.1038/s41590-021-01083-0 (2021)

Credit: Janet Hudson/Getty

In sepsis, the interaction of platelets with neutrophils promotes NETosis, which in turn favours disseminated intravascular coagulation and organ failure. Consistent with a regulatory role for NFAT in this pathway, the authors showed that NFAT inhibition (through FK506 treatment or *Nfat1* deletion) increased the capacity of activated platelets to interact with neutrophils and induce NETosis, through upregulation of P-selectin.

The platelet-intrinsic role for NFAT was confirmed using transgenic mice in which the VIVIT peptide is specifically expressed in platelets (iNFATuation mice). Compared with control platelets, platelets from iNFATuation mice showed reduced NFAT1 dephosphorylation, and increased aggregation and P-selectin expression, leading to increased platelet–neutrophil complexes and NET formation. Accordingly, these mice had shorter bleeding times and increased severity of thromboembolic events. Moreover, selective inhibition of NFAT in platelets worsened morbidity of iNFATuation mice during lipopolysaccharide-induced septic shock and Gram-negative bacterial septicemia, by establishing a detrimental feedback loop between hyperactive platelets and neutrophils. Together, these data suggest that NFAT modulates the ability of platelets to induce and sustain pathophysiological responses and may be a useful therapeutic target in hyporesponsive platelet disorders.

Lucy Bird

ORIGINAL ARTICLE Poli, V. et al. Inhibition of transcription factor NFAT activity in activated platelets enhances their aggregation and exacerbates Gram-negative bacterial septicemia. *Immunity* https://doi.org/10.1016/j.immuni.2021.12.002 (2022)

COVID-19

Omicron, the great escape artist

The sequence of the SARS-CoV-2 Omicron variant was first announced on 24 Nov 2021. Less than a month later, a number of articles in *Nature* and *Cell* report the immune evasion characteristics of the heavily mutated variant.

Compared to the ancestral Wuhan-Hu-1 strain, Omicron contains over 30 mutations in its spike protein, with 15 located in the receptor binding domain (RBD), one of the main targets of neutralizing antibodies (nAbs). Some of these confer tighter binding to human ACE2 (Cameroni et al. show a 2.4-fold increase in binding affinity and Garcia-Beltran et al. show that Omicron-spike containing pseudovirus with was twice as efficient at infecting cells as Delta), while other mutations drive immune escape. Interestingly, they also allow for binding to ACE2 from a broader range of species (Hoffmann et al., Cameroni et al.).

Overall, the studies agree that sera from convalescent as well as fully vaccinated individuals (BNT162b2, mRNA-1273, Ad26.COV2.5 or ChAdOx1-nCoV19, Sputnik V or BBIBP-CorV) contain very low to undetectable levels of nAbs against Omicron. Recent boosting with a third dose of mRNA vaccine (even though these encode ancestral spike) appears to restore neutralizing activity, potentially by increasing the breadth of humoral immunity and cross-reactivity to variants. Some of the studies also show that double vaccination followed by Delta breakthrough infection, or prior infection followed by mRNA vaccine double vaccination, appear to generate increased and potentially protective levels of neutralizing antibodies (Dejnirattisai et al., Cele et al., Carreño et al.).

Several studies also demonstrate that Omicron evades binding and neutralization by most therapeutic SARS-CoV-2 monoclonal antibodies (mAbs), with the exception of some broadly neutralizing mAbs such as sotrovimab (Cao et al., Hoffmann et al., Dejnirattisai et al., Cameroni et al., Planas et al., Liu et al.). Cao et al. show that out of a panel of 247 human RBD-targeted mAbs, 85% fail to bind Omicron.

Although viral escape from nAbs can facilitate breakthrough infections in vaccinated and convalescent individuals, it is worth noting that pre-existing cellular and innate immunity, non-neutralizing antibodies, as well as residual neutralizing antibodies are still likely to protect from severe disease.

Alexandra Flemming

ORIGINAL ARTICLES Cao, Y. et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *Nature* https://doi.org/10.1038/d41586-021-03796-6 (2021) | Cameroni, E. et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *Nature* https://doi.org/10.1038/d41586-021-03825-4 (2021) | Planas, D. et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature* https://doi.org/10.1038/d41586-021-03827-2 (2021) | Liu, L. et al. Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2. *Nature* https://doi.org/10.1038/d41586-021-03826-3 (2021) | Cele, S. et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. *Nature* https://doi.org/10.1038/d41586-021-03824-5 (2021) | Garcia-Beltran, W. et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *Cell* https://doi.org/10.1016/j.cell.2021.12.033 (2021) | Hoffmann, M. et al. The Omicron variant is highly resistant against antibody-mediated neutralization – implications for control of the COVID-19 pandemic. *Cell* https://doi.org/10.1016/j.cell.2021.12.032 (2021) | Carreño, J. M. et al. Activity of convalescent and vaccine serum against SARS-CoV-2 Omicron. *Nature* https://doi.org/10.1038/d41586-021-03846-z (2021) | Dejnirattisai, W. et al. SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. *Cell* https://doi.org/10.1016/j.cell.2021.12.046 (2021)