High-speed delivery to neutrophils

Neutrophils are the ‘first responders’ of the circulating immune system, being recruited rapidly to sites of inflammation by tissue-resident mast cells. Dudeck et al. describe a mechanism to ensure this high-speed response, involving direct delivery of mast cell mediators into the blood.

On the basis of previous studies suggesting a role for mast cell-derived tumour necrosis factor (TNF) in neutrophil recruitment, the authors investigated hapten-induced skin inflammation in mice lacking mast cell-derived TNF (MCΔ^TNF^ mice). The number of neutrophils infiltrating inflamed skin was markedly reduced in MCΔ^TNF^ mice and the ratio of extravascular to intravascular tethered neutrophils suggested reduced diapedesis. This was confirmed by the decreased number of neutrophils attached to vessel walls and their reduced crawling velocity in MCΔ^TNF^ mice.

The effect of TNF deficiency on neutrophil diapedesis did not result from changes to endothelial cell activation; expression levels of chemokines and adhesion molecules by vascular endothelial cells were not affected in MCΔ^TNF^ mice. By contrast, hapten-induced upregulation of CD11b and Ly6G by neutrophils, which are required for blood vessel adhesion and crawling, did not occur in MCΔ^TNF^ mice. Mice lacking neutrophil expression of the TNF receptor TNFR1 had similarly reduced hapten-induced CD11b expression.

Adoptive transfer experiments were used to show that the reduced expression of CD11b and Ly6G by neutrophils from hapten-stimulated MCΔ^TNF^ mice resulted in a reduced ability to extravasate into inflamed skin in wild-type recipient mice, whereas ‘activated’ wild-type neutrophils having high levels of CD11b expression extravasated normally in MCΔ^TNF^ mice. Together, the results indicate a direct effect of mast cell-derived TNF on the extravasation of neutrophils.

So how is TNF delivered directly and rapidly from mast cells to neutrophils? The authors identified perivascular mast cells that are not only attached to the exterior wall of the blood vessel but also are embedded within the endothelial cells and have intravascular extensions making direct contact with the bloodstream that are increased in number and size during inflammation. Furthermore, they showed that these perivascular mast cells can degranulate directly into the bloodstream and they were able to observe this happening in real time. Mast cell granules isolated in vitro then injected intravenously into hapten-challenged mice increased the number of skin-infiltrating neutrophils. This ability of mast cells to degranulate into the bloodstream, and thus prime neutrophils with TNF, was confirmed in two other models of skin inflammation.

Although these results remain to be verified in humans, they suggest that this pathway could be a therapeutic target for inflammation-associated anaphylactic shock or cytokine storm syndromes.

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ORIGINAL ARTICLE Dudeck, J. et al. Directional mast cell degranulation of tumor necrosis factor into blood vessels primes neutrophil extravasation. Immunity https://doi.org/10.1016/j.immuni.2020.12.017 (2021)

COVID-19

SARS-CoV-2 variant evades antibodies whilst maintaining fitness

The SARS-CoV-2 N439K mutation, located in the receptor-binding motif (RBM) of the spike protein, has emerged multiple times independently and was the first RBM variant to spread significantly. Thomson et al. now demonstrate that the RBM, which is the primary target for neutralizing antibodies, is structurally plastic and that the N439K mutation confers an approximately twofold enhanced binding affinity for human ACE2 (the viral entry receptor), without a loss in replication fitness and with similar clinical outcomes to infection with the ancestral virus. They also show that the mutation confers resistance to several neutralizing monoclonal antibodies and allows for immune escape from some polyclonal sera derived from individuals who recovered from infection. The fact that the RBM can readily mutate without loss of fitness indicates that despite the slow mutation rate of the virus, potentially immune-evading variants will continue to emerge — which has indeed been observed since the completion of this study.

ORIGINAL ARTICLE Thomson, E. C. et al. Circulating SARS-CoV-2 spike N439K variants maintain fitness whilst evading antibody-mediated immunity. Cell https://doi.org/10.1016/j.cell.2021.01.037 (2021)

COVID-19

Do rogue antibodies make the difference between mild versus severe COVID-19?

To shed light on the immunological mechanisms underlying the mild/severe distinction in COVID-19 pathology, Combes et al. performed single-cell RNA-seq analysis on blood samples from patients with mild/moderate or severe COVID-19. In patients with mild/moderate COVID-19, they found populations of immune cells that displayed a coordinated pattern of interferon-stimulated gene (ISG) expression, but these cells were systemically absent in patients with severe disease. Surprisingly, patients with severe disease had higher virus-specific antibody titres and lower viral loads than patients with mild/moderate disease. However, they uniquely produced antibodies that appeared to functionally block the production of ISG-expressing cells by engaging FcγRIIB. This Fc receptor antagonizes IFNα and IFNγ signalling and thereby disrupts a positive-feedback loop that would otherwise enhance interferon responses.

ORIGINAL ARTICLE Combes, A. J. et al. Global absence and targeting of protective immune states in severe COVID-19. Nature https://doi.org/10.1038/s41586-021-03234-7 (2021)

COVID-19

Intracranial inflammatory mediators involved in SARS-CoV-2 neurological manifestations?

COVID-19 is frequently associated with a wide spectrum of neurological dysfunction that can persist long after the acute infection. Remsk et al. analysed cerebrospinal fluid from patients with cancer who had neurological manifestations after SARS-CoV-2 infection. They found an increase in intracranial patients with cancer who had neurological manifestations after acute infection. Remsik et al. analysed cerebrospinal fluid from neurological dysfunction that can persist long after the COVID-19 is frequently associated with a wide spectrum in SARS-CoV-2 neurological manifestations?

MMP10 correlated with the degree of neurological dysfunction. They found an increase in intracranial patients with cancer who had neurological manifestations after acute infection. Remsik et al. analysed cerebrospinal fluid from neurological dysfunction that can persist long after the COVID-19 is frequently associated with a wide spectrum in SARS-CoV-2 neurological manifestations?