COVID-19

Mapping the interferon response

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Severe COVID-19 is characterized by the overproduction of inflammatory mediators and cytokines such as interleukin-1 (IL-1), IL-6 and granulocyte–macrophage colony-stimulating factor (GM-CSF); however, the part played by interferons (IFNs) — the signature antiviral cytokines — is complex. In *Cell*, Zanoni and colleagues investigate the expression of IFNs along the upper and lower respiratory tract (URT and LRT, respectively) to understand their effect on COVID-19 severity. Within the URT of patients under 70, most, but not all, IFNs correlate with viral load; however, viral load in the UTR per se does not correlate with the severity of the disease. By contrast, patients older than 70 show a general dysregulation of IFN production in which even low viral burdens can associate with very high IFN expression. High expression of IFN-III (IFNλ), and to a lesser degree IFN-I (IFNβ), in the URT compared with the LRT associates with a milder disease course. IFNλ1 in particular seems to be beneficial, and efficiently triggers the induction of antiviral genes by human bronchial epithelial cells. Furthermore, high relative expression of IFNs in the LRT associates with the activation of cell death pathways. The URT and LRT also differ in their source of IFN production. In the URT, epithelium is the primary producer of IFNs and this occurs directly in response to SARS-CoV-2 infection. By contrast, in the LRT, hematopoietic cells such as conventional dendritic cells are the main source of IFNs and do so in response to SARS-CoV-2-infected epithelium. This study therefore suggests that a robust and prompt IFN-III response in the URT can reduce CoV-2 infection before it reaches the lungs, where IFNs instead exert an immunopathological role. *ZF*

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IMMUNOMETABOLISM

How ILC2s can fight obesity

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Beyond its storage function, white adipose tissue (WAT) is widely considered to be an important secondary immune organ owing to the abundance of leukocytes, but this tissue is also surprisingly well innervated by sympathetic neurons. How local adipocytes, immune cells and nerve fibres interact is an emerging area of research that is important for our understanding of metabolic syndrome, type 2 diabetes and obesity. Research published in *Nature* now shows how group 2 innate lymphoid cells (ILC2s) in the WAT contribute to this tripartite regulation of obesity and its sequelae.

Using various methods, the authors ablated peripheral sympathetic neurons in adult mice resulting in a reduction in ILC2 functionality in the gonadal WAT, as measured by the percentage of cells that were positive for the characteristic ILC2 cytokines interleukin-5 (IL-5) and IL-13. The opposite result occurred in response to pharmacological stimulation of the β2-adrenergic receptor (encoded by *Adrb2*). However, this link between β-adrenergic signaling and adipose ILC2 function seems to be indirect as the deletion of *Adrb2* in lymphoid cells had no effect. The authors instead show that platelet-derived growth factor receptor-α (PDGFRA)-positive mesenchymal stromal cells (MSCs) in the WAT, which have high *Adrb2* expression and are located near sympathetic axons, seem to be this missing link, partly as mice with *Adrb2*-specific deletion in PDGRA$^+$ cells had dysfunctional ILC2s. The authors also show how MSCs communicate with ILC2s. The MSCs seem to pump out glial-derived neurotrophic factor (GDNF) that activates its receptor RET, which is highly expressed by the neighboring ILC2s, and RET then drives ILC2 production of IL-5 and IL-13.

Notably, the authors also show that RET signaling in these adipose ILC2s controls the response to a high-fat diet (HFD). $Ret^{\Delta Vav1}$, $Ret^{\Delta Il5}$ and RET-deficient ILC2 chimeric mice fed with a HFD all had more extreme levels of obesity and lower glucose tolerance than wild-type HFD-fed mice, which the authors attribute to the known effect of type 2 cytokines on WAT 'beigeing' of adipose tissue, with its characteristic increased energy expenditure and reduced lipid storage. *NJB*

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