Monocytes

Fasting affects monocyte lifespan and migration

Fasting has been shown to affect the distribution of leukocytes in the body, but the underlying mechanisms are poorly understood. A report in *Immunity* investigated the mechanisms of monocyte migration during fasting and re-feeding and their consequences for host responses.

Janssen et al. detected large shifts in leukocyte distribution in 24 h fasted mice, with a notable accumulation of monocytes in the bone marrow (BM). The authors found that fasting induced a corticosterol (CORT)-mediated stress response via the hypothalamic–adrenal–pituitary axis. CORT, which is produced by neurons in the paraventricular hypothalamus, binds the glucocorticoid receptor NR3C1 on monocytes, upregulating the chemokine receptor CXCR4 and inducing homing to the BM. Upon re-feeding, these cells re-appear in the circulation (the authors suspect this is due to a fall in CORT levels), causing monocytosis. They form a population of chronologically older monocytes with a distinct transcription profile that is not found in mice fed freely.

Upon intranasal challenge with LPS, fasted then re-fed mice showed more pronounced monocyte recruitment to the lung, and when challenged with *Pseudomonas aeruginosa*, they had higher levels of plasma cytokines and died earlier and in larger numbers compared to mice fed freely.

These observations suggest that monocytic disequilibrium due to fasting then re-feeding increases inflammation, thereby altering host responses. The authors point out that there are many known protective effects of fasting, but show that there can also be a 'cost' — and suggest that the continuous replenishment of circulating monocytes through hematopoiesis may be a luxury that is sacrificed early during nutrient starvation. Moreover, the role of the central nervous system in orchestrating large-scale leukocyte shifts highlights the importance of brain–body communication.

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Original article: Janssen, J. et al. Monocytes re-enter the bone marrow during fasting and alter the host response to infection. *Immunity* https://doi.org/10.1016/j.immuni.2023.01.024 (2023)

In brief

COVID-19

Autoantibodies against chemokines linked with better disease outcomes in COVID-19

Autoantibodies against interferons and other immune mediators have been linked to negative outcomes following infection with SARS-CoV-2. By contrast, this study suggests that autoantibodies targeting chemokines could have beneficial effects in COVID-19. The authors obtained plasma from three independent cohorts of patients and they measured antibody reactivity against the N-terminal loop of all 43 human chemokines. Interestingly, the presence of autoantibodies against specific chemokines could identify convalescent individuals who had better disease courses in the settings of both acute COVID-19 and long COVID. At 6 months post-infection, individuals who had higher levels of autoantibodies against CCL21, CXCL13 and CXCL16 were less likely to have developed long COVID. Autoantibodies isolated from these patients could block B cell chemotaxis in vitro. The authors propose that these chemokine-targeting autoantibodies could dampen potentially harmful immune responses that drive COVID-19 pathology.

Original article: Muri, J. et al. Autoantibodies against chemokines post-SARS-CoV-2 infection correlate with disease course. *Nat. Immunol.* https://doi.org/10.1038/s41590-023-01445-w (2023)

Immunometabolism

Repurposing metabolic drugs for COVID-19

Patients with obesity and/or diabetes have worse outcomes in SARS-CoV-2 infection, and the virus has been shown to promote insulin resistance and β-cell dysfunction in individuals with no previous history of metabolic disease. As such, there is interest in repurposing anti-diabetic drugs for COVID-19. This study reports that blocking the mitochondrial pyruvate carrier (MPC) with the second-generation insulin sensitizer MSDC-0602 K (MSDC) reduces disease in mice infected with SARS-CoV-2, as well as in mice infected with influenza virus. Mice with a myeloid-restricted deletion of MPC also had better outcomes in these viral infections, and MSDC was shown to restrict the inflammatory activity of both mouse and human alveolar macrophages. In virus-infected obese mice, treatment with MSDC reduced hyperglycaemia as well as airway inflammation. Mechanistically, MSDC improved mitochondrial fitness and reduced succinate and acetyl-CoA levels, which destabilized HIF-1α and limited inflammatory responses driven by the HIF-1α pathway.

Original article: Zhu, B. et al. Inhibition of the mitochondrial pyruvate carrier simultaneously mitigates hyperinflammation and hyperglycemia in COVID-19. *Sci. Immunol.* https://doi.org/10.1126/sciimmunol.adf0348 (2023)

Chemokines

CXCL8 blockade reduces fibrosis in endometriosis

Endometriosis is a common condition that leads to pain and infertility, but treatment options are limited. The disease is associated with chronic inflammation, and several inflammatory chemokines have been implicated in its progression. Here, the authors examined the expression of inflammatory genes in endometriotic tissue samples and identified the chemokine CXCL8 (also known as IL-8) and its receptors CXCR1 and CXCR2 as being highly upregulated in women with endometriosis. CXCL8 was also highly expressed in cynomolgus monkeys that spontaneously developed endometriosis, and preliminary experiments suggested that targeting CXCL8 reduced fibrotic disease in these animals. The authors engineered a long-lasting antibody against CXCL8 (AMY109) and showed that therapeutic delivery of this agent reduced disease in a surgically induced model of endometriosis in cynomolgus monkeys. AMY109 seemed to reduce the fibrotic disease associated with endometriosis, at least in part by blocking neutrophil recruitment and activation. The authors report that trials of AMY109 in humans are now underway.

Original article: Nishimoto-Kakiuchi, A. et al. A long-acting anti–IL-8 antibody improves inflammation and fibrosis in endometriosis. *Sci. Transl. Med.* https://doi.org/10.1126/scitranslmed.abq5858 (2023)