Inflammation

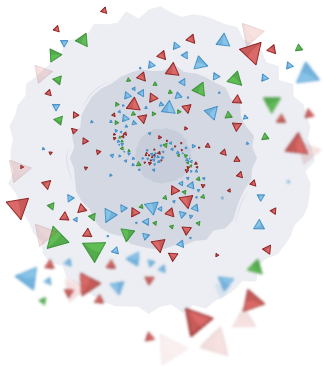
Ferritin-induced NETs lead to cytokine storm in AOSD

The spectrum of hyperferritinaemic syndrome encompasses clinical conditions including adult-onset Still disease (AOSD), macrophage activation syndrome, catastrophic anti-phospholipid syndrome and septic shock, as well as severe COVID-19. Emerging evidence suggests that ferritin, rather than being a biomarker of the inflammatory response, might contribute directly to the pathogenic mechanism that results in systemic inflammation. A study now shows that ferritin promotes neutrophil activation and the formation of neutrophil extracellular traps (NETs) via the ferritin receptor macrophage scavenger receptor 1 (MSR1), and highlights the therapeutic potential of targeting this pathway.

"Hyperferritinaemia and neutrophil activation are hallmarks of AOSD," notes corresponding author Qiongyi Hu. "This study reveals the pro-inflammatory role of ferritin, thereby improving the understanding of the common mechanisms behind the spectrum of hyperferritinaemic syndrome."

In the study, mice treated with intraperitoneally administered ferritin developed systemic inflammation, characterized by a cytokine storm, as well as hepatic inflammation, with increased recruitment of neutrophils and markers of NET formation evident in liver tissue. Further investigations established that neutrophils are essential for ferritin-induced inflammation, and that peptidylarginine deiminase 4, neutrophil elastase and reactive oxygen species are indispensable for NET formation.

Exposure to ferritin increased the expression of MSR1 on



mouse and human neutrophils. Ferritin-induced NET formation was reduced in human neutrophils treated with the MSR1 antagonist fucoidan and in *Msr1*$^{-/-}$ mice, which also displayed attenuated liver inflammation and injury compared with wild-type mice.

Notably, hyperferritinaemia was also shown to contribute to NET formation in neutrophils from patients with AOSD, and treatment with an MSR1 inhibitor abrogated ferritin-induced NET formation in these cells.

The researchers plan to further explore the mechanisms by which ferritin-induced NETs can promote a cytokine storm in patients with AOSD, as well as the potential of targeting the ferritin–MSR1–NET pathway in AOSD and other forms of hyperferritinaemic syndrome.

Sarah Onuora

Original article: Jia, J. et al. Ferritin triggers neutrophil extracellular trap-mediated cytokine storm through Msr1 contributing to adult-onset Still's disease pathogenesis. *Nat. Commun.* **13**, 6804 (2022)

Sjögren syndrome

AhR promotes suppressor cell function in Sjögren syndrome

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells involved in regulating immune responses in many pathological conditions. Emerging evidence suggest that the suppressive activity of MDSCs is impaired in primary Sjögren syndrome. New findings in *Cellular & Molecular Immunology* provide further insight into the underlying mechanisms modulating MDSC responses in this condition, and how these changes might be targeted therapeutically.

Building on previous findings implicating the aryl hydrocarbon receptor (AhR) in MDSC responses, the investigators found that, among various immune cell lineages, the AhR is highly expressed in polymorphonuclear MDSCs (PMN-MDSCs), in both humans and mice. Treatment with indole-3-propionic acid (IPA), a gut-derived tryptophan metabolite and natural ligand for AhR, promoted the differentiation, proliferation and suppressor function of PMN-MDSCs in vitro. By contrast, an AhR antagonist (CH223191) suppressed PMN-MDSC differentiation and proliferation.

In a mouse model of Sjögren syndrome involving immunization with salivary gland proteins, antibody-mediated depletion of PMN-MDSCs, AhR antagonism or a tryptophan-free diet exacerbated disease, including accelerating the reduction in salivary flow rate, increasing the production of autoantibodies and enhancing effector T cell responses. By contrast, dietary supplementation with IPA ameliorated pathology and restored the immunosuppressive function of MDSCs.

Further analysis found that the expression of AhR is decreased during disease in the mouse model and is negatively regulated by the transcription factor IRF4. Deletion or inhibition of IRF4 promoted IPA-mediated PMN-MDSC differentiation and suppressor function in vitro.

> **"AhR is highly expressed in polymorphonuclear MDSCs"**

"Medications targeting the AhR pathway are available and several clinical trials have been initiated to evaluate their safety and efficacy in patients with inflammatory disease," explains Liwei Lu, a corresponding author on the new study. Lu postulates that these medications, or a tryptophan-enriched diet, are possible therapeutic strategies that might be used in combination with DMARDs for the treatment of Sjögren syndrome in future.

Jessica McHugh

Original article: Wei, Y. et al. Aryl hydrocarbon receptor activation drives polymorphonuclear myeloid-derived suppressor cell response and efficiently attenuates experimental Sjögren's syndrome. *Cell. Mol. Immunol.* **19**, 1361–1372 (2022)