Inflammation

Copper boosts pro-inflammatory state of macrophages

Excessive inflammation causes substantial immunopathology. A report in *Nature* now shows that copper ions promote the metabolic and epigenetic remodelling of macrophages and that copper can be targeted to rein in uncontrolled inflammation.

Solier et al. generated monocyte-derived macrophages (MDMs) from human primary monocytes and found that activated MDMs upregulate the glycoprotein CD44, which is linked to cell plasticity.

CD44 can facilitate the endocytosis of hyaluronan-bound metals including copper, and activated MDMs had higher levels of Cu^{2+} ions in their mitochondria compared with non-activated MDMs. This was dependent on CD44 and was unaffected by knockdown of other metal transporters.

Whereas known copper chelators had little effect, the antidiabetic drug metformin, which can also interact with copper, interfered with MDM activation. The authors developed a metformin dimer, LCC-12, with an increased capacity to bind Cu^{2+}, that was 1,000 times more potent than metformin in this assay. LCC-12 also inhibited other processes characterized by CD44 upregulation, such as the epithelial–mesenchymal transition of cancer cells.

Cu^{2+} modulates MDM metabolism by activating hydrogen peroxide, which leads to the oxidation of NADH to NAD^+, which, in turn, activates mitochondrial enzymes and causes metabolic reprogramming. This affects the epigenetic regulation of pro-inflammatory genes by promoting the activity of histone demethylases and acetyltransferases.

In mice, intraperitoneal administration of LCC-12 protected against lipopolysaccharide-induced death, increased survival in a sepsis model, and reduced the expression of inflammatory genes in SARS-CoV-2 infection.

Together, these results indicate that CD44 regulates immune cell activation through the uptake of copper. They also highlight the central role of mitochondrial Cu^{2+} in inflammation, and potentially in cell plasticity in general.

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Original article: Solier, S. et al. A druggable copper-signalling pathway that drives inflammation. *Nature* https://doi.org/10.1038/s41586-023-06017-4 (2023)

In brief

Neuroimmunology

How nociceptors shape dendritic cell responses

Nociceptors and dendritic cells (DCs) are prevalent at barrier tissues, including the skin, and imaging studies have suggested these populations interact to shape local tissue immunity. Using in vitro coculture of primary mouse neurons and bone marrow-derived DCs, Hanc et al. found that nociceptors enhance DC production of inflammatory cytokines following exposure to pathogen-associated molecular patterns (PAMPs) or whole pathogens. This cytokine potentiation required activation of both cell types, as well as physical contact between DCs and electrically competent nociceptors. Further experiments by the authors identified three distinct pathways through which nociceptors regulate DCs. First, when nociceptors (but not DCs) are activated, they produce CGRP and this induces steady state DCs to upregulate 'sentinel' genes, such as pro-IL-1β, without causing overt DC activation. Second, when both nociceptors and DCs are activated, electrical activity from nociceptors is sensed by DCs and this increases the proportion of DCs secreting inflammatory cytokines in response to PAMPs. Third, nociceptors secrete the chemokine CCL2 to retain DCs and prevent them from prematurely leaving inflamed tissues — this increases cytokine production by DCs in the tissue, enhancing local inflammation.

Original article: Hanc, P. et al. Multimodal control of dendritic cell functions by nociceptors. *Science* https://doi.org/10.1126/science.abm5658 (2023)

Allergy

JAKs drive innate-like T_H9 cell activation in allergy

IL-9-producing T helper 9 (T_H9) cells are associated with allergic diseases, including asthma, food allergy and atopic dermatitis. The mechanisms regulating these cells are incompletely understood — for instance, it is not clear why T_H9 cells gradually lose the capacity to secrete IL-9. Here, Son et al. show that the *IL9* locus becomes accessible to STAT5 and STAT6 shortly after T_H9 cell differentiation and this enables TCR-independent 'bystander' activation of resting T_H9 cells in response to IL-2 and IL-4. Such innate-like activation of T_H9 cells promoted allergic airway inflammation in mice. Over time, chromatin remodelling reduces *IL9* locus accessibility and limits *IL9* expression, explaining the instability of T_H9 cells. The authors suggest that intrinsic T_H9 cell instability may act as a negative regulator of bystander activation, but this 'checkpoint' could break down in allergic disease. Notably, treatment with IL-2 and IL-4 induced IL-9 in circulating $CD45RO^+CD4^+$ T cells from patients with atopic dermatitis but not in corresponding T cells from healthy volunteers. Furthermore, expansion of T_H9 cell populations was associated with STAT5 and STAT6 induction and responsiveness to JAK inhibitors both in mouse models and in patients with allergic disease. The authors suggest JAK inhibitors should be considered for patients whose allergic diseases are associated with expansion of T_H9 cell populations.

Original article: Son, A. et al. Dynamic chromatin accessibility licenses STAT5- and STAT6-dependent innate-like function of T_H9 cells to promote allergic inflammation. *Nat. Immunol.* https://doi.org/10.1038/s41590-023-01501-5 (2023)

Tissue repair

Hypoxia and IL-24 drive a sterile wound healing pathway

Here, Liu et al. detail how epithelial stem cells (ESCs) are able to sense injury and initiate tissue repair independently of microbial signals. They show that during skin wounding in mice, ESCs at the wound edge upregulate IL-24, which drives STAT3 activation in an autocrine and paracrine manner to promote wound repair. Notably, this IL-24-mediated process still occurs in germ-free mice and in the absence of adaptive immune cells. Mice in which IL-24 signalling was ablated showed defects in re-epithelialization, in regeneration of blood vessels and in fibroblast responses in the wound bed. The authors found that induction of IL-24 at the wound edge requires both hypoxia-mediated stabilization of HIF1α and autocrine IL-24 receptor signalling. They suggest this leads to natural autoregulation of the repair response, as re-establishment of the vasculature during wound healing will reduce hypoxia- and IL-24-mediated signalling. Interestingly, they highlight that prominent IL-24 expression has been reported in certain diseases that have been associated with dysfunctional tissue repair, including severe COVID-19 and ulcerative colitis.

Original article: Liu, S. et al. A tissue injury sensing and repair pathway distinct from host pathogen defense. *Cell* https://doi.org/10.1016/j.cell.2023.03.031 (2023)