NEUTROPHILS

Defective fibrinolysis in periodontitis

Science **374**, eabl5450 (2021)

Periodontitis is an inflammatory disease that is a major cause of tooth loss. In *Science*, Silva et al. investigate the link between periodontitis and human polymorphisms in the *PLG* gene, which encodes plasminogen and hence causes plasmin-mediated fibrinolysis. The authors show that deficient plasmin generation results in increased fibrin deposition and neutrophil recruitment in gingival tissues, which is necessary but not sufficient to cause bone loss. By using mouse genetic models, they further show that fibrin activates neutrophils via their $\alpha_M\beta_2$ integrin receptor, which induces neutrophil extracellular trap (NET) formation, myeloperoxidase release and reactive oxygen generation, and triggers the immunopathology observed. Similarly, severe gingival disease in humans also correlates with increased fibrin deposition and neutrophil activation. These findings point to potential strategies to blunt this periodontal disease by blocking

fibrin-mediated activation of neutrophils within the oral mucosa. *LAD*

<https://doi.org/10.1038/s41590-022-01133-1>

COVID-19

Young versus old

Nature <https://doi.org/10.1038/04345-x> (2022)

One of the characteristic features of COVID-19 is the much milder disease course seen in children; however, the mechanisms that underlie this are incompletely understood. To address this question, Mayer and colleagues use multi-omics approaches to compare immune responses in matched samples from the respiratory tracts and blood of adults and children. Both children and adults show similar expression of SARS-CoV-2 entry receptors in the respiratory tract but the interferon (IFN) response signature is clearly distinct. In healthy children, the epithelium shows an increased IFN signature with poor induction during COVID-19. By contrast, adults have an initially weak IFN signature that is strongly induced in COVID-19.

Systemically, children show a generally naive immune compartment during COVID-19 whereas adults show a strong cytotoxic and inflammatory signature. Collectively, this suggests that the higher steady-state expression of IFN in children restricts SARS-CoV-2 in the upper respiratory tract and prevents more severe systemic inflammation. *ZF*

<https://doi.org/10.1038/s41590-022-01135-z>

MICROGLIA

High energy, high function

Immunity **55**, 159–173 (2022)

Microglia phagocytose synaptic material to regulate the patterning and wiring of neural circuits. In *Immunity*, He et al. show that IL-33 signaling through the ST2 receptor regulates a specific transcriptional and metabolic program to sustain phagocytosis in microglia. In the postnatal brain, microglia with high metabolic activity have increased phagocytic function, cluster as a distinctive subpopulation and express a transcriptional program that is reflective of activation, which can also be induced by IL-33. Inhibition of mitochondrial bioenergetics diminishes the phagocytic activity of microglia, and IL-33- or ST2-deficient mice have dystrophic microglia, reduced synaptic engulfment, defective synaptic transmission and plasticity and behavioral deficits. IL-33 is expressed by astrocytes and induces mitochondrial activity and the engulfment of synaptosomes via the PI3K–mTOR–AKT pathway. Mitochondrial metabolism and AKT activity are high postnatally and decline in the adult brain, which suggests the temporal regulation of microglia activity in the developing brain. *IV*

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NEUROIMMUNOLOGY

Mediating T_H17 transit

Sci. Transl. Med. <https://doi.org/10.1126/scitranslmed.abj0473> (2022)

T_H17 cells that cross the blood–brain barrier (BBB) are important effectors of neuroinflammation in multiple sclerosis (MS). New data published in *Science Translational Medicine* show that dual immunoglobulin domain-containing cell adhesion molecule (DICAM) can mediate this process. DICAM, already known to be expressed by astrocytes, was shown to be highly expressed by T_H17 cells both in vivo and in cultures of polarizing T helper cells. Neither T_H1 nor T_H2 cells expressed DICAM in these contexts. Furthermore, known ligands for DICAM were highly expressed in brain lesions from patients with MS, and anti-DICAM antibodies could prevent T_H17 cells from sticking to BBB endothelial cultures. Importantly, therapeutic application of these anti-DICAM antibodies reduced the severity of disease in several experimental autoimmune encephalitis mouse models of MS. *NJB*

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