Research highlights

Autoimmunity

STAT3 and autoimmunity

Patients with T cell large granular lymphocytic leukemia (T-LGL) often have expanded CD8 T cells clones bearing gain-of-function (GOF) somatic mutations in *STAT3*, and frequently develop autoimmune disease. In *Immunity*, Masle-Farquhar et al. find that STAT3 GOF somatic mutations in CD8 T cells are a cause, not an effect, of autoimmunity. In mouse models of human STAT3 GOF mutations, in which the mice developed splenomegaly and lymphadenopathy and succumbed to a wasting syndrome, there was an accumulation of CD8 T cells that expressed NKG2D and CX3CR1. This increase in CD8 T cells was mirrored in individuals with STAT3 GOF mutations. $CD8^+$ T cells expressed genes associated with cytotoxicity and proliferation and were highly polyclonal. The $CD8^+$ T cell accumulation was dependent on NKG2D and CD122 (also known as IL-15RB), and depletion of $CD8^+$ T cells reduced inflammation and lethality in mice. Therefore, STAT3 GOF mutations can cause the accumulation of CD8 T cells, resulting in lethal pathology.

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Nature Immunology

Original reference: *Immunity* **55**, 2386–2404.e8 (2022)

COVID-19

SARS-CoV-2 mucosal vaccine

Currently approved SARS-CoV-2 vaccines induce robust systemic immunity but poor immunity at the respiratory mucosa, meaning that they are highly effective against symptomatic disease but do not prevent viral transmission. In *Science*, Mao et al. developed a vaccine strategy that induced mucosal immune memory within the respiratory tract and reduced viral transmission. K18-hACE2 mice were vaccinated with mRNA-LNP (Pfizer/BioNTech BNT162b2) by intramuscular injection, and 14 days later unadjuvanted spike protein was administered intranasally; termed the 'prime and spike regimen'. This resulted in high levels of anti-SARS-CoV-2 IgA and IgG in the nasal wash and bronchoalveolar lavage fluid (BALF), and the accumulation of spike-specific CD8 T cells and antigen-experienced CD4 T cells in the lung and BALF. The prime and spike regimen provided protection from COVID-19-like disease after challenge with a lethal SARS-CoV-2 infection and reduced viral transmission in a hamster model of SARS-CoV-2. Thus, a prime and spike regimen induces a protective mucosal immune response and reduces the transmission of SARS-CoV-2.

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T cells

STAT5 facts

Several cytokines, particularly interleukin 2 (IL-2), signal via the common gamma chain (γc) to activate JAK–STAT5 pathways. In *Science Immunology*, Villarino et al. report a prominent role for the transcription factor STAT5 in the metabolic reprogramming of naive $CD4^+$ T cells into effector cells. STAT5 is required to increase the expression of genes encoding enzymes involved in the glycolysis and oxidative phosphorylation pathways, and amino acid transporters, which are needed to support T cell proliferation and effector function. Increased STAT5 function resulted in increased abundance of key metabolites that fuel T cell proliferation and protein synthesis. Although STAT5 is needed to recruit the histone acetyltransferase p300 to chromatin, not all STAT5-dependent gene expression required p300-mediated epigenetic modifications. Similarly, STAT5 regulated the expression of the transcription factor MYC and promoted cooperative interactions with MYC to enhance metabolic gene expression, although many genes exhibited a greater dependence on STAT5, including those that encode proteins involved in RNA transport. Importantly, the STAT5-dependent transcriptome is also prominent in human T cell malignancies, which suggests that STAT5 could be a potential therapeutic target.

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