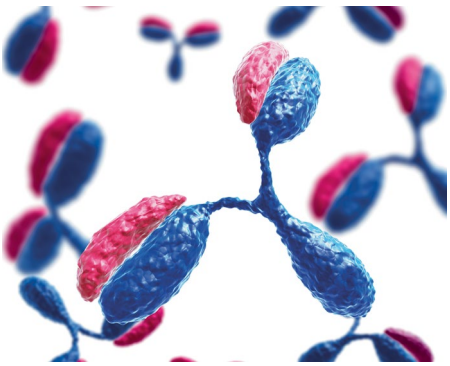
Autoimmunity

Immune dysregulation in Down syndrome



A study in *Nature* from the lab of Dusan Bogunovic has characterized the immune system in individuals with Down syndrome and highlights several unique features that could explain why these individuals are more prone to severe infections and autoimmunity. Specifically, the authors show that the immune system in Down syndrome is characterized by steady state increases in cytokine expression, $CD4^+$ T cell activation, atypical B cell activation and the presence of autoantibodies. Notably, the study highlights immune pathways, such as IL-6 signalling, that could be targeted to prevent disease manifestations in Down syndrome.

Down syndrome, also known as trisomy 21, is a genetic disorder caused by an extra copy of around 200 genes from chromosome 21. Individuals with Down syndrome show developmental defects that affect many physiological systems, but in recent years attention has turned to the immune system disturbances that occur. It has previously been suggested that immune dysfunction in Down syndrome may stem from overactive interferon responses or thymic disturbances, as most interferon receptor subunits and the autoimmune regulator (AIRE) transcription factor are encoded by chromosome 21; however, a proper mechanistic understanding is lacking.

In this study, Malle et al. performed cytokine arrays on plasma from individuals with Down syndrome and age-matched controls and were able to divide Down syndrome individuals into three main groups: one showed marked immune dysregulation and widespread upregulation of 22 out of the 29 cytokines assessed, another group showed significant elevation of a subset of cytokines (including IL-1α, IL-4, IL-6, IL-13 and TNF) and the final group clustered with the controls. Increased cytokine dysregulation in Down syndrome was shown to correlate with greater clinical immune dysfunction. By comparing cytokine profiles seen in Down syndrome and COVID-19, the authors showed that at least one-third of individuals with Down syndrome have elevated baseline cytokine expression levels that resemble those seen in a severe acute viral infection. Therefore, the authors propose that Down syndrome is a cytokinopathy.

Further analyses indicated that individuals with Down syndrome have T cells skewed towards a memory phenotype and show elevated levels of STAT3 phosphorylation in naive, activated and memory $CD4^+$ T cell populations. Treatment with an anti-IL-6 receptor antibody or a JAK inhibitor restored STAT3 phosphorylation to control levels, suggesting IL-6 signalling contributes to aberrant T cell activation in Down syndrome. Disturbances were also seen in the B cell compartment; individuals with Down syndrome showed a profound decrease in total B cells and an almost threefold increase in plasmablasts. In addition, Down syndrome was characterized by increased frequencies of atypical $CD11c^+Tbet^{hi}CD21^{low}$ B cells — these cells are thought to arise from naive B cells that are activated outside of germinal centres and have been linked to various autoimmune diseases. Of note, the frequency of the $CD11c^+$ B cells correlated with higher plasma levels of IL-6 and with the number of autoimmune manifestations seen in the Down syndrome cohort.

When the authors cultured B cells from control individuals with plasma from individuals with Down syndrome or else plasma from controls, they detected markedly higher plasmablast differentiation in the presence of plasma from the Down syndrome cohort. Individual blockade of various cytokines had no effect on this, but JAK inhibitors or combined blockade of IL-6, type I interferon, IFNγ and TNF reduced plasmablast differentiation. The authors also showed that control T cells pre-incubated with plasma from individuals with Down syndrome or else T cells isolated from individuals with Down syndrome promoted increased levels of plasmablast and $CD11c^+$ B cell differentiation when co-cultured with naive $CD11c^-$ B cells. Therefore, aberrant cytokine and T cell responses seem to contribute to the atypical B cell responses seen in Down syndrome.

Further experiments indicated that the $CD11c^+$ B cells that develop in Down syndrome show features associated with autoimmunity, including increased CDR3 length and higher usage of the *IGHV4-34* gene in their B cell receptors. In line with this, microarray analyses identified 365 proteins targeted by autoantibodies from individuals with Down syndrome — by comparison, 257 and 829 proteins, respectively, were found to be targeted by autoantibodies from patients with the autoimmune conditions APS1 or IPEX syndrome. The autoantibodies identified in Down syndrome targeted many different tissues and systems, including the gastrointestinal tract, the CNS and the immune system itself. Of note, the autoantigens identified in Down syndrome largely overlapped with those seen in IPEX syndrome — a disease characterised by defects in regulatory T cells. The authors found that overall T_{reg} cell frequencies were not markedly altered in individuals with Down syndrome, suggesting that aberrant T cell activation is a driver of autoreactivity.

These findings expand our understanding of the immune dysfunction that occurs in Down syndrome. Moreover, they suggest that blocking basal T cell activation, for instance through use of JAK or IL-6 inhibitors, could be used to prevent autoimmune manifestations in Down syndrome.

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Original article: Malle, L. et al. Autoimmunity in Down's syndrome via cytokines, CD4 T cells and $CD11c^+$ B cells. *Nature* https://doi.org/10.1038/s41586-023-05736-y (2023)