Autoimmunity

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Down syndrome: insights into autoimmune mechanisms

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Understanding why individuals with Down syndrome are highly predisposed to autoimmunity has broad mechanistic and therapeutic implications. New work identifies novel potential mechanistic pathways driving increased autoimmunity-relevant CD11c$^+$ B cells and provides the broadest view to date of the repertoire of autoantibodies generated in individuals with Down syndrome.

Refers to Malle, L. et al. Autoimmunity in Down's syndrome via cytokines, CD4 T cells and CD11c$^+$ B cells. *Nature* **615**, 305–314 (2023).

Down syndrome, the most common chromosomal condition (approximately 1 in 700 births), is associated with an increased risk of common autoimmune diseases, including rheumatic diseases[1]. For example, Down syndrome is linked to a four to sixfold increased risk of juvenile idiopathic arthritis, type 1 diabetes, autoimmune thyroid disease and coeliac disease[1]. Hence, there is a growing interest in how trisomy 21 disrupts immune tolerance and promotes autoimmune disease in individuals with Down syndrome, and researchers have begun to identify the key immune genes, pathways and cell types that are dysregulated[2–5]. A new study by Malle and colleagues[6] adds to this knowledge and advances our understanding of the complexity of immune dysregulation in individuals with Down syndrome, which could help pave the way for new and/or personalized treatments of autoimmune diseases in future (Fig. 1).

Previous studies have shown extensive autoimmunity-relevant remodelling of the immune landscape in individuals with Down syndrome, particularly in cytokines and immune subsets[3,4]. An important focus of these investigations has been the enhanced interferon signalling observed in these individuals compared with the general population, arising from overexpression of the four (of six) interferon receptor subunits encoded on chromosome 21 (refs. 2,5). In 2022, IL-6 was implicated as an independent driver of T cell dysregulation in individuals with Down syndrome[3]. Together, these results highlight various molecular changes in individuals with Down syndrome that resemble those seen in autoimmune and rheumatic diseases (Fig. 1). Down syndrome-related cellular changes include increased frequencies of T helper 1 (T_H1) cells, T_H17 cells and CD11c$^+$ B cells[2,3]. By comparison, the role of regulatory T (T_{reg}) cells is less well understood, with conflicting descriptions of intact or impaired suppressive function of T_{reg} cells in Down syndrome[2,7]. Finally, advanced immune ageing in Down syndrome[3] might represent another factor thought to predispose individuals to autoimmune disease.

Malle et al.[6] validate many of these previous findings, particularly the increased plasma concentration of IL-6 and frequency of CD11c$^+$ B cells in individuals with Down syndrome, which have both been linked to ageing and autoimmunity[8]. The researchers provide in vitro evidence supporting both direct and indirect mechanisms that could account for the increased frequency of CD11c$^+$ B cells, including a direct role for serum cytokines (such as IL-6) and a role for T cell help modulated by the cytokine environment of Down syndrome. Importantly, Malle and colleagues demonstrate that the increase in phosphorylated signal transducer and activator of transcription 3 (STAT3; a transcription factor that is activated downstream of various cytokines, including IL-6) in individuals with Down syndrome can be blocked by tocilizumab, implicating IL-6 as a therapeutically tractable promoter of the predisposition to autoimmunity. These data and data from other studies suggest that existing therapies targeting IL-6 and JAK–STAT signalling should be studied to determine their utility in the treatment of autoimmunity in individuals with Down syndrome.

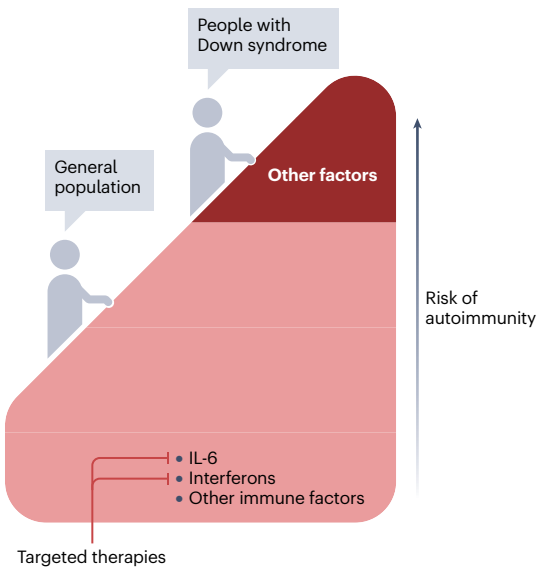

Fig. 1 | How Down syndrome can highlight a path to precision therapy of autoimmunity. Individuals with Down syndrome are at increased risk of common autoimmune diseases compared with the general population owing to dysregulation in specific pathways including IL-6 and interferon signalling. Deep analysis of the immune phenotype of individuals with Down syndrome can help elucidate dysregulated pathways that predispose individuals to autoimmunity and biomarkers of this process. In turn, such insights can point to rational precision therapy strategies (such as targeted biologic therapies) for the prevention and/or treatment of autoimmunity in individuals with and without Down syndrome.

Malle et al.[6] extend our understanding of autoimmunity in Down syndrome through seromic profiling of autoantibodies in individuals with Down syndrome using the CDI HuProt peptide array. These studies revealed an increased number of autoantibodies in Down syndrome, among them autoantibodies that target organs affected in Down syndrome-related autoimmunity, supporting their physiologic relevance. Additionally, the data show that Down syndrome-related autoantibodies overlap with other autoimmune and autoinflammatory conditions including immune polyendocrinopathy enterepathy (IPEX) and autoimmune polyglandular syndrome type 1 (APS1). This overlap might reflect shared pathobiological pathways or downstream effects of failed tolerance. An important observation is the presence of immune-modulating autoantibodies in individuals with Down syndrome, including anti-IFNGR2 antibodies that attenuate IFNγ responses[6]. The presence of antibodies that can drive immune dysregulation and the multiple immune factors that are dysregulated in Down syndrome highlights the value of studying the (complete and integrated) response of participants with Down syndrome, particularly in the context of defined immune perturbations. Malle et al.[6] study these aspects in the context of SARS CoV-2 infection; extending studies of the response to other infections and to vaccinations would be of great future interest. Overall, these findings expand our understanding of how the immune response is dysregulated in individuals with Down syndrome, and open new areas for investigation including acquired causes of immune heterogeneity.

The challenges of studying individuals with Down syndrome overlap with those in non-Down syndrome populations, but often with greater logistical barriers. As with all human immunophenotyping studies, inter-individual heterogeneity is an important variable that ultimately requires larger cohorts and validation studies to confirm initial findings. Importantly, autoimmunity itself can alter the immune architecture, influencing the cytokine profiles and cell compositions, and accelerating immune ageing; moreover, age itself can critically impact immune features in both linear and non-linear ways[3,9]. Thus, future studies in Down syndrome must increasingly examine individuals with Down syndrome across the lifespan, while accounting for potential confounders including age and autoimmunity in the study design. Other key variables might emerge with time; for example, Malle et al.[6] found heterogeneity in the cytokine profiles of individuals with Down syndrome, the cause and effect of which remain to be clearly elucidated. The small pool of participants and high concentration of participants (particularly in the adult Down syndrome population) with multiple co-occurring conditions typically seen in tertiary academic research centres pose challenges to these aspirations. Possible solutions include collaborative efforts, increased outreach and building clinical centres that provide care tailored to adults with Down syndrome. Efforts to enhance Down syndrome research are being promoted by groups including the NIH-INCLUDE Project in the USA and other groups globally.

Establishing larger cohorts that include adults with Down syndrome will considerably enhance Down syndrome-autoimmunity research and has broad implications. In addition to common autoimmune diseases, even apparently Down syndrome-specific conditions such as regression syndrome[10], an immune-related neurologic condition, might share pathophysiology with diseases in individuals without Down syndrome. Continuing efforts to better understand the spectrum of autoimmune diseases affecting individuals with Down syndrome and to identify pathogenic pathways will help identify those individuals with Down syndrome at highest risk of developing autoimmunity, and the triggers likely to precipitate disease. This understanding will help identify the optimal therapeutic approach to mitigate disease in individuals with Down syndrome, establishing Down syndrome as a model for precision therapy of autoimmunity. This approach can then be extended to individuals without Down syndrome who share causal pathways of autoimmunity.

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Competing interests

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