Scientists reveal harmful impacts of immune hyperactivity in Down syndrome and how to normalize it with existing drugs

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People with Down syndrome, the condition caused by an extra copy of

chromosome 21, or trisomy 21, display chronic dysregulation of their immune system, which can contribute to high rates of autoimmune conditions and severe complications from respiratory infections.

In a new study published in *Science Advances*, scientists at the Linda Crnic Institute for Down Syndrome at the University of Colorado Anschutz Medical Campus report the largest and deepest characterization of immune dysregulation in Down syndrome to date. The findings also reveal important connections between immune hyperactivity and other aspects of Down syndrome and provide proof-of-principle evidence for a therapeutic strategy to restore immune balance in this population.

The Crnic Institute's previous research demonstrated that this immune dysregulation is associated with hyperactivity in the interferon response, the main defense against viruses. In addition, they showed interferon hyperactivity contributes to many hallmarks of Down syndrome in a mouse model, including congenital heart defects, developmental delays, cognitive impairments and malformation of the bone structures in the skull.

The most recent study reports the analysis of hundreds of blood samples from research participants enrolled in the Crnic Institute Human Trisome Project, a large cohort study of people with Down syndrome. Using a combination of large-scale data technologies, referred to as multi-omics, they defined associations between the degree of interferon hyperactivity and multiple physiological, metabolic, and immune processes dysregulated by the extra chromosome.

"We observed that interferon hyperactivity really shapes the biology of Down syndrome across the lifespan. Those with the highest interferon activity display increased signs of autoinflammation, stronger dysregulation of important growth factors, profound metabolic changes,

and a vastly different immune system," says Dr. Matthew Galbraith, leader of the Data Sciences Program at the Crnic Institute and one of the co-leading authors of the paper.

"These results clearly demonstrate that persons with Down syndrome with the highest levels of interferon activity show drastic changes in the immune system, such as increases in a type of T cells often involved in the development of autoimmune conditions, or depletion of B cells, which are important for response to vaccines," explains Keith Smith, co-leading author of the paper.

Previous studies have indicated that interferon hyperactivity could be ameliorated with a class of drugs known as "JAK inhibitors" which are approved for the treatment of a wide range of autoinflammatory conditions in the general population. However, the effects of JAK inhibitors on the biological processes modulated by trisomy 21 have not been extensively studied.

To advance this area of research, the Crnic Institute team monitored the effects of JAK inhibition on a research participant with Down syndrome taking the JAK inhibitor known as tofacitinib, or Xeljanz, for the treatment of alopecia areata. Alopecia areata is an autoimmune form of hair loss more common in people with Down syndrome. Over the course of several years and under the care of their dermatologist, the participant provided blood samples while on the medicine and during voluntary interruptions of the treatment.

"We observed a remarkable normalization of interferon hyperactivity when the participant was taking the JAK inhibitor. Consistently, her interferon metrics and other biomarkers of inflammation dropped from the abnormally high levels seen in Down syndrome down to the range observed in the general population, but not any lower. This indicates that the JAK inhibitor provided therapeutic benefit in terms of hair regrowth

without suppressing the immune system below the normal range," explains Dr. Angela Rachubinski, leader of the Clinical and Translational Sciences Program at the Crnic Institute and co-lead author of the study.

According to Dr. Joaquin Espinosa, executive director of the Crnic Institute and senior author of the paper, this study provided the rationale for two additional clinical trials for JAK inhibition in Down syndrome led by the Crnic Institute. "One study is focused on autoimmune skin conditions and another one is focused on Down Syndrome Regression Disorder, a rare but devastating condition characterized by sudden loss of daily living skills and cognitive abilities."

More information: Matthew D. Galbraith et al, Multidimensional definition of the interferonopathy of Down syndrome and its response to JAK inhibition, *Science Advances* (2023). DOI: 10.1126/sciadv.adg6218

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