A new approach to study autoimmune diseases

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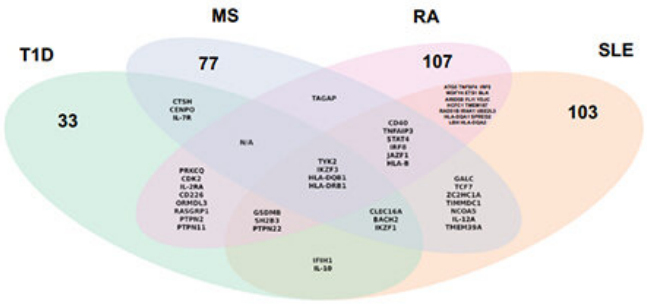

Venn diagrams of risk genes expressed in the target tissues of the fourautoimmune diseases (type 1 diabetes, systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis) shows shared candidate genes among them. Credit: Indiana Biosciences Research Institute

A team of researchers led by the Indiana Biosciences Research Institute Diabetes Center's Scientific Director Decio L. Eizirik, MD, Ph.D., has found that identifying new treatments for autoimmune diseases requires studying together the immune system AND target tissues. This study, "Gene expression signatures of target tissues in type 1 diabetes, lupus erythematosus, multiple sclerosis and rheumatoid arthritis," is featured in the Jan. 6, 2021, edition of *Science Advances*.

"We must move away from the present "immune-centric-only" view of autoimmune diseases," explains Eizirik. "Indeed, trying to understand these diseases focusing on the immune system only, and forgetting the target tissues, may be similar to attempting to fly a plane with only one wing."

Autoimmune diseases, which affect up to 5 percent of the population in different regions, suffer from a case of mistaken identity. The immune system is supposed to protect us from infectious diseases or tumors. Yet, during autoimmune diseases the immune system mistakenly attacks and destroys components of our body, which then causes, for example, type 1 diabetes (T1D), systemic lupus erythematosus (SLE), multiple sclerosis (MS) or rheumatoid arthritis (RA). These four autoimmune diseases share almost half of the same genetic risks, chronic local inflammation and mechanisms leading to target tissue damage.

Despite these common features, autoimmune disorders are traditionally studied independently and with a focus on the immune system rather than on the target tissues. Knowing that there is increasing evidence that the target tissues of these diseases are not innocent bystanders of the immune system attack, but instead are active participants, Eizirik and his team hypothesized that key inflammation-induced mechanisms, potentially shared between T1D, SLE, MS and RA, may drive similar molecular signatures at the target tissue level.

"This research is significant in reaching the JDRF's mission to cure, treat and prevent T1D," said Frank Martin, Ph.D., JDRF director of research. "Discovering the common pathways of tissue destruction across multiple autoimmune diseases will dramatically accelerate our path to a cure for T1D. Drugs that are effective in one autoimmune disease could be equally beneficial for another and quickly repurposed to make a big impact for people living with that disease. Characterizing the similarities and differences between multiple autoimmune diseases has the potential to transform the way we treat and cure these diseases in the future."

To test this hypothesis, the research team obtained gene expression data from diseased tissue sampled from controls or individuals affected by T1D, SLE, MS and RA. This indicated major common gene expression changes at the target tissues of the four autoimmune diseases evaluated. One candidate gene in common between the four diseases is TYK2, a protein that regulates interferon signaling. The team showed in its research that use of TYK2 inhibitors—already in use for other autoimmune diseases—protect ?-cells against immune-mediated damage. This finding reinforces the importance of studying the target tissue of autoimmune diseases, in dialogue with the immune system, to better understand the genetics and natural history of these devastating diseases and to identify novel therapies.

More information: F. Szymczak et al, Gene expression signatures of target tissues in type 1 diabetes, lupus erythematosus, multiple sclerosis, and rheumatoid arthritis *Science Advances* 06 Jan 2021: Vol. 7, no. 2, eabd7600 DOI: 10.1126/sciadv.abd7600

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