Autoimmune diseases: similar molecular signatures in target tissues

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A study conducted by Professor Decio L. Eizirik’s group - ULB Center for Diabetes Research - and published in Sciences Advances shows that autoimmune diseases, including type 1 diabetes, must be studied in their entirety, taking into account not only the immune system but also the target tissues. Indeed, the key mechanisms induced by inflammation, potentially shared between type 1 diabetes, systemic lupus erythematosus, multiple sclerosis and rheumatoid arthritis, could generate similar molecular signatures at the target tissue level. The identification of similar (or, in some cases, divergent) signatures between specific diseases may identify key pathways that could be targeted for therapy, including the reuse of drugs already in clinical use for other diseases. One of these drugs, a TYK inhibitor, shows very promising pre-clinical results for the protection of pancreatic beta cells in type 1 diabetes.

Autoimmune diseases are diseases of “mistaken identity”, where the immune system – which is supposed to protect us against infectious diseases and neoplasias – mistakenly attacks and destroys components of our own body. The incidence of autoimmune diseases is increasing on a worldwide basis, and these diseases - including type 1 diabetes (T1D), systemic lupus erythematosus (SLE), multiple sclerosis (MS) and rheumatoid arthritis (RA) - now affect up to 5% of the population in different regions. There is no cure for autoimmune diseases, and while the immune target of T1D, SLE, MS, and RA are distinct, they share several similar elements, including up to 50% common genetic risk, chronic local inflammation and mechanisms mediating target tissue damage.

In spite of these common features, autoimmune disorders are traditionally studied independently and with a focus on the immune system rather than on the target tissues. There is, however, increasing evidence that the target tissues of these diseases are not innocent bystanders of the autoimmune attack but participate in a deleterious dialogue with the immune system that contributes to their own demise, as first shown by the Eizirik’s group for T1D. Furthermore, in T1D, several of the risk genes for the disease act at the target tissue level – in this case pancreatic β-cells – regulating the responses to viral infections, the dialogue with the immune system and apoptosis. Against this background, the Authors hypothesized that key inflammation-induced mechanisms, potentially shared between T1D, SLE, MS and RA, may drive similar molecular signatures at the target tissue level. Discovering these similar (or, in some cases, divergent) disease-specific signatures may allow the identification of key pathways that could be targeted for therapy, including the re-purposing of drugs already in clinical use for other diseases. To test this hypothesis, they obtained RNA sequencing datasets (i.e. studies
where all genes expressed on a diseased tissue, as compared to a healthy one, are identified, from pancreatic β-cells from controls or individuals affected by T1D, from kidney cells from controls or individuals affected by SLE, from optic chiasm from controls or individuals affected by MS and from joint tissue from controls or individuals affected by RA. These studies indicate major common gene expression changes at the target tissues of the four autoimmune disease evaluated, many of them downstream of interferons, and massive expression of candidate genes (>80% in all cases). One candidate gene in common between the four diseases is TYK2, a protein that regulates interferon signaling, and the Eizirik’s group showed that use of TYK2 inhibitors – already in use for other autoimmune diseases – protect beta-cells against immune-mediated damage in pre-clinical models of diabetes.

These findings, published in Science Advances, change the present “immune-centric-only” view of autoimmune diseases, and indicate 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. 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 one wing only.

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