Autoimmune diseases: why diabetes rather than arthritis?

Most autoimmune diseases share as much as 30-50% of their candidate genes in common: how can we then explain that one specific disease develop instead of another? In a new study published in Nature Genetics, researchers from Université libre de Bruxelles’ Centre for Diabetes Research provide an insight to understand this phenomenon and shed light on the mechanisms leading to type 1 diabetes development.

Autoimmune diseases such as type 1 diabetes, rheumatoid arthritis, multiple sclerosis etc, are a case of “mistaken identity”, i.e., the immune system that is supposed to protect us starts instead to attack our own tissues.

Most autoimmune diseases have a strong genetic component, with candidate genes that increase risk or provide protection against the disease. Several autoimmune diseases have as much as 30-50% of their candidate genes in common, raising the question on why in some individuals the immune system attacks the insulin-producing beta cells, causing type 1 diabetes, while in others it targets for instance joint tissues, leading to rheumatoid arthritis.

A study led by Decio L. Eizirik, a WELBIO researcher at Université libre de Bruxelles’ Centre for Diabetes Research, provides an insight to understand this phenomenon. While most of the research in the field has focused on the role for these candidate genes on the immune system, Decio L. Eizirik’s team has investigated their impact on pancreatic beta cells, the ones producing insulin.

Published in Nature Genetics, this work was done in collaboration with colleagues from Barcelona, Oxford, Pisa and the National Institute of Health (USA). The researchers have discovered that many of these candidate genes affect the function and survival of pancreatic beta cells and the generation of signals that alert and attract the immune system. These dysfunctional signals lead to a misguided dialog between the beta cells and the immune system, rendering beta cells a potential target for the immune system. This immune “attack” happens under special conditions, for instance secondary to local inflammation caused by a viral infection or other “danger signals”.

The teams involved in the project have studied in detail the chromatin behaviour of beta cells exposed to pro-inflammatory signals. The chromatin is a complex of DNA and protein present in the cell nucleus, that allows close packaging of long DNA molecules; for gene transcription to occur, chromatin must “open” and provide access to transcription factors. In the present project, the researchers’ observations indicate that binding of tissue-specific transcription factors (factors that regulate expression of specific genes, such as insulin, in beta cells) “open” the chromatin: this
allows binding of pro-inflammatory transcription factors induced in the beta cells by local inflammation. This is amplified in individuals genetically predisposed to type 1 diabetes and may culminate in progressive beta cell death and diabetes.

The present study has clarified the role for pancreatic beta cells in type 1 diabetes, and provided an explanation for the reasons behind the immune system targeting beta cells. This "amplifying loop" mechanism could also explain other autoimmune diseases: binding of tissue-specific transcription factors, within an inflammatory context, could generate signals that would attract and activate immune cells against specific target tissues. This intriguing hypothesis must be now tested in novel studies comparing different autoimmune diseases.

References

The impact of pro-inflammatory cytokines on the β-cell regulatory landscape provides new insights into the genetics of type 1 diabetes

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