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Press information

Type 1 diabetes: the role of the thymus is not what we thought!

A small revolution has taken place in the world of type 1 diabetes research. A study conducted by an Inserm team led by Roberto Mallone at the Cochin Institute (Inserm, CNRS, Paris Descartes University) is calling into question the role long attributed to the thymus in selecting and eliminating white blood cells associated with type 1 diabetes and reveals that we are all auto-immune. Discoveries which change our understanding of the mechanisms of type 1 diabetes and point to new therapeutic strategies in fighting this disease.

This research has been published in *Science Immunology*.

In the large family of white blood cells, lymphocytes are in charge of immune response during infection. Among them, the T-cells are responsible for the recognition and specific destruction of pathogens. The “T” in T-cells is derived from the thymus, an organ to which the T-cells migrate from their place of birth, the bone marrow, prior to entering the blood circulation. Up until now, it was thought that the thymus was a place for the maturation and selection of T-cells, particularly that of CD8+ T-cells – a rare subset implicated in type 1 diabetes (T1D). So rare in fact that 10 mL of blood contains only 5 to 10 of these cells! These auto-immune lymphocytes become active when they encounter certain characteristic proteins for the first time, such as those of the β cells of the pancreas, subsequently leading them to consider them as undesirable and destroy them.
Up until now, it was accepted that the thymus “presented” to the CD8+ T-cells protein fragments characteristic of pancreatic β cells in order to pre-activate, detect and eliminate them. In T1D, it was thought that the selection by the thymus was altered - that if a healthy thymus filtered virtually all CD8+ T-cells, then that of a person with diabetes allowed many more to pass into the blood circulation. However, by comparing blood samples from healthy subjects and those with T1D, the Inserm researchers observed that not only did the blood of the healthy subjects present CD8+ T-cells but also that it contained as many as that of the diabetic subjects. These unexpected results call into question the role of the thymus in the selection of T-cells: since its presentation of β fragments to the CD8+ T-cells does not lead to their elimination, its selection turns out to be incomplete and inefficient.

The astonishing part of this discovery is that we are all auto-immune. This is the price we pay for being well-protected against the threat of infection, because the CD8+ T-cells spared by the thymus are also capable of recognizing microbial protein fragments that are similar to those of the β cells (a phenomenon known as “cross-recognition”).

But if we are all auto-immune, why then are we not all diabetic? According to Roberto Mallone, Inserm researcher at the Cochin Institute who led this study: *"The next challenge is to better understand the ingredients that transform the "benign" auto-immunity of Mr. Average into T1D. Identifying these ingredients will allow us to diagnose T1D earlier and develop therapies to revert the auto-immunity to its benign state."*

Two principal hypotheses are under investigation: the first one is that non-diabetic individuals may be capable of keeping their CD8+ T-cells under control, either due to a "policing" role played by other regulatory T cells or thanks to low CD8+ T-cell activation. The second is based on potential β cell vulnerability in T1D individuals, leading either to their abnormal recognition by the CD8+ T-cells or to their self-destruction.

Diabetes is a common disease in which complex genetic factors are involved. That is why it is the focus of the French Plan for Genomic Medicine 2025, supported by Aviesan and Inserm. As of 2019, a pilot experiment on diabetes as a common-disease model will be conducted in France to determine how the access to genetic sequencing could lead to earlier and more refined diagnosis than at present and the implementation of suitable treatments. New programs to screen the relatives of T1D patients are also being set up with the studies TRAKR and INNODIA, in order to achieve early diagnosis and the subsequent launch of clinical prevention trials.

Sources

Islet-reactive CD8+ T cell frequencies in the pancreas, but not in blood, distinguish type 1 diabetes from healthy

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