Snapshot turns T cell immunology on its head

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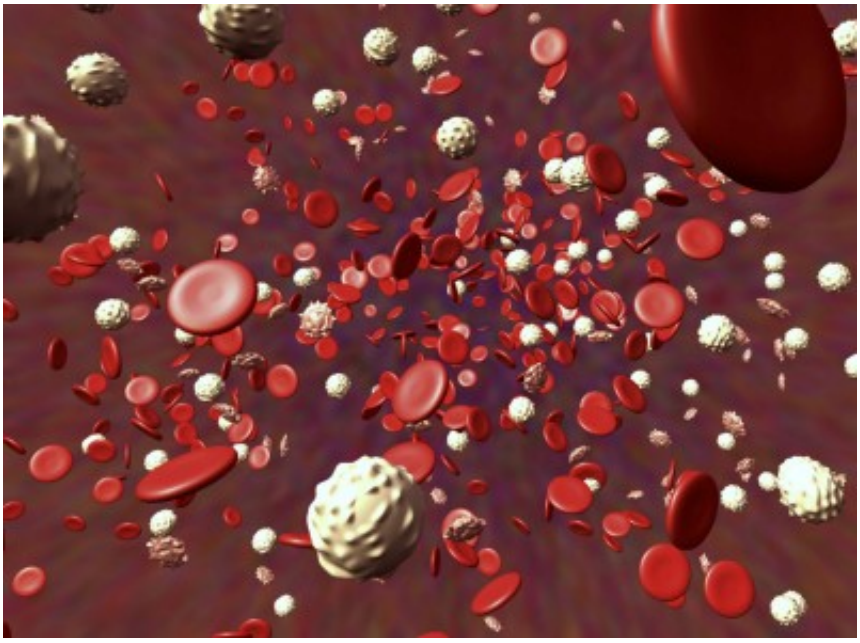

Challenging a universally accepted, longstanding consensus in the field of immunity requires hard evidence. New research from the Australian Research Council Centre of excellence in advanced Molecular imaging has shown the proof is in the picture. And this proof may have implications for type 1 diabetes.

Type 1 diabetes is an autoimmune disease – the body's immune system mistakenly attacks its own cells, leading to the inability to produce enough insulin to regulate glucose levels in the blood. Now, an

unexpected discovery about how these immune cells work at the atomic level may provide avenues to investigate new mechanisms able to short-circuit the inappropriate immune response in patients with type 1 diabetes.

When microorganisms such as bacteria and viruses invade the body, the immune system elicits a response that ensures they are engulfed and destroyed. Central to this response is the molecular-level interaction between the surface receptors of white blood cells (T cells) and immune molecules known as the major histocompatibility complex (MHC). Basically, a cell signals to a T cell that it is infected and the T cells mount a broad immune attack in the area of the infection.

Until now, the assumption has been that the receptors on the T cells (TCRs) must bind to MHC in a specific orientation in order to trigger a signal to the immune system. A team of researchers, led by Professor Jamie Rossjohn at Monash University, has succeeded in turning current immunology on its head, demonstrating for the first time that TCRs can bind with a completely reversed orientation – compared to all previously studied receptors.

Using the national Synchrotron, the team has investigated TCRs associated with a particular type of T cell – a regulatory T cell (Treg) – that prevents the body from attacking its own insulin-producing cells. "We like to call Treg cells 'peacekeeping' cells. They come about to stop the inflammatory response (once infections have been cleared) and false alarms that occur in autoimmune diseases.

In type 1 diabetes there are not enough of these peacekeeping cells and so the immune system continues to attack and destroy insulin-secreting cells," says Dr Hugh Reid, a co-author of the paper published in *Nature Immunology*. "Our atomic snapshots show that TCRs still function when they interact with MHC in a completely different orientation."

Individuals with type 1 diabetes are thought to have a reduced number of the peacekeeping cells. This subsequently triggers an unhelpful immune response in the pancreas, where insulin protein is produced. Using a fragment of this protein and an MHC molecule, the researchers stimulated the production of the peacekeeping cells needed by patients with type 1 diabetes, and they discovered—along with collaborators Tony Tiganis, Monash University and Bart Roep, Leiden University—that despite the reversed mode of connection, the cell still suppressed the attacking response in the presence of insulin.

This 'fixed' orientation of TCR recognition has always been put down to natural selection within the immune system's evolution and immunologists have strongly believed for T cells to be activated they must 'dock' in this fashion. Challenging this conventional understanding of the fixed orientation of TCRs suggests that all types of T cells could be capable of connecting with MHC in completely different ways.

The findings challenge established views and open up many exciting opportunities for further research. Of particular interest is that, despite the TCRs' reversed orientation, the Treg cells are still functional, suppressing the immune response when necessary.

"We will now set out to determine more TCR- MHC interactions of the same regulatory T cell subset and compare them to the other T cell TCR-MHC interactions derived from the inflammatory T cells," reveals Reid.

More information: T cell receptor reversed polarity recognition of a self-antigen major histocompatibility complex, DOI: 10.1038/ni.3271

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