

05 Re-balancing the immune system

Jean Fletcher

The events of the past year have made us all too familiar with the lexicon of immunology and has highlighted the critical importance of our immune system in fighting infection. However, in some individuals genetic and environmental factors conspire to cause the immune system itself to attack their own bodies, resulting in inflammatory diseases such as multiple sclerosis, rheumatoid arthritis, and psoriasis.

In these so-called autoimmune diseases, adaptive immune cells mistakenly recognise antigens (self-antigens) within our own organs, triggering inflammation and tissue damage. Unlike in the case of an infection where our immune system can clear the pathogens and then revert to a resting state, these ever-present self-antigens can perpetuate inflammation and chronic disease. Furthermore, because the same mechanisms that cause autoimmune disease are also required to fight infection, it requires a delicate balancing act to treat the condition without increasing the susceptibility to infection.

Early therapies for autoimmune disease relied on crude, non-specific immune suppression. However, with more detailed knowledge of the role of

the precise immune cells and molecules in these diseases, there are now opportunities for a much more targeted approach, with better results and less adverse effects.

A subset of immune cells known as Th17 cells are highly inflammatory and may be pathological, though these cells are counter-balanced and kept in check by a suppressive cell type called regulatory T (Treg) cells. If we think of inflammation acting as an accelerator, these Treg cells play the role of the brake. In autoimmune diseases the balance between Th17 and Treg cells is frequently off-kilter, allowing Th17 cells to cause uncontrolled inflammation. Understanding how and why the Th17-Treg cell axis becomes dysregulated in autoimmunity, and how it might be manipulated for therapeutic benefit, is the focus of my research. Over the past 10 years my lab in the Trinity Biomedical Sciences Institute has uncovered different ways in which the regulation of Th17 cells goes awry in multiple sclerosis, rheumatoid arthritis, and in skin inflammation.

HS – a debilitating skin condition – More recently, my research has focused on the poorly understood inflammatory skin disease hidradenitis suppurativa (HS). HS is

a severe, debilitating condition which can last for decades. Although it may affect up to 1 in 100 people, it is under-diagnosed and current treatments are inadequate. My research into HS, carried out with Dr Barry Moran in collaboration with dermatologists Professors Brian Kirby (St. Vincent's University Hospital) and Anne Marie Tobin (Tallaght University Hospital), has uncovered Th17 cells as key players in the inflamed skin of these patients. Importantly, this provides a rationale for targeting these cells to treat HS and clinical trials for drugs that block Th17 cells, or their effects, are now underway.

Our research is now examining whether blocking other molecules upstream of the Th17 cells, that influence their development or activation, might be another useful therapeutic option. Further, through detailed analysis of the genes irregularly expressed in inflamed HS skin, we are now learning more about the disease, and hope to identify novel therapeutic targets. Ultimately, the goal in my lab is to contribute substantially to the understanding of HS and other inflammatory diseases, leading to better treatment options.

Jean Fletcher received her BSc from the University of Cape Town and a PhD from University College London. In 2012 she took up an Ussher lectureship in Translational Immunology in the School of Biochemistry and Immunology and the School of Medicine at TCD. She is currently Associate Professor and was elected Fellow of Trinity College Dublin in 2021. Her translational research focuses on understanding the immune dysregulation underlying autoimmune and inflammatory disease with the aim of improving therapies. **Contact:** fletchj@tcd.ie

BELOW – The normal balance between inflammatory Th17 cells and regulatory Treg cells is perturbed in autoimmune diseases including psoriasis, psoriatic arthritis, rheumatoid arthritis, multiple sclerosis and the inflammatory skin disease HS, such that Th17 cells drive uncontrolled inflammation. Therapeutic targeting of the Th17-Treg cell has been very successful in psoriasis and psoriatic arthritis and clinical trials are ongoing for HS.

→ Early therapies for autoimmune disease relied on crude, non-specific immune suppression. However, with more detailed knowledge of the role of the precise immune cells and molecules in these diseases, there are now opportunities for a much more targeted approach, with better results and less adverse effects.

