How the immune system scales its response in proportion to any threat

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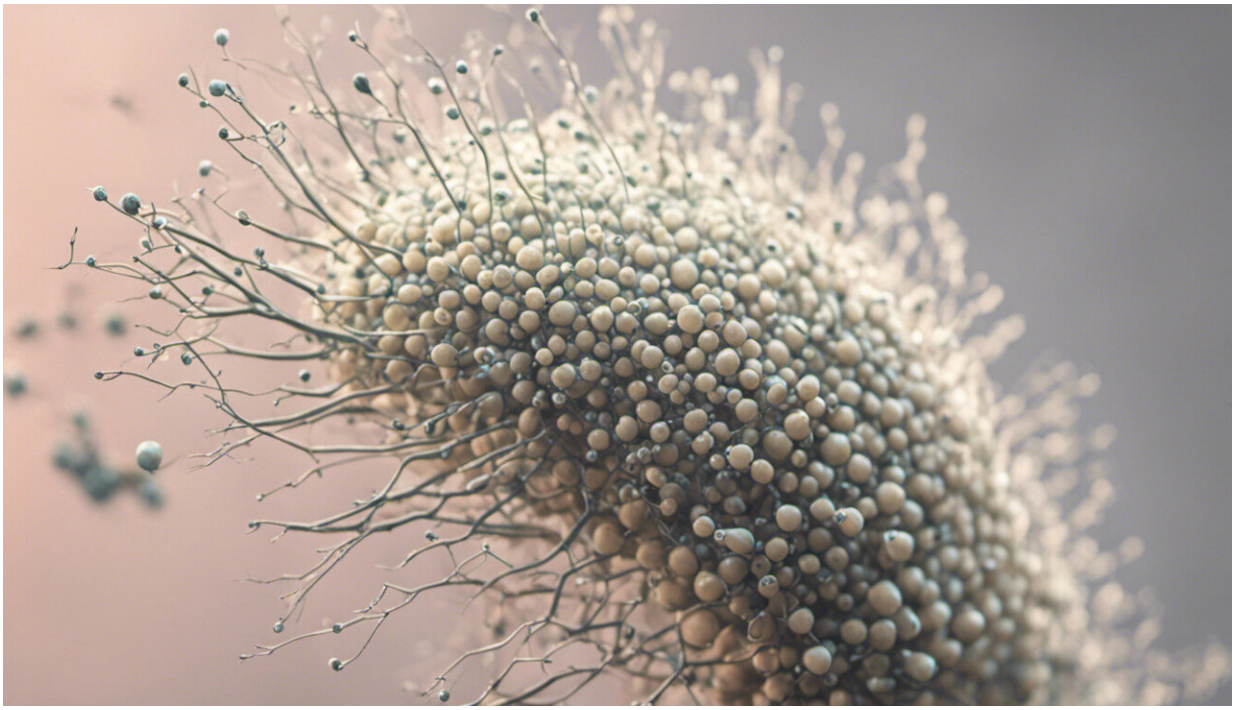

Credit: AI-generated image (disclaimer)

Two Oxford University scientists have proposed a solution to a puzzle of the human immune system: how our immune system scales its response in proportion to any threat to our health to make it 'just right'. Their ideas, published in the journal Trends in Immunology, could support a range of medical research.

Studies by research groups around the world have shown how the T-cells, which are a vital part of our immune system, only perceive the world in a black and white fashion at any moment in time. This means that a minor threat could trigger a response large enough to injure healthy tissue if the T cells acted impulsively on these momentary signals. However, studies also show that the body can match the level of T-cell response to the seriousness of an infection in most situations.

Michael Dustin, Professor of Immunology at Oxford University's Kennedy Institute explained: 'While an overwhelming T-cell response might on the face of it sound effective, it brings risks of immunopathology, where an over-active immune system destroys healthy human tissue, not just the invading disease-causing pathogen.

'Scaling the immune response is therefore a safer option, and we know that is what happens. Until now, however, no one had suggested how the body does that.'

Dr Viveka Mayya, a scientist working with Prof. Dustin, considered the duration of the interactions between T-cells and the dendritic cells that activate T-cell responses as a possible solution to this mystery. Studies from several labs, including Prof. Dustin's, found that as the severity of an infection increased so did the length of these interactions. T-cells are usually 'motile' – they move around the body – but when an infection is happening, they slow down and accumulate around the dendritic cells that help the T cells read the severity of the infection. Longer interactions therefore lead to greater accumulation of T cells over time – a bigger immune response.

This is because the dendritic cells affect proteins called transcription factors in T cells in a time dependent manner. Some of these transcription factors act to reduce the levels of components needed for T-cell movement, causing movement to be slowed and prolonging the

interaction with dendritic cells.

At the same time, other transcription factors are either increased or decreased in a way that prevents the process from 'saturating'. This allows transcription factors that control the growth and metabolism of T cells to accumulate in proportion to the initial microbial threat, allowing a build-up of T cells to the right level.

Dr Viveka Mayya said: 'Many biological processes hit an upper limit, known as saturation. But with T-cell response this effect is suppressed, allowing the response to be just right even if the threat varies over a range of 10,000-fold. Overcoming saturation allows the immune system to keep scaling up its response to meet the demands of severe infection.'

By understanding more about how the immune system works, the pair hope to advance other areas of research.

Prof. Dustin said: 'This knowledge could be applied in vaccine development, where you are looking to cause a strong immune reaction but with minimum risk. It also offers more information for the study of auto-immune diseases: by understanding how the immune system usually gets the response 'just right', we are better placed to see how responses go wrong in autoimmunity and chronic infection and therefore how we can prevent or correct such errors.'

More information: Viveka Mayya et al. What Scales the T Cell Response?, *Trends in Immunology* (2016). DOI: 10.1016/j.it.2016.06.005

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