How Do FOXP3+ Regulatory T Cells Help Fight Infectious Diseases?

T cells are an integral part of the immune system. A subtype of T cell that expresses the CD4, CD25, and forkhead box P3 (FOXP3) proteins on its cell surface is the $CD4^+CD25^+FOXP3^+$ regulatory T cell (Tregs). Tregs help regulate the immune system's responses to pathogens (infectious microorganisms). In this review, we've explored the development and functions of Tregs, highlighting their pivotal role in regulating the immune system's response to infectious microorganisms. Additionally, we've presented the latest research on their involvement in some of the most common infectious diseases.

Tregs can develop as natural Tregs (nTregs) in the thymus (tTregs) or peripheral lymphoid organs (pTregs), or be induced using a cell-signaling molecule (cytokines) called transforming growth factor-β (TGF-β). TGF-β stimulates the expression of FOXP3 in $CD4^+$ T cells to induce their transformation into $FOXP3^+$ Tregs (iTregs).

Tregs play a critical role in protecting the body from overactive immune responses. They release suppressive cytokines that suppress some of the other cells in the immune system called effector T cells, natural killer cells, and antigen-presenting cells. This reduces the overall immune response and thus decreases inflammation, thereby mitigating tissue damage. Disrupting FOXP3 from being expressed in Tregs causes inflammation, autoimmune responses (where the immune system attacks the host), and abnormal metabolism. FOXP3 also regulates the transcription of a number of genes, such as inducing genes for CD25 and suppressive genes for immunosuppressive cytokines.

But while Tregs help reduce the damage caused by immune-response-induced inflammation, they can also suppress the immune response too early or too much, thereby preventing the timely elimination of pathogens and causing chronic, long-term infections. For example, in malarial infections, Tregs decrease at the acute infection stage but increase for chronic infections. In hepatitis B infections, they promote the immune escape of the virus and block the actions of a subtype of T cells called follicular helper T cells (Tfh). Similarly, in cases of hepatitis C, they hinder the clearance of the virus. However, they also limit the scarring of the liver. In COVID-19 infections, people with severe cases were found to have higher levels of Tregs. Tregs also increase during pregnancy, which could create an immunosuppressive environment that increases susceptibility to infections, such as listeria and salmonella. These are just a few of the findings summarized in our review.

Overall, our review highlights the role of FOXP3$^+$ Tregs in the trade-off between infection-fighting pro-inflammatory responses and tissue-protecting anti-inflammatory responses. These findings could help provide new directions for immunotherapies that can treat infectious diseases.

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