# Too Much of a Good Thing: How Anti-Inflammatory FOXP3$^+$ Regulatory T Cells can Prolong Infections

A recent review summarizes the functions of an immune system component called FOXP3$^+$ T cells and the role it plays in common infectious diseases

The immune system is the body's primary defence against infection, tasked with distinguishing between the body's own components (self) and external agents (non-self), such as allergens and infectious microorganisms. Of the various cell types involved in the system, T cells play a crucial role. A specific subtype, CD4+CD25+FOXP3+ regulatory T cells (Tregs), expresses the proteins CD4, CD25, and forkhead box P3 (FOXP3) on their cell surface. These Tregs play a critical role in regulating how the immune system responds to infectious microorganisms.

In a recent review published in *Infectious Microbes & Diseases*, a team of researchers from China summarized the latest research on FOXP3$^+$ Tregs, with a focus on their development, function, and role in some common infectious diseases. "*Tregs play a critical role in mitigating the tissue damage that results from inflammation*," explains Dr. Wenzhi Guo of the First Affiliated Hospital of Zhengzhou, one of the corresponding authors of the study. "*We condensed the available research on the functional regulatory mechanism of Tregs in different tissues and immune microenvironments*."

The major role of Tregs is to protect the body from an overblown immune response. While an immune response causes inflammation in the tissues, too much of this response can cause large amounts of inflammation, leading to tissue damage. For example, too much damage in liver tissue during hepatitis infections can cause permanent scarring (fibrosis), which diminishes liver function. While Tregs develop naturally in the body, they can also be induced using a cell-signaling molecule (cytokine) called transforming growth factor-β (TGF-β).

The review highlights how during an immune response, Tregs release suppressive cytokines that suppress some of the other cell types in the immune system, such as natural killer cells, effector T cells, and antigen-presenting cells. This

immunosuppression reduces the anti-inflammatory response and decreases the damage to tissues. The authors also mention how disrupting FOXP3 expression in Tregs causes inflammation, autoimmune responses (in which the immune system attacks itself/the host body), and metabolic dysfunction. FOXP3 is also responsible for governing the transcription of several genes. These include inducing genes that induce the expression of certain proteins like CD25 and suppressive genes that regulate the release of immunosuppressive cytokines.

A key finding from the review is how Tregs—through their immunosuppressive action—could also prevent the timely elimination of infectious microorganisms from the body. This could contribute to long-term or chronic infections. The authors go on to provide a synopsis of the latest research on Tregs and infectious diseases. Some of these findings include how Tregs decrease during acute malarial infections, but increase during chronic malaria. In cases of hepatitis B, Tregs help the virus escape the immune system. They also block the actions of another type of T cell called T follicular helper cells (Tfh). Tregs similarly hinder the clearance of the hepatitis C virus during Hep-C infections. But at the same time, they limit the scarring of the liver tissue and help to prevent fibrosis. In COVID-19 infections, people with severe cases were found to have higher levels of Tregs.

Higher levels of Tregs are also found in pregnant persons, which could lead to increased susceptibility to infections, because Tregs promote an immunosuppressive environment. For example, the review mentions how in transgenic pregnant mice, Treg expansion led to greater vulnerability to *Listeria* and *Salmonella* infections. The review mentions the role of Tregs in many other infectious diseases, such as tuberculosis, hand-foot-and-mouth disease, HIV-AIDS, and more.

Overall, the review indicates that while FOXP3$^+$ Tregs play an essential role in decreasing inflammation and protecting against tissue damage, there exists a tipping point at which they become unhelpful and prevent the immune system from clearing the infection. The findings of this review could help develop new ideas or strategies for immunotherapies that can target infectious diseases. "*For example, at the early stage of an infectious, enhancing or repairing damaged Tregs can help control the infection or decrease tissue damage*," says the other corresponding author of the study, Dr. Bin Li from the Shanghai Jiao Tong University School of Medicine. *"On the other hand, at later stages of the*

*infection, or in chronic infections, it might be more suitable to suppress the activity of Tregs through targeted therapy. This will enhance the immune response against pathogens."*

This timely, comprehensive review article is sure to serve as a handy primer and kindle new directions of research in the immunotherapeutic treatment of infectious diseases.

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