Master autoimmune regulator gets by with a little help from its friends

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Yongqiang Feng, Ph.D., St. Jude Department of Immunology, investigated the role Foxp3 plays in regulatory T cell function, demonstrating that the protein likely acts as a transcription cofactor, offering new insight into the self vs. non-self discriminatory practices of the immune system. Credit: St. Jude Children's Research Hospital

The protein Foxp3 is vital to the function of immune cells called regulatory T cells, which control immune system activation. Despite its importance, how Foxp3 regulates the immune system using environmental cues has remained unclear.

St. Jude Children's Research Hospital scientists have now discovered that Foxp3 does not work alone; rather, it hijacks DNA-binding proteins that are activated based on the immunological context sensed by regulatory T cells. Through this cooperative interaction, Foxp3 prevents unwanted immune responses, and determines to what extent it needs to suppress the response. The findings, which have implications for future T-cell engineering, were published today in the *Journal of Experimental Medicine.*

The ability of the human body to differentiate its own cells from external attacks is a fundamental process in immune regulation.

"Since the 1950s, the topic of how we distinguish self from non-self has been the key topic in our field," said corresponding author Yongqiang Feng, Ph.D., Department of Immunology. This concept of discriminating between self vs. non-self is controlled by regulatory T cells. The protein Foxp3 is at the center of this discriminatory practice, functioning like a gate keeper in deciding what to hide from immune attack. Loss of this protein leads to a breakdown in this coordination, and lethal systemic inflammation.

Transcription factor or cofactor?

A protein that coordinates expression of genes is called a transcription factor. The tunable nature and broad swath of responses that Foxp3 controls led Feng to question the biochemical nature of how this transcription factor itself was regulated. How did Foxp3 know whether or not to coordinate a suppressive immune response?

The researchers studied the relationship between Foxp3's protein-binding partners and its function, making a surprising discovery.

"We found that when the [environmental] conditions changed, the ability of Foxp3 to interact with DNA also changed," Feng said. "We found the Foxp3 does not directly interact very much with the DNA, but rather binds to other DNA-binding proteins. In this sense, it is a transcriptional cofactor."

It had been speculated for decades that Foxp3 was a transcription factor, with immune suppression coordinated through its expression. However, these findings imply that the environmental trigger which activates regulatory T cells drives the expression of Foxp3's binding partners, which then coordinate with Foxp3 to establish the appropriate immune response. It "swaps out" these binding partners depending on the environmental cue.

'Better protein, better cells, better treatments'

Regulatory T cells are vital to overcoming disease. These cells can be isolated from patients, expanded and engineered to express receptors that allow them to specifically target diseased tissues.

"With regulatory T cells we hope to treat autoimmune diseases such as type 1 diabetes. But we never fully considered how this protein works," said Feng. "As immunologists, we don't just want to understand the protein, we want to know how we can take advantage of this knowledge to engineer better therapies."

Feng aspires to do just that, ultimately utilizing these findings in the design of regulatory T cells with better suppressive function. "With this knowledge, by modifying the different domains within FOXP3, we hope to design a better protein, leading to better regulatory T cells, meaning

better treatments."

More information: Minghong He et al, Dynamic Foxp3–chromatin interaction controls tunable Treg cell function, *Journal of Experimental Medicine* (2024). DOI: 10.1084/jem.20232068

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