

Maintaining Self-Control – The Careful Balance of the Immune System

Researchers from the University of Tsukuba uncover a regulatory mechanism that may help in the fight against autoimmune diseases

Tsukuba, Japan – Autoimmune diseases occur when an individual's immune system fights their own body as if it was a foreign invader. However, in healthy people, these responses are prevented by a process known as immune tolerance. Many complex biological mechanisms maintain the necessary balance between immune activation and suppression to ensure immune tolerance does not prevent the body from effectively fighting pathogens.

In a new study published in *PNAS*, a group of researchers from the University of Tsukuba uncovered how the relationship between two receptors called DNAM-1 and TIGIT helps preserve the balance for optimal immune function. Both of these molecules have previously been studied in a subset of immune cells called regulatory T cells, or Tregs.

Tregs are crucial mediators of immune tolerance and autoimmunity prevention. Treg activity is typically inhibited during inflammatory reactions to infection to allow the body to efficiently fight and clear the invader. However, the molecular mechanisms that control this balance in Treg behavior are not fully understood. When a specific activating molecule (CD155) binds to the receptors DNAM-1 and TIGIT, they trigger signals that tell the T cells how to behave and what functions to perform.

The Tsukuba team found that DNAM-1 and TIGIT compete for CD155 under inflammatory conditions. When CD155 binds to DNAM-1, this receptor sends messages that tell the immune system to wake up and activate. However, when CD155 binds to TIGIT, this receptor acts the opposite way and suppresses the immune system, thereby telling the T cells to stop activating.

To investigate the molecular interplay between DNAM-1 and TIGIT, the researchers studied mice (an acute graft-versus-host disease mouse model) infused with either Tregs lacking DNAM-1 or normal Tregs. "We found that the absence of DNAM-1 resulted in enhanced TIGIT-mediated signaling. This shift in balance occurs because more CD155 is available to bind to TIGIT when DNAM-1 is not present. This helps the Tregs maintain immune suppression during periods of inflammation," explains Professor Kazuko Shibuya, senior author of the study. "We observed similar dynamics in a humanized mouse model, supporting the relevance of these findings to humans." In short, this mechanism helps tell the Tregs to not block the immune system when a true danger is lurking.

Given that Tregs play an important role in autoimmune diseases, the results suggest that the balance between DNAM-1 and TIGIT may be improperly regulated in individuals suffering from autoimmunity. This potential disease mechanism will be the focus of future research. These findings in mice suggest DNAM-1 could be used as a novel molecular target for treating autoimmune diseases.

The article, "DNAM-1 regulates Foxp3 expression in regulatory T cells by interfering with TIGIT under inflammatory conditions," was published in *PNAS* at DOI: 10.1073/pnas.2021309118

Summary: Researchers from the University of Tsukuba determined in mice that a balance between two receptor molecules, called DNAM-1 and TIGIT, helps tell the immune system whether to fight or hold back. In the absence of DNAM-1, TIGIT can produce more signals that suppress activation of certain immune cells, such as regulatory T cells. The balance between these two receptors may be a novel mechanism that can be therapeutically targeted to fight autoimmune diseases.

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