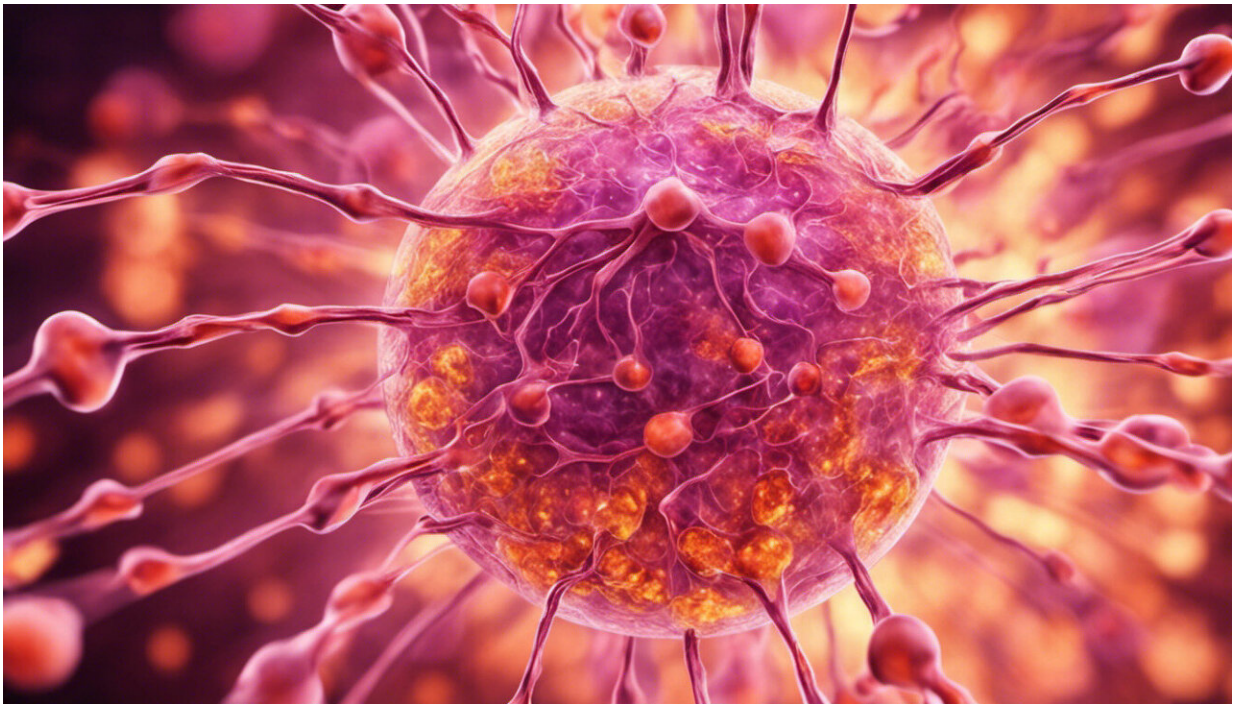


# Controlling inflammation in fat cells to fight obesity-induced diabetes

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Credit: AI-generated image ([disclaimer](#))

The excess fat tissue associated with obesity causes inflammation and reduces glucose tolerance, which increases the risk of diabetes. The mechanism responsible for these physiological effects, however, has been unclear. An international team including researchers from the RIKEN Center for Integrative Medical Sciences (IMS) has now

identified a signaling pathway that is crucial for controlling obesity-associated inflammation, offering hope for a therapeutic target to prevent glucose intolerance.

The researchers focused on [immune cells](#) called regulatory T ( $T_{\text{reg}}$ ) [cells](#). These cells respond to inflammation and proliferate within inflamed tissue. "Whereas most T cells are activated by a specific antigen and induce inflammation,  $T_{\text{reg}}$  cells suppress inflammatory responses," explains Shigeo Koyasu from the Laboratory for Immune Cell Systems at the IMS.

Previous work by the Walter and Eliza Hall Institute (WEHI) of Medical Research in Australia showed that  $T_{\text{reg}}$  cells can be in either an activated state in which they suppress inflammation, or a resting state. In collaboration with the WEHI, Koyasu and his RIKEN colleagues searched for genetic differences between resting and activated  $T_{\text{reg}}$  cells. By analyzing gene expression in the two states, they discovered approximately 2,700 differences.

Interestingly, the researchers discovered that  $T_{\text{reg}}$  cells in fat tissue, known as visceral adipose tissue (VAT), expressed an exceptionally high level of a receptor called ST2 for the signaling molecule interleukin-33 (IL-33). By genetically manipulating the expression of ST2 in mice, the researchers showed that IL-33 signaling is crucial for the development of VAT- $T_{\text{reg}}$  cells. When applied to cultured cells and injected into mice, IL-33 was found to induce the proliferation of VAT- $T_{\text{reg}}$  cells, increasing their population by over ten fold.

" $T_{\text{reg}}$  cells suppress inflammation, which improves [glucose tolerance](#), so an increase in  $T_{\text{reg}}$  cells is beneficial," says Koyasu. "A lack of IL-33 greatly reduced VAT- $T_{\text{reg}}$  numbers, resulting in impaired glucose tolerance. Administration of IL-33 restored glucose tolerance."

Finally, the team administered IL-33 to mice that were either genetically obese or obese owing to a high fat diet. In both cases, IL-33 increased the number of VAT-T<sub>reg</sub> cells and improved glucose tolerance. The findings have therapeutic potential.

"Human T<sub>reg</sub> cells in [fat tissue](#) also express IL-33 receptors, so it is possible that IL-33 could increase T<sub>reg</sub> cells in humans," explains Koyasu. As a possible therapy, however, IL-33 comes with strings attached. "IL-33 also induces allergic [inflammation](#), so it is critical to control the dose to avoid an allergic response while maintaining the ability to control VAT-T<sub>reg</sub> cells."

**More information:** "The transcriptional regulators IRF4, BATF and IL-33 orchestrate development and maintenance of adipose tissue-resident regulatory T cells." *Nature Immunology* 16, 276–285 (2015). doi: [dx.doi.org/10.1038/ni.3085](https://doi.org/10.1038/ni.3085)

Provided by RIKEN

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