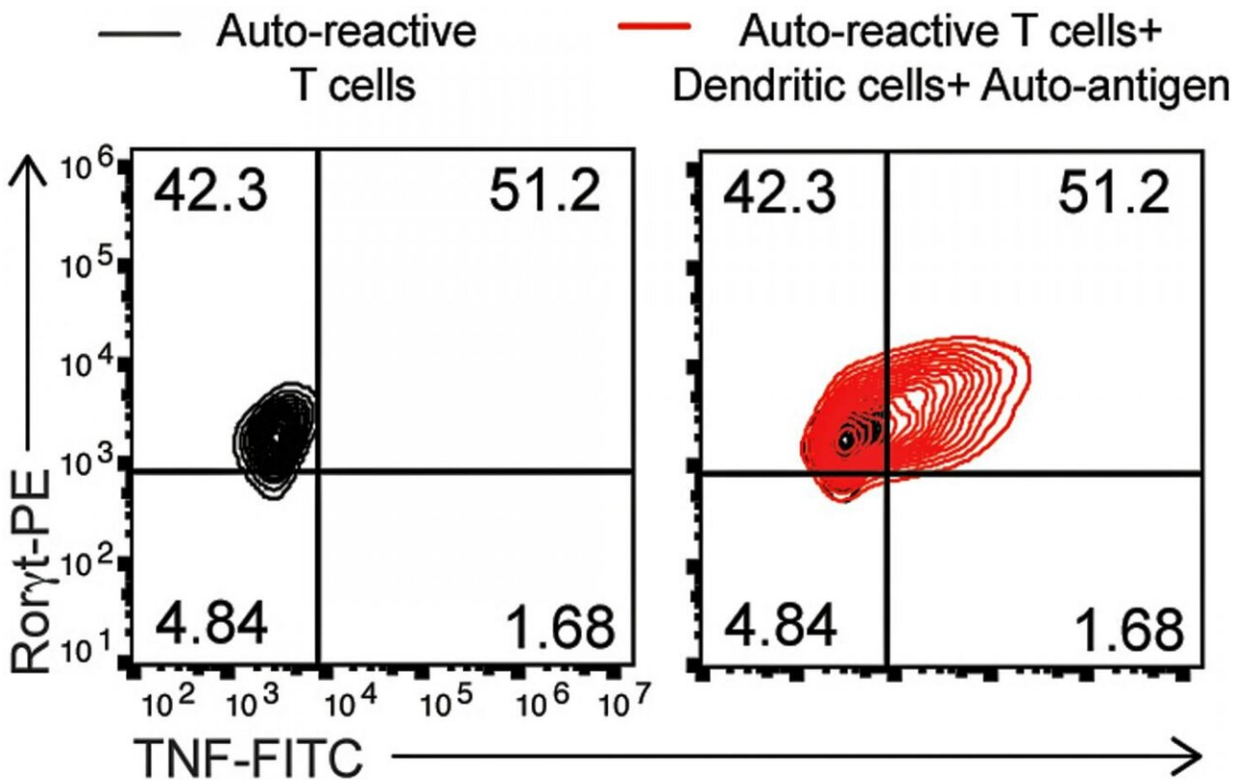


Research adds new twist to fight against autoimmune diseases

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These cell flow cytometry graphs were used by immuno-biologists to illustrate the physical and chemical characteristics of T cells that help drive autoimmunity in mice. Part of a study published by Nature Immunity, the left graph shows resting effector T cell (featured in black) before autoimmune processes are triggered. The right graph shows changes (in red) once the T cells start to produce a pro-inflammatory protein called TNF (tumor necrosis factor). This begins downstream autoimmune processes linked to several diseases in people. Credit: Cincinnati Children's

Scientists describe in *Nature Immunology* an entirely new molecular process in mice that triggers T cell-driven inflammation and causes different auto-immune diseases.

In a study published online Dec. 17, researchers at Cincinnati Children's Hospital Medical Center say their data have implications for Multiple Sclerosis, Type 1 diabetes and Inflammatory Bowel Disease. It also will help efforts to find better treatments for autoimmune disease, still an urgent need in medicine.

"This study opens new avenues for developing more effective autoimmune therapies. To this end, we now are testing the molecular process we identified in different kinds of human cells, including building collaborations with other researchers to collect donated cell samples from people who have multiple sclerosis, arthritis and other autoimmune diseases," said lead investigator Chandrashekar Pasare, DVM, Ph.D., a member of the Division of Immunobiology at Cincinnati Children's and co-director of the Center for Inflammation and Tolerance.

A Mystery Resolved

For the past decade or so, scientists and physicians have linked the immune system protein IL-1b (cytokine interleukin-1 beta) with several autoimmune diseases. Drugs and antibodies that block or inhibit IL-1b are currently used to manage symptoms in people with different types of autoimmune disease, according to researchers.

But until the current study, it wasn't known how IL-1b is made in the body, especially during autoimmunity. This limits the ability to develop effective therapeutics for [autoimmune diseases](#), according to researchers.

Previously it was thought that IL-1b production required activation of a group of immune system protein molecules that make up structures called inflammasomes. It turns out the inflammasomes, which act as system sensors that activate inflammation, can cause what are called auto-inflammatory diseases. These are distinct from auto-immune diseases.

Pasare and his colleagues found out that instead of inflammasomes, a different molecular pathway cranks up inflammation during autoimmunity while working completely independently from inflammasomes. That molecular process was triggered by interactions between myeloid cells and CD4-positive T cells, which become primed to attack harmful bacteria, viruses and other microorganisms. Unfortunately, in the case of autoimmunity, the immune system attacks and eventually destroys healthy tissues erroneously targeted as harmful.

When it's not fulfilling its role in driving autoimmunity, IL-1b usually works as a stimulator of anti-microbial immunity. But during autoimmune processes, the authors report they discovered in their mouse models that autoreactive T cells, macrophage and dendritic cells in the immune system work through two other molecules—TNF ([tumor necrosis factor](#)) and FasL (fas ligand)—to produce overabundant amounts of IL-1b.

"This means our findings have two previously unknown implications," Pasare explained. "We show for the first time that IL-1b can be made in the absence of infection and that T cells are major drivers of IL-1b in an autoimmune setting."

The study also underscores that therapies targeting IL-1b production by inflammasomes are going to be limited in their effectiveness in treating autoimmune disease. This is because the Pasare team's findings show that auto-reactive T [cells](#) have their own mechanisms to drive inflammation and work independently of inflammasomes.

Pasare said that targeting the TNF and FasL pathway of IL-1 β production is more likely to be an effective way of treating auto-immune diseases in humans.

Work Remains Preclinical

The researchers stressed that because the preclinical findings were obtained by studying laboratory models, it is still too early to determine whether the results will translate to treating patients in clinic. A great deal of additional preclinical research is needed first. Anti-TNF therapies are already used in the clinic for some auto-immune diseases, and additional blockade of FasL, as suggested in the current study, may be a more effective way of treating auto-immune diseases. Pasare and his collaborators will continue to test this in their preclinical models.

More information: Jain, A et al. T cells instruct myeloid cells to produce inflammasome-independent IL-1 β and cause autoimmunity. *Nat Immunol* 21, 69 (2020) [DOI: 10.1038/s41590-019-0559-y](https://doi.org/10.1038/s41590-019-0559-y)

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