Researchers identify enzyme key to training cells to fight autoimmune disorders

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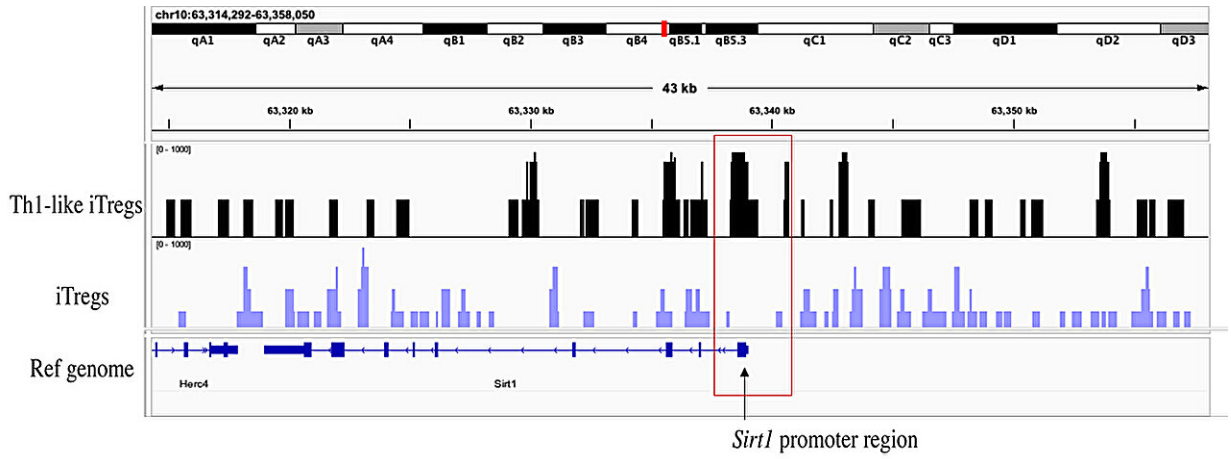

iTregs training in the Th1-like chemical environment appears to block the expression of Sirt1 compared to regular iTregs. Credit: *Frontiers in Immunology* (2024). DOI: 10.3389/fimmu.2023.1292049

Researchers at the University of Massachusetts Amherst recently released a first-of-its-kind study focusing on the rare autoimmune disorder aplastic anemia to understand how a subset of cells might be trained to correct the overzealous immune response that can lead to fatal autoimmune disorders. The research, published in *Frontiers in Immunology*, identifies a specific enzyme known as PRMT5, as a key regulator of suppressive activity in a specialized population of cells.

The human immune system is a marvel of evolution. When a pathogen enters the body, immune cells can identify it, call for backup, attack the pathogen, and then, when the threat has been eradicated, return to a peaceful state. But sometimes, as in the rare autoimmune disorder aplastic anemia, something goes wrong.

In patients with aplastic anemia, the aberrant immune cells, in this case Th1 cells, misidentify healthy stem cells in bone marrow as pathogenic and attack them. Without these bone marrow stem cells, the body can't make white blood cells to fight infections, red blood cells to carry oxygen throughout the body, or platelets that help stop bleeding.

"What we want to do is to make a super-suppressive cell," says Nidhi Jadon, a graduate student in the Department of Veterinary and Animal Sciences at UMass Amherst and the paper's lead author. "If someone is suffering from an autoimmune disorder, we can use these super-suppressive cells to dampen the aberrant immune response instead of drugs."

While drug therapies that manage autoimmune responses can be lifesaving, they also come with a long list of potentially debilitating side effects.

It would be much more effective if the body's own defense system could be retrained—and to see how retraining might happen, Jadon and the paper's senior author, Lisa M. Minter, professor of veterinary and animal sciences at UMass Amherst, relied on a pathbreaking mouse model that Minter developed in 2013 and which closely mimics the human immune responses characteristic of aplastic anemia.

This mouse model has been engineered with Th1 cells that cause aplastic anemia. Jadon, Minter and their colleagues then worked on training the cells responsible for suppressing the immune response—called

iTregs—in the specific chemical environment that the aberrant Th1 cells create around themselves. This chemical environment is one means that Th1 cells use to call for backup, drawing even more Th1 cells into the bone marrow, where they attack and destroy the stem cells.

What Jadon and Minter observed is that the iTregs they created were very effective at reducing the Th1-mediated immune response in their animal model of aplastic anemia. When they looked closer, they discovered that iTregs trained in the Th1-like chemical environment increased production of a specific enzyme called PRMT5, which, in turn, blocked the expression of another specific gene—Sirt1—that destabilizes iTregs and made them less effective.

"No one before us has shown that PRMT5 plays such an important role in mediating the immune suppressive capacity that iTregs display when they are generated under conditions found in a Th1-mediated immune response," says Minter, who is quick to note that it takes a long time to turn a foundational discovery like this one into a therapeutic treatment available in the clinic.

And there's more work to be done: The team wants to focus on additional genes that may be regulated by PRMT5 and how they may also contribute to making iTregs better at suppressing immune responses.

Nevertheless, the mouse models treated with re-trained iTregs showed a significantly extended survival rate. "We're one step closer to finding that super-suppressive cell that can replace drug therapies," says Jadon.

More information: Nidhi Jadon et al, PRMT5 regulates epigenetic changes in suppressive Th1-like iTregs in response to IL-12 treatment, *Frontiers in Immunology* (2024). DOI: 10.3389/fimmu.2023.1292049

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