Medical Xpress

Study reveals molecular mechanism behind multiple sclerosis and other autoimmune diseases

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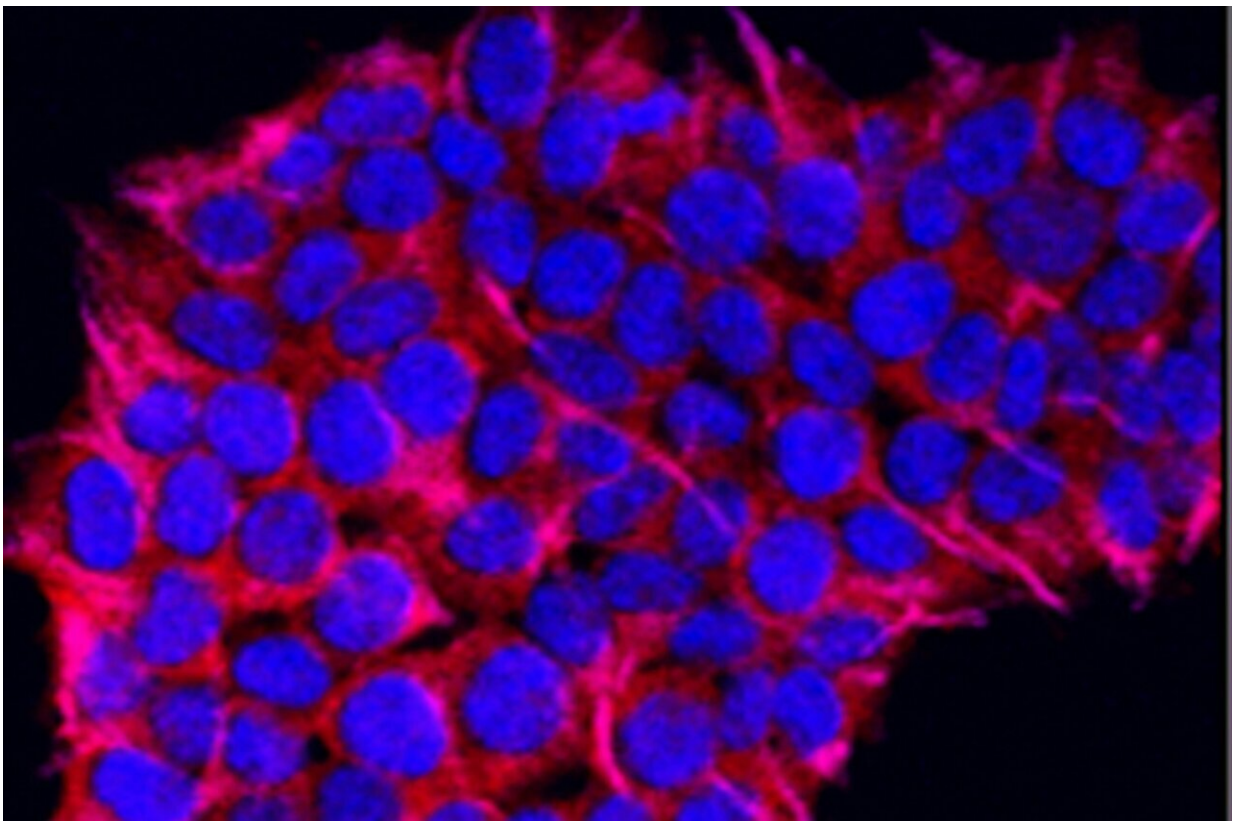

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More than two decades ago, a research team in the lab of David Hafler, a Yale researcher who at the time was at Harvard, discovered a type of T

cell in humans that suppresses the immune system; they later found that these so-called regulatory T cells, when defective, are an underlying cause of autoimmune disease, specifically multiple sclerosis (MS). For many years, however, the mechanism behind this dysfunction has remained unclear.

In a new Yale-led study, a team of researchers finds that this loss of immune regulation is triggered by an increase in PRDM1-S, a protein involved in immune function, triggering a dynamic interaction of multiple genetic and environmental factors, including high salt uptake.

The findings, published in the journal *Science Translational Medicine*, also reveal a new target for a universal treatment for human autoimmune disease.

The research was led by Tomokazu Sumida, an assistant professor at Yale School of Medicine (YSM), and Hafler, the William S. and Lois Stiles Edgerly Professor of Neurology and professor of immunobiology at Yale.

"These experiments reveal a key underlying mechanism for the loss of immune regulation in MS and likely other autoimmune diseases," said Hafler, who is also chair of Yale's Department of Neurology. "They also add mechanistic insight into how Treg [regulatory T cells] dysfunction occurs in human autoimmune diseases."

Autoimmune diseases, among the most common disorders of young adults, are known to be affected by genetic and environmental factors, including vitamin D deficiency and fatty acids. In an earlier study, Sumida and Hafler found that high levels of salt also contribute to the development of multiple sclerosis, an autoimmune disease of the central nervous system. Specifically, they observed that high salt induces inflammation in a type of immune cell known as CD4 T cells, while also

causing a loss of regulatory T cell function. This, they found, is mediated by a salt-sensitive kinase, or enzyme critical for cell signaling, known as SGK-1.

For the new study, researchers used RNA sequencing to compare gene expression in patients with MS with expression in healthy individuals. In patients with MS, the researchers identified upregulation, or increased expression, of a gene called PRDM1-S (primate-specific transcription factor), also known as BLIMP-1, which is involved in regulating immune function.

Surprisingly, PRDM1-S induced increased expression of the salt-sensitive SGK-1 enzyme, leading to disruption of regulatory T cells, the researchers found. Moreover, they found similar overexpression of PRDM1-S in other autoimmune diseases, suggesting that it may be a common feature of regulatory T cell dysfunction.

"Based on these insights, we are now developing drugs that can target and decrease expression of PRDM1-S in regulatory T cells," Sumida said. "And we have initiated collaborations with other Yale researchers using novel computational methods to increase the function of regulatory T cells to develop new approaches that will work across human autoimmune diseases."

The study was done with Bradley Bernstein and Manolis Kellis, longtime collaborators of Hafler from the Broad Institute of MIT and Harvard, and several other research institutions.

Other authors from the Yale lab include neurologist Matthew R. Lincoln, and post-graduate research assistants Alice Yi, Helen Stillwell, and Greta Leissa.

More information: Tomokazu S. Sumida et al, An autoimmune

transcriptional circuit drives FOXP3^{+} regulatory T cell dysfunction, *Science Translational Medicine* (2024). DOI: 10.1126/scitranslmed.adp1720

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