

Understanding Obesity-Induced Inflammation

Mice lacking SAMHD1 enzyme showed more insulin resistance, inflammation and liver fat buildup and fibrosis.

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At a Glance

- NIH-funded researchers detailed a chain of events through which obesity promotes harmful inflammation.
- The findings point to potential new pathways for treating obesity-related illnesses.

More than one-third of American adults live with obesity. Obesity causes inflammation throughout the body, contributing to many of its health consequences. But the mechanism by which this occurs is unclear, making it difficult to develop effective therapies.

Activation of a structure called the NLRP3 inflammasome promotes the sort of inflammation that occurs in obesity. Inflammasomes are typically found in immune cells called macrophages. An NIH-funded study, led by Dr. Zhenyu Zhong of the University of Texas Southwestern Medical Center, investigated how obesity affects the NLRP3 inflammasome. The results were published on January 15, 2026, in [Science](#).

The researchers began by growing macrophages taken from people with obesity and lean people. They found that activating the NLRP3 inflammasome led to a stronger response in macrophages from the people with obesity. Similarly, the inflammasome's response was stronger in macrophages from mice fed a high-fat diet than those fed a normal diet.

The team's search for a culprit for this hyperactivation led them to an enzyme called SAMHD1. Immune cells from people with obesity contained more phosphorylated SAMHD1, which is an inactive form of the enzyme. The same was true in immune cells from mice fed a high-fat diet.

Immune cells lacking SAMHD1 from mice, zebrafish, and humans all showed inflammasome hyperactivation. When mice without SAMHD1 in their macrophages were fed a high-fat diet, they became more insulin-resistant and had greater NLRP3 inflammasome activation than control mice.

They also had more inflammation, fat accumulation, and scarring in their livers.

Further experiments revealed the chain of events by which loss of SAMHD1 affects the NLRP3 inflammasome. SAMHD breaks down deoxyribonucleotide triphosphates (dNTPs), the building blocks of DNA. Without SAMHD1, dNTPs accumulate and promote synthesis of mitochondrial DNA (mtDNA). Newly synthesized mtDNA is especially vulnerable to oxidation, so the amount of oxidized mtDNA increases. Oxidized mtDNA then activates the inflammasome.

The results suggest that obesity promotes inflammation by reducing SAMHD1's ability to break down dNTPs. Treatments that disrupt one or more of the links in this chain of events could help protect people from obesity's inflammation-related health consequences.

"It's been known for a long time that obesity causes uncontrolled inflammation, but no one knew the mechanism behind it," Zhong says. "Our study provides novel insights about why this inflammation occurs and how we might be able to stop it."

This [research summary](#) was published by the National Institutes of Health on February 10, 2026.