Why Does the Immune System Attack Liver Cells in Those With Metabolic Disorders?

Those with type 2 diabetes and obesity are often at risk.

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Researchers from Weill Cornell Medicine have identified a molecule that causes the immune system to attack the liver in response to the accumulation of fat.

Published in Science Immunology, researchers recreated human metabolic diseases in mice to examine changes within the immune system in response to a high-sugar, high-fat diet. They found that the immune response, which involves B and T cells, damages the organs and tissues instead of protecting them.

"For the longest time, people have been wondering how T and B cells learn to attack liver cells, which are under increased metabolic stress due to a high-fat, high-sugar diet," said lead investigator Laura Santambrogio, PhD, a professor of radiation oncology, physiology and biophysics and associate director for precision immunology at the Englander Institute for Precision Medicine at Weill Cornell Medicine, in a news release. "We have identified one protein—probably the first of many—that is produced by stressed liver cells and then recognized by both B and T cells as a target."

Santambrogio added that in those with such metabolic conditions as type 2 diabetes or obesity, the immune system exacerbates damage already taking place within the liver. In people with these conditions, the liver stores too much fat, causing stress to cells, which in turn causes inflammation that can harm tissue over time. This chain of events sometimes gives rise to non-alcoholic steatohepatitis (NASH), also known as fatty liver disease.

This study found that B- and T-cell activity also contributes to this damage. B cells produce proteins called antibodies that fight against infected cells by honing in on a specific part. T cells also attack unhealthy cells by identifying partial sequences of a target protein. These cells sometimes destroy healthy proteins, as occurs in individuals with autoimmune diseases.

Researchers discovered that when cells are under stress, they create more of a protein called PDIA3, which travels to the cells' surfaces, making it easier for B and T cells to attack healthy cells.

Santambrogio emphasized that, unlike autoimmune diseases, this liver condition can be reversed via lifestyle changes such as improving one’s diet and losing weight.

“We have added a new piece to the puzzle by showing how the immune system starts to attack the liver,” she said.

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