Excess dietary salt identified as autoimmune trigger

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For the past few decades, health officials have been reporting increases in the incidence of autoimmune diseases such as multiple sclerosis (MS). Now researchers at Yale School of Medicine, Harvard Medical School and the Broad Institute have identified a prime suspect in the mystery—dietary salt.

In the March 6 issue of the journal *Nature*, Yale researchers showed that salt can induce and worsen pathogenic immune system responses in mice and that the response is regulated by genes already implicated in a variety of autoimmune diseases.

In accompanying papers in the same issue of *Nature*, researchers from Brigham and Women's Hospital and Harvard identified the key molecular pathway involved in the response to salt, and the Broad Institute sketched out the regulatory network of genes that governs this autoimmune response.

"These are not diseases of bad genes alone or diseases caused by the environment, but diseases of a bad interaction between genes and the environment," said David Hafler, the Gilbert H. Glaser Professor of Neurology, professor of immunobiology, chair of the Department of Neurology, and senior author of the Yale paper.

The research was inspired, in part, by an observation that eating at fast-food restaurants tended to trigger an increase in production of inflammatory cells, which are mobilized by the immune system to respond to injury or pathogens but which, in autoimmune diseases, attack healthy tissue. Researchers at Yale and colleagues in Germany led by Dominik Mueller wanted to know whether high salt content in diet might induce the destructive immune system response that is the hallmark of autoimmunity.

They found that adding salt to the diet of mice induced production of a type of T cells previously associated with autoimmune diseases and that mice on salt diets developed a more severe form of an MS animal model, experimental autoimmune encephalomyelitis.

The research at the Broad Institute, Brigham and Women's Hospital, Harvard University, and Yale University expands the understanding of how one type of immune cell—known as a T helper 17 or Th17 cell—develops, and how its growth influences the development of other kinds of cells involved in the immune system. Reconstruction of this molecular circuitry confirmed the surprising role of salt, said the researchers.

"The question we wanted to pursue was: How does this highly pathogenic, pro-inflammatory T cell develop?" said Vijay Kuchroo, a senior scientist at Brigham and Women's Hospital and a Broad Institute associate member. Kuchroo is also the Wasserstrom Professor of Neurology at Harvard Medical School and co-director of the Center for Infection and Immunity at Biomedical Research Institutes. "Once we have a more nuanced understanding of the development of the pathogenic Th17 cells, we may be able to pursue ways to regulate them or their function."

"Humans were genetically selected for conditions in sub-Saharan Africa, where there was no salt," Hafler said. "Today, Western diets all have high salt content and that has led to increase in hypertension and perhaps autoimmune disease as well."

Hafler noted that all test-tube cell biology is performed based on the salt levels found in blood and not in the tissues where immune cell ultimately travel to fight infections. That may have been a reason salt's role in autoimmunity has gone undetected.

"We may have been using the wrong concentrations of salt in our experiments for the past half-century," Hafler said. "Nature did not want immune cells to become turned on in the pipeline, so perhaps blood salt levels are inhibitory."

Patient trials to assess affects of salt on autoimmune diseases are being planned.

"The value in doing an unbiased analysis is that we're able to understand a lot more about the molecular biology at play and put forth a completely novel process," said Aviv Regev, a Broad Institute core member and an associate professor of biology at MIT. Regev is also an Early Career Scientist at Howard Hughes Medical Institute and the director of the

Klarman Cell Observatory at the Broad.

Hafler is not waiting with his own patients.

"I already recommend that my patients use a low-salt, low-fat diet," he said

Markus Kleinewietfeld was lead author of the Yale-led study.

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