

Starvation signals control intestinal inflammation in mice

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Credit: Martha Sexton/public domain

Intestinal inflammation in mice can be dampened by subjecting them briefly to a diet restricted in amino acids, the building blocks of proteins, research scheduled for publication in *Nature* shows.

The findings, made by Bali Pulendran and colleagues at Emory

University, highlight an ancient connection between cellular mechanisms to sense nutrient availability and control of inflammation. They also suggest that a [low protein diet](#) - or drugs that mimic its effects on immune cells - could be tools for the treatment of inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis.

This protective effect was shown to be mediated by a molecule known as GCN2, which is highly conserved from yeasts to man, and which is a critical sensor of amino acid starvation in cells. The finding grew out of the Emory team's earlier discovery that GCN2 is pivotal for induction of immunity to the yellow fever vaccine.

"We reasoned that the intestine would be a site where the immune system is faced with dynamic changes in nutrient bioavailability," says senior author Bali Pulendran, PhD. "So we wondered whether the amino acid sensing pathway involving GCN2 would impact immune homeostasis in the gut."

Pulendran is Charles Howard Candler professor of pathology and laboratory medicine at Emory University School of Medicine, Emory Vaccine Center and Yerkes National Primate Research Center. The co-first authors of the paper are postdoctoral fellows Rajesh Ravindran, PhD, and Jens Loebbermann, PhD. Co-authors on the paper include Randal Kaufman, PhD, at the Sanford Burnham Prebys Medical Discovery Institute, and Jennifer Martinez, PhD, at the National Institute of Environmental Health Sciences.

The team discovered that mice lacking GCN2 are more sensitive to the chemical irritant DSS (dextran sodium sulfate), often used to model colitis in animals. In the absence of irritants, the intestines in mice lacking GCN2 looked normal.

Mice fed a low [protein diet](#) (2 percent, compared to 16 percent in a

standard diet) or a diet lacking only the amino acid leucine were protected from signs of colitis, such as weight loss and bloody diarrhea. Mice lacking GCN2 were not protected from colitis when fed a low protein diet, which demonstrates that GCN2 is necessary for the protective effect.

The results could have implications for treatment of inflammatory bowel diseases, and autoimmune diseases such as rheumatoid arthritis and psoriasis. The researchers showed that responses of Th17 [immune cells](#), which are important in several autoimmune diseases, are controlled by GCN2.

"It is well known that the immune system can detect and respond to pathogens, but these results highlight its capacity to sense and adapt to environmental changes, such as nutritional starvation, which cause cellular stress," Pulendran says.

"It is interesting to ponder the evolutionary pressures that might have resulted in the coupling of this ancient amino acid starvation pathway with control of inflammation. Perhaps this coupling evolved as a sort of negative feedback mechanism to limit inflammation, by sensing depletion of [amino acids](#) that might occur in cells during the repair and regeneration of tissues, in response to cell death during inflammation."

Pulendran cautions that more research is needed before applying the findings to human inflammatory bowel diseases. For instance, a low protein diet is not advisable for long periods, although a low protein diet is sometimes recommended for people with kidney disease to postpone the need for dialysis. The duration or extent of a low protein diet needed to have the desired effect on [intestinal inflammation](#) in humans is not clear.

More information: The amino acid sensor GCN2 controls gut

inflammation by inhibiting inflammasome activation, [DOI: 10.1038/nature17186](https://doi.org/10.1038/nature17186)

Provided by Emory University

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