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Researchers provide evidence linking 'leaky gut' to chronic inflammation

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With the help of genetically engineered mice, scientists at the Massachusetts General Hospital (MGH) are moving closer to establishing the role that increased intestinal permeability, sometimes called a "leaky gut," plays in chronic inflammatory conditions. Regulated by a protein called zonulin, elevated intestinal permeability has been associated with several chronic conditions including autoimmunity, metabolic disorders, neurodegenerative diseases and even cancer.

In an article published in *Annals of the New York Academy of Sciences*, lead author Craig Sturgeon, a graduate student in the Mucosal Immunology and Biology Research Center (MIBRC) at MGH, and colleagues provide a direct link between increased permeability of the small intestine and chronic inflammatory disease. They describe how inducing colitis in transgenic mice with two copies of the zonulin-producing gene variant led to significantly more severe symptoms and increased mortality compared with inducing colitis in animals without the zonulin gene.

"This is the first time that we have been able to mechanistically link zonulin-dependent modulation of small-intestinal permeability and the resulting enhanced antigen trafficking to the development of an inflammatory disease," says Alessio Fasano, MD, director of the MIBRC and senior author of the article. "When we exposed these two groups of mice to inflammatory stress, the zonulin transgenic mice showed a remarkable increase in colon inflammation and in mortality—up to 70 percent—compared to normal mice."

In a related finding that Fasano calls "even more remarkable," adding a zonulin inhibitor—AT1001, also called larazotide acetate—to the drinking water of the transgenic mice completely protected the animals from colonic inflammation and death, reducing permeability of the small intestine to normal levels, despite continued zonulin expression.

Fasano's group discovered zonulin, which controls the opening of "tight junctions" between cells lining the digestive tract, in 2000. Since then it has been the subject of numerous studies implicating intestinal permeability in chronic inflammatory disease. In 2001 while at the University of Maryland School of Medicine, Fasano developed AT1001 as a therapeutic agent for celiac disease. The zonulin-blocking agent is set to undergo Phase III clinical trials later this year, according to Innovate BioPharmaceuticals, which has licensed development of the drug from Alba Therapeutics, a company co-founded by Fasano.

A professor of Pediatrics at Harvard Medical School, Fasano explains that, while some alternative health care practitioners use the term "leaky gut syndrome" to describe a variety of health problems ranging from gastrointestinal complaints to neurological symptoms, he prefers the concept of loss of intestinal barrier function. "Leaky gut syndrome has been blamed by some non-mainstream practitioners as the reason for almost everything that is wrong with a person. With the development of this mouse model to study inflammation, we'll be able to separate science from speculation," he says.

Lead author Sturgeon adds, "Use of these mice will allow us to gain insight into specific mechanisms by which zonulin-dependent increased intestinal permeability can affect disease onset, clinical severity and outcomes, and even possible prevention." Jinggang Lan, PhD, of the MIBRC is also a co-author of the *Annals of the New York Academy of Science* paper. The study was supported by National Institutes of Health grant DK048373.

More information: Craig Sturgeon et al, Zonulin transgenic mice show altered gut permeability and increased morbidity/mortality in the DSS colitis model, *Annals of the New York Academy of Sciences* (2017). DOI: 10.1111/nyas.13343