Scientists pinpoint critical molecule to celiac disease, possibly other autoimmune disorders

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It was nine years ago that University of Maryland School of Medicine researchers discovered that a mysterious human protein called zonulin played a critical role in celiac disease and other autoimmune disorders, such as multiple sclerosis and diabetes. Now, scientists have solved the mystery of zonulin's identity, putting a face to the name, in a sense. Scientists led by Alessio Fasano, M.D., have identified zonulin as a molecule in the human body called haptoglobin 2 precursor.

Pinpointing the precise molecule that makes up the mysterious protein will enable a more detailed and thorough study of zonulin and its relationship to a series of inflammatory disorders. The discovery was reported in a new study by Dr. Fasano, published the week of September 7, 2009 in the online version of the Proceedings of the National Academy of Sciences. Dr. Fasano is a professor of pediatrics, medicine and physiology and director of the Mucosal Biology Research Center and the Center for Celiac Research at the University of Maryland School of Medicine.

Haptoglobin is a molecule that has been known to scientists for many years. It was identified as a marker of inflammation in the body. Haptoglobin 1 is the original form of the haptoglobin molecule, and scientists believe it evolved 800 million years ago. Haptoglobin 2 is a permutation found only in humans. It's believed the mutation occurred in India about 2 million years ago, spreading gradually among increasing numbers of people throughout the world.

Dr. Fasano's study revealed that zonulin is the precursor molecule for haptoglobin 2 — that is, it is an immature molecule that matures into haptoglobin 2. It was previously believed that such precursor molecules served no purpose in the body other than to mature into the molecules they were destined to become. But Dr. Fasano's study identifies precursor haptoglobin 2 as the first precursor molecule that serves another function entirely — opening a gateway in the gut, or intestines, to let gluten in. People with celiac disease suffer from a sensitivity to gluten.

"While apes, monkeys and chimpanzees do not have haptoglobin 2, 80 percent of human beings have it," says Dr. Fasano. "Apes, monkeys and chimpanzees rarely develop autoimmune disorders. Human beings suffer from more than 70 different kinds of such conditions. We believe the presence of this pre-haptoglobin 2 is responsible for this difference between species."

"This molecule could be a critical missing piece of the puzzle to lead to a treatment for celiac disease, other autoimmune disorders and allergies and even cancer, all of which are related to an exaggerated production of zonulin/pre-haptoglobin 2 and to the loss of the protective barrier of cells lining the gut and other areas of the body, like the blood brain barrier," says Dr. Fasano.

"The only current treatment for celiac disease is cutting gluten from the diet, but we have confidence Dr. Fasano's work will someday bring further relief to these patients. Zonulin, with its functions in health and disease as outlined in Dr. Fasano's paper, could be the molecule of the century," says E. Albert Reece, M.D., Ph.D., M.B.A., dean of the School of Medicine, vice president for medical affairs of the University of Maryland and John Z. and Akiko K. Bowers Distinguished Professor. Dr. Fasano, as a physician scientist, fulfills two of the core missions of the University of Maryland School of Medicine: making basic science

discoveries that can impact human health, and finding ways to translate those discoveries into treatments and diagnostic tools."

People who suffer from celiac disease have a sensitivity to gluten, a protein found in wheat, and suffer gastrointestinal distress and other serious symptoms when they eat it. In celiac patients, gluten generates an exaggerated release of zonulin that makes the gut more permeable to large molecules, including gluten. The permeable gut allows these molecules, such as gluten, access to the rest of the body. This triggers an autoimmune response in which a celiac patient's immune system identifies gluten as an intruder and responds with an attack targeting the intestine instead of the intruder. An inappropriately high level of production of zonulin also seems responsible for the passage through the intestine of intruders other than zonulin, including those related to conditions such as diabetes, multiple sclerosis and even allergies. Recently, other groups have reported elevated production of zonulin affecting the permeability of the blood brain barrier of patients suffering from brain cancer.

"We hope pre-haptoglobin 2 will be a door to a better understanding of not just celiac disease, but of several other devastating conditions that continue to affect the quality of life of millions of individuals," says Dr. Fasano. "This is quite a remarkable molecule that was just flying under the radar. We would have never have thought it would be the key. Now that we have identified this molecule, we are able to replicate it in the lab to use for research purposes. We hope to learn much more about it and its potential for treating and diagnosing celiac disease and other autoimmune conditions. This molecule has opened innumerable doors for our research."

Source: University of Maryland Medical Center