The Gatekeeper

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Wheat and Gluten
May Be in Your Future

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"Every oak tree started out as a couple of nuts who decided to stand their ground."

Anonymous

In the last several years, researchers around the world have focused on potential treatments for wheat sensitive, gluten intolerance, and celiac disease. Specific research on celiac diseases has attempted to understand the mechanism by which gluten causes the presentation of this disease. In the past few years, some exiting new discoveries have been made in this area that may have equally important impacts on other conditions as well, such as diabetes and multiple sclerosis. Recently, scientists at the University of Maryland who were looking for the key to unlock some of the most baffling mysteries about celiac disease shouted a very loud, "Eureka" followed by an equally loud, "Open sesame!"

Zealots for Zonulin

"Zonulin" may sound like a character from a science fiction movie, but it's actually a protein made by the human body, and may represent an important piece of the puzzle in the development of autoimmune diseases, including celiac disease.

The small intestine contains billions of cells that are packed so tightly together that they act as a barrier against toxins, viruses, bacteria, and other foreign invaders, protecting the body's tissues. Between these cells are the "tight junctions" (also referred to as the zonula occludens).

Researchers wondered how gluten, a relative large molecule, was getting through the tightly packed cellular barrier and into the immune system where it caused an autoimmune response. The answer, they discovered recently, is that exposing the small intestine of the celiac patient to gluten causes an increase in the production of the protein zonulin. Zonulin decreases the resistance of the small intestinal barrier by opening the tight junctions, which can then open the spaces between cells, allowing some substances to pass through. In other words, zonulin acts as the gatekeeper for the body's tissues. People with celiac disease and some other disorders have higher levels of zonulin, which, in essence, means that gates are "stuck open," allowing gluten and other harmful substances to pass through.

An Unexpected Discovery

The story of the discovery of zonulin is an interesting and unique example of how scientists can learn from microorganisms (for example, bacteria). Researchers at the Center for Vaccine Development at the University of Maryland were trying to develop a vaccine for the cholera bacterium (cholera is one of the leading causes of death in children worldwide, and it causes a profuse, watery diarrhea). The researchers discovered that cholera causes diarrhea by secreting a toxin called Zot (zonula occludens toxin), which can open the tight junctions (zonula occludens), thereby contributing to the severe, life-threatening diarrhea. Being keen scientists, they realized that these smart bacteria were likely mimicking a natural process in the human body. Using the latest techniques in molecular biology, they identified zonulin, a human protein that binds to the same receptor as Zot and performs similar actions.

The researchers found that zonulin was elevated in the tissue of subjects with many different diseases,

such as celiac disease, type 1 diabetes (insulin-dependent or childhood diabetes, also a autoimmune disorder), and multiple sclerosis. They hypothesized that zonulin opens the tight junctions in these individuals, and allows molecules to pass across the intestinal barrier that normally would not pass through.

In a person with celiac disease, production of zonulin increases in response to eating gluten. This leads to more open tight junctions between the intestinal epithelial cells, allowing the passage of toxic portions of gluten (which are normally too large to pass through). These toxic portions then interact with our friend tTG (tissue transglutaminase; see section on antibody testing for celiac disease), which changes the gluten fraction to a form that can interact with the immune system's lymphocytes (specialized white blood cells).

These interactions lead to the production of cytokines, chemicals that attract more lymphocytes to the affected area. The lymphocytes then attack the small intestine epithelium, leading to blunted or flat villi. Some lymphocytes will also be stimulated to produce specialized antibodies, the antigliadin, antiendomysial, and anti-tissue transglutaminase antibodies. These antibodies do not damage the intestine, but can be used as markers for celiac disease when they are found in the blood in elevated concentrations.

Zonulin and the Blood-Brain Barrier

Researchers at the University of Maryland were on a roll. Having discovered the importance of zonulin in opening the spaces between the cells that serves as a barrier in the small intestine, they turned their attention to the blood-brain barrier. The blood-brain barrier, like the barrier created by tightly packed cells in the small intestine, is a collection of tightly packed endothelial cells that line the blood vessels of the brain and prevent some substances in the blood from entering, while allowing others to pass through. Until now, scientists knew very little about why some molecules were allowed to pass through and other were not. The researchers hypothesized that zonulin could play a similar role in the blood-brain barrier to the one it play in the intestinal epithelial barrier, by opening the tight junctions or gates between the cells in the blood vessels of the brain.

Their theories have been substantiated; they have now verified that the receptor that binds both zonulin and Zot exists in the brain. This discovery may lead to novel treatments of diseases in which there is blood-brain barrier dysfunction, such as multiple sclerosis, brain tumors, and HIV infection.

The fact that zonulin receptors exist in the brain, and that zonulin is increased in the tissues of patients with celiac disease, may provide an explanation for some of the neurological symptoms of the disease. Also, the possibility that doctors may be able to deliver new types of medications (linked to Zot or zonulin) across the blood-brain barrier could open the doors to a whole new world of treatment options for many neurological diseases.

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