



Celiac Disease Research at the University of Chicago

The focus of the University of Chicago Celiac Disease Center and its researchers lies in the nature of the immune response in the small intestine. There are several research studies currently in progress that are examining the way in which gluten activates the epithelium of the intestine and induces a stress response, triggering the immune system. This process is not well understood, and Dr. Bana Jabri, with Dr. Stefano Guandalini and colleagues at the University of Chicago, has made important advances in this area.

Dr. Jabri has developed a series of laboratory techniques which help to analyze tissue samples of celiac patients and controls, and procedures to test how gluten activates the intestinal epithelium and immune system.

Dr. Jabri and her team are committed to translational research—ensuring that advances in the laboratory have an impact on patient care. While it takes years to transfer bench research to every day medical care, they design research initiatives with this in mind. Current research activities at the University of Chicago will help patients who have indeterminate test results by providing additional testing methods to clarify the diagnosis; those who may have refractory sprue to receive an accurate diagnosis and more effective treatments; and on the broadest level to develop treatments for celiac disease that disable the immune response and allow a person with celiac disease to eat without worry.

Gluten: A danger signal

Gluten is a molecule with a unique sequence and structure found in wheat, barley and rye but not in oats, corn or rice. Dr. Jabri's laboratory has gathered strong evidence that gluten can act as a danger signal and induce the same chains of events that a virus infecting the human intestine. She and her colleagues believe that gluten can mimic a viral infection in genetically predisposed individuals, and lead the immune system to attack the intestine and destroy it. Dr. Jabri and her colleagues are pursuing research to determine the part of gluten responsible for the danger signal and the molecular pathways underlying the inappropriate stimulation of the immune system. Furthermore, her laboratory is testing the promising hypothesis that if gluten stresses intestinal epithelial (lining) cells, early markers of stress should be detectable in the intestinal epithelium of patients that are at high risk of developing intestinal lesions.

This research may have a major impact in designing new treatments for celiac disease and creating a modified wheat grain, which would be safe for celiac patients. In addition, the identification of early markers of intestinal stress should help physicians to better determine which patients need a gluten free diet by determining which family members are most likely to develop intestinal damage. Finally, identifying this gluten-induced stress pathway will allow Dr. Jabri and her colleagues to test the implications of yet undefined genes on the development of the disease, 60% of which remain unknown.

Damage to the intestinal epithelium (lining)

The mechanisms leading to intestinal destruction and, for some patients, the development of intestinal lymphoma (a cancer of the immune system which is a unique complication of celiac disease) were not understood until recently. Dr. Jabri and her colleagues made the key discovery, that specialized immune cells located in between intestinal epithelial cells (intraepithelial lymphocytes), were the immune cells mediating the epithelial damage. Her laboratory discovered that the cytokine, interleukin 15, produced by stressed intestinal tissue, was responsible for arming the immune cells to kill the epithelium. This research continues to focus on how the immune system gets activated, the role of interleukin 15 in the development of lymphoma, and how therapies targeting interleukin 15 can prevent the development of resistance to a gluten free diet (a condition called refractory sprue) and lymphoma.

A multi-center effort, led by Dr. Jabri, including Dr. Stefano Guandalini from the University of Chicago Comer Children's Hospital; Dr. Peter Green from Columbia University Medical Center; and Dr. Joseph Murray from the Mayo Clinic, is currently collecting biopsy tissue samples from children and adults (who are in the process of being diagnosed) in order to perform laboratory tests that characterize the nature

of the stress inflicted on the intestine by interleukin 15 and other factors.

This line of research has radically altered the way in which we view the pathogenesis of celiac disease; Dr. Jabri and her colleagues have helped to enumerate the role of the innate immune system in the development of celiac disease. This research is the basis of the mouse models that are currently under development in her laboratory. This research is now funded by NIH.

Development of a mouse model

A mouse model is a type of mouse that is capable of developing a disease or condition under study. In order to create a mouse model, a great deal of experimentation is needed to impart the genetic and immune system factors that are necessary for the development of celiac disease. A mouse that can develop celiac disease under expected conditions will allow researchers to prove a cause and effect response (the relationship between gluten and the immune system cells in the gut), allow for the testing of therapeutic strategies and act as a springboard for future research.

Despite the existence of a humanized mouse model expressing the celiac genetic susceptibility molecules DQ2 and DQ8, there is currently no mouse model that is capable of developing intestinal damage upon gluten ingestion. As Dr. Jabri and colleagues have found that interleukin 15 plays a key role in the development of intestinal lesions, they are developing a mouse model that will over-express interleukin 15 in the intestinal lining that will be crossed to the humanized DQ2 and DQ8 mouse to reconstitute the human disease in a single type of mouse. This research is actively pursued but still in an early phase.

For more information contact the University of Chicago Celiac Disease Center at 773.702.7593 or www.CeliacDisease.net.

Research at the University of Chicago aims to answer the following questions:

- Why does gluten constitute a danger signal that inappropriately stimulates the immune system and leads to tissue damage in celiac patients?
- Is the intestinal epithelium (lining) of celiac patients a target for gluten?
- Why do only 5% of individuals who express the DQ2 or DQ8 molecules develop celiac disease?
- What other genes are involved in celiac disease?
- What is the exact role of transglutaminase in the progression of celiac disease?