

Press Release

Researchers hunt for the causes and basis of wheat sensitivities

German Research Foundation funds joint project of the universities in Mainz and Hohenheim to search for better tolerated wheat varieties

(Mainz/Hohenheim, 14 April 2016) Up to five percent of all people who eat wheat products suffer from wheat sensitivities. These are immunological responses to wheat and related cereals such as spelt, rye, and barley, and include celiac disease, wheat allergy, and non-celiac-non allergy wheat sensitivity (NCWS). This can cause physical symptoms as diverse as diarrhea, fatigue, psychological disorders, and worsening of chronic inflammatory diseases. Certain proteins in wheat are the cause. Now doctors and biomedical and agricultural researchers at Johannes Gutenberg University Mainz (JGU) and the University of Hohenheim have joined forces to study these disorders, especially NCWS. Their findings may contribute to the breeding of new types of wheat that lack these disease causing properties while maintaining the characteristics appreciated in wheat products.

The disorder termed NCWS has long posed a riddle to physicians and science. It apparently affects a large number of people when they eat wheat-based foods. The cause is an innate immune response that is triggered by wheat proteins called alpha-amylase-trypsin inhibitors (ATIs). "It is important to differentiate between NCWS, celiac disease, and wheat allergy," emphasized project coordinator Professor Detlef Schuppan, gastroenterologist, biochemist, and immunologist, head of the Institute of Translational Immunology at the University Medical Center of Johannes Gutenberg University Mainz. "Celiac disease is well defined and relatively easily diagnosed. Gluten proteins elicit an aggressive immune response in the gut, and a gluten free diet is the therapy of choice. Wheat allergy is often more difficult to diagnose, but usually recognized by an immediate reaction to wheat consumption. Here gluten and non-gluten proteins are the trigger."

"The main problem with NCWS was that the trigger as well as the clinical manifestations remained in the dark, until recently in my lab at Harvard Medical School in Boston we were able to identify the ATIs in wheat as mild inflammatory immune activators in the intestine," Schuppan explained. "Since then, it has become highly likely that this family of proteins is the cause of symptoms of NCWS," confirmed PD Dr. Friedrich Longin, scientific head of the Wheat Unit at the University of Hohenheim and co-initiator of the joint research project on "Wheat intolerance: influence of wheat varieties and growing conditions on innate immune reactions," funded by the German Research Foundation (DFG). ATIs are proteins that are naturally present in wheat. Just how many proteins of the ATI family and to what extent their content and composition are determined by the wheat variety and environmental growing conditions are not known, although researchers have first data that these factors can vary widely with wheat variety.

Five to ten percent of Germans may suffer from wheat intolerance

"In some people, a certain level of nutritional ATIs from gluten containing grains, especially wheat, appears to trigger or exacerbate inflammatory reactions in the body. These individuals

then experience intestinal as well as prominent extraintestinal problems, including joint and muscle pain, skin eczema, depression, and generalized worsening of pre-existent chronic diseases, including autoimmune diseases," added Professor Detlef Schuppan. Ingested in high quantities, the wheat ATIs activate that part of the immune system which detects mainly bacterial and viral pathogens. As a result, the innate immune system releases inflammatory proteins and activates specific T lymphocytes which directly cause the symptoms described above in those who suffer from the condition.

Longin points out that it will be extremely important to determine actual levels of ATIs as likely triggers of NCWS in individual wheat varieties. "While about one percent of the population of Germany has celiac disease or wheat allergy, it is probable that at least five percent have NCWS." To date, a genetic and proteomic analysis of ATI content in wheat has only been undertaken in the USA and there only in one of the cultivated wheat types. "As environmental effects such as wheat variety and conditions of cultivation are the main factors that determine the levels of these proteins, we need to perform our own standardized investigation of wheat grown in Germany," emphasized Dr. Stefan Tenzer of the Core Facility for Mass Spectrometry at the Institute of Immunology at the Mainz University Medical Center.

Analysis of 160 wheat and spelt varieties at three locations

And this is the starting point of the DFG-funded joint project involving the universities of Mainz and Hohenheim. The researchers planted 150 varieties of wheat at three different locations in Hohenheim. The varieties ranged from modern elite types, such as those currently used by farmers, to important older wheat varieties grown from the 1960s to the 1990s. Also being included in the experiment are ten different varieties of spelt. The wheat varieties have already been harvested, threshed, and cleaned, and are now being examined in the lab. The Mainz University Medical Center has developed the techniques used for analysis that include the determination of the biological activity and the mass spectrometric identification of the ATI proteins, and is also using methods to assess their *in vivo* potential for causing the symptoms in disease models and even in clinical trials.

The researchers have three main aims. Firstly, they want to find out how the content of ATIs has naturally evolved in the various wheat varieties. For this purpose, they are looking at whether there are differences in ATI content in older and newer varieties, the extent to which this is genetically determined in each variety, and whether environmental influences play a role. They also hope to establish exactly how many proteins belong to the family of ATIs in the wheat varieties examined and which of these proteins mainly cause the immune response. The harvested samples are thus being analyzed for ATI content by genetic and proteome methods, while human cell lines are being used to evaluate their immune system-activating effects in the laboratory. Lastly, the scientists hope to be able to establish how far ATI content affects baking properties and palatability, evaluating the wheat variants on the basis of standard quality criteria. Finally, and outside of the current proposal, "we plan several proof-of-concept clinical studies with patients that suffer from defined chronic diseases to assess how far a significant reduction of ATIs in the diet, for example by approximately 90 percent, may improve their condition", said Schuppan.

The goal over the medium term is to use the findings to breed new varieties of wheat that sensitive population groups will better tolerate. "We thus need to get the balance correct and create wheat varieties with a low ATI content that still have good baking properties and palatability," concluded Longin.

The German Research Foundation is funding the Germany-wide unique project on "Wheat intolerance: influence of wheat varieties and growing conditions on innate immune reactions" with EUR 680,000. Of this, EUR 470,000 has been allocated to the Mainz University Medical Center, while the University of Hohenheim will receive EUR 210,000. The financing was granted in response to a joint proposal submitted by Professor Detlef Schuppan, project coordinator and head of the Institute of Translational Immunology at the Mainz University Medical Center, PD Dr. Friedrich Longin, scientific head of the Wheat Unit at the University of Hohenheim, and PD Dr. Stefan Tenzer, head of the Core Facility for Mass Spectrometry at the Institute of Immunology at the Mainz University Medical Center.

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