Celiac disease : towards new therapeutic modalities

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Summary

SUMMARY

What is known about celiac disease?

Celiac disease is one of the most common food intolerances, approximately 1% of the population being a celiac disease patient. It is now known that celiac disease is precipitated by ingestion of gluten, the major storage proteins in wheat, and similar proteins in related cereals like barley, rye and triticale (hybrid between wheat and rye). The most common complains of patients consuming gluten are abdominal pain, diarrhea and vomiting. Also neurological symptoms, infertility and retardation of growth can occur. For a positive diagnosis of celiac disease a histological examination of a small bowel biopsy and a clinical improvement upon the introduction of a gluten-free diet is required. None invasive, serological assays are available that measure the presence and titer of IgA antibodies specific for gliadin, deamidated gliadin, endomysium and tissue transglutaminase. Almost without exception celiac disease develops only in genetically predisposed individuals: over 98% of the patients express either HLA-DQ2 or HLA-DQ8. Next to the genetic component also other factors especially environmental play a role in disease development.

Celiac disease is an immune mediated disease, in which gluten peptides come in contact at the level of the small intestine with gluten specific T cells. These T cells could only be isolated from the small intestine of patients and not of healthy controls. Specific gluten sequences rich in prolamine and glutamine amino acids, resist degradation in the gastro-intestinal tract and after deamidation by the enzyme tTg are recognized by T cells. As a result of the inflammation, the mucosa loses its villi and strongly diminishes the absorption surface causing specific symptoms associated with the disease.

The current treatment for celiac disease is strict adherence to a life-long gluten-free diet. The wide-spread use of gluten and gluten-derived starch in the food industry makes the gluten-free diet challenging. It is not surprising that a considerable proportion of patients, especially adolescents, are interested in alternative treatments that would allow gluten consumption.

Thesis content

My project, which makes the content of this book, has focused on the development of alternatives to the gluten-free diet. Two different approaches were investigated: the use of enzymatic supplementation and the identification and/or development of a less/non-toxic cereal.

Chapter 1 is a general introduction to celiac disease.

In **chapter 2** the characterization of monoclonal antibodies raised against T cell stimulatory gluten peptides is described. Their reactivity against the prolamins from wheat, barley, rye and oats was determined and compared with that of gluten reactive T cells. The results demonstrate that the antibody and T cell reactivity patterns overlap significantly, indicating that the antibodies can be used to detect toxic sequences in

gluten. Subsequently, these antibodies were used in the studies aimed at the development of alternative to the gluten-free diet.

In **chapter 3** we propose a new strategy to generate non-toxic gluten. Our experiments demonstrated that non-immunogenic epitope variants were present in certain diploid wheat varieties that differ one amino acid with the toxic variant. Moreover, we found that by the introduction of this naturally occurring amino acid substitution in other toxic epitopes their T cell stimulatory activity was likewise eliminated. This approach can thus be used to generate gluten genes that are devoid of any T cell stimulatory activity and presumably safe for consumption by celiac disease patients.

In **chapter 4** we investigate the safety of oats for consumption by celiac disease patients. We confirmed that commercially available oats are without exception contaminated with other cereals. Perhaps more importantly, we demonstrate that variability exists in the level of T cell stimulatory gluten like peptides in a panel of oats varieties tested, opening the way to select and/or breed oats varieties that contain no harmful gluten-like proteins.

In **chapter 5** we investigate the potential of AN-PEP, a prolyl-endoprotease produced by the microorganism *Aspergillus niger*, to degrade gluten in an artificial gastrointestinal tract system. The enzyme proved very efficient in degrading all toxic epitopes in this system, even when a complex meal was introduced. These “in vitro” studies now justify a clinical trial to assess the safety and effectiveness of the enzyme for gluten degradation in patients.

In **chapter 6** I discuss how the results may lead to novel treatment modalities and novel foods in the near future.