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Celiac disease and cereal proteins

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ABSTRACT

Celiac disease is a genetically predisposed disease, and statistics show that approximately 1% of the global population suffer from this disease. The starting point of celiac disease is the ingestion of gluten forming proteins and other homologous proteins that are found in wheat, rye, barley and possibly oat. In this review, demographics of celiac disease, the biochemistry of the disease and the proteins and peptides responsible for the immune reaction associated with this disease will be discussed. Additionally, there is much debate about the safety of oat in a gluten-free diet. In this context, the role of oat avenin proteins in giving rise to celiac disease will be reviewed. Moreover, the varying degree of celiac disease toxicity with reference to ancient/historical and modern wheat will be examined.

1. Introduction

Cereal proteins play a major role in dough rheology. For example, wheat gluten proteins, which are composed on gliadin and glutenin proteins, form a continuous three-dimensional network during the dough development process (Barak, Mudgil, & Khatkar, 2015). According to Wieser (2007), gliadins mainly provide viscosity and glutenins provide elasticity to the dough system. Together these proteins develop a viscoelastic dough system. The gliadin to glutenin ratio has been identified as one of determining factors for dough rheology, thus an optimum ratio between gliadin and glutenin results in the formation of a strong dough network (Khatkar, Bell, & Schofield, 1995). The prolamin proteins in rye are termed secalin proteins. These are homologous to gluten forming proteins in wheat, however, these proteins are not able to form a three-dimensional network due to structural and compositional differences (Gellrich, Schieberle, & Weiser, 2003). Barley hordein proteins are rich in hydrophobic amino acids, leading to high surface hydrophobicity and strong protein aggregation. As such, these proteins are important in stabilization of foams and emulsions (Zhao, Tian, & Chen, 2010). In the foam lamella, the barley proteins interact with other components, specifically the bittering agents of hops to form a matrix, which leads to stable foam in beer (Kapp & Bamforth, 2002).

Celiac disease (CD) is an autoimmune enteropathy, which is prevalent in 0.71% (1 in 141) of adolescents and adults in the United States (Rubio-Tapia, Ludvigsson, Brantner, Murray, & Everhart, 2012). The disease develops in genetically susceptible individuals as a result of ingestion of gluten forming proteins found in cereals such as wheat, rye and barley (Trier, 1998). Wheat ingestion was first recognized as the cause of CD by Willem Karel Dicke in 1950. Celiac disease in principle is a T-cell mediated immunological condition (Wieser & Koehler, 2008). $CD4^+$ T-cells identify peptides formed upon digestion of gluten proteins, which are presented by Major Histocompatibility Complex II (MHC II) molecules and cause an autoimmune reaction. Therefore, those who express the MHC class II Human Leukocyte Antigen (HLA) DQ2 and HLA-DQ8 would develop CD (Schuppan, 2000).

In normal physiological conditions, gastric, pancreatic and small intestinal brush-border enzymes digest most dietary proteins into small peptides and amino acids (Wieser & Koehler, 2008). However, toxic peptides in terms of CD are high in proline content, thus, are resistant to digestion. As a result of non-digestion, proline and glutamine rich fragments accumulate in the small intestine. These peptides are referred to as T-cell epitopes (toxic/immunogenic peptides). The pathological conditions associated with CD begins with the alteration of the barrier function of the intestinal mucosa, allowing dietary gluten peptides to reach the subepithelial lymphatic tissue. Recent studies have demonstrated that the zonulin protein is responsible for causing increased permeability of the intestinal mucosa in CD patients. Gluten peptides that have reached the lamina propia are able to trigger the adaptive and innate

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Table 1
Estimated prevalence of celiac disease.

In the general population:	1 in 133
In symptomatic children:	1 in 322
In symptomatic adults:	1 in 105
In first-degree relatives of people with CD:	1 in 22
In second-degree relatives of people with CD:	1 in 39
In chronic disease (such as type 1 diabetes):	1 in 60
In African, Hispanic and Asian-Americans:	1 in 236
World-wide prevalence:	1 in 266

Source: Niewinski (2008).

immune response associated with CD. The final outcomes of the immune response includes, degradation of matrix proteins, and subsequent mucosal destruction, production of antibodies against gluten peptides, tissue transglutaminase and peptide complexes formed by the activity of the enzyme. The most common symptoms of CD are, diarrhea, vomiting and abdominal pain (Scherf, Koehler, & Wieser, 2016). Due to malabsorption of nutrients, conditions such as, vitamin and mineral deficiencies, anemia, night blindness and weakness of bones could occur. Additionally, CD is reported to slower the growth of children and adolescents and cause issues in the reproductive health of women.

2. Demographics of celiac disease

In the early days CD was thought to be a rare disease that affected children causing diarrhea and food intolerance. As of today, this disease is recognized as a multisystemic disorder. Table 1 shows that CD now is a wide spread disease.

3. Genetic aspects of celiac disease

The MHC genes account for about half of the genetic factors associated with the disease (Sollid & Lie, 2005). The HLA class II alleles HLA-DQ2 and HLA-DQ8 have a very strong association with CD (Wieser & Koehler, 2008). Approximately 90–95% of CD patients are positive for HLA-DQ2 (Scherf et al. 2016). The main isoforms of DQ2, DQ2.5 and DQ2.2 have been identified. The former is the dominant, whereas the latter is rare. However, research suggests that non-HLA genes also play a role in the onset of this disease (Wieser & Koehler 2008). HLA-DQ2/8 are expressed in approximately 25% of healthy individuals, and the difference in concordance between monozygotic twins (80%) supports this premise. The contribution of other genes in the pathogenicity of CD is difficult to determine as the effect of these genes is unique to each individual (Kagnoff, 2007).

4. Adaptive and innate immune response

As previously mentioned, CD is only prevalent in individuals predisposed with HLA-DQ2/8 expressed on the surface of Antigen Presenting Cells (APC) such as, dendritic cells, macrophages and B-cells (Wieser & Koehler, 2008). The pathway for adaptive immune response is triggered when HLA-DQ2/8 bind gluten peptides and present them to T-cells, which are in the lamina propria. T-cell receptors are found in gluten-sensitive $CD4^+$ helper cells. The mechanism by which the immune reaction occurs is depicted in Fig. 1.

The deamidated form of the T-cell stimulatory gluten peptides have a higher affinity for HLA-class II proteins, although deamidation is not a requirement for T-cell activation. The tissue transglutaminase enzyme is a calcium-dependent transamidating enzyme, which deamidates glutamine to glutamic acid by reacting with water (Dieterich et al. 1997). This enzyme only deamidates select glutamine residues according to the enzyme's specificity, which is influenced by the amino acids around the glutamine residue (Molberg et al. 1998). Additionally, the tissue transglutaminase enzyme catalyzes the binding of gluten peptides to extracellular matrix proteins such as collagen (Dieterich et al. 2006). This long-

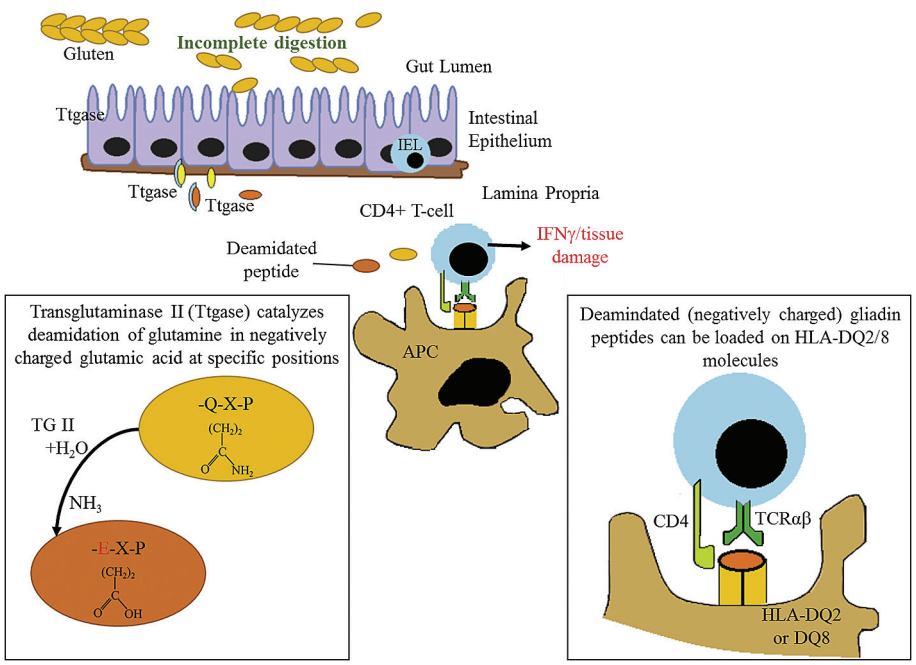

Fig. 1. Immune response associated with celiac disease. Incompletely digested gluten peptides pass through the intestinal epithelium into the lamina propia. Here the peptides undergo deamidation through the action of the tissue transglutaminase enzyme. The deamidated peptides are then recognized as antigens by the antigen presenting cells (APC), which present them to T-cells upon which an immune response in triggered. As a final outcome, interferon-γ (IFN-γ) is produced which leads to tissue damage (Adapted from Meresse, Ripoche, Heyman, & Cerf-Bensussan, 2009).

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