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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Celiac Disease: Role of the Epithelial Barrier

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SUMMARY

Recent findings have suggested that the mucosal barrier is a primary focus of disease activity in celiac disease. Alongside the well-established remodeling of the small intestinal architecture, focal epithelial barrier defects occur with increased apoptosis and an altered tight junction–mediated permeability. Barrier-forming claudins are down-regulated while the channel-forming claudins are up-regulated, both causing a loss of ions and water to the gut lumen. An intimately regulated transcellular passage of gliadin peptides is needed for celiac disease development. As a central organizer of proteins related to barrier function, the role of epithelial polarity regulators is discussed.

In celiac disease (CD) a T-cell–mediated response to gluten is mounted in genetically predisposed individuals, resulting in a malabsorptive enteropathy histologically highlighted by villous atrophy and crypt hyperplasia. Recent data point to the epithelial layer as an underrated hot spot in celiac pathophysiology to date. This overview summarizes current functional and genetic evidence on the role of the epithelial barrier in CD, consisting of the cell membranes and the apical junctional complex comprising sealing as well as ion and water channel-forming tight junction proteins and the adherens junction. Moreover, the underlying mechanisms are discussed, including apoptosis of intestinal epithelial cells, biology of intestinal stem cells, alterations in the apical junctional complex, transcytotic uptake of gluten peptides, and possible implications of a defective epithelial polarity. Current research is directed toward new treatment options for CD that are alternatives or complementary therapeutics to a gluten-free diet. Thus, strategies to target an altered epithelial barrier therapeutically also are discussed. *(Cell Mol Gastroenterol Hepatol 2017;3:150–162; http://dx.doi.org/10.1016/j.jcmgh.2016.12.006)*

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By definition, celiac disease (CD) is an immune-mediated small intestinal disorder with a strong genetic component. In genetically predisposed individuals it is triggered by the ingestion of gluten-containing food. It is assumed that gluten is responsible for CD induction together with one or more other, nondietary factors that have not been identified yet. Gluten is a mixture of proteins found in grains such as wheat, barley, and rye, and includes peptide sequences that have the potential to elicit a small intestinal HLA-DQ2– or HLA-DQ8–restricted T-cell response. The only accepted treatment of CD is the adherence to a strict gluten-free diet (GFD). Diagnosis is established on the basis of the following: (1) a positive transglutaminase-IgA serology; (2) a duodenal histology showing villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis; and (3) by documenting a clinical improvement after introduction of a GFD.[1,2]

As documented by large epidemiologic studies in Europe, North America, and India, the burden associated with CD on the society is significant because it affects approximately 1% of the population and is associated with significant morbidity secondary to malabsorption and a moderately increased risk of developing malignancy.[3–6]

This review focuses on what is known in CD pathophysiology with respect to the intestinal barrier. Barrier function has been shown to be altered in CD for many years already.[7–9] However, it has been a matter of debate regarding its significance ever since (ie, whether barrier function contributes to the development of CD or if it is merely a phenomenon secondary to the CD immune response). Thus, this article summarizes the factors that contribute to barrier function in CD, discusses its presumed functional outcome, and refers to current and future treatment strategies that can be deduced from these insights. In this review we refer to a hierarchy of components of the intestinal barrier. The *mucosal barrier* relates to the barrier the mucosa imposes as a whole (ie, including structures such as lamina propria cells). In contrast, the *epithelial layer* or *epithelial barrier* relates solely to the single layer of intestinal epithelial cells. The term *barrier*

Abbreviations used in this paper: aPKC, atypical protein kinase C; Bmp, bone morphogenetic protein; CBC, crypt base columnar cell; CD, celiac disease; EGF, epidermal growth factor; GFD, gluten-free diet; GI, gastrointestinal; GWAS, genome-wide association studies; IEC, intestinal epithelial cell; IL, interleukin; MIC-A, major histocompatibility complex class I chain–related gene-A; SNP, single-nucleotide polymorphism; TJ, tight junction; ZO, zonula occludens.

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function refers to the functional impact that a structure (eg, the tight junction) imposes on the mucosal immune system.

Genetics

The risk of first-degree relatives being affected by CD was shown to be 7.5% in a recently published meta-analysis.[10] Having at least 2 first-degree relatives with CD in the family increases CD risk to 17%.[11] Importantly, monozygotic twins show a concordance as high as 75% for CD development, which is considerably higher than respective figures in other autoimmune diseases such as multiple sclerosis, Crohn's disease, or type I diabetes mellitus.[12] Forty percent of the genetic risk is conferred by genes encoding for the HLA class II molecules HLA-DQ2 (DQ2.5-DQA1*0501-DQB1*0201 or DQ2.2-DQA1*0201-DQB1*0202) and HLA-DQ8 (DQA1*0301-DQB1*0302).[13–15] The remaining 60% are encoded by non-HLA genes, each of which is estimated to contribute only a small effect.[16]

Making use of single-nucleotide polymorphisms (SNPs) as markers of association, genome-wide association studies (GWAS) were performed to identify further genes responsible for CD. The first GWAS included 778 CD patients and 1422 controls and analyzed 310,605 SNPs, thereby identifying a locus on chromosome 4 harboring the interleukin (IL)2 and IL21 genes.[17] Further GWAS followed with increasing resolution secondary to recruitment of several thousand celiac patients and higher resolving chips that included more than 0.5 million SNPs. These recent chips focused on distinct regions of the genome, thereby uncovering a total of 39 loci that contained 115 genes.[18,19] Several conclusions can be drawn from these GWAS. First, most of the genes identified are implicated in the control of the adaptive immune response, including genes for T-cell activation as well as cytotoxicity, IL21 production, IgA response, and B cells. Second, the function of a considerable number of genes identified in the screen is to date unknown and will be the subject of future research as exemplified by recent work from Kumar et al.[20] The investigators applied a co-expression algorithm and thereby identified 4 CD-associated genes with as-yet unknown function, which now are predicted to be involved in intestinal barrier function, especially in the actin-cytoskeleton rearrangement and cell–cell adhesion pathways. In this regard, an insight published more than 20 years ago should be recalled, namely that healthy first-degree siblings of CD patients also show a significantly altered barrier function.[7] Albeit methodologically different, both studies came to the conclusion that mechanisms determining the intestinal barrier function in CD contribute to disease development rather than being secondary to it. Third, approximately 50% of the associated SNPs affect the expression of nearby genes (ie, expression quantitative traits loci), which implies that deregulated gene expression plays a significant role in CD pathogenesis. Fourth, there is a major overlap of genes involved in CD pathogenesis with genes involved in the development of other autoimmune pathologies including type I diabetes mellitus, rheumatoid arthritis, Crohn's disease, and ulcerative colitis.[21,22] This certainly reflects clinical experience because a high percentage of CD patients suffer from one or more additional autoimmune diseases.

Main Trigger of Celiac Disease: Gluten

Glutens are storage proteins occurring in grains of wheat, barley, rye, and archaic wheats. Although the alcohol-insoluble fraction is referred to as *glutenins* and is responsible for the baking properties of the respective dough secondary to its gluing and dispersing characteristics, the gliadins are alcohol-soluble and carry most of gluten's well-described antigenic properties. Wheat grains express α-, γ-, and ω-gliadins, as well as low- and high-molecular-weight glutenins. The proportion of glutamine and proline is remarkably high (30% and 15% of all amino acids, respectively), which leads to modification by tissue transglutaminase and then contributes to establishing strong interactions of gluten epitopes with the major histocompatibility complex II complex (Figure 1), and results in resistance to degradation by gastrointestinal endopeptidases, thus facilitating the advent of large immunogenic gluten fragments at the epithelial barrier.

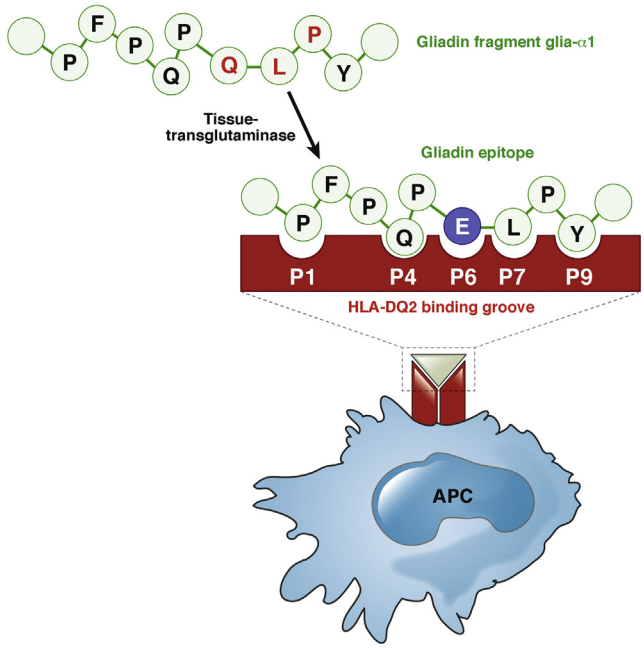

Figure 1. Binding of a gliadin epitope to the HLA complex. Gliadin fragments are deamidated by tissue transglutaminase (ie, a glutamine is transformed to a glutamate), thereby adding an additional negative charge to the epitope (*blue circle*). This facilitates binding to the DQ2 groove of the major histocompatibility complex molecule. Here, binding of the glia-α1 fragment to HLA-DQ2 is exemplified. However, this principle holds true for various oligopeptide sequences within α-, γ-, and ω-gliadin sequences, and also for binding to HLA-DQ8. Amino acids are shown in the 1-letter code with Q, glutamine and E, glutamate. The recognition motif of tissue transglutaminase within the unprocessed gliadin peptide (Q-X-P) is denoted in *red letters*. APC, antigen-presenting cell, P1…P9, binding positions within the DQ2 complex.

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