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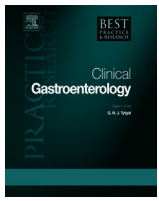

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Therapeutic approaches for celiac disease

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A B S T R A C T

Celiac disease is a common, lifelong autoimmune disorder for which dietary control is the only accepted form of therapy. A strict gluten-free diet is burdensome to patients and can be limited in efficacy, indicating there is an unmet need for novel therapeutic approaches to supplement or supplant dietary therapy. Many molecular events required for disease pathogenesis have been recently characterized and inspire most current and emerging drug-discovery efforts. Genome-wide association studies (GWAS) confirm the importance of human leukocyte antigen genes in our pathogenic model and identify a number of new risk loci in this complex disease. Here, we review the status of both emerging and potential therapeutic strategies in the context of disease pathophysiology. We conclude with a discussion of how genes identified during GWAS and follow-up studies that enhance susceptibility may offer insight into developing novel therapies.

Introduction

Celiac disease is a lifelong autoimmune disease characterized by an aberrant inflammatory response to dietary gluten in genetically susceptible individuals. Currently affecting 0.5–1% in most parts of the world, it is one of the most common chronic digestive disorders, with studies showing the prevalence of the disease is increasing [1,2]. The genetic predisposition to celiac disease is strong but complex. Ninety-five percent of patients are HLA-DQ2 or -DQ8 positive, but the presence of these alleles has a low positive predictive value [3]. The majority of the genetic component of celiac disease, as much as

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65%, may be caused by over 50 non-HLA genes, with each gene slightly contributing to the risk of celiac disease development [4].

The celiac lesion is characterized by villous atrophy, crypt hyperplasia, and infiltration of inflammatory cells, both in the small intestinal epithelium and in the lamina propria. The only current treatment for the disease is strict, lifelong adherence to a gluten-free diet, but many celiac patients experience persistent symptoms and enteropathy despite their best efforts to avoid dietary gluten. Additionally, patients with chronic undetected and untreated celiac disease are at an increased risk for developing enteropathy-associated T-cell lymphoma, small bowel adenocarcinoma, and other gastrointestinal cancers [5–7]. Thus, there is an unmet need for novel, non-dietary therapies that improve both health and quality of life for celiac patients [8–10].

Celiac disease pathogenesis

The design of novel non-dietary therapies to treat celiac disease requires a mechanistic understanding of disease pathogenesis (Fig. 1). At the broadest level, intestinal enteropathy in celiac disease is caused by genetic, immunological, and environmental factors. Gluten, a proline and glutamine rich glycoprotein, is the most critical environmental driver of the disease, while both human leukocyte antigen (HLA) and non-HLA genes are predisposing hereditary factors. MHC locus is the single most important genetic factor of the disease, with the majority of patients carrying a particular variant of HLA-DQ2 (DQA1*05:01, DQB1*02:01; also known as DQ2.5) [4]. Those who are not DQ2.5+ almost all carry HLA-DQ8 (DQA1*03, DQB1*03:02) or another variant of HLA-DQ2 (DQA1*02:01, DQB1*02:02; also known as DQ2.2) [11]. HLA-DQ2 and HLA-DQ8 predispose patients to celiac disease by preferential presentation of gluten peptides to $CD4^+$ helper T cells in the lamina propria. Activation of these T cells with gluten-derived peptides induces the secretion of various inflammatory cytokines dominated by interferon (IFN)-γ [12]. This, in turn, triggers a cascade of inflammatory reactions that leads to the hallmark intestinal enteropathy of celiac disease.

Given that virtually all patients with celiac disease carry particular HLA variants, HLA can be considered a necessary, but not a sufficient, factor for disease development. This claim is substantiated by the fact that while 40% of Caucasians possess one of the two predisposing haplotypes, only 3% of them develop celiac disease [13]. In addition to HLA genes, genome-wide association studies (GWAS) have identified 57 associated non-HLA variants located in 26 regions, with each locus contributing modestly to the overall genetic risk [14]. The majority of these non-HLA loci identified in GWAS harbor genes involved in the biology of T cells and antigen presenting cells. The story that emerges from the genetics of celiac disease bodes well for ongoing drug discovery efforts, given that most are based on the assumption that gluten-reactive T cells play a central role in controlling disease onset and severity. The other genes identified in GWAS reveal additional potential targets for future celiac disease drug discovery efforts.

The principal environmental driver, dietary gluten, contains a number of distinct disease-specific T-cell epitopes. A common feature of these epitopes is the presence of multiple Pro and Gln residues, with the high Pro content rendering these peptides resistant to proteolytic breakdown by gastric, pancreatic, and intestinal digestive proteases [15]. The result is an elevated intestinal concentration of potentially immunoreactive peptides following gluten ingestion. Some of the Gln residues of these immunoreactive peptides can be deamidated by the enzyme transglutaminase 2 (TG2), which is also the dominant autoantigen of celiac disease [16]. Deamidation enhances gluten peptide immunogenicity by increasing the affinity of the interactions between the immunoreactive peptides and specific pockets in the ligand-binding sites of HLA-DQ2 or HLA-DQ8 [17,18].

While the HLA-mediated response to gluten-derived antigens in patients with celiac disease is well understood, several features of gluten enteropathy in celiac disease remain unclear at present. First, dietary gluten reversibly increases small intestinal permeability in many patients with celiac disease. It has been proposed that enhanced paracellular intestinal permeability is the consequence of increased expression of zonulin, a protein released by the small intestinal mucosa after gliadin challenge [19]. Additionally, this phenomenon may be caused by IFN-γ and other cytokines produced by gluten-activated $CD4^+$ T cells [12]. Genomic studies of patients with celiac disease also report involvement of genes that control intestinal permeability, including *MAGI2*, *MYO9B*, and *PARD3* [20,21]. Secondly,