

Coeliac Disease: From Triggering Factors to Treatment

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Abstract Coeliac disease (CD) or gluten sensitive enteropathy is one of the most common inflammatory diseases of the small intestine with estimated prevalence of 1% in the population. Its incidence is increasing and seems to be higher than expected in the pediatric population associated with unfavorable impact on the quality of life. The aim of the present review is to highlight the main triggering factors leading to the development of CD and its pathomechanism with a special outlook to the recent therapeutic approaches.

Keywords: coeliac disease, triggering factors, pathomechanism, therapy


1. Introduction

CD occurs in genetically susceptible individuals triggered by chronic exposure to dietary gluten and related prolamins [1]. Approximately 1% of the population is affected and its prevalence is increased over the last decades [2,3]. This tendency suggests that beside of the genetic predisposition the environmental stress factors also have significant impact on the development of CD [4]. CD often becomes active after surgery, pregnancy, childbirth, viral infection, emotional or other stress situations [5]. The disease leads to intestinal inflammation, villous atrophy, and crypt hyperplasia of the small intestine. In the pathomechanism of CD both the adaptive and innate immunity may be involved 6. Presumed disease is mainly detected by serologic screening for the presence of tissue transglutaminase (tTG) specific immunoglobulin A antibodies [7]. CD may be associated also with various extra-intestinal complications, including isolated iron deficiency anemia, bone and skin disease, infertility, endocrine and neurologic disorders [8].

In the present review we give an overview about the role of genetic and environmental factors in the development of CD and about the major processes of its pathomechanism including the mucosal immune responses and epithelial barrier damage. Finally, we discuss the main strategies to find alternative therapies for CD.

1.1. Role of Genetic and Environmental Factors

The genetic predisposition is associated with the major histocompatibility complex (MHC) region on chromosome 6p21. About 90% of CD patients carry the human leukocyte antigen (HLA) DQ2 and the remainder expresses DQ8 [9]. Patients with CD who are negative for both DQ2 and DQ8 rarely occurs [10].

One of the most important environmental factors which can initiate the exacerbation of the symptoms of CD is gluten and its related prolamins (hordein, secalin, zein). The presence of gliadin, the alcohol-soluble fraction of gluten that contains the majority of toxic components, may initiate inappropriate innate and adaptive immune response leading to the development of CD.

Gliadins are rich in glutamine and proline, which protect them from proteolytic degradation by intestinal brush-border membrane proteases, they cannot be absorbed and remain in the intestinal lumen after gluten ingestion [11]. Due to intestinal infections or other disturbances in the intestinal permeability the undigested gliadin fractions pass through the epithelial barrier [2]. In the lamina propria tTGs become activated and catalyze polyamination or deamidation at selective glutamine residues converting them to negatively charged glutamate [12]. This modification promotes the binding of gliadin-derived fragments to HLA-DQ2 and HLA-DQ8 molecules resulting in antigen presentation and activation of gluten-specific T cells leading to permanent inflammation and mucosal damage [13].

Beside the most relevant gliadins there are also other environmental factors which play crucial role in the pathogenesis of CD including mechanical, chemical or oxidative stress which may all impair epithelial barrier function and facilitate inflammation [14,15].

1.2. Mucosal Immune Responses

Gliadin peptides passing through the damaged epithelial layer induce innate and adaptive immune responses characterized by the infiltration of immune cells in the lamina propria.
The importance of the adaptive immune response to gluten has been well established. After the presentation of deamidated gluten-derived peptides through HLA DQ2 and DQ8 molecules to CD4+ T helper cells further T cells and B lymphocytes become activated which produce anti-gluten and anti-tTG2 antibodies in the lamina propria [13]. Activated T cells express proinflammatory cytokines, e.g. tumor necrosis factor alpha (TNFα) and interferon gamma (IFNγ) triggering the release of matrix metalloproteinases by the local fibroblasts causing epithelial cell damage and tissue remodeling, respectively [16].

Besides the involvement of the components of adaptive immunity the central role of innate immune system has been also suggested in the pathogenesis of CD [6]. Recently increased expression of pattern recognition receptors including Toll-like receptor (TLR) 2 and 4, the well known participants of the innate immune response, was demonstrated in the duodenal mucosa of children with CD [17]. Increased expression of molecular chaperons, heat shock proteins (HSPs) were also demonstrated in patients with CD [18, 19]. It is hypothesized that HSPs as ligands for TLRs induce antigen presentation process and serve as “danger signal” for the immune system [20]. Activation of TLRs on the surface of macrophages and dendritic cells leads to the upregulation of MHC and costimulatory molecules and enhanced expression of proinflammatory cytokines and chemokines [21].

Gliadin-induced innate immune response is also characterized by the increased expression of interleukin-15 produced mainly by enterocytes, which activates intraepithelial CD8+ (cytotoxic) T lymphocytes leading to the destruction of the epithelial cells thus contributing to the damage of the barrier function.

### 1.3. Mucosal Barrier Damage

The intestinal epithelium is a single-cell layer serving as a protective barrier against the external environment. The gastrointestinal tract is frequently challenged by different pathogens and antigens therefore the regulation of intestinal epithelial homeostasis is crucial for the maintenance of the mucosal structure and defensive barrier functions [22]. The gluten induced inflammation, oxidative stress and enhanced epithelial cell apoptosis all lead finally to mucosal damage and consequently to the loss of epithelial barrier function and increased mucosal permeability [6].

Cell adhesion molecules including adherent junction and tight junction proteins (cadherins, claudins, occludin, and junctional adhesion molecules) as well as zonulin as a modulator of tight junctions are crucial regulators of the intestinal barrier function [23,24]. Zonulin is overexpressed in CD and induces an increase in intestinal permeability [25]. Furthermore, the cell adhesion structures are damaged in patients with CD also contributing to the increased mucosal permeability [26].

Recently, it has been demonstrated that gluten peptides can induce the generation of reactive oxygen species (ROS), which then stabilize hypoxia-inducible factor (HIF)-1α by the inactivation of prolyl hydroxylases [27,28]. The increased presence of mucosal HIF-1α and its newly described regulator molecule Parkinson’s disease 7 (PARK7) were demonstrated in patients with newly diagnosed CD [29,30] suggesting their contribution to the pathomechanism of CD. Previously some HIF-1 driven gene, such as trefoil factor 1, multidrug resistance gene 1 of ecto-5-prime nucleotidase was suggested to participate in the regulation of intestinal epithelial barrier function in CD [31]. Therefore it can be hypothesized that the gluten, ROS, HIF/PARK7 axis may play a central role in the pathomechanism of CD.

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**Figure 1.** Alternative therapeutic strategies targeting the pathomechanism of CD. Abbreviations: tTG: tissue transglutaminase; IEL: intraepithelial lymphocytes; IL-15: interleukin-15; APC: antigen presenting cell; HLA: human leukocyte antigen, T: T lymphocyte; B: B lymphocyte; TNF: tumor necrosis factor; IFN: interferon, LPS: lipopolysaccharide
1.4. Therapy

Since undigested gluten and related prolamins are the key triggering factors of CD, it is not surprising that all of the therapeutic interventions aim to eliminate gluten or attenuate its biological effects. At present gluten free diet (GFD) is the accepted treatment for CD, which involves the lifelong elimination of wheat, rye, barley and other gluten-containing foods from the diet. The strict GFD is costly and has an adverse impact on the quality of life [32]. In addition GFD is not fully effective in a significant part of the patients who are unresponsive [4], therefore new therapeutic strategies are under development [33] (Figure 1).

As an alternative therapeutic approach of CD, the use of genetically altered wheat strains lacking harmful gluten epitopes [34] and the detoxification of dietary gluten by enzymatic degradation of gliadin fragments [35] came into the focus and are in preclinical stage. Other therapeutic strategies aim to induce mucosal tolerance by intranasal administration of recombinant α-gliadin, which resulted in the downregulation of the immune response against whole gliadin [36]. Furthermore, immunization with gluten vaccines is under clinical testing showing a well tolerance [37].

Other therapeutic interventions are directed to modulate the immune responses against gliadin peptides and to inhibit the development of inflammation. The blocking of the antigen presentation process through the selective inhibition of ITG2 (e.g. use of cystamine, imidazolium derivates, dihydroisoaxole compounds) are only partly effective because of the risk of undesired interactions with vital biological pathways, thus clinical trials were not undertaken [33, 38]. However, the inhibition of antigen presentation through the blocking of gliadin peptide binding to HLA molecules using gluten peptide analogues is a more effective potential treatment for CD [39]. Likewise the prevention of the recruitment of lymphocytes targeting the chemokine receptor and ligand interactions e.g. CCR9 and CCL25 [40] and CXCR3 and CXCL10 [41] and the modulation of inflammation by monoclonal antibodies against TNF-α (Infliximab) [42] and IFN-γ [43] are another attractive therapeutic options for CD [44].

Another way of action is the preservation of the structure of intestinal barrier: the modulation of the intestinal permeability by zonulin antagonist AT-1001 is a completed phase IIb complementary approach with promising results [45]. Also the administration of a specific anti-IL-15 antibody was able to reverse the intestinal barrier damage through the induction of apoptosis of intraepithelial lymphocytes [46], however clinical studies for CD have been not yet performed. As another strategy to maintain the integrity of the epithelial layer may be the administration of exogenous intestinal alkaline phosphatase (iAP), an enzyme with advantageous bacterial LPS detoxification capacity [47], since its decreased level was reported in CD [48] and when added to newborns with necrotizing enterocolitis significant decrease in inflammatory cytokine expression and intestinal injury were observed [49].

2. Conclusions

CD is a genetically determined autoimmune disease triggered by dietary gluten and related prolamins. The worldwide prevalence of CD is 1% and is still continuously increasing. At present the accepted treatment of CD is a strict and lifelong elimination of gluten from the diet. This therapy is circumstantial and negatively influences the quality of life of both the affected individuals and also their families. In a significant part of the patients GFD is ineffective indicating the need for other alternative therapies. Accordingly different therapies are under development aiming the alternative elimination of gluten from the nutrition or the modulation of the immune responses against gluten.

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Statement of Competing Interests

The authors have no competing interests.

List of Abbreviations

CD: coeliac disease  
tTG: tissue transglutaminase  
MHC: major histocompatibility complex  
HLA: human leukocyte antigen  
TNFe: tumor necrosis factor alpha  
IFNγ: interferon gamma  
TLR: toll-like receptor  
HSP: heat shock proteins  
HIF: hypoxia-inducible factor  
PARK7: Parkinson’s disease  
ROS: reactive oxygen species  
GFD: gluten free diet  
iAP: intestinal alkaline phosphatase

References


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