Crucial role of innate immune system in the pathogenesis of celiac disease

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ABSTRACT

Celiac disease (CD) is a chronic autoimmune disorder caused by ingestion of gluten peptides in genetically predisposed individuals. In susceptible individuals, immune response to gluten results in intestinal damage and a wide range of clinical manifestations. Although both of innate and adaptive immunity is importance for response to gluten but innate system play a critical role in initiation of this process. Thus the main objective of this review is to investigate the role of innate immune system in the pathogenesis of celiac disease.

Keywords: Celiac disease, innate immunity, gluten.

Introduction

Celiac disease (CD) is a gastrointestinal disorder characterized by an abnormal immune response to dietary storage proteins (gluten) of wheat, barley, and rye in genetically predisposed individuals (1-3). It is estimated that around 1% of European and US population are infected with this autoimmune disorder (4). Common reported manifestations of CD is diarrhea, anemia, fatigue, osteoporosis, depression, skin manifestations, and neurologic diseases (5).

Different studies have provided that the presence of human leukocyte antigen (HLA)-DQ2 or HLA-DQ8 is necessary for the initiation of the immune response and followed by inflammation (6). Also damage to the intestinal mucosa in CD patients, result in infiltration of the immune cells such as T cells and plasma cells to the lamina propria, crypt hyperplasia followed by villous atrophy (7).
However, it is now known that adaptive immune response plays a key role in CD pathogenesis but innate immune system is necessary for the initiation of the response to the gluten (8, 9). In the other word, induction of the adaptive response is controlled by innate immunity (Figure 1).

Gliadin peptides by stimulation of innate immune cells type, particularly dendritic cells (DCs) and leukocyte infiltration, induced the inflammation of gut mucosa and breaking immunological tolerance (9). Also another factors such as pro-inflammatory cytokines, receptors and immune cells, plays a role in the induction of CD complications therefore this review was aimed to introduce a critical role of innate immunity in CD.

Immune cells and their role in Celiac disease

The adaptive immune response to gluten is initiated by antigen presenting cells (APCs), particularly DCs, which present to T cell antigen fragments (10), that it key actors in the link between the innate and adaptive immune responses (11). Moreover it is observed that gliadin and the derived peptides can also induce release of inflammatory cytokines and chemokines in DCs (Figure 2). Furthermore, gliadin fragments via p38 mitogen-activated

Figure 1. Overview of the innate immune system components and their function in the pathogenesis of celiac disease.
protein kinases (MAPK) pathway and with upregulation surface C-C chemokine receptor type 7 (CCR7)(13, 14) as well as cytoskeletal remodeling result in DCs migration to mesenteric lymph nodes (LN) (15). Finally trigger DC trafficking leading to clonal expansion of gliadin-specific T cells and increase adverse local and systemic immune responses in CD (13).

Some findings also show that gliadin can increase innate immune responses in monocytes and macrophages via intracellular signaling cascade such as pattern recognition receptors (TLR4) or other MyD88-dependent pathways (12). Maturation of these innate cells and release of inflammatory cytokines such as IL-1β, TNF-α and IL-8 can makes severity the adaptive immune response to gluten (16).

In addition, intestinal enterocytes under inflammatory or cellular stress express MICA/B and HLA-E molecules that are recognized by NKG2D and NKG2C on IELs (17). This process cause of cytotoxicity and apoptosis-inducing activity of IELs and epithelial cells damage via perforin/granzyme and/or Fas/FasL pathways (18).

Cellular stress and innate immunity activation

One of the early events in the pathogenesis of CD is increased cellular stress, particular Heat Shock Proteins (HSPs) (19, 20). HSP, a known cellular chaperone, has biological functions such as epithelial barrier protecting and immune system regulatory effects (21, 22). Several studies have demonstrated that HSP is increased in the duodenal mucosa of CD patients before they develop the disease and play a role in the pathogenesis of CD (20). This protein can binds to APCs and TLRs; and exert immunoregulatory effects by pro-inflammatory cytokines synthesis (21), chemokine, and reactive oxygen species release (22).

In a recent study Sziksz et al. clearly demonstrated that the expression of HSP72 mRNA was significantly increased in the duodenal mucosa of both untreated and treated children with CD compared with controls that may have a role in defense against the gliadin peptides (20).

In fact, HSP72 has a dual role in pathogenesis of CD. Because we know that TLR2 and TLR4 expression is increased in the duodenal mucosa of CD patients (23) and HSP72 is ligand to them (24), thus its might to induce pro-inflammatory cytokine production and co-stimulatory molecule expression that warn the cells of the potential injury (25, 26). In the other side it has an anti-apoptotic effect (27) and can preserve intestinal epithelial and decrease villous atrophy leading to improve the symptoms of the disease (Figure 2).

The role of innate cytokines in the pathogenesis of CD

IL-15

IL-15 is a key mediator of the innate immune system which produced by innate cells such as dendritic cells and macrophages. It exert many biological functions in immune homeostasis (28). Different findings demonstrated that this pro-inflammatory cytokine is upregulate in many organ-specific autoimmune disorders (29, 30).

In celiac disease, upregulation of IL-15 expression in both the lamina propria (LP) and epithelium is hallmark of the disease (28, 31). Some of the gliadin-derived peptides, in particular P31–43, induce intestinal innate immune response and proliferation of celiac enterocytes with IL-15 dependent (12, 32).

In addition to the LP dendritic cells and macrophages, enterocytes and intraepithelial lymphocytes (IELs) also produced IL-15. The function of IL-15 in the pathogenesis of CD include differentiation of dendritic cells (33),
Figure 2. Hypothetic Scheme of CD pathogenesis.
At first, gluten peptides passage into the lamina propria by epithelial transcytosis or increased permeability of epithelial tight junctional by zonulin. In the lamina propria, tissue transglutaminase (tTG) Type 2 with De-amination of gluten result in increases binding affinity to HLA-DQ2 or HLA-DQ8. Subsequently, APCs particularly DCs via IFN-α can induce an adaptive TH1 response that will increase production IFN-γ, release MMPs by myofibroblasts and finally resulting in intestinal changes (crypt hyperplasia and villous flattening). Furthermore innate immune cells and enterocytes produced IL-15 which in the intestinal mucosa with up-regulates the expression of NKG2D and NKG2C on IELs and their ligands MICA/B and HLA-E on epithelial cells, resulting in apoptosis. On the other hand, P31–43 gliadin peptide recognised by TLRs of intestinal APC, leading to increased synthesis of inflammatory cytokines and IL-15. Also, other factors such as HSP72 and PTX3 with induce pro-inflammatory cytokine production leading to tissue inflammation.

proliferation and localization IELs (34), inhibits regulatory T-cells (Treg) and the immunoregulatory transforming growth factor (TGF) signaling (35, 36). Moreover the IL-15 in the intestinal mucosa with up-regulates the expression of NKG2D and NKG2C on IELs and their ligands (MICA/B and HLA-E) on epithelial cells (Figure 2), can induce the apoptosis (37).

In this process, gluten-specific CD4+ T cells with activation of IEL via the production of IL-21 that synergizes with IL-15, promote cytotoxic CD8+ T-cell activation and expansion. Then CD8+ T IELs, in the presence of IL-15, can induce kill epithelial cells via the interactions of their NKG2D and NKG2C with their ligands MICA (37-39). On the other hands, IL-15 can prevent the differentiation of T-reg and upregulation of inflammatory Th1 cell responses leading to the loss of oral tolerance (35). Furthermore IL-15 can inhibit the TGF-β signaling leading to develop intestinal inflammation (36). Finally, all of these factors resulting the development of villous atrophy and epithelial cells damage in celiac disease (37).

**IFN-α**

This cytokine can be secreted by APC in response to enteroviral or intracellular bacterial infections (40); and by activation of DC can upregulate the IFN-γ and IL-15 production (41).

The evidence for the critical role of IFN-α in CD patients show (42) that treatment of chronic myeloid leukemia or hepatitis C patients with IFN-α leads to CD development in two cases (43). Also rotavirus by induce IFN-α production can increased the incidence of CD (44).

Study of Monteleone et al. regarding the role of IFN-α in the loss of tolerance to gluten show that IFN-α with promoting the differentiation and maintenance of Th1 cells can cause villous atrophy and crypt cell hyperplasia (42, 45). They reported that IFN-α was present in mucosal samples of CD patients but not in controls. This research group suggested that IFN-α prevented apoptosis of lamina propria T cells and increased costimulatory molecules on APC (42). Also after binding IFN-α to its receptors on T cells, activates transcription factors such as STAT1 and STAT4 bind to the promoter of IFN-γ (46) and lead to promoting Th1 responses to gluten and increase epithelial cells damage (42) (Figure 2). On the other hands, other finding show that there is an association between IFN-α signaling and expression of IFN-γ; and IFN-γ mediated cellular events are associated to IFN-α signaling (47). However in this regard more effort is needed to better understanding of its mechanism in the pathogenesis of CD.

**Innate receptors & their role of in the pathogenesis of CD**

**• TLR**

Toll-like receptors (TLRs), located in intestinal epithelial cells and lamina propria, is an important group of pattern-recognition receptors that play a crucial role in innate immunity by recognizing pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide, lipopeptides, and bacterial DNA (48, 49). The activation of TLRs leads to the innate immune response and also the induction of the adaptive immune responses (50). Recent findings suggested that these innate immune receptors are involved in pathogenesis of CD (51-53).

In celiac disease, p31-p43 gliadin peptide does not bind to HLA-DQ2 or HLA-DQ8; therefore, this peptide could be recognised by TLRs of intestinal macrophages and dendritic cells. This process leading to increased synthesis of interleukin IL-15 (12) (Figure 2).

In addition, the injured epithelium of patients with celiac disease releases a paracrine zonulin
that opens the intestinal epithelial tight junctions via zonulin receptor (54). This process was depend on myeloid differentiation factor 88 (MyD88), a key adapter molecule in the TLRs signaling pathways in particular TLR4 (55, 56). Moreover, signaling mediated by MyD88 resulting in production of matrix metalloproteases (MMPs), providing evidence that the TLRs signaling system is involved in the pathogenesis of celiac disease (57).

• **NOD2**

  Nucleotide-binding oligomerization domain-containing protein2 (NOD2) is another group of PRRs and cytosolic protein that plays an important role in the inflammatory and immune response at the mucosal level by recognizing peptidoglycan of the bacterial membrane and activating the NF-κB pathway (58). NOD2 is expressed in cytoplasm of intestinal epithelial cells, including Paneth cells and can induce the production of tumor necrosis factor (TNF), interleukin (IL)-6, and IL-8 as proinflammatory mediators (59).

  NOD2 interacts with components of the innate immune system, particularly TLRs (60). The findings show that NOD2 regulate the TLR response and these two molecules have a synergistic effect (60, 61). In addition, NOD2 regulates gut permeability which is mediated by TLRs (62).

  In CD patients, NOD2 expression is increase in the intestinal epithelium, which could correlation with TLRs to generate an innate immune response to gluten (63). Also NOD2 can induce the expression of human leukocyte antigen class II molecules, which have an important role in response of the immune system (64). More research on the role of this receptor in the pathogenesis of CD is needed.

**Function of acute phase proteins in CD**

• **PTX3**

  The long pentraxin (PTX3) is a family member of plasma proteins called acute-phase reactants, plays an important role in innate response and in modulation of the adaptive immunity (65). It is produced by several cell types, such as dendritic cells, macrophages, and endothelial cells, in response to inflammatory cytokines and TLR ligands (66).

  Recent studies point out the possibility that PTX3 is necessary for NF-κB activation and essential role of it in tissue inflammation (67). Assandri et al (68) have reported PTX3 serum level was increased in CD patients with different intestinal mucosa condition.

  Furthermore they demonstrated serum levels of PTX3 correlated with DGP IgA levels but no correlation was seen between PTX3 and tTG IgA levels. They suggested that PTX3 could be overexpress during the exposure to gluten or gliadin, as well as immune response to gluten or others proteins involve NF-κB and TLR pathway.

  Also another evidences recommended that PTX3 could do a crucial role in the several steps of celiac pathogenesis as mediator of inflammation and link gluten ingestion and tissue damage (68).

**Conclusion**

In conclusions this review suggests that celiac disease is a systemic disorder by immune system response. In this autoimmune disorder, undigested peptides of gluten have adverse biological effects in the intestinal mucosa of CD patients such as crypt hyperplasia and villous atrophy.

The result of different studies showed that immune system plays a role in CD pathogenesis; and among the various mechanisms, innate
pathway has a critical role in the development of loss of oral tolerance and damage to the small intestine. Also the importance of understanding among component of innate immunity the role of IL-15 cannot be overstated. Nevertheless another factors is necessary for response to the gluten.

Thus each component of innate immune system that are involved in the pathogenesis of CD can be used as one of the diagnostic markers of disease activates and will help identify therapies target for preventing and treating CD.

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Conflict of Interest
The authors declare no conflict of interest.

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