Review Article
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The role of Th1 and Th17 in the pathogenesis of celiac disease

Abstract

Celiac disease is a chronic autoimmune disease that is associated with genetic, environmental and immunological factors. The disease is closely associated with genes that code for human leukocyte antigens DQ2 and DQ8 haplotypes. In general, celiac disease has been recognized as a T lymphocyte associated disorders in which proteins derived gliadins, in the form of naive or deamidated by tissue Transglutaminase, activate T lymphocytes and as a result, release proinflammatory cytokines Such as IFNγ, IL-17, IL-21 and etc. These cytokines lead to histopathological changes like villous atrophy and crypt hyperplasia In addition, celiac disease has a specific antibody against gluten and an autoantigen of the transglutaminase 2(TG2) that provides strong opportunities to fully understand the adaptive immune response leading to disease. In this review, we investigated the role of Th1 and Th17 as an important mediators in pathogenesis of celiac disease.

Keywords: celiac disease, pathogenesis, Adaptive immunity, Thelper1 (Th1), Thelper17(Th17)

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Introduction

Celiac disease is a chronic autoimmune disease that involves both innate and acquired immunities and is caused by the consumption of specific proteins in genetically susceptible person.[1,2] Such proteins are present in the cereals has different names according to the food source, such as gliadin, hordein and secalin in wheat, rye and barley respectively. Due to structural similarities, they are called gluten.[3,4] The gluten protein is composed of two major parts: the gliadins solution and the insoluble glutenin. Both parts are rich in glutamine and proline contents.[5] Different intestinal and extra-intestinal manifestation such as diarrhea, anemia, bloating, weight loss, osteoporosis, depression, infertility, skin manifestations, and neurologic diseases are associated with celiac disease.[6] Different studies indicated that the incidence of celiac disease is between 0.5% and 2% in the different population.[7–9] Both genetic and environmental factors contribute to the development of celiac disease.[10] The primary HLA relationship for CD is conversed by MHC class II, including HLA-DQ genes. Almost 90 % of the CD patients express the HLA-DQ2 molecules and the majority of the remaining patients express HLA-DQ8.[11,12] Patients with celiac disease have a large number of $CD4^+$ T cell clones that respond to gluten peptides. After detection of gluten by T lymphocyte, a strong immune response develops, and then colony expansion occurs, resulting in symptoms of the disease. Patients undergoing gluten-free diet resulted in loss of clinical and histopathologic symptoms such as increasing IEL level, villous atrophy, intestinal permeability and crypt hyperplasia.[13–16] The glutamate derived from the activity of the transglutaminase enzyme is detected by T lymphocytes during the deamination process.[17] Some gluten peptides cross the intestinal epithelium can be deamidated by the tissue Transglutaminase (tTG), which increases their ability to bind the HLA-DQ2/8 molecules of antigen-presenting cells and to incense Th1, Th2 and Th17 cells that lead to the release of proinflammatory cytokines (IFN-γ, IL21, etc.) and the production of CD antibodies also onset the acquisition of acquired immune response.[18] In this review, we investigated the role of Th1 and Th17 as an important mediators in pathogenesis of celiac disease.

Adaptive immunity

As innate immunity plays a role in the initial defense of the epithelial gut, the acquired immunity in the lamina properia of the intestine provokes a series of immune responses by dendritic cells, macrophages and B cells. On the other hand as APCs initiates the adaptive immune response, antigen presentation is an important and fundamental step in the pathogenesis of celiac disease; and recent studies show that in intestinal lamina properia of patients with celiac disease after 3 days of stimulation with gluten before changing structure of intestinal, the density of macrophages and classical myeloid dendritic cell is decrease although the density of intermediate Dendritic cells ($CD103^+CD11c^+$) have increase. This increasing is linked to tissue structure changes and sudden increase of IEL that play a role in the onset of the disease.

Acquired immune cells can uptake gluten-degraded peptides by HLA-DQ2 or DQ8 and interact with gliadin-specific naive $TCD4^+$ cells which makes them differentiated into Th1/Th17 cells. As a result these cells secrete pre-inflammatory cytokines.[1,14,15,19] Humoral response by B-lymphocyte produces antibodies against the antigen. On the other hand cellular immune response against infection and cancer is applied through two cells. The cytotoxic T cell by detecting target cells by the receptor is causes the cell to die with an apoptotic mechanism. Therefore they led to remodeling and killing the epithelial cells.[20] In the following, the T-helper, which interacts with cell types such as macrophages and dendritic cell, can produce a variety of cytokines. T-helper are divided into two categories Th1 and Th2 based on the type of cytokine produced.[21]

Humoral immune activity has been increased in celiac disease as well as plasma cell levels which increase 2-3 times in active celiac disease.[2] Celiac disease is characterized by a variety of serum

antibodies targeting internal and external molecules.[3] Evaluation of serum antibodies for diagnostic purposes has been carried out about 40 years ago. For a long time, the predominant test has been the measurement of antibody IgA,[22] but today this test in clinical laboratories is used less because of the similarity to antibodies to other diseases, such as rheumatoid arthritis.[23,24] The gluten-deamidated antibody test has been developed based on the role of theTG2 enzyme at the beginning of gluten-derived T-cell epitopes[25] (Figure 1). This test has a great deal of performance, however, the most sensitive and specific test is the serum auto-antibody test.[26,27] The discovery of transglutaminase enzymes as a source of attenuated antigens has led to the development of ELISA, a method for rapid detection of autoantibodies with sensitivity and accuracy of nearly 100%.[28] Both the specific autoantibodies IgA and IgG of the TG2 enzyme can be identified in the serum, but IgA seems is more sensitive. In case of IgA deficiency, the IgG test is the most important diagnostic method.[29] The dependence of the autoimmune response on exposure to the external antigen (gluten) has made celiac disease unique among all autoimmune diseases, and this disease is an interesting model for the study of autoimmune disease.[19]

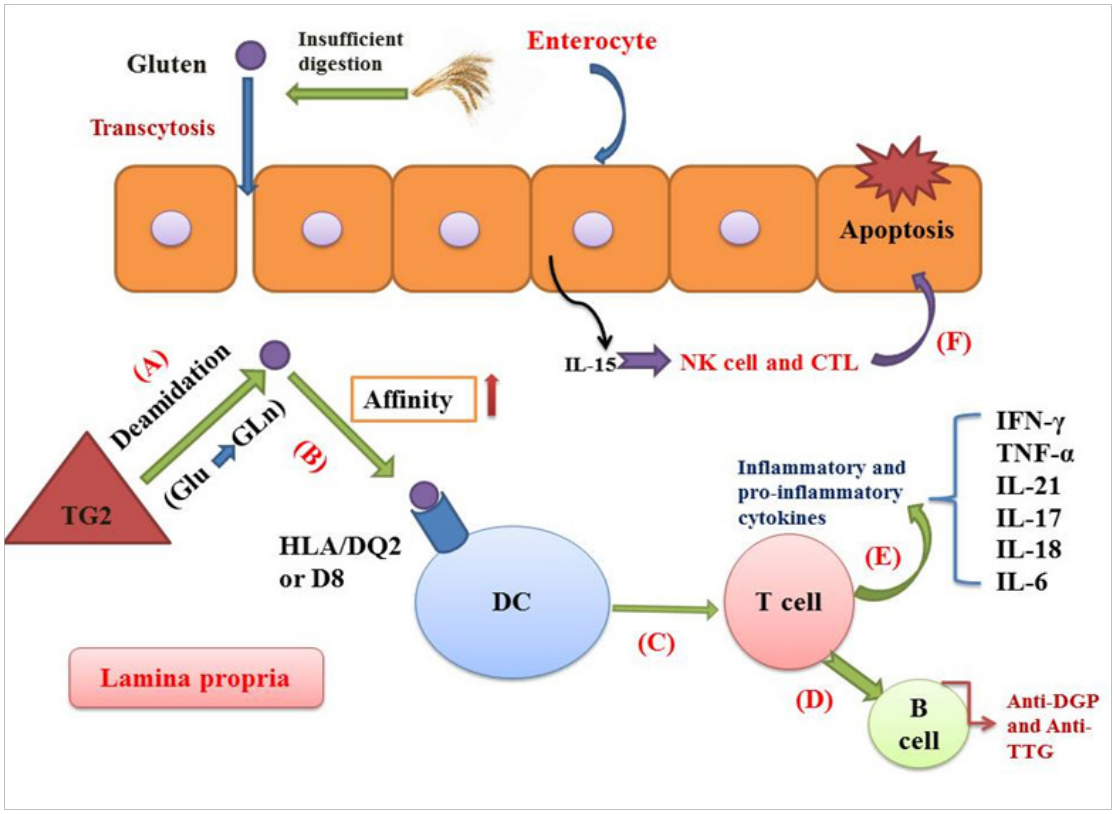

Figure 1 (Simplified schematic depicting the process of humoral and cell-mediated immune responses). TG2 deamidates gluten peptides; (A) Deamidated peptides have high affinities to HLA-DQ2 or DQ8 on antigen presenting cells (B), such as dendritic cells, macrophages, or B cells that leading to presented deamidated peptides to $CD4^+$ T cells(C). These cells then become gluten-reactive and are committed to produce Inflammatory and pro-inflammatory cytokines such as (IFN-γ, TNF-α, IL-18, and IL-21) (E), and could also cooperate with B-cells on antibody synthesis at the time that they differentiate into plasmatic cells in order to secrete specific antibodies against TG2 or gliadin (D). Intestinal epithelial cells (IECs) produce IL-15 after exposure to other gliadin peptides that this in turn activates $CD8^+$ cytotoxic T cells expressing the natural killer receptors, which can target and destroy epithelial cells that carry the stress-induced molecules (F).

Thelper1 (Th1)

$CD4^+$T (Th (lymphocytes show a different population of cells that play a key role in specific immunity. The term "T helper" is a controversial source of research studies that play an important role in helping lymphocyte B to produce antibodies in the early response. Thelper cell (Th1) produces high levels of IFN-γ that is responsible for activating phagocytes, and the production of opsonizing and complement-fixing antibodies. Therefore, they play an important role in protecting against intracellular pathogens.[20,30–33] The first information on human T helper cells has been obtained from studies by Cosmi and colleagues.[34] In the mucosa of patients with celiac disease, histological trauma is associated with marked infiltration of Th1 cells.[35] Intermediates for the development of naïve T-cells into Th1 cells in CD include: T-bet, IFN-α and IL-21, these molecules gene expressions are evaluated by Real-time PCR technique and the results have shown that increased expression in the intestinal biopsy of patients with celiac disease compared to healthy people.[16] Recently, a group showed that IFN-α is another cytokine that can promote T-cell differentiation and produce IFN-γ in humans that is expressed in microsites of untreated celiac patients when anti-IFNα detected by Western blotting analysis. In addition, they have reported the incidence of clinical CD in patients receiving IFN-a therapy, suggesting a role for this cytokine in promoting the local immune response in CD.[20,36] T-bet a special T

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box transcription factor that cooperates with IFN-γ expression in Th1 and natural killer cells. T-bet is responsible for Th1 development from naive Th cells and acts both by initiating Th1 genetic programs and by repressing the opposing Th2 cell development. In this study they showed that T-bet was more prominent in CD mucosa in comparison with normal duodenum. The fact that T-bet was found in the normal duodenum and clinical colon manifestations display that human intestinal lamina propria is penetrated with IFN-γ secreting cells.[13,16,37] In the lamina properia of normal individuals the main cytokines of Th1 is not detectable. The secretion of interferon gamma from the Peyer's patches increases interleukin-12 and led to differentiation of Th1.[38] In fact, mRNA for IFN-γ in the untreated patients shows an even greater increase compared to the messengers for IL-2, IL-18, and TNF-α. Moreover, IFN-γ may have a much greater role in producing mucosal damage of gliadin in CD, indicating the effectiveness of anti-IFN-γ antibodies in preventing villous atrophy of the intestinal.[16] In addition, it has already been shown that T-bet RNA transcripts are up-regulated in CD mucosa, Therefore, the role of this transcription factor is to promote the proliferation of Th1 cells during this disease.[35] In this study, the excessive increase in IFN-γ and the expression of a defective SOCS-1 protein result in the continuous activation of STAT1 in CD, thereby promoting and maintaining local inflammatory responses.[16] In the duodenal normal biopsy IFN-γ stimulates the T-bet via a mechanism dependent on STAT-1. Transcription factors such as STAT-1 and STAT-4 are associated with IFN-γ production and play an important role in the production of a specific Th1 cytokine. Challenge of treated CD but not control biopsies with gliadin increased T-bet and this effect was also inhibited by STAT-1 inhibition. Intestinal mucosa in patients with celiac disease contains large amounts of Th1-related cytokines such as IFN-α, IL-18 and IL-15; the contribution of each of these cytokines is determined in response to Th1.[35] In summary, these evidence indicate that IFN-γ stimulate various effector mechanisms, such as the up-regulation of HLA expression, promoting T cell priming and expansion, release of tissue-damaging MMPs from fibroblasts, improved cytotoxicity of IELs against enterocytes with increased enterocyte apoptosis and villous atrophy (Table1) (Figure1).[16]

Table 1 Comparison of Th1 and Th17 cells and their role in celiac disease

Subtype of T helper	Transcription factor and cytokines	Function in celiac disease
Th1	T-bet,STAT1,STAT4	Release proinflammatory cytokines(IFNγ, IFNα, IL-15, IL-18, IL-12)
Th17	ROR-γt	Plasticity function (release both inflammatory and anti inflammatory cytokine such as IL-17, IL-21, IL-22,TGFβ)

Thelper17 (Th17)

Th17 cells have an important role in several autoimmune diseases. Also recent studies shows that these cells are involved in CD pathogenesis, evidenced by using real-time qRT-PCR showing increased expression of Th17-related cytokines in patients with active CD compared to normal group. Recent studies indicate that the source of these cytokine are $CD4^+$cells and $CD4^+CD8^+$ cells as flow cytometry analysis is confirmed this fact.[39–43] Th17 cells secrete different cytokines such as (IL-17A, IL-17F, IL-21, IL-22) and these are high expression in active CD. Also they need transforming growth factor-β (TGF-β) combined with IL-6 or IL-21 and ROR-γt to be differentiated. CCR6, the receptor for CCL20, is highly expressed on Th17 cells that Involves these cells in the inflammation site.[44] Another study indicate that IL-17A, the specific product of Th17 cells, is highly released in inflamed intestinal of untreated CD than to potential CD mucosa.[45] IL-21 is a member of the IL-2 family of cytokines that is require in the differentiation of Th17 cells and the maintenance of ongoing Th1 response. In the following recent studies show that expression of IL-21RNA and number of $IL\text{-}21^+$cells are increased in deudenom culture of active CD than control group.[46,47] Moreover, studies showed that IL-17A-producing T cells express IFN-γ, and inhibition of IL-21 activity by neutralizing IL-21 Ab decreased IL-17A, IFN-γ and T-bet expression in deodenum cultures of active CD.[41] importantly, stimulation of treated duodenum biopsy of CD By gliadin Leads to an increase in expression of IL-21 in $CD4^+$ T cells. Therefore, IL-21 increase IFN-γ production through positive feedback and has important role in extend of Th17 cells.[48] Another study, show that potential CD has lower number of $IL\text{-}21^+$ cells in the lamina propria compared to active CD.[45] IL-21 may be involved in enhancing intraepithelial $CD8^+$ T cells as well as leading to contribute to CD-associated autoantibody production, since IL-21 effect on B cells to regulate Bcl-6 expression.[48] In 2010, Bood and colleagues[49] indicate that major source of IL-17 production is not gliadin-specific $CD4^+$T cells. In contrast to recent study this evidence show that gluten-specific IL-17A-producing cells have been observed in the duodenum of CD patients.[41,49] Bood et al.[49] show that the gluten- reactive T cells do not produce significant amounts of IL-22[49] but another study indicate that both IL-17 and IL-21 have a role in mucosal immunity so proves that an active role for Th17 cells in the pathogenesis of CD.[50,51] Furthermore, it was indicated that gliadin-specific Th17 cells also produce IFN-γ and IL-21 proinflammatory cytokines, mucosa-protective IL-22, and TGF-β. This evidence suggests that Th17 cells in CD, secreting both proinflammatory and anti-inflammatory cytokines, thus have a functional plasticity (Figure1).[52]

Several studies showes that TGF-β require as a critical signaling cytokine in Th17 differentiation.[53,54] However, TGF-β signaling pathways have importatnt role in the development of Treg and Th17 that in low concentration of TGF-β with IL-6 leading to differentiation of Th17 in contrast to T-reg. Therefore, these cells are opposite and cytokines around the microenvironment of intestine play a decisive role. However, in CD, TGF-β activity is impaired due to IL-15, thus have an importatnt role in Th17 differentiation.[55,56]

Conclusion

In general, by the presented information some key aspects of the immune pathogenesis of celiac disease have been identified. Adaptive immune system seems to play a central role in the pathogenesis of celiac disease. The current understanding suggests that $CD4^+$ T cell regulate immune response to gluten, which is an antibody response against the self-acting transglutaminase enzyme. We know that the HLA-DQ protein complex induces Th1 response, which includes increased production of cytokines, especially IFNγ, a cytokine that is

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the key to initiating injury to intestinal mucosa. However, evidences suggested the role of Th17 in immune response to celiac disease[16] and indicated a plasticity function in pathogenesis of celiac disease. As a result, the complexity of the mucosal cytokines is highlighted. Anti-cytokine approaches that target a pro-inflammatory cytokine, suppression of T cells, targeting B cells with anti-CD20 and etc., offer important constraints in providing an effective treatment for celiac disease.[57]

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Conflict of interest

The author declares no Conflict of interest.

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