Chapter 4

Pathogenesis of Celiac Disease

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Abstract

Celiac disease is a chronic, immune-mediated inflammatory disorder of the small intestine that affects genetically susceptible individuals after ingestion of gluten proteins in wheat, barley and rye cereals. The interaction of genetic and environmental factors leads to loss of tolerance to these proteins and to the development of intestinal lesions characterised by intraepithelial lymphocytosis, enterocyte destruction, mucosal remodelling and the presence of auto-antibodies to the enzyme tissue transglutaminase (TG2). The most widely-accepted pathogenic model includes altered digestion and transport of gluten across the epithelium. This focuses on adaptive immunity mechanisms that depend on stimulation of gluten-reactive CD4+ T cells, which are capable of recognising TG2-deamidated gluten peptides presented by HLA-DQ2/DQ8 molecules, and proinflammatory cytokine production, especially interferon (IFN)-γ. Furthermore, in the innate immune response, gluten has a direct toxic effect on the epithelium, in which the main mediator is interleukin (IL)-15. This is manifested by the expression of stress molecules in enterocytes and activation of CD8+ intraepithelial T-cell cytotoxic function. Some aspects still need to be clarified, especially regarding the nonspecific interaction between gluten and epithelial cells, passage of gluten peptides into the *lamina propria* mucosa, TG2 activation, mechanisms that regulate IL-15 expression, and auto-antibody production.

Keywords

Tolerance breakage, transepithelial transport, IL15, IFNγ, intraepithelial lymphocytosis, CD8+ T lymphocytes, TG2, HLA-DQ.

1. Introduction

Celiac disease (CD) is an inflammatory disorder with autoimmune features that affects genetically predisposed individuals. It is triggered by the ingestion of gluten and other related proteins in barley, rye and possibly oats. The interaction of genetic and environmental factors leads to loss of gluten tolerance and the development of intestinal lesions characterised by increased number of lymphocytes in the epithelium and *lamina propria* (LP), villi loss, destruction of epithelial cells and mucosal remodelling, in addition to the presence of auto-antibodies to the enzyme tissue transglutaminase type 2 (TG2). The lesion and inflammatory bowel changes resolve when gluten is removed from the diet[1]. Patients with CD have also been found to have other changes that affect gut lumen digestion[2,3], the direct action of the gluten peptides on the epithelium and gluten protein transport across the epithelium to the LP mucosa[4,5].

The inappropriate immune response to gluten proteins observed in celiac patients involves both innate and adaptive immunity[6,7]. The key element in the pathogenesis of CD is the activation of the CD4+ T-cells in the LP mucosa after the recognition of TG2-deamidated gluten peptides bound to major histocompatibility complex class II (MHC-II) molecules, called HLA-II in humans. TG2 action consists of transforming certain glutamine residues into glutamic acid, resulting in the exposure of negative charges and enhanced affinity between HLA-DQ2 and/or HLA-DQ8 molecules and these peptide fragments that are resistant to proteolytic digestion by digestive enzymes. CD4+ T-cell activation triggers a pro-inflammatory Th1 cytokine response, with a predominance of interferon (IFN)-γ, other cytokines such as tumour necrosis factor [TNF]-α, interleukin [IL]-18 and IL-21, with the absence of IL-12, together with a proportionate decrease in the expression of immunoregulatory cytokines IL-10 and transforming growth factor (TGF)-β[8,9]. Accordingly, a lesion occurs in the mucosa of the proximal small intestine that causes malabsorption and reduced uptake of nutrients. The clinical and functional consequences vary depending on the degree of mucosal atrophy and transformation[10,11.]

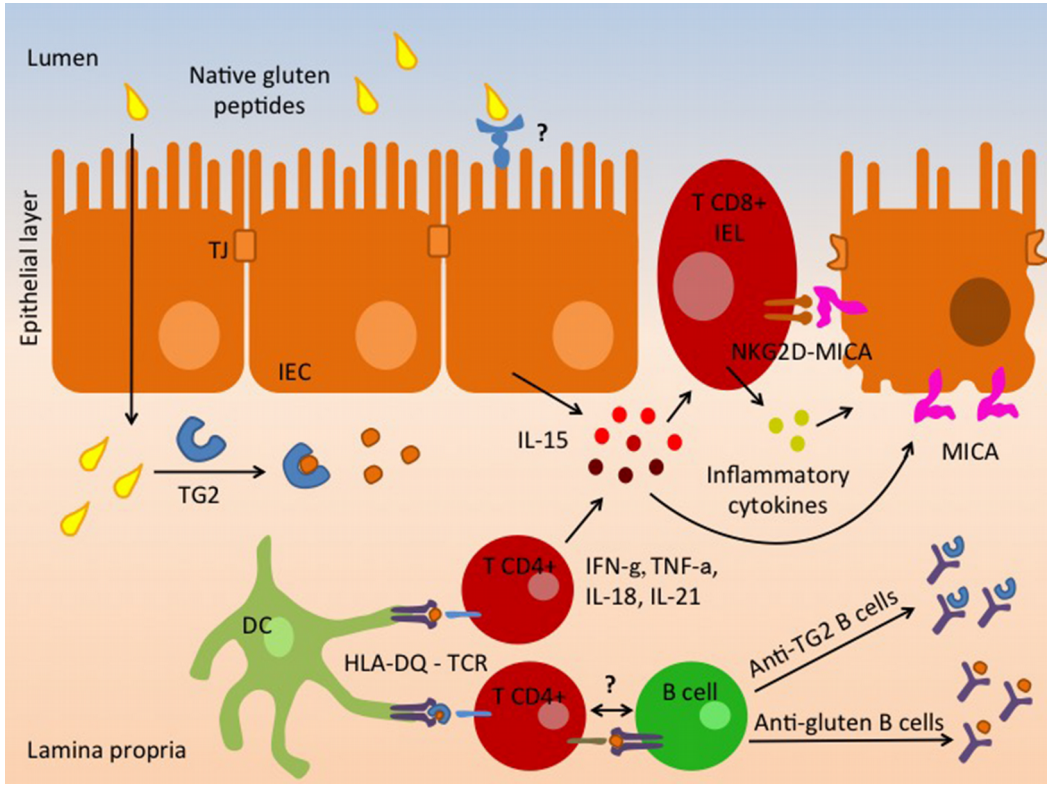

Figure 1. Immunological response to gluten peptides. TG2 modifies gluten peptides by deamidation, thus, HLA-DQ molecules are more likely to bind peptides and these are presented to LP T CD4+ lymphocytes for a longer period of time. T CD4+ lymphocytes are activated and committed to produce Th1 cytokines (IFN-γ, TNF-α, IL-18 and IL-21); they could also help to antibody synthesis by B cells. B cells differentiate into plasmatic cells and secrete specific antibodies against TG2 or gliadin. IECs can produce IL-15 after exposure to other gliadin peptides. Altogether, inflammatory cytokines induce IECs to express stress molecules (MICA), the ligand of NKG2D receptors on activated IELs. Finally, IELs destroy IECs, increasing intestinal permeability. IECs, intestinal epithelial cells; TJ, tight-junctions; TG2, tissue transglutaminase 2; DC, dendritic cell; IELs, intraepithelial lymphocytes; LP, lamina propria; TCR, T-cell receptor; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; IL, interleukin; MICA, MHC class I polypeptide-related sequence A; NKG2D, natural killer cell activating factor 2D.

However, the activation of a gluten-specific CD4+ T-cell response (adaptive immunity) is not sufficient to trigger the mucosal lesion that is characteristic of CD. Some gluten peptides, such as α-gliadin p31-43 and p31-49, induce changes in the innate immunity by acting directly on the epithelium, irrespective of the CD4+ T-cells and HLA-DQ2/DQ8 molecule restriction. This is manifested through an increase in expression of IL-15, cyclooxygenase (COX)-2 and CD25 and CD83 activation markers in the mononuclear cells of the LP[12]. In CD, intestinal intraepithelial lymphocytes in the intestine lose the expression of inhibitory CD94/NKG2A receptors, while increasing the expression of the activating receptors NKG2D and CD94/NKG2C. At the same time, epithelial cells increase the expression of ligands MIC and HLA- E, respectively[13,14]. Epithelial damage leads to increased gut permeability, which may permit the passage of larger, partly-digested gliadin peptides, thereby triggering a positive feedback loop that maintains the inflammatory reaction and intestinal lesion[1] (Figure 1).

2. Intestinal Epithelium

The intestinal epithelium lines the gastrointestinal tract. It is the body's largest mucosal surface and it separates the intestinal lumen from the underlying tissue, where the gut-associated lymphoid tissue (GALT) is located. This physical barrier consists of a single layer of polarised columnar cells (intestinal epithelial cells [IECs]), held together by tight junctions, which prevent the activation of systemic immune responses that can promote the progression of chronic infections and metabolic diseases[15]. Furthermore, the intestinal epithelium has self-protecting and self-regulating properties, not only because it controls new cell growth and old cell replacement, but also because some IECs are specialised to secrete mucus (which is mainly composed of MUC2 protein) and antimicrobial peptides[16], which regulate the levels of commensal and pathogenic bacteria, at the same time as limiting their resistance to an antimicrobial response[15].

The intestinal epithelium may also be directly involved in the immune response due to the ability of microfold cells (M cells) and goblet cells to sample luminal contents and regulate responses through membrane expression of different pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs)[17], which recognise common patterns in pathogenic micro-organisms; NOD-like receptors (NLRs)[18], which detect foreign molecules or cell damage markers in the cytosol; and RIG-I-like receptors (RLRs)[19], which recognise viral ribonucleic acid (RNA). However, the need to tolerate commensal micro-organisms and harmless dietary antigens means that immune responses depend more on the presence of danger signals in infection and stress induced by invasive microorganisms. The term vita-PAMP has been coined to refer to viability receptors and pathogen-associated molecular pattern receptors involved in these processes[20]. Under normal conditions (absence of infection and/or danger signals), the epithelium expresses a repertoire of molecules that maintain homeostasis in the intestinal mucosa. These molecules include thymic stromal lymphopoietin (TSLP)[21,22], TGF-β [21,22], retinoic acid[21], IL-25[23], B-cell activating factor (BAFF)[24] and the B-cell proliferation-inducing ligand (APRIL)[25].

2.1 Gluten Transport Across the Epithelium

Under normal conditions, proteins are mostly hydrolysed by gastric and pancreatic peptidases in the gastrointestinal tract, resulting in smaller peptides or isolated amino acids, which then cross the intestinal epithelium through hydrogen ion-dependent co-transport and sodium-coupled secondary active transport[26]. In CD, gluten proteins are not fully digested. Residual fragments are resistant to enzymatic proteolysis[3] and due to their size, they are not readily absorbed and accumulate in the gut lumen to cross the epithelium through four alternative routes: (1) the paracellular pathway, through the tight junctions between enterocytes[4]; (2) the transcellular pathway, by a mechanism involving enterocyte endocytosis and lysosome degradation during their transit to the basement membrane (a pathway that appears to be altered in CD because intact peptides are allowed to cross the

epithelium to reach the LP)[5,27-29]; (3) retrotranscytosis, a mechanism that depends on gliadin fragments binding to secretory immunoglobulin A1 (sIgA1-peptide) and then CD71, which is a transferrin receptor that is overexpressed in the apical region of the mucosa in active CD[30]; or (4) direct access through extensions of dendritic cells (DCs) derived from monocytes (phenotype CD11c^{low} F4/80+ CX3CR1^{high}), which are sandwiched between epithelial cells[31,32] (Figure 2).

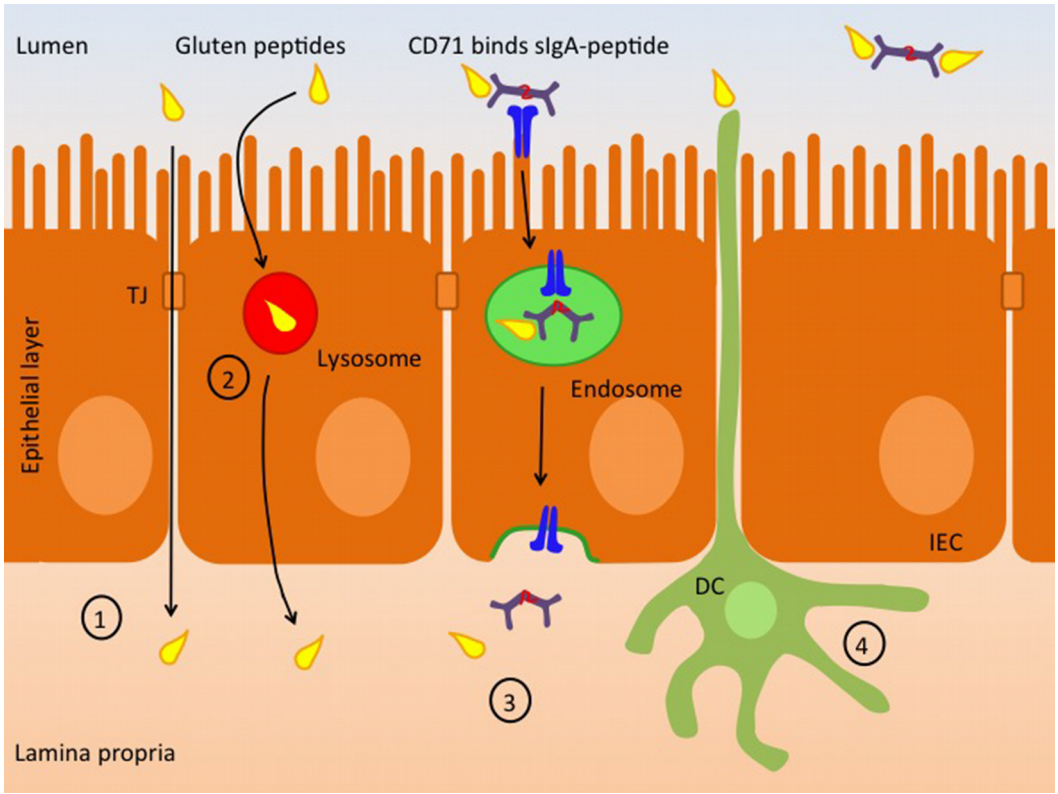

Figure 2. Gliadin transport across the epithelial layer. 1) Paracellular route: gluten cross the epithelial layer through the tight-junctions between enterocytes. 2) Transcellular route: Enterocytes perform endocytosis and degrade proteins in the lysosomes; this route is altered in coeliac disease patients. 3) Retrotranscytosis: secretory IgA binds gliadin peptides, by interaction with the transferrin receptor, CD71, in the apical zone of enterocytes. 4) Dendritic cells can sample antigens directly from the intestinal lumen through dendrites. TJ, tight-junctions; IEC, intestinal epithelial cell; DC, dendritic cell; sIgA, secretory immunoglobulin A.

The passage of gluten peptides across the epithelium not only affects intestinal barrier function, but also the profiles of gene expression and the phosphorylation cascades of metabolic processes, cell proliferation and adhesion, among others[33,34]. Using two *in vitro* culture models and gluten-sensitive macaques, it has been observed that the IFN-γ secreted by activated T-cells in the LP increases gut permeability and promotes immunoreactive α-gliadin (p57-89) peptide 33-mer passage across the epithelium[27,35,36].

Depending on the degree of intestinal inflammation, paracellular transport may also influence peptide transport across the epithelium, because gliadin is able to bind to chemokine receptor CXCR3 and this activates the MyD88 adapter, resulting in the release of zonulin, a protein that rearranges the cell cytoskeleton and modifies tight junctions[37,38]. An increase in mRNA expression of CXCL10 and CXCL11 has been observed in biopsies of patients with active phase CD, as well as elevated serum levels of CXCL10 in these patients[39]. The same study confirmed that CXCL10 is produced by plasma cells and enterocytes, and that its expression increases in the presence of IL-15. It also found increased CXCR3 expression in cells that infiltrate gut mucosa (T-cells in the epithelium and LP, and plasma cells)[39].

3. Adaptive Response to Gluten

Tissue transglutaminase (TG2) is the key component that explains the activation of the adaptive immune response to gluten. TG2 plays a fundamental role in the pathogenic mechanism because it induces enzymatic modification of immunodominant gliadin peptides, leading to the expression of negative charges in amino acid residues in certain positions, thereby increasing affinity for the HLA-DQ2/DQ8 molecules[40]. In addition, TG2 is the main self-antigen of the specific serum antibodies that are of great value in diagnosing CD[41] (Figure 2).

TG2 is found throughout the body. This enzyme catalyses the formation of covalent bonds between glutamine carboxyl groups and lysine amino groups.

It is involved in cell apoptosis because it prevents the exit of cytoplasmic material and, when secreted outside the cell, it collaborates in the remodelling of the extracellular matrix during tissue repair[42]. It is mostly located intracellularly, but appears extracellularly in response to tissue injury. In the normal gut, TG2 is expressed in subepithelial areas, in the LP mucosa and in connective tissue around the crypts; however, in CD, TG2 is also expressed on the apical surface of enterocytes, which may be a gluten-dependent effect[43]. In addition, this enzyme may play a role in the retrotranscytosis mechanism and in gliadin peptide passage through the epithelium, because it has been demonstrated that TG2 can interact with CD71 and sIgA on the apical surface of enterocytes in biopsies of patients with CD. Furthermore, TG2 inhibitors appear to block the transport of gliadin peptide p31-49 via this pathway[44].

TG2 effects on gluten peptides take place under non-physiological conditions (more donor than acceptor molecules) or at a pH of less than 7.0. In these situations, gliadin, which has a glutamine content of more than 30%, is susceptible to TG2-induced changes[42,45]. This is highly relevant in CD, because deamidated peptides have a higher affinity for HLA-DQ molecules, and HLA-DQ2 in particular[1,46,47]. The core structure of the HLA-DQ2 peptide pocket binds these negatively charged amino acids at positions P4, P6 and P7, whereas the HLA-DQ8 molecule does so more externally, at positions P1, P4 and P9[1,46,47]. The fact that the deamidated residues are positioned differently in each gluten peptide suggests that the specific immune response to gluten may be activated for several different pathogenic reasons. The TG2-induced enzymatic change that unmasks the most immunogenic epitopes of gliadin and other prolamines, or that leads to new epitopes due to interaction with proteins in the extracellular matrix may be responsible for the loss of tolerance and onset of autoimmune diseases[1].

However, although the deamidation of gluten peptides is not an absolute requirement, this reaction helps potentiate the adaptive response not only by increasing immunogenic peptide binding to HLA-DQ molecules, but also by improving their stimulatory capacity to present the antigen and promote the

gluten-specific CD4+ T-cell activation[48]. Another possibility is that TG2 activation is not a primary phenomenon in the immune response to gluten, but is triggered by the presence of native (not deamidated) gluten, causing a local inflammatory reaction capable of activating TG2 and initiating its exit from the cytosol. This would amplify the proinflammatory signal and therefore the immune response to gluten[29,49,50] (Figure 1). Furthermore, the activation of TG2 and other enzymes in the gut mucosa may be the result of other environmental factors such as viral infections[51], previous inflammatory reactions[52] or a tissue damage process[53].

3.1. T-Cell Response to Gluten

The adaptive response mediated by LP specific T-cells requires antigen presentation by antigen-presenting cells (APCs) that carry the HLA-DQ2/DQ8 restriction element. In the normal duodenum, APCs that express HLA-DQ molecules in the membrane may be macrophages (accounting for about 80%) of phenotypes CD163+CD11c-; or DCs (the remaining 20%), which are characterised by having a tolerogenic phenotype CD103+CD11c+. However, in CD, most DCs appear to come from the recruitment of peripheral blood monocytes with subsequent maturation *in situ* and they have a proinflammatory phenotype (CD14+ CD11c+). Conversely, there are reduced cell populations with tolerogenic phenotypes (CD103+CD11c+ DCs and CD163+CD11c- macrophages)[54]. The presence of elevated IFN-α levels in the mucosa of patients with CD may be a critical factor in proinflammatory DC differentiation[55], as is suggested by the onset of CD in patients with hepatitis C treated with IFN-α[56], and the predisposition for CD observed in individuals with Down's syndrome (chromosome 21 contains the gene that codes for the IFN-α receptor)[57].

In addition to their involvement in gliadin epitope presentation in the mesenteric lymph nodes, the HLA-DQ2 and DQ8 molecules can also present neo-epitopes and TG2-gluten-peptide complexes to CD4+ T-cells in the LP mucosa[58,59]. These activated lymphocytes trigger a pro-inflammatory response characterised by the secretion of Th1 cytokines with a predominance of IFN-γ,

as well as TNF-α, IL-18 and IL-21, together with a decrease in regulatory cytokines IL-10 and TGF-β[8,60,61]. This cytokine profile and the production of metalloproteinases that break down extracellular matrix proteins, may contribute to the typical lesions observed in CD[1] (Figure 1).

In the healthy gut, the epithelium and LP mucosa express TGF-β1, but in CD TGF-β1is decreased in the epithelial surface and there is loss of crypts, thus increasing the number of macrophages and activated T-cells in the adjacent LP, where there is no tissue damage[62]. Furthermore, IFN-α may be involved in Th1 cell differentiation by enhancing IFN-γ production. It has been observed that IFN-α administration in susceptible individuals can induce a Th1 response leading to hyperplastic lesions[55]. Although as yet unconfirmed, IFN-α may be secreted by activated fibroblasts and macrophages and even DCs in the LP mucosa after an episode of intestinal infection[63], and that it could contribute to intestinal inflammation by rescuing activated T-cells from apoptosis, maintaining memory T-cells once the stimulus has disappeared, and increasing expression of co-stimulatory molecules in local APCs[55]. IL-18 is a cytokine produced by macrophages, DCs and epithelial cells that acts on memory cells and effector cells, enhancing expression of IL-12- or IFN-α-dependent IFN-γ. Under normal conditions, the intestine expresses IL-18, but this expression increases in CD at the expense of its mature form, which requires the involvement of the IL-1β converting enzyme (ICE) or local proteinases[60] (Figure 1).

3.2. B-Cell Response To Gluten

CD is characterised by the presence of a variety of serum antibodies against self and foreign molecules[64]. In 1997, TG2 was identified as the main self-antigen with anti-endomysial antibody reactivity[41]. Anti-TG2 IgA antibodies are produced by plasma cells that infiltrate the LP mucosa of the duodenum[65]. In active phase CD, a two- to three-fold increase in these antibodies has been observed in the lesion area. TG2-specific IgA deposits in the gut have also been described in all disease stages[66], even before the onset of symptoms or before the pathological intestinal lesion appears[67].

B-cells are professional APCs that interact with the antigen through the BCR receptor. Under normal conditions, the gut contains few virgin or memory B-cells and the majority are plasmablasts or plasma cells in the LP with low expression of HLA-II molecules[68]. B-cells probably play a more important role as APCs in the mesenteric lymph nodes, where they may amplify T-cell response to gluten. Although TG2-specific T-cells have not yet been identified, gluten-specific CD4+ T-cells may assist in B-cell differentiation into plasma cells that produce anti-TG2 IgA and IgG antibodies, which disappear when gluten is removed from the diet. One possible explanation is based on the ability of B-cells to act as APCs, as they may present TG2-gluten-peptide complexes via HLA-DQ to gluten-specific T-cells, which in turn would receive the necessary assistance for antibody synthesis[69]. Furthermore, anti-TG2 antibodies may amplify the inflammatory response by increasing gluten absorption and inducing the activation of Fc receptors on local granulocytes[30] (Figure 1).

In CD, other serum auto-antibodies have also been described that present specifically, for example, to actin, different types of collagen, members of the transglutaminase family (TG3, TG6) and clotting factor XIII[70]. It should be noted that IgA/TG3 complexes have been found in the skin of patients with dermatitis herpetiformis[71,72] and the presence of antibodies to neuronal enzyme TG6 has been associated with gluten ataxia[73]. These findings could explain how the extraintestinal manifestations of CD develop.

4. Innate Response to Gluten

Several gliadin peptides have been described with innate response stimulatory properties that act on IECs and DCs, although clarification is needed regarding how they interact with the epithelium and which signalling pathways they activate. These peptides are not recognised by gluten-specific CD4+ T-cells in the context of HLA-DQ2/DQ8 molecules (such as α-gliadin peptides p31-43 and p31-49), which could alter protein processing and intracellular trafficking in IECs and/or activate a stress pathway that has yet

to be identified[5,28,34]. Increased expression of IL-15, cyclooxygenase (COX)-2 and CD25 and CD83 activation markers in the mononuclear cells of the LP has been described using *ex vivo* culture models from biopsies of patients with CD[12]. An increase has also been observed in the expression of the molecules related to the MHC-class I (MIC) polypeptide in IECs[74]. Moreover, some of these gliadin peptides can behave similarly to epidermal growth factor (EGF) by delaying EGF receptor (EGFR) endocytosis and thus prolonging its activation[75]. Although it has been shown that patients with CD also express EGFR and have an activated EGFR signalling pathway, both EGFR and its signalling pathway are constitutively altered (through enhanced phosphorylation of the ERK kinase), i.e., independently of gluten ingestion, which could explain the highly specific damage that gliadin exerts in the epithelium[34]. Apart from these peptides, others may activate DCs by interacting with TLR4[76], as well as stabilising the non-classical MHC molecule HLA-E in the membrane[77], or they could increase gut permeability after binding to chemokine receptor CXCR3[37], an effect that could also be due to the weakening of the tight junctions between the enterocytes[4].

4.1. Role of the Intraepithelial Lymphocytes

Intraepithelial lymphocytes (IELs) form a heterogeneous population located in the basolateral zone of enterocytes, with varying distribution along the intestine. IELs are divided into two groups, natural IELs (T TCR$\alpha\beta$ and T TCR$\gamma\delta$) and induced IELs (T TCR$\alpha\beta$ CD4+ and T TCR$\alpha\beta$ CD8$\alpha\beta$+), defined by their activation mechanisms and the antigens that they recognise[1, 78] (Table 1). The functions of IELs are to defend against infectious agents, memory acquisition and to control responses to innocuous factors, as well as to maintain epithelial integrity[78] (Table 1).

Despite their tolerogenic and protective role, IELs can exacerbate the severity of pathologies such as CD and inflammatory bowel disease[78-80]. In CD, a correlation has been described between the number of TCR$\alpha\beta$ T-cells and villous atrophy[81]. It has also been observed that IELs undergo transformation, acquiring a cytotoxic phenotype[82]. There is also an increased proportion of

IELs with TCR$\gamma\delta$+, which is maintained even with a gluten-free diet, and this is one of the most characteristic changes of CD[83-85]. Natural IELs share some of the preactivation characteristics of CD4+ T-cells that are present in blood and in the LP mucosa and, although they have a higher activation threshold than the latter, in CD they could actually be activated in the gut in response to proinflammatory molecules, and even become autoreactive cells[78,86,87]. Under these conditions, cytotoxic IELs interact through the innate molecules NKG2D and CD94 with their corresponding ligands, MICA and HLA-E, expressed in the IECs[14]. Intraepithelial lymphocytosis occurs as a result, with enterocyte destruction and other alterations such as villous atrophy and crypt hyperplasia[12,78] (Figure 1).

Table 1. Classification of immune system cells that may be involved in the innate or nonspecific response to gluten in the epithelium. IELs, intraepithelial lymphocytes; NK, natural killer; NKT, NK T-cell; TCR, T-cell receptor; MHC, major histocompatibility complex; N/A, not applicable.

	TCR	Restriction	Differentiation	Functions
Natural IELs	$\alpha\beta$ or $\gamma\delta$	MHC	Thymus	Tolerance and protection against diet and microbiota in early life and later protection.
Induced IELs	$\alpha\beta$	MHC	Peripheral	Adaptation to diet and to microbiota: defence, memory and maintenance of integrity. Prevention of exaggerated responses to innocuous antigens.
NK cells	N/A	N/A	Bone marrow, lymph nodes, spleen, tonsils, thymus.	Response to viruses and tumour cells.
NKT cells	Semi-invariant (vα24β11 and others)	CD1d	Peripheral	Protection against tumour cells and autoimmune diseases. Oral tolerance.

Other cell populations that might be involved in the pathogenesis of CD are natural killer (NK) cells and NKT cells[88]. NK cells are involved in responses to virally infected cells and tumours, independently of MHC and antibody formation[89]. A reduction in the number of NK cells has been observed in patients with active CD compared with a control group or patients on a gluten-free diet[85]. Unlike NK cells, NKT cells are a heterogeneous group that have the TCR complex in the membrane, as well as CD3 and Ig receptors and, in some subsets, they also express a semi-invariant TCR receptor (including TCR vα24β11)[90]. They can be activated through TCRs, but independently of MHC[90], and they induce epithelial IL-10 production[91]. However, the role of NKT cells in CD and other diseases is still not fully understood, since these cells can produce cytokines of any pattern, including regulatory ones[92].

4.2. Role of Interleukin (IL)-15 and IL-21

IL-15 is the main mediator in the gluten-induced innate immune response in the gut. This pleiotropic cytokine binds to its specific receptor, related to the IL-2 receptor, by a high-affinity α chain (IL-15Rα). Binding between IL-15 and IL-15Rα, which is necessary for cytokine function, takes place before IL-15 expression in the membrane[93], and is one of the many processes involved in the complex regulation of IL-15[94]. In CD, IL-15 is produced in large quantities by the IECs in response to gluten, but also by mononuclear cells, macrophages and DCs in the LP mucosa[95]. In this context, IL-15 induces IEL reprogramming[13], as well as increasing the expression of MICA stress molecules in enterocytes[96], DC activation[97,98] and positive modulation of IL-21, a cytokine that also plays an important role in the pathogenesis of CD[99,100] (Figure 1). It has been observed that gliadin peptides increase the release of IL-15 in the gut mucosa not only in patients with CD, but also in non-celiac individuals. However, only the mucosa of patients with CD shows increased expression of the IL-15Rα receptor, which could confer these patients a lower threshold of response to IL-15[101].

The finding of an association between the *IL2/IL21* gene region and susceptibility to CD has focused interest on IL-21, a cytokine that is a key determinant in the onset and persistence of CD gut lesions[100]. Furthermore, an increase in IL-21 expression has been observed in biopsies of patients with active CD[61]. IL-21 production is located in lymphocytes in both LP mucosa and the epithelium alike and it is sometimes co-expressed with IFN-γ. Part of this production is also attributed to NKT cells[102]. As mentioned earlier, IL-21 expression is induced by IL-15[99] and both appear to be responsible for blocking the regulatory mechanisms in CD[103-105]. Although this cytokine is produced by Th17 cells, others that follow this pattern are not found to be increased in CD (except in a small group of adults with CD)[106,107].

The two cytokines, IL-15 and IL-21, can act together through different signalling pathways to enhance CD4+ T-cell resistance to regulatory T cells (Treg) in gut mucosa in patients with CD. It is known that IL-15 can interfere with the TGF-β1/Smad3[104] and PI3K[103] anti-inflammatory signals, but the mechanisms of action of IL-21 has yet to be clarified[105]. Finally, IL-15 may also play an important role in the development of refractory CD (RCD) and enteropathy-associated T-cell lymphoma (EATL), by inducing proliferation and resistance to apoptosis of cytotoxic IELs[95].

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