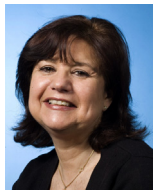
Local Communication Among Mucosal Immune Cells in Patients With Celiac Disease



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In patients with celiac disease, gluten consumption causes inflammation of the duodenum, and, to a lesser extent, the proximal jejunum. Immune-dominant gluten peptides are modified by the enzyme TG2, leading to their high-affinity binding to HLA-DQ2 or HLA-DQ8 molecules (present in people with a predisposition to celiac disease). Gluten peptide−loaded HLA-DQ2 or HLA-DQ8 molecules are recognized by highly conserved receptors on CD4$^+$ T cells in the lamina propria. B cells specific for TG2 and modified gluten peptides are also abundant in the lamina propria of patients with celiac disease. In the epithelium, interleukin-15 activates intraepithelial lymphocytes that promote destruction of epithelial cells. However, it is not clear how the immune responses in the lamina propria and the epithelium, separated by a basement membrane, are linked. We review the immune processes that occur in the lamina propria and their potential effects on epithelial pathology in celiac disease.

Keywords: Celiac Disease; HLA; T Cell; CD4; Intraepithelial Lymphocyte; Intestinal Epithelial Cell; Immunology.

Genetic association studies indicate that most features of celiac disease are ultimately caused by CD4$^+$ T cells.[1–4] The *HLA-DQA1* and *HLA-DQB1* loci, encoding α and β chains of the HLA-DQ proteins, are the main risk factors for the disease.[5,6] Alleles encoding HLA-DQ2.5, and, to a lesser extent, those encoding HLA-DQ8, are strongly associated with disease (Table 1). Unlike other HLA-DQ variants, these HLA-DQ molecules bind an array of gluten peptides with high affinities and slow off rates,[7,8] leading to a CD4$^+$ T-cell response. Genetic studies have also associated 39 non-HLA loci with celiac disease; most are single nucleotide polymorphisms (SNPs) in non-coding regions thought to be involved in gene regulation. Several disease-associated SNPs lie near genes encoding proteins that regulate T-cell function, including *SH2B3, CTLA4, CD28, ICOS, IL2,* and *IL21* (Table 1).

Genetic association studies also suggest that the CD4$^+$ T cells are of the T helper 1 (Th1) type, as many disease-associated SNPs are located near genes that regulate Th1 responses. These responses are mediated by cytokines, such as interferon (IFN) gamma, interleukin (IL)12, and IL18. For example, SNPs near the *IL12A*, *IL18R1*, and *IL18RAP* genes are associated with celiac disease (Table 1). However, the risk allele near *IL18R1* and *IL18RAP* reduces expression of these genes,[9] and is therefore expected to reduce responses to IL18. Although there is no evidence for direct involvement of the *IFNG* locus (which encodes IFN gamma), analyses that combined celiac disease-associated SNPs with mapping of nearby expression Quantitative Trait Loci (cis-eQTL) revealed an interesting connection between susceptibility genes and IFN gamma.[9] Of note, these analyses also indicated that B cells are involved in pathogenesis.[9] In short, genetic association studies indicate the involvement of HLA-DQ2- (and/or HLA-DQ8)-restricted CD4$^+$ T cells, Th1-type cytokines, and B cells in celiac disease.

Immune Responses in the Lamina Propria

The cellular events observed in lamina propria tissues of patients with celiac disease support findings from genetic association studies. First, CD4$^+$ T cells that recognize gluten can be isolated from biopsies from patients, but not from tissues of individuals without celiac disease.[10] These CD4$^+$ T cells recognize gluten peptides bound to HLA-DQ2.5 or

Abbreviations used in this paper: IEC, intestinal epithelial cells; IEL, intraepithelial lymphocytes; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; MMP, matrix metallopeptidase; NK, natural killer; SNP, single nucleotide polymorphism; TCR, T-cell receptor; TG2, transglutaminase; Th1, T helper 1; TLR4, Toll-like receptor 4.

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Table 1. Top 15 Loci Associated with Celiac Disease[1–9]

Chromosome	Candidate gene	Function	Estimated odds ratio
6p21	*HLA*	Antigen presentation	6.23
4q27	*IL2, IL21*	Lymphocyte activation and proliferation	1.41
3q25-26	*IL12A*	Th1 differentiation	1.36
3q28	*LPP*	Cell shape or maintenance?	1.32
1q31	*RGS1*	GTPase-activating protein	1.30
6q23	*TNFAIP3*	Inhibits TNF signaling	1.29
1q24	*FASLG, TNFSF18*	Apoptosis induction	1.28
2q32	*STAT4*	Cytokine signal transduction	1.27
6q22	*PTPRK*	Protein tyrosine phosphatase	1.21
3p21	*CCR1-3, LTF*	Chemokines	1.20
2q11-12	*IL18R1, IL18RAP*	Th1 differentiation	1.20
12q24	*SH2B3, ATXN2*	Lymphocyte signaling	1.19
2q33	*CD28,CTLA4, ICOS*	Lymphocyte co-stimulation	1.19
Xq28	*HCFC1, TMEM187, IRAK1*	IRAK1: TLR and IL1R signaling	1.18
7p14	*ELMO1*	Phagocytosis	1.18

HLA-DQ8.[11,12] HLA-DQ2.2, which is highly similar to HLA-DQ2.5, can bind and present a smaller subset of gluten peptides that have a higher off rate. HLA-DQ2.2 therefore does not increase risk for celiac disease unless it is co-expressed with HLA-DQ2.5. Importantly, tissue transglutaminase (TG2), an enzyme released upon tissue damage, converts glutamine residues in gluten peptides into glutamic acid (a process termed *deamidation*), which greatly increases binding of such peptides to HLA-DQ2.5 and HLA-DQ8, thereby amplifying the T-cell response.[13–15] Responding $CD4^+$ T cells proliferate and produce cytokines such as IFN gamma, IL2, and IL21, but not IL17 (Figure 1).[16–18] These events can take place very early in life, especially in children homozygous for HLA-DQ2.5.[19]

In addition, most patients produce antibodies specific for deamidated gliadin and TG2. The duodenal lamina propria contains a large number of plasma B cells; a large proportion of these produce TG2-specific IgA or deamidated gliadin-specific IgA.[20,21] In line with this, the presence of TG2-specific antibodies in serum is the most specific and sensitive diagnostic marker of active celiac disease.[22–25] Because TG2-specific antibodies are found only in individuals carrying HLA-DQ2 or HLA-DQ8,[26] and because serum antibody levels decrease in individuals on gluten-free diets, antibody production depends on the gluten-specific $CD4^+$ T-cell response. These $CD4^+$ T cells are able to provide help to B cells expressing antigenic HLA-DQ-gluten complexes. In the case of TG2-specific B cells, this would rely on the crosslinking of TG2 to gluten, allowing TG2-specific B cells to internalize gluten and generate complexes of gluten peptides and HLA-DQ on their cell surface.

In short, genetic and immune analyses of patients with celiac disease each support the concept that a gluten-specific $CD4^+$ T-cell response in the duodenal lamina propria is a key step in pathogenesis, regulating the local TG2-specific and deamidated gliadin-specific B-cell response. Intriguingly, the T- and B-cell responses are characterized by heavily biased T-cell receptor (TCR) and B-cell receptor repertoires. Remarkably large fractions of T cells specific for immunodominant HLA-DQ2 and HLA-DQ8 epitopes express TRBV7-2[27,28] and TRBV9,[29] respectively. Furthermore, the CDR3 regions of these TCRs almost invariably encode an arginine, either in the α or in the β chain.[27–30]

Structural studies have shown that specific amino acids in TRBV9 and TRBV7-2, together with conserved arginines in the CDR3, regulate the interaction with HLA-DQ−gluten complexes, and that the TCRs have a relatively high affinity for their cognate ligand.[29,30] Similarly, B cells interact with TG2 via restricted VH and VL chain combinations.[21] These IgA antibodies have high affinities for TG2, despite a limited degree of somatic hypermutation,[20] a programmed process of mutation affecting the variable regions of immunoglobulin genes that allows the selection of B cells with high affinity for antigen Apparently, a high-affinity germline-encoded antibody repertoire specific for TG2 and gluten exists.

It is important to note that celiac disease is diagnosed by the presence of TG2-specific antibodies and/or morphologic features of the small intestine caused by inflammation, after establishment of the disease-associated T- and B-cell responses. It is therefore likely that prolonged exposure to gluten (before diagnosis) selects for T and B cells with the highest affinity receptors for antigen. It is tempting to speculate that celiac disease can develop only when high-affinity gluten-specific TCRs and antibodies are present, and that celiac disease might be treated by eliminating these T cells.

Immune Responses in the Epithelium

Intestinal Epithelial Cells

The duodenal epithelial compartment and architecture are altered in patients with active celiac disease. These changes range from increased numbers of intraepithelial