




Celiac Disease Autoimmunity

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Abstract

Celiac disease is an autoimmune condition triggered by the ingestion of gluten, the protein fraction of wheat, barley and rye. It is not simply an intestinal disease; it is multifactorial caused by many different genetic factors acting together with non-genetic causes. Similar to other autoimmune diseases, celiac disease is a polygenic disorder for which the major histocompatibility complex locus is the most important genetic factor, and is the result of an immune response to self-antigens leading to tissue destruction and the autoantibodies production. Celiac disease exemplifies how an illness can have autoimmune-like features having to be driven by exogenous antigen and how can be reasonably considered as a model of organ-specific autoimmunity.

Keywords Celiac disease · Autoimmunity · Immune tolerance · Autoantibodies

Celiac Disease as an Autoimmune Disorder

Celiac disease (CD) is one of the best-understood immune-related diseases. CD is frequent, with a prevalence of approximately 1:100, and it occurs selectively in individuals expressing HLA-DQ2 or HLA-DQ8. The prevalence of CD is underestimated, as not all cases of CD are symptomatic and thus go undiagnosed (Catassi and Fasano 2008) Celiac disease has many features in common with autoimmune disease.

In CD, there is a massive, pro-inflammatory and pathogenic immune response towards certain parts of gluten and the intestinal tissue itself, resulting in structural changes. The pathogenesis of CD includes the potent and pathogenic CD4⁺ T-cell response towards post-translationally modified gluten and the highly disease-specific B-cell responses towards deamidated gluten and the self-protein transglutaminase 2 (TG2) (Fig. 1).

It is important to consider how epithelial cell stress together with pro-inflammatory adaptive immunity causes cytotoxic T-cell-mediated tissue destruction in CD. The

HLA-DQ molecules predispose to disease by preferential presentation of gluten antigens to CD4⁺ T cells (Bodd et al. 2012; Lundin et al. 1993; Torres et al. 2015). Although these predisposing HLA haplotypes are necessary for disease development, they are not sufficient, as they are highly prevalent in the general population.

The genetic predisposition to CD development has been studied by genome-wide association studies, which have found risk variants in the HLA region, especially HLA-DQ2.5, as well as HLA-DQ2.2 or HLA-DQ8 (Vader et al. 2003; Van Heel et al. 2007). Thirty-nine additional, non-HLA loci have been associated with CD (Hunt et al. 2008; Trynka et al. 2011). Of these genes, many are related to immunity, especially with T-cell and B-cell function. These non-HLA genes may be important determinants of disease susceptibility, as indirectly shown by the high disease concordance rate in monozygotic twins (70%) compared with only 30% in HLA-identical twins (Houlston and Ford 1996).

In general, the similarities between autoimmune diseases are multifaceted, with shared genetic, environmental and immunological factors that may explain the comorbidity. Novel theories have been put forth to explain the possible associations between autoimmune diseases, including the human gut microbiome's influence on the gut-immune system axis, new shared immunological markers, the discovery of common genetic factors, and environmental factors (Wu and Wu 2012; Zhernakova et al. 2009).

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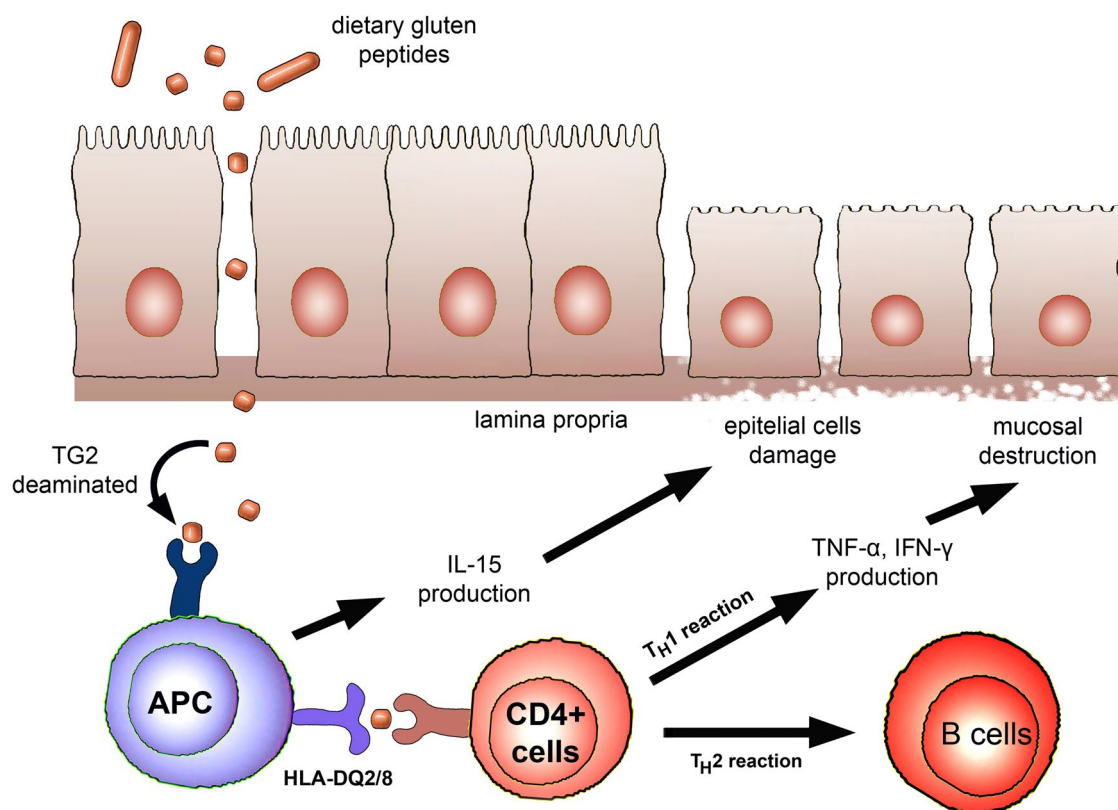


Fig. 1 Schematic representation of celiac disease pathogenesis. Gluten peptides can be transported across the intestinal epithelium. Deamidation by TG2 leads to the production of deamidated gluten that are taken up and presented by antigen-presenting cells (APCs) of HLA-DQ2/HLA-DQ8 molecules. This presentation leads to activated gluten-reactive CD4⁺ Th1 cells that produce high levels of pro-inflammatory cytokines, with aTh1 cytokine pattern dominated by

IFN- γ . Activated CD4⁺ T cells drive the activation and clonal expansion of B cells, which differentiate into plasma cells and produce anti-gliadin and anti-TG antibodies. Gluten peptides induce epithelial and APC cells to secrete IL-15, resulting in an increase in the number of IELs. IFN- γ production, and stimulating cytotoxic effects on epithelial cells (Torres et al. 2015). Re-drawn of Sollid and Jabri (2013)

CD is an excellent model for studying the contribution of genetic factors to immune-related disorders, because (1) the environmental triggering factor is known (gluten); (2) as in other autoimmune diseases, specific HLA types (HLA-DQA1 and HLA-DQB1) are critically involved; (3) there is involvement of non-HLA disease-susceptibility loci, many of which are shared with other autoimmune diseases; (4) there is an elevated incidence of other immune-related diseases both in family members and in CD individuals; and (5) both the innate and the adaptive immune responses play a role in CD (Kumar et al. 2012; Zhernakova et al. 2009).

Autoimmune Features of Celiac Disease

Celiac disease is a unique autoimmune disorder in that the key genetic components (HLA class II genes DQ2 and/or DQ8) are present in almost all patients, the autoantigen is known (tissue transglutaminase), and, most importantly, the environmental trigger is known (gluten) (Lundin et al. 1993).

Gluten is not a pathogen and should not be perceived as immunogenic. Some undigested gluten peptides from *Triticum* species, mainly the 33-mer (LQLQPF-PQPQLPYPQPQLPYPQPQLPYPQPQPF, P57-P89, from α -2 gliadin) and the 25-mer (LGQQPFP-PQQPYPQPQPFPSQQPY, P31-P55 from α -gliadin), have cytotoxic activity or immune-mediated activity (Ciccocioppo et al. 2005). Human TG2 deamidates the 33-mer peptide, increasing its immunogenicity. This enzyme converts glutamine residues into glutamic acid, which results in higher affinity of the peptides to HLA-DQ2/DQ8 molecules and subsequent induction of gluten-specific CD4⁺ T-cell responses in the intestine of CD patients due to a complex interplay between innate and adaptive immune responses to ingested gluten (Barone et al. 2014; Jabri et al. 2005). The adaptive immune response to gluten appears to act in synergy with epithelial cell stress to allow intraepithelial T cells to induce villous atrophy in CD patients.

Gluten peptides, in contrast to other food peptides, are excellent substrates for TG2, and the gluten peptides with

multiple B- and T-cell epitopes can be added onto the surface of multimeric complexes of TG2. CD4⁺ gluten-specific T cells provide help to activate B cells to produce anti-gluten and anti-TG2 antibodies in the plasma cells, which may serve as primary antigen-presenting cells (Lundin et al. 1993; Molberg et al. 1997). This could explain why hypersensitivity to gluten, but not to other food antigens, is established. It is important to understand how gluten-specific HLA-DQ-restricted T cells become pro-inflammatory and why this occurs only in CD patients and not in healthy patients.

It is believed that the interferon (IFN)- γ production from these gluten-specific T cells may be the main cause of mucosal intestinal lesions (Mazzarella et al. 2008). Furthermore, shifts in intestinal permeability, secondary to changes in tight junctions or in food-antigen processing, have been associated with a loss of gluten tolerance (Lerner and Matthias 2015a).

Autoantibodies

TG2 is a deamidating enzyme that can increase the immunostimulatory effect of gluten and is a target autoantigen in the immune response (Di Sabatino et al. 2012). Autoantibodies to TG2 are usually used for diagnosis, showing high CD specificity and sensitivity (Sollid and Jabri 2011). The celiac disease-specific TG2-targeted autoantibodies are deposited in the small-bowel mucosa as well as in other tissues, and interestingly, extra-intestinal manifestations of the disease involving these particular tissues have been reported (Lindfors et al. 2010). As the TG2-targeted autoantibodies have experimentally been shown to modulate the function of different cell types *in vitro* similarly to what has been reported to occur in untreated celiac disease, they could constitute an important contribution to disease progression. So, subjects with negative serum TG2-specific antibodies still seem to produce these antibodies locally, as reflected by small-intestine deposits (Maglio et al. 2011). Antibodies to TG2 include IgA and IgG isotypes. IgA antibodies are more specific than IgG antibodies, and they are produced primarily in the mucosa of the intestine (Marzari et al. 2001). TG2 is involved in the formation of active transforming growth factor (TGF)- β by the crosslinking of the TGF- β binding protein and participates in the motility, as well as attachment, of fibroblasts and monocytes through interactions with fibronectin and integrins, causing CD villous atrophy (Aki-mov and Belkin 2001). Anti-TG2 IgA deposits are detectable in intestinal tissue before the development of overt CD, suggesting that antibody production occurs early in the disease alongside the gluten-specific T-cell response.

Anti-TG2 antibodies may play a part in certain non-intestinal symptoms of CD by interacting with TG2, in addition to cross-reacting with other transglutaminases. In this

sense, deposits of anti-transglutaminase antibody have been detected in the brainstem and cerebellum of a patient showing cerebellar ataxia and gluten sensitivity and in certain idiopathic, neurological, and psychiatric disorders (Hadji-vassiliou et al. 2006). In addition, anti-gliadin antibodies reportedly bind to neural cells and cross-react specifically with synapsin I (Alaedini et al. 2007). Immune reactivity to other autoantigens, including transglutaminase 3, actin, ganglioside, collagen, calreticulin and zonulin, has also been reported in CD (Alaedini and Green 2008). The clinical significance of these antibodies is not known, although some may be associated with specific clinical presentations or extra-intestinal manifestations of celiac disease.

Autoreactive Intraepithelial Lymphocytes

Dysregulated activation of intraepithelial lymphocytes (IELs) is a characteristic of CD that is implicated in the development of villous atrophy and epithelial cell injury. IELs constitute a population of antigen presentation like “innate” T cells that reside between enterocytes in the intestinal epithelium and can be activated by innate signals, acquiring a natural killer-like phenotype and cytotoxic effector functions (Jabri et al. 2000).

CD is characterized (1) by the presence of gluten-specific CD4⁺ T cells in the lamina propria and (2) by a prominent intraepithelial T-cell infiltration in the epithelial layer that promotes the development of small-intestine inflammation. The exact role of CD4⁺ T cells in celiac disease is still not clear, so the excessive production of IFN- γ may enhance HLA-E and MHC-I related chain (MIC) proteins expression by intestinal epithelial cells and promote cytotoxic responses by CD8 $\alpha\beta$ ⁺- and/or CD4⁺TCR $\alpha\beta$ ⁺-induced IELs through the innate CD94-NKG2D pathway (Sollid 2000). The upregulation of these NKG2 receptors seems to be driven by interleukin (IL)-15, which is expressed by CD enterocytes (Mention et al. 2003; Roberts et al. 2001). IL-15 seems to play a critical role in the expansion of IELs and in the induction of MIC molecules on intestinal epithelial cells (Hü et al. 2004).

IELs bearing the $\gamma\delta$ T-cell receptor (TCR) are more abundant in the small intestinal mucosa of patients with CD compared with healthy individuals. Increased numbers of TCR $\gamma\delta$ ⁺ IELs have also been observed in the small intestinal mucosa of CD patients with latent CD, or those on gluten-free diet (GFD) and in some first-degree relatives of CD patients with HLA-DQ2 (Holm et al. 1992). Additionally, the increase of intraepithelial TCR $\gamma\delta$ ⁺ T cells is more pronounced in children than in adults with active CD (Savilahti et al. 1997). It has been proposed that the intraepithelial infiltration of TCR $\gamma\delta$ ⁺ T cells could be used as a diagnostic marker to identify early stage CD (Jarvinen et al. 2003) or to predict the risk of CD development among at-risk subjects

with positive CD-specific autoantibodies and normal intestinal biopsy (Paparo et al. 2005).

Similar to gluten-reactive T cells, gluten-specific B cells preferentially recognize deamidated gluten peptides (Iversen et al. 2015). Close interactions between CD4⁺ T cells and B cells may be important for amplifying the inflammatory response, as B cells can present antigen to T cells and they in turn can provide help for autoantibody production. Gluten-reactive CD4⁺ T cells provide help to both TG2-reactive B cells and deamidated gluten-reactive B cells. TG2-gluten complexes are internalized by TG2-reactive B cells through B-cell receptor-mediated endocytosis. After internalization, deamidated gluten peptides can be released and can bind to HLA-DQ2 or HLA-DQ8 to be presented to T cells. Cooperation between gluten-reactive T-cell and B-cell results in activation of both the T cells and B cells, leading the B cells to differentiate into antibody-producing plasma cells and the T cells to proliferate and clonally expand.

Genetics of Celiac Disease

The genetics of autoimmune diseases include the intracellular signaling that drives the activation of T and B cells, signaling by cytokines and their receptors, and pathways that mediate innate immunity and microbial responses, such as Toll-like receptors and nucleotide-binding oligomerization domain receptors (Sollid and Jabri 2013).

Similar to other autoimmune diseases, celiac disease is a polygenic disorder for which the MHC locus is the single most important genetic factor. The MHC locus accounts for 40–50% of the genetic variance in the disease. The great majority of patients carry a particular variant of HLA-DQ2 (DQA1*05:01, DQB1*02:01; also known as DQ2.5). Those who are not DQ2.5 are almost all HLA-DQ8 (DQA1*03, DQB1*03:02) or carry another variant of HLA-DQ2 (DQA1*02:01, DQB1:02:02; also known as DQ2.2) (Megiorni and Pizzuti 2012; Smyth et al. 2008; Sollid and Lie 2005). HLA can be considered a necessary, but not sufficient, factor for disease development. HLA testing is much used in the clinic to exclude the diagnosis of celiac disease.

Many of the susceptibility loci for celiac disease are shared with those for other autoimmune diseases, such as type 1 diabetes (T1D) and rheumatoid arthritis (RA) (Gutierrez-Achury et al. 2011; Zhernakova et al. 2011), most of which encode genes involved in inflammatory and immune responses (Kumar et al. 2012). Some of them may act as regulators of proliferation and activity of T lymphocytes (*CTLA-4*, *ICOSLG*, and *IL18RAP*). Other genes have also been implicated in the activity of nuclear factor kappa B (REL, UBE2LE) and in signaling processes (SOCS1, SH2B3) or in more than one function, as in the activities of T lymphocytes and cytokines (IL2, IL21, IL12A and IL23R)

(Anaya et al. 2012; Larizza et al. 2012). The HLA locus still presents the most important association in individuals affected by more than one autoimmune disorder (double autoimmunity), and that carry more of the genetic risk markers that are shared between the two diseases independently. In this sense, the *CTLA4* and *IL2RA* loci were more strongly associated with double autoimmunity than with either T1D or CD alone. HLA analyses indicated that the T1D high-risk genotype, *DQ2.5/DQ8*, provided the highest risk for developing double autoimmunity.

The HLA and non-HLA loci can be used as stratification factors in the construction of risk models to predict double autoimmunity appearance and for pathway enrichment analysis to enhance our understanding of the pathophysiology involved in the development of both autoimmune diseases.

Environmental Factors in Celiac Disease

Gluten is the environmental factor required to trigger the disease, but other factors may be involved in a model of a complex multifactorial disease. The intestinal infections, the amount and quality of ingested gluten, the composition of intestinal microbiota, and infant-feeding practices are all possible triggers of the switch from tolerance to an immune response to gluten (Prescott et al. 2008). In this sense, two randomized controlled trials have been performed to clarify the relationship between the age at which gluten is introduced to a child's diet and the risk of CD, showing that timing of gluten introduction does not modify the risk of CD (Lionetti et al. 2014; Vriezinga et al. 2014). Also showed that breastfeeding duration or breastfeeding during gluten introduction have no effect on the risk of CD.

The study of Bouziat et al. (2017) provides support for the concept that viruses can disrupt intestinal immune homeostasis and initiate loss of oral tolerance and Th1 immunity to dietary antigen. The authors propose that viruses elicit pro-inflammatory immune responses to dietary antigen altering immune homeostasis and in particular outfit dendritic cells (DCs) with pro-inflammatory properties at sites, where oral tolerance is induced (Bouziat et al. 2017). Although reovirus infections may trigger development of Th1 immunity to gluten as well as activation of TG2, additional events will be required for induction of anti-TG2 antibodies and villous atrophy.

Many of the implicated environmental factors may act by altering the composition of the microbiome (Verdu et al. 2015). Epidemiological data support an association between dysbiosis and increased risk of CD but there is little understanding of how it might influence gluten-specific immunity in vivo. In vitro data supports the influence of microbes on immune responses to gluten, including roles in modifying T regulatory cells induction, epithelial cell stress and IEL

activation, phenotypic and functional maturation of DCs and pro-inflammatory cytokine production (Verdu et al. 2015).

The Human Microbiome as a Modulator of Autoimmunity in Celiac Disease

The high increase in the incidence of autoimmune disorders cannot be explained only by genetic drift and is thought to be the result of changes in the environment.

The microbiota plays an important role in immune maturation and homeostasis; alterations in microbial composition or colonization may influence intestinal homeostasis and, consequently, immune responses to food antigens.

CD has been linked to alterations in microbial composition (named intestinal dysbiosis) that could promote the disease onset and progression, as for other autoimmune disorders, such as T1D, multiple sclerosis and RA (Edwards 2008; Leirisalo-Repo 2005). It is unknown whether dysbiosis is a disease-promoting factor.

Differences in microbial metabolites between faecal samples of CD patients and healthy controls point to a functional role of the microbiota in the pathogenesis of CD (Di Cagno et al. 2009; Tjellstrom et al. 2005). A significantly higher number of Gram-negative and potentially pro-inflammatory bacteria were found to be associated with the symptomatic presentation of CD (Nadal et al. 2007). The unbalanced microbiota in children with untreated CD seems only partially restored after long-term treatment with a gluten-free diet (Collado et al. 2008; Sanz et al. 2007).

Little is known about the association between dysbiosis and gluten-specific T-cell responses. The functional relevance of these associations in CD remains unclear. The dysbiosis in CD is hallmarked by an increase in gram-negative and *Bacteroides* species and by a decrease in *Bifidobacteria* and *Lactobacilli* (Cheng et al. 2013). As the intestinal microbiota is able to modulate the cytokine environment, an unfavourable microbiota could amplify the immune response to gliadin in individuals with CD. Dysbiosis could represent an important trigger in CD pathogenesis, along with genetic (HLA haplotypes) and environmental (antibiotic administration, mode of delivery, and breastfeeding) factors (Losurdo et al. 2016).

Many studies have shown the presence of bacteria-derived proteolytic activities with the ability to hydrolyse gluten peptides in saliva, the duodenum and faeces (Caminero et al. 2012; Helmerhorst et al. 2010). *Lactobacillus* strains have the ability to completely hydrolyse the 33-mer peptide. However, the degradation products generated after the 33-mer hydrolysis are unknown and could also be highly immunogenic. It is fundamental to test these degradation products to determine whether the immunogenic epitopes are destroyed (Caminero et al. 2016). The opportunistic pathogens and

core gut commensals generate distinct breakdown patterns of gluten with increased or decreased immunogenicity that could influence autoimmune risk. Gluten proteins are resistant to mammalian protease degradation but are good substrates for bacterial metabolic activity (Caminero et al. 2016). Proteases produced by environmental microorganisms have been proposed as pharmacologic therapy in CD (Lahdeaho et al. 2014; Tack et al. 2013).

Gluten-Free Diet and Autoimmune Disorders

It has been suggested that the intestinal-barrier dysfunction associated with undiagnosed CD might promote the onset of other autoimmune disorders by increasing the intestinal permeability to certain triggers (Shan et al. 2004). Diet intervention is a multifactorial approach, because gluten may affect not only the immune system and the gut microbiota but also other organs, such as the pancreas and liver. Ventura et al. (2012) were the first to report gluten-associated autoimmunity. The longer the duration of exposure to gluten before diagnosis of CD is, the higher the risk of developing autoimmune disorders later in life.

Epidemiological evidence suggests that a GFD may have a positive effect in the protection against T1D in humans with CD (Cosnes et al. 2008). However, the evidence is conflicting, as other studies found no protection (Viljamaa et al. 2005). The importance of gluten in T1D is highlighted by cohort studies finding that early introduction of gluten in the diet (before 3 months of age) increases the prevalence of diabetes autoantibodies in high-risk individuals (Ziegler et al. 2003). One of these studies showed signs of improved insulin sensitivity and insulin secretion in the GFD group compared to the group on a normal diet (Pastore et al. 2003).

Kaukinen et al. (2002) have described CD patients with severe liver injury displaying improvement after a GFD. One of these patients had early cirrhosis, and institution of a GFD led to the disappearance of ascites, although the micronodular cirrhosis persisted.

A later onset of CD is related to greater intestinal-barrier integrity and diminishing antigen triggers in the case of several autoimmune diseases. More large-scale prospective studies would be helpful to elucidate the way in which CD is related to other autoimmune conditions to clarify the possible influence that a GFD exerts on these conditions.

Others Autoimmune Disorders Associated with Celiac Disease

CD tends to coexist with several autoimmune diseases, including T1D, autoimmune thyroiditis, inflammatory bowel disease, rheumatoid arthritis, connective tissue disorders

Table 1 Celiac disease and associated autoimmune disorders

Liver diseases	Connective tissue diseases
Primary biliary cirrhosis	Rheumatoid arthritis
Autoimmune hepatitis	Sjogren's syndrome
Primary sclerosing hepatitis	Systemic lupus erythematosus
Endocrine diseases	Cardiological diseases
Diabetes mellitus	Dilated cardiomyopathy
Autoimmune thyroid disease	Autoimmune pericarditis
Addison's disease	
Dermatological diseases	Others
Dermatitis herpetiformis	Psoriasis
Alopecia areata	Sarcoidosis
Vitiligo	Microscopic colitis
Dermatomyositis	Pancreatitis
	Enteropathy-T-cell lymphoma
	Immune thrombocytopenic purpura
Neurological diseases	
Gluten ataxia	
Peripheral neuropathies	

and psoriasis between others (Birkenfeld et al. 2009; Lerner and Matthias 2015a, b; Viljamaa et al. 2005) (Table 1). The prevalence of co-existing autoimmune disease is estimated to be 3–10 times higher in CD patients than in the general population (Kakleas et al. 2015; Sategna Guidetti et al. 2001). In CD patients, a diagnosis of the disease early in life and a positive family history of autoimmunity are risk factors for developing other autoimmune diseases, while a GFD has a protective effect (Collin et al. 1994). More than 60% of CD-associated susceptibility loci are shared with at least one other autoimmune condition, such as T1D and RA (Rossi and Bot 2011), suggesting common pathogenic mechanisms. In particular, the recognition of peptides by HLA molecules, post-translational modifications of self-antigens (PTMs) required for optimal peptide binding, and immune mechanisms leading to tissue damage have been found. PTMs allow the generation of neo-self epitopes in the development of autoimmunity (Doyle and Mamula 2005). PTMs can occur spontaneously or arise by enzymatic modification, altering the protein structure, biological functions and modifications of the proteolytic degradation. PTMs of self-proteins to which the immune system has not developed tolerance, include enzyme-dependent glycosylation, deamidation, citrullination, iodination, phosphorylation, methylation or chemical modifications such as disulfide bridge formation, oxidative modification or nitration, and many others (Arentz-Hansen et al. 2000; Collado et al. 2013).

Individuals affected by more than one autoimmune disorder may have an immune response more disturbed than

those with only one disease. There may be an overlap in their aetiology due to shared genetic risk factors (Zhernakova et al. 2009) or due to synergistic effects of the genes involved in each disease separately (Cotsapas et al. 2011). The larger percentage of individuals developing more than one autoimmune disorder than expected suggests that common genetic loci and common biological pathways are involved in their pathogenesis. Regular screening in patients with one autoimmune disease for autoantibodies of other autoimmune diseases will be important for the clinical care of these patients and may provide some insights into the disease pathogenesis.

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