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Celiac disease: From gluten to autoimmunity

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ABSTRACT

Celiac disease, also known as gluten-sensitive enteropathy and nontropical sprue, is a prevalent autoimmune disorder that is triggered by the ingestion of wheat gluten and related proteins of rye and barley in genetically susceptible individuals. The immune response in celiac disease involves the adaptive, as well as the innate, and is characterized by the presence of anti-gluten and anti-transglutaminase 2 antibodies, lymphocytic infiltration in the epithelial membrane and the lamina propria, and expression of multiple cytokines and other signaling proteins. The disease leads to inflammation, villous atrophy, and crypt hyperplasia in the small intestine. In addition to the intestinal symptoms, celiac disease is associated with various extra-intestinal complications, including bone and skin disease, anemia, endocrine disorders, and neurologic deficits. Gluten-free diet is currently the only effective mode of treatment for celiac disease, but better understanding of the mechanism of the disease is likely to add other choices for therapy in the future.

Contents

The earliest known descriptions of symptoms consistent with celiac disease were by the Greek physician Aretaeus in the second century. In the 19th century, Samuel Gee and other physicians further defined the symptoms and characteristics of the disease and offered various ideas about treatment. However, Willem Karel Dicke was the first to recognize the

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importance of the removal of offending grains from diet in celiac disease in the 1940s, while John W. Paulley described the associated histologic changes in the intestine. The discovery of the association of the disease with specific HLA markers and gluten-specific T cells, and the recognition of transglutaminase 2 (TG2) as the target autoantigen of anti-endomysial antibodies took place in the 1980s and 1990s.

1. Epidemiology and genetics of celiac disease

Once considered to be a rare disease limited to the pediatric population, it is now estimated that as many as one in every 100 persons in the United States and many other parts of the world has celiac disease [1]. While it can occur at any age, it is, as with many other autoimmune diseases, more predominant among females than males by a ratio of 3 to 1 [2]. Celiac disease is a multigenic disorder, with genes for specific class II human leukocyte antigens (HLA) conferring about 40% of the genetic susceptibility. The primary HLA association is with DQ2 (DQA1 *05/DQB1 02) and DQ8 (DQA1 *0301/DQB1 *0302) [3]. These cell surface proteins of antigen-presenting cells confer susceptibility for celiac disease by having the important role of presenting specific immunogenic gluten peptides to gluten-specific T cells in the small intestine. While the presence of these HLA proteins is necessary for developing celiac disease, it is not enough. Multiple non-HLA genes also contribute to the genetic risk for celiac disease and have been reported in a number of studies, although their identities and functions remain to be confirmed [4,5].

2. Clinical presentation

The clinical presentation of celiac disease is highly variable. In childhood, the disease commonly presents with failure to thrive, short stature, delayed puberty, chronic diarrhea, steatorrhea, abdominal distension, and anemia. In adults, symptomatic or classical cases of the disease may present with chronic diarrhea, abdominal distention and pain, weakness, and malabsorption [6]. However, many patients have little or no gastrointestinal symptoms, while presenting with extra-intestinal features, such as dermatitis herpetiformis, anemia, osteoporosis, infertility, and neurologic problems, among others (Table 1) [1]. It is therefore more appropriate to consider celiac disease as a multisystem disorder, rather than a mainly gastrointestinal one.

Table 1
Some of the disorders believed to be associated with celiac disease

Endocrine disorders	Neurologic disorders	Liver diseases	Other
Type 1 diabetes	Cerebellar ataxia	Primary biliary cirrhosis	Anemia
Autoimmune thyroid disorders	Peripheral neuropathy	Autoimmune hepatitis	Osteoporosis
Addison disease	Cognitive impairment	Autoimmune cholangitis	Dermatitis herpetiformis
Reproductive disorders	Psychosis		Selective IgA deficiency
	Epilepsy		Turner syndrome
	Migraine		Idiopathic dilated cardiomyopathy
			Down syndrome
			Malignancies

While some of the extra-intestinal manifestations of celiac disease, such as anemia and osteoporosis, are primarily due to nutritional deficiencies that result from the mucosal lesion, others have a much more complex connection to celiac disease that involves genetic and immunologic factors. Some of the most commonly encountered, but sometimes overlooked, manifestations of celiac disease or associated disorders are worth discussing in more detail here.

2.1. Dermatitis herpetiformis

Dermatitis herpetiformis is the skin manifestation of celiac disease, affecting about 10–20% of celiac patients [7]. It is characterized by papulovesicular lesions and presence of granular deposits of IgA in the dermal papillae [7,8]. The prevalence of HLA-DQ2 and -DQ8 markers in dermatitis herpetiformis is the same as in celiac disease, and patients often have intestinal histologic changes that are identical to those in celiac disease, even in the absence of gastrointestinal symptoms. Pharmacological treatment, usually with dapsone, is beneficial for quick resolution of skin manifestations, but gluten-free diet is the only long-term treatment. The antibody profile in dermatitis herpetiformis is similar to that for celiac disease [9]. However, in addition to anti-TG2 antibodies, antibody reactivity that is specific to transglutaminase 3 (TG3, or epidermal transglutaminase, eTG), has also been demonstrated [10].

2.2. Neurologic disorders

Neurologic deficits are among the most common and debilitating extra-intestinal manifestations of celiac disease, affecting between 10–30% of patients [11–13]. Cerebellar ataxia and peripheral neuropathy are the most common neurologic complications that might accompany celiac disease, but seizures, chronic headache, depression, and psychiatric disorders have also been reported [12]. Several studies report elevated levels of anti-gliadin antibody in patients with neurologic deficits, even in the apparent absence of the characteristic mucosal pathology [14–16]. The nature of the connection between celiac disease and neurologic complications is still largely unknown. However, immunologic abnormalities in the nervous system, including lymphocytic infiltration in the central and peripheral nervous system of affected individuals, as well as response to gluten-free diet and immunomodulatory treatment in some patients, point to an immune-mediated mechanism of pathogenesis in at least some of the associated neurologic symptoms [16–19].

2.3. Endocrine disorders

Celiac disease has been reported to be associated with a number of autoimmune endocrine disorders, most commonly type 1 diabetes and thyroid disease, each affecting approximately 5% of patients [20]. The link is primarily a result of common genetic background, most importantly in the HLA region of chromosome 6 [5,20]. The effect of gluten-free diet on these disorders is currently believed to be limited at best [20].

2.4. Malignancies

There is an increase in the incidence of certain cancers among celiac disease patients, including non-Hodgkin lymphoma, enteropathy-associated T-cell lymphoma, small intestinal adenocarcinoma, and esophageal and oropharyngeal squamous carcinoma [21]. However, strict adherence to gluten-free diet has been found to be effective at reducing the risk of some malignancies [21].

3. Diagnosis

Accurate diagnosis of celiac disease is achieved by following the current diagnostic guidelines and keeping in mind that intestinal biopsy remains the only widely accepted diagnostic gold standard. We will discuss the diagnosis of celiac disease, based on the recommendations of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) [22], and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) [23], which is also summarized by the algorithm in Fig. 1.

3.1. Serologic tests

Celiac disease is usually suspected in a patient either because of the presence of characteristic symptoms (discussed above), or due to being in an at-risk group. Individuals in the at-risk group include 1) those with celiac disease-associated disorders (Table 1), and 2) first- and second-degree relatives of celiac patients. Once celiac disease has been suspected, the patient should be tested for serologic markers of the disease.

The single most sensitive and specific serologic marker of celiac disease is the IgA anti-transglutaminase 2 (anti-TG2) or anti-endomysial antibodies [24]. While two different types of test are used for anti-TG2 and anti-endomysial antibodies, they detect antibodies to the same antigen, namely TG2 [1]. A review of literature does not indicate a statistically significant difference between the human anti-TG2 antibody and anti-endomysial antibody tests [25], and either one can therefore be considered in the initial panel of serologic tests. The IgA isotype is more sensitive and specific (over 90%) for celiac disease than the IgG, and is recommended for initial screening [25]. However, as IgA deficiency has an increased prevalence among celiac patients [6], care should be taken in interpreting the results of IgA antibody tests. In the case of IgA deficiency, measurement of IgG anti-TG2/endomysial and IgG anti-gliadin antibodies should be substituted. Although the presence of the anti-gliadin antibody is historically considered to be an important hallmark of celiac disease, lower figures for its sensitivity and specificity in comparison to IgA anti-TG2 antibody have led to a diminished utility of the

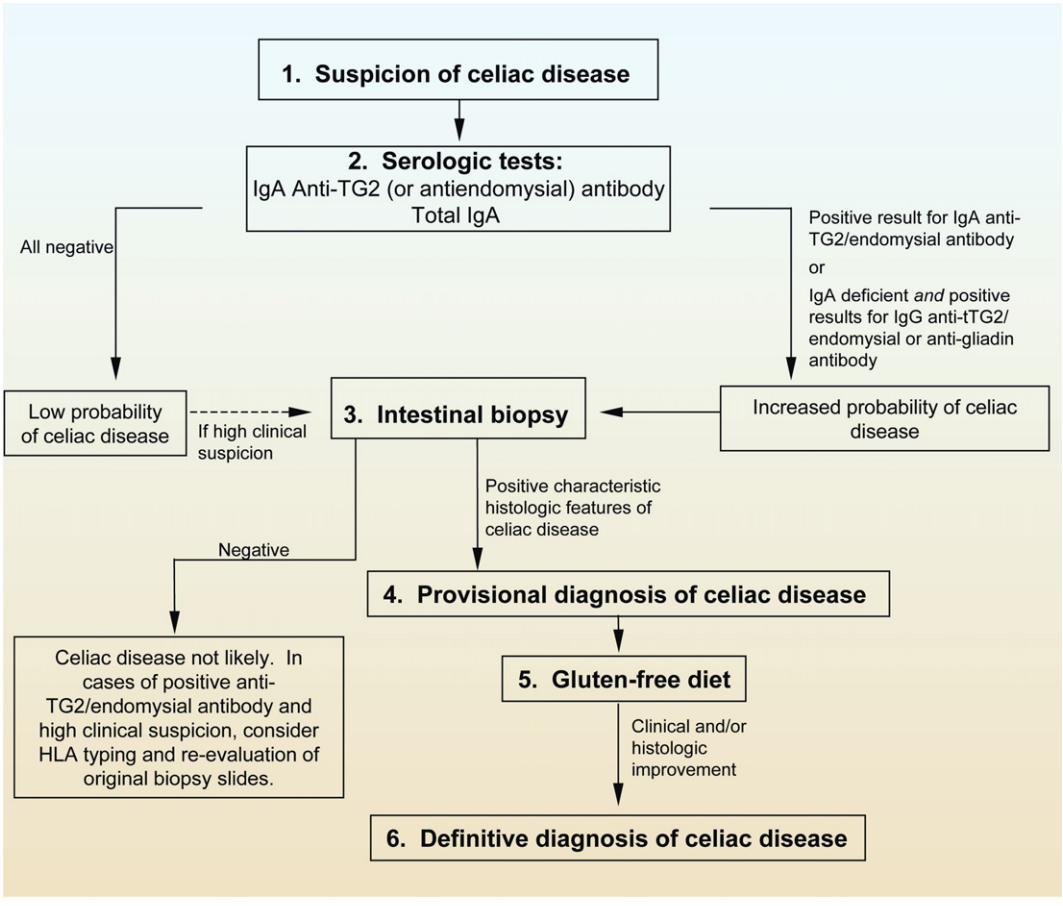

Fig. 1. Proposed plan for evaluation of patients suspected of having celiac disease.

marker for diagnosis. However, in cases of IgA deficiency, use of the anti-gliadin antibody in addition to the IgG anti-TG2 antibody will increase sensitivity. In addition, newer generations of anti-gliadin antibody tests that use celiac disease-specific deamidated gliadin peptides instead of whole gliadin protein mixtures are now considered to have sensitivity and specificity that rival those of the anti-TG2 antibody test [26]. These tests are likely to find wide use once their performance has been further confirmed in more studies.

3.2. Intestinal biopsy

A positive result for IgA anti-TG2/endomysial antibody, or IgG anti-TG2/endomysial and anti-gliadin antibody in case of IgA deficiency should be followed by intestinal biopsy. A biopsy might also be done in cases of negative serology but high clinical suspicion (Fig. 1). The characteristic histologic features of celiac disease range from near-normal villous architecture with increased intraepithelial lymphocytosis to total villous atrophy [27]. Positive identification of these abnormalities leads to a presumptive diagnosis of celiac disease, which should be followed by institution of gluten-free diet. A definitive diagnosis is made only after clear improvement in response to diet has occurred. A second biopsy to confirm histologic improvement is not necessary, except in cases where the clinical symptoms of celiac disease are not present.

What if the biopsy report is negative, while there is positive serology or a high clinical suspicion of celiac disease? In such cases, a careful review and discussion of the results of the biopsy with an expert gastrointestinal pathologist should be made before considering additional biopsy. In addition, it is useful in such cases to consider HLA typing. Because nearly all celiac patients (and approximately 25%–40% of the general population) carry the HLA-DQ2 and/or HLA-DQ8 alleles, the absence of both markers has a very high negative predictive value, helping to rule out the disease in cases of equivocal biopsy results [25].

4. Treatment

The only currently available treatment for celiac disease is complete elimination of gluten and related proteins from diet, whereby food products containing wheat, rye, and barley are avoided. Improvement of symptoms is generally seen within days to weeks after the initiation of gluten-free diet, while full mucosal recovery usually takes longer [28]. Anti-TG2 and anti-gliadin antibody titers will go down with the elimination of gluten from diet, but may require many months or even years to completely disappear. Future therapeutic options may include enzymatic treatment of gluten to break down toxic peptides, selective modulation of TG2 activity, or blocking of the binding of gliadin peptides to HLA molecules, but for now the gluten-free diet remains the only choice for treatment. As was mentioned, treatment of patients with dermatitis herpetiformis can combine the gluten-free diet with the application of dapsone for a fast resolution of the itching and rash.

What should be done when a patient does not respond to the gluten-free diet? In such a case a careful review of the diagnosis, as well as the diet, should be undertaken. First, it is important to determine if the patient actually has celiac disease by re-evaluating the results of the serologic tests, and by careful re-examination of the original biopsy slides. Consulting with a gastrointestinal pathologist and testing for HLA DQ2/DQ8 markers will be helpful in resolving doubts about the diagnosis. Specifically, it is important to rule out other conditions that may share similar symptoms, including pancreatic insufficiency, lymphocytic colitis, bacterial overgrowth, and refractory sprue with a clonal T cell population [1]. Second, a reassessment of the diet with the help of an expert dietician may be needed to find out if the patient is on a true gluten-free diet. Considering that wheat and wheat derivatives are used in many food products, effective adherence to a gluten-free diet is not a trivial task. While all of the mentioned toxic cereals and any derivatives should be eliminated from diet, they can be substituted by other grains, such as rice, corn, quinoa, amaranth, sorghum, and buckwheat, which are found to be safe [6]. Although oat is considered to be well-tolerated by the majority of patients, it should be noted that some commercial preparations are reported to contain contamination from gluten-containing cereals [29].

5. Pathogenesis

The pathogenesis of celiac disease involves a complex interplay between environmental, genetic, and immunologic factors. Wheat gluten and related proteins elicit innate and adaptive immune responses in the small intestine that lead to mucosal damage. Genes encoding class II human leukocyte antigens HLA-DQ2 and -DQ8 are closely linked to the disease and are found in nearly all celiac patients. Non-HLA genes clearly play a role in celiac disease as well. The immunologic response to gluten includes antibody reactivity to gluten proteins and the autoantigen TG2, $CD4^+$ T cell reactivity to gluten, increased number of intraepithelial $CD8^+$ T cells, and elevated levels of a number of cytokines and chemokines [30].

The term gluten refers to the main storage proteins of wheat and probably includes more than 100 different molecules. The gluten proteins are divided on the basis of solubility into gliadins and glutenins, both of which are implicated in celiac disease. Rye and barley contain proteins that are similar to wheat gluten and which also can trigger the disease [30]. Some incompletely digested peptides of wheat gluten and related proteins of rye and barley can cross the epithelium and enter the lamina propria of the small intestine under certain conditions. It has been speculated that stress factors can lead to changes in intestinal permeability that give the gluten peptides access to the lamina propria [1]. For example, gastrointestinal infections have been found to increase the risk of triggering celiac disease [31]. The innate immune response to gluten (discussed below) might also be a precursor to mucosal changes that increase intestinal permeability. Meanwhile, neutral glutamine residues in the gluten peptides can be converted to negatively charged glutamic acids through deamidation by TG2. Antigen presenting cells expressing the HLA-DQ2 and HLA-DQ8 molecules have an increased affinity for these deamidated peptides. Subsequent binding of the generated immunogenic peptides to the HLA molecules results in peptide complexes that can activate host gluten specific $CD4^+$ T cells in the lamina propria. Activation of

these T cells is accompanied by the production of a number of cytokines that can in turn promote inflammation and villous damage in the small intestine through the release of metalloproteinases by fibroblasts and inflammatory cells [1,30].

Activated gluten-specific $CD4^+$ T cells can also stimulate B cell production of anti-gluten, as well as anti-TG2 antibodies. In the absence of TG2-specific T cells, the anti-TG2 antibody response is believed to be driven by intermolecular help, whereby gluten-specific T cells are proposed to provide help to TG2-specific B cells, granted that TG2-gluten complexes are formed [32]. Such a gluten-specific T cell-driven mechanism would lead to an anti-TG2 immune response without the need for TG2-specific T lymphocytes. In fact, the dependence of anti-TG2 antibodies on gluten intake in celiac disease patients appears to support such a mechanism [33]. While TG2 can form complexes with gluten peptides, it can also cross-link gluten to matrix proteins, thereby retaining gluten in the tissue environment and generating molecular complexes that can elicit an immune response to additional autoantigens [34].

Whether the antibodies of celiac disease play a role in the mucosal pathology or any of the extra-intestinal manifestations is less clear. In some autoimmune disorders, autoantibodies can specifically interfere with the biologic activities of a specific antigen, while in others they can cause tissue injury by forming immune complexes that activate the complement system. It has been shown that the anti-TG2 antibodies in celiac disease can interfere with TG2 activity and have a

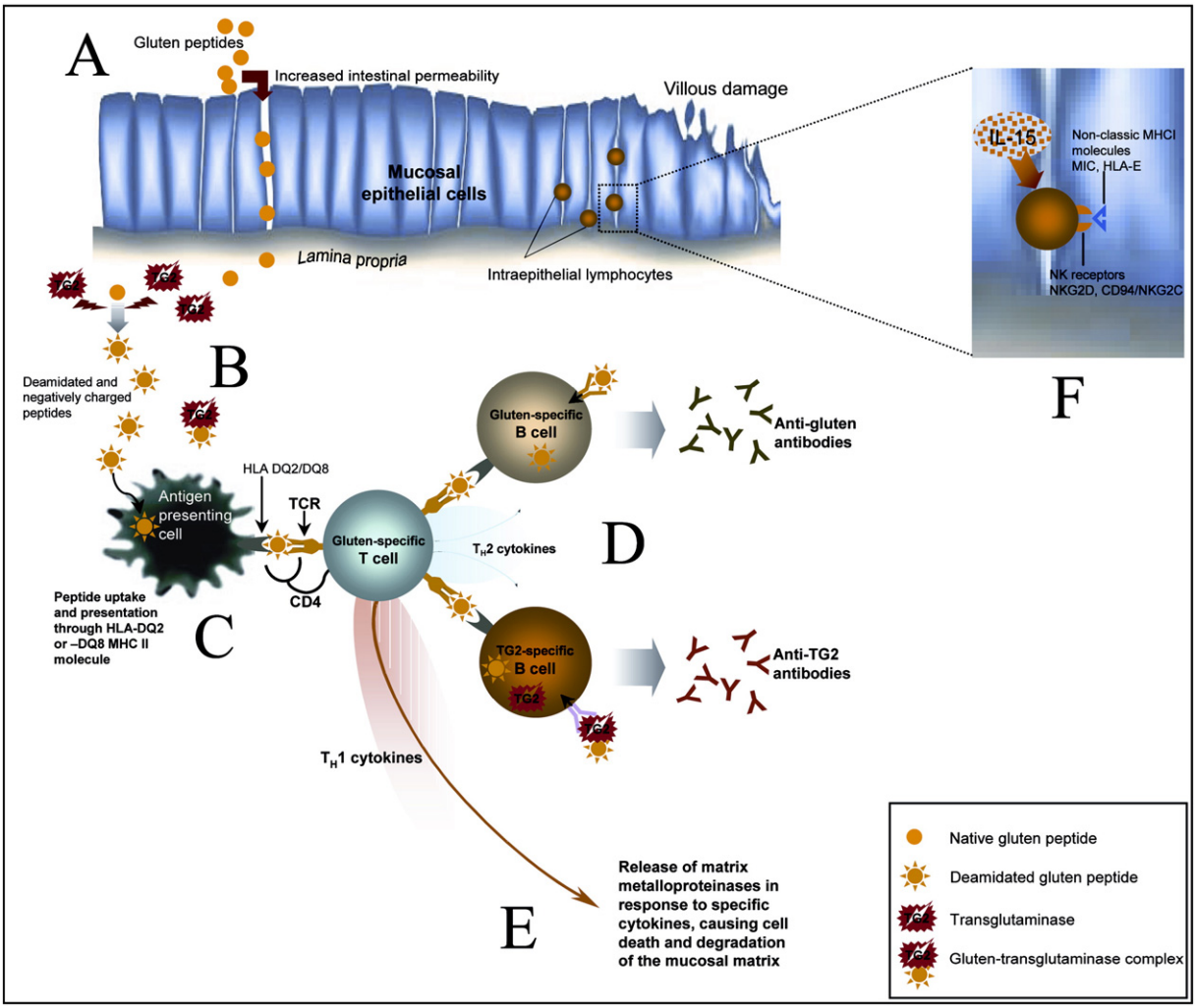

Fig. 2. Simplified schematic depicting the process of humoral and cell-mediated immune responses and subsequent mucosal injury in celiac disease. A) Gluten peptides resistant to digestive enzymes cross the epithelial barrier following an increase in intestinal permeability. B) Relevant gluten peptides are deamidated by TG2, creating epitopes with increased immunostimulatory potential. The gluten peptides may also become covalently linked to TG2 or other proteins through the enzymatic activity of TG2. C) Deamidated peptides are presented by antigen presenting cells, such as dendritic cells, macrophages, or B cells to $CD4^+$ T cells. D) Help from gluten-specific T cells leads to B cell clonal expansion and release of anti-gluten antibodies. TG2-specific B cells might also become activated by gluten-specific T cells through intermolecular help. E) Expression of pro-inflammatory cytokines by activated T cells promotes the release of matrix metalloproteinases that cause epithelial cell damage and tissue remodeling. F) The response to gluten also involves the innate immune system, as epithelial cells secrete IL-15 and express non-classic MHC class I molecules in response to gluten exposure. 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. TCR: T cell receptor; APC: antigen-presenting cell.

deleterious impact on epithelial cell differentiation [35,36]. The anti-TG2 antibodies have also been shown to increase epithelial cell permeability in an intestinal cell line and to induce monocyte activation upon binding to Toll-like receptor 4, which might contribute to the intestinal damage [37]. Anti-TG2 antibodies might also play a role in some of the extra-intestinal manifestations of celiac disease, through interaction with TG2, as well as cross-reaction with other transglutaminases. In fact, deposits of anti-transglutaminase antibody have been observed in the cerebellum and brainstem of a patient with gluten sensitivity and cerebellar ataxia, as well as in the papillary dermis of patients with dermatitis herpetiformis [34].

Evidence for direct involvement of anti-gliadin antibodies in the pathogenesis of the mucosal lesion is scarce. As these antibodies are increased in certain idiopathic neurologic and psychiatric disorders, some investigators have focused on their potential for cross-reactivity towards neural antigens. The anti-gliadin antibodies have been shown to bind to neuronal cells and to specifically cross-react with synapsin I [38,39]. Serum from an ataxia patient with anti-gliadin antibodies has also been shown to cause motor coordination deficits when injected into the brain of mice [40]. Therefore, the anti-gliadin antibodies can be envisioned to have a role in some neurologic complications of celiac disease, but probably only if they are able to cross the blood-brain or blood-nerve barriers and reach their target in affected individuals.

While the adaptive immune response to gluten that we have so far discussed has been studied intensely, the innate immune reaction, which involves the activation of intraepithelial T cells and cytolytic activity towards enterocytes, has only recently begun to receive attention. It is now known that gluten induces the expression of IL-15 cytokine and non-classical MHC class I ligands MIC and HLA-E by stressed epithelial cells in the small intestine [30]. This appears to activate antigen non-specific intraepithelial $CD8^+$ lymphocytes expressing the natural killer receptors NKG2D and CD94/NKG2C. Specifically, the interaction of these lymphocytes with epithelial cells that express the stress-induced MIC and HLA-E molecules results in the release of IFN-γ and cytotoxic molecules that contribute to epithelial cell death [30] (Fig. 2).

6. Conclusion

As the awareness of celiac disease has increased in the last two decades, there has been a sharp increase in the number of newly diagnosed individuals. It is now clear that celiac disease affects about 1% of the population in many regions of the world. The discovery of sensitive and specific serologic markers of the disease has significantly contributed to more efficient diagnosis and follow-up of patients. However, celiac disease remains underdiagnosed in many countries, and we are still far from gaining a clear understanding of many aspects of its pathogenic mechanism. Nevertheless, as the disease receives increasing attention from physicians and scientists, significant progress is likely to take place in the next few years to better understand the mode of pathogenesis, determine the nature of its relationship with various extra-intestinal manifestations, and find novel and effective ways of treating patients.

Take-home messages

- Celiac disease is a prevalent autoimmune disorder that is characterized by an improper immune response to ingested wheat gluten and related cereal proteins in genetically predisposed individuals.
- Celiac disease manifests itself in multiple intestinal and extra-intestinal complications.
- Both arms of the immune system, innate and adaptive, are involved in the pathogenesis of the disease.
- The IgA anti-TG2 antibody is currently considered to be the most sensitive and specific serologic marker of the disease.
- The intestinal biopsy remains the only widely accepted gold standard for diagnosis of celiac disease.
- Gluten-free diet is an effective treatment, leading to complete recovery in patients and reducing the risk of developing certain additional complications.

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Novel autoantigens in multiple sclerosis

B cells play a role in multiple sclerosis, however there is not a specific autoantibody used to diagnose this disease. In a recent paper, Somers *et al.* **(J Immunol 2008;180:3957-63)** using a phage display library, from multiple sclerosis brain plaques, tried to select potential autoantigens in cerebrospinal fluid from ten patients with relapsing-remmitting multiple sclerosis. The authors identified eight possible autoantigens and processed a more extensive evaluation in more 63 cerebrospinal fluid from multiple sclerosis. The sensitivity was 86% and specificity 45% when all 8 antigens were used. Interestingly, they reach a high specificity (100%), however a low sensitivity (23%), when four of these antigens were applied. The authors identified a novel antigen (SPAG16) using bio-informatic analysis. This study brings a panel of new autoantigens in multiple sclerosis that may have a role in the future research for diagnosis of this disorder.

Abnormal T cell differentiation predicts relapse in rheumatoid arthritis

Rheumatoid arthritis is an inflammatory chronic and autoimmune disorders with various pathogenic mechanisms. One of these is the existence of an abnormal CD4+ T cell subset associated with inflammatory conditions, mainly rheumatoid arthritis. In this line, Burgoyne *et al.* **(Ann Rheum Dis 2008;67:750-7)** have studies these abnormal cells in different chronic inflammatory disorders (rheumatoid arthritis, Crohn`s disease, and osteoarthritis). The authors found these T cells in rheumatoid arthritis (RA) and Crohn`s disease, but not in osteoarthritis. During remission of RA, hyperproliferation of CD4+ cells was blocked and interestingly high frequency of these inflammatory related T cells in remission was a good predictor of relapse within 18 months. This study suggest that T cells are an important factor in RA pathophysiology , despite the lack of inflammation during remission, these cells persist and they may play a role as circulating precursosrs of pathogenic cells.