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REVIEW

Antibodies in celiac disease: implications beyond diagnostics

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Celiac disease is a multisystemic dietary, gluten-induced autoimmune disorder characterized by the presence of transglutaminase (TG) 2 serum autoantibodies. Distinct autoantibodies targeting members of the TG family (TG2, TG3 and TG6) are found deposited in small-bowel mucosa and in extraintestinal tissues affected by the disease. Serum autoantibodies against other self-antigens also emerge in untreated celiac disease patients. Although villous atrophy and crypt hyperplasia in small-bowel biopsy samples are still the gold standards in diagnostics, celiac disease-specific antibodies are widely used as diagnostic aids. Gluten-induced small-bowel mucosal T-cell response is the cornerstone in the pathogenesis of the disorder, but humoral immunity may also play a central role. This review article is focused on the autoantibodies that occur in the context of celiac disease. The article summarizes the diagnostic utility of different celiac-related antibodies and discusses their roles in the pathogenesis of the disease.
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AN OVERVIEW OF CELIAC DISEASE: THE PLAYERS IN THE GAME

Celiac disease is an autoimmune disorder that occurs in genetically susceptible individuals in response to dietary gluten in wheat, rye and barley. In clinical and pathological terms, our understanding of the disease has considerably improved in recent decades. Traditionally, celiac disease has been considered a fairly uncommon gastrointestinal disorder affecting mainly children, but according to current knowledge, the disease has evolved to become a common systemic condition affecting individuals of all age groups. In many Western countries, the disease affects approximately 1% of the population, but it has recently been shown that the true prevalence of celiac disease is increasing over time.[1] The prevalence also increases by age within a country; for example, in Finland, the prevalence is 1.5% in children,[2] 2% in adults[1]and 2.7% in the elderly.[3] The symptoms and signs of celiac disease vary from mild to severe, and some with celiac disease can be asymptomatic for years or decades. The classical symptoms include the following: malabsorption, chronic diarrhea, iron deficiency anemia and weight loss. In children, short stature is also a symptom. In addition to gastrointestinal symptoms, the disease has extraintestinal manifestations, such as osteoporosis,[4] dermatitis herpetiformis,[5] neurological problems,[6] liver disorders,[7] arthritis[8] and obstetric problems.[9] Celiac disease is also associated with other autoimmune disorders, such as type one diabetes mellitus and autoimmune thyroid diseases.[10]

Celiac disease is associated with major histocompatibility complex class II genes and the alleles encoding the human leukocyte antigen molecules (HLA)-DQ2 and HLA-DQ8. Almost all patients with celiac disease carry these HLA alleles.[11] However, 30–40% of healthy individuals also carry the DQ2 and DQ8 alleles. The majority of these individuals never develop the disorder. To explain this discrepancy, genome-wide linkage and association studies have been conducted, and a set of chromosomal regions that may harbor gene variants or polymorphisms conferring additional risk for developing celiac disease has been identified.[12,13]

Although other environmental factors ('second hits') in addition to gluten may be involved in triggering celiac disease, the disease goes into remission when gluten is removed from the diet. This suggests that gluten is a major player in the pathogenesis of the disease. Gluten-containing cereal prolamins, such as gliadin in wheat, secalin in rye and hordein in barley, have a high number of repetitive glutamine- and proline-rich sequences, making them highly resistant to proteolytic degradation by human gastric, pancreatic and intestinal brush-border enzymes, even in healthy individuals.[14,15] Such proteolytic resistance results in the persistence of relatively large peptides, which are thought to activate the small-bowel mucosal immune system, thereby leading to the development of celiac disease. Under normal physiological conditions, intestinal epithelium is fairly impermeable to long peptides, such as wheat-derived gliadin peptides. However, in untreated celiac disease, the epithelial barrier function is compromised, and gliadin peptides gain access across the epithelial layer.[16] Studies performed with small-bowel biopsy organ cultures and different *in vitro* cell cultures support the idea that gluten can activate the innate immunity mechanisms. This activation is thought to be mediated by toxic gluten-derived gliadin peptides (the α-gliadin peptide 31–43), which eventually results in intestinal epithelial cell damage.[17–20]

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However, a different set of gliadin peptides, the so-called immunogenic peptides (peptides within the α-gliadin 33-mer peptide 56–89), activate the adaptive immune response. First, these peptides are post-translationally modified by a ubiquitously expressed multifunctional enzyme, transglutaminase (TG) 2, which catalyzes the deamidation of distinct glutamine amino acids to glutamic acid residues.[21,22] Such deamidation greatly enhances the ability of the peptides to bind to HLA-DQ2, which thereby potentiates celiac patient T-cell stimulation.[21,23] As a result, proinflammatory cytokines are secreted during small-bowel mucosal tissue remodeling and damage, which is characterized by villous atrophy, crypt hyperplasia and inflammation. During this process, B cells start to secrete antibodies against the trigger, gliadin and various self-antigens.[24] This review is focused on the importance of gluten-induced disease-pathognomonic antibodies as a diagnostic tool and discusses their roles in celiac disease pathogenesis in the intestinal and extraintestinal environment.

CELIAC DISEASE ANTIBODIES: DIFFERENT TARGETS, DIFFERENT CLINICAL UTILITY

Serum antibodies

The gold standard in diagnosing celiac disease is the presence of histological changes in small-bowel mucosal biopsies. In other words, villous atrophy, crypt hyperplasia and profound inflammation characterize celiac disease. However, because of the multifaceted nature of the disease, clinicians have long used various serum-based antibody tests in case finding (Table 1) before proceeding to diagnostic upper gastrointestinal endoscopies with multiple small-bowel mucosal biopsies. Among the first serum-based antibody tests applied in celiac disease, diagnostics are the antigliadin antibody (AGA) assays. Currently, these tests are no longer used as diagnostic aids because their sensitivities and specificities are fairly poor.[25] In addition, individuals suffering from gastrointestinal conditions other than celiac disease and healthy individuals without celiac-type genetics have been reported to have elevated AGA levels.[29]

The problems with the AGA tests were overcome by the advent of the gluten-dependent IgA-class R1-type reticulin (ARA) and endomysial autoantibody (EMA) tests.[27,30–33] These tests are based on indirect immunofluorescence using rodent (ARA) or primate (EMA) tissues as antigens. In most studies, their sensitivities and specificities are both reported to be above 90% (Table 1), though these tissue-based autoantibody tests are often subjective and laboratory dependent. It has been suggested that symptomatic patients, both children and adults, could be diagnosed based on a positive serum EMA finding.[34,35]

In 1997, Dieterich and co-workers identified TG2 as the autoantigen of celiac disease.[36] As various TG2-based enzyme-linked immunosorbent assays (ELISA) became available, a new era in celiac disease case finding by serology began.[27,37] Thereafter, it was shown that TG2 was also the specific protein antigen in the ARA and EMA tests,[38] indicating that the abovementioned three tests in fact do measure the same autoantibodies. Currently, TG2 ELISA tests are widely used in diagnostic workup of celiac disease.[25] However, it is important to bear in mind that the performance of the commercial ELISA TG2-antibody assays may vary depending on the quality of the TG2 antigen and thus, may yield false-positive and false-negative results.[25,39,40] Therefore, the EMA test appears to hold its place as the gold standard celiac disease-specific antibody test. The superiority of the EMA test in celiac disease diagnostics is also supported by a high concordance between EMA positivity and the presence of the celiac-type HLA-DQ2 or -DQ8, which is not always seen with TG2 ELISA seropositivity.[2,32,34] Furthermore, the compromised specificity of the TG2 ELISA and the high specificity and sensitivity of the EMA tests suggest that the epitope in the EMA test is somehow specific for celiac disease autoantibodies.

An indication of the constant development of serological tests for celiac disease is the introduction of an ELISA test using deamidated gliadin peptides (DGPs) as antigens. The rationale behind the test is based on the finding that TG2 is known to deamidate gliadin peptides during the pathogenesis of celiac disease.[21] It has been shown that selective deamidation specifically increases circulating antibody recognition of gliadin peptides in celiac patients, and such serum DGP antibodies have been proven to be highly accurate indicators of untreated celiac disease (Table 1).

Celiac disease patients with selective IgA deficiency are by definition negative for serum antibodies in the IgA class. Therefore, IgG-based EMA, TG2 and DGP antibody test are esed in such class[26,41,42]. To avoid using total serum IgA measurements, the IgA-class antibody tests have been combined with the IgG-class tests in a single screen assay.[43]

A common feature for the above listed celiac disease antibodies is that they are gluten-dependent and their levels decrease and become negative within 1 year of being on a strict gluten-free diet. However, it is important to keep in mind that seronegativity in patients consuming gluten does not rule out the possibility of celiac disease.

Antibodies found in the serum of celiac disease patients are not only restricted to the antigen triggering the disease (gliadin, DGP) or the major celiac-specific autoantigen, TG2. Patients have also been reported to have circulating antibodies against other self-antigens, exemplifying a further breakdown of immune tolerance. However, such autoantibodies are generally independent of endomysial staining.[24,38] For instance, celiac patients have gluten-dependent IgA-class autoantibodies against cytoskeletal actin. The presence of these autoantibodies correlates with the severity of the small-bowel villous atrophy.[44] Other identified targets for celiac autoantibodies include the following: calreticulin, zonulin and desmin. However, studies on their applicabilities in celiac disease diagnostics are scarce.[24]

Table 1 Sensitivities and specificities of IgA-class serological tests in untreated celiac disease

Antibodies	*Sensitivity*	*Specificity*	*References*
AGA	75–95%	80–95%	25
ARA	78–97%	98–100%	26 and 27
EMA	80–97%	97–100%	25
Anti-TG2	85–98%	95–99%	25
Anti-DGP	74–98%	90–99%	28

Abbreviations: AGA, anti-gliadin antibodies; anti-DGP, deamidated gliadin peptide antibodies; anti-TG2, transglutaminase 2 antibodies; ARA, R1-type reticulin antibodies; EMA, endomysial antibodies.

Intestinal autoantibodies

The first evidence of antibody deposits in the intestinal environment was produced in the 1970s by Shiner and Ballard, who reported an increase in extracellular deposits of immunoglobulins, especially IgA, in jejunal mucosa of celiac children after a gluten challenge.[45] Immediately thereafter, similar IgA deposits in the basement membrane area were reported in the small-bowel mucosa of untreated celiac patients in conjunction with increases in the number of immunoglobulin-containing cells.[46–49] Immunoelectron microscopic studies revealed heavy deposits of IgA in the basement membrane of surface epithelial cells, in crypt epithelium, around the subepithelial fibroblasts and in the walls of blood vessels in the intestinal mucosa of

celiac patients. Such findings differed considerably from those in healthy individuals.[46–51] It was also found that during a gluten-free diet, the antibody deposits disappeared, but when gluten was reintroduced in the diet of celiac disease patients, the antibody deposition rapidly reappeared.[49,52,53]

After the identification of TG2 as the celiac disease autoantigen,[36] it was demonstrated that the patient autoantibodies also target the autoantigen TG2 in tissues.[54,55] Furthermore, the IgA deposits in celiac disease patient small-bowel biopsies had the ability to bind external TG2 when added to the tissues.[56] Interestingly, it has been shown by phage-display technology that celiac disease autoantibodies are produced locally in the small-bowel mucosa.[57]

Staining of IgA deposits, which are small-bowel mucosal TG2-targeted autoantibodies, has extensively been used in the diagnostic workups of celiac disease. There are several studies showing that all untreated celiac disease patients, even seronegative ones, characteristically have these deposits in their small-bowel mucosa.[55,56,58] These deposits appear early on during disease development when the mucosa is still morphologically normal. These deposits appear in the mucosa even before they are detectable in the periphery.[55,59,60] In IgA-deficient celiac disease patients, these mucosal autoantibody deposits appear in the IgM-class instead.[61]

Autoantibodies associated with extraintestinal manifestations of celiac disease

Interestingly, in some cases, autoantibodies against distinct self-molecules in addition to TG2 have been reported to coincide with specific clinical manifestations of celiac disease. Even more intriguing is the fact that these autoantigens belong to the same TG protein family as TG2, which is the major celiac disease autoantigen.

Dermatitis herpetiformis is regarded as a dermal manifestation of celiac disease.[5] Dermatitis herpetiformis is an autoimmune, blistering, pruritic papulovesicular gluten-dependent skin rash typically located on the elbows, forearms, buttocks, knees and scalp. Moreover, dermatitis herpetiformis and celiac disease have identical genetic backgrounds that include the presence of HLA-DQ2 or HLA-DQ8.[62] The diagnosis of dermatitis herpetiformis is established by the demonstration of granular IgA deposits in the dermal papillae of uninvolved skin. In 2002, Sardy and colleagues identified the epidermal TG, TG3, as the autoantigen of dermatitis herpetiformis.[63] Moreover, serum TG3-targeted autoantibodies are found in patients with dermatitis herpetiformis, and they seem to be gluten dependent.[64,65]

Celiac disease may also present with neurological complications, such as dementia, brain atrophy, cerebellar ataxia, peripheral neuropathy and epilepsy with occipital calcifications.[6] Gluten ataxia is a sporadic cerebellar ataxia associated with the presence of AGA without other apparent etiologies for the ataxia. It can manifest with or without enteropathy.[6] It has been shown that gluten ataxia patients have celiac-specific TG2-targeted IgA deposits in the duodenal mucosa as well as in brain blood vessels.[66] Interestingly, it was recently shown that serum autoantibodies in gluten ataxia patients also recognize a novel neuronal TG, TG6.[67] However, contradictory results exist as to its suitability in clinical practice.[67,68]

THE ROLE OF CELIAC DISEASE ANTIBODIES IN THE PATHOGENESIS

Antibodies in the intestinal environment

Although the applicability of celiac disease-specific antibodies in the diagnostics of the disease is well established, the question remains as to how the antibodies are linked with the pathogenesis of the disease (Figure 1), especially considering that gliadin peptides or TG2, which are the targets of the antibodies, have important roles in disease progression. Table 2 lists known biological effects of celiac-type antibodies.

The epithelium in the small-bowel mucosa of untreated celiac disease patients is characterized by an increased number of proliferating cells, a decreased number of differentiated cells, augmented cellular turn over and compromised barrier function. Although proinflammatory cytokines and gliadin are known to induce such features in intestinal epithelial cells,[85] there are emerging data suggesting that celiac disease antibodies have similar effects in cell culture conditions. To modulate small-bowel mucosal epithelial biology *in vivo* in the intestines of celiac disease patients, the celiac-type antibodies are located (deposited) in strategically correct places, such as below the epithelial layer. These antibodies then target extracellular TG2 on subepithelial fibroblasts and on the basement membrane.[29,51,55] Furthermore, the antibodies are translocated by specific mechanisms to the intestinal lumen.[29]

Serum IgA in patients with untreated celiac disease and patient-derived anti-TG2 autoantibodies produced by recombinant technology have been shown to induce epithelial cell proliferation.[69,70] Celiac patient IgA is also capable of inhibiting intestinal epithelial cell differentiation.[69] In addition, several studies suggest that celiac antibodies also modulate epithelial barrier function.[71,72] In accordance with these results, our recent data demonstrate that IgA derived from untreated celiac disease patients specifically increase the transepithelial passage of gliadin peptides *in vitro*.[73] All of the abovementioned cellular effects are also seen in small-bowel mucosal lesion that is characteristic of untreated celiac disease. Thus, celiac antibodies could collectively promote the development of small-intestinal damage. Yet, based on the aforementioned experiments, it is not completely clear which celiac-type antibody populations are responsible for the effects on epithelial cell biology. It is therefore conceivable that the effects could be exerted by antibodies against DGPs and autoantibodies targeted against self-molecules.

In addition to being deposited below the intestinal epithelium, TG2 autoantibodies also target blood vessel TG2 in the intestinal lamina propria.[86] The intestinal vascular network plays important roles in intestinal biology. One of these roles is to provide mechanical support to the villi. Duodenal biopsies derived from untreated celiac patients show disorganization in the vascular network as well as a reduction in vessel maturity.[86] Interestingly, the target of the disease-specific autoantibodies, TG2, has been reported to modulate angiogenesis.[87] In this context, it is tempting to speculate first that the described defects in the mucosal vasculature of celiac disease patients contribute to the disease pathogenesis and also that the blood vessel TG2-targeted autoantibodies take part in the aberrant organization of the mucosal vasculature. In this respect, our group has shown that celiac patients' autoantibodies that specifically target TG2 have the ability to inhibit angiogenesis *in vitro*[75] by increasing endothelial cell TG2 enzyme activity.[76] Moreover, our studies have also demonstrated that blood vessel permeability to macromolecules and lymphocytes *in vitro* is increased in the presence of patient-derived TG2 autoantibodies.[77] Therefore, the celiac disease-specific TG2-targeted autoantibodies deposited around mucosal blood vessels in the patients could contribute to the disorganization of the small-bowel vasculature and their increased permeability.

Although there are data available from *in vitro* studies that antibodies from celiac disease patients could take part in the remodeling of the small-bowel mucosal architecture and development of villous atrophy and crypt hyperplasia, there are unfortunately no studies demonstrating this *in vivo*. Neither passive transfer of IgG-class gliadin

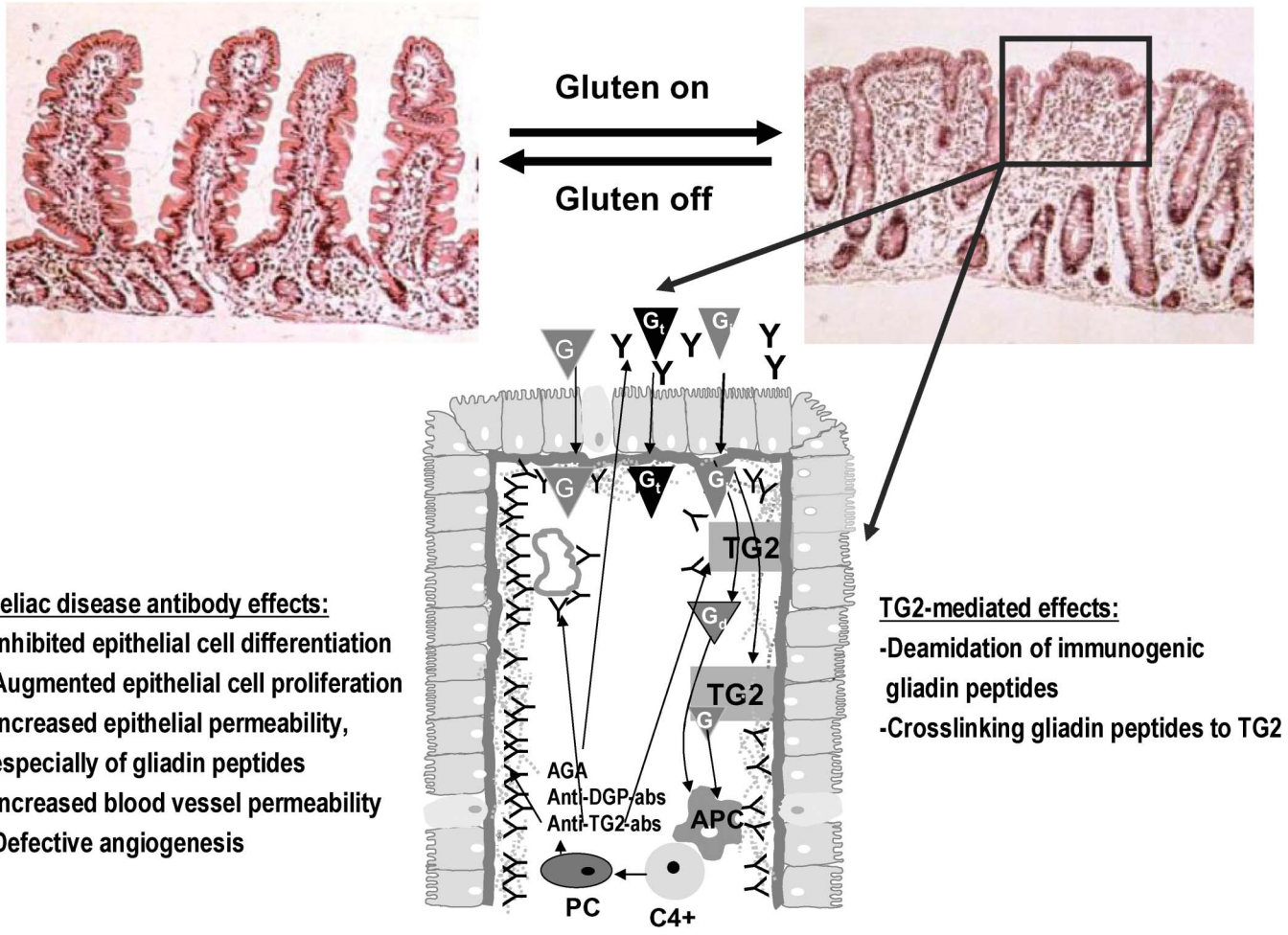

Figure 1 The pathogenesis of celiac disease. In celiac disease patients, the gluten-induced small-bowel mucosal deterioration occurs gradually from normal morphology (shown in the left) to villous atrophy with crypt hyperplasia and inflammation (shown in the right). The schematic presentation (below) shows what happens in the small-bowel mucosa at the cellular level in untreated celiac patients. G_t evoke an innate immunity response, which eventually lead to epithelial cell death and increased epithelial permeability. This enables the G_i to enter the lamina propria where TG2 either deamidates or crosslinks the peptides to themselves. G_d or gliadin-TG2 complexes are taken up by APCs. This is followed by DQ2-/DQ8-dependent activation of $CD4^+$ T cells and the subsequent secretion of antibodies by mucosal PCs. TG2 autoantibodies are found to be deposited in the small-intestinal mucosa below the epithelial basement membrane and around capillaries, but antibodies are also present in the lumen (indicated by Y in the figure). In these distinct locations, the antibodies, which are also targeted against other molecules than TG2, could take part in the disease pathogenesis, and their effects are listed in the figure. When the exogenous trigger gluten is removed, the mucosal damage recovers. AGA, anti-gliadin antibody; anti-DGP-abs, deamidated gliadin peptide antibodies; anti-TG2-abs, TG2 autoantibodies; APC, antigen-presenting cell; G, gliadin; G_d, deamidated gliadin peptide; G_i, immunogenic gliadin peptide; G_t, toxic gliadin peptide; PC, plasma cell; TG2, transglutaminase 2.

Table 2 Biological effects of celiac disease autoantibodies

	Effect describe	*References*
In vitro		
	Induction of epithelial proliferation	69 and 70
	Inhibition of epithelial differentiation	69
	Increase in epithelial permeability	71–73
	Interference with gliadin up-take	74
	Inhibition of angiogenesis	75 and 76
	Increase in vascular permeability	77
	Induction of neuronal apoptosis	78
	Binding to placental tissue	79
	Induction of trophoblast apoptosis	80
In vivo		
	Induction of ataxia	81
	No effect	82–84

antibodies[83] nor adenovirus vector-mediated expression of celiac patient-derived TG2-specific autoantibodies in mice[82] have resulted in any kind of intestinal pathology resembling that seen in human celiac disease. Similarly, experiments to immunize mice with the celiac disease autoantigen TG2 failed to induce any morphological changes in the small bowel.[84] Taken together, the participation of celiac disease antibodies in the development of the disease-characteristic small-bowel mucosal lesions remains unclear. It is noteworthy, however, that transgenic mice expressing celiac-type HLA with gluten-specific $CD4^+$ T cells from intestinal biopsies of patients neither developed celiac disease-like conditions.[88] As there is currently no animal model for celiac disease that presents with all features of the disorder, this issue certainly warrants further studies.

Antibodies in the extraintestinal environment

As we previously described, dietary gluten leads to the production of a wide range of antibodies in celiac patients once B cells are stimulated

(Table 1), and sometimes specific autoantibodies correlate with distinct extraintestinal manifestations (e.g., TG3 with dermatitis herpetiformis and TG6 with gluten ataxia).[63,67] However, patients also have circulating autoantibodies against TG2 in the serum and/or TG2-autoantibody deposits in the small-bowel mucosa, as discussed previously.

Even if TG3 has been identified as the autoantigen in dermatitis herpetiformis and patients produce IgA-class anti-TG3 autoantibodies, neither serum TG3 nor TG2 autoantibodies are able to bind to papillary skin structures.[63] This would suggest that the circulating antibodies are not directed against dermal targets and that the IgA/TG3 aggregates in the dermis of patients with dermatitis herpetiformis may represent immune complexes. The prevailing hypothesis for the pathogenesis of dermatitis herpetiformis postulates that the dermal IgA originates in the form of immune complexes from the small intestine, binds to the skin and activates the subsequent inflammatory response.[63] Although, to our knowledge, there are no *in vivo* studies directly proving that dermally deposited IgA is the cause of skin lesions; it is of great interest that a proportion of HLA-DQ8 transgenic mice in a non-obese diabetic background develop skin pathology reminiscent of dermatitis herpetiformis with dermal IgA deposits.[89]

The other extraintestinal manifestation of celiac disease that results in an additional autoantigen to TG2 is gluten ataxia, as already mentioned. Gluten ataxia is characterized by for instance a substantial loss of Purkinje cells.[6] Interestingly, it has been reported that in cell culture, patient anti-TG2 autoantibodies induce neuronal cell apoptosis, which is mediated by mitochondria-dependent mechanisms.[78] The authors reported that the apoptotic effect was more pronounced in cultures supplemented with antineuronal antibodies than in those supplemented with combined antigliadin and anti-TG2 antibodies. As this finding was published before TG6 was identified as an autoantigen in gluten ataxia, it would be interesting to know whether the anti-TG6 autoantibodies were responsible for the phenomena. It was later reported that only distinct celiac disease patient-derived anti-TG2 autoantibodies recognize neurons, and interestingly, such autoantibodies crossreact with both TG3 and TG6.[81] In the elegant study of Boscolo and co-workers, it was shown that intraventricular injection of both the anti-TG2 or the anti-TG2/3/6 crossreactive autoantibodies provoked transient, but equally intensive, ataxia in mice.[81] Although the previous study clearly demonstrates the pathogenetic potential of celiac-specific TG2-targeted autoantibodies to induce gluten ataxia, the precise contribution of TG6 autoantibodies still remains to be elucidated.

The various extraintestinal manifestations of celiac disease are not always characterized by specific autoantibodies other than those targeting TG2. TG2-targeted deposits have been reported to exist, for instance, in the liver of untreated celiac disease patients,[55] and interestingly, liver problems are reported as one extraintestinal manifestation of celiac disease. To date, there are no studies addressing the effects of disease-specific TG2 autoantibodies on hepatocytes or liver function.

Celiac disease is sometimes associated with poor pregnancy outcomes, including increased incidence of miscarriages and intrauterine growth restriction.[9] Although IgA, the characteristic class of celiac disease-specific autoantibodies is not able to pass from the maternal to the fetal site of the placenta, it has been show that celiac patient IgA-class autoantibodies *in vitro* bind to placental TG2.[79] However, the IgG-class TG2 autoantibodies in an undiagnosed pregnant woman do cross the placental barrier and may target the autoantigen, causing ill health to the fetus and newborn. Recently, Di Simone and colleagues showed that IgG-class anti-TG2 antibodies, both commercial and celiac disease patient derived, bind to cultured human primary trophoblasts and cause increased time- and dose-dependent apoptosis of these cells.[80] In pregnancy, the umbilical cord and placental vasculature are vitally important as they assure efficient delivery of nutrients and other essential compounds to the growing embryo. Therefore, it can be envisaged that the effects of the celiac-specific autoantibodies on vascular biology[75–77] also contribute to adverse pregnancy outcomes.

Following the same logic, the celiac patient TG2 autoantibodies have been suggested to be involved in the development of other celiac disease-related extraintestinal manifestations. For instance, celiac disease-specific autoantibodies recognize TG2 in bone,[90] thyroidal gland[91] and heart muscle tissues,[92] and furthermore, celiac disease has been associated with osteoporotic fractures and with thyroidal and cardiac autoimmunity and dysfunction.[90–92] Currently, we can only speculate that the disease-specific autoantibodies may have an active role in the pathophysiology of these conditions; although this suggestion is attractive, its validity awaits verification.

CONCLUSIONS

A hallmark of celiac disease is the presence of distinct autoantibody populations both in the patient's serum and in different tissues. Some of these autoantibodies (EMA and anti-TG2) are highly disease-specific and are used in clinics for presumptive diagnosis. Today, evidence is emerging in favor of their pathogenic potential, as discussed in the present review. However, it remains to be determined which antibody populations contribute to the disease progression at

Box 1. Role of B cells in autoimmunity, return to the past

Over the past few years, concepts in autoimmunity and immunology have changed so that some researchers are starting to think that the role of B cells in the regulation of immunology is different than was previously thought. In fact, some researchers in the areas of rheumatology or endocrinology have concluded that B cells have a central role in autoimmunity. This concept is based on Burnett's forbidden clone hypothesis, which states that an indolent lymphoproliferative disorder of B cells underlines the development of autoimmune disease. This event could be a consequence of a mutation in the regulatory genes of B-cell precursors. Thus, the precursors could have relevance in autoimmunity through their B-cell receptors, which could match self-antigens. Such cells would escape the homeostatic mechanisms and then proliferate, differentiate to plasma cells and produce relevant quantities of antibodies. The antibodies could modulate the physiology of the target tissue either by themselves or together with T cells and other inflammatory cells to produce the final damage. Because B-cell receptors have different specificities, their effects would be different. This intriguing hypothesis is supported by experimental evidence. In many autoimmune diseases, such as rheumatoid arthritis, Sjögren's syndrome, myositis, Grave's disease or even insulin-dependent diabetes mellitus, B cells have been recognized as key players that are essential for disease progression.[93] The most convincing data speaking in favor of this hypothesis are those demonstrating B-cell depletion to be an effective from of intervention in many autoimmune conditions.[93]

the small-bowel mucosal and extraintestinal levels and the mechanism involved.

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