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REVIEW ARTICLE

A role for anti-transglutaminase 2 autoantibodies in the pathogenesis of coeliac disease?

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Abstract Coeliac disease is an autoimmune-mediated disorder with both innate and adaptive immune components. The disease is triggered by dietary gluten, which provokes the development of a massive immune reaction leading to the destruction of the small-intestinal mucosal morphology and intestinal dysfunction. Besides the typical small-bowel symptoms extraintestinal manifestations may also arise in a subset of coeliac disease patients. In addition, gluten evokes the production of antibodies mainly targeting deamidated gluten peptides or transglutaminase 2. Although coeliac disease has traditionally been regarded as a T cell-mediated disorder, this review discusses the role of the gluten-induced disease-specific anti-transglutaminase 2-autoantibodies in the pathogenesis of the disease.

Keywords Coeliac disease · Transglutaminase 2 · Autoantibodies · Pathogenesis

Introduction

Coeliac disease is an autoimmune-mediated enteropathy triggered by the ingestion of gluten-containing cereals (including wheat, rye and barley) in genetically susceptible persons. Of the genetic factors contributing to susceptibility, the strongest recognized association is with human leukocyte antigen (HLA) genes. Approximately 95% of coeliac patients carry the HLA DQ2 molecule and the rest HLA DQ8 (Sollid 2002). The disease is classically characterized by diarrhoea, malabsorption and failure to thrive in childhood. Nowadays, however, the clinical symptoms are highly variable (Visakorpi and Mäki 1994) and the disease also manifests itself in a wide range of extraintestinal organs such as bone (osteopenia and osteoporosis), brain (gluten ataxia) and skin (dermatitis herpetiformis) (Mustalahti et al. 1999; Hadjivassiliou et al. 2006; Collin et al. 2007). The diagnosis is based on the histological finding of small-bowel mucosal villous atrophy with crypt hyperplasia together with profound inflammation. However, the presence of such a lesion is not specific for coeliac disease, since villous atrophy with crypt hyperplasia also occurs in conjunction with other enteropathies such as giardiasis and rotavirus gastroenteritis (Freeman 2004). Thus the mucosal lesion can rather be regarded as a general protective mechanism of the organism against the environmental insult to get rid of the pathogenetic "bug", which in the case of coeliac disease is gluten. The most obvious feature distinguishing coeliac disease from the other enteropathies is the presence of circulating antibodies against deamidated gliadin peptides (Ankelo et al. 2007; Kaukinen et al. 2007; Niveloni et al. 2007) or IgA-class autoantibodies targeted against transglutaminase 2 (TG2) during a gluten-containing diet (Dieterich et al. 1997). In addition to anti-TG2-antibodies, autoantibodies against other "self-antigens" such as desmin and actin are found in some patients (reviewed in Shaoul and Lerner 2007).

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The pathogenesis of coeliac disease

Although the exact mechanism underlying the development of gluten-induced mucosal lesion is not fully understood, coeliac disease pathogenesis is thought to progress through both innate and adaptive immunity mechanisms (Maiuri et al. 2003; Gianfrani et al. 2005). When gluten enters the human gastrointestinal tract it is only partially cleaved by gastrointestinal enzymes (Hausch et al. 2002; Shan et al. 2002). This partial digestion leads to the appearance of a large repertoire of peptides, of which some are toxic and others immunogenic to coeliac disease patients (Beissbarth et al. 2005). In susceptible individuals, the toxic peptides are thought to evoke an innate immunity response presumably mediated by interleukin (IL) 15 (Maiuri et al. 2000), resulting in epithelial cell damage (Hue et al. 2004). Subsequent entry of the immunogenic peptides into the lamina propria initiates the adaptive immunity response. TG2, present in the small-intestinal mucosa, is known to deamidate immunogenic gliadin peptides, this increasing their affinity to the HLA DQ2 molecules (Molberg et al. 1998). The result is lamina propria T cell activation, secretion of a legion of proinflammatory cytokines and eventually extensive tissue remodeling. In addition to launching massive mucosal inflammation, the activated T cells are thought to induce the production of coeliac disease-specific autoantibodies by B cells (reviewed in Jabri and Sollid 2006). The mucosal autoantibodies have nevertheless usually been given no role in the disease pathogenesis.

The production of coeliac disease-specific antibodies

Interestingly, while gliadin/gluten is the trigger of coeliac disease, the autoantibodies in addition to being targeted against deamidated gliadin peptides also recognize TG2. How can this be achieved? Already in the early 1990s Mäki suggested that coeliac disease autoantibodies could be generated in a mechanism involving the hapten-carrier model (Mäki 1994). At that time, when the target of coeliac disease autoantibodies had yet to be identified, it was speculated that gliadin could be complexed to the coeliac disease autoantigen and both would be processed together by the antigen-presenting cells but the autoantibodies would be directed against self and not only gliadin. After the discovery of TG2 as the major coeliac disease autoantigen and the indication that TG2 might form complexes with gliadin (Dieterich et al. 1997), the hapten-carrier model was reintroduced as a possible mechanism explaining the existence of anti-TG2-specific autoantibodies (Sollid et al. 1997). The proposed model assumed that in the small-intestinal mucosa gliadin is complexed with TG2 and that this complex is processed by B cells. The gliadin-specific CD4+ helper T cells present in the mucosa of untreated coeliac disease patients (Lundin et al. 1993; Molberg et al. 1997) would give the necessary help to activate autoantibody production by B cells.

Data published since the introduction of the hapten-carrier model as the possible mechanism explaining the existence of TG2 autoantibodies in fact speak in favour of this hypothesis. It has been shown that the coeliac disease autoantigen TG2 can crosslink gliadin peptides to itself (Skovbjerg et al. 2004; Dieterich et al. 2006). Furthermore, the presence of gliadin-specific T cells is already well established (Lundin et al. 1993; Molberg et al. 1997), while nobody has been able to identify TG2-specific T cells in the small-intestinal mucosa of untreated coeliac disease patients. It was also very recently shown that when TG2 is complexed with an inhibitor mimicking a gluten peptide, the active site of TG2 is exposed (Pinkas et al. 2007) and interestingly, the majority of coeliac patient IgA-class autoantibodies loose their affinity to TG2 if the catalytic amino acid triad is mutated (Byrne et al. 2007). Thus, when gliadin peptides are bound to TG2, neo-epitopes of TG2 would become uncovered, as suggested by Pinkas and coworkers (Pinkas et al. 2007), allowing autoantibodies against the active site to be generated through the hapten-carrier model.

It has very recently, been suggested that in coeliac disease antibodies against deamidated gliadin peptides might in fact precede the appearance of anti-TG2 autoantibodies (Ankelo et al. 2007; Korponay-Szabo et al. 2008), the conception being that initially the antibodies might be targeted against gliadin peptides and that autoantibodies against TG2 would be produced only after epitope spreading through molecular mimicry.

The epitope spreading theory could also apply in the development of extraintestinal manifestations. It has been reported that dermatitis herpetiformis patients have autoantibodies targeted against TG3 (Sardy et al. 2002), and it has recently been pointed out that gluten ataxia patients have autoantibodies against TG6 (Aeschlimann et al. 2007). It is thus conceivable that initially coeliac disease patients produce autoantibodies against deamidated gliadin peptides and subsequently against TG2. After the appearance of autoantibodies against other members of the transglutaminase family, these patients would develop extraintestinal manifestations depending on the type of transglutaminase the novel autoantibodies are targeted against.

The role of coeliac disease-specific autoantibodies in the development of the small intestinal mucosal lesion

It has been shown that the coeliac disease-specific autoantibodies against TG2 are produced locally in the

small-intestinal mucosa (Marzari et al. 2001) and probably drift into the circulation by "spilling over" from the intestine. These autoantibodies, in addition to being present in the circulation, are also sequestered at the site of their production. In untreated coeliac disease patients they can be found deposited in the small-bowel mucosa on extracellular TG2 below the epithelial layer and around blood vessels (Korponay-Szabo et al. 2004; Kaukinen et al. 2005; Salmi et al. 2006). Interestingly, also patients with early stage coeliac disease with normal small-bowel mucosal villous morphology (Korponay-Szabo et al. 2004; Kaukinen et al. 2005) and even seronegative patients evince these mucosal TG2-targeted autoantibody deposits when on a gluten-containing diet (Salmi et al. 2006).

Are the coeliac disease-specific circulating autoantibodies and the small-bowel mucosal autoantibody deposits targeting TG2 merely innocent bystanders or could they actually play a role in the disease pathogenesis? The first report on the biological effects of coeliac disease autoantibodies on distinct cellular functions was published in 1999, when it was shown that untreated coeliac patient IgA inhibits the in vitro differentiation of intestinal epithelial cells (Halttunen and Mäki 1999). In line with these findings are results showing that commercial anti-TG2 antibody and anti-TG2 monoclonal antibodies derived from coeliac disease patients induce a cell cycle S-phase entry of coeliac patient epithelial cells in biopsy samples *ex vivo* (Barone et al. 2007). It has also been reported that a subset of coeliac patient autoantibodies increase the permeability of the epithelial layer (Zanoni et al. 2006). Thus the action of the autoantibodies on the intestinal epithelium could well contribute to the development of crypt hyperplasia with the lack of differentiation and enhanced proliferation of the epithelium (Juuti-Uusitalo et al. 2007) as well as to the increased epithelial permeability seen in the small intestine of untreated coeliac patients (Smecuol et al. 1997).

The autoantibodies also affect the function of mesenchymal cells by increasing S phase entry (Barone et al. 2007), inhibiting cell motility and enhancing matrix degradation (Halttunen 2000). Consequently the effects exerted by coeliac disease-specific autoantibodies on mesenchymal cells could participate in the mucosal damage for instance by inducing extracellular matrix breakdown, which is indicated by the increased expression of certain matrix metalloproteinase in the small-intestinal mucosa of untreated coeliac disease patients (Bister et al. 2005; Ciccocioppo et al. 2005).

Recently it was found that autoantibodies derived from coeliac disease patients are able to activate monocytes upon binding to toll-like receptor 4 (Zanoni et al. 2006). Moreover, serum from untreated coeliac children is reported to induce monocyte-mediated antibody-dependent cytotoxicity (Saalman et al. 1998). Although the role of monocytes in coeliac disease is but poorly understood, it has been reported that monocytes activated by exogenous gliadin secrete cytokines such as IL-8 and tumour necrosis factor α (Jelinkova et al. 2004). Thus, activation of monocytes by the coeliac disease-specific autoantibodies could participate in the pathogenesis by attracting immune cells to the inflamed tissue and by activating matrix metalloproteinases through the secretion of the above-mentioned inflammatory cytokines. Furthermore, the autoantibodies could promote tissue damage by inducing monocyte-mediated cytotoxicity in target cells together with gliadin. Altogether, these findings suggest that the coeliac disease-specific TG2-targeted autoantibodies might in fact be a link between the innate and adaptive immune response in the pathogenesis of coeliac disease, as suggested by Zanoni and coworkers (Zanoni et al. 2006).

Recent findings indicate that in coeliac disease anti-TG2-specific autoantibodies are deposited around the small-bowel mucosal blood vessels (Korponay-Szabo et al. 2004; Kaukinen et al. 2005; Salmi et al. 2006) and interestingly, TG2 has a role in angiogenesis (Haroon et al. 1999; Jones et al. 2006). These observations set the basis for studies which demonstrated that coeliac patient autoantibodies specifically targeted against TG2 inhibit several steps in the process of angiogenesis in vitro (Myrsky et al. 2008). The small-bowel mucosal vasculature has been reported to be disorganized in untreated coeliac disease (Cooke and Holmes 1984), although this aspect has been largely ignored. Thus, the anti-angiogenic effects of the TG2-targeted autoantibodies could well lead to the abnormal appearance of the entire vasculature network seen in the small-intestinal mucosa of untreated coeliac disease patients and thereby participate in small-bowel mucosal remodeling.

The contribution of the coeliac type autoantibodies to the development of neurological manifestations

Neurological manifestations occur in approximately 7% of coeliac disease patients (Luostarinen et al. 1999). These manifestations are highly variable and include disorders such as neuropathy, memory impairment as well as epilepsy, brain atrophy and gluten ataxia (Collin et al. 1991; Hadjivassiliou et al. 1996; Luostarinen et al. 1999). The presence of serum antibodies against gliadin has been indicated in these conditions, but whether autoantibodies against TG2 or other coeliac disease antigens exist in the circulation is less well established. Interestingly, however, a paper by Hadjivassiliou and coworkers (Hadjivassiliou et al. 2006) reported that all gluten ataxia patients included in their study had IgA-class autoantibodies targeted against TG2 in the small-intestinal mucosa regardless of the fact

that only one-third of them had these antibodies in the serum. In the same study it was further shown that the autoantibodies were in fact also deposited in the brain vasculature of a gluten ataxia patient. Recently it has also been shown that injection of serum derived from gluten ataxia patients or recombinant anti-TG2-specific antibodies from coeliac disease patients to mouse brain causes ataxia-like symptoms in these animals (Boscolo et al. 2007).

Moreover, coeliac disease patients evincing neurological symptoms have been reported to have circulating neuronal antibodies, although such antibodies have also been found in neurological conditions unrelated to coeliac disease (Volta et al. 2002). These antibodies are mainly IgG class and recognize either enteric or central nervous system neurons such as Purkinje cells and thus form an antibody population distinct from the TG2-targeted autoantibodies (Volta et al. 2002). Interestingly, however, sera from untreated coeliac disease patients with neurological disorders evincing both neuronal and anti-TG2-autoantibodies have been reported to induce neural cell apoptosis (Cervio et al. 2007). Although sera from patients without neuronal antibodies but with TG2-targeted antibodies could also induce significant apoptosis, sera also containing the neuronal antibodies were more efficient in this respect (Cervio et al. 2007). Taken together, the coeliac patient autoantibodies targeted against TG2 and neuronal antigens possibly other than TG2 might lead to the development of neurologic impairment via a hitherto undescribed mechanism. This might involve increased permeability of the blood-brain-barrier due to the TG2-targeted autoantibody binding, as suggested by Boscolo and coworkers, as well as neuronal cell apoptosis induced by the neuronal antibodies (Boscolo et al. 2007; Cervio et al. 2007).

The mechanism behind the coeliac disease autoantibody function

The main target of coeliac disease-specific autoantibodies, TG2, is a multifunctional protein with cross-linking as well as G protein function (Fesus and Piacentini 2002). In addition, the protein has been implicated in non-enzymatic processes such as cell adhesion and signaling (Akimov et al. 2000; Balklava et al. 2002). There are reports that IgA fractions from untreated coeliac patients are not able to inhibit the enzymatic activity of TG2, while affinity-purified patient anti-TG2 antibodies are partially inhibitory (Dieterich et al. 2003). The remaining activity was nonetheless still sufficient for crosslinking (Dieterich et al. 2003). Furthermore, it has been demonstrated that IgA and IgG antibody fractions from untreated coeliac disease patients reduce the in vitro enzymatic activity of TG2 by 20% (Esposito et al. 2002). More recently it has been reported that coeliac disease patient autoantibodies actually enhance the transamidating activity of TG2 in conditions mimicking the in vivo situation more than those used in the two above-mentioned publications (Kiraly et al. 2006). It is of note that the same group also showed patient autoantibodies to be able to inhibit the G protein function of TG2 (Kiraly et al. 2006). As mentioned above, TG2 has also nonenzymatic functions, but up to date the effects of coeliac patient autoantibodies on these functions have not been thoroughly addressed experimentally in any study and the possible modulatory effects of the patient autoantibodies on these nonenzymatic functions have only been discussed.

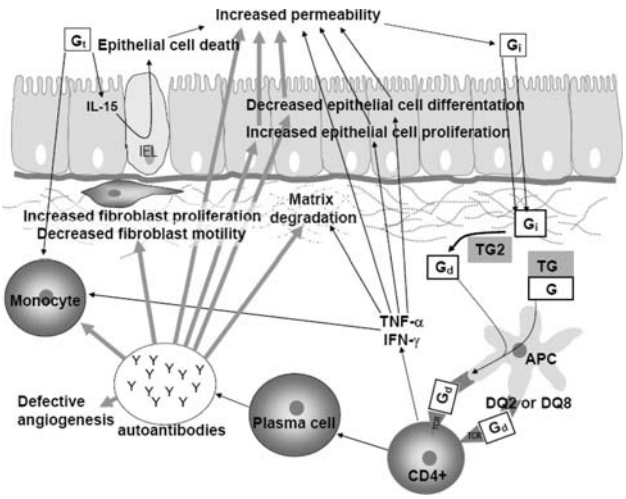

Fig. 1 Autoantibody involvement in coeliac disease pathogenesis. Toxic gliadin peptides (G_t) evoke an innate immunity response through the secretion of interleukin (*IL*) 15 which eventually leads to epithelial cell death and increased epithelial permeability. This enables the immunogenic gliadin peptides (G_i) to enter the lamina propria, where they are thought to be deamidated by transglutaminase 2 (*TG2*). Deamidated peptides (G_d) are endocytosed and processed by antigen-presenting cells (*APC*) either alone or complexed to TG2 (the hapten-carrier model). The APCs then present the peptides bound to DQ2 or DQ8 grooves to T cells. T cell receptors (*TCR*) on the surface of helper T cells recognize the deamidated gliadin in the context of DQ2 or DQ8, which leads to a strong T cell response with secretion of several inflammatory cytokines such as tumour necrosis factor (*TNF*) α and interferon (*IFN*) γ. The action of these cytokines is traditionally thought to result in mucosal disruption by enhancing the proliferation and reducing the differentiation of epithelial cells as well as increasing the permeability of the epithelium. Furthermore, these cytokines are also thought to contribute to matrix degradation and activation of monocytes. In addition to inducing the secretion of inflammatory cytokines the T cells are also thought to induce the secretion of anti-TG2-targeted autoantibodies by mucosal B cells. Experimental evidence shows that the autoantibodies produced have effects on epithelial cell function, matrix degradation and activation of monocytes similar to those of the gluten-induced secreted proinflammatory cytokines. Moreover, these autoantibodies also modulate the function of fibroblasts by increasing their proliferation and inhibiting their motility. Furthermore, the anti-TG2-targeted autoantibodies inhibit angiogenesis, which could well be an additional contributor in small-bowel mucosal remodeling

Conclusions

In summary, the coeliac disease-specific autoantibodies targeted against TG2 interfere with or modulate the function of different cell types (summarized in Fig. 1) and, interestingly, some of these effects resemble the action of the coeliac-toxic gliadin or the gliadin-induced proinflammatory cytokines. We thus conclude that the coeliac disease-specific autoantibodies altogether and specifically targeted against TG2 are pathogenetically relevant and therefore constitute an important contribution to disease progression in addition to the T-cell driven mechanism. In fact, since the autoantibodies are present in the small-intestinal mucosa at an early stage in the disease when the mucosal morphology is still normal and there is as yet no appreciable inflammation in the lamina propria (Korponay-Szabo et al. 2004; Kaukinen et al. 2005; Salmi et al. 2006), we suggest that the TG2-targeted autoantibodies might constitute a pathogenic factor acting in the early disease phase together with gliadin. All in all, coeliac disease could be included in the group of autoimmune diseases such as myastenia gravis and pemphigus vulgaris in whose pathogenesis the disease-specific autoantibodies have been experimentally shown to play a fundamental role (Vincent et al. 1998; Aoki-Ota et al. 2004).

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