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REVIEW ARTICLE

Tissue transglutaminase in celiac disease: role of autoantibodies

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Abstract In celiac disease (CD), gluten, the disease-inducing toxic component in wheat, induces the secretion of IgA-class autoantibodies which target tissue transglutaminase (tTG). These autoantibodies are produced in the small-intestinal mucosa, and, during gluten consumption, they can also be detected in patients' serum but disappear slowly from the circulation on a gluten-free diet. Interestingly, after adoption of a gluten-free diet the serum autoantibodies disappear from the circulation more rapidly than the small-intestinal mucosal autoantibody deposits. The finding of IgA deposits on extracellular tTG in the liver, kidney, lymph nodes and muscles of patients with CD indicates that tTG is accessible to the gut-derived autoantibodies. Although the specific autoantibody response directed against tTG is very characteristic in celiac patients, their role in the immunopathology of the celiac mucosal lesion is a matter of debate. Here we report a brief summary of anti-tTG antibody effects demonstrating that these antibodies are functional and not mere bystanders in the disease pathogenesis. In fact, they inhibit intestinal epithelial cell differentiation, induce intestinal epithelial cell proliferation, increase epithelial permeability and activate monocytes and disturb angiogenesis.

Keywords Celiac disease · Tissue transglutaminase · Autoantibodies · Autoimmunity

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Abbreviations

CD	Celiac disease
tTG	Tissue transglutaminase
TGF β	Trasforming growth factor β
GA	Gluten ataxia

Tissue transglutaminase—biological aspects

Tissue transglutaminase (tTG), a member of the vast TG enzyme family, is a ubiquitously expressed multifunctional protein (Griffin et al. 2002; Lorand and Graham 2003). tTG prevalently catalyzes the formation of isopeptide linkages between the γ-carboxamide group of protein-bound glutamine residue and the ε-amino group of protein-bound lysine residue. Its catalytic activity requires millimolar concentration of Ca^{2+} and it is inhibited by guanine nucleotides. Glutamine residues can be deamidated to glutamic acid as a side-reaction in the absence of suitable amines or at low pH. Furthermore, tTG is capable of both binding and hydrolyzing GTP, so that the enzyme can function as a cell signal transducer, promoting the activation of the α_{1B}-adrenoreceptor (Im et al. 1997). At present, however, the physiological consequences remain unclear. The binding of GTP or Ca^{2+} causes opposite functions of tTG. These enzymatic activities of the protein appear to be mutually exclusive in vivo. This hypothesis has been supported by very recent results on the large conformational changes observed upon treatment with the allosteric effectors Ca^{2+} and GTP/GDP (Pinkas et al. 2007). Besides cross-linking and GTP-hydrolyzing activity, additional functions, such as disulphide isomerase activity (Hasegawa et al. 2003) and kinase activity (Mishra and Murphy 2004), have been attributed to tTG.

The intriguing properties of this enzyme are related not only to its cellular and tissue distribution (Griffin et al. 2002; Lorand and Graham 2003), but also to the nature of the target protein substrates. A number of protein substrates for TGs and in particular for tTG have been identified in vitro as well as in vivo (Esposito and Caputo 2005). However, in many cases the importance of tTG-catalyzed modifications are still to be demonstrated.

tTG is prevalently an intracellular enzyme mainly localized in the cytosol and, in some cell types such as neuroblastoma cells, it is also be found in the nuclear compartment (Lesort et al. 1998). Moreover, tTG has been detected on the cell surface (Akimov et al. 2000; Akimov and Belkin 2001; Barone et al. 2007), and in the extracellular matrix (Aeschlimann and Thomazy 2000) indicating a wide range of possible biological activities. tTG contributes to the organization of the cytoskeleton by cross-linking various cytoskeleton proteins, i.e. beta-tubulin, actin, myosin, vimentin. This extensive polymerization, which occurs during the final steps of apoptosis, stabilizes the structure of the dying cells thereby preventing release of cell components that might give rise to inflammatory or autoimmune responses. Recent studies have focused on the role of tTG in apoptosis via activation of the transforming growth factor β1 (TGF-β1) (Falasca et al. 2005). The release of the activate cytokine allows macrophages to recognize and internalize apoptotic cells without causing an inflammatory response. In $tTG^{-/-}$ mice the clearance of apoptotic cells is defective leading to autoimmunity (Falasca et al. 2005).

tTG is constitutively externalized from undamaged cells into the extracellular space where it plays an important role in cell-matrix interactions (Lorand and Graham 2003; Zemskov et al. 2006). Since there is no leader peptide domains in tTG (Gentile et al. 1991), the mechanisms of tTG translocation across the membrane and the pathway of externalization remain unknown. Likewise, it is unknown the subsequent fate of externalized tTG, which will be in part removed from the cell surface and in part will constitute the pool of the membrane-bound protein. Recently, a novel mechanism of regulation of surface tTG through internalization and subsequent lysosomal degradation, has been reported. tTG endocytosis occurs by means of a dynamin-dependent process that involves clathrin- and caveolin-dependent pathways and requires lipoprotein receptor-related protein 1 (Zemskov et al. 2007). As an outside membrane-bound protein, tTG could be catalitically inactive under physiological conditions and could mediate the interaction of β1 and β2 integrins with fibronectin in a catalytic independent manner (Akimov et al. 2000). Through this interaction, tTG seems to modulate cell-matrix adhesion, spreading, integrin-mediated signaling, cell migration, proliferation or differentiation (Akimov et al. 2000; Akimov and Belkin 2001; Balklava et al. 2002; Mangala and Mehta 2005).

Finally, tTG has been directly implicated in a number of diseases, such as tissue fibrosis and scarring (liver and renal fibrosis), inflammation, neurodegenerative diseases, dermatitis herpetiformis, tumor growth, and autoimmune disorders such as celiac disease (CD) (Kim et al. 2002; Verderio et al. 2004; Ruan and Johnson 2007).

Tissue transglutaminase as autoantigen in celiac disease

CD is an immune-mediated disease that is triggered by the ingestion of gliadin and of other toxic prolamines in genetically susceptible individuals (Sollid 2000, 2002). It is characterized by a dysregulated immune response at the gut level dominated by T cells of the Th1 type. This abnormal mucosal immune response results in the enteropathy. CD can be considered an autoimmune disease because of the presence of autoantibodies in both the serum and the intestinal mucosa of patients. The mechanisms leading to development of autoimmunity in CD are still largely unknown. It appears that long-term exposure of the immune system to gluten can lead to an increased incidence of autoimmunity in CD (Ventura et al. 1999); nevertheless, whether there is a direct correlation between gluten ingestion and the outcome of autoimmune diseases in CD patients is still under debate. The most evident expression of autoimmunity is the presence of serum antibodies to tTG (Dieterich et al. 1997).

In accordance with the upregulation of tTG in intestinal inflamed sites, tTG may generate additional antigenic epitopes by crosslinking gliadin peptides to itself and/or to other protein substrates. tTG-gliadin complexes bind to tTG-specific B cells, are endocytosed and processed. Gliadin-DQ2 complexes are then presented by the tTG-specific B cells to gliadin-specific T cells which provide the necessary help to produce anti-tTG antibodies (Sollid et al. 1997; Schuppan et al. 1998; Molberg et al. 2000). Since the existence of tTG specific T cells in the intestinal mucosa of untreated patients is not proven, it is hypothesized that the production of anti-tTG antibodies is driven completely by intestinal gliadin-specific T cells. The observation that anti-tTG antibody titers fall and can become undetectable during a gluten-free diet suggests that B cell activity depends on persistent antigen presentation.

A novel proposal to explain the autoantibody response to tTG in CD patients comes from Pinkas et al. The authors show that tTG undergoes a large-scale structural rearrangement in its closed (GTP-bound) and open (Ca^{2+}-activated) conformations. In a normal stress-free environment, most extracellular tTG is predominantly in a closed conformation despite relatively high extracellular Ca^{2+} concentrations. Some innate immune signals can trigger

rapid activation of tTG into its catalitically active, open conformation that exposes self-epitopes that are ordinarily inaccessible to the immune system. These "neo-epitopes" trigger an autoantibody response (Pinkas et al. 2007).

It is possible to isolate anti-tTG antibodies from all intestinal lymphocyte libraries, but not from those obtained from peripheral lymphocytes (Marzari et al. 2001). This is in contrast to antibodies against gliadin, which can be obtained from all libraries, indicating that while the humoral response against tTG occurs at the local level, that against gliadin occurs both peripherally and centrally. tTG antibodies are typically deposited in the small bowel mucosa below the basement membrane and around capillaries. These antibodies find their way into the circulation occasionally, even before architectural changes occur and the formation of the mucosal lesion and before $\gamma\delta$ T-cells are driven to the intraepithelial compartment in morphologically normal mucosa.

tTG is also the antigen for the in vitro and in vivo binding of celiac IgA antibodies to extraintestinal normal tissues, such as the liver, kidney, appendix, oesophagus, and umbilical cord sections (Korponay-Szabó et al. 2004) thus demonstrating that tTG is widely accessible to the intestinal produced circulating autoantibodies throughout the body. These findings suggest that IgA anti-tTG antibodies may be contributing factors in extraintestinal organ manifestations in celiac patients.

The presence of IgA anti-tTG antibodies in untreated CD patients has had a large diagnostic impact; serological tests based on the presence of anti-tTG antibodies have acquired a great importance, in particular for the possibility of generating effective tools for a wide non-invasive mass screening program (Crovella et al. 2007).

Although much is known about the role of tTG in CD (Stenberg et al. 2008), it is unclear if anti-tTG antibodies play a role in the pathogenesis of the mucosal lesion typical of the disease or if they represent bystanders in CD. Therefore investigation from different laboratories have been performed to understand whether tTG autoantibodies contribute or not to the intestinal lesion in CD.

Anti tissue transglutaminase antibodies effects on the enzymatic activity

The putative involvement of tTG in the pathogenesis of CD could be due to two distinct but interdependent pathways. The tTG-mediated deamidation of specific gliadin peptides transforms the ingested gliadin from non-stimulatory to efficient T-cell antigens (Molberg et al. 1998; Arentz-Hansen et al. 2000) able to evoke a massive secretion of local cytokines, thereby leading to alterations in enterocyte proliferation and differentiation. The tTG-mediated crosslinking between gliadin peptides and the enzyme itself leads to the formation of tTG-gliadin complexes that may contain neoepitopes that trigger mucosal T cells with the production of autoantibodies against tTG and gliadin (Molberg et al. 2000). Both reactions could be involved in the breakdown of tolerance and precipitation of disease. It is worth noting that the increase of both tTG activity in vivo and tTG protein have been detected at critical sites of CD, such as the intestinal brush border and subepithelial compartments (Esposito et al. 2003). In this context it one could hypothesize that tTG antibody inhibition would ameliorate the intestinal damage initiated by the enzyme.

With different experimental approach as several groups have addressed this issue, with quite different results as to the degree of inhibition (Esposito et al. 2002; Dieterich et al. 2003; Roth et al. 2003; Byrne et al. 2007; Király et al. 2006). In general, it is possible to conclude that IgA and IgG from serum of CD patients as well as monoclonal anti-tTG antibodies, especially those obtained from CD patients, display a partial and dose-dependent inhibitory effect on the transamidating activity of human tTG, both in vitro and in situ. It is interesting to underline that the degree of inhibition of tTG activity may vary significantly among patients. This result is probably due to the fact that these antibodies isolated from CD patients recognize different conformational tTG epitopes not located at the active site of the enzyme (Marzari et al. 2001; Esposito et al. 2002), or as suggested by Roth et al. the active site may be concealed from the immune system in vivo via the formation of the intermediary thioester with the substrate (Roth et al. 2003).

Recently, it has been described that celiac antibodies did not have significant inhibitory effects on transamidation/deamidation activity of tTG but, in contrast, they were able to enhance, in a dose-dependent manner, the reaction velocity to 105.4–242.2%. The authors suggest that celiac antibodies may stabilize the enzyme in a catalitically advantageous conformation (Király et al. 2006). Therefore, depending on binding epitopes and functional consequences, these antibodies may be harmful or protective.

Finally, our study on the effect of anti-tTG antibodies on the enzymatic activity associated with the extracellular surface shows that anti-tTG antibodies only partially inhibit the transamidating activity of tTG (Barone et al. 2007). This finding suggests that anti-tTG antibodies from patients with CD may not bind epitopes related to substrate recognition sites of extracellular membrane-bound tTG.

Anti tissue transglutaminase antibodies effects on cell cycle

The digestive epithelium is characterized by constant cell renewal and differentiation. Epithelial cells proliferate in

the crypts, where the undifferentiated epithelial stem cells are located, and then migrate toward the villus while differentiating into absorptive enterocytes. Since the most important characteristic of CD mucosal damage is both morphological alteration and cryptic disregulated proliferation, it is possible that anti-tTG antibodies have an effect on the cell morphology and on the cell cycle.

A study published in 1999, using a three-dimensional fibroblast—epithelial cell co-culture model mimicking the in vivo crypt-villus axis, provided indirect evidence of a contribution of tTG autoantibodies to the mucosal transformation observed in celiac patients (Halttunen and Mäki 1999). In that study it was demonstrated that anti-tTG IgA, as well as commercial anti-tTG monoclonal antibodies, inhibit fibroblast-induced TGF-β-mediated differentiation with a simultaneous increase in the proliferation rate of intestinal crypt-like T84 epithelial cells. TGF-β is considered to be the major autocrine/paracrine inhibitory regulator in the intestinal epithelium. It induces proliferation arrest in epithelial cells, often with simultaneous signaling for the terminal differentiation pathway. Since tTG is involved in the activation of latent TGF-β the authors suggested that blocking the bioactivity of tTG prevented the generation of the active form of TGF-β thus affecting the differentiation of the celiac epithelium (Halttunen and Mäki 1999). More recently, the same authors showed that celiac disease-specific autoantibodies targeted against tTG interfere with fibroblast–extracellular matrix interaction by inhibiting fibroblast motility and collagen gel contraction, as well as by increasing type I collagen degradation in vitro. In view of this, the authors suggested that celiac disease-specific IgA targeted against tTG decrease the level of matrix stabilization rather than increase matrix degradation per se (Haltunnen et al. personal communication).

More recently, we demonstrated that, like growth factors that drive arrested cells into S phase and so induce cell proliferation, anti-tTG antibodies cause $G_0 \rightarrow S$ transition in arrested NIH 3T3 fibroblasts. Similar results were obtained by using commercial antibodies, or antibodies from CD patients or from healthy individuals. Interestingly, both CUB 7402 and a monoclonal antibody from a CD patient induced S-phase entry in epithelial cells from intestinal biopsies of CD patients but not in non-celiac control patients (Barone et al. 2007).

The finding that these antibodies stimulate cell cycle progression suggests that they, by interacting with tTG on the cell surface, could modulate the tTG-integrin interaction that is required to mediate adhesion in the regulation of cell fate and maintenance of normal epithelial homeostasis or, more generally, to mediate processes that lead to DNA synthesis in the nuclei.

As proper actin dynamics is a prerequisite for the epithelial cell proliferation, tTG autoantibodies both commercially available and from CD patients are implicated in the regulation of cytoskeleton rearrangement in different cell lines. Using actin staining, it is possible to observe that the treatment with increasing amounts of CUB 7402 produces a dose-dependent enhancement of membrane ruffling formation with respect to untreated cells, which maintained a regular geometrical shape. These effects are not limited to intestinal cells, but occur also in epithelial cells of mammary origin as MCF7 cells and even in NIH 3T3 fibroblasts (Barone et al. 2007).

Anti tissue transglutaminase antibodies effects on angiogenesis

Angiogenesis, the process of new blood vessel formation, is dependent on the proliferation, migration, and differentiation of endothelial cells into tubular structures. tTG seems to play a crucial role in the remodeling of small arteries (Bakker et al. 2005; Bergamini et al. 2005). On the basis of the presence of tTG targeted antibody deposits around blood vessels in vivo (Korponay-Szabó et al. 2004), Myrsky et al. demonstrated that CD disease-specific IgA class autoantibodies targeting tTG disturb angiogenesis (Myrsky et al. 2008). The expression of vascular α-smooth muscle actin, a differentiation marker for mesenchymal vascular smooth muscle cells, is reduced in untreated CD patients resulting in a disorganized vasculature. In CD patients on a gluten free diet, the expression of vascular α-smooth muscle actin increases. In particular anti-tTG antibodies inhibit all the initial steps of angiogenesis such as sprouting of endothelial cells, migration of endothelial cells along the formed sprout and the formation of the endothelial tubes. Moreover, these antibodies are able to inhibit the migration of mesenchymal cells from the surrounding connective tissue to surround the endothelial tubes. However, they did not inhibit the last step of angiogenesis, that of differentiation of mesenchymal cells into vascular smooth muscle or pericytes. In addition, the autoantibodies causing the disorganization of the actin cytoskeleton in capillary cells types, as we have demonstrated in fibroblast cells (Barone et al. 2007), might inhibit cell migration (Myrsky et al. 2008).

Anti tissue transglutaminase antibodies effects on apoptosis

Increased enterocyte apoptosis has been associated with the celiac lesion (Moss et al. 1996). IL-15 production, which in turn is thought to cause intra epithelial lymphocytes

expansion in CD (Jabri et al. 2000) has been implicated in the increased expression of tTG and MICA in enterocytes, and of NKG2D on lymphocytes. The interaction between MICA and NKG2D is at least in part responsible for intra epithelial lymphocytes-induced enterocyte apoptosis and villus atrophy (Meresse et al. 2006). Several studies have been performed to evaluate whether antibodies to tTG affected cell apoptosis.

Using a TUNEL assay, we demonstrate that antibodies to tTG, whether commercial (CUB 7402) or from a CD patient, did not modify the basal apoptotic rate in NIH 3T3 fibroblasts and Caco-2 cells (Barone et al. 2007). Neither did they affect apoptosis in cultured intestinal CD biopsies, which suggests that tTG autoantibodies are unrelated to CD enterocyte apoptosis (Barone et al. 2007). However, Maiuri et al. reported that in a different system (T84 cells), a monoclonal anti-tTG antibody, namely 6B9, protected against apoptosis induced by the alpha-gliadin peptide 31–43, while CUB 7402 was not as effective (Maiuri et al. 2005).

In a recent study, Cervio et al. tested the hypothesis that sera containing antineuronal antibodies present in a subset of CD patients may evoke neuronal damage (Cervio et al. 2007). The authors used a neuroblastoma cell line of human origin (ie, SH-Sy5Y) to demonstrate that antineuronal antibodies from patients with CD and neurologic promote apoptosis by activating a mitochondrial-dependent pathway. Interestingly, this proapoptotic mechanism is likely to depend on the combination of anti-gliadin and anti-tTG antibodies. In fact, anti-gliadin- and anti-tTG-depleted CD sera had an apoptotic effect similar to controls (Cervio et al. 2007).

Anti tissue transglutaminase antibodies effects on intestinal permeability

One fundamental question is how "toxic" gliadin peptides go through intestinal epithelial layer and gain access to immuno-competent cellular compartments. In normal condition, intestinal epithelium represent a barrier to the entrance of external antigens thanks to the intracellular gates of tight junctions. Therefore, any disorder compromising the tight junction structure must have a dramatic effect on the integrity of epithelium barrier and, as a consequence, on antigenic load in the intestinal mucosa. It is worth to note that a key feature of the early stages of CD as well as in autoimmune disease is the presence of increased intestinal epithelial cell permeability (Watts et al. 2005; Kagnoff 2005). Recently, it has been demonstrated that in active CD, a subset of anti-tTG IgA antibodies are functionally active increasing intestinal permeability. Moreover, anti-tTG antibody are able to induce monocyte activation by production of proinflammatory cytokines (Zanoni et al. 2006). Such antibodies recognize the viral protein VP-7, suggesting a possible involvement of rotavirus infection in the pathogenesis of the disease, through a mechanism of molecular mimicry.

Anti tissue transglutaminase antibodies effects on extraintestinal manifestations of CD

Gluten sensitivity in CD causes intestinal atrophy resulting in a malabsorption syndrome. However, gluten sensitivity may involve several organs and is often associated with extraintestinal manifestations (Kagnoff 2005). Among the most common neurological manifestations associated with CD are peripheral neuropathy, cerebellar ataxia, the so-called gluten ataxia (GA), epilepsy, and migraine. In patients with GA, anti-tTG antibodies cross-react with neurons but additional anti-neuronal antibodies are present. Recently, it has been demonstrated that monoclonal anti-tTG antibodies from CD patients when injected into mouse brain, localize at the level of the brain blood vessels and cause GA (Boscolo et al. 2007). Since there are deposits of anti-tTG antibodies around vessels in the brain of GA patients but not in the control brain (Marzari et al. 2001; Hadjivassiliou et al. 2006), Boscolo et al. hypothesized that such antibodies affect the functioning of the blood–brain barrier. By investigating the mechanisms underlying neurologic impairment in CD another research group observed that antineuronal antibodies and, to a lesser extent, combined antigliadin and anti-tTG antibodies in CD sera contribute to neurologic impairment via apoptosis (Cervio et al. 2007).

The association between CD and autoimmune liver disorders such as primary biliary cirrhosis, autoimmune hepatitis, and primary sclerosing cholangitis is well documented (Kaukinen et al. 2002). Anti-tTG antibodies deposits have been found around blood vessels in the liver of CD patients with severe liver disease (Korponay-Szabó et al. 2004). Furthermore, there are data suggesting that hepatic disturbances can be reversed with dietary treatment (Kaukinen et al. 2002). Further studies are needed to clarify the relationship between the CD specific anti-tTG antibodies and the extraintestinal manifestations.

Anti-idiotype antibodies

The existence of an idiotype-anti-idiotypic network focused on tTG in CD has recently been observed (Ferrara et al. 2007). Anti-anti-tTG antibodies were found in both the intestinal mucosa and in the sera of several subjects genetically predisposed to CD and with intact intestinal mucosa. Interestingly, the ratio between anti-anti-tTG antibodies and anti-tTG was higher in asymptomatic subjects than in

subjects with CD with typical intestinal lesions. In addition, it has been demonstrated that an animal model (mice C56B1/6J), artificially induced to produce anti-tTG antibodies, develops a strong anti-idiotype response (Di Niro et al. 2008). Also in the mouse model, high anti-tTG titers coupled to low anti-idiotype and vice versa (Di Niro et al. 2008). Such findings are opening the way to a new field of investigation focused on the effects of the interaction between the autoimmune response (anti-tTG) and the anti-idiotype response (anti-anti-tTG) in the pathogenesis of CD. The hypothesis that an idiotypic network is involved in sequestering anti-tTG antibodies to modulate their biological and pathological roles is attractive and requires further investigation.

Conclusions

A characteristic feature for CD is the presence of specific anti-tTG antibodies in the serum as well as in the small-intestinal mucosa of patients not on a diet. Mucosal antibody deposits disappear slowly from both serum and mucosal deposits as the mucosa begins to heal (Stenman et al. 2008). Hence the question: are tissue tTG antibodies only bystanders in the disease pathogenesis or are pathogenetic? Several data suggest that tTG autoantibodies might themselves be pathogenic. In fact, they inhibit intestinal epithelial cell differentiation (Halttunen and Mäki 1999), induce intestinal epithelial cell proliferation (Barone et al. 2007), increase epithelial permeability and activate monocytes (Zanoni et al. 2006) and disturb angiogenesis (Myrsky et al. 2008).

These key aspects of cell behavior involve surface tTG, therefore, we hypothesize that tTG autoantibodies, by interacting with the extracellular membrane-bound tTG, may play an important role in the progression and maintenance of the mucosal lesion typical of celiac disease.

The finding of IgA deposits on extracellular tTG in the liver, lymphnodes and muscles indicates that tTG is accessible to the gut-derived autoantibodies (Korponay-Szabó et al. 2004). Therefore, several intestinal and extraintestinal clinical manifestations of CD (e.g. liver, heart, nervous system) are possibly related to the presence of autoantibodies in situ. In conclusion, the results reported here support the hypothesis that gluten-induced disease-specific autoantibodies might constitute an important contributor in the development and persistence of the flat mucosal lesion seen in CD.

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