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Review

# Transglutaminase 2-targeted autoantibodies in celiac disease: Pathogenetic players in addition to diagnostic tools?

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ABSTRACT

Celiac disease comprises intolerance against dietary gluten present in wheat, rye and barley, and it belongs to the most common food-related life-long disorders in Western countries. Nowadays celiac disease is conceived as an autoimmune-mediated systemic disorder commonly presenting as enteropathy in genetically susceptible individuals. The most obvious feature distinguishing celiac disease from other small-intestinal enteropathies is the presence of autoantibodies against transglutaminase 2 (TG2) during a gluten-containing diet. The gluten-derived gliadin peptides and the self, TG2, have established and well-accepted role in celiac disease pathogenesis. TG2 is known to deamidate, and crosslink gluten-derived gliadin peptides to itself, thereby favoring disease progression. The celiac disease-specific TG2-targeted autoantibodies are deposited in the small-bowel mucosa as well as in other tissues, and interestingly, extraintestinal manifestations of the disease involving these particular tissues have been reported. As the TG2-targeted autoantibodies have experimentally been shown to modulate the function of different cell types *in vitro* similarly to what has been reported to occur in untreated celiac disease, they could constitute an important contribution to disease progression. In this review we discuss the role of TG2, the autoantigen and the autoantibodies targeted against it in the pathogenesis of celiac disease.



**Contents**



## 1. Introduction

Celiac disease, an autoimmune-mediated systemic disorder commonly presenting as enteropathy, is provoked in genetically predisposed individuals by the ingestion of wheat, barley and rye proteins i.e. gluten. The best characterized genetic factors contributing to disease predisposition are the human leukocyte antigen (HLA) molecules DQ2 and DQ8. Approximately 95% of patients carry the alleles encoding the DQ2- and most of the rest the DQ8-molecule [1]. In celiac patients the ingestion of gluten leads to small-intestinal mucosal inflammation and villous atrophy together with crypt hyperplasia as well as the appearance of clinical symptoms. A wide variety of extraintestinal manifestations occurring with or without enteropathy have also been described in the context of celiac disease. These include dermatitis herpetiformis (skin disorder), osteopenia and osteoporosis, neuronal problems (for example gluten ataxia) and several hepatic disorders, to

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name a few [2]. In addition to clinical symptoms and the typical small-intestinal mucosal damage, the consumption of gluten evokes the production of pathognomic antibodies targeted against the enzyme transglutaminase 2 (TG2) [3] and gluten-derived gliadin peptides [4]. The value of the disease-specific antibodies in the diagnostics of celiac disease is fully acknowledged and as the tests are highly accurate they offer a convenient means of selecting patients to undergo diagnostic small-bowel endoscopy and biopsy [5]. The targets of the celiac disease-specific antibodies TG2 and gliadin peptides have established and well-accepted roles in celiac disease pathogenesis, whereas the role of the disease-specific antibodies themselves remains obscure. This review highlights the importance of TG2 and discusses the role of the gluten-induced disease-specific antibodies in the pathogenesis of celiac disease.

## 2. Celiac disease autoimmunity

In celiac disease all the elements crucial for autoimmunity have been identified: the environmental trigger and driving force; food gluten, the susceptibility of major histocompatibility complex (MHC) class II genes (DQA and DQB) and the self; TG2. Celiac disease is self-perpetuating, similar to other autoimmune disorders if the specific trigger, gluten, is not removed. When the trigger is removed, the clinical condition and the small-bowel mucosal lesion recovers and also the production of TG2 autoantibodies declines [6,7]. It is intriguing to hypothesize that the disease-specific TG2-targeted autoantibodies, which appear very early during the disease process even before the development of villous atrophy, are disease inducing, as discussed below. In fact, nature might have meant the celiac disease-specific autoantibodies to have biological functions (Fig. 1) instead of merely being an epiphenomenon, and perhaps even to play a role in protection against disease.

## 3. Overview of celiac disease pathogenesis

Gluten in wheat, barley and rye has a high content of glutamine and proline residues rendering it resistant to gastrointestinal proteolytic enzymes. The incomplete hydrolysis of gluten during

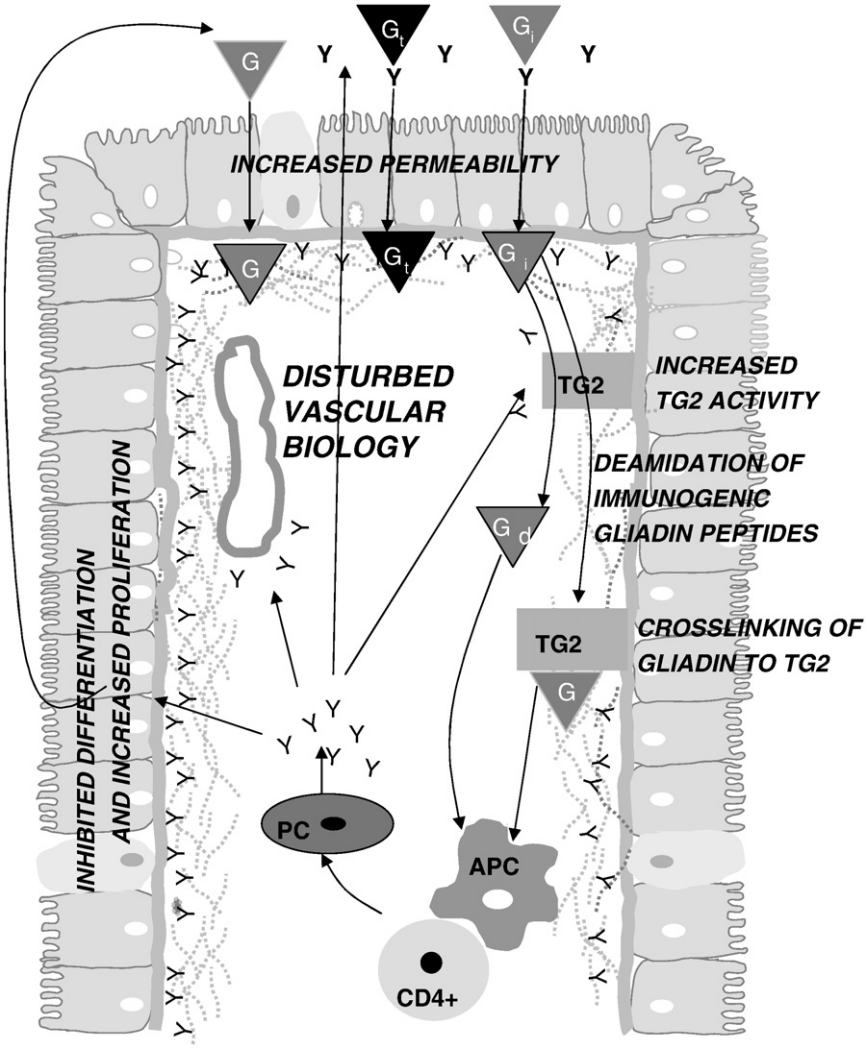


**Fig. 1.** The contribution of transglutaminase 2 (TG2) and the celiac disease-specific autoantibodies in the disease pathogenesis. Disease-specific IgA class autoantibodies present in the intestinal lumen (indicated by bolded Y) bind to toxic and immunogenic gliadin peptides (Gt and Gi, respectively) and enable their transepithelial passage to the lamina propria. In the lamina propria TG2 deamidates the immunogenic peptides and crosslinks gliadin peptides to itself. Deamidated gliadin peptides (Gd) and gliadin–TG2-complexes are taken up by antigen-presenting cells (APC) and presented to CD4+ T cells (CD4+). This could lead to the production of celiac disease-specific autoantibodies against gliadin as well as TG2 by plasma cells (PC). TG2 autoantibodies are found to be deposited in the small-intestinal mucosa below the epithelial basement membrane and around capillaries. Below the epithelial sheet, the autoantibodies could increase the activity of TG2, leading to augmented deamidation and crosslinking of gliadin peptides by TG2. In addition, these subepithelially located autoantibody deposits could partly account for increased epithelial permeability, inhibited differentiation and increased proliferation. Further, the TG2-targeted autoantibodies located around mucosal capillaries could disturb vascular biology by inhibiting locally ongoing angiogenesis and by increasing vascular permeability. G indicates any type of gliadin peptide.