

Review

Microbial Transglutaminase is Beneficial to Food Industries but a Caveat to Public Health

Aaron Lerner^{1,2,*}, Torsten Matthias²

¹ B. Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, 31096, Israel

² AESKU.KIPP Institute, Wendelsheim, 55234, Germany

* Correspondence: Aaron Lerner, Email: aaronlerner1948@gmail.com; Tel.: +49-6734-9622-1010; Fax: +49-6734-9622-2222.

ABSTRACT

Microbial transglutaminase (mTG) is a survival factor for bacteria that is heavily used as a protein glue in the processed food industries. Despite the manufacturers' claims for its safe usage, scientific observations are accumulating for its unwanted effects on human health. The enzyme can cross link proteins, imitating its family member, tissue transglutaminase, the autoantigen of celiac disease. Its gliadin cross-linked complexes are immunogenic in celiac disease. In the intestinal lumen, mTG exerts anti protease activity and forms resistant isopeptide bonds, it is anti-phagocytic, thus suppressing luminal protective pathways. It increases intestinal permeability, is trans-epithelialy transported and faces the enteric mucosal immune cells. Finally, mTG-containing products can react as emulsifiers and mucolytic agents thus compromising barriers' integrities. The present review summarizes and updates on the potential detrimental effects of mTG, aiming to protect the public from the enzyme's unwanted effects.

KEYWORDS: microbial transglutaminase; processed food; food additive; food industry; celiac disease; public health

INTRODUCTION

Transglutaminases (TGs) (EC 2.3.2.13), *i.e.*, protein-glutamine γ -glutamyltransferase, are multi-functional, pleiotropic enzymes, expressed ubiquitously and extensively in living organisms. They are active in all mammalian tissues, in invertebrates, plants, yeasts and bacterial cells. Presently, nine members of the TG family have been characterized in human tissues, playing a crucial role in physiological homeostasis, as well as in pathological disorders [1]. All TGs, catalyze the formation of an isopeptide bond, cross-linking an amine group (acyl acceptor) and the acyl group (acyl donor). They are an example of enzyme's induced posttranslational modification of proteins/peptides, involving a plethora of common chronic human diseases [2,3]. Deamidation or cross-linking of proteins are the main mechanisms through which they exert their biological functions. The human tissue

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transglutaminase (tTG) is celebrating its diamond anniversary, since its discovery 60 years ago. It evolved from a pedestrian protein to a talented promising therapeutic target [4,5].

The present review will concentrate on the prokaryotic TGs, the microbial TG (mTG), highlighting its massive uses in the processed food industries, as a food additive. It appears that mTG, a bacterial survival factor, is beneficial for the food industry, but, its public safety is under investigation where various potential detrimental effects were recently described or suggested.

Characteristics of Microbial Transglutaminase

Prokaryotic mTG is a member of the extended TG family, exerting deamidation and cross-linking of multiple substrates [6]. Its versatility spans a wide bacterial kingdom, was firstly isolated and characterized in *Streptomyces mobaraense* [2,3,7–9]. It is 331 amino acids long with a molecular weight of 37.9 kDa. Since its first characterization, a plethora of additional microbes were described to secrete mTG, with variable enzymatic yield capacities [3]. The most frequently used industrial mTG is secreted from *Streptoverticillium mobaraense* [3]. Novel mTGs are continuously described using ultrahigh-throughput screening and other biotechnological systems [10]. A recent new one, for example that exerts anti-phagocytic activity was reported in *Streptococcus suis* [11].

mTG and tTG are Structurally Different but Functionally Similar

Inversely to the human tTG, considered as the autoantigen in celiac disease (CD) [12], mTG is not dependent on calcium for activation nor on nucleotides for deactivation. Instead of four domains, it has only a single structural domain and a lower molecular weight than the tTG. It exhibits less substrate specificity and operates in a wider pH range [6,13]. Bonds created by the mTG are relatively resistant to proteases degradation, the enzyme operates at a higher reaction rate, delivering a higher transamidation/deamidation ratio due to its improved cross-linking capacity. Notably, tTG is endogenous, while mTG is exogenous, a common enzyme of the prokaryotic kingdom, considered as an environmental factor that potentially can affect human health, as detailed below. Considering its protein modifying abilities, exerting deamidation and transamidation, it imitates functionally the endogenous tTG [2,3,6,13]. Based on its fundamental features and its wider enzymatic activity, it represent a prime candidate, extensively used by multiple and constantly developing industries. The tissue engineering, textile, leather, biomedical diagnostic, labeling, biotechnological, pharmaceutical, food processing and nutraceutical industries [6,8,14–22].

Applications of Microbial Transglutaminase in the Food Processing Industries

The industrial applications of mTG is constantly expanding and diverging. Since the present review zooms on human health and mTG ingestion, from now on it will focus on the food processing industries.

The surge in eight food additives, increasingly used by the processed food industries, mTG included, was summarized recently [14]. It appears that the net percent increase per year of total enzyme usage in the processed food industries is estimated to be 21.9%, mTG being a major one [14]. It is estimated that for each kilogram of food material, the processed food industry is using 50–100 mg of the mTG enzyme, ending up in a 15 mg daily intake [15,18,23].

The frequently used nickname of mTG is “protein glue” but scientifically, it is a clear posttranslational modifier of proteins. This results in a three-dimensional structural change consequently creating new epitopes on the complexes’ surface [2,3,6,13]. In fact, the enzyme is consumed by most of the processed food industries, including bakeries, dairy, meat, surimi, sea food and fish, salad, casein and gelatin, myosin and actin, confection, convenience and many more industrial food applications [6,8,14–21,24–26]. The industrial manufacturers’ benefits, using mTG were reported extensively. In brief, the mTG enzymatic action affects viscosity, gelation, foaming, thermal stability, elasticity, water-holding capacity, binding ability, emulsification, consistency, texture, resilience and above all, elongate the life time in the groceries, public markets and supermarkets shelves and improve palatability [6,13,15]. The enzyme is considered as an industrial processing aid, thus, escaping the regulation of a food additive.

Celiac Disease and Tissue Transglutaminase

Celiac disease (CD) is a gluten dependent autoimmune disease elicited in genetically predisposed individuals by the consumption of prolamine grains (*i.e.*, wheat, barley, rye and oat) or ingredients of them. It affects 1–1.5% of Western populations and improves on gluten free diet. Pathophysiologically, gluten is partially digested in the enteric lumen, resulting in partial degradation till proteolytic-resistant peptides are formed. After trans-epithelial transport, gliadin peptides are deamidated/transamidated by the sub-epithelial tTG, leading to the formation of deamidated gliadin peptides, have a stronger binding capacity to MHC II, thus, stimulating the T and B cells to damage the epithelium, induce inflammation and secrete CD associated autoantibodies [27]. It should be emphasized that often forgotten is that transamidation occurs at a higher rate (75%) than deamidation (25%) in the tTG-gliadin cross talks [28]. After transamidation, tTG is covalently linked to gliadin peptides to create neo-epitopes complexes [29]. Interestingly, these neo-epitopes were described *in vivo* in small intestine biopsies of CD patients where a

pathogenic role was attributed to them [30–32]. Formation of tTG-neo epitopes and presentation to the immune system, would support the hypothesis of epitope spreading and the ensuing development of autoantibodies against tTG and against the neo-epitope tTG cross linked complex [13,30,33]. In summary, tTG is a key player in CD initiation and progression by modifying naive gliadins to immunogenic molecules and complexes, thus losing the tolerance to gluten/gliadin containing nutrients. The transamidation capacities of the tTG is imitated by the exogenous mTG.

MICROBIAL TRANSGLUTAMINASE—GLIADIN CROSS-LINKED COMPLEXES ARE IMMUNOGENIC IN CELIAC DISEASE

Several potential aspects associate mTG to celiac disease. At present, it should be stressed that we are dealing with an associative correlation and no causality was yet determined. Epidemiologically, the annual increased consumption of the enzyme goes parallel with the increased incidence of autoimmune conditions and CD, in the last decades [14,34,35]. Pathophysiologically, mTG imitates functionally the tTG, both posttranslation modifiers of gluten/gliadin peptides, by deamidation and transamidation [6]. Chemically, gluten and gliadin peptides are ideal substrates for the two enzymes due to their rich glutamine and lower lysine contents. Sequence-wise, no sequence homology but active site similarity were detected upon alignment of the two TGs [13].

Those associations were at the basis to explore the immunogenicity of the mTG and its gliadin-docked complexes, in CD patients. When the serological titers of mTG, tTG, gliadin complexed mTG (mTG neo-epitope) and gliadin complexed tTG (tTG neo-epitope) were studied in 95 pediatric celiac patients, compared to 99 normal children, 79 normal adults and 45 children with nonspecific abdominal pain, the following results were obtained: (1) mTG-neo IgA, IgG and IgA combined with IgG antibody titers exceed significantly the comparable mTG ones. The anti mTG positive patients were negligible and with a very low activity. (2) All levels of mTG-neo and tTG-neo isotypes were significantly higher in CD patients compared to controls. (3) Comparing all studied antibodies, tTG-neo IgA+IgG, tTG-neo IgA and mTG-neo IgG correlated best with patient's intestinal pathology ($r^2 = 0.6454$, $r^2 = 0.6165$, $r^2 = 0.5633$; $p < 0.0001$, $p < 0.0001$, $p < 0.0001$, respectively). (4) mTG-neo IgG+IgA showed an increased immunoreactivity compared to single mTG and gliadin ($p < 0.001$) but similar immunoreactivity to the tTG-neo IgG and IgA ELISA. (5) Using competition ELISA, the mTG neo-epitopes and tTG neo-epitopes antibodies had identical outcomes when checked on CD sera, both showing a decrease in optical density of $55 \pm 6\%$ ($p < 0.0002$). The author's summary was: "mTG is immunogenic in children with CD and, by complexing to gliadin, its immunogenicity is enhanced" [13].

Comparing 17 CD associated serological biomarkers, mTG-neo IgG correlated closely to the mucosal injury and was summarized as a new

reliable serological biomarker for CD diagnosis and enteric damage reflection [27]. Finally, when a Swedish pediatric CD population was studied for CD related antibodies, mTG-neo IgG had a good area under curve on ROC analysis (0.877) and an acceptable sensitivity (0.88%) and specificity (90%) for CD diagnosis [36].

PATHOGENIC ASPECTS OF MICROBIAL TRANSGLUTAMINASE

The potential pathogenic proofs for the environmental mTG involvement in chronic human disease induction are still being explored, but some of them were already published. Figure 1 summarizes schematically the various pathogenic pathways of mTG, representing potential mechanisms for mTG pathogenicity.

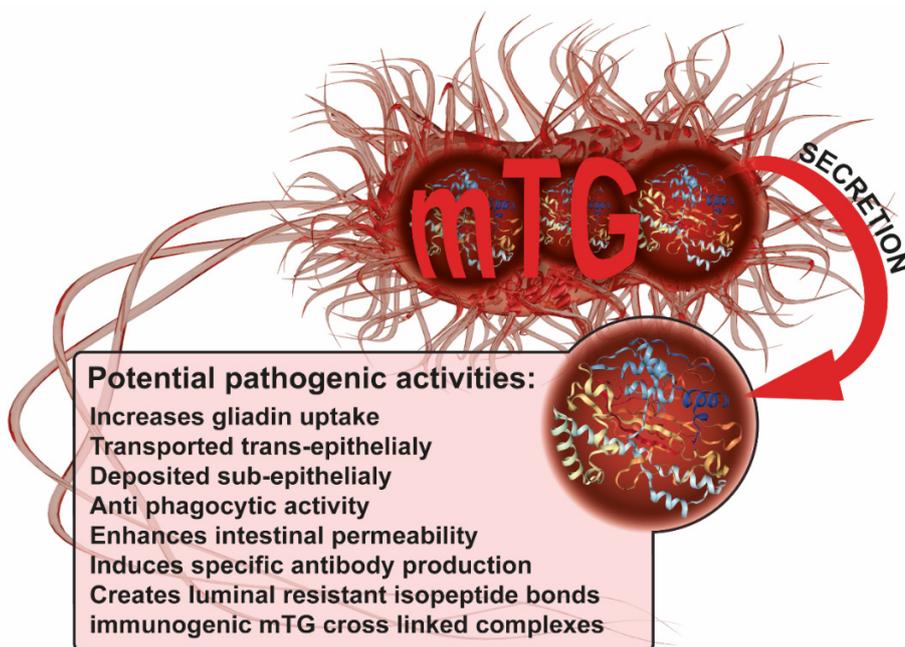


Figure 1. mTG activities representing potential mechanisms for mTG pathogenicity in human.

mTG can Potentially Enhance Intestinal Permeability

mTG is a survival factor that protects bugs against us, thus, enhancing the survival of dysbiotic or pathogenic bacteria in the gut lumen [2,3]. Microbial infections are a well-described etiology for compromising tight junction integrity and increasing intestinal permeability [37]. Gluten ingestion and gliadin peptides induce increased intestinal permeability, not only in CD patients [38]. Being a gluten-based peptide, mTG cross-linked gliadin can duplicate the effect on the tight junction. Additionally, actin, e-cadherin and adherens junctions are integral part of the enteric, inter-epithelial permeability machinery. They can be modified by TGs, including mTG that imitate functionally TGs, thus perturbing their protective ability [6,14,39]. mTG has emulsifying properties by cross-linking different proteins. Emulsifiers, heavily used in the process food industries, are enhancers of gut permeability [14,40].

The same reasoning apply to the mTG capacity to lipidate proteins, thus augmenting their emulsifying ability [41]. Much more, proteins originate from nutrients like casein, pork myofibrils, peanut and fish, cross-linked by mTG acquired emulsifying properties [39,42]. The same holds true for hydrolyzed gluten, known to increase emulsification [43]. Other food additive, heavily consumed by food industries, the nanoparticles, can be cross linked by mTG to improve their luminal delivery systems [44,45]. Nanoparticles also are disruptors of tight junction integrity [14].

Finally, Glutamine and sulfur-containing amino acids (cystine, cysteine and methionine) regulate the intestinal originated cell line (Caco-2) tight junction proteins. mTGs cross-linking those glutamine/sulfur containing amino acid peptides can induce a deprivation state of those amino acids, thus declining intestinal permeability regulation [46,47].

mTG Effects on Epithelial Gliadin Uptake and Transportation

tTG facilitates apical-basal passage of gliadins, a process helped by apical transferrin receptors and secretory IgA [48]. Imitating tTG functions, mTG potentially can facilitate this epithelial gliadin uptake pathway, thus enhancing CD [6]. Very recently, Stricker P. *et al.*, shed a new aspect of mTG pathogenic potential [32]. They followed tagged mTG and gliadin, applied to CD intestinal biopsies and RACE cells (rapid uptake of antigen into the cytosol of enterocytes), *ex vivo* and *in vitro*, respectively. mTG and gliadin were transported to the enterocytes' and to the of RACE cells' endoplasmic reticulum. Furthermore, mTG strongly localized at the basolateral membrane and the enteric lamina propria. Those interesting observations suggest cross presentation of exogenous antigens, like mTG and gliadins, in CD patients and more importantly, indicating a potential antigenic interaction with cells of the immune system. The cited basic science study support our clinical studies of mTG-gliadin neo-epitope complexes, being immunogenic in CD patients [13,27]. Actually, the mechanism of those antibodies production is clearer, since foreign antigens like mTG and gliadin peptides, find their way from the intestinal lumen and after trans-enterocyte transport, deposited and exposed to the immune sub-epithelial system.

mTG Suppresses Intestinal Luminal Protective Barriers

Being exposed to the environment, the intestinal compartment evolved multiple protective mechanisms. Some of them can be disrupted by mTG, thus giving the bugs a survival advantage on us, in the enteric extremely hostile compartment.

A novel mTG was lately described in *Streptococcus suis* that represent a virulent factor that suppresses phagocytic activities, thus suppressing a crucial component of human immunity [49–51]. Not less significant is the mucus layer. Recently tTG was found to stabilize, by cross-linking glutamine rich compounds, the MUC2 Mucin intra cellular isopeptide bonds, before being secreted extracellularly [52]. Since the human gut

lumen is rich in mTG activity, and the mucus is rich in acyl donors and acceptors, it is foreseeable that mTG can alter mucus stability, enabling pathogenic microbes to approach their attached receptors. Finally, the isopeptide bonds formed by mTG are extremely resistant to any human luminal enzyme, escaping the enzymatic degradation, reducing agents and multiple detergents. Even immunoglobulins, bile acids or antimicrobial molecules cannot break down those bonds [3,53,54]. In summary, luminal mTG has the capacity to counteract highly conserved evolutionary protective intestinal mechanisms.

Additional Observations Related to Potential mTG Pathogenicity in CD

One of the main important aspect is the availability of mTG in commercial food products. When 60 meat and meat products on the supermarket shelves were double-checked by different sensitive analytical methods, many of them contained mTG [55]. Although only associative, epidemiological survey showed a correlation between the increased CD incidence and the continuous surge in consumption of enzymes in the bakery industries, mTG being a major one [6,14]. Finally, wheat or gluten containing products enzymatically treated by mTG were shown to be immunogenic, inducing antibodies when consumed by humans [56–65], thus substantiating the serological studies on mTG immunogenicity [13,27].

THE POTENTIAL INTESTINAL SOURCES OF MTG LOAD

In order to exert its immunogenic and pathogenic activities (Figure 1), mTG needs to enter the human gut lumen. A portion of mTG is environmentally generated, some of it is introduced in the form of food additives and the rest is produced by the luminal prokaryotes [2,3]. Table 1 summarizes the extra and intra intestinal sources of mTGs. Taken together, a plethora of extra intestinal and enteric luminal sources of mTGs, capable to cross-link numerous substrates, including the glutamine rich gliadins, exist. The final result is that the mTG mobilomic cargo can posttranslational and modify proteins, rendering naive to non-tolerated ones, potentially driving autoimmunity [2,3,6,32].

Table 1. The extra and intra-intestinal sources of mTG.

	mTG Source	References
Extra-intestinal	Processed food additive	[2,3,6,8,13–17,24]
	Pathobionts	[2,3,14,50,66–68]
	Probiotics	[67,69–71]
	Plants	[65,72]
	Vegetables	[65,72]
Intra-intestinal	Microbiome	[2,3,6,13–17]
	Dysbiome	[2,3,6]
	Yeasts	[73–76]

SUMMARY

mTGs are considered, at least by producers, to be safe, non-toxic, non-allergenic, non-immunogenic and non-pathogenic for public health [6]. The present review summarizes the epidemiological, scientific and clinical proofs for this food additive and bacterial survival factor's immunogenic and pathogenic potentials. Actually, there is enough background knowledge to address mTGs' safety in a multi-disciplinary approach, aiming to protect the public against its potential detrimental effects. If substantiated, the findings will affect food product labeling, processed food additive policies, regulatory authorities' product control, consumer health education and public health safety. A.L. designed and wrote the manuscript, T.M. overviewed, searched and analyzed the literature and edited the manuscript.

AUTHOR CONTRIBUTIONS

A.L. conceived the original idea, designed and wrote the manuscript, T.M. overviewed, searched and analyzed the literature and edited the manuscript.

CONFLICTS OF INTEREST

No grant support and no conflicting interests.

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