**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 49601

**Manuscript Type:** LETTER TO THE EDITOR

**Microbial transglutaminase should be considered as an environmental inducer of celiac disease**

Lerner A *et al*. mTG and CD

Aaron Lerner, Torsten Matthias

**Aaron Lerner, Torsten Matthias,** AESKU.KIPP Institute, Wendelsheim 55234, Germany

**ORCID number**: Aaron Lerner (0000-0002-6779-4090); Torsten Matthias ([0000-0002-6779-4090](http://orcid.org/0000000267794090)).

**Author contributions**: Lerner A and Matthias T wrote the letter.

**Conflict of interest**: The authors declare no conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Corresponding author: Aaron Lerner, MD, Academic Research, Associate Professor, Chief Scientist,** AESKU.KIPP Institute, Mikroforum Ring 2, Wendelsheim 55234, Germany. [aaronlerner1948@gmail.com](mailto:aaronlerner1948@gmail.com)

**Fax:** +49-6734-96222222

**Received:** June 4, 2019

**Peer-review started:** June6, 2019

**First decision:** August 1, 2019

**Revised:** October 9, 2019

**Accepted:** October 15, 2019

**Article in press:**

**Published online:**

**Abstract**

Due to the recent interest in food additives that can act as triggering factors in autoimmune diseases including celiac disease (CD), the present letter to the editor expands on the microbial transglutaminase (mTG). It is heavily consumed by a plethora of food processing industries as “glue of proteins” thus improving product’s stability, texture and shelf life. However, more and more information is accumulated lately, questioning its safety. Its cross-linked gliadin complexes are immunogenic in CD. The enzyme increases gliadin uptake, is transported in a trans-epithelial way and deposited below the enterocyte’s line, has anti- phagocytic activity, enhances intestinal permeability and creates luminal resistant isopeptide bonds. No doubt that mTG is beneficial to food industries but a caveat to public health is highly recommended.

**Key words:** Microbial transglutaminase; Transglutaminase 2; Celiac disease; Processed food; Food additive; Food industry; Immunogenicity; Pathogenicity; Food safety; Public health

**© The Author(s) 2019.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Recently, various food additives were suspected to trigger autoimmunity, including celiac disease (CD). Microbial transglutaminase (mTG), a heavily used one that imitates functionally the autoantigen of CD is a prime environmental candidate to induce the disease. The enzyme increases gliadin uptake, is transported in a trans-epithelial way, has anti- phagocytic activity, enhances intestinal permeability and creates luminal resistant isopeptide bonds. Its gliadin cross-linked complexes are immunogenic and reflect the degree of intestinal injury in CD patients. The present letter updates and explains why the protein linker, mTG, is beneficial to food industries but a caveat to public health.

Lerner A, Matthias T. Microbial transglutaminase should be considered as an environmental inducer of celiac disease. *World J Clin Cases* 2019; In press

**TO THE EDITOR**

We congratulate Mancuso and Barisani for their mini review discussing the place of food additives as triggers of celiac disease (CD)[1]. Gluten-based and metallic nanoparticles are rather discussed extensively, but, microbial transglutaminase (mTG) quite sparely. Since much more data is available in the literature, the purpose of the present letter is to expand on the immunogenicity and potential pathogenicity of the mTG-gliadin cross-linked complexes. Based on biochemical, enzymatic functional similarities, industrial food applications and usage, epidemiological, immunological and clinical data, mTG was hypothesized to play a role in CD initiation and evolvement, in 2015[2]. Since then multiple observations gradually closed the gaps between the mTG and CD and those are the reasons of the present update.

The enzyme itself is extensively used in the processed food industries as a protein cross linker and gluten/gliadins are ideal substrates since they contain acyl donors and acceptors[2,3].

Contrary to the industrial claims that the enzyme and its cross-linked proteins are safe, non-toxic, not allergenic, not immunogenic and not pathogenic, the published scientific literature is neither fully supportive nor confirmative of those declarations. In their review, the authors describe the immunogenicity of the mTG-gliadin cross-linked complexes and their activity correlation to the enteric damage in CD[1,4]. This cross-linked complexes’ immunogenicity was substantiated in additional studies[5,6].

Following are some additional published observations which are pointing against the Generally Recognized As Safe labelling of the mTG usage in the processed food industries, that were summarized recently[7-10].

Meat products on supermarket shelves contain mTG[11] so that after consumption the enzyme reaches the gut. The gastrointestinal luminal compartment contains TG activity, unfortunately mTG activity was not explored in those years[12] and mTG facilitates gliadin uptake when checked on intestinal originated cell line[13]. It is important to remember that gliadin, a major compromiser of tight-junction integrity is a part of the cross-linked complex, that mTG possess emulsifier activity, that it is a survival factor for the luminal microbes, including pathobionts, all of them are known to increase intestinal permeability[2-4,7-10]. In this sense, Stricker *et al*[14] recently shed new light on mTG pathogenic capacity. By tagging gliadin and mTG they demonstrated trans-enterocyte transportation through the endoplasmic reticulum, to be deposited at the basolateral membrane. The sub-epithelial presentation of the two exogenous antigens indicate their potential interaction with the local immune systems, including antigen presenting macrophages. Notably, mTG is known to suppress enteric mucosal mechanical or immune protective mechanisms. By its cross linking capabilities, mTG can break mucus stability, enabling pathobionts to adhere to their receptors[9]. mTG has anti phagocytic activity thus counter-acting a major immune protective barrier[15-17]. More so, the covalent isopeptide bonds created by the mTG are extremely resistant to the luminal proteases, bile acids, reducing agents, immunoglobulins and detergents, thus, elongating their half-life to exert their detrimental functions[2,7-9]. Finally, multiple clinical studies have shown that mTG treated wheat or gluten are immunogenic, inducing antibodies and generating T cell stimulatory epitopes involved in CD, when consumed[18-20].

Two main critical issues, raised recently[21], deserve discussion and should be clarified: temperature and pH dependency of the enzyme and its gliadin cross-linked neo-complex.

mTG is active till 60 ℃Celsius but various food products are not boiled during the production processes. On contrary to the enzyme activity, its mTG gliadin docked complexes turn more immunogenic when heated to 900. Most probably, during denaturation, more epitopes are exposed to the immune system.

Concerning the pH impact on mTG activity, the enzyme is active at pH 4.0 and above (Ramesh A, personal unpublished communication). It should be stressed that: (1) During meal intake the gastric acidity is neutralized, pH can reach 4.5; (2) Many children and adults consume acid suppression medications; (3) Infants and elderly have a higher gastric pH; (4) Between meals the pH is differentially distributed in the stomach; and (5) Alkaline reflux is not a rare phenomenon.

So, despite the acidity, the mTG enzyme can still execute its functions, in the gastric passage. Above all, it is not the intra corporal enzyme activity which is critical, rather, it is the resulting cross-linked immunogenic/pathogenic complexes that are more important to human safety and health. After all, the complexes are created extra corporally, during the industrial process and those are quite resistant to the enteric intra-luminal offending agents.

In summary, Mancuso *et al*[1] tried to summarize the “current knowledge based on critical review of the literature”. The present letter to the Editor, extends the knowledge and hopefully, brings some additional information for the readers to weigh before conclusions.

It is correct that many observations are associative and conclusive direct cause and effect relationships, still have to be established. No doubt mTG is beneficial to food industries but a caveat to public health is highly recommended[9].

**REFERENCES**

1 **Mancuso C**, Barisani D. Food additives can act as triggering factors in celiac disease: Current knowledge based on a critical review of the literature. *World J Clin Cases* 2019; **7**: 917-927 [PMID: 31119137 DOI: 10.12998/wjcc.v7.i8.917]

2 **Lerner A**, Matthias T. Possible association between celiac disease and bacterial transglutaminase in food processing: a hypothesis. *Nutr Rev* 2015; **73**: 544-552 [PMID: 26084478 DOI: 10.1093/nutrit/nuv011]

3 **Lerner A**, Matthias T. Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease. *Autoimmun Rev* 2015; **14**: 479-489 [PMID: 25676324 DOI: 10.1016/j.autrev.2015.01.009]

4 **Matthias T**, Jeremias P, Neidhöfer S, Lerner A. The industrial food additive, microbial transglutaminase, mimics tissue transglutaminase and is immunogenic in celiac disease patients. *Autoimmun Rev* 2016; **15**: 1111-1119 [PMID: 27640315 DOI: 10.1016/j.autrev.2016.09.011]

5 **Lerner A,** [Patricia](https://www.researchgate.net/profile/Wusterhausen_Patricia) W, Neidhöfer S, Matthias T. Comparison of the reliability of 17 celiac disease associated bio-markers to reflect intestinal damage. *J Clin Cell Immunol* 2017; **8**: 1 [DOI: 10.4172/2155-9899.1000486]

6 **Agardh D.** Diabetes and Celiac Disease Unit, Department of Clinical Sciences, Lund University, Malmo, Sweden. Personal communication.

7 **Torsten M**, Aaron L. Microbial Transglutaminase Is Immunogenic and Potentially Pathogenic in Pediatric Celiac Disease. *Front Pediatr* 2018; **6**: 389 [PMID: 30619787 DOI: 10.3389/fped.2018.00389]

8 **Aaron L**, Torsten M. Microbial transglutaminase: A new potential player in celiac disease. *Clin Immunol* 2019; **199**: 37-43 [PMID: 30543926]

9 **Lerner A,** Matthias T. Microbial Transglutaminase is Beneficial to Food Industries but a Caveat to Public Health. *Med One* 2019; **4**: e190001 [DOI: 10.20900/mo.20190001]

10 **Lerner A,** Matthias T. Gluten and autoimmunogenesis. In: Musaic of Autoimmunity, The novel factors of autoimmune diseases revisited. 2nd edition, Eds: Shoenfield Y, Perricone C. Pub; Elsevier. 2019 pp:315-321.

11 **Kaufmann A,** K**ö**ppel R, Widmer M. Determination of microbial transglutaminase in meat and meat products. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2012; **29**: 1364-1373 [PMID: 22747363 DOI: 10.1080/19440049.2012.691557]

12 **Bruce SE**, Bjarnason I, Peters TJ. Human jejunal transglutaminase: demonstration of activity, enzyme kinetics and substrate specificity with special relation to gliadin and coeliac disease. *Clin Sci (Lond)* 1985; **68**: 573-579 [PMID: 2858282 DOI: 10.1042/cs0680573]

13 **Lerner A,** Aminov R, Matthias T. Intestinal dysbiotic transglutaminases are potential environmental drivers of systemic autoimmunogenesis. *Front Microbiol* 2017; **8**; article 66

14 **Stricker S**, de Laffolie J, Rudloff S, Komorowski L, Zimmer KP. Intracellular Localization of Microbial Transglutaminase and Its Influence on the Transport of Gliadin in Enterocytes. *J Pediatr Gastroenterol Nutr* 2019; **68**: e43-e50 [PMID: 30320664 DOI: 10.1097/MPG.0000000000002171]

15 **Fittipaldi N**, Segura M, Grenier D, Gottschalk M. Virulence factors involved in the pathogenesis of the infection caused by the swine pathogen and zoonotic agent Streptococcus suis. *Future Microbiol* 2012; **7**: 259-279 [PMID: 22324994 DOI: 10.2217/fmb.11.149]

16 **Xu B,** Zhang P, Li W, Liu R, Tang J, Fan H. hsdS, Belonging to the Type I Restriction-Modification System, Contributes to the Streptococcus suis Serotype 2 Survival Ability in Phagocytes. *Front Microbiol* 2017; **8**: 1524

17 **Pian Y,** Wang P, Liu P, Zheng Y, Zhu L, Wang H, Xu B, Yuan Y, Jiang Y. Proteomics identification of novel fibrinogen-binding proteins of Streptococcus suis contributing to antiphagocytosis. *Front Cell Infect Microbiol* 2015; 5: 19 [PMID: 25789245 DOI: [10.3389/fcimb.2015.00019](https://dx.doi.org/10.3389%2Ffcimb.2015.00019)]

18 **Lerner A,** Matthias T. Food Industrial Microbial Transglutaminase in Celiac Disease: Treat or Trick. *Int J Celiac Dis* 2015; **3**: 1-6

19 **Dekking EHA,** Van Veelen PA, de Ru A, Kooy-Winkelaara EMC, Gröneveld T, Nieuwenhuizen WF, Koning F. Microbial transglutaminase generate T cell stimulatory epitopes involved in celiac disease. *J Cereal Sci* 2008; **47**: 339-346 [DOI: 10.1016/j.jcs.2007.05.004]

20 **Gerrard JA,** Sutton KH. Addition of transglutaminase to cereal products may generate the epitope responsible for coeliac disease. *Trends Food Sci Technol* 2008; **16**: 510-512 [DOI: 10.1016/j.tifs.2005.07.002]

21 **Chander AM**, Yadav H, Jain S, Bhadada SK, Dhawan DK. Cross-Talk Between Gluten, Intestinal Microbiota and Intestinal Mucosa in Celiac Disease: Recent Advances and Basis of Autoimmunity. *Front Microbiol* 2018; **9**: 2597 [PMID: 30443241 DOI: 10.3389/fmicb.2018.02597]

**P-Reviewer:** Ghoch ME, Gabriel S, Kai K, Nag DS **S-Editor:** Dou Y **L-Editor: E-Editor:**

**Specialty type:** Medicine, Research and Experimental

**Country of origin:** Germany

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): E