

Microbial Transglutaminase as a Candidate Nutritional Adjuvant: An Evidence-Based Evaluation Using ASIA Syndrome Criteria

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Abstract: Microbial transglutaminase (mTG) is a food-processing enzyme widely used for protein cross-linking in processed foods. Experimental, serological, and disease-specific studies suggest that mTG and mTG-modified protein complexes may possess immunogenic and pro-inflammatory properties, particularly in the context of celiac disease. Through transamidation and cross-linking, mTG can generate post-translationally modified protein complexes and neo-epitopes that may interact with host immune pathways. This review critically evaluates the available evidence relevant to mTG within the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) framework. The evidence is strongest for dietary exposure and mTG-associated immunogenicity, whereas evidence for mTG-specific clinical manifestations, improvement after selective withdrawal, systemic autoimmunity, and causal ASIA induction remains limited or indirect. Accordingly, mTG should currently be considered a candidate nutritional/environmental adjuvant rather than a clinically validated ASIA-inducing factor. These observations warrant further independent investigation of human exposure, gastrointestinal biological activity, dose-response relationships, susceptible populations, immunological biomarkers, and long-term safety.

Keywords: microbial transglutaminase; autoimmune diseases; processed food additives; ASIA syndrome; nutritional adjuvants; protein cross-linking

1. Introduction

1.1. The Microbial Transglutaminase Enzyme

In microorganisms, the enzyme microbial transglutaminase (mTG) acts primarily as a survival factor. Unlike its human counterpart, tissue transglutaminase (tTG/TG2), mTG is a calcium-independent enzyme that modifies proteins by its capacity to transamidate or deamidate them. The result is to strengthen the microbial organism's structural integrity and suppress the host immunity thus, protect it against hostile environments [1,2].

The specific biological functions of mTG in various microbes include: A. Structural integrity, by catalyzing cross-linking of cell wall proteins in species like *Streptomyces*, *Saccharomyces cerevisiae* and *Candida albicans* [3]. B. Immune evasion and pathogenicity, by acting as a virulent factor, exerting anti-phagocytic activity, hence, helping the pathogen to evade the host's immune system [4]. C. Spore protection, by cross-linking proteins within spore coats, exerting added protection [5]. D. Pathogenic support, by increasing intestinal permeability of the host, the enzyme can enhance the activity and proliferation of other pathogenic bacteria. E. Luminal resistance, by formation of stable proteinic isopeptide bonds extremely resistant to host proteolytic degradation, bile acids, and pH changes. These mTG cross-linked peptides allow pathobionts to survive longer in harsh environments of the human intestinal lumen [1,2].



1.2. Objective and Review Approach

The objective of this narrative, hypothesis-driven review is not to establish mTG as clinically validated cause of ASIA, but to critically evaluate whether currently available evidence supports its consideration as a candidate nutritional/environmental adjuvant within the ASIA framework. We assess the validity and strength of evidence corresponding to individual ASIA criteria, distinguish disease-specific observations from mTG-specific evidence, identify major uncertainties and alternative interpretations, and define the experimental and clinical studies required to validate or refute the hypothesis.

1.3. Literature Selection and Evidence Assessment

It is a narrative, hypothesis-driven review. As such the review draws on literature addressing mTG biology, industrial food usage and exposure, gastrointestinal effects, immunogenicity, celiac disease, other proposed autoimmune or neuroinflammatory associations, and the ASIA framework. A comprehensive literature search was conducted across the PubMed/MEDLINE, Embase, and SciELO databases, covering publications from January 2000 to August 2026. We used the following Medical Subject Heading terms in our search: “microbial transglutaminase”, “food industry enzyme”, “autoimmune disease”, “ASIA syndrome”, along with keywords related to applications, industrial usage, human consumption, side effects, harmful effects, toxic effects, regulation, safety, and public health. This search was inclusive of all languages. Additionally, the reference lists of selected articles were reviewed to identify other relevant studies. The corresponding author was responsible for conducting the literature survey, screening abstracts, and reviewing full-text articles as necessary. Evidence was interpreted according to its source, quality and directness: human clinical evidence, experimental/mechanistic evidence, serological findings, exposure data, bioinformatic observations, and hypothesis-generating associations. Terms such as “strong”, “moderate”, “limited”, “indirect”, and “context-specific” refer to the quality and directness of evidence supporting the proposed mTG-ASIA relationship, rather than to the strength of evidence for the underlying disease itself.

1.4. Microbial TG Is Widely Used in the Processed Food Industries

It acts as a “protein glue” or by its more popular name “meat glue”, to cross-link proteins, significantly improving texture, elasticity, water-holding capacity, and stability in meat, fish, dairy and bakery products. It combines and restructures the meats, improves gelation in dairy products, strengthens dough, and enables the neo-creation of textured plant-based alternatives. But above all, it extends the half-life of the products on the supermarket shelves. This represents a major economic benefit for the food industry [6]. The enzyme is consumed by a wide range of food manufacturers: meat and fish, bakery and noodles, dairy, desserts, tofu preparations, production of edible protein films and soy or plant-based meat substitutes, allowing them to better mimic traditional meat products [7].

1.5. Increased Consumption of Exogenous mTG in the Processed Food Industries

Global industrial consumption of mTG is rapidly increasing, representing the most rapidly growing industrial enzyme. The enzyme global market for the food manufacturers was valued at approximately \$2.3 billion as of 2020. However, the specific market for mTG was estimated at around \$200 million that same year, representing an annual net growth rate of approximately 21.9% [8]. The mTG market is mainly driven by its pivotal role as a “protein glue”. Based on the literature, daily intake of mTG used by Western diets, in the processed food products, can range up to 15 mg, where every kg of mTG processed product contains around 50–100 mg of mTG [9,10]. Interestingly, approximately eight million pounds of “meat glue” are used annually in the United States alone. A most recent publication projected that the compound annual growth rate, between 2024 to 2033, will be 4.8%, reaching 361.17 million \$, in 2033 [7]. The author mentioned growing concerns about the “enzyme safety, particularly regarding potential immunogenic reactions and its long-term impact on consumer health”.

1.6. Environmental and Putative Sources of mTG Activity in the Human Gut

Before embarking on the mTG as a new environmental factor consistent with ASIA syndrome criteria, its external, non-endogenous luminal sources, compared to the endogenous ones, should be detailed (Table 1).

Table 1. Established and putative sources of transglutaminase activity or transglutaminase-like proteins relevant to the human intestinal environment.

Source Category	Specific Sources	Evidence Type	Key References
Exogenous (Dietary)	Processed food additives (meat, dairy, bakery, plant-based products)	Direct evidence (industrial use, intake estimates)	[1,2,6–10]
	Probiotics (engineered or natural producers)	Experimental/applied	[7,11–14]
	Plant-derived transglutaminases	structural/functional similarity	[15–17]
Endogenous (Luminal microbiota)	Commensal microbiota	Indirect/inferred	[1,2,7,8,10,13,14,18–21]
	Dysbiotic microbiome	Indirect/hypothesis-driven	[1–4,6,10,16,18,19,22]
	Pathobionts (e.g., <i>Streptomyces</i> , <i>Candida</i>)	Experimental evidence	[1–6]
Putative/Emerging sources	Yeasts	Experimental evidence	[1–4,7,23,24]
	Viral homologs (transglutaminase-like proteins)	Bioinformatic/evolutionary	[23,24]

Multiple potential dietary and luminal sources may contribute to total intestinal transglutaminase exposure; however, their relative quantitative contributions remain largely unknown. Measurements in meat products confirm the presence of industrial mTG in selected foods [12], and estimates cited in the literature suggest that Western processed-food intake may contain up to approximately 15 mg mTG per day [9,10]. In contrast, the quantities contributed by commensal or dysbiotic microbiota, pathobionts, probiotics, plants, yeasts, and other putative sources have not been adequately quantified. These sources should therefore not be treated as equivalent to documented dietary exposure. Transglutaminase-like sequences reported in bacteriophages and viruses represent bioinformatic/evolutionary observations rather than evidence of quantitatively meaningful intestinal mTG exposure [23,24].

Transglutaminase activity or transglutaminase-like proteins occur across diverse biological systems, but the relevance of each potential source to human intestinal exposure differs substantially. Documented dietary mTG exposure should be distinguished from inferred microbial sources and from bioinformatic homology. The broad substrate cross-linking capacity of mTG provides a mechanistic basis for post-translational modification of proteins and formation of potentially immunogenic neo-epitopes; however, the extent to which these processes occur in vivo in humans at typical dietary exposure levels remains uncertain [1,2,10,19,25–28]. Sequence similarity and cross-reactive antibodies may contribute to molecular mimicry, but these observations support biological plausibility rather than establishing clinical causality [2,10,28–31].

1.7. Fate and Biological Activity of Dietary mTG during Food Processing and Gastrointestinal Transit

A key unresolved issue is the amount of biologically active dietary mTG that reaches the intestinal lumen and mucosal surface after food processing and gastrointestinal transit. Thermal processing, technological conditions, gastric acidity, and proteolytic enzymes may alter enzyme activity and exposure. The current evidence base does not establish that sufficient active mTG reaches the human intestine to initiate all proposed effects in vivo. Importantly, two mechanistically distinct questions should be considered separately: whether active mTG enzyme survives gastrointestinal transit, and whether proteins previously cross-linked or transamidated by mTG persist after digestion and retain immunological relevance. Future studies should quantify both residual enzymatic activity and the persistence of mTG-modified protein products under physiologically relevant conditions.

Noteworthy is the scientific contribution of Stricker et al., regarding the mTG and gliadin peptide transepithelial transport. It appears that mTG and gliadin peptides are transported through the endoplasmic reticulum of human enterocytes and by RACE cells, suggesting cross-presentation of those exogenous nutritional antigens to the sub-epithelial immune systems [28,29,31]. This strong localization of mTG at the basolateral membrane below the lamina propria may also indicate a potential antigenic recognition of foreign epitopes by the local immune networks. Since mTG may not only be taken up with food stuffs but could also be released by bacteria within the intestinal microbiota, further investigations are needed regarding the role of mTG in CD pathogenesis and its safety for human use. Moreover, the unregulated use of mTG in food production might therefore pose a potential threat for consumers [28–30]. Intriguingly, Stricker et al. reported that mTG is much more resistant to exogenous oxidative stress compared to the endogenous tTG, thus, mTG may persist longer and potentially contribute to the accumulation of foreign immunoactive peptides within the gut lumen [31]. These mechanistic findings warrant further investigation.

2. ASIA Syndrome

Since 2011, several medical entities related to environmental adjuvants, including the post-vaccination phenomena, Gulf war syndrome, silicosis, the macrophagic myo-fasciitis syndrome, artificial implants induced inflammations or autoimmune diseases (ADs) and chronic fatigue syndrome, which share comparable symptoms and signs, were highlighted in the medical literature [31]. These observations laid the background for a new entity, namely: ASIA syndrome, known as Shoenfeld's syndrome (autoimmune/inflammatory syndrome induced by adjuvants) [32–36]. Since then, numerous publications extended the list of the environmental adjuvants, thus, establishing a continuously evolving syndrome [37–39].

The common thread shared between those environmental adjuvants is their capacity to induce autoimmune and inflammatory mechanisms resulting in a well characterized clinical entity. Parallely to the growing list of specific immune adjuvants, the ensuing involved clinical and pathological diseases expanded vastly. Multiple ADs, undifferentiated connective tissue disease, immune-related adverse events, silicone implant incompatibility syndrome, biomaterial injections and prostheses (mainly silicone, hyaluronic acid, methacrylate compounds and acrylamides), squalene, mesh Implants, gluteal biopolymer remodeling injections, chronic fatigue syndrome, fibromyalgia, sick-building syndrome, post-orthostatic tachycardia syndrome and the list continues to expand [40–43].

More recently, COVID-19, post-infectious immune phenomena, and vaccine-associated observations have also been discussed within the expanding ASIA literature [39–47]. These examples illustrate the evolving scope of the ASIA framework but are not central to the present evaluation of mTG and are therefore not discussed in detail here.

2.1. The Pathophysiology of ASIA Syndrome

ASIA syndrome is a multi-etiological, involving various mechanistic pathways [32–35,48–50]. As in ADs involvement, genetics and environment play a pivotal role, but the dominant ones driving the syndrome are environmental factors, playing a major duty as adjuvants [32–35,48–50]. Genetically, HLA class I and II haplotypes, containing the DR/DQ groups are associated with ADs induced by environmental adjuvant. Indeed HLA-DR4, DRB1, DR53, DQA1*0102 and HLA DR2DQ6, DR4DQ8, and DR3DQ2 are associated with susceptibility to ASIA syndrome [32–35,49–51]. HLA-DRB1 is associated with silicone breast implants and vaccinations. HLA-DRB1*01 or HLA-DRB4 are linked to predisposition to developing ASIA syndrome. HLA-B27 predispose to post vaccine ADs. PTPN22 (Protein Tyrosine Phosphatase Non-Receptor Type 22) is associated with increased susceptibility to ASIA syndrome. HLA-DR5 and HLA DQ2 is associated with silicone implant incompatibility [32–35,49–51].

In addition to genetic factors, sequence similarity, cross-reactive antibodies, molecular mimicry, immune hyperstimulation, innate immune dysregulation, T cell failure, release of pro-inflammatory cytokines, imbalance between the Th1/Th2 immune response ratio or excessive Th1 response, B cell overactivation, enhanced Th17 cell activation and finally, epigenetic modifications were reported to drive the autoimmunogenesis [32–36,49–53].

2.2. The Diagnostic Criteria for ASIA Syndrome

ASIA syndrome, also called Shoenfeld syndrome, has been described using major and minor diagnostic criteria, with two major criteria or one major plus one minor criterion commonly proposed for classification [32–35,39,48–54]. Nutritional factors such as gluten have also been discussed as potential environmental adjuvants [26,55–57]. In the present review, these criteria are used as an analytical framework to evaluate the mTG hypothesis; correspondence with individual criteria should not be interpreted as proof that dietary mTG independently causes ASIA. Table 2 outlines the reported ASIA criteria [32–35,39,48–54].

Table 2. Diagnostic criteria for ASIA syndrome.

Criteria Type	Description	References
Major criteria	Exposure to an external stimulus (infection, vaccine, silicone, adjuvant) prior to symptom onset	[32–35,39,48–54]
	Typical clinical manifestations (myalgia, arthralgia, chronic fatigue, neurological symptoms, cognitive impairment, fever)	[32–35,48–50,54]
	Improvement after removal of inciting agent	[32–35,48–50,54]
	Typical biopsy of affected organs	[32–35,48–50,54]
Minor criteria	Autoantibodies or antibodies against suspected adjuvant	[32–35,48–50,54]
	Additional clinical manifestations	[32–35,48–50,54]
	Specific HLA (e.g., DRB1, DQB1)	[32–36,49–51]
	Development of autoimmune disease	[32–35,48–50,54]

3. Evidence Relevant to the Proposed Relationship between Microbial Transglutaminase and the ASIA Framework

Table 3 evaluates the available evidence relevant to individual ASIA criteria, emphasizing the directness, disease context, and major limitations of each line of evidence. Figure 1 provides a graphical synthesis of the proposed mechanistic relationship between dietary mTG exposure, intestinal and immune pathways, disease-associated observations, and the corresponding evidence relevant to the ASIA framework. Both the table and figure should be interpreted as an assessment of a testable hypothesis rather than as confirmation that mTG fulfills the diagnostic criteria of ASIA.

Table 3. Evidence relevant to the proposed mTG-ASIA relationship: Strength, directness, and limitations.

ASIA Criteria	Evidence for mTG	Strength of Evidence	Key References
Major Criteria			
Exposure to external stimulus	Widely consumed processed food additive	Strong for dietary exposure	[1,2,6–11]
Typical clinical manifestations	Celiac disease-associated findings; proposed links to neuroinflammation and PBC remain indirect and require independent validation	Moderate (primarily celiac disease-based)	[1,2,18,21]
Improvement after removal	A gluten-free diet may concomitantly reduce exposure to mTG-containing processed foods and mTG-modified gluten proteins, but selective mTG withdrawal has not been tested	Insufficient direct evidence; no selective mTG withdrawal/rechallenge studies	[2,10,26,55–57]
Typical biopsy	Duodenal pathology and mTG neo-epitope antibody associations reported in celiac disease; not demonstrated as an mTG-specific ASIA lesion	Disease-specific/indirect for mTG-ASIA	[58–61]
Minor Criteria			
Autoantibodies	Anti-mTG/neo-epitope antibodies described	Strong for antibody detection; causal significance uncertain	[1,2,10,18,58,62]
Specific HLA	HLA-DQ2/8 predisposition (celiac context)	Strong for celiac HLA susceptibility; indirect for mTG-specific ASIA susceptibility	[60,61]
Development of autoimmune disease	Celiac disease provides the strongest disease-specific context; independent mTG causality is unproven and evidence in other diseases is speculative	Limited/indirect for mTG-specific autoimmune disease induction	[1,2,18,25,26]
Additional manifestations	Reported extra-intestinal associations; no evidence that these manifestations are specifically induced by dietary mTG	Limited/indirect; no challenge/withdrawal evidence	[1,2,18,26]

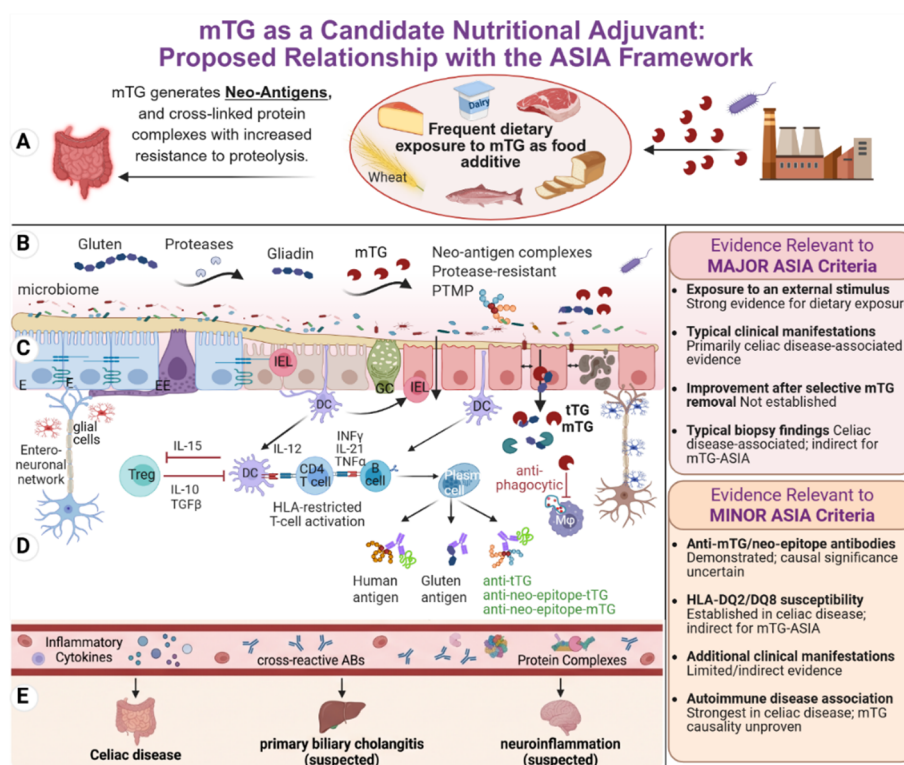


Figure 1. Proposed relationship between mTG and the ASIA framework. (A) Frequent dietary exposure to mTG-containing processed foods represents a potential external stimulus. (B) mTG-mediated cross-linking generates protease-resistant neo-antigen complexes. (C) Increased intestinal permeability may facilitate their interaction with

the mucosal immune system. **(D)** HLA-restricted T-cell activation and B-cell differentiation may promote antibody production and inflammatory responses. **(E)** The strongest disease-specific evidence derives from celiac disease, whereas associations with primary biliary cholangitis and neuroinflammation remain indirect. The right panel summarizes the strength and limitations of evidence relevant to individual ASIA criteria.

In summary, available evidence shows varying degrees of correspondence between mTG-related observations and individual ASIA criteria. Evidence is strongest for dietary exposure and for immunogenicity in the celiac disease context [62]. Evidence for mTG-specific clinical manifestations, improvement after selective withdrawal, systemic autoimmune disease induction, and extra-intestinal ASIA-like manifestations remains indirect, disease-specific, or insufficient. Thus, mTG should currently be considered a candidate nutritional/environmental adjuvant whose relationship to ASIA requires prospective experimental and clinical validation.

4. Limitations and Alternative Interpretations

Several limitations constrain the interpretation of the current evidence. First, much of the human evidence derives from celiac disease and cannot be assumed to demonstrate mTG-specific systemic ASIA. Second, association, immunogenicity, or molecular mimicry does not by itself establish causation. Third, dietary mTG exposure is difficult to separate from gluten exposure and from broader changes in processed-food consumption. Fourth, selective mTG withdrawal/rechallenge studies and human dose-response studies are lacking. Fifth, the amount of biologically active mTG reaching the human intestinal mucosa remains insufficiently characterized. Sixth, proposed associations with primary biliary cholangitis, neuroinflammation, and other extra-intestinal conditions require independent confirmation. Finally, a substantial portion of the supporting literature originates from overlapping author groups; independent replication and critical literature representing alternative interpretations are therefore particularly important. Concerning the self-citation of the authors, multiple publications of other authors support the adverse effects and the risks for public health, using mTG in processed foods, mainly for celiac patients [18,27,29,31,63–71].

5. Research Priorities for Testing the mTG-ASIA Hypothesis

The mTG-ASIA hypothesis is testable. Priority studies should determine: (1) the amount and enzymatic activity of mTG remaining after food processing and gastrointestinal digestion; (2) the persistence and immunological properties of mTG-modified protein complexes; (3) dose-response relationships between dietary mTG exposure and immune or inflammatory biomarkers; (4) whether effects are restricted to genetically susceptible individuals or also occur in the general population; (5) whether the gut microbiota metabolizes or inactivates mTG; and (6) how industrial mTG differs functionally and immunologically from transglutaminases produced by intestinal microorganisms.

Appropriate experimental approaches include physiologically relevant digestion models, intestinal epithelial and immune co-culture systems, genetically susceptible animal models, prospective HLA-stratified human cohorts, and ultimately controlled dietary exposure or selective withdrawal/rechallenge studies where ethically and practically feasible. Candidate outcomes may include residual mTG activity, intestinal permeability, inflammatory mediators, anti-mTG antibodies, antibodies to mTG-modified neo-epitopes, disease-specific autoantibodies, and clinical outcomes. Evidence of a reproducible exposure-response relationship and reversal after selective mTG withdrawal would substantially strengthen causality; failure to reproduce these effects would argue against the hypothesis.

6. Regulatory and Risk-Benefit Considerations

The widespread technological benefits of mTG in food production should be weighed against unresolved questions concerning cumulative exposure, gastrointestinal biological activity, immunogenicity, and susceptible populations. The present evidence does not by itself establish that current mTG consumption causes ASIA or systemic autoimmunity. It does, however, support further independent safety assessment, improved exposure characterization, and transparent evaluation of potential risks and benefits.

7. Conclusions

The available evidence supports consideration of microbial transglutaminase as a candidate nutritional/environmental adjuvant whose immunological properties show varying degrees of correspondence with the ASIA framework. Evidence is strongest for dietary exposure and mTG-associated immunogenicity, particularly in the context of celiac disease, whereas evidence for mTG-specific clinical manifestations, selective

withdrawal response, systemic autoimmunity, and causal ASIA induction remains limited or indirect. Controlled exposure, withdrawal/rechallenge, dose-response, mechanistic, and prospective clinical studies are required before mTG can be classified as a clinically validated ASIA-inducing environmental adjuvant. Nevertheless, its widespread use in processed foods, the existing evidence of immunological activity and its transepithelial passage justify further independent investigation of its long-term safety and potential effects in susceptible populations.

Author Contributions

A.L. screened the literature, designed, wrote and edited the manuscript. C.B. screened the literature, revised the manuscript, designed the figures with BioRender.com. Both authors contributed to the interpretation of the literature. All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT and Claude for literature search, improving style and reading Comprehension. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Abbreviations

mTG—microbial transglutaminase, tTG—tissue transglutaminase, PTMP—post-translational modification of proteins, ASIA—The autoimmune/inflammatory syndrome induced by adjuvants, ADs—autoimmune diseases.

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