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Supplement Article

Is the microbiome important in celiac disease?

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Abstract

Celiac disease (CeD) is an autoimmune condition driven by gluten in genetically predisposed individuals. CeD is characterized by small intestinal villous atrophy but presents with a spectrum of gastrointestinal and systemic manifestations. Its only treatment is a strict, life-long adherence to a gluten-free diet, which is difficult to manage and does not always lead to symptomatic or mucosal recovery. About 40% of the population express the CeD-associated risk genes, but only 1%-2% of the worldwide population has CeD. This, along with the rising prevalence of CeD suggests other cofactors in disease pathogenesis. The gut microbiome has been implicated in CeD based on epidemiology studies and clinical associations. Mechanistic studies using relevant *in vitro* and *in vivo* preclinical models have begun to elucidate mechanisms through which microbes can influence CeD. Ultimately, a better understanding of these cofactors and their mechanisms will provide rationale intervention strategies and novel therapeutic targets to prevent or treat CeD.

Key words: celiac disease; microbiome; gluten.

Introduction

Celiac disease (CeD) is an autoimmune condition, with an average worldwide prevalence of 1%-2% that has gastrointestinal and systemic manifestations. A recent review analyzed the prevalence and variable burden of CeD by continent or country.[1] In Canada testing rates have remained stable, but its incidence has increased from 2015 to 2020.[2] Growing number of cases are reported in areas of the world with previously unknown CeD burdens such as Africa, South, and East Asia, as well as in Black, Latino, and native populations of the Americas.[1,3,4]

The hallmark pathological feature is small intestinal villous atrophy. CeD is unique in that the driving antigen, gluten, has been identified, along with the major disease-associated susceptibility genes, that code for HLA-DQ2 and HLA-DQ8. Large, immunogenic gluten peptide fragments, that result from incomplete degradation in the intestinal lumen, are deamidated by tissue transglutaminase (TG2) and cross the small intestinal barrier where they can interact with antigen-presenting cells (APCs). The structure of gluten peptides allows them to bind to HLA-DQ2 or -DQ8 heterodimers on APCs, and this affinity is increased following deamidation of gluten peptides by TG2.[5,6] This triggers a pro-inflammatory gluten-specific T-cell response leading to the IFN-γ producing CD4+ T cells, as well as anti-gliadin and anti-TG2 producing plasma cells. In addition to a gluten-specific immune response, an innate immune response that results in the activation of cytotoxic intraepithelial lymphocytes (IELs) and epithelial cell death is required for the development of villous atrophy.[7]

Although strict avoidance of gluten in the diet (gluten-free diet, GFD) improves symptoms and pathology in a majority of patients, small amounts of gluten exposure reactivate inflammation. Indeed, immunological evidence supports the chronic nature of CeD, where both circulating gluten-specific CD4+ T cells[8] and tissue-resident IELs[9] reach a chronically altered phenotype after initiation of a GFD. Moreover, gluten challenge in patients on a GFD will induce rapid mucosal gluten-specific CD4+ T cells, with systemic recirculation.[10,11] This insight has led to rapid development of new diagnostic approaches based on short-term gluten challenge and blood tests for the determination of T cell-derived cytokines.[12,13] While a GFD is currently the only way symptoms can be managed by patients with CeD, it is not a cure, as it does not always lead to complete symptomatic or mucosal recovery.

HLA-DQ2 and -DQ8 genes are prevalent with approximately 30%-40% of the population expressing one or both of the CeD-associated HLA-DQ heterodimers.[14] This, together with the rapid increase in prevalence in the past decades, implicates environmental cofactors in disease onset.[15] While not completely understood, these cofactors provide opportunities for therapeutic intervention. Epidemiological studies, showing associations with infections and disease,[16–18] or changes in the gut microbiota composition,[7,15] support a role for the gut microbiome in CeD. However, determining causality or mechanisms from epidemiological studies is difficult. To better understand which microbial cofactors and how they are involved in CeD pathogenesis, a translational approach, using relevant *in vitro* and *in vivo* models, is needed. Only then are we in a place to target these microbial pathways using novel therapeutics. Here, we will focus on the specific mechanisms through which microbial co-factors have been implicated in CeD (Figure 1).

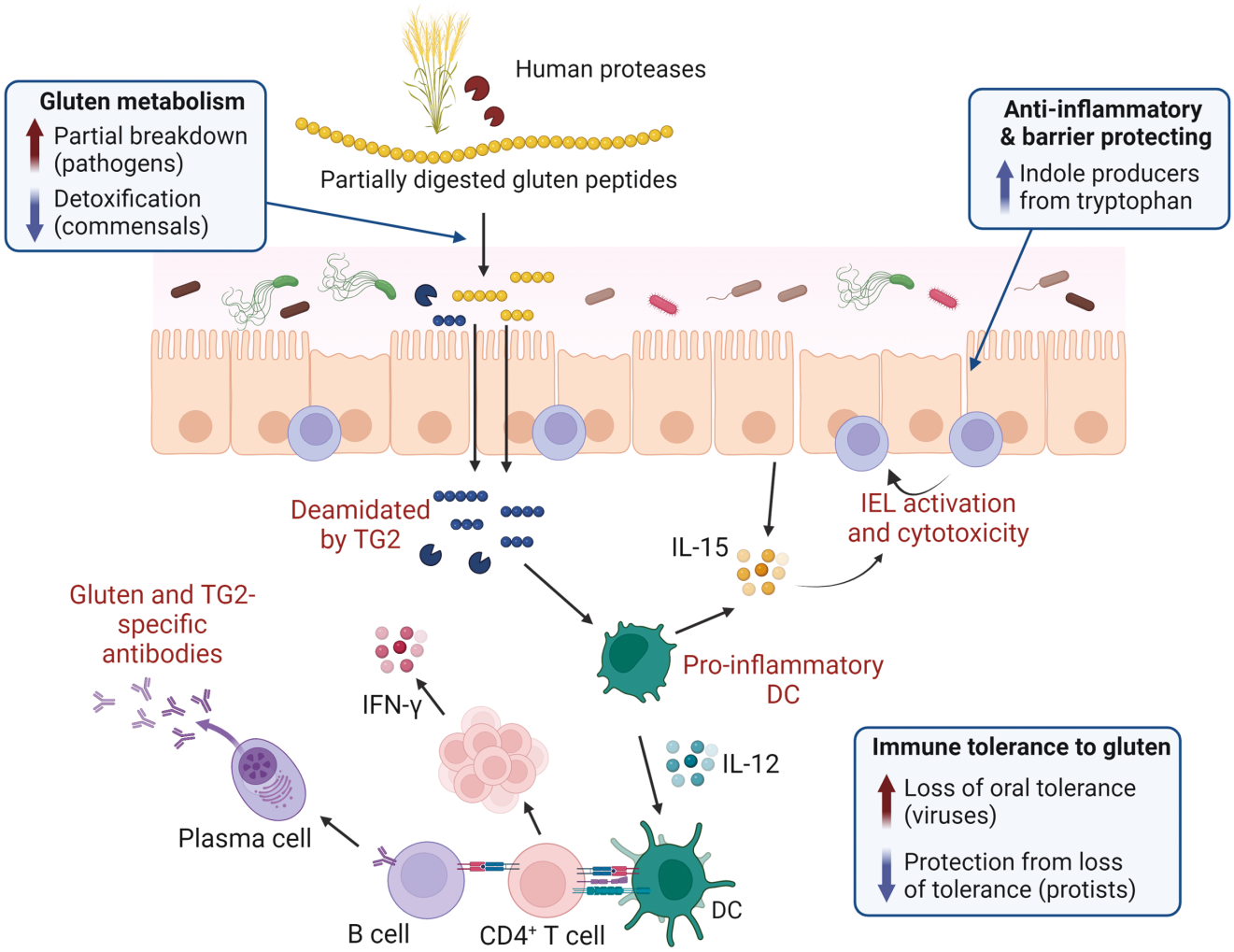

Figure 1. Celiac disease (CeD) pathogenesis and microbial mechanisms. Gluten peptides are partially digested by host and microbial enzymes in the small intestinal lumen. These peptides translocate the epithelial barrier and are deamidated by tissue transglutaminase (TG2), after which they bind with high affinity to HLA-DQ2 or -DQ8 on antigen-presenting cells, such as dendritic cells (DC), leading to the activation and proliferation of IFN-γ producing gluten-specific CD4+ T cells. In addition, activation of cytotoxic intraepithelial lymphocytes culminates in enterocyte cell death and villous atrophy. While gluten is the main driver, microbes have emerged as important modulators of immune responses in CeD. Microbes can participate in gluten metabolism by increasing or decreasing peptide immunogenicity, they can influence nonspecific immune responses through microbial metabolism of dietary tryptophan to indoles, or they can influence the process of oral tolerance. Created using BioRender.com.

Microbial mechanisms that target gluten-specific immunity

One key feature of gluten, the main protein fraction of cereal grains such as wheat rye or barley, is its resistance to digestion by human enzymes in the gastrointestinal tract. This results in large gluten peptides that have retained immunogenicity-that is, they are capable of stimulating gluten-specific CD4+ T cells. However, bacteria within the human gastrointestinal tract can also participate in gluten metabolism.[19–21] Its important to note that microbial gluten metabolism results in a variety of peptides with varying degrees of immunogenicity. For instance, the opportunistic pathogen *Pseudomonas aeruginosa* produces the enzyme LasB, which can generate highly immunogenic peptides that can easily translocate across the epithelial barrier and stimulate gluten-specific T cells. On the other hand, further digestion of these *P aeruginosa* generated peptides by other members of the gut microbiota, such as lactobacilli, can reduce peptide immunogenicity.[21] This highlights the importance of the metabolic function of the microbial community as a whole within the small intestinal environment.

Indeed, differences in the overall gluten-degrading capacity of the fecal[22] and, importantly, the small intestinal microbiota[23–25] have been observed in CeD patients. In support of this, variations in the quantity and types of gluten peptides in the urine have been reported between CeD patients and controls consuming wheat.[26] While microbiome alterations have been described in CeD,[15] Constante et al.[24] demonstrated biogeographical niches in luminal versus mucosal microbiota, and along the duodenal segments and feces. Moreover, the study revealed an impaired capacity of mouse intestinal contents to degrade immunogenic gluten peptides after colonization with microbiota from CeD patients versus healthy individuals who had similar HLA-DQ backgrounds. A lower abundance of microbial glutamate carboxypeptidase genes in colonized mice was associated with impaired gluten-degrading capacity,[24] supporting the hypothesis that CeD patients have

altered microbial metabolism of gluten. Whether altered microbial gluten-degrading capacity is present prior to CeD development, or is a result of active disease remains to be determined, but could be addressed using small intestinal microbial samples from longitudinal cohorts of at-risk individuals. Efficient, and complete degradation of peptides that are no longer capable of inducing gluten-specific T-cell responses is a therapeutic target of interest.[27]

Based on sequence similarities between microbial antigens and gluten peptides, molecular mimicry has been suggested in the pathogenesis of CeD.[15] In support of this, there are similarities between gluten and a variety of microbial antigens including the viral protein E1b found in human adenovirus type 12,[28] the *Candida albicans* adhesion Hwp1,[29] and the bacterial peptide succinylglutamate desuccinylase found in certain *Pseudomonas* strains, including *P fluorescens*.[30] Notably, peptides from succinylglutamate desuccinylase induced a potent, although varying, IFN-γ response from gluten-reactive CD4+ T cells isolated from CeD patients undergoing a gluten challenge.[30] Together this data supports the concept that microbial antigens could drive or maintain gluten-specific T-cell responses.[31]

Pro-inflammatory gluten-specific immune responses may also be influenced by inter-kingdom communication between different members of the gut microbiome. The loss of oral tolerance, an active process of local and systemic immune unresponsiveness to food antigens, is a key step in CeD development. In mice, it has been shown that several viruses can disrupt the process of oral tolerance, leading to pro-inflammatory antigen-specific, including gluten-specific, immune responses. This process is dependent on the capacity of the virus to trigger very specific inflammatory signalling pathways (interferon regulatory factor 1) in dendritic cells.[32,33] Interestingly, this viral-induced inflammatory pathway in dendritic cells (DCs) can be influenced by the presence or absence of other gut microbiome members. Protists are unicellular eukaryotes whose role in the gut microbiome has been underappreciated and understudied. Medina Sanchez et al.[34] found that the presence of a specific commensal protist, *Tritrichomonas arnold*, could protect mice against viral-mediated loss of oral tolerance to gluten. This effect was mediated through still unknown *T arnold* produced metabolites that prevented the viral-induced inflammatory signalling pathways in DCs, and the subsequent loss of oral tolerance to food antigens like gluten. Using human stool samples, the authors found that protists of the *Parabasalia* family, to which *T arnold* belongs, are underrepresented in CeD patients compared to healthy controls.[34] Future studies will determine whether this could be a therapeutic target in individuals who already have CeD, in addition to a preventative approach for CeD.

Microbial mechanisms that target non-specific host immunity and barrier function

Microbial mechanisms that target nonspecific immune pathways have also been implicated in CeD.[15,35] One such immune pathway involves IELs, which are not gluten-specific, but are key to CeD pathogenesis. IELs mediate the tissue destruction that results in villous atrophy. Despite the critical role they play, little is known about the signals that lead to their activation and cytotoxicity. Their location within the intestinal epithelium implies that they are constantly exposed to commensal microbes, pathogens, and dietary antigens and it is suggested that these signals from the microenvironment play an important role in IEL maintenance, activation, and cytotoxicity. Indeed, in recent years, microbial pathways have been suggested to influence IEL phenotype and proliferation. For instance, the microbial protease LasB from *P aeruginosa* was shown to induce the proliferation of cytotoxic IEL subsets in mice.[23] When combined with gluten, the presence of LasB led to more severe small intestinal inflammation in gluten-immunized mice that express human HLA-DQ8. IL-15 is another signal that is critical for IEL regulation. IL-15, which can be induced by viruses[36] and through bacterial signalling pathways,[37,38] or during stress,[39] can transform IELs into cytotoxic tissue destroying cells.[40] In gluten-immunized mice, IL-15 was required for the IEL-mediated destruction of the intestinal epithelium,[41] and heightened IL-15 levels have been reported in CeD patients. Exactly how altered microbial signalling and IL-15 contribute to altered IEL homeostasis and CeD pathogenesis requires additional research.

Finally, microbial metabolism of dietary components, other than gluten, may impact host immunity and barrier function. The microbial metabolism of dietary tryptophan results in the production of indole and indole derivatives that can activate the aryl hydrocarbon receptor (AhR).[42] The AhR is widely expressed within the intestinal microenvironment, including epithelial cells and immune cells, where it contributes to mucosal immunity and barrier function homeostasis.[43] AhR signalling can also promote tissue-protective IEL phenotypes.[44,45] Clinical studies indicate that the microbiota from active CeD patients has an impaired capacity to metabolize tryptophan to indoles, resulting in downregulation of the AhR pathway in the small intestine of celiacs.[46] In mice expressing human HLA-DQ8, a low tryptophan diet was associated with reduced indoles, reduced AhR activity in the small intestine, as well as increased paracellular permeability, altered IELs and more severe gluten-immunopathology. Restoring tryptophan metabolism through a high tryptophan diet in mice improved gluten-immunopathology, including intestinal permeability. Similar findings were observed in a model of food allergy.[47] AhR has a variety of immune-modulating properties, and more studies are needed to determine the mechanisms through which AhR can modulate CeD pathogenesis. Nevertheless, these findings are promising and implicate tryptophan metabolism and the AhR pathways as a potential therapeutic target for CeD. Indeed, a recent clinical trial demonstrated that the AhR pathway in the small intestine can be activated by tryptophan supplementation in healthy individuals.[48]

Future perspectives

This growing knowledge of host–microbe–diet interactions in CeD pathogenesis highlights the importance of the function of the microbial community as a whole within the small intestine. Despite the duodenum being the site of active disease, the small intestinal microbiome has been understudied, particularly the inter-kingdom and host–microbe interactions that could either promote or protect from CeD development. However, as we learn more about these interactions, we have the opportunity to leverage these pathways to develop novel therapeutics.[27] For instance, engineered or microbial-derived enzymes that are capable of fully detoxifying immunogenic gluten peptides

are currently in clinical trials.[49,50] Understanding the microbial metabolites or antigens involved in oral tolerance induction or its loss, will also provide novel therapeutic opportunities. Finally, dysregulated microbial pathways in CeD could also be targeted using specific intervention strategies. For instance, tryptophan supplementation could be utilized to activate the AhR pathway[48] in CeD patients who present with altered microbial tryptophan metabolism. While more research using clinical cohorts and small intestinal microbial samples is needed, translational research using relevant *in vitro* and *in vivo* models will be important for elucidating host–microbe–diet mechanisms involved in CeD. With this knowledge and well-designed clinical trials, preventative or adjuvant therapies for the GFD are within reach.

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Conflicts of interest

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Data availability

There are no data associated with this manuscript.

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