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# The microbiome in celiac disease: Beyond diet-genetic interactions

**I**NHERITING THE WRONG GENES and eating the wrong food (ie, gluten) are necessary for celiac disease to develop, but are not enough by themselves. Something else must be contributing, and evidence is pointing to the mix of bacteria that make our guts their home, collectively called the *microbiome*.

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Celiac disease is a highly prevalent, chronic, immune-mediated form of enteropathy.<sup>1</sup> It affects 0.5% to 1% of the population, and although it is mostly seen in people of northern European descent, those in other populations can develop the disease as well. Historically, celiac disease was classified as an infant condition. However, it now commonly presents later in life (between ages 10 and 40) and often with extraintestinal manifestations.<sup>2</sup>

In this issue of *Cleveland Clinic Journal of Medicine*, Kochhar et al provide a comprehensive updated review of celiac disease.<sup>3</sup>

## ■ GENES AND GLUTEN ARE NECESSARY BUT NOT SUFFICIENT

Although genetic factors and exposure to gluten in the diet are proven to be necessary for celiac disease to develop, they are not sufficient. Evidence of this is in the numbers; although one-third of the general population carries the HLA susceptibility genes (specifically *HLA-DQ2* and *DQ8*),<sup>4</sup> only 2% to 5% of people with these genes develop clinically evident celiac disease.

Additional environmental factors must

be contributing to disease development, but these other factors are poorly understood. Some of the possible culprits that might influence the risk of disease occurrence and the timing of its onset include<sup>5</sup>:

- The amount and quality of gluten ingested—the higher the concentration of gluten, the higher the risk, and different grains have gluten varieties with more or less immunogenic capabilities, ie, T-cell activation properties
- The pattern of infant feeding—the risk may be lower with breastfeeding than with formula
- The age at which gluten is introduced into the diet—the risk may be higher if gluten is introduced earlier.<sup>6</sup>

More recently, studies of the pathogenesis of celiac disease and gene-environmental interactions have expanded beyond host predisposition and dietary factors.

## ■ OUR BODIES, OUR MICROBIOMES: A SYMBIOTIC RELATIONSHIP

The role of the human microbiome in autoimmune disease is now being elucidated.<sup>7</sup> Remarkably, the microorganisms living in our bodies outnumber our body cells by a factor of 10, and their genomes vastly exceed our own protein-coding genome capabilities by a factor of 100.

The gut microbiome is now considered a true bioreactor with enzymatic and immunologic capabilities beyond (and complementary to) those of its host. The commensal microbiome of the host intestine provides benefits that can be broken down into three broad categories:

- Nutritional—producing essential amino acids and vitamins

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- Metabolic—degrading complex polysaccharides from dietary fibers
- Immunologic—shaping the host immune system while cooperating with it against pathogenic microorganisms.

The immunologic function is highly relevant. We have coevolved with our bacteria in a mutually beneficial, symbiotic relationship in which we maintain an active state of low inflammation so that a constant bacterial and dietary antigenic load can be tolerated.

Is there a core human microbiome shared by all individuals? And what is the impact of altering the relative microbial composition (dysbiosis) in physiologic and disease states? To find out, the National Institutes of Health launched the Human Microbiome Project<sup>8</sup> in 2008. Important tools in this work include novel culture-independent approaches (high-throughput DNA sequencing and whole-microbiome “shotgun” sequencing with metagenomic analysis) and computational analytical tools.<sup>9</sup>

An accumulating body of evidence is now available from animal models and human studies correlating states of intestinal dysbiosis (disruption in homeostatic community composition) with various disease processes. These have ranged from inflammatory bowel disease to systemic autoimmune disorders such as psoriasis, inflammatory arthropathies, and demyelinating central nervous system diseases.<sup>10–14</sup>

## RESEARCH INTO THE MICROBIOME IN CELIAC DISEASE

Celiac disease has also served as a unique model for studying this biologic relationship, and the microbiome has been postulated to have a role in its pathogenesis.<sup>15</sup> Multiple clinical studies demonstrate that a state of intestinal dysbiosis is indeed associated with celiac disease.

Specifically, decreases in the abundance of *Firmicutes* spp and increases in *Proteobacteria* spp have been detected in both children and adults with active celiac disease.<sup>16,17</sup> Intriguingly, overrepresentation of *Proteobacteria* was also correlated with disease activity. Other studies have reported decreases in the proportion of reportedly protective, anti-inflammatory bacteria such as *Bifidobacterium* and increases in the proportion of *Bacteroides* and *Escherichia coli* in patients with active disease.<sup>18,19</sup> Altered diversity

and altered metabolic function, ie, decreased concentration of protective short-chain fatty acids of the microbiota, have also been reported in patients with celiac disease.<sup>19,20</sup>

To move beyond correlative studies and mechanistically address the possibility of causation, multiple groups have used a gnotobiotic approach, ie, maintaining animals under germ-free conditions and incorporating microbes of interest. This approach is highly relevant in studying whether the bacterial community composition is capable of modulating loss of tolerance to gluten in genetically susceptible hosts. A few notable examples have been published.

In germ-free rats, long-term feeding of gliadin, but not albumin, from birth until 2 months of age induced moderate small-intestinal damage.<sup>21</sup> Similarly, germ-free nonobese diabetic-*DQ8* mice developed more severe gluten-induced disease than mice with normal intestinal bacteria.<sup>22</sup>

These findings suggest that the normal gut microbiome may have intrinsic beneficial properties capable of reducing the inflammatory effects associated with gluten ingestion. Notably, the specific composition of the intestinal microbiome can define the fate of gluten-induced pathology. Mice colonized with commensal microbiota are indeed protected from gluten-induced pathology, while mice colonized with *Proteobacteria* spp develop a moderate degree of gluten-induced disease. When *Escherichia coli* derived from patients with celiac disease is added to commensal colonization, the celiac disease-like phenotype develops.<sup>23</sup>

Taken together, these studies support the hypothesis that the intestinal microbiome may be another environmental factor involved in the development of celiac disease.

## QUESTIONS AND CHALLENGES REMAIN

The results of clinical studies are not necessarily consistent at the taxonomy level. The fields of metagenomics, which investigates all genes and their enzymatic function in a given community, and metabolomics, which identifies bacterial end-products, characterizing their functional capabilities, are still in their infancy and will be required to further investigate functionality of

**In small studies, people with celiac disease had fewer *Firmicutes* and *Bifidobacteria* and more *Proteobacteria*, *Bacteroides*, and *E coli***

the altered microbiome in celiac disease.

Second, the directionality—the causality or consequences of this dysbiosis—and timing—the moment at which changes occur, ie, after introducing gluten or at the time when symptoms appear—remain elusive, and prospective studies in humans will be essential.

Finally, more mechanistic studies in animal models are needed to dissect the host immune response to dietary gluten and perturbation of

intestinal community composition. This may lead to the possibility of future interventions in the form of prebiotics, probiotics, or specific metabolites, complementary to gluten avoidance.

In the meantime, increasing disease awareness and rapid diagnosis and treatment continue to be of utmost importance to address the clinical consequences of celiac disease in both children and adults.

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