EDITORIAL

The Gut, Intestinal Permeability, and Autoimmunity

The gut is the largest surface of the body, approximately the size of a tennis court that is continually and persistently exposed to bacterial and dietary antigens. This exposure applies to every human being, as we all eat, drink fluids, and inadvertently put things in our mouths, starting at birth. The gut houses the largest collection of immune cells, consisting of 70% of all lymphoid tissues in the body.[1] Inside the gut are approximately 130 trillion bacteria, consisting of thousands of species, known as microbiota or commensals.[2] The total number of cells of the human body is approximately 10 trillion, so this gives us a perspective into the size and the importance of the microbiota. Of these bacteria, the predominant phylotypes being *Bacteroidetes* and *Firmicutes*, 70%, cannot be cultivated by current microbiological methods.[2,3] These bacteria break down dietary components and are a defense mechanism against colonization with pathogens.[4]

This rich bacterial community is kept in check by 1 thin layer of interconnected epithelial cells, the first point of contact for gut bacteria and part of the mucosal immune system, which provides digestive, absorptive, neuroendocrine, and immunological functions. The layer of epithelial cells is reinforced by tight junctions (TJs) in the paracellular spaces between the epithelial cells. These TJs are a highly regulated entry that open and close depending on signals, such as cytokines and bacterial components from the lumen, lamina propria, and epithelium, and they are essential to the intestinal diffusion mechanisms.[5] The epithelial cells line the lamina propria of the small and large intestines and Peyer's patches, which are organized lymphoid tissues. The Peyer's patches are critical for the direct antigen sampling from the gut and are where immune responses are induced and regulated. Secretory immunoglobulin A helps prevent the adherence of bacteria to the mucosal surface and also the penetration of antigens.[6,7] The main cells that present antigens to the adaptive arm of the mucosal immune system are dendritic cells. Different populations of dendritic cells are responsible for the activation of T-cell subpopulations and, therefore, the immune response, either one of tolerance or one of stimulation.[8]

Zonulin is the modulator of intercellular TJs and participates in the balance between tolerance and immune response. In genetically susceptible patients with zonulin dysregulation, autoimmunity can occur. The important point is that the interplay and progression between genetics and environmental triggers can be stopped when the zonulin-dependent intestinal barrier function is reestablished.[9]

Let us examine some autoimmune conditions affected by zonulin dysregulation. We have seen the serious and worrisome upsurge of celiac disease (CD), a chronic enteropathy triggered by the gluten fraction from wheat, rye, or barley—mainly gliadin, glutenin, and transglutaminase. This can cause damage in any organ. There are other important components as well, including different epitopes of gliadin and types of transglutaminases and cross-reactive foods. An entire chapter can be written about these but would be too long for this editorial. Patients with CD have elevated serum levels of zonulin.[10] The inflammatory enteropathy in CD is further aggravated by tumor necrosis factor alpha (TNF-α) and interferon gamma (INF-γ), leading to increased permeability.[11] Some patients suffer from nonceliac gluten sensitivity (NCGS) and have a prevalence of nongastrointestinal (GI) symptoms, which can appear days after ingestion of gluten.

Inflammatory bowel diseases, including ulcerative colitis and Crohn's disease, are associated with abnormal intestinal permeability that precedes the development of either disorder.[12,13] This can be seen with asymptomatic Crohn's disease patients who develop increased intestinal permeability up to 1 year prior to relapse.[14] The production of inflammatory cytokines, such as TNF-α, INF-γ, and others, promotes the leakage of more intestinal content across the epithelial layer, creating a chronic sequence.

Type 1 diabetes (T1D), an autoimmune disease sometimes linked to CD and thyroiditis, can also manifest itself with GI symptoms. TJ permeability has been associated with these GI symptoms and the onset of T1D.[15] Approximately 50% of T1D patients have elevated levels of zonulin, further implicating intestinal permeability into its pathogenesis of this autoimmune disorder.[16] Studies have also linked gliadin to T1D autoimmunity.[17]

The GI system is monitored by the brain via neural, immunological, and endocrine mechanisms. The enteric nervous system controls the GI system and is influenced by

the intestinal microbiota.[18] There are more neurons in the enteric nervous system than in the spinal cord, mainly in the myenteric and submucosal plexus. Neuropeptides are able to upregulate the permeability of TJs via this mechanism and modify the function of the mucosal barrier.[19,20] Multiple sclerosis (MS) is one of the most common and severe demyelinating neurological diseases, affecting principally young people, ultimately leading to disability. Studies have shown an increase in intestinal permeability of TJs in 25% of MS patients.[21] Gluten ataxia can be found in patients with CD and NCGS presenting with myoclonus, opsoclonus, and palatal tremor.[22] Neuromyelitis optica, a form of MS characterized by acute transverse myelitis and optic neuritis, also can be seen in these patients.[23] The formation of Lewy bodies, consisting mainly of aggregated and phosphorylated α-synuclein, can be caused by gut dysbiosis and the resulting inflammatory environment from bacterial toxins, leading to Parkinson's disease.[24,25]

There are a few laboratories in the United States that perform accurate antibody measurements, allowing the clinician to predicts sometimes several years in advance the development of an autoimmune disorder prior to the appearance of symptoms. The results of antibody testing can shed light on the responsible triggers of the autoimmune response, which can then be removed, helping the patient avoid autoimmunity. With the removal of gluten from the diet, patients with CD and NCGS have a gradual decline in symptoms, intestinal damage is eventually restored, and the antibody titers return to normal, including zonulin."

There is a trend toward providing consumers with more gluten-free foods and drinks. The sales of these have increased from $5.4 billion to $8.8 billion in the past 2 years according to Mintel,[26] a market research firm. Gluten, however, is sometimes difficult to eliminate from the diet as it can found not only in foods and beverages, but also in medicines, vitamins and supplements, lip balm, and even the glue on stamps and envelopes.[27]

The above demonstrates one small facet of autoimmune diseases that affects more than 50 million Americans. There is much more, of course, as we barely touched on aquaporin, molecular mimicry, the immunological mechanisms involved, and many other factors. Some of these will be discussed in subsequent editorials.

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