

The Connection between gut microbiota and multiple sclerosis

Gut microbiota in MS

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system with a pathogenesis involving a dysfunctional blood-brain barrier and myelin-specific, autoreactive T cells. Nouri *et al.* showed that the increased intestinal permeability and dysfunction may act to support disease progression. Multiple sclerosis (MS) is one of the inflammatory autoimmune disorders with an increasing incidence. MS is characterized by breakdown of the blood-brain barrier (BBB) and demyelization of the central nervous system (CNS) due to infiltrating self-reactive T cells recognizing myelin antigens [1].

The pathogenic reaction leading to MS is an autoimmune response attacking myelin sheets of the nerve cells of the CNS requires the coincidence of at least three factors:

1. A permissive genetic predisposition
2. A pro-inflammatory intestinal microbial profile
3. An accumulation of autoreactive T cells in the gut-associated lymphatic tissue

It now turns out that, the microbes profoundly influence the body's functions on a global level. Microbial dialogues with the immune system are indispensable in helping to develop and maintain the system's full functionality. In particular circumstances, our commensal gut microbiota can trigger autoimmune responses. Gut bacteria form societies that differ greatly, dependent on their location. Some bacteria populate the inner gut lumen beyond the mucus layer, while others thrive within mucus.

Unsurprisingly, the gut flora has a central role in initiating and modulating inflammatory bowel disease. However, the discovery that intestinal microbiota are able to trigger autoimmune disease in organs far away from the gut, in the CNS, was less anticipated. Epidemiological analyses indicate that particular risk genes are required in order to allow environmental stimuli to initiate the inflammatory pathogenesis of multiple sclerosis (MS) [2].

Expression of zonulin in auto immune diseases:

Zonulin has been reported as a biomarker of several pathological conditions, including autoimmune diseases [3], Zonulin is over expressed in tissues and sera of subjects affected by autoimmune diseases like celiac disease (CD) and multiple sclerosis (MS) [4, 5]. Besides an increase in blood-brain barrier permeability, MS patients may also experience an increased permeability of intercellular tight junctions (TJ) of the enterocytes. To challenge this hypothesis, we measured serum levels of zonulin in MS patients with different subtypes of MS, relapsing-remitting (RRMS) vs. secondary-progressive (SPMS) and activities to

ascertain whether expression of zonulin into peripheral circulation can differentiate these two groups. Approximately **29% of patients with either RRMS or SPMS had elevated serum zonulin** levels (a percentage similar to increased intestinal permeability in MS patients reported by Yacyshyn et al. : High levels of CD45RO were found on circulating CD20+ B cells from patients with MS, with overall average serum levels ~2.0-fold higher than in controls. [6]. Interestingly, patients with RRMS in remission showed serum zonulin levels comparable to controls [7].

Zonulin expression was raised in intestinal tissues during the acute phase of **celiac disease** (CD) [5]. Zonulin is activated by gliadin, which is a component of gluten. Gliadin activates and induces the zonulin release from enterocytes into the intestinal lumen. The activation of the zonulin pathway is mediating cytoskeletal reorganization and the opening of tight junctions leading to a rapid increase of intestinal permeability provoking auto immune diseases. Like celiac disease (CD) and multiple sclerosis (MS) [4, 5]. One of the autoimmune targets of CD is tissue transglutaminase (TTG) [4]. This process activates a cascade of events in which cytokines and matrix metalloproteinase's are up-regulated and the intestinal mucosa is destroyed [6,7]. CD is currently regarded as a paradigm of autoimmune disease [8]

Zonulin-Summary

Zonulin over expression leads to an increased intestinal barrier permeability, which is also known as the **“leaky gut syndrome”** [7]. The authors identified Zonulin as a pre-**Haptoglobin**. Haptoglobins are released in the serum. Their function is to form stable complexes with hemoglobin (Hb) to prevent oxidative tissue damage [9].

Since Fasano *et al.* reported previously that the key biological effect of zonulin is to affect the integrity of intercellular tight junctions (TJ), Fasano and colleagues specifically focused their efforts on demonstrating, that the recombinant pre-Haptoglobin2 (HP-2) alters intestinal permeability. These results were validated independently in an *in vivo* intestinal permeability assay in which zonulin induced a significant and reversible increase in both, gastroduodenal and small intestinal permeability. Fasano reported for the first time the novel characterization of zonulin as pre-HP2, a multifunctional protein that regulates intestinal permeability caused by EGFR. This increase of intestinal barrier permeability leads to the development of auto immune diseases since the immune system in the gut is weakened by the barrier permeability [7].The production of a similar factor from pathogenic bacteria, like *V. cholera* (named ZOT for zonula occludens toxin) correlates with diarrheagenicity of *V. cholerae* strains. Zot, an enterotoxin from *Vibrio cholera* opens reversibly intercellular tight junctions. In summary the data from these studies demonstrate that the same anti-Zot antibodies used detect zonulin in the serum as well [10].

Probiotics and intestinal neuroimmunology

The human gastrointestinal tract contains a large and complex neural network called the enteric nervous system, whose main purpose is to regulate the physiological function of the gut and to modulate communication between the gut and the central nervous system. [11]. Unsaturated fatty acids from plant and fish diets are enriched in ω -3 fatty acids regulate the immune reactivity [12]. **Probiotics** are defined as microorganisms that are believed to provide health benefits when consumed [13, 14]. Probiotics possess well documented decay properties in the prevention and treatment of diarrhoeal diseases [15, 16] as well as modulating immune responses [17].

The Gut flora, gut microbiota or gastrointestinal microbiota are a complex community of microorganisms providing a barrier to pathogenic organisms [18, 19]. The gut-associated lymphoid tissue (GALT), forms part of the intestinal epithelium and detects and reacts to pathogens appearing and developing during the time that the gut flora develops and establishes [19]. Even more, if the gut flora is disturbed and not homeostasis, can provoke auto immune diseases like rheumatoid arthritis, diabetes and multiple sclerosis [20].

The direct connection between the development of MS and the gut flora was demonstrated in animal models of MS by Wekerle and colleagues [21].

Literature

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