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EVIDENCE OF A CLOSE RELATIONSHIP BETWEEN GUT MICROBIOTA DYSBIOSIS AND MULTIPLE SCLEROSIS

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Abstract

The intestinal barrier is a functional unit organized in several layers whose function is to maintain a normal permeability of the intestine and prevent the passage of the luminal content in the bloodstream in order not to activate an abnormal immune response and not to induce an inflammatory state and its alterations are found in many diseases, such as inflammatory bowel disease, graft versus host disease and celiac disease. Also, the central nervous system (CNS) is equipped with an anatomical-functional unit, the blood-brain barrier, whose function is to protect brain tissue from harmful elements present in the blood. Alterations of this barrier are an essential feature of the pathophysiology of multiple sclerosis. Immune dysregulation mediated by the blood brain barrier allows the migration of activated inflammatory cells in the brain, which in turn induces demyelination, axonal loss and other tissue damage and many molecules present in the tight junctions of the endothelial cells of the blood brain barrier are identical to those in the intestinal tissues. In these areas, various studies have shown that alterations in the intestinal microbiome can be found in patients with multiple sclerosis, strengthening the concept of the intestine-brain-microbiome axis. A common immunopathogenic element between MS and intestinal microbiota could be linked to mechanisms of molecular mimicry where specific autoreactive lymphocytes could be cross-activated by antigens present in microorganisms of the microbiota. Furthermore, various gastrointestinal diseases which are characterized by alterations of the intestinal barrier are frequently found in comorbidity with demyelinating diseases. Alterations of intestinal homeostatic mechanisms in multiple sclerosis could result in an increase in bacterial translocation through a compromised intestinal barrier. Furthermore, the use of therapies modifying the progression of multiple sclerosis represents a further crucial element since the intestinal barrier is essential for the absorption of drugs. The intestinal barrier is the physical and functional area of interaction between the luminal microbiome and the organism and is also responsible for the modulation of multiple biochemical processes and the immune modulation of the mucosa. All of this directly affects microglia and neuroinflammation. Therefore studies on the relationships between microbiome, intestinal barrier and neuroimmunological changes are needed to identify a single integrative model.

Keywords: *multiple sclerosis, microbiome, neuroinflammation*

Introduction

Our body has several biological barriers whose function is to separate the external environment from the internal environment in order to maintain homeostasis. One of these barriers is present in the intestine, the intestinal barrier, a functional unit organized in several layers, whose function is to maintain a normal permeability of the intestine and prevent the passage of the luminal content into the bloodstream in order not to activate a abnormal immune response and not induce an inflammatory state. This barrier is able to recognize commensal microorganisms and distinguish them from pathogens by having an adequate immune response (1). Alterations in the functionality of the intestinal barrier are found in many diseases, such as inflammatory bowel disease, transplant disease against the host and celiac disease (2-3-4). The CNS, extremely sensitive to homeostatic variations, has a blood-brain barrier, an anatomical-functional unit whose function is to protect brain tissue from harmful elements present in the blood. Alterations of the blood-brain barrier are an essential feature of the pathophysiology of multiple sclerosis. Immune dysregulation mediated by the blood-brain barrier allows for the migration of activated inflammatory cells into the brain, which in turn induces demyelination, axonal loss and other tissue damage (5-6). Many molecules present in the tight junctions of the endothelial cells of the blood-brain barrier (occludin, claudine and zone occludens-1) are identical to those in the intestinal tissues (6).

The intestinal barrier

The intestinal barrier is a functional unit organized in several layers (Fig. 1): a physical surface barrier that hinders bacterial adhesion by preventing its spread in the underlying tissues, a secretory barrier that includes antimicrobial peptides, mucus and liquid and an immunological barrier deeper functional able to discriminate the microorganisms between pathogens and commensals inducing an immune response or a tolerance. The integrity of the barrier is also maintained by the low pH of the bactericidal gastric juice (8). One of the main causes of increased intestinal barrier permeability (9) is inflammation where inflammatory cytokines (interferons, interleukin (IL)-17, alpha tumor necrosis factor), calcium-dependent oxidative stress, alter the molecules present in the tight junction of endothelial cells and induce greater intestinal permeability (10-11).

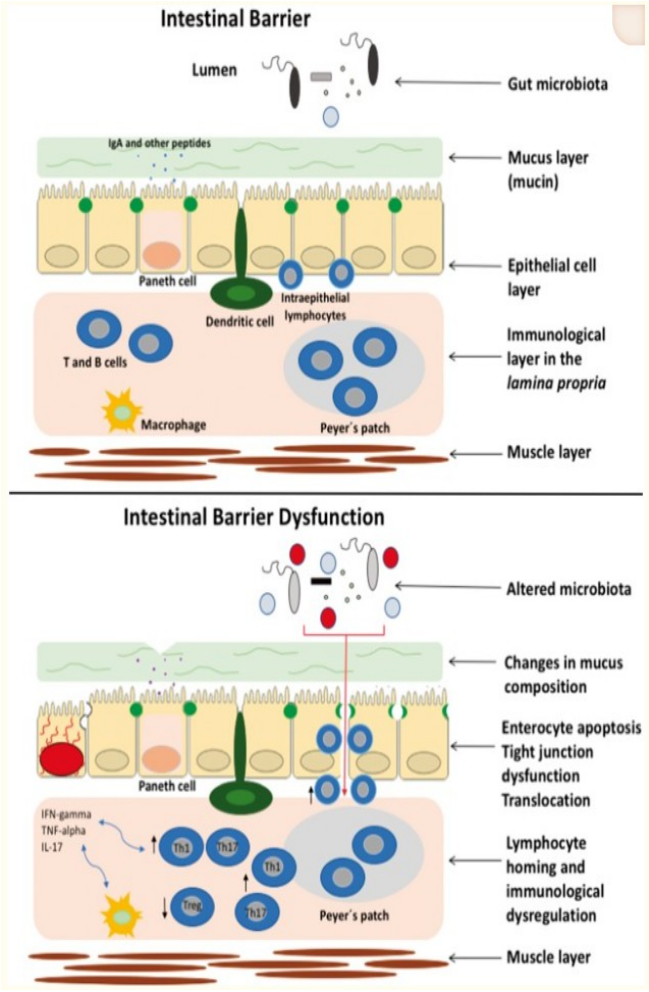

Fig.1: Intestinal barrier homeostasis, microbiome and neuroinflammation (9).

The interaction between the microbiome and the intestinal barrier is of fundamental importance for its integrity and homeostasis, the alterations of which would favor neuroinflammation. In this regard, several studies have shown that alterations in the intestinal microbiome can be found in patients with multiple sclerosis, strengthening the concept of the intestine-brain-microbiome axis. To date, multicenter studies are underway to define a "central microbiome" as a specific "phenotype of the multiple sclerosis microbiome" has not been

described "(19). There is an abundance of Streptococcus, Anaerostipes, Faecalibacterium, Pseudomonas, Mycoplasma, Haemophilus, Blautia and Dorea and a relative reduction of Clostridia, Bacteroides, Prevotella, Parabacteroides and Adlercreutzia (17). In pediatric multiple sclerosis, patients have higher levels of Desulfovibrionaceae members and depletion in Lachnospiraceae and Ruminococcaceae (18). Immunological disorders related to cytokines, interferon or proinflammatory intestinal cells (TH17) may be at the basis of changes in the microbiome (TH17) (20-21).

In this regard, intestinal germ-free mice have been shown to have an attenuated form of experimental autoimmune encephalomyelitis (EAE). (22) In these experimental models, low levels of Inteleukin-17 (proinflammatory cytokine produced by TH17) and an increase in Tregs expressing the ectonucleotidase CD39 with immunomodulatory and anti-inflammatory action (molecule capable of splitting the 'Extracellular ATP blocking its inflammatory action and increasing the production of adenosine which has anti-inflammatory properties recognized). Colonization with segmented filamentous bacteria that use a hook structure to attach to intestinal cells and release vesicles full of molecules that can prevent the immune system from attacking microbes, leads to an increase in IL-17 production and the development of severe EAEs . In contrast, other intestinal diners such as P. histicola or B. fragilis are able to suppress EAE severity, decreasing the pro-inflammatory Th1 and Th17 cells and increasing the Treg (23).

An altered microbiome also leads to changes in some products associated with bacteria known to influence intestinal homeostasis and neuroimmune responses such as short chain fatty acids (SCFA - butyrates, propionates and acetates), produced by the anaerobic bacterial fermentation of food carbohydrates and dietary fiber. SCFA regulate the transport of sodium at the level of intestinal epithelial cells, activate the inhibition of histone deacetylase, responsible for cell apoptosis (24), control the structure and immune function of microglia and astrocytes (25), also reduce the proliferation of T cells and the production of cytokines in the intestine. They also activate together with the metabolites of dietary tryptophan, indoxyl-3-sulfate and indole-3-propionic acid, the aryl hydrocarbon receptor (AHR) which act on the astrocyte and reduce inflammation through type I interferons (26). In this regard, it was observed that in MS patients, the circulating levels of AHR agonists were decreased. In EAE models, SCFA administration led to an improvement in disease severity in association with a decrease in Th1 cells and an increase in Tregs (27). SCFAs could also modulate the permeability of the blood-brain barrier by acting at the level of molecules present in the tight junctions of endothelial cells (occludin) (28) (Fig.2).

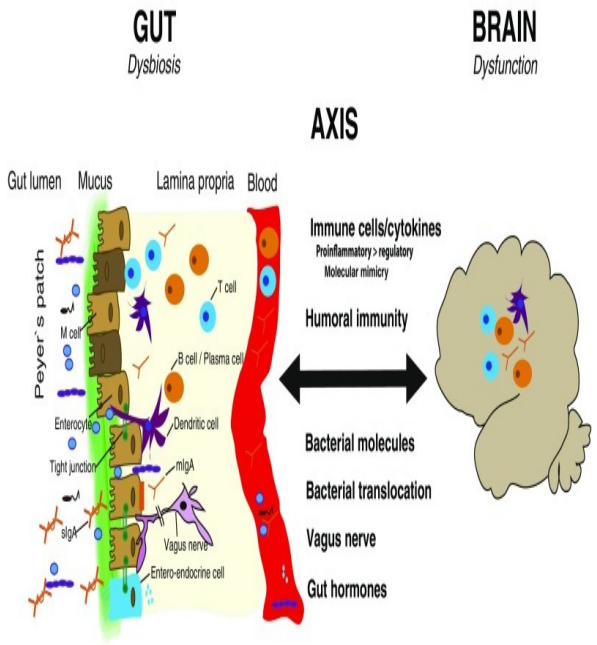

Fig.2: The interface of the intestinal mucosa is an area of intense interaction between the intestinal microbiota in the luminal space and the immune cells located in the lamina propria and enriched with lymphoid follicles, the Peyer plaques. Putative mechanisms by which dysbiosis in the gut can affect inflammation of the central nervous system in MS patients pass through immune cells through an imbalance of pro and anti-inflammatory cytokines Other routes of communication include humoral immunity, bacterial molecules (acids fats, etc.), Direct bacterial translocation leading to activation of the innate immune system, and direct communication through the vagus nerve or the release of intestinal hormones (e.g. 5-hydroxytryptamine). mIgA = monomeric IgA; sIgA = secretory IgA (19).

A common immunopathogenic element between MS and intestinal microbiota could be linked to molecular mimicry mechanisms where specific autoreactive lymphocytes could be cross-activated by antigens present in microbiota microorganisms such as Bacteroides spp and Enterococcus faecalis and myelin (29).

Alteration of the intestinal barrier and demyelinating diseases

Various gastrointestinal diseases that are characterized by alterations of the intestinal barrier are frequently in comorbidity with demyelinating diseases. In particular, IBD (inflammatory bowel disease) shares common epidemiological, genetic and immunological aspects with multiple sclerosis (12) and more specifically a higher incidence of IBD among MS patients and of MS among IBD patients (13). Both IBD and MS patients appear to have a 50% increased risk of comorbidity with MS or IBD, respectively, without any difference between Crohn's disease and ulcerative colitis. In patients with IBD there is a 3-fold increase in hyperintense white matter lesions in magnetic resonance imaging, a reduction in the volume of gray matter and a reduced axial diffusivity in the main white matter traits (14-15). The lesions of the white matter in IBD can be of various nature (ischemic, vasculitic) but the finding of demyelination in more than 70% is indicative compared to 30% in controls by age and sex (16).

These elements could highlight a connection between the intestinal barrier and the demyelination of the CNS not only in relation to the commensal intestinal microbiome but also with the integrity of the barrier itself. The lactulose / mannitol permeability test was observed to be abnormal in a large percentage of MS patients while not detecting any association between alterations in permeability and brain injury load (30).

Similar findings were also found in the experimental models of EAE (experimental autoimmune encephalomyelitis (EAE), animal model of multiple sclerosis) where altered intestinal permeability, reduced thickness of the submucosa and alterations of tight junctions in intestinal epithelial cells in relation to gravity were observed EAE. The alterations of the intestinal barrier may be related to systemic or CNS infections, a common complication in patients with multiple sclerosis, to anomalies of the microbiota-barrier interaction from which improper variation of the immune response with neuroimmune dysregulation due to abnormal transmucosal passage of harmful antigens or immunogenic (Fig.3).

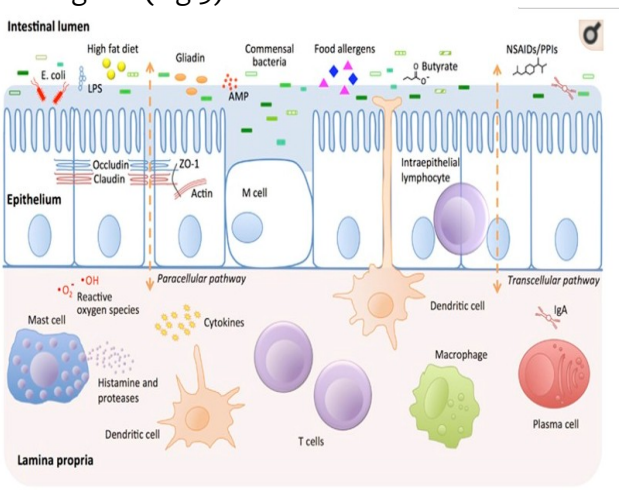

Fig. 3: The intestinal barrier is made up of several layers that provide protection against microbial invasion. The intestinal lumen contains antimicrobial peptides (AMP), IgA and commensal bacteria that inhibit the colonization of pathogens. A layer of mucus covers the intestinal surface providing a physical barrier. The epithelial layer is made up of a single layer of epithelial cells that are sealed by tight junction proteins such as occludin, claudine and zonulin-1 which prevent the paracellular passage. This layer also houses intraepithelial lymphocytes, M cells (overlying Peyer plaques and lymphoid follicles), calyx cells that produce mucus and Paneth cells that produce bacteriocin. The lamina propria contains a large amount of immune cells, both from the innate immune system (eg Macrophages, dendritic cells, mast cells) and the adaptive immune system (eg T cells, plasma cells that produce IgA). In addition, the cells of the central and enteric nervous system innervate in the lamina propria. Factors influencing intestinal barrier function include pathogenic bacteria such as E. Enteropathogenic coli, high fat diet, lipopolysaccharides (LPS), medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPI), as well as various food allergens and the gluten component gliadin (31).

Alterations of intestinal homeostatic mechanisms in multiple sclerosis could result in an increase in bacterial translocation through a compromised intestinal barrier.
A correlation has been observed between plasma endotoxin levels [lipopolysaccharide (LPS)] with production of IL-6, a multifunctional cytokine, both pro-inflammatory and anti-inflammatory, and EDSS scale (32) from which the hypothesis of an endotoxemia of low grade that may be present in patients with multiple sclerosis, probably due to bacterial translocation in the context of an altered intestinal barrier.
Finally, the use of oral disease modifying therapies and/or symptomatic drugs in multiple sclerosis is also a concern, since the intestinal barrier is essential for drug absorption (33).

Disease Modifying Treatments and intestinal barrier

The DMTs normally used in MS can modify the microbiome but we do not know exactly if their possible effects on the intestinal barrier can contribute to therapeutic efficacy (34) (Fig. 4) Disease Modifying Treatments and intestinal barrier. The DMTs normally used in MS can modify the microbiome but we do not know exactly if their possible effects on the intestinal barrier can contribute to therapeutic efficacy (34) (Fig. 4)

Interferons

There is evidence to suggest that endogenous interferons could affect the intestinal barrier. Type I interferons, including IFNα and IFNβ, are an integral part of the innate host's immune response to the gut microbiota and modulate bilateral interactions between epithelial cells and commensal flora (35). They would act by stabilizing biological barriers (intestinal barrier, BEE) by acting on the tight junctions of endothelial cells, inhibiting the continuous proliferation of the intestinal epithelium and increasing the proportion of intestinal Treg. The intestinal microbiota also stimulates the production of IFNβ at the dendritic level (36).

Glatiramer acetate

Various studies have shown that glatiramer acetate reduces colon injury in animal models of colitis, through the reduction of TNFα signaling, the elevation of regulatory T cells and the increase of anti-inflammatory mediators such as IL-10 and TGFβ. GA also induces a modification of the microbiota with quantitative variations of Bacteroidaceae, Faecalibacterium, Ruminococcus, Lactobacillaceae, Clostridium and other Clostridiales (34).

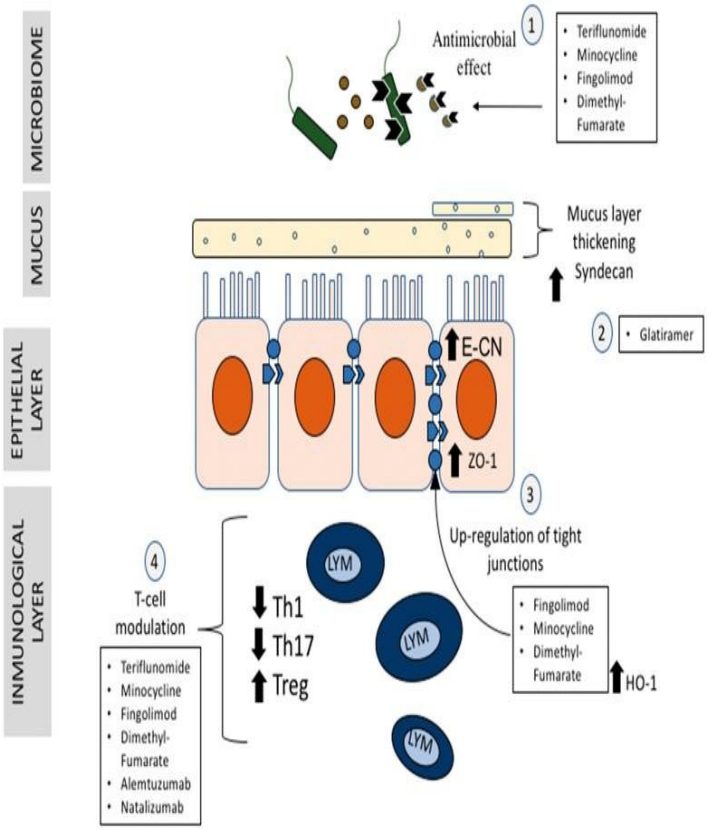

Fig. 4: Different disease-modifying therapies in clinical use can advantageously modulate intestinal barrier function through a variety of mechanisms (9).

Natalizumab

Natalizumab blocks integrins, glycoproteins involved in the immune-inflammatory process in IBDs by their recruitment action of T lymphocytes at the site of inflammation (37), being able to modulate the inflammatory response in this area in multiple sclerosis. In mouse EAE models, an increase in pro-inflammatory Th17 cells and a decrease in Treg in the intestine are observed. Integrins promote the differentiation of Th17 cells by acute EAE (38).

In patients with multiple sclerosis, treatment with natalizumab reduces the α-4-positive Th1, Th17 and Tregs integrin populations in a differentiated way assuming the intestine as a reservoir and activation site for Th17 and other T cells. It is possible that the therapeutic properties of natalizumab in multiple sclerosis may depend, at least in part, on these intestinal effects on integrins and on the circulation of lymphocytes, in addition to those observed in the blood-brain barrier. The intestine could act as a control point, a reservoir and an activation site for Th17 and other T cells, a process regulated in part by intestinal integrins. Natalizumab and its non-selective blockade of integrin could lead to changes in the way lymphocytes interact with intestinal tissue (39).

Fingolimod

Another drug that acts by regulating leukocyte trafficking is fingolimod, a functional sphingosine 1-phosphate receptor (S1P) antagonist. S1P1 receptors are highly expressed on lymphocyte membranes and are essential for the exit of T and B cells from secondary lymphoid organs. S1P can influence the intestinal barrier by modulating endothelial cell tight junction proteins, particularly in inflammatory conditions (40). Fingolimod can also directly influence the microbiota. Both sphingosine and fingolimod inhibit C. perfringens growth and endotoxin production in vitro, suggesting an intrinsic antibacterial property

Dimethylfumarate

Dimethyl fumarate (DMF) is derived from simple fumaric acid and acts as an immunomodulator by promoting apoptosis of T cells, switching to a Th2 response and acting as an antioxidant. There is limited but interesting evidence suggesting that DMF could positively affect both the intestinal barrier and the intestinal microbiota. DMF alleviates experimentally induced colitis by reducing the Th1 response in mouse models and protecting human intestinal epithelial cells from oxidative barrier alterations while preserving the occludens-1 area and occludin expression in vitro (41). DMF also preserves the morphology of the intestinal mucosa after exposure to mycotoxins, decreases intestinal permeability by strengthening tight junctions and has anti-mold and antibacterial properties. Also, DMF has also led to greater diversity of the microbiome, with an increased abundance of bacteria producing SCFA (42).

Alemtuzumab

Alemtuzumab is an anti-CD52 antibody that causes significant lymphocyte contraction. Despite its specific mechanism of action, there is evidence to suggest that it has harmful effects on the integrity of the intestinal barrier by increasing its permeability for ultrastructural alterations of tight junctions (43) and could alter the intestinal microbiome.

Teriflunomide

Teriflunomide selectively and reversibly inhibits dihydroorotate dehydrogenase, leading to a reduction in the number of activated lymphocytes that enter the central nervous system. This substance could alter the microbiome and the host's response to enteral pathogens. Treatment of porcine intestinal epithelial cells with teriflunomide has led to a reduced ability to fight bacterial infections by suppressing STAT-6 signaling (44).

Possible therapies for intestinal barrier alterations

There are few therapeutic strategies for alterations of the intestinal barrier and are directed towards different elements of the same:

- tight junction of endothelial cells

larazotide acetate, a synthetic octapeptide developed for celiac disease that can reduce intestinal permeability by acting on zonulin and actin (45)

- enrichment of the intestinal mucus layer

lecithins, in particular phosphatidylcholine (46), stem cells (study therapies for IBD) (47)

- immune homeostasis

Vit. D: protection of intestinal permeability, reduction of cell apoptosis, action on tight junctions (48)

- probiotics

barrier stabilization, faecal microbiota transplantation, modulation of the immune response in the mouse EAE model

- short chain fatty acids (SCFA)

tight junction protection, action on mucin with mucoprotective improvement on intestinal epithelial cells (49).

Conclusion

The intestinal barrier is the physical and functional area of interaction between the luminal microbiome and the organism and is also responsible for the modulation of multiple biochemical processes and the immune modulation of the mucosa. All of this directly affects microglia and neuroinflammation. Without any doubt, future studies will have to consider the microbiome, the intestinal barrier and the neuroimmunological changes downstream to adapt them to them in a single integrative model.

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