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EDITORIAL

Focus on the gut-brain axis: Multiple sclerosis, the intestinal barrier and the microbiome

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Abstract

The brain-gut axis serves as the bidirectional connection between the gut microbiome, the intestinal barrier and the immune system that might be relevant for the pathophysiology of inflammatory demyelinating diseases. People with multiple sclerosis have been shown to have an altered microbiome, increased intestinal permeability and changes in bile acid metabolism. Experimental evidence suggests that these changes can lead to profound alterations of peripheral and central nervous system immune regulation. Besides being of pathophysiological interest, the brain-gut axis could also open new avenues of therapeutic targets. Modification of the microbiome, the use of probiotics, fecal microbiota transplantation, supplementation with bile acids and intestinal barrier enhancers are all promising candidates. Hopefully, pre-clinical studies and clinical trials will soon yield significant results.

Key words: Multiple sclerosis; Microbiome; Intestinal barrier; Bile acids; Gut-brain axis

Core tip: Many studies suggest that the brain-gut connection can contribute to our knowledge of the pathophysiology of neurological conditions. Recent evidence suggests that people with multiple sclerosis have changes in their gut microbiome, their intestinal barrier and even in the metabolism of bile acids. All of these represent relevant therapeutic targets that could feasibly be addressed by pre-clinical and clinical studies. This knowledge acquired in the bench might soon be translated to the bedside.

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INTRODUCTION

Clinical and preclinical studies have shown bidirectional interactions within the brain-gut axis and the gut microbiome, the intestinal barrier and the immune system, both in health and disease. These complex interactions might be relevant for the pathophysiology of inflammatory demyelinating diseases, and in particular, multiple sclerosis, where much interest has been placed in the recent literature.

THE GUT MICROBIOME

Much interest has been placed recently on the possible role of the gut microbiome in multiple sclerosis (MS) pathophysiology. Many review articles on this subject have recently been published[1-3], perhaps more than original research articles that actually characterize the gut microbiome in patients with MS. This research is in keeping with the essential role that the gut microbiome has in regulating the development of the immune system[4]. This area of research has also been the subject of recent symposia in international MS conferences[5,6].

Much of the experimental evidence is derived from studies using the experimental autoimmune encephalomyelitis (EAE) mouse model of MS. Modifying the gut microbiota with either antibiotic cocktails or probiotics leads to EAE attenuation as well as a multitude of regulatory immune responses[7-9]. Animals bred in germ-free conditions are resistant to EAE induction and show an attenuated immunological response[10,11], an effect lost when mice are repopulated with gut commensals[11]. In recent intriguing experiments, transgenic mice prone to spontaneous brain autoimmunity developed severe disease when transplanted with fecal microbiota from MS patients, as opposed to mice that received fecal microbiota from healthy matching twins[12]. Germ-free mice receiving similar transplants also developed severe EAE, while showing altered peripheral immune responses[13].

From studies attempting to characterize the composition of the microbiome, it is clear there are some differences in people with MS compared to controls. People with relapsing-remitting MS (RRMS) have an abundance of *Anaerostipes*, *Faecalibacterium*, *Pseudomonas*, *Mycoplasma*, *Haemophilus*, *Blautia*, and *Dorea* and a relative decrease of *Bacteroides*, *Prevotella*, *Parabacteroides* and *Adlercreutzia*[14-16]. In pediatric MS, patients have higher levels of members of *Desulfovibrionaceae* and depletion in *Lachnospiraceae* and *Ruminococcaceae*[17,18]. Issues are further complicated by complex analyses at the taxa, phylum and species levels, and a myriad of microbes have been implicated. For example, studies have found a significant depletion in clostridial species[15,19], *Butyricimonas*[20], *Roseburia*[21] and an increase in *Streptococcus*[22], *Methanobrevibacter*, *Akkermansia* and *Coprococcus*[14,20].

However, there are some limitations to these studies. The methods used to analyze the microbiome have been heterogeneous, with most (but not all) studies using a variation of 16S sequencing. There are differences in sample processing, DNA extraction, choice of primers, databases and hyper-variable regions analyzed across studies. Furthermore, close to two thirds of patients with MS have gastrointestinal symptoms such as constipation, dyspepsia and other functional gastrointestinal disorders[23], and many of these have been also associated with an altered gut microbiota[24]. Studies so far have not properly accounted for these symptoms or other relevant variables such as diet. An ongoing International MS Microbiome study aims to define a "core microbiome"[3]. It might shine some light into this complicated field.

Nonetheless, there is mounting experimental evidence that the gut microbiome may play a role in MS pathophysiology and human studies suggest that patients have a different microbiome compared to controls. Of course, the true significance of the results obtained so far is unclear, considering that there has often been a failure to replicate microbiome animal studies in humans. But the next question that comes to mind is whether this can also constitute a relevant therapeutic target. Although this appears to be the case in experimental models, translation to clinical practice may prove challenging.

Modifying the microbiome through medications, possibly antibiotics, could be the simplest method, but several issues arise that question the feasibility of this approach. Targeting specific commensals might prove difficult and requires appropriate identification of these targets. The case of minocycline is an interesting example. Recently shown to delay the occurrence of a second demyelinating event in patients with a clinically isolated syndrome[25], minocycline is an antibiotic known to alter the gut microbiome[26]. Whether this is an additional mechanism of action remains unknown; it is noteworthy that the initial rationale for testing minocycline in early MS is based on its various immune-modifying properties[27]. On the other hand, there is also evidence that MS disease modifying therapies (DMTs) may alter the microbiome directly[26], and indeed, it also appears that a multitude of other medications such as antidepressants, antipsychotics and immune modulators may also do so[28]. Issues such as the generation of resistant strains are also worthy of consideration.

Probiotics are a popular option but there are various issues with their practical implementation. Probiotics do not modify the host microbiome in a robust and persistent manner, although they are purported to be able to influence gut immunity and homeostasis. Despite success

in showing a benefit for probiotics in animal models[29,30], there are only a handful of clinical trials in MS. Results have been preliminary, with some modest beneficial trends in clinical variables and some biochemical markers of changes in peripheral immune function[31-33]. However, they have included very small numbers of patients and the duration of these trials have been too short to shed any light onto clinically meaningful outcomes. There are many barriers to be overcome, such as selecting the appropriate formulation, dose and study design. There is also a lesson to be learned from the multiple clinical trials in inflammatory bowel disease (IBD), where despite a wealth of available studies (although heterogeneous in design and quality), the evidence supporting their clinical use is limited to carefully selected subpopulations[34,35].

Fecal microbiota transplantation (FMT) would constitute the optimal strategy to modify the gut microbiome. It has proven to be remarkably effective in managing *C. difficile* colitis, and isolated case reports describe beneficial effects over MS disease course, through mechanisms that remain unclear[36,37]. A clinical trial of FMT is underway[38], but even before its completion, many questions arise. It is unclear which population should be studied and what characterizes an ideal donor, not to mention the dose, route of administration and dose scheduling (single dose *vs* multiple doses). Patient with *C. diff* colitis who undergo FMT have been previously treated with antibiotics such as vancomycin and metronidazole, and presumably, have had some of their microbiota depleted. Would patients with MS require "ablation" of their microbiome before FMT? DMTs have immune modulating properties and they may also directly alter the microbiome[26], so their possible effects on the "engraftment" cannot be underestimated.

THE INTESTINAL BARRIER

The intestinal barrier is the physical and functional zone of interaction between the gut microbiome and the organism. It is a complex multi-layered structure that includes major portions of the gut immunological system and is essential for homeostasis[26]. However, it has been comparatively ignored regarding its possible role in MS pathophysiology.

In experimental models, mice undergoing EAE show an altered intestinal barrier, with increased permeability and various gross morphological changes, as well as alterations in the expression of tight junction proteins in the intestinal mucosa[39]. The peak of intestinal barrier dysfunction mirrors the peak of EAE clinical severity and preventing intestinal barrier breakdown leads to attenuation of EAE[40]. These alterations have also been associated with several abnormal immunological responses.

Patients with MS also have an altered intestinal barrier. Almost 2 decades ago, investigators found that patients with MS had increased intestinal permeability when compared to controls, using an *in vivo* mannitol/lactulose ratio test[41]. Increased intestinal permeability was also found to be associated with the number of peripheral CD45RO+ B cells[41]. A more recent study confirmed this finding; up to 70% of MS patients had increased intestinal permeability[42]. It has been hypothesized that an altered intestinal barrier might lead to bacterial translocation thus allowing the passage of noxious molecules such as microbial associated molecular patterns. This could then alter peripheral immune responses or allow these molecules to enter the CNS and alter neuroimmunity[26,43].

Although the evidence linking the intestinal barrier with MS is much more limited than evidence linking MS with alterations of the gut microbiome, the question of whether it constitutes a viable therapeutic target is the same. Of course, the issue is complicated by the fact that the microbiome is essential in the regulation of intestinal barrier function, so it could be arbitrary to think of them as separate entities. An altered intestinal barrier is also a crucial aspect of the pathophysiology of IBD and celiac disease, so research from these fields has shed light on possible strategies to maintain intestinal barrier integrity.

One of the first components of the intestinal barrier is a thick mucus layer forming a protective film, enriched by secretory IgA and antimicrobial peptides and proteins. Oral supplementation with lecithin and phosphatidylcholine can adhere to the intestinal mucosa, strengthening the mucus layer and improving barrier function[44-46]. Regulators of tight junctions, such as larazotide, are under development. Larazotide is a peptide able to re-arrange tight junctions and prevent intestinal barrier dysfunction. It has been studied in patients with celiac disease with promising results[47-49]. Designing pre-clinical studies using these methods to enhance barrier function in the setting of autoimmune neurological disease should be straightforward.

Although probiotics may not be the ideal method to modify the microbiome, they have been suggested to play a significant role in modulating barrier function. *E. coli* strain *nissle* has been marketed in Europe for many years as a probiotic with beneficial effects on the intestinal barrier[50]. It has moderate evidence from randomized trials showing it may lead to remission in ulcerative colitis[51] and in the EAE mouse model of MS it reduced disease severity by maintaining intestinal barrier function[40]. VSL#3 is another probiotic mixture with putative barrier-protecting properties[52]. There is evidence of clinical effectiveness in the management of chronic pouchitis in patients with ulcerative colitis[35,53]. VSL#3 administered to a small number of MS patients leads to an anti-inflammatory peripheral immune response[33]. These two probiotic agents would be good candidates for a large, well-designed clinical trial.

Finally, we go full circle and return to FMT. It is believed that after successful modification of the microbiome, this strategy might lead to improved intestinal barrier function[54]. The gut microbiome is essential for the regulation of intestinal barrier homeostasis[55], partly through the production of short chain fatty acids (SCFA) such as butyrate, propionate and acetate. SCFAs can modulate tight junctions in the gut and modulate inflammatory responses in the intestinal mucosa[44,55]. Other interesting alternatives have also recently been described

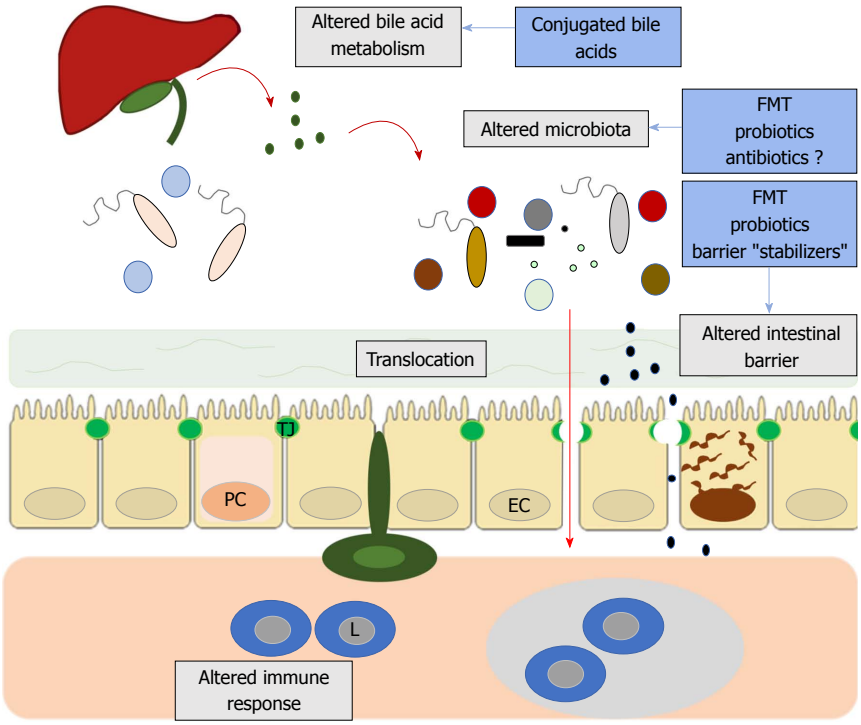

Figure 1 Alterations in intestinal homeostasis described in multiple sclerosis as therapeutic targets. Altered bile acid metabolism, altered microbiota and alterations in intestinal barrier function all lead to local and systemic alterations in immune responses that could negatively impact MS pathophysiology (grey squares). Bile acid supplementation, fecal microbiota transplantation, probiotics, antibiotics and barrier protectors are all possible therapeutic interventions (blue squares). MS: Multiple sclerosis; FMT: Fecal microbiota transplantation; PC: Paneth cells; EC: Epithelial cells; TJ: Tight junctions; L: Lymphocytes.

including the use of stool substitute preparations made from purified intestinal bacterial cultures derived from a single healthy donor[56]. Of course, many questions would need to be settled before clinical trials as discussed above.

BILE ACIDS

Bile acids are the main regulators of fat and fat-soluble vitamins digestion. They also significantly affect gut physiology and homeostasis. Bile acids can modulate the intestinal barrier function through complex mechanisms[57,58], and can shape the gut microbiota community. In turn, the microbiome can change bile acid metabolism[59]. Remarkably, bile acids may also modulate inflammatory signaling in the central nervous system. Ursodeoxycholic acid can inhibit the inflammatory activity of microglia *in vitro*[60], and tauroursodeoxycholic acid can shift microglia phenotypes towards an anti-inflammatory state through activation of the G protein-coupled bile acid receptor 1/Takeda G protein-coupled receptor 5[61]. Bile acids are also agonists of the nuclear hormone receptor farnesoid X receptor. Bile acid farnesoid X agonism led to attenuation of EAE and modulation of neuroinflammatory responses[62]. Mice fed a high-fat diet show dysregulated bile acid synthesis, gut dysbiosis and increased microglial activation[63]. Furthermore, metabolomics studies have found alterations in bile acids in patients with MS compared to healthy controls[64]. Conjugated bile acids such as ursodeoxycholic acid have been used in the management of some gastrointestinal diseases for decades. A clinical trial of bile acid supplementation in MS is underway[65].

CONCLUSION

Exciting research suggests that the brain-gut axis, once an almost esoteric concept, might yield novel therapeutic targets in neuroimmunological diseases such as MS (Figure 1). The often-symbiotic roles of the gut microbiome, intestinal barrier and even bile acids in the regulation of neuroimmune responses is beginning to be elucidated. If future pre-clinical and clinical studies confirm the relevance of intestinal barrier dysfunction, bile acid metabolism and the gut microbiome in the pathophysiology of MS, the next step will be to translate these findings into therapeutics. Only well designed clinical trials will answer whether interventions such as FMT, probiotics or barrier protectors yield clinically meaningful results. The time is right to assess whether the gut-brain axis can be transferred from the bench to the bedside.

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