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Role of Gut Microbiota in Multiple Sclerosis (MS)

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Abstract

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) characterized by inflammation, demyelination, and neurodegeneration. The pathogenesis of MS is complex, involving a combination of genetic, environmental, and immunological factors. Recent research has revealed the potential role of the gut microbiota in the development and progression of MS. The gut microbiota, a diverse and dynamic community of microorganisms, influences immune system function, metabolism, and the integrity of the blood-brain barrier. Dysbiosis, or an imbalance in the gut microbial composition, has been observed in MS patients, with certain bacterial species implicated in the modulation of CNS inflammation and autoimmune responses. Animal models of MS, such as experimental autoimmune encephalomyelitis (EAE), have demonstrated that gut microbiota can significantly affect disease severity and progression. Mechanisms underlying this interaction include the modulation of T-cell responses, regulatory immune cells, and gut-brain signaling pathways. Furthermore, diet and probiotics have been suggested as potential therapeutic strategies to restore microbiota balance and mitigate MS symptoms. However, more research is needed to fully understand the intricate relationship between gut microbiota and MS, and how these findings may be translated into clinical interventions. This review highlights the current understanding of the gut-brain axis in MS and its implications for future therapeutic approaches.

Keywords: Multiple sclerosis (MS); Gut Microbiota.

Introduction

Multiple sclerosis (MS)

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system that is commonly caused by immune mediation, characterized by multiple lesions throughout the brain and spinal cord and dissemination in time, which results in a constellation of neurological deficits that eventually lead to accumulated disability. MS remains one of the most common causes of neurological disability in young adults aged 18-40[1].

The disease has three main stages, a pre-clinical stage where the combination of genetics and environmental factors could trigger the pathology, an inflammatory stage where attacks of neurological dysfunction, such as optic neuritis, pyramidal, cerebellar or brainstem impairment, sensory symptoms, bladder dysfunction, and a final neurodegenerative stage of disease progression .The disease has many clinical forms: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS) [2]

The burden of MS is very high. Over 2.5 million people throughout the world are affected. It is common knowledge that the immunological dysregulation and self-reactive response that led to antibody attacks on the central nervous system are the fundamental pathological components of multiple sclerosis. [3].

The etiology of MS is multi factorial. It has been widely reported that increased intestinal permeability, disruption of BBB integrity, chronic inflammation, and altered T cells differentiation have a key role in MS onset and progression[4]. evidence suggests a functional alteration of regulatory T cells (Tregs) and/or effector B and T cells. Such changes compromise peripheral tolerance mechanisms, leading to the activation of peripheral autoreactive B and T cells. As a result, cellular entities, including $CD8^+$ T cells, $CD4^+$ T helper (TH) 1 cells, TH17 cells, and B cells, breach the blood-brain barrier and infiltrate the central nervous system (CNS). This infiltration promotes the activation of both microglia and astrocytes, culminating in extensive demyelination and axonal injury [5]. Growing evidence links the microbial communities in the gut to the pathophysiological processes underlying multiple sclerosis. Any changes Alterations in the gut microbiota impact immune function and the course of MS [6].

Gut Microbiota:

The gut microbiota is a complicated and ever-changing population of bacteria that inhabits the gastrointestinal system(GIT). It is crucial to human health and disease. The gut microbiota is made up of bacteria, viruses, fungi, and archaea, plays a major

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role in many physiological functions, as digestion, immunological function, body metabolism, and even behavior. the intestinal microbiota participates in the production of essential nutrients such as vitamin K and vitamin B [7]. Then are taxonomically classified into species, genus and phyla, containing both beneficial and pathogenic[8].
Recent Advances in sequencing techniques, as 16S rRNA and metagenomics, helped us identify certain intestinal microbiota in close association with human health, such as Phyla Firmicutes, Bacteroidetes, Pseudomonadota, and Actinomycetota [9].
Microbiota populations inhabit not just the gastrointestinal tract but also the epidermis, respiratory system, and reproductive system, affecting several physiological processes, including nutrition, cancer, and immunological homeostasis. The composition and quantity of gut microbiota are influenced by a number of factors, including environmental conditions, diet, and the immune system of the host.The gut microbiota changes with time rather than remaining the same throughout a person's life. [10]

Gut-Brain Axis
Recent evidence has highlighted the bidirectional communication between the gut microbiome and central nervous system (CNS), referred to as the "microbiota–gut–brain axis" [11]. The gut and brain are anatomically separate but there are several pathways by which the gut microbiota communicates with the CNS. These communication channels include modulation of the immune system, vagus nerve, enteric nervous system (ENS), neuroendocrine system, and circulatory system through the production of neuroactive substances, metabolites, and hormones [12]. Intense research highlighted the fact that the gut microbiota is capable of producing or stimulating the production of neurotransmitters, including serotonin, dopamine, and γ-aminobutyric acid (GABA).
Some of the microbial metabolites for example short-chain fatty acids (SCFA) particularly butyrate, tryptophan and its derivatives, and bile acid metabolites], can affect directly or indirectly brain functions, and immunological factors. It was shown that Butyrate, have anti-inflammatory effects and promote the differentiation of Treg cells, which are crucial for maintaining immune tolerance [13]. It is believed that the consumption of a diet with high fiber intake may increase the production of butyrate, thus leading to improved outcomes in patients with CNS disorders[14].
As for Tryptophan, its metabolism by gut microbiota produces metabolites (e.g., indole derivatives) that modulate immune responses and protect against neuroinflammation [15].
Both the composition of the gut microbiota and the integrity of the intestinal barrier are central players in this axis[16]. Under standard conditions, signaling from the gastrointestinal microbiota entails complex communication among diverse cellular entities, including dendritic cells, macrophages, and lymphocytes, thereby coordinating a multitude of physiological processes. Both the innate and adaptive immune systems intricately regulate these processes. [17]

Gut Microbiota and MS
The complex relationship between the gut microbiome and human immune responses has been studied immensely recently and it is becoming increasingly clear, particularly the role of the gut-brain axis plays in the development of MS[17].
Galluzzo et al. (2021) [18]documented an increased abundance of Ruminococcaceae in MS patients compared to healthy controls. Ruminococcus is associated with an increased risk of MS [19]. it is suggested that Ruminococcus may be involved in oxidative stress responses, which amplify an inflammatory milieu in the gut[10].
Other findings that were recorded along with the emerging research, Actinomycetales, Desulfovibrionales, Verrucomicrobiales, Gemmiger sp were all downregulated in MS[20]. Anaerostipes sp., Lachnospiracea were up regulated. Faecalibacterium is one of the most common health-promoting bacteria. Faecalibacterium was significantly lower in patients with MS[21].
Also, an increase in the abundance of Clostridium bolteae, Ruthenibacterium lactatiformans, and Akkermansia, along with a decrease in Blautia wexlerae, Dorea formicigenerans, and Erysipelotrichaceae CCMM, was found in 2 different forms of MS , the progressive MS and the relapsing-remitting MS as compared to the healthy controls [21, 22].
Bifidobacterium induces an anti-inflammatory immune response [23].Bifidocbacterium is decreased along MS patients [2].The *Akkermansia muciniphila* may contribute to exacerbation of chronic inflammation and exacerbation of MS symptoms either directly by shifting the immune response to the Th1 phenotype or indirectly by interacting with other bacteria and reducing the ability to differentiate against Treg [20].

Prevotella has a protective effect on MS.
In observational studies, Prevotella is frequently found to be reduced in patients with MS compared to the healthy controls [24]. Prevotellais one of the most abundant genus in the healthy gut [5]. Multiple complex pathways between the gut microbiota and the immune system were found. These pathways include pattern recognition receptor systems, serotonin, antimicrobial peptides and metabolites. The signals from microbiota starts the cascade, involving epithelial cells, dendritic cells, macrophages, and innate lymphoid cells, and then cells of the adaptive immune system. It is followed by homeostasis, regulation of immune system development and maturation [25]. Gut dysbiosis has been associated with a variety of disorders including MS, due to its ability to modulate the immune responses in the gut-associated lymphoid tissues (GALT) .
Dysbiosis, defined as an imbalance in the gut microbiota, can suppress Tregs and promote the proliferation of inflammatory T cells, such as TH1 or TH17 cells therefore enhancing the neuroinflammatory process. This leads to a disturbance in the immune system balance and a flare of systemic inflammatory response that speeds up the progression of MS course. On the other hand, a balanced or specific microbial composition may slow the development of MS [10].

Disease modifying therapy and Gut microbiota

MS medications have an impact on the Gut microbiota. Patients treated with disease modifying therapies, such as glatiramer acetate (GA) and dimethyl fumarate (DMF), displayed distinct microbiota composition compared to non-treated patients [26]. Interferon beta inhibits T cells and proinflammatory cytokines, stimulates Tregs and suppressive B cells, modulates the interaction between the microbes and epithelial cells and stabilize the intestinal barrier by upregulating tight junction proteins in endothelial cells[2] Teriflunomide inhibits dihydroorotate dehydrogenase, pyrimidine synthesis and proinflammatory cytokines and could influence the gut microbiome by suppressing the STAT-6 signaling pathway, increasing specific T reg cells [2].

The role of Probiotics, Prebiotics and postbiotics

Probiotics:

Probiotics have antimicrobial and anti-inflammatory properties and they reduce intestinal permeability, so they can contribute to improve the homeostasis of the intestinal microbiota [27]. Probiotics can affect the immune system by inducing a flare of anti-inflammatory cytokines and Tregs and a reduction of pro-inflammatory cytokines. Probiotics, such as Lactobacillus and Bifidobacterium, have shown in modulating gut microbiota and reducing inflammation in MS patients [28]. Kouchaki et al. reported improvement in extended disability status scale and decrease in inflammatory markers in patients with MS who were treated with probiotic supplementation.

Prebiotics:

Prebiotics are substrates that are selectively used by host microorganisms conferring a health benefit [29].They have an ability to beneficially manipulate the host's microbiota .They are resistant to digestion in the gut, they are fermented by the GM, and they stimulate the growth and activity of bacteria connected with a state of health and well-being.data have shown the beneficial effect of prebiotics in the CNS by improving neuroinflammation and modulating cognitive impairment, anxiety, and depression[30].

Postbiotics

Postbiotics, or the metabiotics, are the structural components of probiotic microorganisms and/or their metabolites and/or signaling molecules with determined chemical structures that can optimize host-specific physiological functions, regulation, and metabolic and/or behavior reactions connected to the activity of host indigenous microbiota such as SCFAs, enzymes, cell surface proteins, and vitamins [31] and butyrate was positively associated with the frequency of IL-10-producing B cells .The decreased serum concentration of butyrate seen in MS correlated with alterations in barrier permeability and inflammation.

Fecal Microbiota Transplantation (FMT)

Faecal microbiota transplantation (FMT) as an alternative and effective approach aimed at restoring eubiosis in a variety of diseases. FMT involves transplanting faecal matter from healthy donors into the patient's intestine. Within the MS setting, the benefits of FMT are associated with the induction of functional and compositional alterations in the GM, which impact immunity. Specifically, GM's ability to control the activity of Treg and Th cells is crucial to improving MS symptoms [32].

Dietary Interventions

Diet has been shown to have a significant impact on the gastrointestinal tract, as it regulates the composition and functionality of the gastrointestinal tract (GM). Additionally, the influence of inadequate nutrition on the development and progression of a number of disorders, including neurodegenerative diseases, has been well proven.

Diets composed of high intake of fat, sugar, salt, and animal proteins may lead to the development of specific pathogenic bacteria, which in turn promotes and increases gut dysbiosis, inflammation, and damage to the intestinal barrier.

Dietary habits can lead to an increase in the permeability of the blood-brain barrier, which then can trigger central nervous system autoimmunity. On the other hand, a diet that is rich and abundant in vegetables and fibers, with the administration of probiotics and vitamin D, results in the restoration of gut microbiota and an increase in microbiota-associated anti-inflammatory factors such as SCFAs [33].

Considering the major role that diet and dietary habits play in shaping GM helping to preserve brain health, reduce risk, modulate symptoms, and improve pathophysiology related to neurodegenerative diseases, dietary intervention in conjunction with pharmacological treatment could be a strategy to restore GM dysbiosis and improve symptoms of multiple sclerosis.[32].

Conclusion

Probiotics, prebiotics, and postbiotics are emerging as major players in the therapies for multiple sclerosis (MS). This is due to their capacity to induce anti-inflammatory effects by acting on the immune system as well as the microbiota that is found in the digestive tract.

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