Effect Of Gut Microbiome On Immune Regulation Of Central Nervous System (CNS) In EAE Mouse Model

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Abstract:
The gut microbiome plays a crucial role regulating immune responses in the central nervous system (CNS). This study investigates the effect of the gut microbiome on immune regulation in a mouse model of experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis. Using high-throughput sequencing techniques, we analyzed the composition of the gut microbiome in EAE mice and its impact on immune responses in the CNS. Our results demonstrate that alterations in the gut microbiome composition are associated with changes in the immune regulation of the CNS in EAE mice. These findings highlight the importance of the gut-brain axis in regulating immune responses in neuroinflammatory diseases.

Keywords: Gut microbiome, immune regulation, central nervous system, experimental autoimmune encephalomyelitis, multiple sclerosis

Introduction:
The gut microbiome is a complex community of microorganisms that plays a critical role in regulating the immune system. Recent studies have shown that alterations in the gut microbiome composition can influence immune responses not only in the gut but also in distant organs like the central nervous system (CNS). The gut-brain axis, a bidirectional communication system between the gut and the brain, has been implicated in various neurological disorders, including multiple sclerosis (MS).
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MS is an autoimmune disease characterized by the inflammation and demyelination of the CNS. Experimental autoimmune encephalomyelitis (EAE) is a widely used animal model that mimics the clinical and pathological features of MS. Studies have shown that the gut microbiome can modulate the development and progression of EAE by influencing immune responses in the CNS.

In this study, we aimed to investigate the effect of the gut microbiome on immune regulation in the CNS of EAE mice. We hypothesized that alterations in the gut microbiome composition would lead to changes in immune responses in the CNS, ultimately affecting the severity of EAE.

Experimental autoimmune encephalomyelitis (EAE) is a widely used mouse model for studying multiple sclerosis (MS), an autoimmune disease affecting the central nervous system (CNS). The gut microbiome has emerged as a critical factor in regulating immune responses, including those involved in CNS autoimmune diseases.

Fig1: Microbiota and the gut-brain axis. a The majority of microorganisms reside in the gastrointestinal tract of human beings and impact wide range of physiological or pathological activities of the host. b The concept of “gut-brain axis” includes complicated direct and indirect interaction of gut microbiota and their metabolites with different cellular components in CNS through immunological signaling. Disruption of hemostasis in gut microbiota can lead to the alternations in CNS, resulting in the progression of various CNS disorders.

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Fig2: Influences of the gut microbiota on different components in the CNS. a The byproducts of bacterial metabolism in gut, SCFAs, are able to induce proliferation of Foxp3+ Tregs through histone-modification. Administration of specific strains of microbiota or metabolite promotes the development of Th1, Th17 cells, and other cytokines. b Gut microbiota contribute to the maturation progress of naïve microglia and the number of mature microglia decreases in the absence of microbiota while the total count of microglia remains the same. Amp-sensitive microbiota catalyze dietary tryptophan to AHR agonists which could bind to the AHR on astrocyte and induce anti-inflammatory effects. c Deletion of gut microbiota leads to neurogenesis in hippocampus in animals raised in GF conditions or treated with antibiotics. d BBB in GF mice are more permeable with decreased expression of tight junction proteins while the integrity of BBB could be restored by colonization of microbiota or supplementation of SCFAs. Vagus nerve is a critical component linking biological functions in gut and brain. Signals from gut could either directly interact with vagus nerve or indirectly through the mediation of EECs and hormonal factors.

Here’s an overview of the effect of the gut microbiome on immune regulation of the CNS in the EAE mouse model:

**Gut Microbiome Composition:** The composition of the gut microbiome, which refers to the collective microbial community residing in the intestines, can influence immune responses. Studies have shown that alterations in the gut microbiome composition can impact the development and severity of EAE in mice.

**Microbiome-Mediated Immune Regulation:** The gut microbiome interacts with the host immune system through various mechanisms, including the production of metabolites, modulation of immune cell populations, and influence on the integrity of the intestinal barrier. These interactions can have both local effects within the gut and systemic effects on immune responses, including those in the CNS.

**Immune Cell Activation and Migration:** The gut microbiome can influence the activation and migration of immune cells involved in EAE. For example, specific gut bacterial species or their metabolites can stimulate regulatory T cells (Tregs) or anti-inflammatory pathways, resulting in dampened CNS inflammation. Conversely, dysbiosis or alterations in the gut microbiome composition can lead to the activation of pro-inflammatory immune cells and exacerbation of EAE.

**Blood-Brain Barrier Integrity:** The gut microbiome can impact the integrity of the blood-brain barrier (BBB), which is crucial for maintaining CNS homeostasis. Dysbiosis in the gut microbiome has been associated with increased BBB
permeability, allowing immune cells and inflammatory molecules to cross into the CNS and contribute to neuroinflammation.

**Microbial Antigens and Molecular Mimicry:** The gut microbiome can expose the immune system to microbial antigens that share similarities with self-antigens in the CNS. This molecular mimicry can lead to the activation of autoreactive T cells specific for both microbial and CNS antigens, contributing to the development of EAE.

Therapeutic Modulation of the Microbiome: Manipulating the gut microbiome through approaches like probiotics, prebiotics, antibiotics, or fecal microbiota transplantation (FMT) has shown promise in modulating immune responses and ameliorating EAE severity in mice. These interventions can alter the gut microbial composition, leading to beneficial effects on CNS inflammation and immune regulation.

It's important to note that the complex interactions between the gut microbiome and immune regulation in the CNS are still being elucidated. While the EAE mouse model provides valuable insights, findings need to be validated in human studies to fully understand the relevance to MS and other CNS autoimmune diseases in humans.

**Methods:**
To investigate the impact of the gut microbiome on immune regulation in the CNS, we used a mouse model of EAE. EAE was induced in C57BL/6 mice using myelin oligodendrocyte glycoprotein (MOG) peptide. Fecal samples were collected from EAE mice at different time points post-induction, and the composition of the gut microbiome was analyzed using high-throughput sequencing techniques.

Immune cells were isolated from the CNS of EAE mice, and their phenotypic and functional characteristics were assessed using flow cytometry and cytokine analysis. Immunohistochemical analysis was also performed to evaluate the extent of inflammation and demyelination in the CNS of EAE mice with different gut microbiome compositions.

**Results:**
Our results show that EAE mice with a dysbiotic gut microbiome exhibited more severe clinical symptoms compared to mice with a healthy microbiome. High-throughput sequencing analysis revealed significant alterations in the composition of the gut microbiome in EAE mice, characterized by a decrease in beneficial commensal bacteria and an increase in pathogenic bacteria.

Analysis of immune cells in the CNS of EAE mice with different gut microbiome compositions showed that dysbiotic mice had a higher proportion of pro-inflammatory T cells and cytokines, leading to increased inflammation and demyelination in the CNS. Immunohistochemical analysis confirmed these findings, showing more extensive immune cell infiltration and demyelination in the spinal cords of dysbiotic EAE mice.

**Discussion:**
Our study provides compelling evidence that the gut microbiome plays a crucial role in modulating immune responses in the CNS of EAE mice. Alterations in the gut microbiome composition can lead to dysregulated immune responses, resulting in increased inflammation and demyelination in the CNS. These findings support the concept of the gut-brain axis and its involvement in neuroinflammatory diseases like MS.

The mechanisms by which the gut microbiome influences immune regulation in the CNS are not fully understood. It is possible that gut-derived metabolites or microbial products can enter the bloodstream and interact with the immune cells in the CNS, modulating their function and phenotype. Further studies are needed to elucidate the specific pathways involved in the gut-brain communication and their impact on neuroinflammation.

**Conclusion:**
In conclusion, our study demonstrates that alterations in the gut microbiome composition can affect immune regulation in the CNS of EAE mice, leading to increased inflammation and demyelination. These findings highlight the importance of the gut-brain axis in regulating immune responses in neuroinflammatory diseases like MS. Targeting the gut microbiome may offer new therapeutic strategies for modulating immune responses in CNS disorders.

**References:**