The Dynamics of the Gut Microbiome in Multiple Sclerosis in Relation to Disease

Ellen M. Mowry, MD, MCR[a], Justin D. Glenn, PhD[b,*]

KEYWORDS

- Gut microbiome • Multiple sclerosis • Neuroinflammation • Gut bacteria
- Experimental autoimmune encephalomyelitis

KEY POINTS

- Preclinical and clinical case-control studies indicate that multiple sclerosis (MS) is associated with gut microbial dysbiosis, although its role in MS development is unknown.
- Alterations of the MS gut microbiota may include reduction of bacteria species that generate immune-modulatory molecules, including short-chain fatty acids, and increases in some immune-stimulatory and neurotoxic species.
- Preliminary studies suggest that gut immunity could be biased toward inflammation in MS and may promote immune responses targeting central nervous system tissue.
- There is no current established therapy for targeting the gut microbiome for MS therapy, but several lines of intervention are under investigation, including vitamin D supplementation, probiotic consumption, and diet modification.

INTRODUCTION

Multiple sclerosis is a chronic, inflammatory autoimmune disease of the central nervous system characterized by attacks on and degradation of myelin sheaths, axonal dropout, and gradual neuron loss. Its pathogenesis has been extrapolated mainly through the understanding of disease-causing mechanisms comprising its classical mouse model, experimental autoimmune encephalomyelitis (EAE).[1] EAE induction involves subcutaneous immunization of mice with an emulsion composed of a myelin component, such as myelin oligodendrocyte glycoprotein (MOG) peptide/protein or proteolipoprotein (PLP) peptide and complete Freund adjuvant in addition to pertussis toxin administration. In response, myelin peptide-specific T cells become activated as

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[a] Department of Neurology, Johns Hopkins School of Medicine, 600 North Wolfe Street, Pathology 627, Baltimore, MD 21287, USA; [b] Department of Neurology, Johns Hopkins School of Medicine, 600 North Wolfe Street, Meyer Building, Room 6-138, Baltimore, MD 21287, USA
* Corresponding author.
E-mail address: jglenn7@jhmi.edu

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proinflammatory T cells (including T_H1 and T_H17) and attack once in the CNS. EAE immunization results in a reliable and reproducible ascending paralysis that can be evaluated with a well-defined severity score point-based system. EAE can also be induced by adoptively transferring activated $CD4^+$ T cells from EAE-immunized mouse donors into naïve recipients.

Although EAE gives insight into the possible cellular and molecular mechanisms that underlie MS pathogenesis, it does not reflect MS etiology, which is only partially understood. As is the case with many autoimmune diseases, heritable, genetic components and environmental factors are thought to contribute to MS development. In addition to sex differences, smoking, viral infection (with Epstein-Barr virus), lower vitamin D levels, and obesity, particularly in adolescence, appear to increase MS risk.[2–5] A growing body of studies and literature is centered on the association of gut microbial dysbiosis and the development of MS, and this topic will be the remaining focus of this article.

NORMAL COMPOSITION OF THE HUMAN GUT MICROBIOTA

The gut microbiota refers to the total number and composition of microbes that inhabit the gut, while the microbiome comprises the total genetic makeup of the microbiota. Its bacterial component has received the most attention and study due in part to its great density within the gut. The adult human intestine contains over 70% of the body's microbes, up to 100 trillion, and the microbiome number is 10 times larger than that of somatic and germ cells.[6,7] Gut commensal bacteria perform a large range of indispensable tasks for the promotion of human health, beginning with energy extraction.[7] The gut sits as an anaerobic bioreactor in which bacteria break down complex, otherwise indigestible, polysaccharides into monosaccharides and eventually fatty acids. Moreover, gut bacteria play integral roles in other forms of nutrient and xenobiotic metabolism; normal development of intestinal stroma, parenchyma, and the immune system; and the steady-state release of antimicrobial and immune-modulatory molecules.

Of the 55 known bacterial divisions, only 8 have been identified in the gut, 5 of which are rare.[7,8] The remaining 3 divisions include cytophaga-flavobacterium-bacteroides, firmicutes, and proteobacteria, with the former two composing around 30% each of bacteria isolated from feces and the mucus covering intestinal epithelium. Proteobacteria is present but not as prominent. The composition of a healthy gut contains large fractions of the phyla Firmicutes and Bacteroidetes, including the genera *Bacteroides*, *Prevotella*, and *Ruminococcus*, followed by Actinobacteria and Verrucomicrobia, but low in Proteobacteria phyla members.[9,10]

Factors that contribute to the formation and stable establishment of the normal human gut microbiota include mode of delivery in parturition, type of infant feeding (breast vs bottle), and diet.[11] Going into adulthood, diet is arguably the primary determinant of gut microbial composition and shapes the prospective interactions between the host and microbiota. Diets rich in fruits, vegetables, and fibers promote gut bacterial diversity and enrich for phyla involved in insoluble carbohydrate metabolism such as Firmicutes, while diets heavy in meat consumption are enriched for bile-metabolizing bacteria.[12,13]

EVIDENCE LINKING GUT DYSBIOSIS AND MODELS OF MULTIPLE SCLEROSIS

First, gut bacteria are required for induction of EAE. Mice housed in germ-free facility conditions, in which the gut is devoid of bacterial pathogens, developed a significantly less severe course of EAE compared with those in specific pathogen-free (SPF)