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REVIEW

The Microbiome–Gut–Behavior Axis: Crosstalk Between the Gut Microbiome and Oligodendrocytes Modulates Behavioral Responses

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Abstract

Environmental and dietary stimuli have always been implicated in brain development and behavioral responses. The gut, being the major portal of communication with the external environment, has recently been brought to the forefront of this interaction with the establishment of a gut–brain axis in health and disease. Moreover, recent breakthroughs in germ-free and antibiotic-treated mice have demonstrated the significant impact of the microbiome in modulating behavioral responses in mice and have established a more specific microbiome–gut–behavior axis. One of the mechanisms by which this axis affects social behavior is by regulating myelination at the prefrontal cortex, an important site for complex cognitive behavior planning and decision-making. The prefrontal cortex exhibits late myelination of its axonal projections that could extend into the third decade of life in humans, which make it susceptible to external influences, such as microbial metabolites. Changes in the gut microbiome were shown to alter the composition of the microbial metabolome affecting highly permeable bioactive compounds, such as p-cresol, which could impair oligodendrocyte differentiation. Dysregulated myelination in the prefrontal cortex is then able to affect behavioral responses in mice, shifting them towards social isolation. The reduced social interactions could then limit microbial exchange, which could otherwise pose a threat to the survival of the existing microbial community in the host and, thus, provide an evolutionary advantage to the specific microbial community. In this review, we will analyze the microbiome–gut–behavior axis, describe the interactions between the gut microbiome and oligodendrocytes and highlight their role in the modulation of social behavior.

Key Words Gut microbiome • myelin plasticity • social behavior • metabolites • oligodendrocytes • prefrontal cortex

Introduction

While neurogenesis and gliogenesis occur during the early stages of development, the formation of myelin around the axons is a long process that continues to develop well into adult life [1]. Myelin is the specialized membrane of cells called oligodendrocytes, which derive from progenitor cells. The differentiation of these progenitors into myelinating oligodendrocytes is defined by a complex and long-lasting transcriptional program, which is orchestrated by modification of the epigenome, caused by intrinsic and environmental factors. One of the major portals of environmental exposure for the mammalian body is the gut, and the role of a gut–brain axis in health and disease has recently been established, with multiple implications for brain physiology and pathology, as well as behavioral responses [2–4].

The most protracted changes in myelination occur in the prefrontal cortex (PFC), the association cortex of the frontal lobe, which exhibits late myelination of its axonal connections [1]. PFC has a crucial role in adjusting an organism's behavior to the environment and shapes social behavior [5, 6]. Therefore, changes in the development and function of the PFC could significantly affect behavioral responses of mice and humans. In this review, we will describe the importance of

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PFC myelination in shaping social behavior and highlight the concept of myelin plasticity in the adult PFC. We will then decipher the microbiome–gut–behavior axis and provide the latest evidence regarding the crosstalk between microbiota, PFC oligodendrocytes, and social behavior.

Myelin Plasticity and Social Behavior

Myelin Formation in the PFC Shapes and is Shaped By Social Experiences

While neurons have long been considered central nervous system cells that can adapt in response to environmental stimuli, oligodendrocytes have also been shown to adapt in response to environmental changes. More specifically, social experiences in early life have been shown to shape myelin formation in the PFC [7, 8]. This is of high relevance, as this is also the brain region where external stimuli are integrated and translated into several complex behaviors [9]. Myelin changes in the PFC have been reported in a wide range of psychiatric illnesses, including autism, anxiety, schizophrenia, and depression, and abnormal myelination has been associated with numerous behavioral phenotypes, including social avoidance [10, 11]. In many instances, early life experiences have been associated with long-lasting white matter changes and suggest that myelination changes induced by childhood events are relatively stable and possibly unfavorably modulate the onset of psychiatric disorders [12–15].

Behavioral Responses can be Modified By Exogenous Regulators of Myelin Plasticity

The adult PFC has also been shown to undergo myelination in adult jugglers, further underlying the role of myelin plasticity as an adaptation to novel experiences [16]. Protracted social isolation of adult mice was also shown to impair myelination and induce epigenetic changes in oligodendrocytes, which were highlighted by ultrastructural studies of the PFC [11]. From a mechanistic standpoint, the way by which external experiences modulate the transcriptional program remain unclear. However, it was recently reported that clemastine, a muscarininc inhibitor, was sufficient to prevent the onset of social avoidance behavior induced by social isolation by favoring myelin formation and the deposition of correct epigenomic marks in oligodendrocytes [17]. Among the factors that could affect myelination in the PFC, the gut microbiome has recently emerged as a key player in the regulation of myelin formation and the pathogenesis of neurobehavioral disorders [18–23].

The Microbiome–Gut–Behavior Axis: A Novel Regulatory Pathway of PFC Myelination and Social Behavior

The microbiome–gut–behavior axis is an intricate network of dynamic and bidirectional signaling pathways that provide a link between dietary and environmental stimuli, myelination in the PFC, and behavioral responses. The gut–brain axis is broadly defined as inclusive of gut microbiota, gut epithelium, liver, enteric, parasympathetic and sympathetic nervous systems, brain and spinal cord, neuroendocrine connections, metabolites, cytokines, neuropeptides, and signaling molecules [24, 25]. The majority of gut–brain communication, however, is being facilitated via 4 distinct routes: 1) vagal afferents; 2) gut hormones; 3) cytokines; and 4) microbial metabolites [24, 26, 27]. Microbial metabolites have recently come to the forefront of the gut–brain axis after the demonstration of a surprisingly large effect of the gut microbiome on mammalian blood metabolites, especially short-chain fatty acids (e.g., butyrate) and amino acid degradation products (e.g., phenols and indoles) [28].

The gut–brain axis has been implicated in the regulation of microglial activity [29], blood–brain barrier integrity [30], hippocampal neurogenesis [31], myelination [20, 21], neuroendocrine response to stress, and neurotransmitter production [24, 25, 32]. The regulatory effect of the gut–brain axis on behavior in mice has been uncovered more recently and shown to be dependent on the formation of bioactive microbial metabolites, such as p-cresol, a phenol produced by microbial degradation of dietary tyrosine (Fig. 1) [21].

The Effect of the Gut Microbiome on Social Behavior

The profound impact of the gut microbiota on the modulation of behavioral responses has recently been recognized mainly through work on germ-free (GF) and antibiotic-treated mice [21, 32]. GF mice have been found to have reduced anxiety-like and depressive behaviors [33, 34] and have altered stress and amygdala-dependent fear responses [35]. In addition to these changes, GF mice, particularly males, exhibit autism-like social impairments accompanied by reduced preference for novel social situations and increased repetitive behaviors [33]. Interestingly, patients with autism spectrum disorder have been found to have altered gut microbiome with differences in species richness and diversity *versus* controls [3, 36]. Moreover, it was recently shown that the transfer of gut microbiota from socially withdrawn mice was sufficient to induce the same phenotype in the recipient mice [21], suggesting that gut microbiota have a central role in the modulation of their host's social behavior. This behavioral effect could, in turn, provide the microbial community with an evolutionary advantage by eliminating incoming competition from the

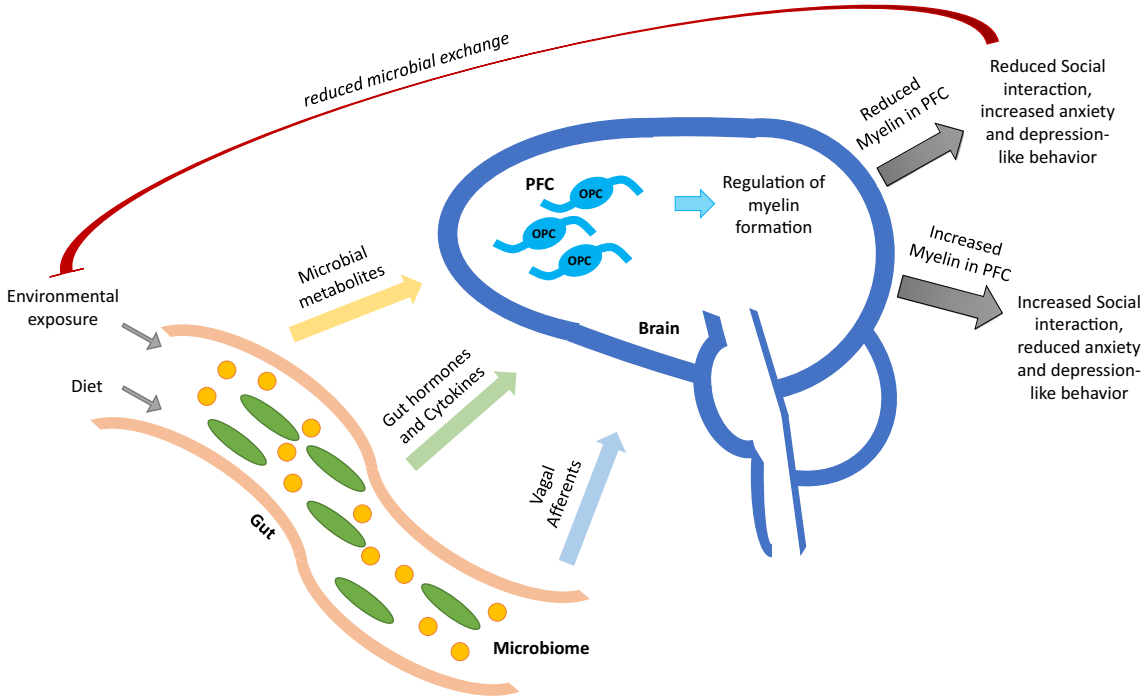

Fig. 1 The microbiome–gut–behavior axis. The gut is one of the major portals of environmental exposure of the mammalian body and is the site where the gut microbiome integrates the environmental and dietary signals to produce certain secondary messengers that can reach and affect brain development and behavior. These second messengers can be in the form of unique microbial metabolites, gut hormones, cytokines, and vagal afferent signals. One well-studied mechanism of modulation of behavioral responses by the gut microbiome involves certain microbial metabolites that can reach the brain and affect myelin formation in the prefrontal cortex (PFC) of the brain by interfering with differentiation of oligodendrocyte progenitor cells (OPC), possibly via modulating *Sox10* or *MYRF*. Increased production of these metabolites by the microbial community of the gut can inhibit OPC differentiation and reduce the formation of myelin in the PFC. Reduced myelination in the PFC is then associated with increased anxiety and depression-like behavior and reduced social interaction. This social isolation could then benefit the microbial community by limiting incoming competition from the external environment, as social isolation could also lead to less microbial exchange. However, decreased production of these metabolites by the gut microbial community would allow OPCs in the PFC to differentiate and increase myelination, which could lead to increased social interactions, and reduced anxiety and depressive-like behaviors, at least in mice

external environment, as socially withdrawn mice that do not interact with other mice also have less microbiome exchange.

Myelination is the Link Between the Gut and Social Behavior

Current evidence in mouse models suggests that the microbiome–gut–behavior axis exerts its regulatory effect on social behavior mainly by affecting myelination in the PFC [20, 21]. Gacias et al. [21] demonstrated that daily gavage of antibiotics could protect nonobese diabetic (NOD) mice from social avoidance and despair-like behaviors that were observed when NOD mice were gavaged with water, suggesting a role of the gut microbiota in determining the behavioral response of mice to a stressful stimulus. To further corroborate that, the transfer of gut microbiota from water-gavaged NOD donors, which included members of the Clostridiales order and Lachnospiraceae and Ruminococcaceae families, to microbiota-depleted C57BL/6 recipients was sufficient to induce the same socially withdrawn behavioral phenotype. Interestingly, it was shown that socially withdrawn mice had impaired myelination in the PFC with a reduction in all major myelin gene transcripts, which was then linked to a disturbed gut microbial metabolome. More specifically, socially withdrawn mice had changes in their gut microbiome that allowed the production of increased concentrations of p-cresol, a highly permeable product of microbial degradation of dietary tyrosine, which can inhibit oligodendrocyte differentiation *in vitro* [21].

However, p-cresol is not the only microbial metabolite that could potentially mediate the effects of the gut microbiome on myelination and behavior. Several other studies have investigated the role of butyrate, a short-chain fatty acid produced by the gut microbiome via dietary fiber fermentation, has been implicated in the regulation of microglial activity [37], which, in turn, could regulate myelination. Butyrate could also directly affect oligodendrocyte progenitor cell (OPC) differentiation and myelination as it has histone deacetylase inhibitory activity similar to valproic acid, a mood stabilizing drug that can inhibit OPC differentiation *in vitro* and *in vivo* [38]. These findings emphasize the importance of the microbiome–gut–behavior axis in modulating myelination and social behaviors and emphasize the role of microbial metabolites as one of the

main routes of gut microbiota–oligodendrocyte communication.

The Microbiome–Gut–Behavior Axis Targets PFC Myelination Via Regulation of Myelin Regulatory Factor and Sry-Related HMg-Box Gene 10

The importance of gut microbiota in regulating PFC myelination was also shown by Hoban et al. [20]. GF mice exhibited hypermyelinated axons and marked upregulation of genes linked to myelination at the PFC. At the molecular level, myelin regulatory factor (MYRF) was identified as a major driver of the observed hypermyelination, which was also accompanied by increased Sry-related HMg-box gene 10 (*Sox10*) expression in GF mice. Interestingly, *Sox10* was found to be downregulated by p-cresol, the microbial metabolite identified by Gacias et al. [21]. Interestingly, p-cresol has been found to be absent in GF mice [28], a finding that could potentially explain the observed increase in *Sox10* expression in those mice.

Hoban et al. [20] also found that neural activity-induced transcriptional pathways were upregulated in the PFC of GF mice. This is in agreement with a previous report of hyperactive amygdala (which connects to the PFC via glutamatergic projections) in GF mice [39]. This increased neural activity could also play a role in regulating myelin formation at the PFC in GF mice, as myelination has been shown to be regulated by neuronal activity and glutamate release from synaptic vesicles [40, 41]. These data reinforce the central role of microbiota in regulating myelin plasticity and bring the PFC at the center of the microbiome–gut–behavior axis.

Microbial Neurotherapeutics: Modulation of the Microbiome–Gut–Behavior Axis

The existence of a microbiome–gut–behavior axis in various neurobehavioral diseases brings out the potential of therapeutic manipulation of the gut microbiome. The effort to leverage the therapeutic effect of microbes is still in the early stages of development and further research is needed to establish such an effect. Preliminary evidence has shown that daily supplementation with *Lactobacillus* and *Bifidobacterium* strains could exert a positive effect in mood, anxiety, and cognitive symptoms of depression, with the most benefit observed in anxiety-related symptoms [42]. Distinct probiotic preparations, however, may display batch effects and differ among various manufacturers, thereby highlighting the need for a better understanding of the probiotic-mediated modulation of microbial communities to regulate behavior. In addition to probiotics, a future microbial neurotherapeutic intervention could be targeting the early-life microbiome. It is now possible to restore the microbiome of newborn infants delivered by cesarean section to resemble that of infants delivered vaginally [43], and, thus, potentially correct the aberrant early-life microbiome composition that has been associated with deregulated brain development in other studies [3].

Finally, a future consideration for potential intervention on the gut microbiome in humans is direct fecal microbiota transplantation, a procedure that has been successfully performed for the treatment of antibiotic-resistant gastrointestinal infections. In mice, transfer of microbiota from socially withdrawn mice to microbiota-depleted recipients was sufficient to transfer the behavioral phenotype, suggesting that fecal microbiome transplantation could effectively manipulate the microbiome–gut–behavior axis [21]. Despite the fact that evidence to support the effectiveness of this method for the treatment of neurological disorders in humans is scant, the increased interest on microbiota characterization in neurological disorders highlights the need for additional studies on the therapeutic efficacy of such microbial neurotherapeutic interventions in the future.

Conclusion

The microbiome–gut–behavior axis, as part of the gut–brain axis, is being increasingly recognized as an important regulator of PFC myelination and a modulator of social behavior. PFC is a key brain region for driving behavioral responses, which has also been implicated in depression and autism [20]. Current evidence suggests that microbial transfer can transmit social behaviors in mice and unique microbial metabolites, such as p-cresol, are at the core of this microbiome–gut–behavior axis [21]. Such microbial metabolites modulate myelin plasticity at the PFC by changing the expression of *MYRF* and *Sox10* at the molecular level. This alteration in myelination at the PFC then regulates behavioral responses to stressful or social stimuli. Moreover, regulation of the amygdala–PFC glutamatergic activity by the gut microbiome could also influence myelin plasticity at the PFC and modulate anxiety-related and social behaviors [20]. More research is needed, however, to further elucidate the components of the microbiome–gut–behavior axis with the ultimate goal of identifying potential probiotics and microbial neurotherapeutic interventions that could rescue the microbiome–gut–behavior axis deregulation that has been observed in different neurobehavioral diseases.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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