Review

The Gut–Myelin Axis: Microbial Metabolites in Oligodendrocyte Biology and Remyelination

Enso O. Torres Alegre * and Diana E. Mora Jiménez

Posted Date: 27 February 2026

doi: 10.20944/preprints202602.1855.v1

Keywords: microbiota–gut–brain axis; oligodendrocytes; myelination; short-chain fatty acids; epigenetic regulation; multiple sclerosis; remyelination; postbiotics

 doi:10.20944/preprints202602.1855.v1

Review

The Gut–Myelin Axis: Microbial Metabolites in Oligodendrocyte Biology and Remyelination

Enso O. Torres Alegre [1,*] and Diana E. Mora Jiménez [2]

[1] Pontifical Catholic University of Chile, Santiago, Chile
[2] University of Notre Dame, South Bend, IN, USA
* Correspondence: onill@uc.cl

Abstract

Background: The gut microbiota–brain axis has emerged as an important regulator of central nervous system (CNS) development and function. Beyond its established roles in immunity and behavior, accumulating evidence suggests that microbial-derived metabolites influence glial biology, including oligodendrocyte development and myelination. **Scope:** In this review, we summarize current evidence supporting a role for microbial metabolites—particularly short-chain fatty acids (SCFAs), tryptophan-derived indoles, and secondary bile acids—in regulating oligodendrocyte precursor cell (OPC) proliferation, differentiation, and myelin formation. We discuss the molecular and cellular mechanisms involved, including epigenetic regulation, G-protein–coupled receptor signaling, nuclear receptor activation, and metabolic support pathways. **Key Findings:** Available studies indicate that butyrate can modulate oligodendrocyte lineage progression through histone deacetylase inhibition, thereby influencing chromatin accessibility at myelin-related gene loci. Tryptophan-derived indoles act through the aryl hydrocarbon receptor (AhR) to dampen neuroinflammatory signaling and support glial homeostasis, while secondary bile acids signal via receptors such as TGR5 and the vitamin D receptor to promote pro-remyelinating environments. In parallel, microbial acetate contributes to acetyl-CoA pools required for lipid biosynthesis and epigenetic regulation within oligodendrocytes. **Clinical Implications:** Alterations in gut microbiota composition and reduced availability of microbial metabolites have been consistently reported in Multiple Sclerosis, a disease characterized by impaired remyelination. These observations suggest that microbiome-targeted interventions, including dietary modulation and postbiotic supplementation, may complement existing therapeutic strategies. **Conclusions:** Together, current evidence supports the concept that microbial metabolites act as systemic modulators of CNS myelination, linking dietary and microbial inputs to oligodendrocyte biology. Further mechanistic and translational studies are needed to define how these pathways can be effectively harnessed for therapeutic benefit in demyelinating disorders.

Keywords: microbiota–gut–brain axis; oligodendrocytes; myelination; short-chain fatty acids; epigenetic regulation; multiple sclerosis; remyelination; postbiotics

1. Introduction

The myelin sheath represents one of the most remarkable evolutionary innovations of the vertebrate nervous system. This multilayered lipid membrane, produced by oligodendrocytes in the central nervous system (CNS), enables saltatory conduction of action potentials, increasing nerve impulse velocity by up to 100-fold while reducing metabolic costs [1,2]. Beyond its insulating function, myelin provides essential metabolic support to axons through the transfer of lactate and other energy substrates, establishing a symbiotic relationship critical for neuronal survival [3,4].

1.1. The Oligodendrocyte Lineage: A Developmental Overview

Oligodendrocyte development proceeds through a well-characterized sequence of cellular stages. Oligodendrocyte precursor cells (OPCs), identified by expression of NG2, PDGFRα, and Olig2, arise

 doi:10.20944/preprints202602.1855.v1

from ventricular zone progenitors and migrate extensively throughout the CNS [6,7]. Upon receiving appropriate environmental cues, OPCs exit the cell cycle and differentiate into pre-myelinating oligodendrocytes, characterized by elaboration of complex membrane processes. Terminal differentiation yields mature myelinating oligodendrocytes expressing myelin structural proteins including myelin basic protein (MBP), proteolipid protein (PLP), and myelin-associated glycoprotein (MAG) [8,9].

This developmental trajectory was traditionally viewed as governed primarily by intrinsic genetic programs and local signaling from the neurovascular niche, including growth factors (PDGF, FGF), axonal signals (neuregulin-1), and extracellular matrix components [10,11]. However, emerging evidence has broadened this perspective to include systemic influences originating from an unexpected source: the gut microbiota.

1.2. The Microbiota-Gut-Brain Axis: A Paradigm Shift

The human gut harbors approximately 10^{14} microorganisms representing over 1,000 species, collectively termed the gut microbiota [12]. This microbial community functions as a virtual endocrine organ, producing an extraordinary diversity of metabolites that enter systemic circulation and influence distant organ systems, including the brain [13,14]. The bidirectional communication network linking gut microbiota to brain function—the microbiota-gut-brain axis—has emerged as a critical determinant of neurodevelopment, behavior, and neurological disease [15,16].

The significance of the microbiota for CNS myelination was first revealed by studies in germ-free (GF) mice, which are raised in sterile isolators and lack any microbial colonization. These animals exhibit striking defects in myelin gene expression and white matter structure, particularly in the prefrontal cortex [17]. Importantly, many of these defects can be rescued by post-natal colonization with a complex microbiota, demonstrating that microbial signals are not merely correlative but causally related to myelination [18].

Recent work further demonstrates that gut microbiota composition directly influences optic nerve fiber maturation and myelination in germ-free and gnotobiotic mice [5].

1.3. Microbial Metabolites: The Molecular Messengers

Among the myriad molecules produced by gut bacteria, three classes have emerged as particularly important regulators of oligodendrocyte biology:

1. **Short-chain fatty acids (SCFAs):** Produced by bacterial fermentation of dietary fiber, SCFAs—primarily acetate, propionate, and butyrate—reach millimolar concentrations in the gut and micromolar concentrations in systemic circulation [19,20].
2. **Tryptophan metabolites:** Gut bacteria metabolize the essential amino acid tryptophan into various indole derivatives, including indole-3-aldehyde, indole-3-propionic acid (IPA), and indole-3-acetic acid [21,22].
3. **Secondary bile acids:** Microbial transformation of primary bile acids produces secondary bile acids such as lithocholic acid (LCA) and deoxycholic acid (DCA), which function as signaling molecules throughout the body [23,24].

1.4. Scope and Objectives of This Review

This comprehensive review aims to synthesize current knowledge regarding the mechanisms by which microbial metabolites regulate oligodendrocyte lineage dynamics and myelination. We will examine:

- The pathways through which metabolites access the CNS
- Epigenetic mechanisms, particularly HDAC inhibition by SCFAs
- G-protein coupled receptor (GPCR) signaling cascades
- Metabolic support of myelin lipid biosynthesis
- Clinical implications for Multiple Sclerosis and other demyelinating disorders
- Therapeutic frontiers including postbiotics and dietary interventions

 doi:10.20944/preprints202602.1855.v1

2. The Microbiota-Gut-Brain Axis: Pathways of Metabolite Delivery

For microbial metabolites to influence oligodendrocyte biology, they must first traverse multiple physiological barriers to access the CNS parenchyma. Understanding these pathways is essential for appreciating how gut-derived signals reach their cellular targets.

2.1. Intestinal Absorption and Systemic Distribution

SCFAs are absorbed across the colonic epithelium through multiple mechanisms. Passive diffusion of protonated forms occurs at the acidic luminal pH, while active transport is mediated by monocarboxylate transporters (MCT1, MCT4) and the sodium-coupled transporter SMCT1 (SLC5A8) [25,26]. Once absorbed, SCFAs enter the portal circulation and are partially metabolized by the liver, with remaining fractions reaching systemic circulation at concentrations of 100-400 μM for acetate and 1-10 μM for propionate and butyrate [27,28].

Tryptophan metabolites and secondary bile acids similarly enter systemic circulation through specific transporters. Indole derivatives are absorbed via passive diffusion and reach plasma concentrations of 0.5-10 μM [29]. Secondary bile acids utilize the apical sodium-dependent bile acid transporter (ASBT) and organic solute transporters (OSTα/OSTβ) [30].

2.2. Blood-Brain Barrier Penetration

The blood-brain barrier (BBB) represents a selective interface that restricts molecular traffic between systemic circulation and the CNS. Critically, the gut microbiota itself influences BBB integrity. Germ-free mice exhibit increased BBB permeability due to reduced expression of tight junction proteins including occludin, claudin-5, and ZO-1 [31]. Colonization with SCFA-producing bacteria or direct butyrate administration restores BBB integrity, creating a regulatory feedback loop wherein the microbiota controls access of its own metabolites to the brain.

SCFAs cross the BBB primarily via MCT1, which is expressed on brain endothelial cells. Brain concentrations reach approximately 17.0 μM for acetate, 2.1 μM for propionate, and 2.8 μM for butyrate in rodents [32]. These concentrations, while lower than systemic levels, are within the range reported to activate cellular receptors and modulate enzymatic activity in experimental systems.

Indole derivatives, being lipophilic, can cross the BBB via passive diffusion. IPA reaches brain concentrations sufficient to activate the pregnane X receptor (PXR) and provide neuroprotection [29,148]. Secondary bile acids utilize organic anion transporting polypeptides (OATPs) expressed at the BBB, though their CNS concentrations remain less well characterized [34].

2.3. Microglial and Astrocytic Intermediaries

Microbial metabolites do not always act directly on oligodendrocytes; their effects are frequently mediated through other glial populations. This indirect signaling represents a crucial amplification mechanism.

As summarized in Figure 1, microbial metabolites target multiple glial cell types through specific transport mechanisms.

 doi:10.20944/preprints202602.1855.v1

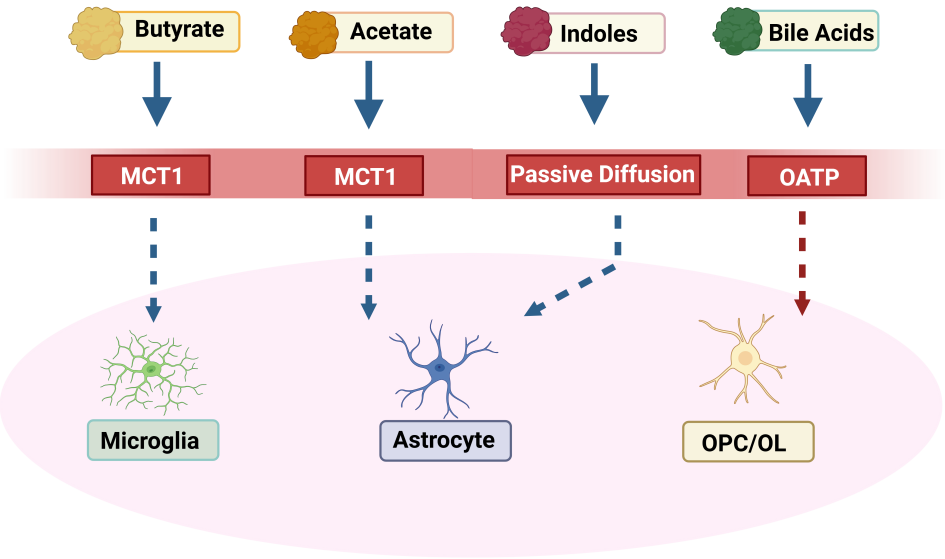

Figure 1. Transport mechanisms and cellular targets of microbial metabolites in the CNS. Butyrate, acetate, indoles, and bile acids cross the blood-brain barrier via specific transporters (MCT1, OATP) or passive diffusion. Once in the CNS parenchyma, these metabolites act on multiple glial populations: microglia, astrocytes, and oligodendrocyte precursor cells (OPCs)/oligodendrocytes (OLs). This multi-cellular targeting enables coordinated regulation of myelination through direct and indirect signaling pathways.

2.3.1. Microglial Maturation and Function

Microglia, the resident macrophages of the CNS, are exquisitely sensitive to microbial signals. Germ-free mice exhibit immature microglia characterized by altered morphology, reduced ramification, and impaired responses to pathological stimuli [35]. SCFA supplementation rescues microglial maturation, restoring their capacity for phagocytosis and cytokine production.

Since efficient remyelination requires microglial clearance of myelin debris from demyelinated lesions, the microbial regulation of microglial function indirectly influences OPC differentiation and myelin repair [36,37]. Microglia also secrete factors that directly influence OPC behavior, including IGF-1 and activin-A, creating a complex signaling network linking microbial inputs to oligodendrocyte responses [38].

2.3.2. Astrocyte-Oligodendrocyte Crosstalk

Astrocytes represent another critical intermediary in microbiota-oligodendrocyte communication. Tryptophan-derived indoles activate the aryl hydrocarbon receptor (AhR) in astrocytes, suppressing production of pro-inflammatory cytokines including IL-6, TNF-α, and IL-1β [39]. Since these cytokines inhibit OPC differentiation and can be directly toxic to oligodendrocytes, the anti-inflammatory effects of microbial indoles on astrocytes create a permissive environment for myelination.

Astrocytes also provide metabolic support to oligodendrocytes through gap junction-mediated transfer of metabolites. The panglial syncytium, formed by connexin-based coupling between astrocytes and oligodendrocytes, enables direct metabolic communication [40,41]. Microbial metabolites that influence astrocyte metabolism may therefore indirectly affect oligodendrocyte bioenergetics.

 doi:10.20944/preprints202602.1855.v1

3. Short-Chain Fatty Acids: Epigenetic and Metabolic Regulation

Short-chain fatty acids represent the most extensively studied class of microbial metabolites in the context of CNS myelination. Their mechanisms of action span epigenetic regulation, G-protein coupled receptor signaling, and direct metabolic contribution.

3.1. SCFA Biosynthesis and Distribution

SCFAs are produced in the cecum and colon through bacterial fermentation of non-digestible carbohydrates, primarily dietary fiber and resistant starch. The major fermentation pathways include:

- **Acetate:** Produced via acetyl-CoA and the Wood-Ljungdahl pathway by diverse bacterial taxa including *Bacteroides*, *Bifidobacterium*, and *Akkermansia* [42].
- **Propionate:** Synthesized through the succinate, acrylate, and propanediol pathways, primarily by *Bacteroidetes*, *Veillonella*, and *Propionibacterium* [43].
- **Butyrate:** Produced via butyryl-CoA:acetate CoA-transferase and phosphotransbutyrylase/butyrate kinase pathways by *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Roseburia* species [44,45].

Table 1. SCFA Concentrations in Different Physiological Compartments.

SCFA	Colon (mM)	Portal Vein (μM)	Systemic (μM)	Brain (μM)
Acetate	60-80	260-375	100-400	15-20
Propionate	15-25	20-88	1-13	1.5-2.5
Butyrate	10-20	12-40	1-12	2-4

Data compiled from [19,20,27,32].

3.2. Butyrate as a Histone Deacetylase Inhibitor

Molecular Mechanism

Butyrate inhibits Class I and Class IIa histone deacetylases (HDACs), leading to increased histone acetylation and enhanced accessibility of chromatin at pro-myelinating gene loci. This epigenetic "priming" coordinates the transcriptional program required for OPC differentiation and myelin synthesis.

The most profound mechanism by which SCFAs regulate oligodendrocyte biology is through inhibition of histone deacetylases (HDACs). Butyrate acts as a non-competitive inhibitor of Class I HDACs (HDAC1, 2, 3, 8) and Class IIa HDACs (HDAC4, 5, 7, 9), with IC_{50} values in the low micromolar range [46,47].

3.2.1. HDAC Function in Oligodendrocyte Development

The role of HDACs in oligodendrocyte development is paradoxically complex. During the transition from OPC to mature oligodendrocyte, HDAC1 and HDAC2 are required to repress genes that maintain the progenitor state, including *Sox2*, *Id2*, *Id4*, and *Hes5* [48]. Genetic deletion of both HDAC1 and HDAC2 in the oligodendrocyte lineage severely impairs differentiation and myelination.

However, the timing of HDAC activity is critical. Sustained HDAC activity can prevent terminal differentiation by maintaining repressive chromatin states at myelin gene promoters. The transient inhibition of HDACs by butyrate may therefore facilitate a permissive epigenetic state favoring the release of pro-myelinating genes (including *Mbp*, *Plp1*, *Mag*, and *Mog*) from epigenetic repression while allowing completion of the differentiation program [49,50].

3.2.2. Experimental Evidence for HDAC Inhibition in Myelination

Multiple lines of evidence support the pro-myelinating effects of HDAC inhibition:

1. Systemic butyrate administration enhances myelin gene expression in the prefrontal cortex of mice [17,18].

 doi:10.20944/preprints202602.1855.v1

2. In vitro treatment of OPCs with butyrate or other HDAC inhibitors (valproic acid, trichostatin A) promotes expression of MBP and PLP [50].
3. Cuprizone-induced demyelination models show accelerated remyelination following butyrate supplementation [51].
4. Chromatin immunoprecipitation (ChIP) studies demonstrate increased histone H3 and H4 acetylation at myelin gene promoters following SCFA treatment [18].

3.3. G-Protein Coupled Receptor Signaling

Beyond epigenetic effects, SCFAs activate specific G-protein coupled receptors (GPCRs) that trigger intracellular signaling cascades.

3.3.1. GPR41 and GPR43

GPR41 (FFAR3) and GPR43 (FFAR2) are the primary SCFA receptors, with distinct expression patterns and ligand preferences [52,53]:

- **GPR43:** Highest affinity for acetate and propionate; expressed on microglia and immune cells
- **GPR41:** Highest affinity for propionate and butyrate; expressed on neurons and enteroendocrine cells

Activation of these receptors triggers $G\alpha_i$-mediated inhibition of adenylyl cyclase and $G\beta\gamma$-mediated activation of phospholipase C, leading to decreased cAMP and increased intracellular calcium [54]. In microglia, GPR43 activation promotes an anti-inflammatory phenotype that supports remyelination [35].

3.3.2. GPR109A (Hydroxycarboxylic Acid Receptor 2)

Butyrate also activates GPR109A (HCA2), a receptor expressed on microglia, astrocytes, and intestinal epithelium [55]. GPR109A signaling in microglia suppresses NF-κB activation and promotes production of anti-inflammatory mediators, contributing to a neuroprotective environment [56].

3.4. Acetate and the Acetyl-CoA Hub

Acetate, the most abundant SCFA in systemic circulation, serves as a direct metabolic substrate with implications for both lipid synthesis and epigenetic regulation.

3.4.1. Acetyl-CoA Synthetase Pathways

Upon entering cells, acetate is converted to acetyl-CoA by acetyl-CoA synthetases (AceCS1 in the cytoplasm/nucleus; AceCS2 in mitochondria) [57]. This acetyl-CoA serves multiple functions:

As illustrated in Figure 2, microbial acetate contributes to both epigenetic regulation and metabolic support of myelination through its conversion to acetyl-CoA.

1. **Fatty acid synthesis:** Cytoplasmic acetyl-CoA is carboxylated to malonyl-CoA, initiating fatty acid biosynthesis essential for myelin membrane production [58].
2. **Histone acetylation:** Nuclear acetyl-CoA provides acetyl groups for histone acetyltransferases (HATs), promoting gene activation [57,59].
3. **Energy metabolism:** Mitochondrial acetyl-CoA enters the tricarboxylic acid (TCA) cycle for ATP production [60].

 doi:10.20944/preprints202602.1855.v1

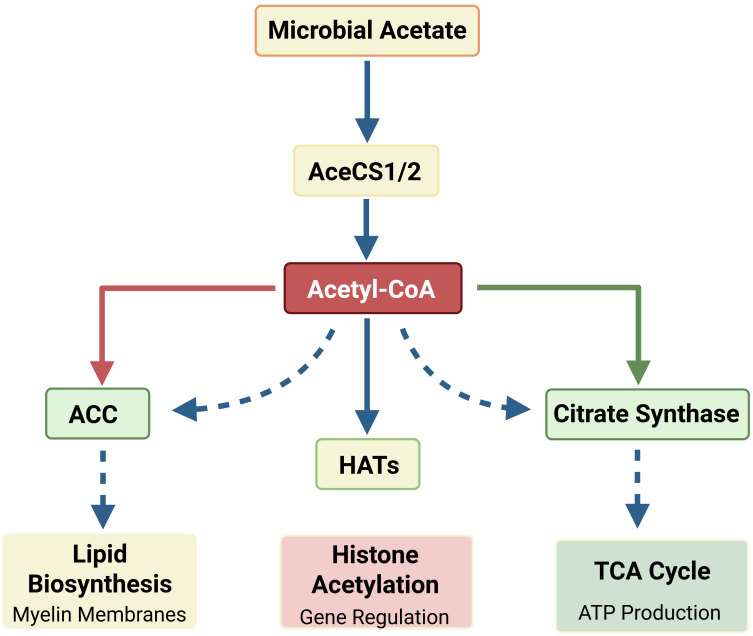

Figure 2. Metabolic fate of microbial acetate in oligodendrocytes. Acetate is converted to acetyl-CoA by acetyl-CoA synthetases (AceCS1/2). This central metabolite serves three key functions: (1) entry into the TCA cycle for ATP production; (2) provision of acetyl groups for histone acetylation via histone acetyltransferases (HATs), regulating gene expression; and (3) serving as a precursor for lipid biosynthesis, including myelin membrane components. This multi-faceted role positions acetate as a critical link between microbial metabolism and oligodendrocyte function.

3.4.2. Implications for Myelination

The metabolic link between gut-derived acetate and oligodendrocyte function is particularly significant given the extraordinary lipid demands of myelination. Myelin is approximately 70-80% lipid by dry weight, requiring massive biosynthetic capacity [61]. The flux of microbial acetate into acetyl-CoA may contribute to supporting this demand, while simultaneously providing acetyl groups for the epigenetic regulation of myelin genes.

Recent work has demonstrated that dietary interventions increasing acetate availability enhance myelin lipid synthesis in rodent models [62]. Conversely, depletion of SCFA-producing bacteria reduces brain acetyl-CoA levels and impairs myelination [18].

3.5. Propionate: Immunomodulation and Beyond

Propionate, while less studied than butyrate in the CNS, exerts important immunomodulatory effects that indirectly support myelination.

3.5.1. Regulatory T Cell Induction

Propionate promotes the differentiation of regulatory T cells (Tregs) in the gut-associated lymphoid tissue through HDAC inhibition and GPR43 activation [63,64]. These Tregs can migrate to the CNS or release systemic anti-inflammatory signals that suppress Th17-mediated autoimmunity—a key pathogenic mechanism in Multiple Sclerosis [65].

Clinical trials have demonstrated that oral propionate supplementation increases circulating Treg populations in MS patients and correlates with reduced relapse rates [66]. This systemic immunomodulation creates a permissive environment for remyelination by reducing ongoing immune-mediated damage.

 doi:10.20944/preprints202602.1855.v1

4. Tryptophan-Derived Metabolites and AhR Signaling

Tryptophan is an essential amino acid that serves as a precursor for multiple bioactive compounds. While host metabolism primarily directs tryptophan toward serotonin and kynurenine pathways, gut bacteria produce a distinct repertoire of indole derivatives with potent neuroactive properties [21,22,67].

4.1. Microbial Tryptophan Metabolism

Gut bacteria metabolize tryptophan through several pathways:

1. **Indole pathway:** Tryptophanase (TnaA) converts tryptophan to indole, which can be further modified to produce indole-3-aldehyde, indole-3-acetic acid, and indole-3-propionic acid (IPA) [68].
2. **Tryptamine pathway:** Decarboxylation produces tryptamine, a neuroactive amine [69].
3. **Kynurenine pathway:** Some bacteria possess indoleamine 2,3-dioxygenase (IDO) homologs that produce kynurenine metabolites [70].

Key bacterial genera involved in tryptophan metabolism include *Lactobacillus*, *Clostridium*, *Bacteroides*, and *Peptostreptococcus* [22].

4.2. The Aryl Hydrocarbon Receptor (AhR)

The aryl hydrocarbon receptor is a ligand-activated transcription factor belonging to the basic helix-loop-helix/Per-ARNT-Sim (bHLH-PAS) family. Originally characterized as a xenobiotic sensor, AhR is now recognized as a key mediator of microbial-host communication in the CNS [39,71].

4.2.1. Mechanism of AhR Activation

In the absence of ligand, AhR resides in the cytoplasm complexed with HSP90, XAP2, and p23. Ligand binding (e.g., by indole derivatives) triggers conformational changes, nuclear translocation, and heterodimerization with ARNT (AhR nuclear translocator). The AhR-ARNT complex binds xenobiotic response elements (XREs) in target gene promoters, modulating transcription [72].

4.2.2. AhR in Astrocytes: Suppression of Neuroinflammation

A seminal series of studies by Rothhammer and colleagues demonstrated that microbial tryptophan metabolites activate AhR in astrocytes, triggering anti-inflammatory transcriptional programs [39,73]. Specifically:

- AhR activation suppresses NF-κB signaling in astrocytes
- Production of pro-inflammatory cytokines (IL-6, TNF-α, CCL2) is reduced
- Astrocytes adopt a neuroprotective phenotype supporting oligodendrocyte survival

In experimental autoimmune encephalomyelitis (EAE), a mouse model of MS, dietary tryptophan supplementation or direct indole administration reduces disease severity through AhR-dependent mechanisms [39].

4.2.3. AhR in Microglia

AhR signaling in microglia modulates their activation state and phagocytic capacity. Microbial metabolites acting through microglial AhR suppress production of inflammatory mediators while maintaining the capacity for myelin debris clearance [73]. This balance is critical for efficient remyelination.

4.3. Indole-3-Propionic Acid: A Potent Neuroprotectant

Indole-3-propionic acid (IPA) is produced exclusively by gut bacteria, primarily *Clostridium sporogenes*, and is one of the most potent naturally occurring antioxidants [29,74].

4.3.1. Antioxidant Properties

IPA scavenges reactive oxygen species (ROS) with efficiency comparable to melatonin. Given that oligodendrocytes are exceptionally vulnerable to oxidative stress due to their high iron content

 doi:10.20944/preprints202602.1855.v1

and low antioxidant enzyme levels, the neuroprotective effects of IPA may be particularly relevant to myelin maintenance [75].

4.3.2. Pregnane X Receptor Activation

Beyond its antioxidant function, IPA activates the pregnane X receptor (PXR), a nuclear receptor that regulates xenobiotic metabolism and intestinal barrier function [148]. PXR activation enhances expression of tight junction proteins, potentially contributing to BBB integrity.

4.4. Clinical Relevance: Tryptophan Metabolism in MS

Multiple Sclerosis patients exhibit altered tryptophan metabolism characterized by:

- Reduced circulating levels of indole derivatives [76]
- Increased kynurenine/tryptophan ratio indicative of inflammatory IDO activation [77]
- Decreased abundance of tryptophan-metabolizing bacteria including *Lactobacillus* species [78,79]

These observations suggest that restoration of microbial tryptophan metabolism could represent a therapeutic strategy for promoting remyelination and suppressing neuroinflammation.

5. Secondary Bile Acids: Emerging Regulators of Remyelination

Secondary bile acids, produced by microbial transformation of host-derived primary bile acids, have recently emerged as potent signaling molecules with implications for oligodendrocyte biology.

5.1. Bile Acid Metabolism and the Microbiota

Primary bile acids (cholic acid and chenodeoxycholic acid) are synthesized in the liver from cholesterol and secreted into the intestine to facilitate lipid absorption. A fraction escapes enterohepatic recirculation and reaches the colon, where bacteria perform various modifications [23]:

- **Deconjugation:** Bile salt hydrolases remove glycine/taurine conjugates
- **7α-dehydroxylation:** Produces lithocholic acid (LCA) from chenodeoxycholic acid and deoxycholic acid (DCA) from cholic acid
- **Epimerization and oxidation:** Generate additional bile acid species

Key bacterial genera performing these transformations include *Clostridium*, *Bacteroides*, *Lactobacillus*, and *Bifidobacterium* [80,81].

5.2. Bile Acid Receptors in the CNS

Secondary bile acids activate multiple receptors expressed in the brain:

5.2.1. TGR5 (GPBAR1)

TGR5 is a G-protein coupled receptor activated by LCA and DCA. In the CNS, TGR5 is expressed on microglia, astrocytes, and neurons [82]. TGR5 activation:

- Suppresses microglial inflammatory responses via cAMP elevation
- Reduces production of TNF-α and IL-1β
- Promotes neuroprotective microglial phenotypes

5.2.2. Vitamin D Receptor (VDR)

The vitamin D receptor, a nuclear hormone receptor, is activated by both 1,25-dihydroxyvitamin D_3 and secondary bile acids, particularly LCA [83]. VDR is expressed in oligodendrocytes and OPCs, and its activation:

- Promotes OPC differentiation into mature oligodendrocytes
- Enhances expression of myelin genes
- Provides neuroprotection against inflammatory damage

 doi:10.20944/preprints202602.1855.v1

The connection between VDR signaling and myelination is particularly intriguing given the well-established epidemiological link between vitamin D deficiency and MS risk [84,85].

5.3. Bile Acids and Remyelination

Emerging evidence suggests that secondary bile acids can promote remyelination:

1. Tauroursodeoxycholic acid (TUDCA) administration in EAE models reduces demyelination and enhances OPC differentiation [86].
2. Ursodeoxycholic acid (UDCA) is being evaluated in clinical trials for progressive MS based on its neuroprotective and immunomodulatory properties [87].
3. MS patients show altered bile acid profiles with reduced secondary bile acids, suggesting dysbiosis-driven deficiency [88].

6. Metabolic Support of Axonal Integrity and Bioenergetics

The relationship between oligodendrocytes and axons extends far beyond simple insulation. Oligodendrocytes are active metabolic partners that provide trophic support essential for axonal survival and function.

6.1. The Monocarboxylate Transporter Shuttle

Myelinated axons depend on oligodendrocyte-derived metabolic substrates for their energy needs. The monocarboxylate transporter (MCT) shuttle is the primary mechanism for this metabolic coupling [3,4]:

1. Oligodendrocytes take up glucose via GLUT1 or utilize glycogen stores
2. Glycolytic metabolism produces pyruvate, which is converted to lactate
3. MCT1 on the oligodendrocyte membrane exports lactate into the periaxonal space
4. Axonal MCT2 imports lactate for mitochondrial oxidation

Disruption of this shuttle—through MCT1 knockout or oligodendrocyte damage—leads to axonal degeneration even in the absence of demyelination [4].

6.2. Microbial Contribution to the Metabolic Axis

Microbial metabolites contribute to this bioenergetic relationship through multiple mechanisms:

6.2.1. Direct Fuel Provision

SCFAs, particularly acetate, can be directly oxidized by oligodendrocytes to generate ATP. Acetate enters the TCA cycle via acetyl-CoA, providing an alternative carbon source to glucose [89]. This may be particularly relevant during periods of high metabolic demand or when glucose availability is limited.

6.2.2. Support of Lipid Synthesis

The extraordinary lipid demands of myelination require substantial metabolic resources. Acetyl-CoA derived from microbial acetate contributes to:

- Cholesterol biosynthesis (the mevalonate pathway)
- Fatty acid synthesis (via malonyl-CoA)
- Sphingolipid production (ceramide and galactocerebroside)

Studies in germ-free mice show reduced expression of cholesterol biosynthesis genes in the prefrontal cortex, suggesting that microbial metabolites support myelin lipid production [17].

6.3. Mitochondrial Function and Oxidative Stress

Myelination is metabolically demanding and generates significant reactive oxygen species (ROS). Oligodendrocytes are particularly vulnerable to oxidative damage due to:

 doi:10.20944/preprints202602.1855.v1

- High iron content (required for myelin synthesis enzymes)
- Low levels of antioxidant enzymes (catalase, superoxide dismutase)
- Abundant polyunsaturated fatty acids in myelin membranes

Recent evidence indicates that mitochondrial metabolic programming is not merely supportive but instructive for oligodendrocyte maturation. During the transition from pre-oligodendrocytes to mature oligodendrocytes, mitochondrial respiration increases alongside enhanced pyruvate dehydrogenase (Pdh) activity, promoting acetyl-CoA production and facilitating terminal differentiation and remyelination [155]. These findings suggest that intact mitochondrial flux is essential for effective oligodendrocyte lineage progression.

Microbial metabolites provide several layers of antioxidant protection:

1. **IPA:** Direct ROS scavenging and Nrf2 activation [73]
2. **Butyrate:** Upregulation of antioxidant gene expression through HDAC inhibition [90]
3. **Indoles:** AhR-mediated induction of antioxidant enzymes [39]

By maintaining mitochondrial health and cellular redox balance, microbial metabolites ensure that OPCs retain the bioenergetic capacity required for the membrane expansion and protein synthesis of myelination.

7. Clinical Implications: Multiple Sclerosis and Demyelinating Disorders

Multiple Sclerosis (MS) affects approximately 2.8 million people worldwide and is characterized by inflammatory demyelination, neurodegeneration, and accumulating disability [91]. The recognition of microbiota-oligodendrocyte interactions has profound implications for understanding MS pathogenesis and developing new therapies.

7.1. Dysbiosis in Multiple Sclerosis

Multiple independent studies have documented characteristic alterations in the gut microbiome of MS patients:

Table 2. Gut Microbiome Alterations in Multiple Sclerosis.

Bacterial Taxon	Change in MS	Metabolic Impact
Faecalibacterium prausnitzii	↓↓	Reduced butyrate
Prevotella species	↓	Reduced propionate
Butyricimonas	↓	Reduced butyrate
Lactobacillus species	↓	Reduced indoles
Clostridium clusters IV/XIVa	↓	Reduced SCFAs/bile acids
Methanobrevibacter	↑	Altered fermentation
Akkermansia muciniphila	Variable	Context-dependent

Data compiled from [78,79,112–114].

The consistent finding of reduced SCFA-producing bacteria suggests that MS patients experience a systemic deficiency in metabolites required for optimal oligodendrocyte function.

7.2. The Differentiation Block in Chronic Lesions

In chronic MS lesions, OPCs are often present in the lesion vicinity but fail to differentiate into mature myelinating oligodendrocytes—a phenomenon termed the "differentiation block" [92–94]. This failure of endogenous repair represents a major therapeutic challenge and has been attributed to multiple factors:

- **Inhibitory signaling:** Accumulation of myelin debris, chondroitin sulfate proteoglycans (CSPGs), and semaphorins creates a non-permissive microenvironment [95,96].
- **Epigenetic dysregulation:** OPCs in chronic lesions exhibit altered chromatin states with reduced accessibility at pro-myelinating gene loci [97,98].

 doi:10.20944/preprints202602.1855.v1

- **Metabolic insufficiency:** Impaired bioenergetic capacity may prevent the massive membrane synthesis required for myelination [99,100].
- **Chronic inflammation:** Persistent low-grade inflammation maintains an anti-regenerative environment [101,102].

The deficiency of microbial-derived HDAC inhibitors and AhR ligands in MS patients may directly contribute to this differentiation block by failing to provide the epigenetic "priming" signals required for OPC maturation. Supporting this hypothesis, circulating SCFA levels negatively correlate with MS disease activity and disability progression [103,104].

The integrated actions of these metabolites, summarized in Figure 3, provide both epigenetic priming and anti-inflammatory signaling that collectively support remyelination.

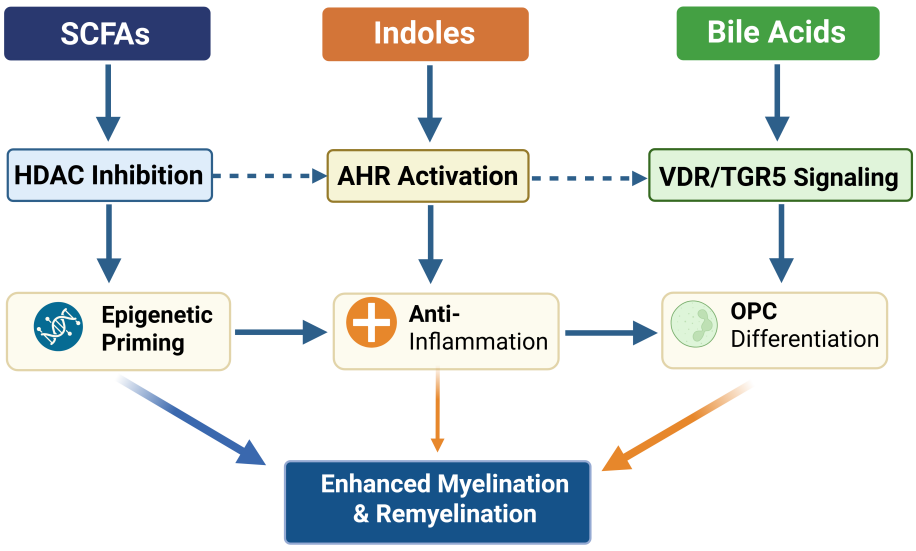

Figure 3. Integrated mechanisms by which microbial metabolites promote myelination. SCFAs (particularly butyrate) inhibit histone deacetylases (HDACs), leading to epigenetic priming of OPCs for differentiation. Indoles activate the aryl hydrocarbon receptor (AhR), suppressing neuroinflammation. Bile acids signal through receptors such as VDR and TGR5, promoting anti-inflammatory and pro-differentiation pathways. Together, these coordinated actions enhance OPC differentiation, reduce inflammation, and promote both developmental myelination and remyelination after injury.

7.3. Modulation of Neuroinflammation

Beyond direct effects on oligodendrocytes, microbial metabolites regulate myelination indirectly through modulation of CNS inflammation.

7.3.1. The Treg-Th17 Balance

The balance between regulatory T cells (Tregs) and pro-inflammatory Th17 cells is critical in MS pathogenesis. Th17 cells produce IL-17 and GM-CSF, which promote inflammatory demyelination, while Tregs suppress autoimmune responses [105,106].

Microbial SCFAs, particularly propionate, promote Treg differentiation through multiple mechanisms:

1. **HDAC inhibition:** Enhanced acetylation of the Foxp3 locus stabilizes Treg identity [64,107].
2. **GPR43 activation:** SCFA signaling through GPR43 on T cells promotes Treg differentiation [63].

 doi:10.20944/preprints202602.1855.v1

3. **Dendritic cell modulation:** SCFAs promote tolerogenic dendritic cells that favor Treg induction [108,109].

Clinical evidence supports this mechanism: oral propionate supplementation in MS patients significantly increased circulating Treg frequency and function, correlating with reduced annualized relapse rate [66].

7.3.2. Microglial Polarization

Microglia can adopt pro-inflammatory (M1-like) or anti-inflammatory/pro-regenerative (M2-like) phenotypes, though this classification is increasingly recognized as oversimplified [110]. Similarly, astrocyte activation in demyelinating disease does not conform to a strict binary paradigm but instead represents a spectrum of context-dependent reactive states balancing protective and pathological functions [171]. Microbial metabolites promote microglial states conducive to remyelination:

- SCFAs suppress microglial production of TNF-α, IL-1β, and iNOS [35,111]
- Indoles via AhR reduce microglial inflammatory activation [73]
- Bile acids through TGR5 promote anti-inflammatory microglial phenotypes [86]

Since activated microglia can directly damage oligodendrocytes through release of reactive oxygen species and inflammatory cytokines, microbial modulation of microglial states is critical for creating a permissive environment for remyelination.

7.4. Gut-Brain Axis in MS: Clinical Evidence

Several lines of clinical evidence support the relevance of the gut-brain axis in MS:

Key Points

Clinical Evidence for Microbiome Involvement in MS:

1. Gut microbiome composition differs significantly between MS patients and healthy controls across multiple cohorts [78,79,113]
2. Fecal transplantation from MS patients into germ-free mice exacerbates experimental autoimmune encephalomyelitis [112,113]
3. Circulating SCFA levels correlate inversely with MS disease activity [103,104]
4. Probiotic and dietary interventions show promise in preliminary clinical trials [141]
5. MS disease-modifying therapies alter gut microbiome composition [159,160]

8. Experimental Models: Evidence from Germ-Free and Intervention Studies

The most compelling mechanistic evidence for microbial regulation of myelination comes from controlled experimental models that manipulate the microbiome or its metabolites. Recent morphometric analyses of optic nerves from germ-free (GF), gnotobiotic (OMM12), and conventionally colonized mice revealed significant alterations in axon diameter, fiber density, and g-ratio in young adult animals, supporting a direct role of gut microbiota in CNS myelination [5].

8.1. Germ-Free Mouse Studies

Germ-free (GF) mice, raised in sterile isolators without any microbial colonization, have proven invaluable for understanding microbiome-brain interactions.

8.1.1. Myelination Defects in GF Mice

GF mice exhibit multiple abnormalities in CNS myelination:

1. **Prefrontal cortex hypomyelination:** Reduced MBP and PLP expression; thinner myelin sheaths on electron microscopy [17,18]
2. **Transcriptomic changes:** RNA-seq reveals downregulation of cholesterol biosynthesis genes (*Hmgcr*, *Fdft1*, *Sqle*) and myelin structural genes [17]

 doi:10.20944/preprints202602.1855.v1

3. **Altered white matter volume:** MRI studies show reduced white matter in prefrontal regions [115]
4. **OPC differentiation defects:** Reduced numbers of mature CC1+ oligodendrocytes in corpus callosum [18]

8.1.2. Reversibility and Critical Windows

Critically, many myelination defects in GF mice can be rescued by microbial colonization, but timing matters:

- **Early colonization (weaning):** Nearly complete rescue of myelin gene expression and white matter structure [17]
- **Adult colonization:** Partial rescue, suggesting a critical developmental window [18]
- **SCFA supplementation alone:** Substantial rescue even without live bacteria, demonstrating metabolite sufficiency [35]

These findings suggest that while the developing brain is most sensitive to microbial cues, some plasticity persists into adulthood—an encouraging observation for therapeutic applications.

8.2. Antibiotic Perturbation Studies

Antibiotic treatment provides a complementary approach to studying microbiome-myelination interactions in conventionally raised animals.

8.2.1. Effects of Antibiotic-Induced Dysbiosis

Broad-spectrum antibiotic treatment in adult mice produces:

- Reduced circulating SCFA levels (>80% reduction) [35,116]
- Impaired microglial maturation similar to GF mice [35]
- Altered myelin gene expression in prefrontal cortex [18]
- Behavioral changes consistent with prefrontal dysfunction [117,118]

8.2.2. Recovery Following Antibiotic Cessation

Upon antibiotic withdrawal, the gut microbiome gradually recovers, and microbial metabolite levels normalize over 2-4 weeks. Importantly, myelination markers also recover, demonstrating the dynamic responsiveness of oligodendrocytes to microbial signals [18]. This reversibility has important implications for understanding how transient dysbiosis (e.g., from illness or dietary changes) might temporarily impact CNS myelination.

8.3. Demyelination-Remyelination Models

Several experimental models allow direct assessment of microbial effects on remyelination following demyelinating injury.

8.3.1. Cuprizone Model

Cuprizone (bis-cyclohexanone-oxaldihydrazone) is a copper chelator that, when administered in the diet, causes selective oligodendrocyte death and demyelination, particularly in the corpus callosum [121]. Upon cuprizone withdrawal, spontaneous remyelination occurs over 2-4 weeks.

Studies using this model have demonstrated:

- GF mice show delayed remyelination compared to conventionally raised controls [119]
- Butyrate supplementation accelerates remyelination and improves motor function [51]
- High-fiber diets enhance endogenous SCFA production and promote myelin repair [120]

8.3.2. Experimental Autoimmune Encephalomyelitis (EAE)

EAE, induced by immunization with myelin antigens or adoptive transfer of myelin-reactive T cells, models the inflammatory demyelination of MS [122].

Microbiome interventions in EAE have shown:

 doi:10.20944/preprints202602.1855.v1

1. **GF protection:** GF mice are relatively protected from EAE, likely due to impaired effector T cell development [123,124]
2. **Probiotic effects:** Administration of specific bacterial strains (e.g., *Bacteroides fragilis*, *Prevotella histicola*) reduces EAE severity [125,126]
3. **SCFA supplementation:** Propionate administration reduces disease severity and enhances Treg responses [65]
4. **Dietary fiber:** High-fiber diets protect against EAE through enhanced SCFA production [127]

Table 3. Summary of Experimental Evidence Linking Microbiota to Myelination.

Model System	Manipulation	Myelination Outcome	Key References
Germ-free mice	Absence of microbiota	Hypomyelination (PFC)	[17,18]
Antibiotic-treated	Broad-spectrum ABx	Reduced myelin genes	[18,35]
Cuprizone + GF	Demyelination in GF	Delayed remyelination	[119]
Cuprizone + butyrate	SCFA supplementation	Accelerated repair	[51]
EAE + GF	Autoimmune model	Reduced severity	[123,124]
EAE + propionate	SCFA supplementation	Reduced severity; ↑ Tregs	[65,66]
EAE + probiotics	Live bacteria	Reduced severity	[126,169]

8.4. Colonization Studies with Defined Communities

Moving beyond GF versus conventionalized comparisons, researchers have begun using defined microbial communities to dissect specific bacterial contributions:

- **Altered Schaedler Flora (ASF):** An 8-member defined community that partially rescues GF phenotypes [128]
- **Synthetic communities:** Custom-designed consortia enriched in SCFA producers show enhanced myelination support [129]
- **Monocolonization:** Single-strain colonization identifies specific bacterial contributions [130]

These approaches are revealing that not all bacteria contribute equally to myelination support, with butyrate-producing *Clostridia* species appearing particularly important [131].

9. Therapeutic Frontiers: From Probiotics to Precision Postbiotics

The recognition of microbial metabolites as systemic regulators of myelination has catalyzed development of novel therapeutic strategies targeting the gut-brain axis.

9.1. Dietary Interventions

9.1.1. High-Fiber Diets

Dietary fiber provides the substrate for microbial SCFA production. Increasing fiber intake represents a simple, low-risk intervention with potential CNS benefits:

- **Mechanisms:** Enhanced fermentation increases colonic SCFA concentrations; systemic levels rise proportionally [20,132]
- **Fiber types:** Resistant starch, inulin, pectin, and β-glucans are particularly effective at increasing butyrate [133]
- **Clinical evidence:** High-fiber diets associate with reduced MS risk in epidemiological studies [134]; intervention trials are ongoing

9.1.2. Ketogenic and Low-Carbohydrate Diets

Paradoxically, ketogenic diets—which are low in fiber—may also benefit myelination through alternative mechanisms:

- Ketone bodies (β-hydroxybutyrate) are HDAC inhibitors structurally similar to butyrate
- Ketogenic diets show neuroprotective effects in MS animal models [135,136]

 doi:10.20944/preprints202602.1855.v1

- Pilot clinical trials suggest potential benefits in MS patients [137,138]

9.1.3. Mediterranean Diet

The Mediterranean diet, rich in fiber, polyphenols, and omega-3 fatty acids, promotes a diverse, SCFA-producing microbiome:

- Associated with reduced MS risk and disease activity [139]
- Increases circulating SCFA levels [140]
- The MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay) is being evaluated for MS

9.2. Probiotic and Synbiotic Approaches

9.2.1. Traditional Probiotics

Administration of live beneficial bacteria aims to restore healthy microbiome composition:

- ***Lactobacillus* and *Bifidobacterium* species:** Reduce pro-inflammatory cytokines; enhance intestinal barrier function [141,142]
- ***Prevotella histicola*:** Suppresses EAE through Treg induction [126]
- **VSL#3 consortium:** Multi-strain probiotic showing immunomodulatory effects in MS patients [141]

Clinical trials of probiotics in MS have shown modest benefits on inflammatory markers and quality of life, though effects on myelination per se remain to be demonstrated [143].

9.2.2. Next-Generation Probiotics

Emerging approaches focus on bacteria specifically selected for their metabolite-producing capacity:

- **Engineered strains:** Bacteria genetically modified for enhanced SCFA or indole production [144,145]
- **Spore-forming *Clostridia*:** Potent butyrate producers with improved survival through the stomach [131]
- ***Akkermansia muciniphila*:** Produces propionate and enhances intestinal barrier function; shows promise in metabolic disease [146]

9.2.3. Synbiotics

Synbiotic formulations combine probiotics with prebiotic substrates to enhance bacterial survival and metabolite production:

- Butyrate-producing bacteria paired with resistant starch [133]
- *Lactobacillus* strains with inulin or fructooligosaccharides [141]
- Custom formulations optimized for individual patient microbiomes [147]

9.3. Postbiotic Supplementation

Molecular Mechanism

Postbiotics are defined as "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" (ISAPP consensus, 2021). In the context of myelination, this includes direct supplementation with SCFAs, indole derivatives, or bile acids to bypass the variability of microbial production.

9.3.1. SCFA Supplementation

Direct administration of SCFAs offers precise control over metabolite exposure:

- **Oral butyrate:** Sodium butyrate or tributyrin (a butyrate prodrug) can be administered orally; shows efficacy in demyelination models [51]
- **Oral propionate:** Clinical trials in MS show increased Tregs and reduced relapse rates [66]

 doi:10.20944/preprints202602.1855.v1

- **Challenges:** Rapid metabolism limits systemic exposure; enteric coating or prodrug formulations improve bioavailability [28]

9.3.2. Indole Derivatives

Tryptophan metabolites represent another postbiotic avenue:

- **Indole-3-propionic acid:** Potent antioxidant; activates PXR; being evaluated for neuroprotection [148,149]
- **Indole-3-carbinol:** AhR agonist; used as dietary supplement; shows anti-inflammatory effects [150]

9.3.3. Bile Acid Therapeutics

Secondary bile acids and their derivatives are entering clinical development:

- **Ursodeoxycholic acid (UDCA):** FDA-approved for primary biliary cholangitis; being repurposed for MS [87]
- **Tauroursodeoxycholic acid (TUDCA):** Shows neuroprotection in ALS trials; MS trials planned [151]
- **TGR5 agonists:** Synthetic agonists under development for metabolic disease may have CNS applications

9.4. Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT), involving transfer of stool from healthy donors to patients, represents the most comprehensive microbiome intervention:

- **Rationale:** Restores entire microbial ecosystem including metabolite-producing capacity
- **MS case reports:** Anecdotal reports of improvement following FMT [152]
- **Clinical trials:** Phase I/II trials in MS are underway (ClinicalTrials.gov identifiers NCT03594487, NCT04203017)
- **Challenges:** Standardization, safety (infection risk), and donor selection remain obstacles [153]

9.5. Personalized Approaches and Biomarkers

The substantial inter-individual variation in gut microbiome composition suggests that personalized approaches may be necessary:

- **Microbiome profiling:** 16S rRNA or metagenomic sequencing to identify individual deficiencies [147]
- **Metabolomic biomarkers:** Circulating SCFA, indole, and bile acid levels as treatment targets [103]
- **Pharmacomicrobiomics:** Individual microbiome composition influences drug metabolism and efficacy [154]

10. Critical Discussion and Future Perspectives

While the evidence linking microbial metabolites to oligodendrocyte biology is compelling, several critical questions remain to be addressed.

These findings are reinforced by recent ultrastructural studies of optic nerve fibers demonstrating hypermyelination and altered axon dimensions in germ-free and simplified microbiota models [5].

Beyond multiple sclerosis, converging evidence across neurodegenerative disorders underscores the central regulatory role of glial populations—including astrocytes, microglia, and oligodendrocytes—in shaping disease trajectories and therapeutic responsiveness [172].

10.1. Translational Challenges

10.1.1. Species Differences

Most mechanistic studies have been conducted in rodents, which differ from humans in:

- Microbiome composition and diversity [156]
- Relative brain size and white matter proportion [157]
- Developmental timing of myelination [158]

 doi:10.20944/preprints202602.1855.v1

- Metabolite concentrations reaching the CNS [20]

Human studies measuring CNS metabolite concentrations (e.g., via magnetic resonance spectroscopy) and correlating them with myelin imaging metrics are needed.

10.1.2. Causality vs. Correlation

While dysbiosis is consistently observed in MS, establishing causality is challenging:

- Disease-modifying therapies alter the microbiome [159]
- Dietary changes accompanying chronic illness affect microbial composition
- Reverse causation (CNS inflammation affecting gut) is possible [161]

Longitudinal studies following at-risk individuals (e.g., those with clinically isolated syndrome) could help establish temporal relationships.

10.2. Mechanistic Gaps

10.2.1. Direct vs. Indirect Effects

The relative contribution of direct metabolite effects on oligodendrocytes versus indirect effects through microglia, astrocytes, and immune cells remains unclear. Cell-specific conditional knockouts of metabolite receptors could address this question.

10.2.2. Metabolite Synergies

Metabolites do not act in isolation. The combinatorial effects of SCFAs, indoles, and bile acids likely create a "metabolic milieu" whose properties exceed the sum of individual components. Systems biology approaches integrating multi-omics data are needed to capture these interactions [162].

10.2.3. Timing and Critical Windows

The observation that early-life colonization is more effective than adult colonization at rescuing GF myelination defects suggests critical developmental windows [17]. Key questions include:

1. Can these windows be "reopened" in adults through pharmacological or environmental interventions?
2. Are there distinct windows for initial myelination versus remyelination after injury?
3. How do early-life antibiotic exposures affect long-term myelination capacity?

10.3. Future Directions

10.3.1. Advanced Imaging

Integration of gut microbiome profiling with advanced neuroimaging could reveal brain-microbiome correlations:

- Myelin water imaging and quantitative magnetization transfer for myelin content [163]
- Diffusion tensor imaging for white matter microstructure [164]
- PET imaging with myelin-specific tracers

10.3.2. Single-Cell Approaches

Single-cell RNA sequencing of the oligodendrocyte lineage following microbiome perturbations could reveal:

Recent advances in spatial transcriptomics further extend these approaches by preserving anatomical context while resolving region-specific glial transcriptional programs, enabling identification of spatially defined inflammatory and pro-regenerative niches within CNS lesions [170,173].

- Specific OPC subpopulations responsive to microbial signals [165]
- Transcriptional trajectories altered by metabolite exposure
- Novel therapeutic targets [166]

 doi:10.20944/preprints202602.1855.v1

10.3.3. Organoid Systems

Human brain organoids offer new opportunities for studying microbiome-oligodendrocyte interactions:

- Myelinating organoids recapitulate human oligodendrocyte development [167,168]
- Co-culture with microbial metabolites or conditioned media
- Patient-derived organoids for personalized medicine approaches

10.3.4. Clinical Trial Design

Future clinical trials of microbiome-targeted interventions for MS should incorporate:

- Stratification by baseline microbiome composition
- Metabolomic endpoints (circulating SCFA, indole levels)
- Myelin-specific imaging outcomes
- Long-term follow-up for disability progression

11. Conclusions

The recognition that microbial metabolites serve as systemic regulators of oligodendrocyte lineage dynamics represents a paradigm shift in our understanding of CNS myelination. Through HDAC inhibition, GPCR signaling, AhR activation, and direct metabolic support, gut-derived molecules—particularly SCFAs, tryptophan derivatives, and secondary bile acids—coordinate the complex transcriptional and metabolic programs required for myelin synthesis and maintenance.

This integrated view of the gut-brain axis in myelination has profound implications for understanding demyelinating diseases such as Multiple Sclerosis. The characteristic dysbiosis observed in MS patients, with depletion of SCFA-producing bacteria and altered tryptophan metabolism, may directly contribute to the failure of endogenous remyelination that characterizes progressive disease.

Therapeutically, the gut-brain axis opens multiple intervention points. Dietary modifications, probiotics, and direct postbiotic supplementation all show promise for promoting remyelination and suppressing neuroinflammation. The ongoing clinical trials of propionate, UDCA, and FMT in MS patients will provide critical evidence for the translational potential of these approaches.

As we move toward precision medicine, integration of microbiome profiling with neuroimaging and clinical outcomes will enable personalized therapeutic strategies. The next decade promises to reveal the full therapeutic potential of harnessing the gut microbiota for CNS regeneration.

Summary of Key Conclusions

1. Microbial metabolites (SCFAs, indoles, bile acids) are essential regulators of oligodendrocyte differentiation and myelination
2. Butyrate acts as a systemic HDAC inhibitor, epigenetically "priming" pro-myelinating gene expression
3. Tryptophan-derived indoles suppress neuroinflammation through astrocytic AhR signaling
4. MS patients exhibit characteristic dysbiosis with reduced SCFA-producing bacteria
5. Dietary, probiotic, and postbiotic interventions represent promising therapeutic strategies
6. Personalized approaches integrating microbiome profiling may optimize treatment outcomes

Abbreviations

AhR Aryl Hydrocarbon Receptor
BBB Blood-Brain Barrier
CNS Central Nervous System
DCA Deoxycholic Acid
EAE Experimental Autoimmune Encephalomyelitis
FMT Fecal Microbiota Transplantation

 doi:10.20944/preprints202602.1855.v1

GF	Germ-Free
GPCR	G-Protein Coupled Receptor
HDAC	Histone Deacetylase
IPA	Indole-3-Propionic Acid
LCA	Lithocholic Acid
MBP	Myelin Basic Protein
MCT	Monocarboxylate Transporter
MS	Multiple Sclerosis
OL	Oligodendrocyte
OPC	Oligodendrocyte Precursor Cell
PLP	Proteolipid Protein
SCFA	Short-Chain Fatty Acid
TGR5	Takeda G-Protein Receptor 5
Treg	Regulatory T Cell
VDR	Vitamin D Receptor

References

1. Nave, K. A. (2010). Myelination and support of axonal integrity by glia. *Nature*, 468(7321), 244-252. doi: 10.1038/nature09614
2. Simons, M., & Nave, K. A. (2015). Oligodendrocytes: Myelination and axonal support. *Cold Spring Harbor Perspectives in Biology*, 8(1), a020479. doi: 10.1101/cshperspect.a020479
3. Fünfschilling, U., et al. (2012). Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. *Nature*, 485(7399), 517-521. doi: 10.1038/nature11007.
4. Lee, Y., et al. (2012). Oligodendroglia metabolically support axons and contribute to neurodegeneration. *Nature*, 487(7408), 443-448. doi: 10.1038/nature11314
5. Ronchi, G., Pellegrino, D., et al (2025). Gut microbiota regulates optic nerve fiber myelination. *Frontiers in Cell and Developmental Biology*, 13:1526855. https://doi.org/10.3389/fcell.2025.1526855
6. Kessaris, N., et al. (2006). Competing waves of oligodendrocytes in the forebrain and postnatal elimination of an embryonic lineage. *Nature Neuroscience*, 9(2), 173-179. doi: 10.1038/nn1620
7. Richardson, W. D., et al. (2006). Oligodendrocyte wars. *Nature Reviews Neuroscience*, 7(1), 11-18. doi: 10.1038/nrn1826
8. Emery, B. (2010). Regulation of oligodendrocyte differentiation and myelination. *Science*, 330(6005), 779-782. doi: 10.1126/science.1190927
9. Zuchero, J. B., et al. (2015). CNS myelin wrapping is driven by actin disassembly. *Developmental Cell*, 34(2), 152-167. doi: 10.1016/j.devcel.2015.06.011
10. Fancy, S. P., et al. (2011). Myelin regeneration: A recapitulation of development? *Annual Review of Neuroscience*, 34, 21-43. doi: 10.1146/annurev-neuro-061010-113629
11. Mitew, S., et al. (2014). Mechanisms regulating the development of oligodendrocytes and central nervous system myelin. *Neuroscience*, 276, 29-47. doi: 10.1016/j.neuroscience.2013.11.029
12. Sender, R., et al. (2016). Revised estimates for the number of human and bacteria cells in the body. *PLoS Biology*, 14(8), e1002533. doi: 10.1371/journal.pbio.1002533
13. Cryan, J. F., et al. (2019). The microbiota-gut-brain axis. *Physiological Reviews*, 99(4), 1877-2013. doi: 10.1152/physrev.00018.2018
14. Sharon, G., et al. (2016). The central nervous system and the gut microbiome. *Cell*, 167(4), 915-932. doi: 10.1016/j.cell.2016.10.027
15. Mayer, E. A., et al. (2015). Gut microbes and the brain: Paradigm shift in neuroscience. *Journal of Neuroscience*, 35(41), 13857-13867. doi: 10.1523/JNEUROSCI.3299-14.2014
16. Dinan, T. G., & Cryan, J. F. (2017). Gut instincts: Microbiota as a key regulator of brain development, ageing and neurodegeneration. *Journal of Physiology*, 595(2), 489-503. doi: 10.1113/JP273106
17. Hoban, A. E., et al. (2016). Regulation of prefrontal cortex myelination by the microbiota. *Translational Psychiatry*, 6(4), e774. doi: 10.1038/tp.2016.42
18. Gacias, M., et al. (2016). Microbiota-driven transcriptional changes in prefrontal cortex override genetic differences in social behavior. *eLife*, 5, e13442. doi: 10.7554/eLife.13442
19. Cummings, J. H., et al. (1987). Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut*, 28(10), 1221-1227. doi: 10.1136/gut.28.10.1221

 doi:10.20944/preprints202602.1855.v1

20. Dalile, B., et al. (2019). The role of short-chain fatty acids in microbiota-gut-brain communication. *Nature Reviews Gastroenterology & Hepatology*, 16(8), 461-478. doi: 10.1038/s41575-019-0157-3
21. Agus, A., et al. (2018). Gut microbiota regulation of tryptophan metabolism in health and disease. *Cell Host & Microbe*, 23(6), 716-724. 10.1016/j.chom.2018.05.003
22. Roager, H. M., & Licht, T. R. (2018). Microbial tryptophan catabolites in health and disease. *Nature Communications*, 9(1), 3294. doi: 10.1038/s41467-018-05470-4
23. Wahlström, A., et al. (2016). Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. *Cell Metabolism*, 24(1), 41-50. doi: 10.1016/j.cmet.2016.05.005
24. MahmoudianDehkordi, S., et al. (2019). Altered bile acid profile associates with cognitive impairment in Alzheimer's disease - An emerging role for gut microbiome. *Alzheimer's & Dementia*, 15(1), 76-92. doi: 10.1016/j.jalz.2018.07.217
25. Sivaprakasam, S., et al. (2017). Short-chain fatty acid transporters: Role in colonic homeostasis. *Comprehensive Physiology*, 8(1), 299-314. doi: 10.1002/cphy.c170014
26. Borthakur, A., et al. (2008). Regulation of monocarboxylate transporter 1 (MCT1) promoter by butyrate in human intestinal epithelial cells. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 294(1), G241-G247. doi: 10.1002/jcb.21532
27. Bloemen, J. G., et al. (2009). Short chain fatty acids exchange across the gut and liver in humans measured at surgery. *Clinical Nutrition*, 28(6), 657-661. 10.1016/j.clnu.2009.05.011
28. Boets, E., et al. (2017). Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 312(1), G37-G47. doi: 10.1113/JP272613
29. Wikoff, W. R., et al. (2009). Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proceedings of the National Academy of Sciences*, 106(10), 3698-3703. doi: 10.1073/pnas.0812874106
30. Dawson, P. A., et al. (2009). Bile acid transporters. *Journal of Lipid Research*, 50(12), 2340-2357. doi: 10.1194/jlr.R900012-JLR200
31. Braniste, V., et al. (2014). The gut microbiota influences blood-brain barrier permeability in mice. *Science Translational Medicine*, 6(263), 263ra158. doi: 10.1126/scitranslmed.3009759
32. MacFabe, D. F. (2012). Short-chain fatty acid fermentation products of the gut microbiome: Implications in autism spectrum disorders. *Microbial Ecology in Health and Disease*, 23, 19260. doi: 10.3402/mehd.v23i0.19260
33. Venkatesh, M., et al. (2014). Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and Toll-like receptor 4. *Immunity*, 41(2), 296-310. doi: 10.1016/j.immuni.2014.06.014
34. Mertens, K. L., et al. (2017). Bile acid signaling pathways from the enterohepatic circulation to the central nervous system. *Frontiers in Neuroscience*, 11, 617. doi: 10.3389/fnins.2017.00617
35. Erny, D., et al. (2015). Host microbiota constantly control maturation and function of microglia in the CNS. *Nature Neuroscience*, 18(7), 965-977. doi: 10.1038/nn.4030
36. Lampron, A., et al. (2015). Inefficient clearance of myelin debris by microglia impairs remyelinating processes. *Journal of Experimental Medicine*, 212(4), 481-495. doi: 10.1084/jem.20141656
37. Lloyd, A. F., et al. (2019). Central nervous system regeneration is driven by microglia necroptosis and repopulation. *Nature Neuroscience*, 22(7), 1046-1052. doi: 10.1038/s41593-019-0418-z
38. Miron, V. E., et al. (2013). M2 microglia and macrophages drive oligodendrocyte differentiation during CNS remyelination. *Nature Neuroscience*, 16(9), 1211-1218. doi: 10.1038/nn.3469
39. Rothhammer, V., et al. (2016). Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and CNS inflammation via the AhR. *Nature Medicine*, 22(6), 586-597. doi: 10.1038/nm.4106
40. Orthmann-Murphy, J. L., et al. (2011). Gap junctions couple astrocytes and oligodendrocytes. *Journal of Molecular Neuroscience*, 35(1), 101-116. doi: 10.1007/s12031-007-9027-5
41. Tress, O., et al. (2012). Panglial gap junctional communication is essential for maintenance of myelin in the CNS. *Journal of Neuroscience*, 32(22), 7499-7518. doi: 10.1523/JNEUROSCI.0392-12.2012
42. Louis, P., et al. (2014). The gut microbiota, bacterial metabolites and colorectal cancer. *Nature Reviews Microbiology*, 12(10), 661-672. doi: 10.1038/nrmicro3344
43. Reichardt, N., et al. (2014). Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. *The ISME Journal*, 8(6), 1323-1335. doi: 10.1038/ismej.2014.14
44. Louis, P., & Flint, H. J. (2010). Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. *FEMS Microbiology Letters*, 294(1), 1-8. doi: 10.1111/j.1574-6968.2009.01514.x
45. Vital, M., et al. (2014). Revealing the bacterial butyrate synthesis pathways by analyzing (meta) genomic data. *mBio*, 5(2), e00889-14. doi: 10.1128/mBio.00889-14

 doi:10.20944/preprints202602.1855.v1

46. Davie, J. R. (2003). Inhibition of histone deacetylase activity by butyrate. *The Journal of Nutrition*, 133(7), 2485S-2493S. doi: 10.1093/jn/133.7.2485S
47. Waldecker, M., et al. (2008). Inhibition of histone-deacetylase activity by short-chain fatty acids and some polyphenol metabolites formed in the colon. *The Journal of Nutritional Biochemistry*, 19(9), 587-593. doi: 10.1016/j.jnutbio.2007.08.002
48. Shen, S., et al. (2008). Age-dependent epigenetic control of differentiation inhibitors is critical for remyelination efficiency. *Nature Neuroscience*, 11(9), 1024-1034. doi: 10.1038/nn.2172
49. Conway, G. D., et al. (2012). Histone deacetylase activity is required for human oligodendrocyte progenitor differentiation. *Glia*, 60(12), 1944-1953. doi: 10.1002/glia.22410
50. Shen, S., et al. (2005). Histone modifications affect timing of oligodendrocyte progenitor differentiation in the developing rat brain. *Journal of Cell Biology*, 169(4), 577-589. doi: 10.1083/jcb.200412101
51. Chen, T., et al. (2019). Butyrate suppresses demyelination and enhances remyelination. *Journal of Neuroinflammation*, 16(1), 165. doi: 10.1186/s12974-019-1552-y
52. Brown, A. J., et al. (2003). The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *Journal of Biological Chemistry*, 278(13), 11312-11319. doi: 10.1074/jbc.M211609200
53. Le Poul, E., et al. (2003). Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *Journal of Biological Chemistry*, 278(28), 25481-25489. doi: 10.1074/jbc.M301403200
54. Kimura, I., et al. (2011). Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proceedings of the National Academy of Sciences*, 108(19), 8030-8035. doi: 10.1073/pnas.1016088108
55. Thangaraju, M., et al. (2009). GPR109A is a G-protein–coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. *Cancer Research*, 69(7), 2826-2832. doi: 10.1158/0008-5472
56. Fu, S. P., et al. (2015). Anti-inflammatory effects of BHBA in both in vivo and in vitro Parkinson's disease models are mediated by GPR109A-dependent mechanisms. *Journal of Neuroinflammation*, 12(1), 9. doi: 10.1186/s12974-014-0230-3
57. Mews, P., et al. (2017). Acetyl-CoA synthetase regulates histone acetylation and hippocampal memory. *Nature*, 546(7658), 381-386. doi: 10.1038/nature22405
58. Camargo, N., et al. (2017). Oligodendroglial myelination requires astrocyte-derived lipids. *PLoS Biology*, 15(5), e1002605. doi: 10.1371/journal.pbio.1002605
59. Wellen, K. E., et al. (2009). ATP-citrate lyase links cellular metabolism to histone acetylation. *Science*, 324(5930), 1076-1080. doi: 10.1126/science.1164097
60. Pietrocola, F., et al. (2015). Acetyl coenzyme A: A central metabolite and second messenger. *Cell Metabolism*, 21(6), 805-821. doi: 10.1016/j.cmet.2015.05.014
61. Saher, G., et al. (2011). Cholesterol in myelin biogenesis and hypomyelinating disorders. *Biochimica et Biophysica Acta*, 1811(12), 698-703. doi: 10.1016/j.bbalip.2015.02.010
62. Mews, P., et al. (2019). Alcohol metabolism contributes to brain histone acetylation. *Nature*, 574(7780), 717-721. doi: 10.1038/s41586-019-1700-7
63. Smith, P. M., et al. (2013). The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science*, 341(6145), 569-573. doi: 10.1126/science.1241165
64. Arpaia, N., et al. (2013). Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature*, 504(7480), 451-455. doi: 10.1038/nature12726
65. Haghikia, A., et al. (2015). Dietary fatty acids directly impact central nervous system autoimmunity via the small intestine. *Immunity*, 43(4), 817-829. doi: 10.1016/j.immuni.2015.09.007
66. Duscha, A., et al. (2020). Propionic acid shapes the multiple sclerosis disease course by an immunomodulatory mechanism. *Cell*, 180(6), 1067-1080. doi: 10.1016/j.cell.2020.02.035
67. Gao, K., et al. (2020). Tryptophan metabolism: A link between the gut microbiota and brain. *Advances in Nutrition*, 11(3), 709-723. doi: 10.1093/advances/nmz127
68. Zelante, T., et al. (2013). Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity*, 39(2), 372-385. doi: 10.1016/j.immuni.2013.08.003
69. Williams, B. B., et al. (2014). Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. *Cell Host & Microbe*, 16(4), 495-503. doi: 10.1016/j.chom.2014.09.001

 doi:10.20944/preprints202602.1855.v1

70. Gao, J., et al. (2018). Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism. *Frontiers in Cellular and Infection Microbiology*, 8, 13. doi: 10.3389/fcimb.2018.00013
71. Quintana, F. J., & Sherr, D. H. (2013). Aryl hydrocarbon receptor control of adaptive immunity. *Pharmacological Reviews*, 65(4), 1148-1161. doi: 10.1124/pr.113.007823
72. Denison, M. S., & Nagy, S. R. (2003). Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. *Annual Review of Pharmacology and Toxicology*, 43(1), 309-334. doi: 10.1146/annurev.pharmtox.43.100901.135828
73. Rothhammer, V., et al. (2018). Microglial control of astrocytes in response to microbial metabolites. *Nature*, 557(7707), 724-728. doi: 10.1038/s41586-018-0119-x
74. Dodd, D., et al. (2017). A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites. *Nature*, 551(7682), 648-652. doi: 10.1038/nature24661
75. Thorburne, S. K., & Bhagat, S. (1996). Low glutathione and high iron govern the susceptibility of oligodendroglial precursors to oxidative stress. *Journal of Neurochemistry*, 67(3), 1014-1022. doi: 10.1046/j.1471-4159.1996.67031014.x
76. Lim, C. K., et al. (2017). Kynurenine pathway metabolomics predicts and provides mechanistic insight into multiple sclerosis progression. *Scientific Reports*, 7(1), 41473. doi: 10.1038/srep41473
77. Hartai, Z., et al. (2005). Kynurenine metabolism in multiple sclerosis. *Acta Neurologica Scandinavica*, 112(2), 93-96. doi: 10.1111/j.1600-0404.2005.00442.x
78. Chen, J., et al. (2016). Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. *Scientific Reports*, 6(1), 28484. doi: 10.1038/srep28484
79. Jangi, S., et al. (2016). Alterations of the human gut microbiome in multiple sclerosis. *Nature Communications*, 7(1), 12015. doi: 10.1038/ncomms12015
80. Ridlon, J. M., et al. (2006). Bile salt biotransformations by human intestinal bacteria. *Journal of Lipid Research*, 47(2), 241-259. doi: 10.1194/jlr.R500013-JLR200
81. Gérard, P. (2013). Metabolism of cholesterol and bile acids by the gut microbiota. *Pathogens*, 3(1), 14-24. doi: 10.3390/pathogens3010014
82. Keitel, V., et al. (2019). The G-protein coupled bile salt receptor TGR5 is expressed in liver sinusoidal endothelial cells. *Hepatology*, 70(3), 982-997. doi: 10.1002/hep.21458
83. Makishima, M., et al. (2002). Vitamin D receptor as an intestinal bile acid sensor. *Science*, 296(5571), 1313-1316. doi: 10.1126/science.1070477
84. Munger, K. L., et al. (2006). Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA*, 296(23), 2832-2838. doi: 10.1001/jama.296.23.2832
85. Mokry, L. E., et al. (2015). Vitamin D and risk of multiple sclerosis: A Mendelian randomization study. *PLoS Medicine*, 12(8), e1001866. doi: 10.1371/journal.pmed.1001866
86. Yanguas-Casás, N., et al. (2017). TUDCA: An agonist of the bile acid receptor GPBAR1/TGR5 with anti-inflammatory effects in microglial cells. *Journal of Cellular Physiology*, 232(8), 2231-2245. doi: 10.1002/jcp.25742
87. Parry, G. J., et al. (2010). Safety, tolerability, and cerebrospinal fluid penetration of ursodeoxycholic acid in patients with amyotrophic lateral sclerosis. *Clinical Neuropharmacology*, 33(1), 17-21. doi: 10.1097/WNF.0b013e3181c47569
88. Bhargava, P., et al. (2020). Bile acid metabolism is altered in multiple sclerosis and supplementation ameliorates neuroinflammation. *Journal of Clinical Investigation*, 130(7), 3467-3482. doi: 10.1172/JCI129401
89. Moschen, A. R., et al. (2012). Dietary factors: Major regulators of the gut's microbiota. *Gut & Liver*, 6(4), 411-416. doi: 10.5009/gnl.2012.6.4.411
90. Dong, W., et al. (2014). Sodium butyrate activates NRF2 to ameliorate diabetic nephropathy possibly via inhibition of HDAC. *Journal of Endocrinology*, 223(1), 27-36. doi: 10.1530/JOE-16-0322
91. Walton, C., et al. (2020). Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Multiple Sclerosis Journal*, 26(14), 1816-1821. doi: 10.1177/1352458520970841
92. Kuhlmann, T., et al. (2008). Differentiation block of oligodendroglial progenitor cells as a cause for remyelination failure in chronic multiple sclerosis. *Brain*, 131(7), 1749-1758. doi: 10.1093/brain/awn096
93. Franklin, R. J. (2002). Why does remyelination fail in multiple sclerosis? *Nature Reviews Neuroscience*, 3(9), 705-714. doi: 10.1038/nrn917
94. Chang, A., et al. (2002). Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. *New England Journal of Medicine*, 346(3), 165-173. doi: 10.1056/NEJMoa010994
95. Syed, Y. A., et al. (2011). Inhibition of CNS remyelination by the presence of semaphorin 3A. *Journal of Neuroscience*, 31(10), 3719-3728. doi: 10.1523/JNEUROSCI.4930-10.2011

 doi:10.20944/preprints202602.1855.v1

96. Fancy, S. P., et al. (2009). Dysregulation of the Wnt pathway inhibits timely myelination and remyelination in the mammalian CNS. *Genes & Development*, 23(13), 1571-1585. doi: 10.1101/gad.1806309
97. Moyon, S., et al. (2017). Demyelination causes adult CNS progenitors to revert to an immature state and express immune cues that support their migration. *Journal of Neuroscience*, 37(5), 1197-1210. doi: 10.1523/JNEUROSCI.0849-14.2015
98. Koreman, E., et al. (2018). Chromatin remodeling and epigenetic regulation of oligodendrocyte myelination and myelin repair. *Molecular and Cellular Neuroscience*, 87, 18-26. doi: 10.1016/j.mcn.2017.11.010
99. Rone, M. B., et al. (2016). Oligodendrogliopathy in multiple sclerosis: Low glycolytic metabolic rate promotes oligodendrocyte survival. *Journal of Neuroscience*, 36(17), 4698-4707. doi: 10.1523/JNEUROSCI.4077-15.2016
100. Schirmer, L., et al. (2019). Neuronal vulnerability and multilineage diversity in multiple sclerosis. *Nature*, 573(7772), 75-82. doi: 10.1038/s41586-019-1404-z
101. Absinta, M., et al. (2021). A lymphocyte–microglia–astrocyte axis in chronic active multiple sclerosis. *Nature*, 597(7878), 709-714. doi: 10.1038/s41586-021-03892-7
102. Lassmann, H. (2018). Multiple sclerosis pathology. *Cold Spring Harbor Perspectives in Medicine*, 8(3), a028936. doi: 10.1101/cshperspect.a028936
103. Zeng, Q., et al. (2019). Gut dysbiosis and lack of short chain fatty acids in a Chinese cohort of patients with multiple sclerosis. *Neurochemistry International*, 129, 104468. doi: 10.1016/j.neuint.2019.104468
104. Park, J., et al. (2015). Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases. *Mucosal Immunology*, 8(1), 80-93. doi: 10.1038/mi.2014.44
105. Korn, T., et al. (2009). IL-17 and Th17 cells. *Annual Review of Immunology*, 27, 485-517. doi: 10.1146/annurev.immunol.021908.132710
106. Kleinewietfeld, M., et al. (2013). Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature*, 496(7446), 518-522. doi: 10.1038/nature11868
107. Furusawa, Y., et al. (2013). Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*, 504(7480), 446-450. doi: 10.1038/nature12721
108. Nastasi, C., et al. (2015). The effect of short-chain fatty acids on human monocyte-derived dendritic cells. *Scientific Reports*, 5(1), 16148. doi: 10.1038/srep16148
109. Kaisar, M. M., et al. (2017). Butyrate conditions human dendritic cells to prime type 1 regulatory T cells via both histone deacetylase inhibition and G protein-coupled receptor 109A signaling. *Frontiers in Immunology*, 8, 1429. . doi: 10.3389/fimmu.2017.01429
110. Ransohoff, R. M. (2016). A polarizing question: Do M1 and M2 microglia exist? *Nature Neuroscience*, 19(8), 987-991. doi: 10.1038/nn.4338
111. Wenzel, T. J., et al. (2020). Short-chain fatty acids (SCFAs) alone or in combination regulate select immune functions of microglia-like cells. *Molecular and Cellular Neuroscience*, 105, 103493. doi: 10.1016/j.mcn.2020.103493
112. Berer, K., et al. (2017). Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. *Proceedings of the National Academy of Sciences*, 114(40), 10719-10724. doi: 10.1073/pnas.1711233114
113. Cekanaviciute, E., et al. (2017). Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models. *Proceedings of the National Academy of Sciences*, 114(40), 10713-10718. doi: 10.1073/pnas.1711235114
114. Tremlett, H., et al. (2016). Gut microbiota in early pediatric multiple sclerosis: A case-control study. *European Journal of Neurology*, 23(8), 1308-1321. doi: 10.1111/ene.13026
115. Lu, J., et al. (2018). Microbiota influence the development of the brain and behaviors in C57BL/6J mice. *PLoS One*, 13(8), e0201829. doi: 10.1371/journal.pone.0201829
116. Thion, M. S., et al. (2018). Microbiome influences prenatal and adult microglia in a sex-specific manner. *Cell*, 172(3), 500-516. dio: 10.1016/j.cell.2017.11.042
117. Desbonnet, L., et al. (2015). Gut microbiota depletion from early adolescence in mice: Implications for brain and behaviour. *Brain, Behavior, and Immunity*, 48, 165-173. doi: 10.1016/j.bbi.2015.04.004
118. Leclercq, S., et al. (2017). Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior. *Nature Communications*, 8(1), 15062. doi: 10.1038/ncomms15062
119. McMurran, C. E., et al. (2019). The microbiota regulates murine inflammatory responses to toxin-induced CNS demyelination but has minimal impact on remyelination. *Proceedings of the National Academy of Sciences*, 116(50), 25311-25321. doi: 10.1073/pnas.1905787116

 doi:10.20944/preprints202602.1855.v1

120. Langley, M. R., et al. (2020). High fat diet consumption results in mitochondrial dysfunction, oxidative stress, and oligodendrocyte loss in the central nervous system. *Biochimica et Biophysica Acta-Molecular Basis of Disease*, 1866(3), 165630. doi: 10.1016/j.bbadis.2019.165630
121. Matsushima, G. K., & Morell, P. (2001). The neurotoxicant, cuprizone, as a model to study demyelination and remyelination in the central nervous system. *Brain Pathology*, 11(1), 107-116. doi: 10.1111/j.1750-3639.2001.tb00385.x
122. Constantinescu, C. S., et al. (2011). Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). *British Journal of Pharmacology*, 164(4), 1079-1106. doi: 10.1111/j.1476-5381.2011.01302.x
123. Lee, Y. K., et al. (2011). Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. *Proceedings of the National Academy of Sciences*, 108(Suppl 1), 4615-4622. doi: 10.1073/pnas.1000082107
124. Berer, K., et al. (2011). Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. *Nature*, 479(7374), 538-541. doi: 10.1038/nature10554
125. Ochoa-Repáraz, J., et al. (2010). A polysaccharide from the human commensal Bacteroides fragilis protects against CNS demyelinating disease. *Mucosal Immunology*, 3(5), 487-495. doi: 10.1038/mi.2010.29
126. Mangalam, A., et al. (2017). Human gut-derived commensal bacteria suppress CNS inflammatory and demyelinating disease. *Cell Reports*, 20(6), 1269-1277. doi: 10.1016/j.celrep.2017.07.031
127. Mizuno, M., et al. (2017). The dual role of short fatty acid chains in the pathogenesis of autoimmune disease models. *PLoS One*, 12(2), e0173032. . doi: 10.1371/journal.pone.0173032
128. Dewhirst, F. E., et al. (1999). Phylogeny of the defined murine microbiota: Altered Schaedler flora. *Applied and Environmental Microbiology*, 65(8), 3287-3292. doi: 10.1128/AEM.65.8.3287-3292.1999
129. Faith, J. J., et al. (2014). Identifying gut microbe-host phenotype relationships using combinatorial communities in gnotobiotic mice. *Science Translational Medicine*, 6(220), 220ra11. doi: 10.1126/scitranslmed.3008051
130. Tan, J., et al. (2016). The role of short-chain fatty acids in health and disease. *Advances in Immunology*, 121, 91-119. doi: 10.1016/B978-0-12-800100-4.00003-9
131. Atarashi, K., et al. (2013). Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature*, 500(7461), 232-236. doi: 10.1038/nature12331
132. So, D., et al. (2018). Dietary fiber intervention on gut microbiota composition in healthy adults: A systematic review and meta-analysis. *The American Journal of Clinical Nutrition*, 107(6), 965-983. doi: 10.1093/ajcn/nqy041
133. Baxter, N. T., et al. (2019). Dynamics of human gut microbiota and short-chain fatty acids in response to dietary interventions with three fermentable fibers. *mBio*, 10(1), e02566-18. doi: 10.1128/mBio.02566-18
134. Fitzgerald, K. C., et al. (2018). Diet quality is associated with disability and symptom severity in multiple sclerosis. *Neurology*, 90(1), e1-e11. doi: 10.1212/WNL.0000000000004768
135. Kim, D. Y., et al. (2012). Inflammation-mediated memory dysfunction and effects of a ketogenic diet in a murine model of multiple sclerosis. *PLoS One*, 7(5), e35476. doi: 10.1371/journal.pone.0035476
136. Storoni, M., & Plant, G. T. (2015). The therapeutic potential of the ketogenic diet in treating progressive multiple sclerosis. *Multiple Sclerosis International*, 2015, 681289. doi: 10.1155/2015/681289
137. Brenton, J. N., et al. (2019). Phase II study of ketogenic diets in relapsing multiple sclerosis: Safety, tolerability and potential clinical benefits. *Journal of Neurology, Neurosurgery & Psychiatry*, 93(6), 637-644. doi: 10.1136/jnnp-2022-329074
138. Swidsinski, A., et al. (2017). Reduced mass and diversity of the colonic microbiome in patients with multiple sclerosis and their improvement with ketogenic diet. *Frontiers in Microbiology*, 8, 1141. doi: 10.3389/fmicb.2017.01141
139. Katz Sand, I., et al. (2018). The role of diet in multiple sclerosis: Mechanistic connections and current evidence. *Current Nutrition Reports*, 7(3), 150-160. doi: 10.1007/s13668-018-0236-z
140. De Filippis, F., et al. (2016). High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut*, 65(11), 1812-1821. doi: 10.1136/gutjnl-2015-309957
141. Tankou, S. K., et al. (2018). A probiotic modulates the microbiome and immunity in multiple sclerosis. *Annals of Neurology*, 83(6), 1147-1161. doi: 10.1002/ana.25244
142. Kouchaki, E., et al. (2017). Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled trial. *Clinical Nutrition*, 36(5), 1245-1249. doi: 10.1016/j.clnu.2016.08.015

 doi:10.20944/preprints202602.1855.v1

143. Salami, M., et al. (2019). How probiotic bacteria influence the motor and mental behaviors as well as immunological and oxidative biomarkers in multiple sclerosis? A double blind clinical trial. *Journal of Functional Foods*, 52, 8-13. doi: 10.1016/j.jff.2018.10.023
144. Mimee, M., et al. (2015). Programming a human commensal bacterium, Bacteroides thetaiotaomicron, to sense and respond to stimuli in the murine gut microbiota. *Cell Systems*, 1(1), 62-71. doi: 10.1016/j.cels.2015.06.001
145. Charbonneau, M. R., et al. (2020). Developing a new class of engineered live bacterial therapeutics to treat human diseases. *Nature Communications*, 11(1), 1738. doi: 10.1038/s41467-020-15508-1
146. Depommier, C., et al. (2019). Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: A proof-of-concept exploratory study. *Nature Medicine*, 25(7), 1096-1103. doi: 10.1038/s41591-019-0495-2
147. Zmora, N., et al. (2018). Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. *Cell*, 174(6), 1388-1405. doi: 10.1016/j.cell.2018.08.041
148. Venkatesh, M., et al. (2014). Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and Toll-like receptor 4. *Immunity*, 41(2), 296-310. doi: 10.1016/j.immuni.2014.06.014
149. Konopelski, P., et al. (2022). Indole-3-propionic acid, a tryptophan-derived bacterial metabolite, reduces weight gain in rats. *Nutrients*, 14(7), 1507. doi: 10.3390/nu11030591
150. Busbee, P. B., et al. (2013). Use of natural AhR ligands as potential therapeutic modalities against inflammatory disorders. *Nutrition Reviews*, 71(6), 353-369. doi: 10.1111/nure.12024
151. Elia, A. E., et al. (2016). Tauroursodeoxycholic acid in the treatment of patients with amyotrophic lateral sclerosis. *European Journal of Neurology*, 23(1), 45-52. doi: 10.1111/ene.12664
152. Makkawi, S., et al. (2018). Fecal microbiota transplantation associated with 10 years of stability in a patient with SPMS. *Neurology-Neuroimmunology Neuroinflammation*, 5(4), e459. doi: 10.1212/NXI.0000000000000459
153. Allegretti, J. R., et al. (2019). The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. *The Lancet*, 394(10196), 420-431. doi: 10.1016/S0140-6736(19)31266-8
154. Zimmermann, M., et al. (2019). Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature*, 570(7762), 462-467. doi: 10.1038/s41586-019-1291-3
155. Sajad, M., et al. (2024). Pyruvate Dehydrogenase-Dependent Metabolic Programming Affects the Oligodendrocyte Maturation and Remyelination. *Molecular Neurobiology*. doi: 10.1007/s12035-024-03965-9
156. Xiao, L., et al. (2015). A catalog of the mouse gut metagenome. *Nature Biotechnology*, 33(10), 1103-1108. doi: 10.1038/nbt.3353
157. Ventura-Antunes, L., et al. (2013). Different scaling of white matter volume, cortical connectivity, and gyrification across rodent and primate brains. *Frontiers in Neuroanatomy*, 7, 3. doi: 10.3389/fnana.2013.00003
158. Miller, D. J., et al. (2012). Prolonged myelination in human neocortical evolution. *Proceedings of the National Academy of Sciences*, 109(41), 16480-16485. doi: 10.1073/pnas.1117943109
159. Storm-Larsen, C., et al. (2020). Gut microbiota composition during a 12-week intervention with delayed-release dimethyl fumarate in multiple sclerosis. *Multiple Sclerosis and Related Disorders*, 39, 101898. doi: 10.1177/2055217319888767
160. Cantarel, B. L., et al. (2015). Gut microbiota in multiple sclerosis: Possible influence of immunomodulators. *Journal of Investigative Medicine*, 63(5), 729-734. doi: 10.1097/JIM.0000000000000192
161. Wunsch, M., et al. (2022). The enteric nervous system is a potential autoimmune target in multiple sclerosis. *Acta Neuropathologica*, 144(5), 871-888. doi: 10.1007/s00401-017-1742-6
162. Shoaie, S., et al. (2015). Quantifying diet-induced metabolic changes of the human gut microbiome. *Cell Metabolism*, 22(2), 320-331. doi: 10.1016/j.cmet.2015.07.001
163. MacKay, A. L., & Laule, C. (2016). Magnetic resonance of myelin water: An in vivo marker for myelin. *Brain Plasticity*, 2(1), 71-91. doi: 10.3233/BPL-160033
164. Alexander, A. L., et al. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics*, 4(3), 316-329. doi: 10.1016/j.nurt.2007.05.011
165. Marques, S., et al. (2016). Oligodendrocyte heterogeneity in the mouse juvenile and adult central nervous system. *Science*, 352(6291), 1326-1329. doi: 10.1126/science.aaf6463
166. Jäkel, S., et al. (2019). Altered human oligodendrocyte heterogeneity in multiple sclerosis. *Nature*, 566(7745), 543-547. doi: 10.1038/s41586-019-0903-2
167. Madhavan, M., et al. (2018). Induction of myelinating oligodendrocytes in human cortical spheroids. *Nature Methods*, 15(9), 700-706. doi: 10.1038/s41592-018-0081-4

 doi:10.20944/preprints202602.1855.v1

168. Marton, R. M., et al. (2019). Differentiation and maturation of oligodendrocytes in human three-dimensional neural cultures. *Nature Neuroscience*, 22(3), 484-491. doi: 10.1038/s41593-018-0316-9
169. Lavasani, S., et al. (2010). A novel probiotic mixture exerts a therapeutic effect on experimental autoimmune encephalomyelitis mediated by IL-10 producing regulatory T cells. *PLoS One*, 5(2), e9009. doi: 10.1371/journal.pone.0009009
170. Stacho, R., Zucha, D., Kirdajova, D., & Valihrach, L. (2026). Applications of Spatial Transcriptomics in Ischemic Stroke Research. *American Journal of Pathology*. doi: 10.1016/j.ajpath.2026.01.008
171. Abulaban, A. A., Al-Kuraishy, et al. (2025). The Janus Face of Astrocytes in Multiple Sclerosis: Balancing Protection and Pathology. *Brain Research Bulletin*, 226, 111356. doi: 10.1016/j.brainresbull.2025.111356
172. Jubair, H. (2026). Glial Cells in Dementia: From Cellular Dysfunction to Therapeutic Frontiers. *Cell Transplantation*. doi: 10.1177/09636897251414216
173. Deng, X., Zhao, M., et al. (2025). New insights into acute ischemic stroke from the perspective of spatial omics. *Theranostics*, 15(15), 7902-7924. doi: 10.7150/thno.113396