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REVIEW

Gut–Spinal Cord Axis in Spinal Cord Injury: Bidirectional Inflammatory Mechanisms and Microbiota-Targeted Therapeutic Strategies

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Abstract: Spinal cord injury (SCI) is a complex neurological disorder characterized not only by localized neuroinflammation but also by systemic immune dysregulation and multiorgan dysfunction. Emerging evidence has identified the gut microbiota as a critical extrinsic regulator of neural homeostasis, giving rise to the concept of the "gut–spinal cord axis". This review systematically examines the dynamic and bidirectional alterations in the gut microbial composition following SCI, with a particular emphasis on the role of microbiota-derived metabolites in the gut–spinal cord axis. These metabolites are recognized as key mediators that shape the spinal inflammatory milieu by modulating specific signaling pathways. In addition, the mechanistic basis of the gut–spinal cord axis is further dissected through neural, immune, and metabolic regulatory frameworks, highlighting how gut dysbiosis following SCI contributes to spinal inflammation via the modulation of vagal nerve signaling, immune cell polarization, and metabolic homeostasis. Moreover, the translational potential of microbiota-targeted interventions—such as probiotics and fecal microbiota transplantation (FMT)—is evaluated in terms of their ability to suppress inflammatory amplification and restore the disrupted bidirectional gut–spinal cord feedback loop. By integrating multiomics approaches and adopting a spatiotemporal perspective, this review underscores the importance of cross-system therapeutic strategies in SCI, aiming to provide a theoretical foundation and practical guidance for future precision interventions and translational research.

Keywords: spinal cord injury, gut–spinal cord axis, gut microbiota, neuroinflammation, probiotics, fecal microbiota transplantation

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Introduction: From a Single-Injury Model to a Systemic Regulatory Framework

The Dual Challenge of Spinal Cord Injury Epidemiology

Spinal cord injury (SCI) is a severe and debilitating condition that commonly results from traffic accidents, falls, and sports-related trauma. It is caused primarily by compression, traction, or contusion of the spinal cord, leading to partial or complete loss of motor, sensory, and autonomic functions.[1] Globally, it is estimated that 2 to 3 million individuals are living with SCI, with 250,000 to 500,000 new cases reported annually.[2] The lifetime cost of medical care and assistance for SCI patients can range from $500,000 to $2 million.[3] While paralysis represents the most visible consequence of SCI, its associated systemic complications are equally significant, including cardiovascular disease, metabolic syndrome, urogenital and gastrointestinal dysfunction, chronic pain, immunosuppression, anxiety, and depression.[4,5] However, most current therapies are limited in their ability to modulate systemic inflammatory responses or address long-term multi-system dysfunctions, highlighting the need for novel interventions that target upstream drivers of secondary injury.

The prognosis of SCI is closely linked to the severity of the primary injury, the timing of therapeutic interventions, and the progression of secondary pathological responses.[6] Surgical decompression within 24–36 hours after injury is recognized as an effective and critical treatment for improving neurological outcomes in SCI patients.[7] Adjunctive therapies such as hyperbaric

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oxygen, pulsed electrical stimulation, mild hypothermia, acupuncture, and laser puncture have also been employed to support functional recovery.[8] Pharmacological treatments, neurotrophic factor administration, cell transplantation, gene therapy, and signaling pathway modulation hold therapeutic promise but still require extensive clinical validation.[7,9]

SCI poses dual therapeutic challenges: minimizing secondary damage in the acute phase and promoting functional restoration in the chronic phase. In the early stage, the focus was on neuroprotection and the preservation of spinal cord integrity. In contrast, the chronic stage requires sustained strategies that target neural regeneration, control of inflammation, and systemic recovery. This multifaceted progression suggests that SCI treatment cannot depend on a single modality but rather demands interdisciplinary, multimodal strategies tailored to different stages of recovery.

Evolution and Scientific Significance of the "Gut–Spinal Cord Axis" Concept

The concept of the "gut–spinal cord axis" is built upon extensive research into the interactions between the gut microbiota and the central nervous system (CNS). Early studies focused on the regulatory mechanisms of the neuroendocrine–immune network within the "gut–brain axis", revealing that gut microbes can influence brain function via the vagus nerve, short-chain fatty acids (SCFAs), and various cytokines.[10–12] However, accumulating evidence has indicated that the influence of the gut microbiota extends beyond the brain, playing a pivotal role in modulating the spinal cord microenvironment as well.[13,14] Through metabolites, immune signaling molecules, and neuroactive compounds, the gut microbiota can directly or indirectly regulate spinal cord inflammation, oxidative stress, and axonal regeneration, thus giving rise to the theoretical framework of the gut–spinal cord axis (Figure 1).[15,16]

The bidirectional regulation of the gut–spinal cord axis exhibits significant spatiotemporal dynamics. Temporally, gut dysbiosis triggered by acute SCI can aggravate secondary injury through the activation of proinflammatory signaling

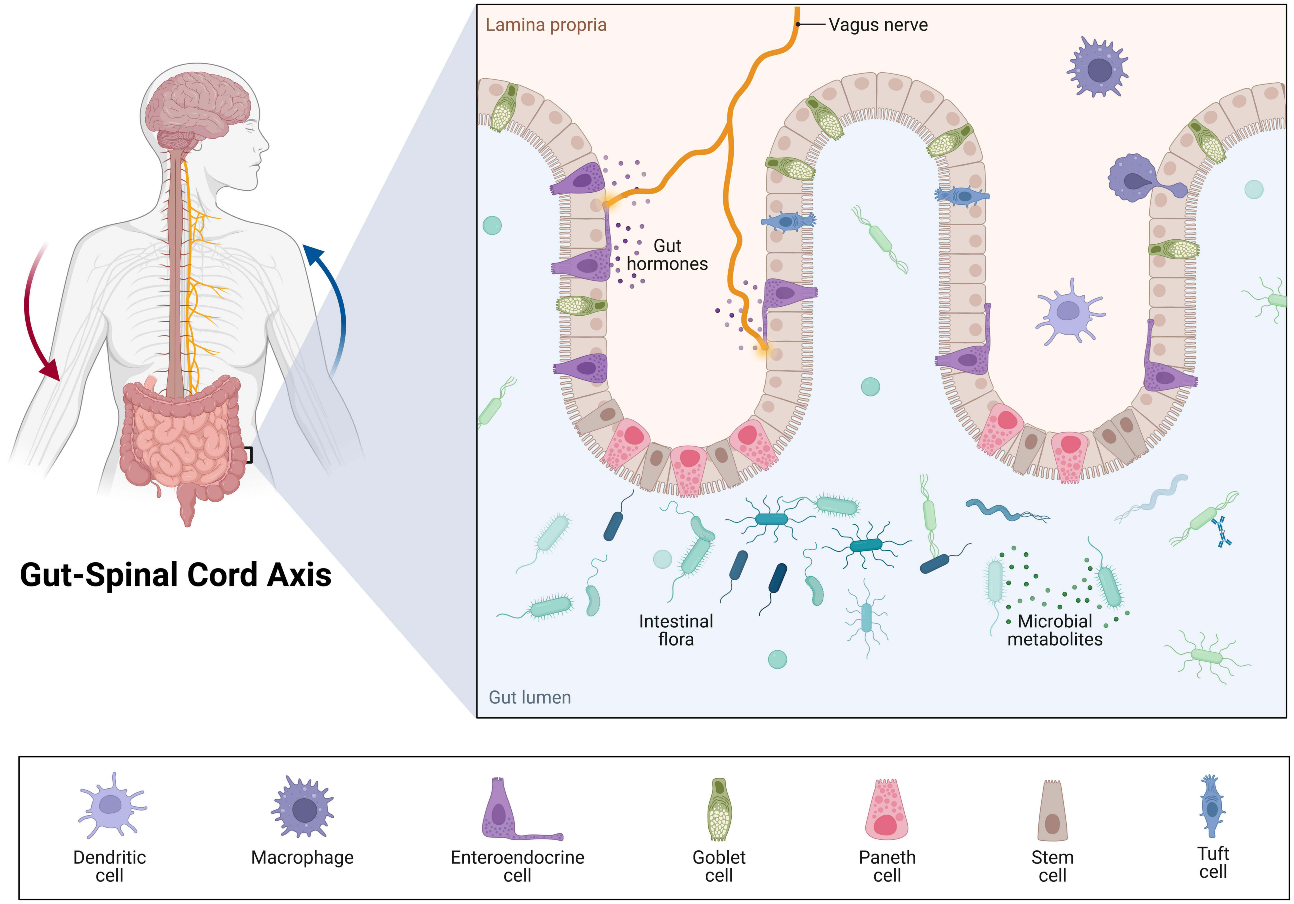

Figure 1 Conceptual framework of the gut–spinal cord axis. A schematic illustration showing the bidirectional communication between the gut microbiota and the spinal cord. Red arrows indicate the influence of the spinal cord on the gut, while blue arrows indicate the influence of the gut on the spinal cord.

cascades. Disruption of the gut microbiota after SCI facilitates microbial translocation and systemic dissemination of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), which activate Toll-like receptor (TLR) and inflammasome pathways in the injured spinal cord.[17] This immune activation contributes to sustained microglial activation, cytokine production, and blood–spinal cord barrier breakdown, thereby amplifying secondary neuroinflammatory damage.[18] In contrast, the restoration of microbial metabolic homeostasis during the chronic phase contributes critically to neuroregeneration.[19] Spatially, alterations in the spinal cord microenvironment—such as aberrant neuronal excitability and glial activation—can provide feedback to influence gut barrier integrity and microbiota composition via autonomic and humoral pathways. This bidirectional communication creates a cross-system cascade of "neurotrauma–gut dysbiosis–inflammatory amplification".[20] This spatiotemporal interplay suggests that the gut–spinal cord axis is not a static or linear pathway but rather a dynamic regulatory network involving both local and systemic mechanisms. The emergence of this concept challenges the traditional paradigm that treats the neural, immune, and metabolic systems as independent entities. Instead, it highlights their systemic crosstalk, particularly in the complex pathophysiology following SCI. The gut microbiota and their metabolites not only contribute to neurorepair but also actively regulate immune responses during the recovery process. Immune and neural interactions occurring at distinct time points and spatial scales converge into a dynamic feedback loop, underscoring the interdependence of multisystem coordination in SCI pathology. This conceptual advancement offers new insights into therapeutic strategies, emphasizing the necessity of integrating neuroimmune and microbial modulation in SCI management.

The dynamic interplay between post-SCI inflammatory progression and gut microbiota homeostasis represents a critical regulatory nexus that determines the outcome of neural repair. This review systematically examines the spatiotemporal associations between neuroinflammation and gut dysbiosis following SCI, with a focus on the bidirectional modulation exerted by the gut–spinal cord axis on the cascading pathological events initiated by SCI. By integrating multidisciplinary evidence from neuroimmunology, metabolomics, and microbiome research, we aim to deconstruct the multidimensional network through which the gut microbiota influences spinal microenvironmental homeostasis via metabolic–immune–neural circuits. On this basis, we further evaluated the therapeutic potential of microbiota-targeted interventions—such as probiotics and fecal microbiota transplantation (FMT)—in disrupting the vicious cycle of inflammation–regeneration imbalance. This analytical framework not only offers new perspectives for overcoming the limitations of conventional monodimensional therapies but also advances SCI research toward a translational paradigm rooted in multisystem integration.

Inflammatory Responses Following SCI: Local Initiation and Systemic Amplification

Mechanisms Underlying the Local Initiation of Inflammation After SCI

The pathological mechanisms of SCI are complex and generally categorized into primary and secondary injuries.[21,22] Primary injury results from mechanical compression or external forces that cause immediate disruption of spinal cord structures such as axons, blood vessels, and cells. The severity and extent of the primary injury directly influence the prognosis and overall outcome of SCI.[1] As the damage caused by primary injury is often irreversible, current research efforts—both domestically and internationally—are focused primarily on targeting secondary injury.[23] Among the various mechanisms of secondary injury, neuroinflammation plays a central role, and its spatiotemporal dynamics critically shape the microenvironment for neuronal survival.[24]

At the molecular level, neuroinflammation following SCI involves a complex hierarchical regulatory network.[25] Damage-associated molecular patterns (DAMPs), which are released from necrotic cells at the injury site, have been identified as key initiators and accelerators of proinflammatory mediator release.[26] These DAMPs activate TLR signaling pathways, thereby triggering rapid responses from microglia and astrocytes.[27] Activated glial cells secrete proinflammatory cytokines such as IL-1β, TNF-α, and IL-6, along with chemokines such as CCL2 and CXCL1, which collectively recruit peripheral neutrophils and monocytes to the lesion site, initiating a neuroinflammatory cascade.[14] Further studies have shown that a variety of mediators—such as matrix metalloproteinase-8 (MMP-8), cyclooxygenase-2 (COX-2), and interferon-gamma (IFN-γ)—are released in a sequential manner, contributing not only to neuronal apoptosis but also to the remodeling of blood–spinal cord barrier (BSCB) permeability, thereby forming a self–amplifying loop.[28]

Temporally, post-SCI neuroinflammation is typically divided into three phases: acute, subacute, and chronic.[21,29] In humans, the transition from the acute to subacute phase generally occurs within several hours to 48 hours after injury, whereas progression to the chronic phase is expected to take place within six months.[1] In the subacute and chronic stages, neuroinflammatory responses are key contributors to ongoing cell death and tissue degradation, thus constituting a fundamental component of secondary injury.[30] Different types of immune cells are involved at distinct time points in the injury process. Neutrophils, as early responders, are rapidly recruited to the injury site within one hour via the release of the chemokines IL-1β and CXCL1/CXCL2 by activated microglia and astrocytes[31] The infiltration of these cells becomes detectable within three hours, peaks at 1–3 days, and resolves by approximately day seven.[32] These cells exacerbate tissue damage by releasing reactive oxygen species (ROS) and matrix metalloproteinases (MMPs) and further propagate the inflammatory cascade by recruiting peripheral monocytes through proinflammatory signals.[33] By day three postinjury, monocytes infiltrate the lesion and differentiate into macrophages.[34] These monocyte-derived macrophages (MDMs) predominantly exhibit a proinflammatory M1 phenotype and are typically restricted to the first week after SCI. In contrast, microglia serve as the primary source of anti-inflammatory M2 cells.[34] As intrinsic immune cells of the central nervous system, microglia are rapidly activated following injury, reach peak activity between days 3–7, and remain persistently activated for more than 180 days, spanning the entire course from acute to chronic inflammation.[32,35] During the chronic phase of SCI, adaptive immunity becomes increasingly dominant. T-cell subsets, such as Th1 and Th17 cells, participate in the regulation of neuroinflammation. Hyperactivation of Th1 cells has been implicated in the disruption of the BSCB, thereby aggravating demyelinating injury.[36] Concurrently, B cells can initiate systemic autoimmune responses, ultimately leading to the amplification of local inflammation and systemic immune dysregulation.[37] Collectively, the spatiotemporal dynamics of local neuroinflammation, orchestrated by a coordinated interplay of diverse cellular and molecular mediators, drive the progression of secondary injury. This not only shapes the pathological microenvironment at the lesion site but also lays the groundwork for the subsequent propagation of systemic inflammation and involvement of distal organs.

Spatiotemporal Expansion of Systemic Inflammation and Effects on Distant Organs After SCI

SCI is not confined to local neuroinflammation but also induces systemic immune dysregulation and multiorgan dysfunction. The resulting inflammatory cascade exhibits both time-dependent and spatially expansive characteristics.[30] The intensity, extent, and duration of the systemic inflammatory response are closely associated with the severity of the injury. During the acute phase, the levels of proinflammatory cytokines such as IL-1β and TNF-α are rapidly elevated, accompanied by massive infiltration of immune cells, including monocytes/macrophages and microglia.[38] As the injury progresses into the chronic phase (>40 days), persistent activation of inflammatory cells, such as Ly6C^{+} macrophages, can still be detected in cases of severe injury, whereas inflammatory responses tend to subside in mild injuries.[38] Furthermore, spinal cord injury-induced immune depression syndrome (SCI-IDS) is characterized by a profound decline in peripheral immune function in patients with severe SCI. Although this may reduce the risk of autoimmune responses, it significantly increases susceptibility to infections.[39] The sustained state of chronic inflammation not only hampers neural repair but also contributes to distal organ damage, such as neuropathic pain and gastrointestinal dysfunction, thereby forming a vicious cycle of “inflammation–neuroimbalance”.[40]

One of the key mechanisms underlying the systemic dissemination of inflammation is the hemodynamic disturbance caused by SCI. The descending sympathetic vasomotor fibers originating from the spinal cord are disrupted, resulting in diminished sympathetic tone, systemic arterial hypotension, and redistribution of peripheral blood flow.[41] It has been reported that up to 22% of patients with acute SCI develop gastrointestinal bleeding (GIB), which poses a significant risk to both morbidity and mortality.[42] Margo et al[43] described a 21-year-old female with traumatic SCI who died from asymptomatic yet fatal GIB due to autonomic dysfunction, highlighting the high-risk nature of SCI-associated gastrointestinal pathology. In addition to reducing gastrointestinal perfusion and inducing ischemia–reperfusion injury, hemodynamic instability may impair the autonomic regulation of gastrointestinal function.[41] Under normal conditions, gastrointestinal motility and secretion are coregulated by the enteric nervous system (ENS) and the autonomic nervous system (ANS), with the ANS primarily modulating rather than directly controlling ENS activity.[44] Following SCI, disruption of spinal sympathetic axons impairs central signaling, resulting in colonic dysrhythmia, disrupted sensory transmission, and sphincter dyssynergia.[44,45] Moreover, autonomic imbalance exacerbates gastrointestinal dysmotility, manifesting as prolonged intestinal transit time, decreased peristaltic frequency, and vascular tone dysregulation.[46] Consequently, more than 60% of SCI patients experience constipation or fecal incontinence.[47,48] These pathological manifestations are defined as neurogenic bowel dysfunction (NBD), which is clinically classified into upper motor neuron (UMN) and lower motor neuron (LMN) types on the basis of the degree of injury.[49] Both forms involve ENS impairment and persistent intestinal inflammation. Although the ENS possesses intrinsic neuroplasticity in response to physiological stimuli,[50] experimental models have shown that SCI leads to structural atrophy (ie, decreased neuronal density) and functional impairment (ie, reduced intestinal myoelectric activity) of the ENS.[51] These pathological changes result in minimal recovery over long-term follow-up[52] It is hypothesized that SCI-induced systemic imbalances, such as the activation of inflammatory cascades and gut microbial dysbiosis, may alter the local intestinal microenvironment and hinder the regenerative capacity of the ENS.[53,54] This pathological cascade may result in persistent NBD, contributing significantly to increased hospitalization rates and long-term mortality.[55–57]

The traumatic nature of SCI provides a unique therapeutic window for early intervention in NBD. However, current first-line therapies, including laxatives and stool softeners, are poorly effective in the context of SCI and may even worsen fecal incontinence,[58] indicating that symptom-based management fails to address the core pathophysiological mechanisms of the gut–spinal axis. Numerous studies have revealed a strong association between gut microbiota dysbiosis and NBD symptoms in SCI patients. Zhang et al[59] emphasized the disrupted gut microbial ecology in NBD patients and its correlation with prolonged defecation time. Moreover, patients with quadriplegia had significantly longer defecation times than paraplegic patients and healthy individuals did. Yu et al[60] further demonstrated that gut microbiota diversity was significantly lower in patients with complete SCI than in those with incomplete SCI and that reduced microbial diversity was correlated with higher NBD scores. These findings suggest that SCI may aggravate NBD not only by affecting autonomic and ENS function but also by altering the composition of the gut microbiota.

Gut Microbiota Dysbiosis: A Systemic Inflammation Amplifier in SCI

Onset and Dynamic Characteristics of Gut Microbiota Dysbiosis Following SCI

Significant Alterations in Microbiota Composition

The gut microbiota plays a crucial role in maintaining bidirectional communication between the gastrointestinal tract and the central nervous system, as well as in regulating immune responses and metabolic homeostasis.[14] Most current studies investigating gut microbiota alterations in SCI patients utilize fecal samples because of their noninvasive nature and lower risk of cross-contamination than do tissue biopsies.[61] However, even for the same condition, the results across different studies often vary significantly. These discrepancies may stem from factors such as individual variability, sampling techniques, and sequencing depth but also reflect the methodological limitations of the current research. For example, the majority of studies rely on 16S rRNA sequencing, which offers limited taxonomic resolution—typically at the genus level—thus constraining our understanding of the functional changes in the microbiota associated with SCI.[62]

Despite these limitations, numerous clinical and animal studies have consistently demonstrated characteristic alterations in the gut microbiota composition following SCI, with alpha diversity changes receiving particular attention. Some clinical studies have reported significantly reduced Shannon, Chao1, and phylogenetic diversity (PD) indices in patients with complete or incomplete SCI, indicating decreased richness and evenness.[63] However, other studies have reported increased Chao1 and decreased Simpson indices in patients with chronic thoracolumbar or cervical injuries, suggesting increased richness but reduced evenness.[59,64] Some even report higher overall alpha diversity (Chao1, PD, Shannon, and Simpson indices) in SCI patients than in healthy controls.[65] These contradictions may result not only from differences in species abundance estimation methods (eg, OTU clustering bias) but also from variations in the injury stage—acute disruptions may be followed by compensatory microbiota remodeling during the chronic phase.[66] Notably, discrepancies between animal and human studies are further influenced by research design. Rodent models (eg, homogenized female samples under controlled interventions) often show no significant differences in alpha diversity,[49,67–70] whereas human studies (typically male-dominated and confounded by disease duration, medications, and diet) are more likely to reveal heterogeneous patterns, although causality remains unclear owing to the observational nature of these data.[71,72] Although alpha diversity is often regarded as an indicator of gut health,[73] microbiota reconstruction following SCI frequently involves the expansion of proinflammatory bacteria, highlighting that shifts in diversity metrics alone cannot fully reflect ecosystem functional stability.[66]

The gut microbiota composition after SCI is typically evaluated at both the phylum and genus levels.[74] At the phylum level, the dominant taxa include Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia,[75] with Firmicutes and Bacteroidetes together accounting for approximately 90% of total gut bacteria and playing essential roles in intestinal homeostasis.[76] A reduced Firmicutes/Bacteroidetes (F/B) ratio is widely considered a hallmark of dysbiosis and is frequently observed in patients with inflammatory bowel disease (IBD)[77] and similarly reported in patients with SCI.[78] In a cohort study involving 54 Turkish SCI patients, Gungor et al[49] reported significantly reduced Firmicutes abundance compared with that in healthy controls. Kong et al[71] confirmed this trend and reported an increase in Synergistota. Conversely, a Chinese cohort study revealed elevated levels of Proteobacteria and Verrucomicrobia alongside reduced Bacteroidetes in patients with chronic complete SCI.[59] Findings from animal models partly mirror those of human studies. For example, Jing et al[79] reported reduced Firmicutes and increased Bacteroidetes in SCI mice, with Firmicutes abundance inversely correlated with motor recovery. Myers et al[80] reported increased Proteobacteria and elevated systemic inflammation marker CD14 in a C57BL/6 mouse SCI model. At the genus level, although species-specific changes vary among studies, a consistent core pattern emerges: expansion of proinflammatory taxa and loss of anti-inflammatory genera. Multiple studies have reported significant reductions in *Lactobacillus, Allobaculum, Sutterella, Prevotella, Faecalibacterium*, and *Dialister* and enrichment of proinflammatory genera such as *Bacteroides, Blautia, Escherichia-Shigella, Alistipes, Rikenella, Staphylococcus, Anaerotruncus*, and *Mucispirillum*.[49,63,78,81] Notably, host specificity strongly influences the trajectory of certain genera. For example, *Blautia* abundance is elevated in patients with SCI, particularly during the chronic phase,[49,59,64] whereas it tends to decrease in animal models.[79] Similarly, *Bacteroides* is not emphasized in animal studies but is consistently enriched in human SCI cohorts,[59,64] likely reflecting host-specific regulatory effects on the gut microbiome. Differences in microbial shifts may also be shaped by SCI severity, diet, environmental factors, and antibiotic usage.[71] However, most human studies to date are cross-sectional and observational in design, which limits their ability to establish causal relationships between microbiota changes and SCI pathophysiology. Although specific microbial signatures have been associated with injury severity, disease stage, and systemic inflammation, it remains unclear whether these alterations are causative or merely reflective of host responses and confounding variables. To address these challenges, future research should prioritize longitudinal cohort studies and multi-omics integration—including metagenomics, metabolomics, and host immune profiling—to unravel the temporal dynamics and functional relevance of microbiota shifts in SCI.

While current SCI microbiome studies have predominantly focused on bacterial populations, recent work in murine models has demonstrated that the virome also undergoes significant shifts after SCI. Specifically, Du et al[81] applied genome-resolved metagenomic and viromic profiling to SCI mice and observed decreases in phages associated with beneficial commensals and increases in phages linked to potentially pathogenic bacteria. Although direct evidence in human SCI is still lacking, insights from gastrointestinal diseases such as inflammatory bowel syndrome suggest that mycobiome and virome alterations may influence intestinal barrier integrity, immune activation, and microbial composition.[82,83] Future multiomics studies in SCI should therefore aim to include viromic and mycobiomic analyses to better understand gut–CNS interactions across microbial kingdoms.

Time-Dependent Shifts in the Gut Microbiota Post-Injury

The temporal dynamics of gut microbiota dysbiosis following SCI are markedly time dependent, and inconsistencies across studies may stem from variability in sampling time points. Initial alterations appear as early as 3 days postinjury, becoming more pronounced between days 7 and 40.[38,80,84] However, some studies report partial microbiota recovery during the subacute phase, with certain taxa returning to baseline levels.[13,68,69,85] For example, O'Connor et al[67] reported decreased Clostridium abundance and increased IL-1β levels at 8 weeks post-SCI, whereas Jing et al[86] reported increased *Clostridium* abundance at 4 weeks, underscoring the temporal sensitivity of microbiota changes. Doelman et al,[85] using a porcine model, delineated distinct shifts between the acute (0–14 days) and subacute (>14 days) phases, with phyla such as Firmicutes and Spirochaetes exhibiting dynamic changes, indicating that dysbiosis represents an ongoing, adaptive process. Acute-phase changes (3–40 days) tend to stabilize progressively, with an increase in Sutterella potentially linked to heightened inflammation, whereas a decline in Burkholderiaceae in the chronic phase (>41 days) correlates with persistent motor deficits.[85] Although some studies report partial restoration of specific bacterial taxa, the gut microbial ecosystem rarely returns to a preinjury homeostatic state, emphasizing the critical importance of early therapeutic interventions.[87]

Injury Severity–Associated Patterns of Microbial Dysbiosis

The pattern of gut microbiota dysregulation after SCI is influenced by both the anatomical location of the injury (cervical vs thoracolumbar) and the extent of neurological impairment (complete vs incomplete injury), with both factors contributing to microbial community heterogeneity.[88] Among patients categorized as AIS grade A or B by the American Spinal Injury Association, higher abundances of Lactobacillus have been observed, whereas Bacteroides, Faecalibacterium, and Helicobacteraceae were more prevalent in AIS grade C or D patients.[89] A comparative study of complete (CTSCI) and incomplete (ITSCI) injuries revealed nine significantly different genera: Coriobacteriaceae, Synergistetes, Eubacterium, and Cloacibacillus were enriched in CTSCI, whereas Lactobacillaceae, Lachnospiraceae, Eubacterium, Clostridium, and Sutterella were more abundant in ITSCI[60.] Different severities of injury also result in distinct microbial profiles. Zhang et al[59] reported increased Bacteroides abundance in tetraplegia patients and increased Blautia, Porphyromonadaceae, and Lactobacillus abundance in paraplegia patients. Another study revealed reduced Firmicutes at the T10 level and increased Actinobacteria at both T4 and T10.[81] Together, injury severity and progression time jointly shape microbiota dynamics, accounting for interstudy variability. For example, during the early postinjury stages (day 3), the abundance of the orders Bifidobacteriales and Lactobacillales increased, whereas that of Bifidobacterium decreased significantly; by day 13, Akkermansia had nearly disappeared. By day 41, more severe injuries were associated with more pronounced microbiota disruptions.[13]

Mechanisms of Gut Microbiota Dysbiosis Following SCI

The mechanisms underlying gut microbiota dysbiosis following SCI are multifaceted and involve a range of interrelated factors, including disrupted neural regulation, intestinal immune imbalance, compromised epithelial barrier integrity, and prolonged antibiotic use (Figure 2). Collectively, these factors disrupt intestinal homeostasis and ultimately lead to microbial dysbiosis.

Disruption of Central and Enteric Neural Control of Gastrointestinal Function

SCI disrupts supraspinal regulation of sympathetic preganglionic neurons, impairing postganglionic control of gastrointestinal (GI) function and systemic homeostasis.[20] The loss of autonomic neural input compromises gastrointestinal motility, mucus secretion, immune activation, and epithelial barrier integrity, facilitating bacterial translocation and contributing to gut microbial dysbiosis.[49] This may be attributed to damaged sympathetic regulation of the stomach, small intestine, and colon, subsequently leading to imbalances in the ENS.[14] Lefèvre et al[90] reported that in mice with T8 SCI, nitrergic neurons were diminished, and acetylcholine levels decreased, although the proportion of cholinergic neurons remained unchanged. Conversely, White et al[91] reported reductions in both nitrergic and cholinergic neurons in T3 SCI mice. These findings suggest that SCI perturbs intestinal motility and secretion by altering ENS neuronal subtypes. Moreover, prolonged bed rest in SCI patients exacerbates GI dysmotility, impairs mucosal secretion, and compromises immune function, thereby further disrupting the gut microenvironment.[39] This chronic dysfunction not only undermines gastrointestinal physiology but also interacts with microbial dysbiosis to increase infection risk and the immune burden, ultimately impeding patient recovery and quality of life.

Immune Dysregulation in Gut-Associated Lymphoid Tissue (GALT)

Approximately 70–80% of the body's immune cells reside in GALT, which is under sympathetic regulation.[92] SCI disrupts this neural control, destabilizing immune homeostasis within the GALT.[92] Kigerl et al[93] demonstrated increased expression of TNF, IL-10, IL-1β, and TGF-β in mesenteric lymph nodes by day 3 postinjury. Temporal analysis revealed that acute-phase alterations in microbial composition were associated with IL-12-driven Th1 immune responses, whereas chronic-phase changes were linked to IL-1β-associated OTUs (n = 23),[67] indicating the dynamic participation of inflammatory mediators in microbiota remodeling. These findings imply that sympathetic dysregulation following SCI alters GALT reactivity, thereby impacting the gut microbial balance.

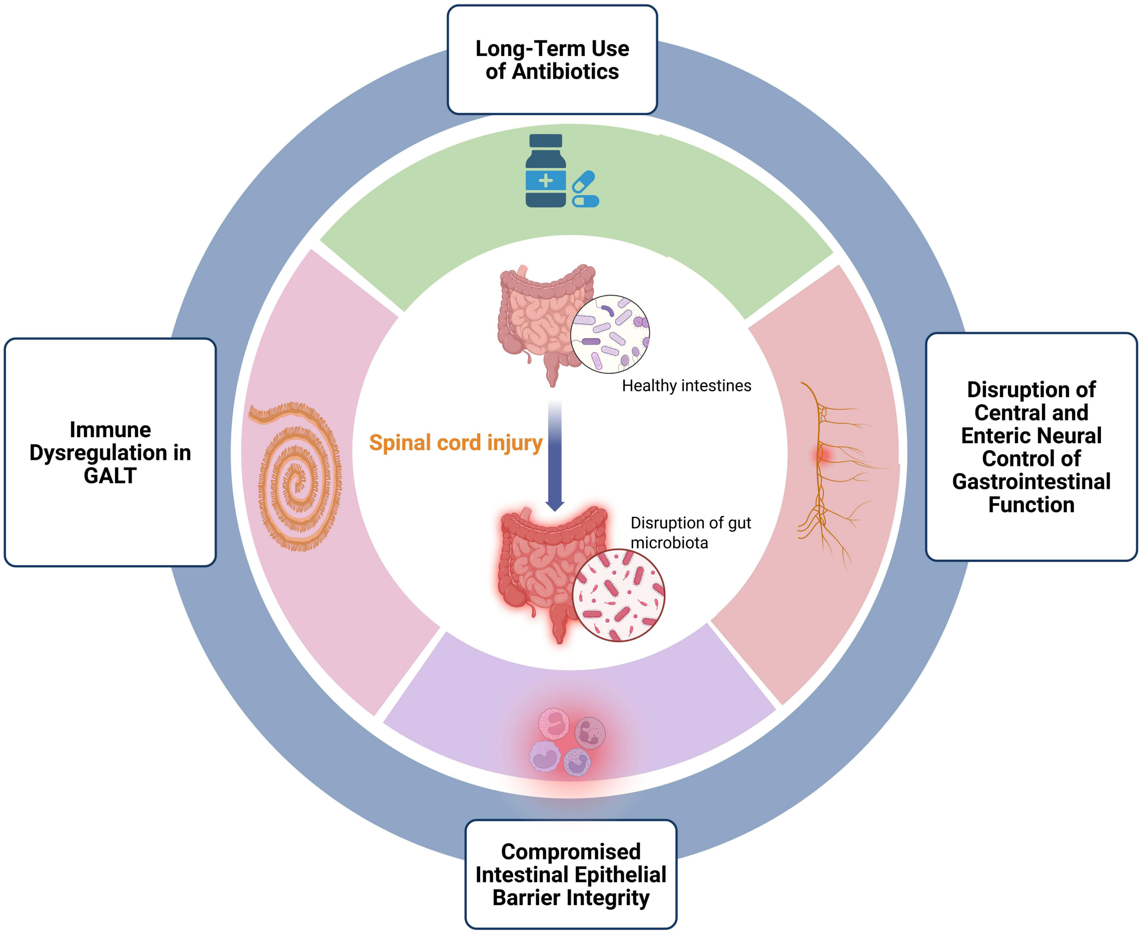

Figure 2 Mechanisms underlying gut microbiota dysbiosis following SCI.

Compromised Intestinal Epithelial Barrier Integrity

The ENS maintains the intestinal barrier by segregating the sterile lamina propria from antigen-rich luminal contents.[94] Tight junctions, comprising claudins, occludins, and members of the TAMP (tight junction-associated MARVEL protein) family, are essential for barrier integrity.[95] Occludin, a key tight junction protein, is downregulated by proinflammatory cytokines such as TNF-α via transcriptional suppression.[96] Barrier dysfunction following SCI has been well reported.[97,98] Jing et al[86] reported reduced expression of zonula occludens-1 (ZO-1), occludin (OCLN), claudin-3 (CLDN3), and claudin-5 (CLDN5) in the colonic tissues of SCI mice, accompanied by increased intestinal permeability. This disruption facilitates the translocation of bacteria and their metabolites into systemic circulation, increasing susceptibility to enterogenic infections and intestinal diseases. SCI-induced barrier impairment also delays locomotor recovery in mice.[93] Notably, FMT was shown to restore occludin expression and reduce TNF-α, NF-κB, and IL-1β levels in colon tissue, suggesting a regulatory role for inflammatory cytokines in barrier function.[99] Additionally, hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis post-SCI increases glucocorticoid release, which further increases intestinal permeability and exacerbates dysbiosis.[100]

Long-Term Use of Antibiotics

Antibiotics are frequently administered after SCI because of their anti-inflammatory and neuroprotective properties.[101] However, accumulating evidence indicates that prolonged antibiotic use exacerbates microbial dysbiosis, which is characterized by increased relative abundances of Firmicutes, Proteus, and Actinobacillus and decreased Bacteroides, ultimately impairing functional recovery.[86,89,102] Furthermore, SCI itself induces autonomic dysfunction, fostering microbial imbalance and immunosuppression, which increases susceptibility to infection.[103] This vulnerability often necessitates repeated antibiotic interventions, establishing a vicious cycle that further disrupts microbial homeostasis.[20] Notably, recent findings suggest a synergistic effect between SCI-induced dysbiosis and antibiotic-mediated microbial depletion, leading to increased variability in microbiota composition.[67]

Gut Microbiota-Mediated Mechanisms Regulating Inflammatory Responses After SCI

Microbiota-Derived Metabolites and Their Signaling Roles in Neuroinflammation After SCI

The gut microbiota exerts profound immunomodulatory effects through the production of various metabolites, which serve as critical signaling mediators in the pathogenesis of neuroinflammation following SCI. Among these, representative classes such as LPS, SCFAs, tryptophan-derived compounds and bile acid have been the most extensively studied. Although these metabolites differ in origin and mode of action, they converge upon key immunological and neuroinflammatory pathways. In this section, we comprehensively review each major class of microbiota-derived metabolites, their signaling mechanisms, and their roles in mediating peripheral and central inflammation after SCI.

LPS–TLR Signaling: A Proinflammatory Axis Amplified by Gram-Negative Bacteria

LPS, a major component of gram-negative bacterial cell walls, is released upon bacterial lysis in the gut.[104] In the context of gastrointestinal dysfunction and compromised intestinal barrier integrity, LPS may translocate across the intestinal epithelium into the systemic circulation, thereby eliciting systemic inflammatory responses.[105] This translocation occurs primarily via paracellular leakage due to tight junction disruption, as well as increased epithelial permeability following microbial dysbiosis, inflammation, and enterocyte apoptosis.[106] Circulating LPS activates innate immune receptors in peripheral tissues, sustaining a systemic proinflammatory state characterized by elevated cytokine production and immune cell infiltration.[107] LPS activates pattern recognition receptors such as TLR4,[108] promoting the systemic translocation of bacterial products and inducing both local and systemic inflammation.[109] While LPS cannot cross the intact blood–brain barrier (BBB), traumatic insults such as SCI increase BBB permeability, allowing LPS infiltration into the CNS, where it activates resident immune cells such as microglia, initiating neuroinflammatory responses.[110,111] MYERS et al[80] demonstrated that SCI leads to expansion of the phylum Proteobacteria—rich in gram-negative species—concomitant with systemic endotoxemia and endoplasmic reticulum stress within the injured spinal cord. These findings highlight that microbial-derived endotoxins influence both peripheral and central inflammation following SCI. In the spinal cord, LPS binds to TLR4 on microglia, activating the MyD88/NF-κB signaling cascade and increasing the levels of proinflammatory cytokines such as TNF-α and IL-1β, thereby exacerbating neuroinflammation and neuronal damage.[112–115] In addition to TLR4, microglia express a wide array of TLRs (1–9), whereas astrocytes express TLR3 under basal conditions and upregulate TLR2 and TLR4 upon activation.[27] LPS-induced TLR4 activation leads not only to NF-κB signaling but also to NLRP3 inflammasome activation and pyroptosis.[116] Dong et al[117] reported that oral administration of curcumin in a TBI model modulated gut microbial diversity, reduced serum LPS levels, and suppressed the TLR4/MyD88/NF-κB pathway, leading to decreased inflammatory cytokine production. These findings support the existence of a pathological gut–LPS–neuroinflammation axis following SCI, wherein microbiota-derived LPS breaches the compromised intestine and BBB to activate neuroimmune responses, thus contributing to the secondary progression of spinal cord pathology.

SCFAs and Multitarget Pathways: Multifaceted Modulators of Neuroinflammation

SCFAs, including acetate, propionate, and butyrate, are microbial fermentation products of dietary fiber and complex carbohydrates.[118] SCFAs not only serve as an energy source for colonic epithelial cells but also act as signaling molecules that confer numerous health benefits.[119] Physiological concentrations of SCFAs are essential for maintaining intestinal and blood–brain barrier integrity, immune homeostasis, and CNS health.[120,121] In SCI patients, a marked reduction in Firmicutes and altered Firmicutes-to-Bacteroidetes ratios are correlated with diminished SCFA production.[89] Acetate, propionate, and butyrate levels are strongly positively correlated with beneficial taxa such as Faecalibacterium, Agathobacter, and Megamonas.[122] SCFAs may cross the intestinal barrier into the circulation and influence CNS cells either directly or indirectly via immune and endocrine signaling.[20,93,123,124]

In germ-free mice colonized with SCFA-producing Clostridium butyricum and Bacteroides thetaiotaomicron, BBB permeability was reduced, and the expression of tight junction proteins in the cortex and hypothalamus was elevated.[125] Similar protective effects extend to the BSCB, where SCFAs—particularly valproic acid—have been shown to increase the expression of tight junction proteins and reduce paracellular leakage following SCI, which helps preserve BSCB integrity and prevents the infiltration of peripheral immune cells into the injured spinal cord.[126,127] These effects are attributable to the direct actions of SCFAs on epithelial and endothelial barriers and neuronal structures, as well as their ability to regulate immune responses.[128] Jing et al[79] demonstrated that FMT from healthy mice into SCI models increased microbial diversity, restored SCFA levels, suppressed NF-κB activation, and improved motor function. Mechanistically, SCFAs act as endogenous inhibitors of histone deacetylases (HDACs), thereby suppressing NF-κB signaling in glial cells and downregulating proinflammatory cytokine expression.[119,129] Among them, sodium butyrate is a potent HDAC inhibitor that directly modulates glial cell states. It reduces microglial activation, promotes anti-inflammatory M2-like polarization, and suppresses astrocytic reactivity, thereby mitigating glial-driven neuroinflammation.[130] Other HDAC inhibitors such as valproic acid have shown similar anti-inflammatory effects, acting through the STAT3/NF-κB axis to suppress microglia-mediated neuroinflammation in SCI models.[126] Similarly, pentanoate-labeled chitosan nanoparticles have been shown to repair the blood–spinal cord barrier and reduce astrocyte activation after SCI,[131] mirroring findings in TBI models.[132] SCFAs also modulate immune responses via G protein–coupled receptor 43 (GPR43), facilitating the differentiation of Th17 cells into Treg cells and mitigating CNS inflammation.[133,134] In animal models, oral SCFA administration promotes anti-inflammatory T-cell phenotypes, enhances Treg-derived IL-10 secretion, and facilitates Treg migration to the lesion site, thereby suppressing neuroinflammation via Treg–γδT cell interactions.[121] Collectively, these findings suggest that SCFAs serve as pivotal mediators in the gut–spinal cord axis and represent potential therapeutic targets for modulating neuroinflammation in SCI.

Tryptophan Metabolites and AHR Signaling: Microbial Pathways in Neuroimmune Regulation

Tryptophan (TRP) is an essential amino acid whose metabolites play critical roles in numerous neurological disorders.[135] TRP is primarily catabolized through the kynurenine pathway (KP), serotonin pathway, and indole pathway, yielding bioactive compounds such as kynurenine (KYN), 5-hydroxytryptamine (5-HT), and various indole derivatives.[136] Gut microbes are indispensable in mediating these metabolic routes.[137] TRP metabolism is enriched among taxa such as Actinobacteria, Firmicutes, Bacteroidetes, Proteobacteria, and Clostridia, with genera such as Clostridium, Burkholderia, Streptomyces, Pseudomonas, and Bacillus exhibiting robust metabolic capacities.[138] Consequently, alterations in the composition of the gut microbiota substantially impact TRP metabolic outputs and associated immune regulatory functions.

In the indole pathway, approximately 4–6% of dietary TRP is converted into indoles (eg, indole-3-acetic acid [IAA] and indole-3-propionic acid [IPA]) by commensal bacteria such as *Escherichia coli*, Bacteroides, and Clostridia via the enzyme tryptophanase (TnaA).[139,140] IPA is synthesized predominantly by Lactobacillus spp. and other members of Firmicutes.[141] Clostridium sporogenes is capable of producing both IAA and IPA via oxidative and reductive routes, processes that are crucial for maintaining intestinal homeostasis and mitigating inflammation.[142] Microbial dysbiosis can disrupt these pathways, thereby exacerbating neuroinflammatory responses. Within the KP, probiotics such as Lactobacillus and Bifidobacterium downregulate the expression of indoleamine 2,3-dioxygenase (IDO), a key enzyme that catalyzes the formation of neurotoxic metabolites, including 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN), thus offering neuroprotection[141,143] For example, Roseburia intestinalis has been reported to effectively suppress the accumulation of KYN and QUIN,[144] whereas species such as Clostridium and Burkholderia promote the conversion of TRP to QUIN.[138,145] This skewed metabolic direction has been closely linked to the pathogenesis of several neurodegenerative and neuropsychiatric disorders, including Alzheimer's disease,[146] major depressive disorder,[147] and Parkinson's disease.[148] Within the 5-HT pathway, Lactobacillus and Bifidobacterium species have been shown to facilitate the conversion of TRP into 5-HT, modulating both central and peripheral serotonergic signaling. They also increase 5-HT synthesis by upregulating the expression of tryptophan hydroxylase 1 (TPH1), a rate-limiting enzyme in 5-HT biosynthesis.[149,150] A reduced abundance of lactic acid bacteria has been associated with decreased plasma and intestinal 5-HT levels.[151,152] Specific strains, such as Lactobacillus plantarum DR7 and Roseburia intestinalis, have been demonstrated to increase TPH1/2 expression and alleviate depression-like behaviors in animal models.[144,153] However, some studies also suggest that the ingestion of certain Lactobacillus strains may lead to reductions in both 5-HT and brain-derived neurotrophic factor (BDNF) levels, indicating that the neuromodulatory effects of these bacteria are likely strain-specific.[154]

In addition to metabolic regulation, tryptophan-derived metabolites also exert potent anti-inflammatory effects via activation of AHR, forming the basis of a "tryptophan–AHR–anti-inflammatory signaling axis". Rothhammer et al[155] reported that TRP metabolites, in concert with type I interferons (IFN-Is), activate AHR in astrocytes, thereby inducing the expression of suppressor of cytokine signaling 2 (SOCS2). SOCS2, in turn, downregulates the NF-κB signaling pathway, effectively dampening neuroinflammation.[150] Notably, SOCS2-deficient mice exhibit exaggerated NF-κB activation upon LPS stimulation, underscoring the essential role of SOCS2 in mediating AHR-dependent anti-inflammatory responses.[156] Thus, the TRP metabolite–AHR–SOCS2–NF-κB signaling cascade not only elucidates the molecular crosstalk between the gut microbiota and its metabolic products and the central immune system but also presents a promising therapeutic target for interventions along the gut–spinal cord axis.[157]

Bile Acid and the FXR/TGR5 Pathways: Microbial Modulators of Neuroimmune Homeostasis

Bile acids, steroid metabolites synthesized in the liver and modified by the gut microbiota, extend their role beyond lipid digestion to crucial immune and inflammatory regulation.[158] Primary bile acids such as cholic acid are transformed by intestinal bacteria into secondary bile acids such as deoxycholic acid and lithocholic acid.[159] The composition of this bile acid pool depends heavily on gut microbial communities, including genera such as Lactobacillus, Clostridium, and Bacteroides, which express bile salt hydrolases and 7α-dehydroxylases that modulate bile acid metabolism and signaling.[160,161] In SCI animal models, gut dysbiosis and bile acid metabolism disturbances occur alongside altered signaling of bile acid receptors—TGR5, a G protein-coupled receptor, and FXR, a nuclear receptor.[162–164] TGR5 activation inhibits spinal microglial and macrophage NF-κB signaling and NLRP3 inflammasome-mediated pyroptosis, reducing secondary inflammation and facilitating recovery.[163] FXR regulates bile acid homeostasis, maintains intestinal barrier integrity, modulates the gut microbiota, and suppresses proinflammatory cytokines, thereby mitigating neuroinflammation and neuropathic pain.[162] Bile acid derivatives such as tauroursodeoxycholic acid (TUDCA) and ursodeoxycholic acid (UDCA) exert neuroprotective effects by activating antioxidant pathways, inhibiting MAPK signaling, and supporting bone marrow mesenchymal stem cell survival and differentiation, which together promote tissue repair and functional recovery in SCI.[165–168] Additionally, bile acids suppress proinflammatory glycolytic pathways (eg, PKM2), further attenuating neuroinflammation.[169] Overall, bile acid metabolism and FXR/TGR5-mediated signaling form a key mechanistic axis linking gut microbiota alterations to central nervous system inflammation via the gut–spinal cord axis.

Systemic Pathway Regulatory Mechanisms: Multilevel Crosstalk Among Metabolic, Neural, and Immune Pathways

The gut–spinal cord axis constitutes a complex bidirectional communication system, primarily orchestrated through neural, immune, and metabolic pathways that enable dynamic regulation between the gut and the CNS.[33] Under physiological conditions, the gut microbiota interacts with the vagus nerve, the intestinal immune system, and host metabolic networks via microbial metabolites, thereby jointly maintaining neurohomeostasis, immune balance, and metabolic assimilation.[170] Following SCI, disruptions in neural regulation, microbial dysbiosis, and compromised intestinal barrier integrity synergistically drive inflammatory cascades and metabolic dysregulation, exacerbating the process of secondary injury.[171] Elucidating the integrative neuroimmune-metabolic mechanisms of this axial system could offer novel insights into SCI pathogenesis and lay the theoretical foundation for microbiota-targeted therapeutic strategies (Figure 3).

Neural Regulatory Mechanisms

The vagus nerve serves as a central conduit for bidirectional communication within the gut–spinal cord axis. Anatomically, it comprises approximately 80% afferent and 20% efferent fibers, enabling direct transmission of information between the gut and CNS.[172] Physiologically, the vagus nerve regulates gastrointestinal motility, peristaltic reflexes, and emptying functions, thereby preserving digestive homeostasis.[173] It is also sensitive to changes in the intestinal environment, as it can detect microbial metabolites such as SCFAs, γ-aminobutyric acid, and 5-HT.[174] These

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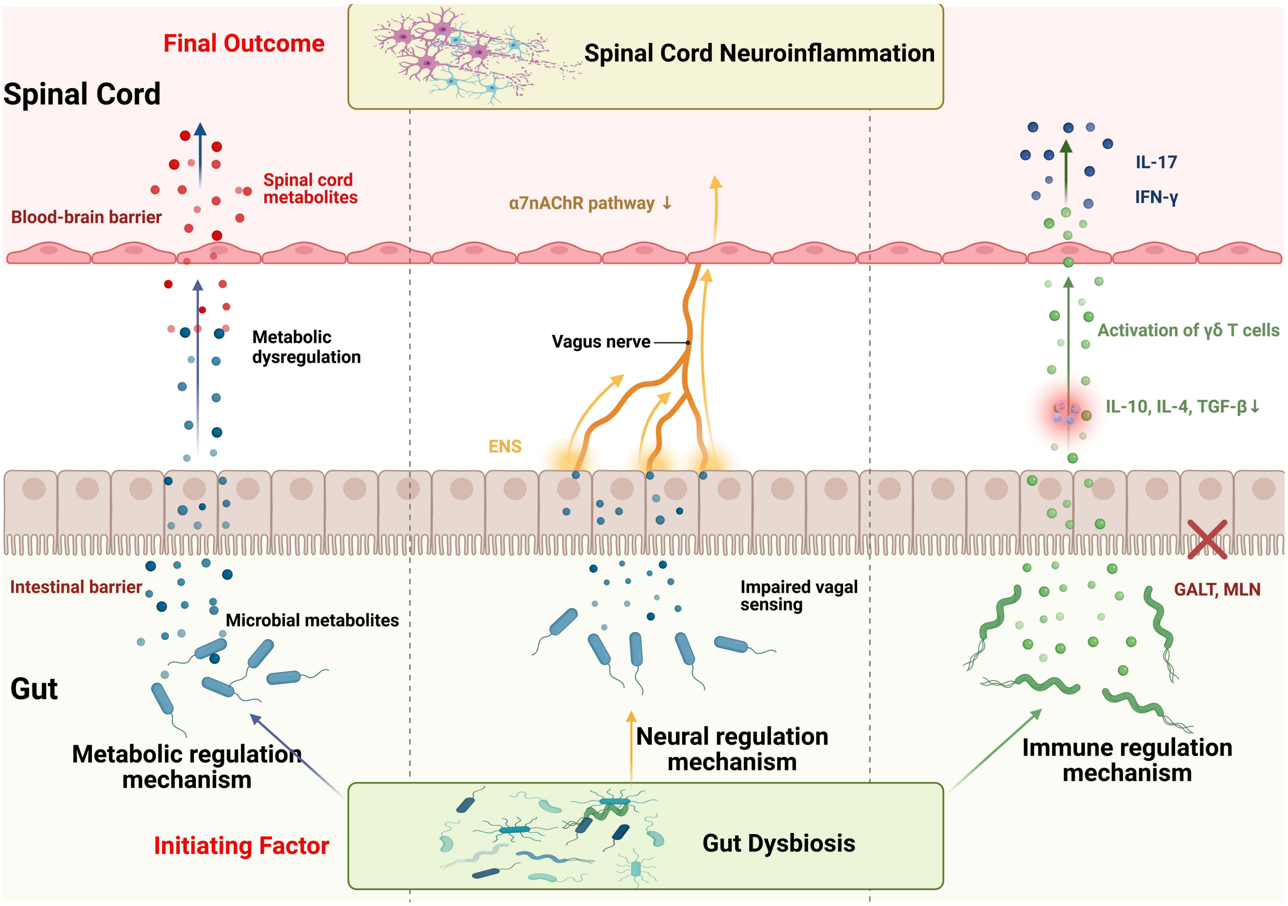

Figure 3 Mechanistic insights into gut microbiota–mediated exacerbation of spinal cord inflammation. Gut dysbiosis acts as an initiating factor that drives pathological changes along the gut–spinal cord axis. Through neural, metabolic, and immune pathways, microbial imbalance disrupts systemic homeostasis and promotes inflammatory responses within the injured spinal cord, ultimately exacerbating neuroinflammation and impeding recovery. Orange arrows indicate neural signaling via the enteric nervous system and vagus nerve; blue arrows represent the transport and effects of microbial metabolites; green arrows indicate immune signaling pathways, including cytokine release and immune cell activation.

Abbreviations: GALT, gut-associated lymphoid tissue; MLN, mesenteric lymph nodes; ENS, enteric nervous system.

metabolites interact with receptors expressed on vagal afferents, including free fatty acid receptors (FFARs) and 5-HT receptors (eg, 5-HT3 and 5-HT4), thereby modulating CNS activity.[175] Notably, SCFAs such as butyrate significantly increase vagal afferent firing frequency, strengthening gut-to-brain signaling.[176] Furthermore, the vagus nerve plays an essential role in immune regulation through the α7 subunit of nicotinic acetylcholine receptors (α7nAChRs), which mediate the cholinergic anti-inflammatory pathway by promoting the shift of M1-polarized Iba-1+/CD86+ microglia to M2-polarized Iba-1+/CD206+ microglia.[177,178] Upon detection of peripheral inflammatory signals by afferent fibers, the dorsal motor nucleus integrates this information and activates efferent cholinergic output, thereby suppressing the release of TNF-α, IL-1β, and IL-6 and limiting systemic inflammation.[178,179] Pathologically, SCI-induced autonomic dysfunction diminishes vagal tone, leading to gastrointestinal dysmotility, increased permeability, and microbial imbalance.[180] Pathogenic metabolites (eg, aberrant α-synuclein) may enter the vagus nerve through a compromised intestinal barrier, initiating CNS inflammatory cascades—a mechanism supported by Parkinson's disease models.[181] Preserving vagal integrity is therefore critical: vagotomy abolishes the anxiolytic effects of probiotics (eg, Bifidobacterium and Lactobacillus) and exacerbates inflammation and endothelial apoptosis after SCI.[179,182] In contrast, vagus nerve stimulation mitigates blood–spinal cord barrier disruption and promotes functional neurological recovery.[183]

In parallel, the ENS—a semi-autonomous network of enteric neurons and glial cells—modulates gut barrier function and mucosal immunity through close interaction with epithelial and immune cells.[184] ENS neurons regulate intestinal permeability by influencing tight junction protein expression, mucus secretion, and epithelial cell turnover.[185] Moreover, they can sense microbial signals and release neuropeptides such as vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP), which exert anti-inflammatory effects locally.[186] Enteric glial cells also contribute to intestinal homeostasis by producing cytokines and neurotrophic factors that influence immune cell behavior and epithelial repair.[187] Disruption of these neuroimmune interactions after SCI may aggravate gut dysbiosis, barrier dysfunction, and systemic inflammatory responses.[53] Overall, neural circuits such as the vagus nerve and ENS function as central integrators of neural, immune, and metabolic signals, playing pivotal roles in maintaining gut–CNS homeostasis and modulating the pathophysiological progression of SCI.

Metabolic Regulatory Mechanisms

The gut microbiota plays a critical role in regulating host energy metabolism and lipid homeostasis, all of which are profoundly disrupted following SCI.[71,188] Patients with paraplegia or quadriplegia often exhibit features of metabolic syndrome, including visceral adiposity and insulin resistance, which are consistent with the metabolic disturbances induced by microbiota transplantation in animal models.[64] Specific alterations in microbial composition are closely associated with these metabolic abnormalities. For example, Yu et al[60] reported that an enrichment of Synergistetes may contribute to increased susceptibility to metabolic dysregulation in CTSCI patients. Synergistetes is an opportunistic bacterial phylum implicated in the pathogenesis of periodontitis and peri-implantitis,[189] and previous studies have shown positive correlations between Synergistetes abundance and cholesterol, nicotinic acid, and selenium intake.[190] Changes in Synergistetes levels, such as increased low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL) cholesterol, may be linked to dysregulated lipid profiles in SCI patients.[191] Conversely, nicotinamide derivatives have demonstrated neuroprotective effects in SCI models [38]. Heller et al[192] and Seelig et al[193] reported that patients with traumatic SCI presented with elevated serum selenium (Se) at admission, followed by a rapid decline within 24 hours. This redistribution of Se may facilitate anti-inflammatory responses and neuronal regeneration, contributing to improved clinical outcomes. Moreover, SCI-associated dysbiosis—characterized by reduced Clostridiales and increased Akkermansia—correlates with metabolic inflammation and aberrant glucose and lipid metabolism. Notably, the role of Akkermansia appears context dependent: while it is typically beneficial in metabolic disorders owing to its low abundance,[194,195] its function in the SCI setting may differ owing to gut environmental adaptations.[196] Additional dysbiosis, such as increased Bifidobacterium and reduced Prevotella, along with altered systemic metabolites (eg, decreased HDL), further supports the notion that the gut microbiota modulates neuroinflammation through complex metabolic pathways.[59,60,64] In summary, microbiota dysregulation following SCI is intricately linked to systemic metabolic alterations, ultimately contributing to the amplification of neuroinflammatory processes.

Immunomodulatory Mechanisms

The gut microbiota plays a pivotal role in maintaining immune homeostasis. As the largest immune organ, GALT comprises approximately 70–80% of the body's immune cells, encompassing both innate and adaptive immune populations.[197] Commensal microbes present antigenic epitopes to immune cells within the GALT via pattern recognition receptors (PRRs), subsequently activating downstream signaling pathways to orchestrate the balance of local and systemic immune responses.[198] Notably, the sympathetic innervation of the GALT positions it as a critical interface for neuroimmune communication. SCI-induced dysregulation of sympathetic tone can disrupt the immunological microenvironment of the GALT, impairing mucosal immune surveillance over the intestinal microbiota.[199] This autonomic dysfunction initiates a vicious cycle of microbial dysbiosis and immune disarray, ultimately compromising host immune defense and leading to increased susceptibility to infections and impaired tissue repair.[103] Rong et al[112] elucidated the molecular basis of microbiota–immune axis disruption in a murine model of SCI. Postinjury dysbiosis was accompanied by the upregulation of proinflammatory cytokines (TNF-α, IL-1β, and IL-6), which was driven primarily by sustained activation of the TLR4/MyD88 signaling cascade. Concurrently, the suppression of anti-inflammatory mediators (IL-4, TGF-β, and IL-10) exacerbates the imbalance of immune regulatory networks. Importantly, SCI-induced gastrointestinal motility disorders further impair microbiota–immune interactions, leading to dysfunction of immune organs such as mesenteric lymph nodes (mLNs). This is characterized by aberrant activation of T and B lymphocytes, which in turn aggravate neuroinflammation and hinder functional recovery.[200] As a key hub for intestinal immune surveillance, the mLN system utilizes dendritic cells (DCs) to continuously sample gut antigens and maintain a delicate equilibrium between immune tolerance and activation under physiological conditions.[201] These findings reveal how localized intestinal immune disruption can propagate systemic inflammation and exacerbate neural tissue damage, providing a rationale for multitargeted therapeutic strategies.

As central modulators of immune homeostasis, the gut microbiota can profoundly influence the differentiation and function of various lymphocyte subsets, including γδ T cells and regulatory T (Treg) cells—both of which play key roles in SCI pathogenesis.[121,202,203] Pang et al[65] reported associations between gut microbial taxa and lymphocyte subsets in SCI patients. Specifically, five bacterial genera—Lachnospiraceae UCG-008, Lachnoclostridium 12, Tyzzerella 3, Trueperella, and Ruminococcaceae UCG-002—were correlated with T lymphocyte subpopulations and NK cells. Additionally, Prevotella 9, Lachnospiraceae NC2004 group, Veillonella, and Sutterella were positively correlated with B cells, whereas Clostridium and Akkermansia were negatively correlated. Moreover, Roseburia and Ruminococcaceae UCG-003 were positively associated with cytokine-induced killer (CIK) cells. These observations underscore the close interdependence between the gut microbial composition and immune cell distribution, where dysbiosis may directly precipitate immune surveillance failure and uncontrolled inflammation.[204,205] Mechanistically, microbial homeostasis is critical for maintaining basophil populations and guiding T-cell differentiation.[206] Certain strains, such as Lactobacillus reuteri, can modulate tryptophan metabolism to induce the generation of $CD4^+CD8\alpha\alpha^+$ double-positive T cells in the intestinal epithelium, thereby reprogramming immunoregulatory pathways and enhancing anti-inflammatory responses.[141,207] While Treg cells are traditionally considered protective through peripheral immunosuppression, their functionality is highly dependent on a dynamically balanced intestinal immune milieu.[208,209] Treg cells can directly influence the activation state of γδ T cells,[210] which are central players in the gut–spinal cord immune axis. Owing to their unique migratory capacity across organ systems, γδ T cells may serve as a crucial link between intestinal and spinal pathophysiology.[121] Neuroinflammation following SCI is largely driven by the proinflammatory cytokine IL-17, which recruits neutrophils and other inflammatory cells to exacerbate tissue damage and neurodegeneration.[211,212] Therapeutically targeting IL-17 signaling—either by inhibiting its production or function—significantly alleviates pathological inflammation and promotes neurofunctional recovery.[213] Activated γδ T cells, as a primary source of IL-17, proliferate and secrete both IL-17 and IFN-γ, thereby amplifying inflammatory cascades.[214–216] The immunopathology of SCI appears to be predominantly fueled by the infiltration of peripheral γδ T cells, as these cells rarely reside in the uninjured CNS, suggesting that peripheral organs—especially the gut—may regulate cross-organ injury responses by circulating immune networks.[217,218] Indeed, analogous to the "gut–brain axis" described in ischemic stroke models,[219] SCI prompts the targeted recruitment of gut-derived γδ T cells to the injury site, a process tightly regulated by the composition of the gut microbiota.[220] The CCL2/CCR2 signaling axis has been identified as a key mechanism mediating γδ T-cell homing to spinal cord lesions, suggesting that the CCL2/CCR2 signaling axis is a promising therapeutic target for SCI.[202] Taken together, these findings not only highlight potential immunotherapeutic strategies for SCI but also emphasize the fundamental role of the gut–spinal cord axis in the immunopathogenesis of neural trauma.

Therapeutic Strategies Targeting the Gut–Spinal Cord Axis

As described above, gut dysbiosis following SCI contributes to the exacerbation of secondary spinal inflammation via multiple pathways. Consequently, modulation of the gut microbiota represents a promising therapeutic avenue to ameliorate the inflammatory microenvironment of the injured spinal cord—an approach termed gut microbial therapy. Current interventions, such as probiotics and FMT, have demonstrated potential in the treatment of SCI (Figure 4).

Probiotics

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer health benefits to the host. When these effects extend to behavior and mental states, such microbes are further classified as "psychobiotics".[10,221,222] Among the most studied genera are Lactobacillus, Bifidobacterium, Streptococcus, Escherichia, Enterococcus, and Clostridium butyricum. Much of the research in this field has focused on the influence of these microbes on the nervous, endocrine, humoral, and immune systems, particularly in the context of anxiety, stress, and depression.[223–225] Through modulation of the gut microbial composition and immune homeostasis, probiotics have been shown to promote host health.[226] In the context of SCI, probiotic administration has been shown to normalize the gut microbial architecture and mitigate the detrimental feedback loop between intestinal barrier damage and central neuroinflammation via bidirectional signaling along the microbiota–CNS axis.[227] Experimental models indicate that certain strains can normalize microbial architecture, repair

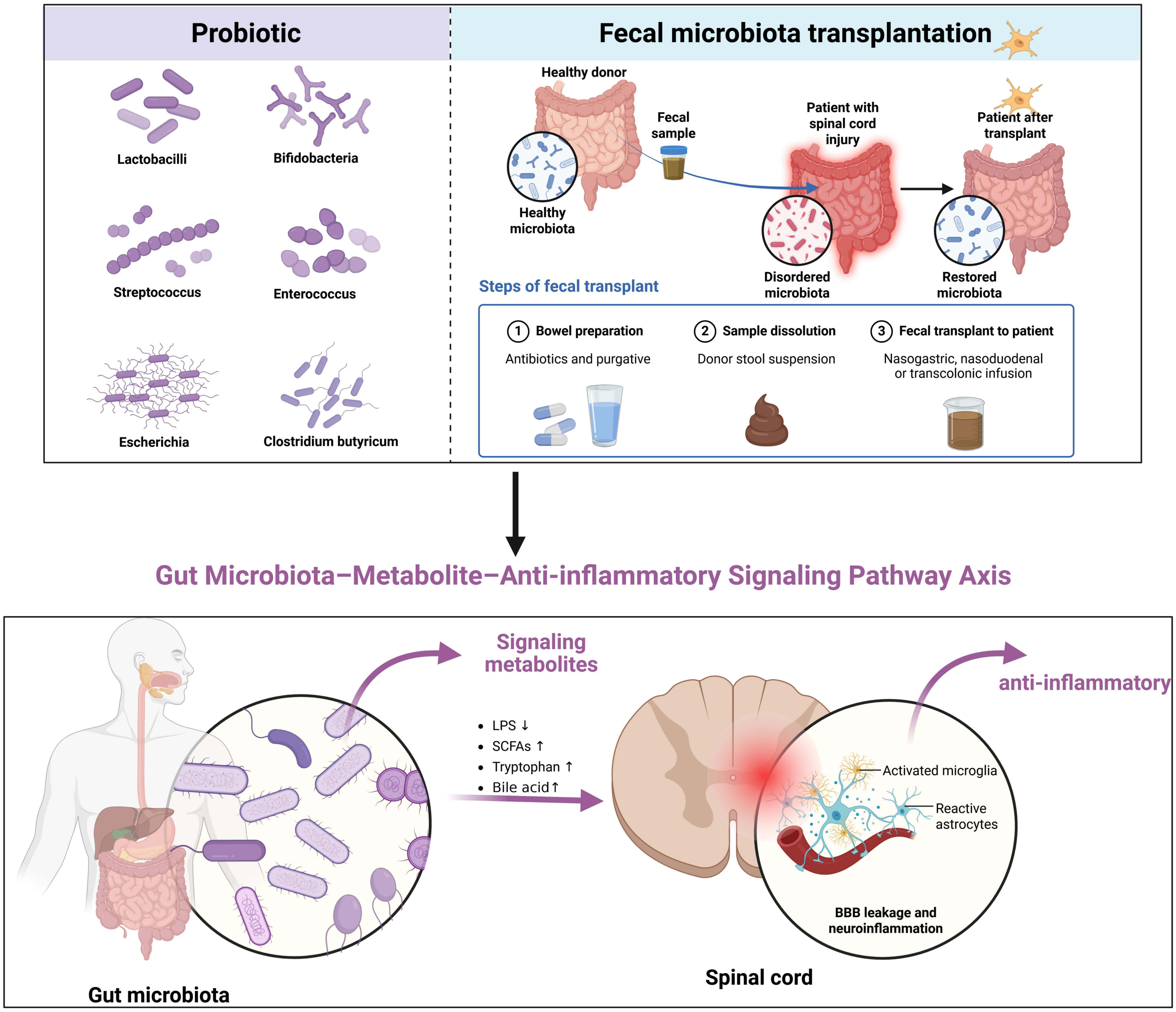

Figure 4 Therapeutic Strategies Targeting the Gut–Spinal Cord Axis. Therapeutic strategies such as probiotic supplementation and FMT aim to restore gut microbial balance and reestablish gut–spinal cord axis homeostasis. By modulating systemic signaling and reducing neuroinflammation, these interventions offer promising avenues for improving outcomes after SCI. Purple arrows illustrate the gut microbiota–metabolite–spinal cord signaling axis, which promotes anti-inflammatory responses in the injured spinal cord.

intestinal barrier integrity, and attenuate central neuroinflammation via bidirectional microbiota–CNS signaling. For example, oral administration of the multistrain formulation VSL#3 (5×10^9 CFU/day for 35 days) improved locomotor coordination, reduced lesion volume, and enhanced myelin preservation in SCI model mice.[93] Similarly, local injection of conditioned medium from Lactobacillus rhamnosus GG (30 mg/kg, post-injury) promoted motor function recovery and microglial M2 polarization, likely through inhibition of the NF-κB pathway.[228] Another strain, Limosilactobacillus reuteri DSM 17938, improved spinal pathology by reducing M1 microglial activation and inflammatory cytokine production, while restoring intestinal barrier function via AhR signaling and tight junction reinforcement.[229] These findings underscore the potential of probiotics not only as microbial modulators but also as immunoregulatory and barrier-protective agents in SCI recovery.

Clinical data further support that such interventions can significantly increase patients' health indices.[230,231] In the ECLISP randomized controlled trial, daily supplementation with Lactobacillus casei Shirota ($\geq 6.5 \times 10^9$ CFU) reduced the incidence of antibiotic-associated diarrhea (AAD) in SCI patients who regularly used proton pump inhibitors, suggesting a protective effect in at-risk populations.[232] However, no overall benefit was observed in unselected patients, and a separate study revealed that a commercial probiotic cocktail failed to improve functional outcomes and even delayed microbiota normalization.[233] These inconsistencies highlight the importance of strain specificity, host conditions, and treatment context. While no major adverse effects have been reported, rigorous evaluation of safety, including donor screening and patient immune status, remains essential.[234] Overall, probiotics represent promising adjuncts in SCI management, but further investigations are needed to refine strain selection, dosage regimens, and clinical applicability.

In addition to live microbial supplementation, prebiotics—nondigestible dietary fibers such as inulin and oat bran—support gut health by selectively promoting the growth of beneficial microbes and enhancing the metabolic activity of commensal bacteria.[235] While they do not directly inhibit pathogenic species, prebiotics improve microbial diversity and contribute to intestinal barrier integrity, indirectly modulating host immunity.[236] Synbiotics, defined as synergistic combinations of probiotics and prebiotics, aim to maximize microbial engraftment and functionality.[237] Although most studies on SCI focus on probiotics alone, early-stage clinical evidence suggests the feasibility and safety of both prebiotic and synbiotic interventions in individuals with SCI.[72] A randomized crossover trial in elite wheelchair athletes with SCI demonstrated the feasibility and safety of both probiotic (3 g/day) and prebiotic (5 g/day oat bran) supplementation over a 4-week period. Although both interventions were well tolerated, probiotics elicited greater reductions in systemic inflammatory markers and improved gut microbiota diversity.[231] These findings suggest that synbiotics, which combine probiotics and their preferred substrates, may offer additive or synergistic benefits by enhancing microbial colonization and immune regulation. Despite encouraging preclinical and pilot data, the therapeutic utility of prebiotics and synbiotics in SCI requires further investigation to clarify strain–substrate compatibility, optimal dosing, and long-term efficacy across diverse patient populations.

Fmt

FMT, an emerging therapeutic strategy, aims to restore the gut microbial balance and reshape metabolite profiles to regulate host immunity and neurological function. It has shown promise across a range of CNS disorders.[238,239] In SCI models, FMT has been shown to reconstruct dysbiotic microbial communities and promote neuronal survival and axonal regeneration. For example, Jing et al[79] demonstrated that probiotic transplantation in SCI mice significantly elevated motor-evoked potential (MEP) amplitudes and increased the expression of NeuN+ neurons, NF-200+ axons, and synaptic proteins, indicating the restoration of neural function. Rodenhouse et al[102] further confirmed that preoperative FMT could prevent post-SCI functional deficits and reverse antibiotic-induced dysbiosis. Mechanistically, FMT appears to modulate the gut–immune–brain axis to ameliorate the chronic inflammatory microenvironment, for example, by suppressing proinflammatory IL-1β/NF-κB signaling and restoring neurotrophic factor expression (eg, BDNF, NT-3, NGF), thereby enhancing synaptic plasticity and neurorepair.[240,241] Moreover, Jing et al[242] reported that FMT inhibited the overactivation of microglia and macrophages in the CNS, promoted their shift toward anti-inflammatory phenotypes, and reduced aberrant astrocyte activation. Additionally, microbial-derived metabolites such as β-alanine were shown to inhibit matrix metalloproteinase-9 (MMP-9) activity, thus preserving the integrity of the blood–spinal cord barrier and mitigating oxidative stress and secondary damage. Notably, FMT has shown therapeutic benefits in a range of CNS diseases, including Parkinson's disease, Alzheimer's disease, stroke, autism spectrum disorders, and multiple sclerosis.[243–248] For example, germ-free mice receiving FMT from Parkinson's disease patients developed motor deficits, whereas healthy donor FMT reduced neuroinflammation and TLR/TNF-α signaling in Parkinson's disease mice, demonstrating a neuroprotective effect.[243,244] In APP/PS1 transgenic mice, FMT improved cognitive function and synaptic plasticity while attenuating neuroinflammation, thereby alleviating Alzheimer's disease-like pathology.[245] In a middle cerebral artery occlusion (MCAO) rat model, FMT reduced infarct volume, alleviated cerebral edema, and lowered blood lipid levels.[247]

Despite these encouraging results, the clinical translation of FMT for SCI remains challenging. One major concern is safety: although most adverse events (eg, abdominal discomfort, bloating) are mild and self-limiting, serious complications such as transmission of multidrug-resistant organisms (eg, drug-resistant Escherichia coli) have been reported, prompting FDA safety alerts.[249–251] Rigorous donor screening and standardized protocols are therefore essential. Encouragingly, a recent study in SCI patients colonized with carbapenemase-producing Enterobacteriaceae or vancomycin-resistant enterococci revealed that FMT achieved decolonization in most cases without adverse effects, supporting its feasibility in high-risk populations.[252] Collectively, these findings provide compelling evidence for the therapeutic potential of FMT in SCI.

Nonetheless, further research is needed to refine treatment protocols, ensure safety, and explore long-term efficacy across diverse patient populations.

Conclusion and Future Perspectives

SCI is a complex neurological disorder characterized by localized neuroinflammation, immune dysregulation, and dysfunction of distal organs. In recent years, the regulatory role of the gut microbiota in SCI has garnered increasing attention. The emerging concept of the "gut–spinal cord axis" offers a novel framework for understanding the pathophysiology of SCI and developing new therapeutic strategies. This review summarizes the dynamic alterations in the gut microbiota following SCI, elaborates on their critical roles in modulating inflammation, promoting neuroregeneration, and maintaining metabolic homeostasis, and explores the underlying mechanisms through which microbiota-derived metabolites—such as LPS, SCFAs and tryptophan metabolites—affect the spinal microenvironment. Additionally, we systematically evaluated microbiota-targeted interventions, including probiotics and FMT, highlighting their therapeutic potential and current progress in SCI recovery. Despite promising preclinical and early clinical evidence supporting the role of gut microbiota modulation in SCI, several key questions remain unresolved. The precise mechanisms of action require further elucidation, and microbial interventions must be optimized and rigorously tested in translational settings to advance precision therapy in SCI.

As research into the gut–spinal cord axis has progressed, the critical influence of the gut microbiota on SCI pathogenesis and recovery has become increasingly evident. However, current investigations face considerable challenges, including interindividual variability in microbial composition, the complexity of microbiota–host interactions, and the need for precise modulation strategies. Future research should prioritize the following areas. First, the integration of multiomics technologies—particularly metagenomics, metabolomics, and transcriptomics—will be essential for comprehensively characterizing the dynamic shifts in the gut microbiota after SCI and unraveling how metabolic–immune–neural networks shape spinal homeostasis. Second, to address limitations associated with existing microbial interventions—such as strain selection, dosage control, and individual variability—synthetic biology and bioengineering approaches could be harnessed to develop next-generation, highly targeted and stable microbiota-based therapies. Moreover, the neuroprotective and immunomodulatory effects of microbiota-derived metabolites, particularly SCFAs and tryptophan catabolites, warrant further investigation. These molecules may serve not only as biomarkers for disease progression and therapeutic response but also as the basis for novel metabolite-based treatment strategies. Finally, translating microbiome-based interventions into clinical practice will require large-scale, longitudinal studies to evaluate long-term efficacy and safety, alongside the application of artificial intelligence and big data analytics to personalize treatment protocols. We suggest that human cohort studies include follow-up durations of at least 12 months to capture stable microbial reconstitution and delayed neurological responses. In conclusion, with the continued convergence of microbiology, neuroscience, and artificial intelligence, microbiota modulation holds promise as an innovative and precise therapeutic approach for SCI. Harnessing this axis may lead to more effective strategies for improving patient outcomes and advancing the field of neuroregenerative medicine.

Consent for publication

All the authors agree with the publication of this work.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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