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Research Progress on Fecal Microbiota Transplantation in Regulating Neuroinflammation and Microglial Activation After Spinal Cord Injury

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Abstract: Spinal cord injury (SCI) causes neurological dysfunction and systemic complications, among which secondary neuroinflammation and gut-related immune alterations have increasingly been recognized as interrelated pathological processes. Beyond the initial mechanical insult, persistent neuroinflammation, microglial activation, disruption of the blood-spinal cord barrier (BSCB), and imbalance of the lesion microenvironment substantially influence neurological recovery and neuropathic pain development. Gut microbiota has recently been incorporated into the mechanistic framework of SCI because injury-induced autonomic dysfunction, bowel impairment, and antibiotic exposure may reshape intestinal microbial ecology. SCI-associated gut dysbiosis may further contribute to intestinal barrier dysfunction, altered microbial metabolite profiles, peripheral immune activation, and central neuroinflammatory responses through the gut-spinal cord axis. Fecal microbiota transplantation (FMT) introduces a complex donor-derived microbial ecosystem into the recipient intestine and aims to restore microbial diversity and functional balance. In preclinical SCI models, FMT has been associated with microbial reconstruction, improved gut barrier integrity, reduced inflammatory signaling, and a more permissive lesion microenvironment. However, the causal relationship among FMT, microbiota-derived metabolites, neuroinflammation, and microglial regulation remains insufficiently defined. This review summarizes current evidence linking FMT, gut microbiota, neuroinflammation, and microglial activation after SCI, with particular emphasis on the potential mechanisms connecting microbial remodeling with central immune regulation.

Keywords: Fecal microbiota transplantation; Spinal cord injury; Gut microbiota; Neuroinflammation; Microglial activation

1. Introduction

Spinal cord injury (SCI) is a highly disabling injury of the central nervous system, commonly caused by traffic accidents, falls from height, sports-related trauma, or violence. Patients may develop varying degrees of motor and sensory dysfunction, as well as neurogenic bladder, neurogenic bowel dysfunction, autonomic dysfunction, chronic pain, and psychological problems. A broad SCI primer describes traumatic SCI as a condition with severe physical and social consequences and limited intrinsic recovery potential [1]. These complications often persist throughout rehabilitation and long-term survival, exerting sustained effects on quality of life, mental health, and social participation. The intrinsic regenerative limitation of spinal cord tissue, together with persistent secondary injury cascades, largely restricts functional recovery after SCI. Therapeutic approaches capable of reshaping the post-injury inflammatory microenvironment are therefore central to current SCI research.

Pathologically, SCI is generally divided into primary and secondary injury. Primary injury is mainly caused by direct mechanical trauma, including spinal cord contusion, compression, hemorrhage, axonal disruption, and immediate death of neurons and glial cells. Secondary injury refers to a series of pathological cascades that gradually develop after the initial insult, including inflammation, oxidative stress, apoptosis, ischemia, hypoxia, BSCB disruption, glial scar formation, and local microenvironment imbalance. Inflammation has been proposed as a major therapeutic target within this secondary injury cascade [2]. Because secondary injury evolves over hours to weeks and involves modifiable inflammatory, vascular, and cellular responses, it represents a more accessible therapeutic window than the initial mechanical insult.

The inflammatory response after SCI is stage-dependent and context-dependent, displaying both debris-clearing and tissue-damaging properties. A moderate inflammatory response contributes to necrotic tissue clearance, repair initiation, and local defense. Persistent or excessive inflammation may aggravate neuronal and oligodendrocyte injury, inhibit axonal regeneration, promote glial scar formation, and impair neurological recovery. Long-lasting inflammation may also participate in abnormal neural network remodeling and neuropathic pain development. Thus, inflammation after SCI should be evaluated in relation to injury stage, cellular composition, inflammatory intensity, and the local microenvironment.

Within this inflammatory network, microglia are central immune cells that deserve particular attention. As resident immune sentinels of the central nervous system, microglia rapidly respond to damage-associated signals released after SCI. Reviews focusing on SCI microglia emphasize their central role in neuroinflammatory modulation and their dynamic interactions with other cells in the lesion environment [3,4]. Activated microglia may contribute to tissue repair by phagocytosing necrotic tissue, clearing myelin debris, and secreting repair-associated factors. Conversely, they may also release pro-inflammatory mediators, including TNF-alpha, IL-1beta, IL-6, and reactive oxygen species, thereby aggravating local inflammation and neuronal injury.

Microglial activation is also relevant to chronic pain after SCI. Evidence from neuropathic pain research indicates that spinal microglia contribute to pain sensitization through neuroimmune signaling [5,6]. For this reason, microglia provide a cellular bridge between SCI-related inflammation and long-term sensory dysfunction. However, their responses should be interpreted as dynamic state transitions rather than fixed pro-inflammatory or anti-inflammatory phenotypes.

Although the initial insult occurs within the spinal cord, SCI rapidly produces systemic consequences, particularly in organs regulated by autonomic pathways. Reduced intestinal motility, defecation disorders, dietary changes, decreased physical activity, and antibiotic exposure may all alter the gut microbial ecosystem after injury. Experimental evidence first demonstrated that gut dysbiosis after SCI can impair recovery and amplify intraspinal pathology [7]. A later review further described gut microbiota as disease-modifying factors after traumatic SCI [8]. Accordingly, gut microbiota have increasingly been regarded as an important link between systemic alterations after SCI and local neuroinflammation.

FMT refers to the transfer of functional microbial communities from healthy donor feces into the recipient intestine to restore intestinal microbial homeostasis. Compared with supplementation with a single probiotic strain, FMT involves more complex reconstruction of microbial communities and may therefore be more suitable for diseases characterized by marked dysbiosis. This review focuses on the relationship among FMT, gut microbiota, neuroinflammation, and microglial activation, aiming to clarify the potential role of microbiota-based interventions in secondary injury modulation after SCI.

2. Neuroinflammation and Microglial Activation After Spinal Cord Injury

2.1 Neuroinflammation as an Important Component of Secondary Injury After SCI

Primary mechanical trauma directly damages neurons, glial cells, vascular endothelial cells, and axonal structures. Local hemorrhage, edema, ischemia, hypoxia, and cell necrosis occur rapidly at the lesion site. As the pathological process progresses, the integrity of the BSCB is disrupted, vascular permeability increases, peripheral immune cells infiltrate the injured area, and the local inflammatory response is further amplified. Inflammatory mediator release, immune cell recruitment, and glial cell activation together constitute an important pathological basis of secondary injury after SCI [2].

Neuroinflammation is not mediated by a single cell type or a single factor. Rather, it is a dynamic process involving microglia, astrocytes, infiltrating macrophages, neutrophils, T cells, and multiple inflammatory mediators. In the early stage of injury, inflammatory responses are mainly associated with necrotic tissue clearance, chemokine release, and immune cell recruitment. When inflammation persists, however, local pro-inflammatory cytokine levels increase, oxidative stress intensifies, neurons and oligodendrocytes undergo further damage, axonal regeneration is inhibited, and glial scars gradually form.

Neuroinflammation after SCI is closely associated with neuropathic pain. Inflammatory mediators released by glial cells and immune cells can alter the excitability of neurons in the spinal dorsal horn and promote sensitization of pain pathways. Chronic pain after SCI has been reviewed as a process involving gut-brain and neuroimmune interactions, which supports the need to connect inflammatory mechanisms with pain outcomes [6]. Thus, neuroinflammation affects not only histological repair and locomotor recovery, but also long-term nociceptive dysfunction.

2.2 The Dual Role of Microglia in SCI

Microglia participate in microenvironmental surveillance, phagocytosis of cellular debris, regulation of synaptic function, and immune defense. Under physiological conditions, they remain in a relatively resting surveillance state and continuously sense changes in the surrounding environment. In the injured spinal cord, damage-associated molecular patterns, inflammatory cytokines, cellular debris, and blood-derived components can all activate microglia. Activated microglia may show enlarged cell bodies, shortened processes, enhanced migratory ability, and increased expression of inflammatory mediators [3,4].

Microglia exhibit a clear dual role during SCI progression. Excessively activated microglia can produce TNF-alpha, IL-1beta, IL-6, reactive oxygen species, and proteases, thereby enhancing local inflammation and causing additional injury to neurons and oligodendrocytes. In contrast, microglia can also participate in tissue repair and microenvironmental stabilization by phagocytosing necrotic tissue and myelin debris and by secreting anti-inflammatory and neurotrophic factors. These findings indicate that the role of microglia is shaped by injury stage and the local microenvironment, rather than remaining fixed throughout disease progression.

Microglia have often been classified into M1 and M2 phenotypes to describe their pro-inflammatory and anti-inflammatory functions. However, microglial states after SCI are far more complex than this binary classification. In the injured spinal cord, microglial responses vary across lesion regions and pathological stages, making static phenotype labels insufficient to describe their functional diversity. Suppressing excessive pro-inflammatory responses while preserving repair-associated functions is therefore a key issue in neuroinflammatory regulation.

2.3 Microglial Activation and Neuropathic Pain

Neuropathic pain after SCI is an important complication that substantially affects quality of life. Its mechanisms involve altered neuronal excitability, synaptic remodeling, spinal dorsal horn sensitization, and glial activation. Spinal microglia are implicated in the establishment and maintenance of neuropathic pain through neuroimmune interactions [5]. Because neuropathic pain is closely related to central sensitization and chronic inflammation, explaining its pathogenesis solely from the perspective of abnormal neuronal excitability is insufficient.

After injury, microglia in the spinal dorsal horn may be activated and enhance neuronal excitability through the release of pro-inflammatory cytokines, chemokines, and neuromodulatory substances. Inflammatory mediators released by microglia can affect synaptic transmission, lower pain thresholds, and promote mechanical allodynia and hyperalgesia. As inflammation persists, abnormal interactions between microglia and neurons may further stabilize central sensitization, transforming pain from an acute response into a chronic pathological state.

From this perspective, microglia not only participate in tissue destruction and repair after SCI, but may also serve as an important cellular target linking neuroinflammation and chronic pain. For FMT, regulation of gut microbiota and microbial metabolites may provide a potential route for influencing microglial activation and SCI-induced neuropathic pain. Studies directly using pain behavior as a major endpoint remain relatively limited, and incorporating pain-related behavioral endpoints would allow a more complete assessment of whether FMT affects not only locomotor recovery but also SCI-associated nociceptive dysfunction.

3. Gut dysbiosis After Spinal Cord Injury and its Immunological Significance

3.1 SCI-induced Alterations in Gut Microbiota Composition

SCI can induce systemic changes across multiple organ systems, especially those under autonomic regulation. Post-injury autonomic dysregulation may impair intestinal motility, disturb defecation rhythm, and contribute to neurogenic bowel dysfunction. Clinical studies have identified altered gut microbiota in patients with SCI, supporting the relevance of intestinal microbial changes in this population [9,10]. Reduced physical activity, dietary changes, antibiotic use during hospitalization, and increased susceptibility to infection may also affect the intestinal microbial ecosystem.

Human and animal studies have reported SCI-associated microbial shifts characterized by reduced abundance of SCFA-producing bacteria and enrichment of taxa linked to inflammatory or mucin-degrading profiles. A rat model study reported microbiota alterations and intestinal inflammation after SCI [11]. In the acute clinical stage, microbiota changes have also been shown to correlate with injury severity [12]. These findings suggest that gut dysbiosis after SCI may not be merely an accompanying phenomenon, but may participate in the pathological process following injury.

Gut dysbiosis may be associated with injury severity, disease course, bowel function, and inflammatory markers after SCI. A systematic review of animal and human evidence concluded that SCI populations show consistent differences in microbiome composition compared with able-bodied controls [13]. Patient-based studies have also reported altered gut microbiota and serum metabolite profiles, while rehabilitation-related evidence suggests that microbial recovery may remain incomplete after SCI [14,15]. However, microbial alterations reported in different studies are not completely consistent. This inconsistency may be related to differences in study populations, injury level, injury severity, sampling time, diet, antibiotic use, and detection methods.

3.2 Intestinal Barrier Dysfunction and Peripheral Immune Responses

The intestinal barrier is essential for maintaining the balance between luminal microorganisms and the host internal environment. Under physiological conditions, the intestinal barrier restricts the entry of luminal bacteria and bacterial components into the circulation while allowing orderly absorption of nutrients and metabolites. In the context of SCI, gut dysbiosis has been linked to intestinal permeability and systemic immune alterations in experimental studies [7]. After SCI, abnormal intestinal motility, local inflammation, and gut dysbiosis may collectively disrupt intestinal barrier integrity, resulting in increased intestinal permeability.

When the intestinal barrier is impaired, bacterial components and metabolites are more likely to enter the circulation. These gut-derived inflammatory signals may activate peripheral immune cells, promote pro-inflammatory cytokine release, and affect central nervous system inflammation through blood circulation or immune signaling. Because the BSCB at the lesion site is often disrupted after SCI, peripheral inflammatory signals may more readily interact with the injured region, thereby aggravating local inflammation.

This gut-derived inflammatory route may help explain how intestinal dysbiosis is translated into immune signals capable of influencing the injured spinal cord. Reviews of gut microbiota and SCI-related immune responses have emphasized the potential involvement of both innate and adaptive immunity in this process [16]. Therefore, when discussing the role of FMT, it should be considered a comprehensive intervention that may simultaneously affect gut microecology, intestinal barrier function, and immune status.

3.3 Microbial Metabolites in Neuroimmune Regulation

Gut microbiota produces a variety of bioactive metabolites, among which SCFAs are among the most extensively studied. Acetate, propionate, and butyrate are mainly produced by bacterial fermentation of dietary fiber. These metabolites help maintain intestinal barrier integrity, regulate immune cell differentiation and inflammatory responses, and may influence the central nervous system through humoral circulation. Host microbiota and SCFAs have been shown to regulate microglial maturation and function in the central nervous system [17].

In the context of SCI, metabolomic evidence indicates that gut microbiota and serum metabolite profiles are altered in patients, suggesting that microbial metabolic function may be involved in post-injury pathology [14]. If dysbiosis reduces SCFA levels, their anti-inflammatory and barrier-protective effects may be weakened, thereby aggravating neuroinflammation. This supports a mechanism in which microbial metabolites act as mediators between intestinal dysbiosis and central immune responses.

In addition to SCFAs, amino acids, bile acids, and tryptophan metabolites may also participate in communication between gut microbiota and neuroimmunity. A broad gut-brain axis review has summarized immune, neural, endocrine, and metabolic communication routes between intestinal microbes and the central nervous system [18]. Future research should therefore move beyond descriptive analysis of microbial composition and focus more on microbial metabolic function and its relationship with neuroinflammation.

3.4 Bridging Mechanisms Between Gut Dysbiosis and Microglial Activation

Gut dysbiosis and microglial activation do not have a simple direct one-to-one relationship. After SCI, alterations in gut microbiota may first affect intestinal barrier integrity and microbial metabolite profiles, subsequently changing peripheral immune responses and circulating inflammatory factors. In the context of BSCB disruption, these peripheral inflammatory signals and metabolic changes may more easily interact with the lesion microenvironment, thereby affecting the inflammatory conditions surrounding microglia.

This framework is important for interpreting the potential role of FMT. If FMT can ameliorate dysbiosis, restore certain beneficial metabolites, protect the intestinal barrier, and reduce peripheral inflammatory input, it may indirectly reduce persistent pro-inflammatory stimulation in the injured spinal cord and thereby attenuate excessive microglial activation. Accordingly, the axis of gut microbiota-intestinal barrier-peripheral immunity-lesion microenvironment-microglial activation may serve as a principal logical framework for discussing the mechanisms of FMT.

4. Application of Fecal Microbiota Transplantation in Spinal Cord Injury

4.1 FMT Reshapes Gut Microbiota After SCI

FMT introduces a complex donor-derived microbial ecosystem into the recipient intestine, with the aim of restoring microbial diversity and functional balance. Unlike supplementation with one or several probiotic strains, FMT attempts to restore the overall balance of intestinal microecology. Microbiota-targeted modulation beyond FMT also supports the modifiability of post-SCI dysbiosis; for example, melatonin treatment alleviated SCI-induced gut dysbiosis in mice [19]. In a rat SCI model, fecal transplant prevented gut dysbiosis and anxiety-like behavior, suggesting that microbial reconstruction may affect both intestinal and behavioral outcomes [20]. Therefore, for complex dysbiosis after SCI, FMT has a certain theoretical advantage.

Relevant studies have shown that after FMT, SCI mice exhibit reshaped gut microbiota, accompanied by improvements in locomotor function, body weight recovery, metabolic status, intestinal barrier integrity, and gastrointestinal motility. FMT improved neurological restoration in a mouse SCI model and was linked to the brain-gut axis in a key preclinical study [21]. Collectively, these observations place microbial reconstruction and metabolite recovery upstream of systemic immune modulation and local neural repair.

The influence of FMT on gut microbiota provides a foundation for mechanistic research, but microbial changes induced by FMT do not mean that the underlying mechanisms are fully clarified. Current research still needs to distinguish which microbial alterations are closely related to functional recovery and which are merely accompanying phenomena. For this review, whether FMT can further influence neuroinflammation and microglial activation through gut microbiota remodeling is a more targeted issue.

4.2 FMT Improves the Lesion Microenvironment

Deterioration of the lesion microenvironment after SCI is an important factor limiting tissue repair. The injured area is often characterized by insufficient vascular perfusion, BSCB disruption, inflammatory cell infiltration, excessive glial responses, and insufficient neurotrophic support. Although gut microbiota are located outside the central nervous system, their potential influence on the lesion microenvironment through immune, metabolic, and barrier-related pathways deserves attention.

FMT has been reported to improve spinal cord tissue preservation, vascular perfusion, pericyte coverage, and BSCB integrity, while also suppressing activation of microglia and astrocytes [22]. These findings extend the role of FMT from improving gut microbiota to modulating the local microenvironment after SCI. This point is particularly important because it suggests that FMT may not act only in the intestine, but may also influence inflammatory conditions at the lesion site through systemic regulation.

Nevertheless, current studies still rely largely on immunofluorescence, inflammatory factor detection, and histological assessment. They do not fully explain which specific bacterial populations or metabolites directly affect microglia. Existing evidence supports an association between FMT and reduced microglial activation, but the complete causal chain remains to be verified. Future research may focus on the relationships among microbial metabolites, peripheral inflammatory factors, BSCB status, and microglial responses.

4.3 Potential Effects of FMT on Functional Recovery

Most FMT-related SCI studies have used locomotor recovery as an important outcome. Common evaluation methods include Basso Mouse Scale scores, footprint analysis, inclined plane tests, electrophysiological assessment, and histological staining. Available evidence suggests that after FMT intervention, animals may show improved locomotor scores, increased neuronal survival, enhanced axonal regeneration, and better tissue preservation, indicating that FMT may create more favorable conditions for functional recovery.

Recent studies have further combined 16S rRNA sequencing, immunofluorescence, and RNA sequencing to show that FMT can restore gut microbial balance in SCI mice, reduce inflammation, promote extracellular matrix remodeling, and establish a more favorable local microenvironment for neural recovery. A recent study reported that FMT promoted functional recovery in mice with SCI by modulating the spinal cord microenvironment [23]. These results suggest that the effects of FMT on SCI involve multi-level interactions among gut microecology, immune inflammation, metabolic status, and local tissue repair.

The translational value of FMT in SCI remains uncertain because most evidence is derived from rodent models, whereas controlled clinical data in SCI patients are still lacking. FMT protocols also differ substantially among studies. Donor source, preparation method, administration route, timing of intervention, duration of treatment, and antibiotic pretreatment may all affect experimental outcomes. Because these factors have not yet been standardized, FMT should currently be described as a potential microbiota-based intervention strategy rather than a mature therapeutic method.

4.4 Boundaries of Current Evidence on FMT

When evaluating the role of FMT, it is necessary to clarify the level and boundaries of existing evidence. Current studies consistently suggest that SCI is associated with gut dysbiosis and that FMT can improve gut microbial structure, intestinal barrier function, and certain neurological function indicators in animal models. Some studies have also observed that FMT reduces inflammatory responses, improves the lesion microenvironment, and is accompanied by decreased glial activation.

However, these results cannot be equated with a fully established causal mechanism. Existing studies have not sufficiently determined which specific bacterial populations, metabolites, or inflammatory pathways determine the protective effects of FMT. Therefore, this review positions FMT as a multi-step microbiota-based intervention rather than a single-target therapeutic strategy. Such positioning is more consistent with the current evidence and helps avoid overinterpretation of the mechanisms underlying FMT.

5. Potential Mechanisms by which FMT Regulates Neuroinflammation and Microglial Activation

Current evidence supports a multi-step model in which FMT-related microbial remodeling may affect neuroinflammation through metabolic, barrier-protective, and immune-regulatory pathways. The initial effect may involve remodeling of gut microbial structure and metabolic function. This may subsequently influence SCFAs and other microbial metabolites, intestinal barrier protection, peripheral immune responses, and inflammatory pathways such as NF-kappaB, ultimately affecting the lesion microenvironment and microglial activation. Because these processes may interact with one another, FMT should not be understood as an intervention targeting a single molecule. Rather, it may represent an integrated strategy that modulates systemic and local inflammatory status through gut microecology.

5.1 Regulation of Microglial Function Through Restoration of SCFAs and Other Microbial Metabolites

Among microbial metabolites, SCFAs provide a plausible mechanistic link between FMT-induced microbial reconstruction and reduced inflammatory activation after SCI. SCI-induced gut dysbiosis has been shown to influence neurological recovery partly through SCFAs [24]. Gut dysbiosis after SCI is often accompanied by a reduction in SCFA-producing bacteria, resulting in decreased levels of acetate, propionate, and butyrate. Based on current evidence, FMT may indirectly attenuate excessive pro-inflammatory microglial activation by restoring SCFA-producing bacteria and increasing SCFA levels.

This mechanism is biologically plausible. Gut microbiota can influence microglial homeostasis through SCFAs, and microbiota-derived SCFAs are known to participate in central immune regulation [17]. FMT-related increases in SCFA levels have also been associated with functional recovery and intestinal barrier improvement in preclinical SCI models [24]. Together, these findings suggest that SCFAs may occupy an intermediate position between microbial remodeling and neuroinflammatory regulation.

However, direct evidence for the complete chain of specific SCFA-specific receptor-microglial state-functional recovery after SCI remains insufficient. Existing studies suggest that SCFAs participate in the protective effects associated with FMT, but they do not prove that these metabolites are the only or decisive mechanism. Therefore, SCFAs should be described as possible mediators of FMT rather than as the sole mechanism.

5.2 Reduction of Peripheral Inflammatory Input Through Intestinal Barrier Protection

Intestinal barrier dysfunction after SCI may allow gut-derived inflammatory signals to enter the circulation, thereby aggravating peripheral immune activation and central neuroinflammation. When intestinal permeability increases, bacterial components and pro-inflammatory metabolites are more likely to enter the bloodstream and trigger systemic inflammatory responses. In the injured spinal cord, where the BSCB is already disrupted, peripheral inflammatory signals may further exacerbate local immune cell activation and glial responses.

FMT may reduce intestinal permeability by reconstructing microbial structure, increasing beneficial bacteria and their metabolites, and improving epithelial tight junctions. FMT-related improvement of intestinal barrier integrity has been reported in a mouse SCI model [21]. After the intestinal barrier is improved, bacterial components and pro-inflammatory metabolites may have fewer opportunities to enter the circulation, which may reduce the transmission of peripheral inflammation to the injured spinal cord.

For microglia, decreased peripheral inflammation may reduce the stimuli that maintain sustained pro-inflammatory activation, thereby favoring a shift of the local spinal cord inflammatory microenvironment toward repair. Intestinal barrier protection is only one possible component of FMT action. It may interact with microbial metabolites, inflammatory pathways, and the lesion microenvironment to jointly influence microglial activation.

5.3 Attenuation of Neuroinflammation Through Regulation of NF-kappaB-related Inflammatory Signaling

NF-kappaB is a classical transcriptional regulatory pathway involved in inflammatory responses. It can regulate the expression of various pro-inflammatory cytokines, chemokines, and inflammation-related enzymes. NF-kappaB signaling has been reviewed as an important pathway in neurological inflammation [25]. After SCI, local injury signals, inflammatory mediators, and cellular stress responses may activate the NF-kappaB pathway, thereby promoting inflammatory mediator release and immune cell activation.

In FMT-related studies, FMT has been found to downregulate NF-kappaB-related inflammatory signals in both the spinal cord and intestine. FMT-mediated improvement in SCI models has been linked to reduced inflammatory signaling and altered microbial metabolism [24]. Mechanistically, FMT may influence intestinal inflammation by restoring microbial balance and improving metabolite profiles. It may also affect local NF-kappaB activation in the spinal cord by reducing peripheral inflammatory input.

However, NF-kappaB is not the only inflammatory pathway involved in SCI. TLR4, MAPK, NLRP3, JAK/STAT, and other signaling pathways may also participate in this process. Therefore, a more appropriate expression is that NF-kappaB may be one of the important molecular links through which FMT-mediated microbiota remodeling regulates neuroinflammation after SCI, rather than the only decisive pathway responsible for FMT effects.

5.4 Influence on Microglial Activation Through Improvement of the Lesion Microenvironment

The regulation of the local lesion microenvironment by FMT may be an important pathway through which it affects microglial activation. After SCI, ischemia, hypoxia, BSCB disruption, inflammatory cell infiltration, and glial responses collectively create an environment unfavorable for neural repair. Microglia within this environment are continuously exposed to injury signals and inflammatory mediators and may therefore remain in a pro-inflammatory activation state.

Studies indicate that FMT may improve vascular perfusion, pericyte coverage, and BSCB integrity, while reducing local inflammation [22]. When the lesion microenvironment improves, microglia may be exposed to fewer pro-inflammatory stimuli, thereby reducing excessive activation. At the same time, increased secretion of neurotrophic factors and improved tissue preservation may provide more favorable conditions for repair in the injured area.

FMT-related metabolomic studies suggest that metabolites other than SCFAs may also participate in modulation of the lesion microenvironment. Supplementation with certain metabolites has been shown to improve neuronal survival and BSCB integrity in experimental SCI research [22]. This suggests that the effects of FMT may not be mediated by a single metabolite, but may involve combined actions of multiple microbiota-derived metabolites.

6. Current Limitations and Future Perspectives

6.1 Direct Evidence for FMT-mediated Regulation of Microglia Remains Insufficient

Current studies indicate that FMT can reduce inflammation and suppress microglial activation, but most evidence remains associative. FMT has been associated with decreased microglial activation, reduced inflammatory factor expression, and improved lesion microenvironment. However, these findings do not fully prove that FMT directly regulates microglia through specific bacterial populations, metabolites, or signaling pathways, thereby improving SCI outcomes.

This limitation is closely related to current research methods. Most studies mainly use immunofluorescence, inflammatory factor detection, behavioral scoring, and histological observation. These methods can reflect overall changes before and after intervention, but they cannot confirm a specific causal chain. Causality could be more rigorously tested by integrating antibiotic depletion, defined bacterial colonization, metabolite supplementation, receptor blockade, and microglia-specific manipulation.

6.2 Microglial Heterogeneity Requires Further Investigation

Many current studies still rely mainly on markers such as Iba1, CD68, TNF-alpha, and IL-1beta to evaluate microglial activation. These indicators can reflect microglial number, activation level, and certain pro-inflammatory features, but they cannot fully characterize the complex functions of microglia at different injury stages. After SCI, microglia and infiltrating macrophages may overlap in morphology and in the expression of some markers [3,4].

Future studies may combine single-cell RNA sequencing, spatial transcriptomics, lineage tracing, and flow cytometry to more accurately distinguish microglia, infiltrating macrophages, and other immune cell populations. These approaches may also clarify the effects of FMT on different microglial subpopulations. For FMT research, it is important to determine whether FMT mainly affects pro-inflammatory microglial states and whether it preserves or enhances repair-associated responses.

6.3 FMT Protocols Remain Non-standardized

Current animal studies of FMT in SCI differ in donor source, preparation method, administration route, timing of intervention, duration of treatment, and the use of antibiotic pretreatment. The main FMT studies in SCI have used different animal models, transplantation schedules, and outcome measures [20,23]. Donor microbial composition, recipient baseline microbiota, and pretreatment strategies may all influence intervention effects. Because of these differences, comparability among studies is limited.

The lack of standardized FMT protocols also affects clinical translation. Patients with SCI often have infections, antibiotic exposure, altered nutritional status, bowel dysfunction, and long-term immobility, all of which may influence recipient microbial engraftment and intervention safety. Therefore, future research needs to establish more standardized FMT protocols and systematically evaluate safety, efficacy, and optimal intervention windows.

6.4 Research on Neuropathic Pain Remains Insufficient

Although the role of microglia in neuropathic pain has received considerable attention, current FMT-related SCI studies mainly focus on locomotor recovery, tissue protection, and changes in inflammatory factors. Studies directly assessing pain behavior are relatively limited. For spinal surgery and SCI rehabilitation, neuropathic pain after SCI is a major clinical issue. Pain not only affects adherence to rehabilitation training, but may also worsen sleep disturbance, anxiety, and depression [5,6].

Mechanistically, microglial activation is closely associated with neuropathic pain, and gut microbiota and their metabolites may influence microglial status. Therefore, whether FMT can affect mechanical allodynia, thermal hyperalgesia, and central sensitization by regulating gut microbiota, SCFAs, and microglial activation warrants further investigation. If future studies combine pain behavioral assessment, inflammatory markers, microglial responses, and microbial metabolite changes, they may provide a more comprehensive evaluation of the potential value of FMT in managing pain after SCI.

6.5 Clinical Translational Evidence Remains Limited

Clinical observational studies on gut dysbiosis after SCI have gradually increased, but direct clinical studies evaluating FMT in patients with SCI remain scarce. Existing clinical and experimental evidence primarily indicates that SCI is associated with altered microbial composition, metabolic abnormalities, and bowel dysfunction [9,15]. It does not directly prove that FMT can improve neurological function or pain outcomes in patients. Therefore, in clinical application, FMT should still be regarded as a promising but unverified microbiota-based intervention strategy.

Patients with SCI are highly heterogeneous. They differ in injury level, injury severity, disease course, nutritional status, infection history, antibiotic exposure, and bowel function. These factors may influence both the efficacy and safety of FMT. In addition, donor screening, infection risk, microbial stability, treatment duration, and long-term follow-up must be carefully evaluated before clinical translation.

7. Conclusion

Neuroinflammation and microglial activation after SCI are important mechanisms involved in secondary injury progression and limited functional recovery. Neuroinflammation participates in tissue clearance and repair initiation after injury, but persistent or excessive inflammation may aggravate neuronal injury, inhibit axonal regeneration, and contribute to neuropathic pain. As resident immune cells of the central nervous system, microglia play a key role in this process, and their response states are dynamic and complex. Regulating excessive pro-inflammatory microglial activation while preserving repair-associated functions is an important direction for intervention in neuroinflammation after SCI.

SCI can induce gut dysbiosis, intestinal barrier dysfunction, and alterations in microbial metabolites. These changes may affect peripheral immune responses and central neuroinflammation through the gut-spinal cord axis. FMT has shown potential in animal models of SCI by improving neurological function, protecting the intestinal barrier, regulating SCFA levels, reducing inflammation, and improving the lesion microenvironment. Based on current evidence, FMT may participate in neuroinflammatory regulation after SCI through a multi-step mechanism involving gut microbiota remodeling, restoration of microbial metabolites, intestinal barrier protection, reduction of peripheral inflammatory input, modulation of NF-kappaB-related inflammatory pathways, and attenuation of microglial activation.

Nevertheless, current research remains mainly preclinical. The direct causal relationship between FMT and microglial regulation has not yet been fully established, and studies on neuropathic pain outcomes remain limited. Future research should integrate multi-omics technologies, cell-specific interventions, and standardized FMT protocols to further clarify the mechanisms by which FMT regulates neuroinflammation and microglial activation after SCI. As the evidence chain becomes more complete, gut microbiota-based intervention strategies may provide new directions for controlling secondary injury, regulating neuroinflammation, and improving long-term outcomes after SCI.

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