Journal of Inflammation Research Dovepress

Open Access Full Text Article REVIEW

Unveiling the Gut-Disc Axis: How Microbiome Dysbiosis Accelerates Intervertebral Disc Degeneration

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Abstract: The gut microbiome (GM), often referred to as the second genome of the human body, plays a crucial role in various metabolic processes and mediates the development of numerous diseases. Intervertebral disc degeneration (IDD) is an age-related degenerative spinal disease characterized by the loss of disc height, hydration, and integrity, leading to pain and reduced mobility. Although the pathogenesis of IDD is not fully understood, recent studies suggest that dysbiosis of the gut microbiome may accelerate the progression of IDD through multiple mechanisms. This article begins by discussing the potential relationship between GM dysbiosis and human diseases, followed by a comprehensive review of the regulatory mechanisms of GM in skeletal diseases within the gut-disc axis framework. Furthermore, it explores three potential pathways through which GM dysbiosis may mediate the development of IDD: immunomodulation, bacterial translocation and colonization, and the decomposition and absorption of intestinal metabolites. These pathways can disrupt disc cell homeostasis and promote degenerative changes. Finally, this paper summarizes for the first time the potential therapeutic approaches for delaying IDD by targeting the gut-disc axis, providing new insights into the pathogenesis and regenerative repair strategies for IDD.

Keywords: intervertebral disc degeneration, microbiome, inflammation, immunity, metabolism

Intervertebral disc degeneration (IDD) is a complex pathological process involving multiple factors, including genetics, obesity, age, and lifestyle. It is primarily characterized by the loss of water content in the disc tissue, reduced elasticity, decreased height, and diminished ability to respond to mechanical loads.[1,2]

The human gut microbiome (GM) is a dynamic and complex ecosystem composed of countless microorganisms interacting with the human host.[3,4] The GM, being the largest micro-ecosystem in the human body, plays a crucial role in maintaining normal physiological functions and metabolic balance. Dysbiosis of the GM, characterized by the overgrowth of pathogenic bacteria, is a micro-ecological imbalance associated with various diseases, including neurological disorders, cancer, and autoimmune diseases.[5] However, the potential influence of this micro-ecological imbalance on IDD is still unclear. Therefore, this review provides a comprehensive narrative summary of the mechanisms by which GM regulates human diseases and explores potential ways in which GM influences IDD from various perspectives. Additionally, it provides the first summary of the latest research on targeting the gut-disc axis for the prevention and treatment of IDD, offering valuable insights into the association between spinal degenerative diseases and GM.

Overview of GM and Human Diseases

The gut microbiome (GM) plays a crucial role in maintaining host health through multiple pathways, including nutrient absorption, energy metabolism, and immune regulation. When the balance of GM becomes disrupted, both its structure and function become disordered, leading to the accumulation of dysregulated metabolic products that can influence the development of various diseases.[6,7] Recent advancements in molecular biology, genomics, and large-scale parallel

Received: 20 July 2024
Accepted: 26 October 2024
Published: 5 November 2024

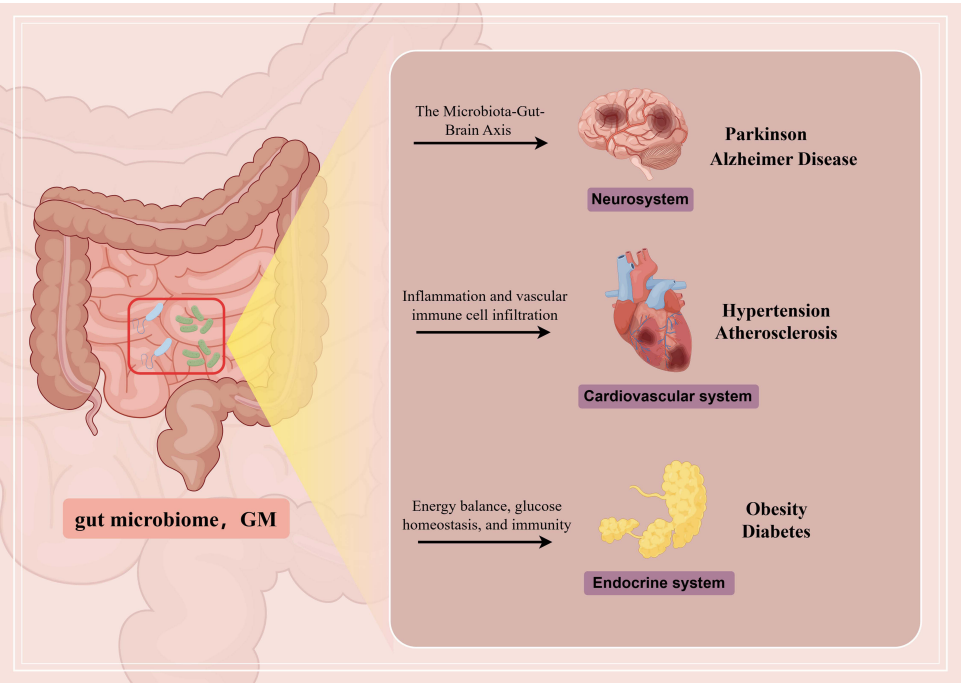

Figure 1 Overview of GM and Human Diseases. GM influences the development of neurological, cardiovascular, and endocrine diseases through multiple pathways.

sequencing technologies have expanded our understanding of GM dysbiosis and its impacts. These imbalances not only disturb the intestinal environment but also mediate the progression of diseases across multiple systems, including the nervous, cardiovascular, and endocrine systems (as illustrated in Figure 1).

In cardiovascular diseases (CVD), for instance, GM dysbiosis contributes to conditions like hypertension and atherosclerosis (ACVD) by influencing inflammation and vascular function through its metabolites. Hypertensive patients exhibit reduced GM diversity and abundance, with an increased Firmicutes/Bacteroidetes ratio.[8] Studies have shown that they have significantly lower abundances of beneficial groups like Roseburia and Faecalibacterium, while pathogenic groups such as Enterobacteriaceae and Streptococcus are elevated.[9,10] In ACVD, patients also demonstrate increased levels of Collinsella and Intestinimonas, contributing to disease progression.[11] Similarly, in nervous system diseases like Parkinson's disease (PD) and Alzheimer's disease (AD), alterations in GM composition are closely linked to disease progression. In PD, increased abundances of Ruminococcaceae and Clostridium XIVa correlate with motor symptoms, while cognitive impairment is associated with changes in Butyricicoccus and Clostridium XIVa.[12,13] In AD patients, the abundances of anti-inflammatory bacteria such as Eubacterium rectale, Bacteroides fragilis, and Faecalibacterium are significantly decreased, while pro-inflammatory genera like Escherichia and Shigella are increased.[14,15] Additionally, AD patients show a lower abundance of Firmicutes and Actinobacteria, with a rise in Bacteroidetes.[16] Endocrine system diseases, including obesity and type 2 diabetes mellitus (T2DM), are also characterized by GM dysbiosis. Obesity is marked by decreased levels of Akkermansia muciniphila, Faecalibacterium prausnitzii, and Bacteroides, while the abundance of Firmicutes is significantly increased.[17,18] In T2DM, patients exhibit reduced gut microbiome diversity and an elevated Firmicutes/Bacteroidetes ratio, along with higher levels of Proteobacteria compared to healthy individuals.[19,20] Understanding these GM shifts provides insights into the mechanisms underlying these multi-system diseases and presents potential avenues for novel therapeutic strategies.

Overview of GM and Bone Diseases

Under normal circumstances, a balanced GM abundance ratio efficiently regulates human metabolism and immune status. Recently, more scholars have proposed the microbiota-gut-bone axis concept to elucidate the complex relationship between gut microbiota and bone diseases.[21,22] Building on this, Rajasekaran et al comprehensively evaluated the microbial composition of intervertebral discs (IVDs) and reported differences between the microbiota of normal and

degenerated IVDs.[23] This led to the gut-disc axis concept, indicating that GM may play a crucial regulatory role in IDD.[24] This section presents an overview of the gut-bone axis and gut-disc axis concepts. Furthermore, it reviews the potential relationship between GM and bone and intervertebral disc tissue, providing insights into GM's role in bone diseases."

Gut-Bone Axis

Bone tissue, as a metabolically active organ of the human body, undergoes bone matrix formation, mineralization, and resorption throughout the entire bone remodeling process.[25,26] This process is tightly regulated by the interaction between osteoblasts and osteoclasts, through direct cell contact or communication via secreted proteins, to regulate cell survival, differentiation, and apoptosis, which is crucial for maintaining bone homeostasis.[27] The development of osteoporosis and osteoproliferative diseases involves immune-inflammatory regulatory mechanisms.[28,29] The gut microbiome (GM) appears to play a role in this context, as it is thought to influence immunity and inflammation—key components of osteoimmunology. For instance, the GM is hypothesized to regulate cytokine secretion during metabolic processes, potentially through the production of short-chain fatty acids and other metabolites. This regulation may stimulate inflammation-mediated bone formation, although the direct association between GM-related cytokine release and disc degeneration remains to be fully established.[30,31] It has been proposed that GM may secrete neurotransmitters that could activate the immune system, potentially leading to increased circulating osteoclast cytokines via T-cell-dependent mechanisms.[32] However, it is important to note that these connections are still under investigation and may not indicate a causal relationship. Additionally, several gut hormones are involved in bone remodeling. After nutrient intake through food, intestinal endocrine cells secrete gut hormones that regulate glucose homeostasis and participate in energy requirements during bone remodeling.[33] For example, gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), which are primarily secreted by enteroendocrine cells, are thought to stimulate insulin secretion, potentially promoting insulin-mediated bone formation.[34] Preclinical studies indicate that GIP receptor knockout mice exhibit significant decreases in bone mineral density (BMD) and bone strength, along with reductions in markers of bone formation such as alkaline phosphatase and osteocalcin.[35] In summary, while the gut microbiome may influence the development of bone diseases through mechanisms such as nutrient absorption, inflammation, and immune regulation, the precise nature of these interactions, particularly their causal relationships, requires further investigation. A more nuanced understanding of the gut-bone axis may provide insights into potential strategies for preventing and treating bone diseases.

The Gut-Disc Axis

IVDs are avascular structures made of fibrocartilage, comprising three components: the central gelatinous nucleus pulposus, the outer fibrous annulus, and the upper and lower cartilaginous endplates. This structure separates vertebral bodies, transmits loads, and provides flexibility and effective stress support to the spine.[36,37] Normally, IVDs are regarded as immune-privileged tissues lacking immune cells. The cells within, including CEP, NP, and AF, have been demonstrated to exhibit classical expression and markers of immune cells.[38] However, the hypoxic environment and loss of immune barrier function in IVDs create conditions for anaerobic bacteria growth in degenerated IVDs. These bacteria produce large amounts of inflammatory factors, recruiting more inflammatory cells such as T cells, B cells, dendritic cells, and macrophages.[39] This results in degenerated IVDs becoming ideal environments for microbial growth, proliferation, and metabolic product accumulation. Here, we explore three potential mechanisms through which gut microbiota dysbiosis accelerates IDD.

Immunomodulation

As mentioned above, the development of IDD have been proven to be associated with the abnormal induction of pro-inflammatory factor secretion by IVD cells and immune cells. These molecules trigger pathogenic and inflammatory responses in IVDs, potentially activating apoptosis, senescence, and autophagy.[40,41] GM and the human immune system interact with each other. The types, abundance, and metabolites of GM regulate immune homeostasis and influence many immune-related diseases.[42] Research has shown that in germ-free mouse models, the absence of GM results in decreased

immune signaling, an imbalanced T(H)1/T(H)2 ratio, and systemic T cell deficiencies compared to mice colonized with the gut bacterium Bacteroides fragilis.[43] Additionally, as a defense mechanism, intestinal epithelial cells produce a mucosal barrier that separates the microbiota from host immune cells, thereby reducing intestinal mucosal permeability.[44] However, GM dysbiosis weakens the epithelial barrier, increasing permeability and contact between GM and the intestinal mucosal immune barrier, leading to an imbalance of potential pathogens.[45] This excessive contact leads to an influx of activated immune cells and inflammatory cytokines, which migrate and accumulate near the IVDs via the bloodstream, thereby regulating bone metabolism and inducing the occurrence and development of IDD.[39] Similarly, immune cells stimulate IVD cells to produce neurogenic factors such as neurotrophin-3 (NT-3), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF), inducing the formation of nociceptive nerve fibers in the dorsal root ganglion (DRG).[46] On the other hand, the persistent inflammatory environment in the degenerating IVD increases the expression of pain-related cation channels in the DRG, mediated by immune responses.[47] Both are common causes of IDD-related low back pain. Therefore, GM dysbiosis may influence IDD development by affecting immune function in three proposed ways. Firstly, GM dysbiosis increases epithelial barrier permeability, allowing activated immune cells to migrate and accumulate near the IVDs via the bloodstream, regulating bone metabolism and inducing IDD. Secondly, the migration of immune cells into the IVDs stimulates IVD cells to produce neurogenic factors, leading to the emergence of nociceptive nerve fibers. Finally, the chronic inflammatory environment in IVDs increases the expression of pain-related cation channels, mediated by immune cells, contributing to IDD-associated low back pain.

Bacterial Translocation and Colonization

Recent studies have shown that inflammatory infiltration resulting from GM dysbiosis is a crucial factor in triggering bone and joint diseases such as osteoporosis and rheumatoid arthritis.[48,49] Therefore, we hypothesize that chronic inflammation caused by GM imbalance may be an important factor in the occurrence and development of IDD. Below, we focus on the potential links among GM, inflammation, and IDD, while emphasizing the possible mechanism mediated by bacterial translocation and colonization.

As stated above, the protective effect of the blood-disc barrier renders healthy IVDs as immune-privileged tissues, effectively preventing the influence of other potential inflammations. However, this also impedes immune surveillance within the IVDs, preventing immune cells from promptly responding to microenvironment changes.[40] Therefore, we propose that the lack of immune surveillance in the IVDs is a precondition for inducing IDD, and the inflammatory response triggered by anaerobic bacterial invasion within the IVDs is a critical factor in IDD. The interaction between these two factors jointly influences the occurrence and development of IDD.

Translocation and colonization of bacteria might mediate the development of IDD in three ways. On the one hand, chronic intestinal inflammatory changes caused by GM dysbiosis can increase intestinal permeability, promoting bacteria to penetrate the epithelial barrier and enter the bloodstream.[50,51] Although most translocated bacteria are eradicated by the immune system, a few can survive the immune response, reaching the vicinity of the IVDs through the bloodstream, colonizing, and releasing pro-inflammatory factors that stimulate vascular proliferation into the IVDs, thereby disrupting their anaerobic environment. On the other hand, abnormal mechanical stress and sustained axial loading can also cause irreversible microdamage to the IVDs.[52] This creates an ideal environment for bacterial growth and proliferation. Bacteria evading immune responses via the gut can enter the IVDs, with their pro-inflammatory factors and harmful metabolites further accelerating IDD progression. Lastly, bacteria entering through damaged IVDs can stimulate IVD cells to secrete inflammatory factors, affecting the balance of cellular synthesis and catabolism, leading to a cascade of reactions that promote chemokine production, ultimately accelerating collagen and proteoglycan inactivation within the IVDs and inducing Extracellular matrix (ECM) degradation.[46]

Decomposition and Absorption of Intestinal Metabolites

Under physiological conditions, intestinal epithelial mucus forms a robust physical barrier preventing pathogens from invading the intestine. Short-chain fatty acids (SCFAs), also known as volatile fatty acids, are organic fatty acids produced by the fermentation of carbohydrates by GM, with various physiological functions including energy provision,

intestinal mucosal protection, metabolic regulation, and immune modulation.[53] The colon is the primary site for SCFA production, mainly from the fermentation of undigested carbohydrates by anaerobic bacteria. Studies have demonstrated that SCFAs are essential metabolites produced by GM.[54,55] The process of IDD is accompanied by vertebral bone remodeling, including endplate thickening and osteophyte formation. Similarly, IVD calcification is associated with the metabolic imbalance of osteoblasts and osteoclasts. Research shows that SCFAs promote the differentiation of immature CD4+ cells into regulatory T cells (Tregs), which preferentially reside on the bone endosteal surface.[56] Furthermore, calcium deposition within IVDs and the expression of the extracellular calcium-sensing receptor (CaSR) are closely related to G-protein-coupled receptors in degenerated IVDs. SCFAs can inhibit bone resorption or osteoclast formation by activating G-protein-coupled receptors (GPCR) or inhibiting histone deacetylases (HDAC).[57] This suggests that SCFAs derived from the gut may diffuse into the IVDs and accelerate the processes of calcification and IDD. Therefore, we believe SCFAs, key metabolites from GM, may play a crucial role in mediating IDD by affecting bone metabolic balance, inducing IVD calcification, and vertebral bone remodeling.

In conclusion, GM dysbiosis mediated by the gut-disc axis can accelerate IDD progression through immune regulation, bacterial translocation and colonization, and intestinal metabolite breakdown and absorption. This provides a reference for the prevention and treatment of IDD centered around GM. However, these three potential mechanisms are based solely on a comparative analysis of various literature sources, and their validity and feasibility require further verification through in-depth animal experiments. Figure 2 illustrates the brief mechanism of action between GM and IDD.

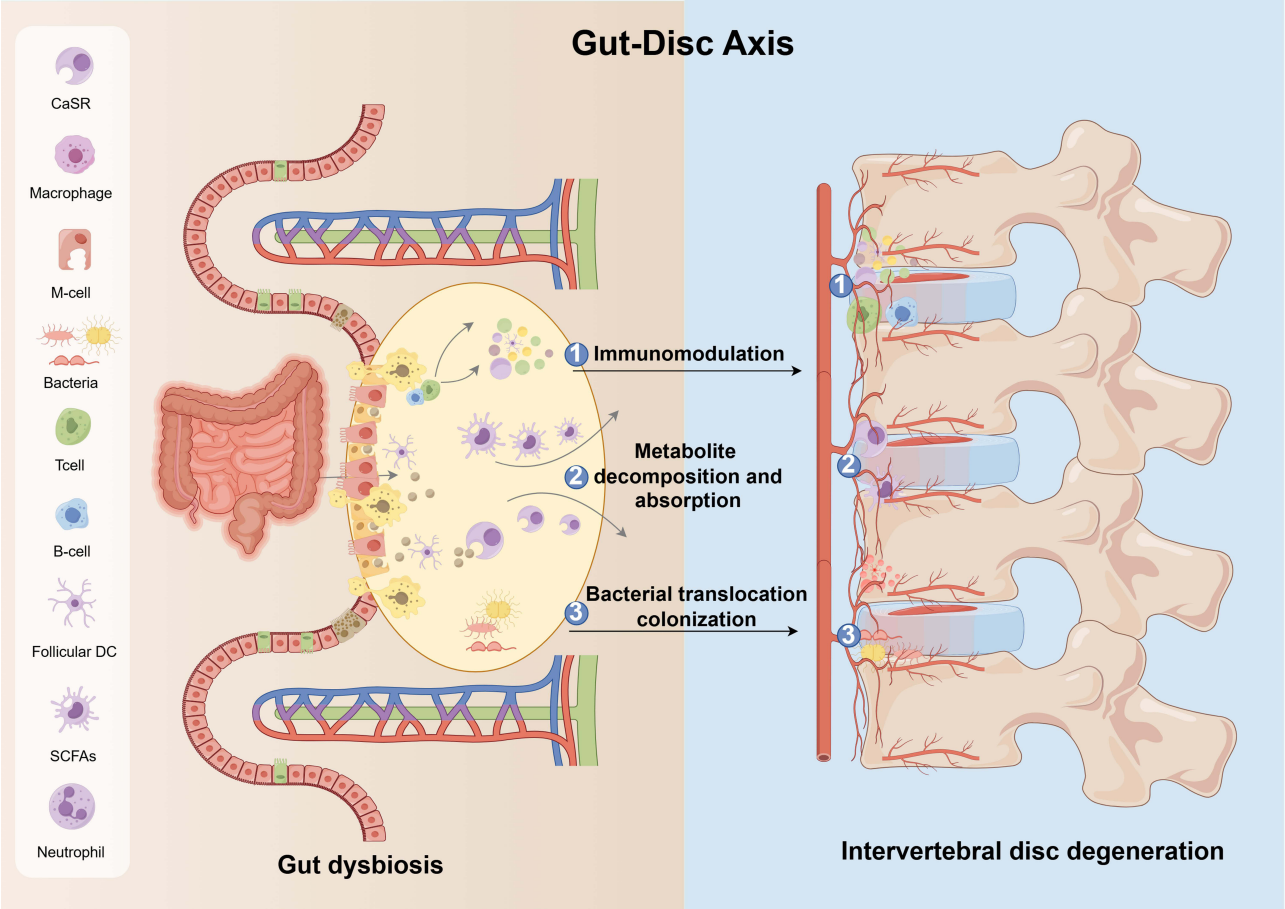

Figure 2 Possible mechanism of GM-mediated IDD. GM imbalance can accelerate the occurrence and development of IDD through immune regulation, bacterial translocation and colonization, and decomposition and absorption of intestinal metabolites.

Modern Research Progress on Targeting GM to Delay IDD

As the largest avascular tissues in the human body, IVDs rely on a crucial nutrient supply for effective function. Metabolic imbalance, ECM component changes, and IVD cell senescence and apoptosis are significant risk factors for IDD. There are numerous treatment options for IDD, primarily surgical and conservative treatments. Surgical treatment can alleviate symptoms such as compression and pain but cannot fundamentally reverse the biomechanical disorders caused by spinal degeneration. Conservative treatment can alleviate some clinical symptoms of IDD patients, but its effectiveness varies, and the treatment course is relatively long. Both treatments cannot effectively reverse the biological progression of IDD.[58] The following is the first review of the potential therapeutic modalities targeting GM to delay IDD in recent years, so as to provide clinical reference.

In recent years, GM colonization has attracted extensive attention as a promising therapeutic target. Lactobacillus paracasei (L. paracasei), mainly in the human oral cavity and intestines, alleviates inflammation-related diseases by regulating anti-inflammatory and pro-inflammatory cytokine secretion.[59] Research has shown that colonizing L. paracasei S16 in IDD mice promotes IVD cell proliferation, reduces cell apoptosis, and significantly improves the behavioral scores of IDD mice compared to the non-intervention group. Furthermore, it alleviates the abnormal inflammatory response in IDD mice.[60] Unlike targeting a single microbial community, fecal microbiota transplantation (FMT) involves colonizing the patient's gut with a suspension of feces from a healthy individual to alter the composition and abundance of the host's GM and restore gut microbiota balance.[61] Compared to a single microbial community, this approach maximizes the maintenance of the host's GM and metabolite integrity, thereby more effectively restoring GM dynamic balance. It has been reported that in an IDD rat model, FMT treatment via fecal suspension gavage not only significantly reduces histopathological damage to IVD tissues, decreases the secretion of inflammatory factors such as TNF-α, IL-1β, IL-6, MMP-3, and MMP-13, but also maintains the stability of IVD cells. Additionally, compared to the IDD group, the FMT intervention group showed improved GM abundance and diversity in rats.[62] This indicates that FMT could effectively target and slow IDD progression. However, research on GM colonization for treating IDD is still limited, and there is controversy over the duration of the effects of this method in slowing IDD progression. Besides GM colonization to slow IDD, researchers are also targeting intracellular modification processes to influence GM ecological balance. N6-methyladenosine (m6A), the most common internal modification of mammalian mRNA, affects gene expression in various transcriptional processes. Methyltransferase-like 3 (METTL3) is a key protein in the m6A methyltransferase complex with specific catalytic activity that regulates RNA splicing and assists in the regulation of various physiological and pathological processes.[63] Studies have found that METTL3 is highly expressed in IDD rats, and knocking out METTL3 can restore specific gut microbiota levels in IDD rats while altering their pathological phenotype. Moreover, inhibiting METTL3 significantly improves IVD cell senescence and damage, potentially involving TLR2 m6A modification and gut microbiota regulation.[64] This suggests that targeting GM to inhibit METTL3 could be a potential therapeutic target for delaying IDD progression.

The development of theories such as the gut-bone axis and gut-disc axis in modern medicine aligns with the holistic concepts of traditional Chinese medicine (TCM). For millennia, Chinese herbal medicines have been employed in Asian countries such as China, Japan, and Korea to treat various orthopedic diseases, including IDD. Recently, researchers have targeted GM with Chinese herbal medicines to inhibit the inflammatory cascade within IVDs, effectively slowing the progression of IDD. Sanbi Decoction, which was first documented in the Song Dynasty's "Women's Comprehensive Prescriptions", has been primarily used for the treatment of degenerative spinal diseases for a long time. Research found that it can broadly regulate GM and serum metabolic homeostasis, reduce inflammatory responses, inhibit ECM degradation, restore IVD height and water content, and significantly slow IDD progression.[65] Similarly, the Qiangjin Zhuanggu Qufeng Mixture can maintain the balance between ECM synthesis and degradation, thus slowing the progression of IDD. This process may involve improving the abundance of GM bacteria like Enterobacteriaceae and Clostridium butyricum, inhibiting NLRP3 inflammasome expression, and preventing nucleus pulposus cell pyroptosis.[66] Additionally, other studies have shown that Yaobishu Capsules and their active components, palmitic acid (PA) and trans-4-methoxycinnamic acid (THMC), can reshape GM balance after IDD in rats, restore metabolic homeostasis, activate autophagy and the Wnt/β-catenin pathway, reduce IDD-induced inflammation and pain, thereby slowing the progression of IDD.[67] Table 1 systematically summarizes three potential therapeutic approaches targeting GM to slow IDD progression.

Table 1 Potential Therapeutic Approaches Targeting GM to Delay IDD

	Intervention Modality	Mechanism	References
Intestinal microflora colonization	L.paracasei S16	Improves inflammatory response in LDH mouse models, alters gut microflora, and regulates serum metabolomics.	[60]
	Fecal microbiota transplantation	Attenuates histopathological damage of IVDs and reduces inflammatory factor secretion, also maintains IVDs cell stability and improves GM abundance and diversity.	[61,62]
Regulation of intracellular modifications	METTL3	Mediated m6A modification and regulation of GM, thereby delayed nucleus pulposus cell senescence.	[64]
Traditional Chinese medicine	Sanbi Decoction	Regulate the dynamic balance of intestinal flora and serum metabolism, reduce inflammatory response, inhibit ECM degradation, and restore the height of IVDs	[65]
	Qiangjin Zhuanggu Qufeng mixture	Maintains the balance of ECM synthesis and degradation, improves GM flora abundance, inhibits NLRP3 inflammasome expression, and prevents myeloid cell pyroptosis.	[66]
	Yaobishu formula	Restoration of GM homeostasis, maintenance of metabolic homeostasis, and activation of autophagy and Wnt/β-catenin pathways	[67]

Discussion

Intestinal dysbiosis is a pathological state characterized by the excessive growth of pathogenic microorganisms in the host. Research has shown that this process is linked to the onset and progression of various inflammatory and immune diseases. However, the potential mechanisms of interaction between GM and IDD remain unclear. Taking the gut - disc axis as the starting point, this paper first summarizes the connections between GM imbalance and human diseases, then comprehensively reviews GM's regulatory mechanisms in skeletal diseases, and finally systematically summarizes the current potential therapies targeting the gut - disc axis to delay IDD for the first time. We found that GM imbalance and disordered metabolite accumulation affect the host's intestinal balance and mediate systemic diseases, including nervous, cardiovascular, and endocrine systems. Similar findings demonstrated that gut microbiota dysbiosis correlates with increased inflammatory markers associated with systemic diseases.[68,69] GM dysbiosis can also accelerate IDD development through immune regulation, bacterial translocation and colonization, and intestinal metabolite breakdown and absorption. In line with this, Studies have highlighted that the inflammatory response elicited by gut dysbiosis contributes significantly to the pathophysiology of disc degeneration.[70] Moreover, the current therapeutic strategies targeting the gut-disc axis to delay IDD can be categorized into three types: gut microbiota colonization, intracellular modification regulation, and traditional Chinese medicine intervention. It is important to note that even the drugs referenced for addressing IDD in this manuscript are based on preclinical studies, which may not result in clinically significant or favorable outcomes. Based on these findings, we believe targeting GM and IVD microbiome inflammation and interrupting the cascade reaction in IVDs may effectively delay IDD progression. Therefore, comprehensive and systematic research on the impact of GM on IDD will significantly broaden our understanding of intestinal microbial ecology and skeletal diseases, offering new perspectives for the prevention and treatment of skeletal diseases under precision medicine.

However, research in this area still has limitations: Currently, most of the literature cited in this article relates to preclinical models, which may not indicate a direct causal relationship between the GM and IDD. Additionally, studies have shown that interventions effective in animal models do not always translate to human subjects, suggesting a need for careful consideration of species differences in future research. As the study highlights, the human microbiome is diverse, stable and resilient, and the differences between animal models complicate the extrapolation of results.[71] Moreover, due to factors such as cost, time, and participation, studies on the relationship between GM and IDD are scarce and primarily limited to animal experiments. Consequently, clinical applications remain unlikely at present.

Additionally, the interactions between the gut ecosystem and the host are often multifactorial, with unknown confounding variables potentially influencing the conclusions drawn from these studies. Thus, further investigations are necessary to explore the benefits of gut microbiome interventions and to elucidate the detailed mechanisms by which GM influences spinal disease progression.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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.

Funding

This article was supported by National Natural Science Foundation of China (82174402).

Disclosure

The authors declare that they have no competing interests in this work.

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