The gut-bone-cartilage triad: Microbial regulation of the Wnt/β-catenin signaling pathway in osteoarthritis joint remodeling (Review)

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Abstract. Osteoarthritis (OA) is a prevalent chronic joint disorder with a notable global health burden, characterized by articular cartilage degeneration, abnormal bone remodeling and synovial inflammation. Traditional treatments mainly focus on symptom management rather than addressing the underlying disease mechanisms. The gut microbiome serves a potential role in OA through the gut-bone-cartilage axis. Notably, the gut microbiome and its metabolites can influence bone and cartilage homeostasis, and the Wnt/β-catenin signaling pathway has been implicated in OA pathogenesis. The present study comprehensively reviews the emerging evidence supporting the gut-bone-cartilage axis in OA and the role of microbial regulation of Wnt/β-catenin signaling in joint remodeling. The current understanding of the influence of the gut microbiome on OA pathogenesis is summarized, discussing the mechanisms underlying the gut-bone-cartilage axis and exploring the therapeutic potential of targeting this axis. Future research should focus on developing targeted therapies that modulate the gut microbiome and the Wnt/β-catenin pathway, as well as exploring the potential of gene editing and carrier technologies for OA treatment.

Contents

1. Introduction
2. Gut microbiota-derived metabolites: Regulators of Wnt/β-catenin signaling
3. Wnt/β-catenin dysregulation: Direct driver of OA structural pathology
4. Gut-joint connection: Evidence, mechanisms and debates
5. Therapeutic strategies and translational medicine prospects
6. Future research directions and challenges
7. Conclusion

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1. Introduction

Osteoarthritis (OA) is a prevalent chronic joint disorder that poses a notable global health burden. With the aging population, the prevalence of OA is expected to rise, making it a critical public health issue (1). According to recent statistics, OA affects >300 million people worldwide, with a higher prevalence in individuals aged ≥60 years (1). The economic cost of OA is substantial, with direct medical expenses and indirect costs due to lost productivity estimated at billions of dollars annually; this underscores the urgent need for effective therapeutic strategies to manage and potentially reverse OA progression (2).

The pathophysiological hallmarks of OA include articular cartilage degeneration, abnormal bone remodeling and synovial inflammation (3). Cartilage degeneration is characterized by the loss of chondrocytes and the breakdown of the extracellular matrix, leading to reduced joint function and increased pain (4). Abnormal bone remodeling manifests as subchondral bone sclerosis and the formation of osteophytes, which further contribute to joint dysfunction (5). Synovial inflammation is characterized by the infiltration of inflammatory cells and the production of proinflammatory cytokines such as IL-1β) and tumor necrosis factor-α (TNF-α), exacerbating cartilage and bone damage. These pathological changes are interconnected, creating a vicious cycle that accelerates OA progression (5).

Despite the notable burden of OA, traditional treatments have limitations (6). Current therapeutic approaches primarily focus on symptom management, such as pain relief and improved joint function, rather than addressing the underlying disease mechanisms (7). Most research has concentrated on local factors within the joint microenvironment, such as chondrocyte apoptosis and inflammatory mediators (8,9). However, these approaches have shown limited efficacy in halting or reversing OA progression; therefore, there is a growing recognition of the need to explore systemic factors that may influence OA development and progression.

One such systemic factor is the gut microbiome, which has emerged as a potential regulator of OA through the

gut-bone-cartilage axis (10,11). The gut microbiome comprises trillions of microorganisms that serve crucial roles in host metabolism, immune function and inflammation (12). Previous studies have shown that the gut microbiota and its metabolites can influence bone and cartilage homeostasis through various mechanisms, including immune modulation and signaling pathways such as Wnt/β-catenin (10,13-15). For example, animal studies have demonstrated that alterations in the gut microbiota composition can lead to changes in bone density and cartilage integrity, suggesting a potential link between gut dysbiosis and OA development (11,16). Additionally, the Wnt/β-catenin signaling pathway has been implicated in OA pathogenesis, with a study showing that its dysregulation can contribute to cartilage degeneration and bone remodeling (17). These findings highlight the potential of targeting the gut microbiome and Wnt/β-catenin signaling as novel therapeutic strategies for OA.

The present study aims to provide a comprehensive review of the emerging evidence supporting the gut-bone-cartilage axis in OA and the role of microbial regulation of Wnt/β-catenin signaling in joint remodeling. The current understanding of the influence of the gut microbiome on OA pathogenesis is summarized, discussing the mechanisms underlying the gut-bone-cartilage axis and exploring the therapeutic potential of targeting this axis. By integrating insights from various studies, the present review aims to provide information on novel options for OA treatment and management.

2. Gut microbiota-derived metabolites: Regulators of Wnt/β-catenin signaling

The gut microbiome, comprising a diverse array of microorganisms, serves a crucial role in host metabolism and immune function (18). These microorganisms, which include bacteria, fungi and viruses, reside primarily in the gastrointestinal tract and contribute to the breakdown of dietary fibers, the production of vitamins and the regulation of immune responses (19). Among the various metabolites produced by the gut microbiome, short-chain fatty acids (SCFAs), bile acids and tryptophan derivatives have garnered marked attention due to their systemic effects on bone and cartilage metabolism (20-22) (Table I).

Key metabolites linking the microbiota to the Wnt pathway [SCFAs, bile acids and lipopolysaccharide (LPS)]. The gut microbiome is characterized by its high diversity, with thousands of different species coexisting in a complex ecosystem (19). Bacteria from the Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria phyla are the most abundant. These microorganisms perform a variety of functions, including the fermentation of indigestible carbohydrates to produce SCFAs, such as acetate, propionate and butyrate (20). These SCFAs not only serve as an energy source for colonic epithelial cells but also have systemic effects on metabolism and inflammation (18,22) (Fig. 1).

The metabolites produced by the gut microbiome notably impact bone metabolism, influencing both bone formation and resorption (23,24). SCFAs, particularly butyrate, have been shown to regulate bone density through multiple mechanisms. Butyrate inhibits osteoclast differentiation, thereby reducing bone resorption and protecting bone density (25). This effect is mediated by the inhibition of histone deacetylases (HDACs), which serve a crucial role in osteoclastogenesis. On the other hand, LPS, a component of the outer membrane of gram-negative bacteria, can promote bone resorption by activating the Toll-like receptor 4 (TLR4) pathway. This leads to the production of pro-inflammatory cytokines such as IL-1β and TNF-α, which stimulate osteoclast activity and bone resorption (26) (Fig. 1).

Vitamin metabolism is another area where the gut microbiome exerts its influence on bone health. Vitamin K2, essential for the activation of bone matrix proteins such as osteocalcin, is influenced by the gut microbiome. Guan *et al* (27) showed that alterations in the gut microbiome can affect the availability of vitamin K2, thereby impacting bone metabolism (Fig. 1).

Metabolite-driven Wnt activation/inhibition mechanisms. The gut microbiome also indirectly influences cartilage metabolism through the induction of systemic inflammation. Dysbiosis, or an imbalance in the gut microbiome, has been associated with increased levels of pro-inflammatory cytokines such as IL-1β and TNF-α (28). These cytokines can promote the degradation of cartilage matrix components, such as collagen and proteoglycans, by stimulating the production of matrix metalloproteinases (MMPs) and aggrecanases in chondrocytes (29). This inflammatory cascade accelerates cartilage degeneration and contributes to the progression of OA.

Moreover, the gut microbiome is implicated in the development of metabolic inflammation and obesity-related OA (30). Obesity is an important risk factor for OA, and studies have shown that the gut microbiome can influence energy metabolism and fat storage (31,32). Dysbiosis can lead to increased energy harvest from the diet and promote adipose tissue expansion, contributing to obesity (33). The resulting mechanical stress on joints, combined with systemic inflammation, exacerbates cartilage degeneration and joint damage in OA.

Butyrate (from Firmicutes) inhibits HDACs, enhancing β-catenin nuclear translocation and activating Wnt signaling in osteoblasts (20). Conversely, LPS (from gram-negative bacteria) binds TLR4, suppressing Wnt via NF-κB-induced sclerostin expression (34), promoting osteoclastogenesis and cartilage breakdown.

Notably, the influence of the gut microbiota on Wnt/β-catenin signaling is not limited to direct metabolic products. The gut microbiota also modulates the immune response of the host, which in turn affects Wnt/β-catenin signaling. For example, probiotics such as *Lactobacillus* have been shown to modulate the immune system and reduce inflammation by regulating the balance between T helper 17 (Th17) and regulatory T (Treg) cells, thereby inhibiting the overactivation of the Wnt/β-catenin pathway (35). This immune-mediated regulation provides another layer of complexity in the role of the gut microbiota in OA pathogenesis.

Additionally, a recent study has highlighted the role of bile acids in regulating Wnt/β-catenin signaling (21). Bile acids, upon metabolism by gut microbiota, can activate farnesoid X receptor (FXR) and other signaling pathways that intersect with Wnt/β-catenin (21). This crosstalk is particularly relevant in the context of bone and cartilage homeostasis, as evidenced by altered bile acid profiles in patients with OA, characterized

Table I. Gut microbial metabolites and their regulation of the Wnt/β-catenin pathway in OA.

First author, year	Metabolite category	Specific metabolite	Source of metabolite	Mechanism of action on Wnt/β-catenin pathway	Model/study type	Key findings	(Refs.)
Montalvany-Antonucci *et al*, 2019	SCFAs	Butyrate	Produced by gut microbiota through fermentation of dietary fibers	Inhibits HDACs, enhancing β-catenin stability; this leads to increased expression of Wnt target genes in osteoblasts, promoting bone formation	Animal model	Butyrate supplementation reduces cartilage degradation and inflammation in animal models of OA by modulating the Wnt/β-catenin pathway	(20)
Hou *et al*, 2023	Bile acids	Secondary bile acids	Metabolized by gut microbiota from primary bile acids	FXR activation inhibits the Wnt/β-catenin pathway in osteoblasts, reducing bone resorption; in chondrocytes, it suppresses Wnt-induced inflammation	Mechanistic study	Altered bile acid metabolism is associated with changes in bone density and cartilage integrity in patients with OA	(21)
Lucas *et al*, 2018	Tryptophan derivatives	Indole-3-propionic acid	Produced by gut microbiota from tryptophan	Acts as an antioxidant and modulates Wnt/β-catenin signaling by interacting with aryl hydrocarbon receptors, reducing inflammatory responses in chondrocytes	Cell culture	Indole-3-propionic acid protects chondrocytes from oxidative stress and inhibits Wnt/β-catenin pathway overactivation	(22)
Lee *et al*, 2019	SCFAs	Propionate	Produced by gut microbiota through fermentation of dietary fibers	It upregulates Wnt inhibitors like DKK1, reducing Wnt activation in osteoblasts and chondrocytes	Animal model	Propionate supplementation has a protective effect on cartilage in animal models of OA	(25)
Rios *et al*, 2019	Bile acids	Deoxycholic acid	Metabolized by gut microbiota from primary bile acids	Activates TLR4 and NF-κB pathways, leading to increased production of pro-inflammatory cytokines	Animal model	Deoxycholic acid administration is associated with exacerbated joint inflammation and cartilage damage in animal models of OA	(26)
Guan *et al*, 2020	Vitamin metabolites	Vitamin K2	Influenced by gut microbiota metabolism	Vitamin K2 deficiency decreases osteocalcin activation, impairing Wnt-mediated bone formation	Animal model	Dysbiosis affects vitamin K2 availability, impacting bone metabolism and potentially contributing to OA	(27)
Collins *et al*, 2021	LPS	Gram-negative bacterial cell wall component	Released by gut microbiota, particularly in dysbiosis	Activates TLR4 pathway, leading to pro-inflammatory cytokine production	Animal model	Elevated LPS levels are associated with increased joint inflammation and cartilage damage in animal models of OA	(28)
Pedersini *et al*, 2020	Vitamin metabolites	Vitamin D	Influenced by gut microbiota metabolism	Regulates Wnt/β-catenin signaling by enhancing the expression of vitamin D receptor and influencing the activity of related proteins	Animal model	Vitamin D deficiency is associated with exacerbated OA progression, while supplementation improves joint health	(29)

Table I. Continued.

First author, year	Metabolite category	Specific metabolite	Source of metabolite	Mechanism of action on Wnt/β-catenin pathway	Model/study type	Key findings	(Refs.)
Xie *et al*, 2020	LPS	Lipid A	Released by gut microbiota, particularly in dysbiosis	Activates TLR4 and NF-κB pathways, leading to increased production of pro-inflammatory cytokines	Animal model	Lipid A administration is associated with increased joint inflammation and cartilage damage in animal models of OA	(33)

DKK1, Dickkopf-1; FXR, farnesoid X receptor; HDACs, histone deacetylases; LPS, lipopolysaccharide; OA, osteoarthritis; SCFAs, short-chain fatty acids; TLR4, Toll-like receptor 4.

by a significant decrease in the levels of secondary bile acids (such as deoxycholic acid and lithocholic acid) and a relative increase in primary bile acids (such as cholic acid and chenodeoxycholic acid) compared to healthy individuals (21).

This crosstalk is particularly relevant in the context of bone and cartilage homeostasis, as evidenced by studies showing altered bile acid profiles in patients with OA, characterized by a significant decrease in the levels of secondary bile acids (such as deoxycholic acid and lithocholic acid) and a relative increase in primary bile acids (such as cholic acid and chenodeoxycholic acid) compared to healthy individuals (21).

In summary, gut microbiota-derived metabolites exert notable effects on Wnt/β-catenin signaling through multiple mechanisms, involving direct metabolic actions, immune modulation and interactions with other signaling pathways. These findings underscore the multifaceted role of the gut microbiome in OA pathogenesis and highlight potential therapeutic targets for modulating joint remodeling in OA.

3. Wnt/β-catenin dysregulation: Direct driver of OA structural pathology

The Wnt/β-catenin signaling pathway serves a crucial role in bone formation, cartilage homeostasis and joint development (36). This pathway is involved in the regulation of cell proliferation, differentiation and survival, and it is thus essential in maintaining the structural integrity of the musculoskeletal system. In OA, the Wnt/β-catenin pathway exhibits a dual role, with both protective and pathological effects (36). Understanding this dual role is essential for developing targeted therapeutic strategies to manage OA progression (Fig. 2).

Wnt hyperactivation. The Wnt/β-catenin signaling pathway is a highly conserved pathway that regulates various cellular processes, including bone formation and cartilage homeostasis (36). In the canonical Wnt pathway, Wnt ligands bind to Frizzled (FZD) receptors and LRP5/6 co-receptors, leading to the accumulation of β-catenin in the cytoplasm (37,38). This accumulated β-catenin translocates to the nucleus, where it interacts with TCF/LEF transcription factors to regulate the expression of target genes involved in OA pathogenesis, such as MMP13, ADAMTS5 (a disintegrin and metalloproteinase with thrombospondin motifs 5), and cyclin D1 (37). These genes are involved in cell proliferation, differentiation and survival, making the Wnt/β-catenin pathway a critical regulator of bone and cartilage metabolism (38). β-catenin accumulation in chondrocytes, driven by canonical Wnt signaling activation, functions as a transcriptional co-activator that directly binds to T-cell factor/lymphoid enhancer factor (TCF/LEF) sites in the promoters of genes encoding catabolic enzymes. This leads to the upregulation of MMP13 and ADAMTS5 (39-41). MMP13 specifically cleaves type II collagen, the primary structural component of articular cartilage, while ADAMTS5 is the major aggrecanase responsible for aggrecan core protein degradation (39,40). This direct degradation of collagen II and aggrecan is a central mechanism driving cartilage matrix loss in OA. Elevated fecal LPS levels, indicative of gut dysbiosis and increased gram-negative bacterial load/intestinal permeability, promote systemic inflammation and can activate TLR4 signaling within joint tissues. TLR4 signaling has been shown

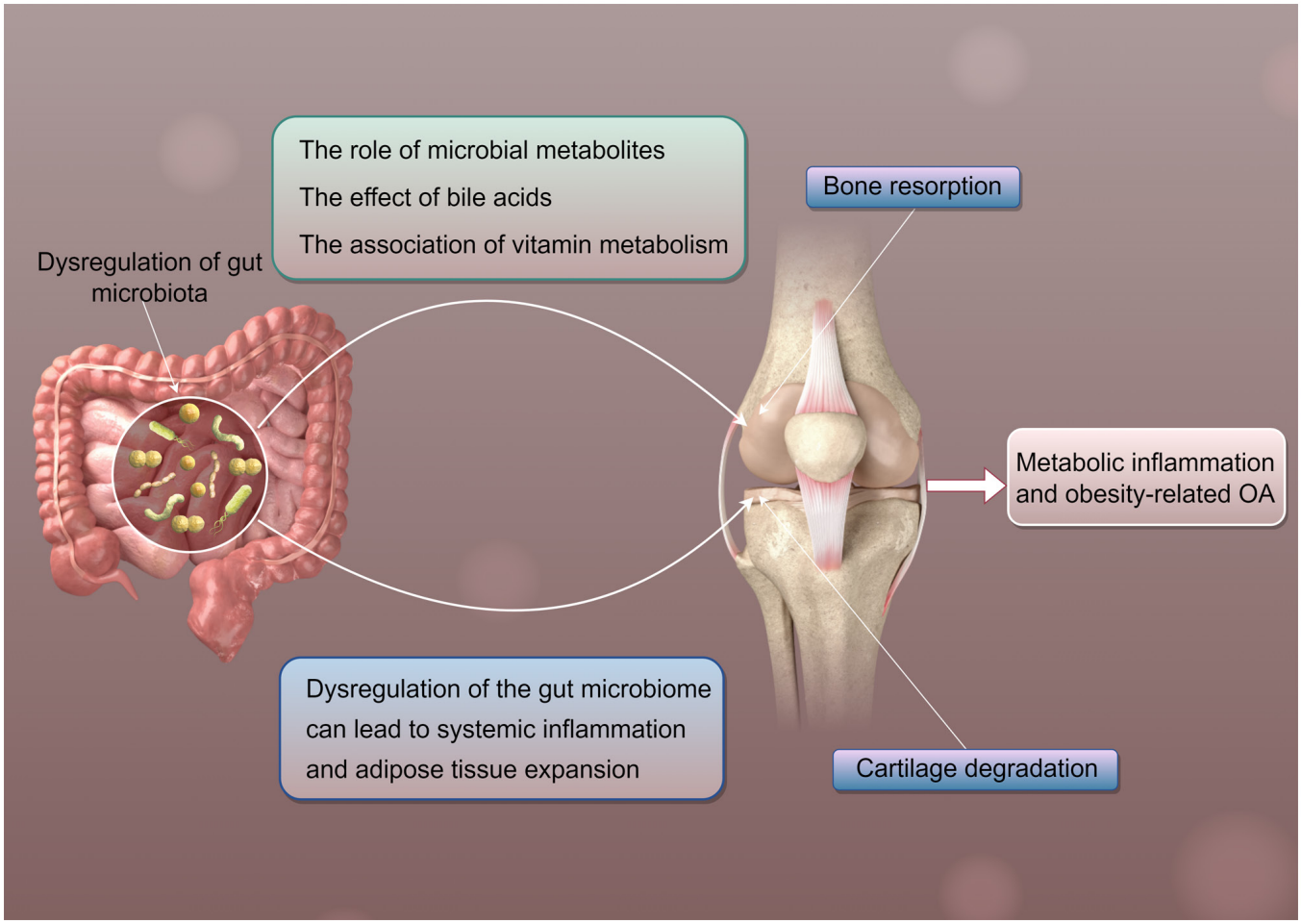

Figure 1. The gut-bone-cartilage triad. Schematic representation of the gut-bone-cartilage triad, illustrating the interactions between gut microbiota, bone and cartilage in OA. This figure was generated by Figdraw (www.figdraw.com; ID no. TIAWO27ea2). OA, osteoarthritis.

to potentiate Wnt/β-catenin signaling and/or induce the expression of inflammatory cytokines (such as IL-1β and TNF-α) that further stimulate chondrocyte catabolism, including MMP13 and ADAMTS5 production (28,34). Thus, the clinical association between elevated fecal LPS levels and accelerated cartilage loss can be mechanistically explained, at least in part, by LPS-mediated enhancement of the Wnt/β-catenin pathway and downstream inflammatory cascades, culminating in the upregulation of these key matrix-degrading enzymes and subsequent cartilage destruction (28,34).

Wnt dysregulation. In OA, the Wnt/β-catenin pathway is often dysregulated, leading to both protective and pathological effects (39). At the chondrocyte level, excessive activation of the Wnt/β-catenin pathway can result in the hypertrophy of chondrocytes and the upregulation of MMPs, which contribute to cartilage degradation (40,41). This process is characterized by the loss of cartilage matrix components, such as collagen and proteoglycans, leading to reduced joint function and increased pain.

On the other hand, the Wnt/β-catenin pathway also serves a role in bone remodeling (42). β-catenin promotes the differentiation of osteoblasts, which are responsible for bone formation (43,44). However, abnormal activation of this pathway can lead to the formation of osteophytes, bony outgrowths that contribute to joint deformity and reduced mobility (45,46). This dual role of the Wnt/β-catenin pathway in OA highlights the complexity of its regulation and the need for targeted therapeutic interventions.

Regulation of the Wnt pathway by the gut microbiome. The gut microbiome has emerged as a key regulator of the Wnt/β-catenin pathway, influencing both bone and cartilage metabolism (47). Furthermore, the gut-brain axis may be involved in the indirect regulation of the Wnt/β-catenin pathway through neural communication, although further research is needed to elucidate its role in bone and cartilage metabolism (48). Overall, these diverse mechanisms highlight the complexity of how gut microbial metabolites modulate the Wnt/β-catenin signaling pathway in distant bones and cartilages, and underscore the potential of targeting this axis for OA treatment.

At the cellular level, the Wnt/β-catenin pathway exhibits distinct effects on different cell types. In osteoblasts, β-catenin promotes differentiation and bone formation by upregulating osteogenic genes such as Runx2 and Osterix (49). Conversely, in chondrocytes, excessive activation of the Wnt/β-catenin pathway can lead to hypertrophy and the upregulation of MMPs, which contribute to cartilage degradation (50). This cell-specific regulation underscores the complexity of the Wnt/β-catenin pathway in OA pathogenesis.

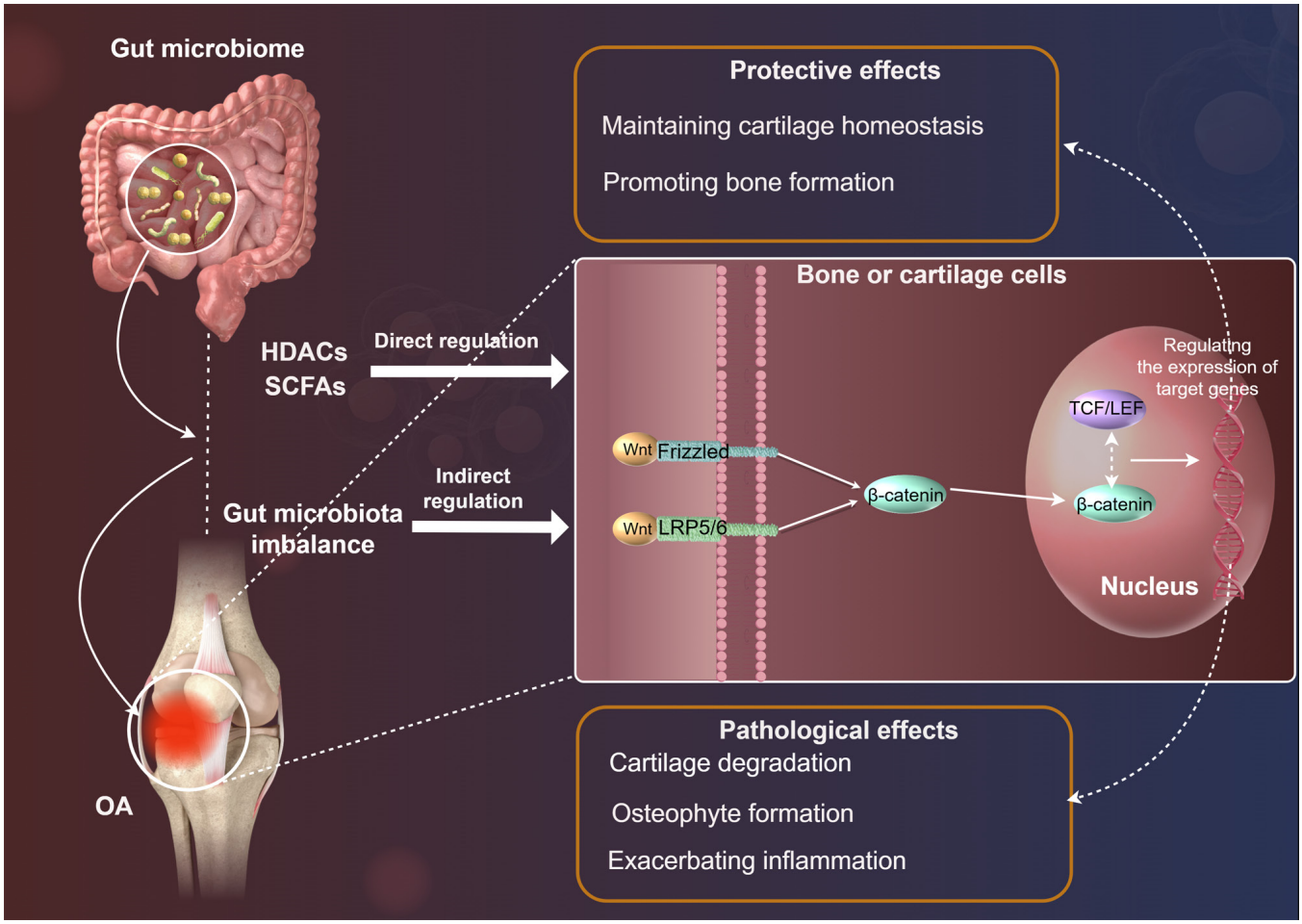

Figure 2. Wnt/β-catenin signaling pathway in OA. The dual role of the Wnt/β-catenin signaling pathway in OA exerts both protective and pathological effects. This figure was generated by Figdraw (www.figdraw.com; ID no. YTOSUdf022). HDAC, histone deacetylases; OA, osteoarthritis; SCFAs, short chain fatty acids.

The gut microbiome can indirectly regulate the Wnt/β-catenin pathway through the immune-metabolic network. Dysbiosis, or an imbalance in the gut microbiome, can lead to increased levels of pro-inflammatory cytokines, such as IL-1β and TNF-α. These cytokines can influence the expression of Wnt pathway-related genes, such as sclerostin, an inhibitor of Wnt signaling (51). Furthermore, the Wnt/β-catenin pathway involves intricate feedback mechanisms. For example, the upregulation of Dickkopf-1 and secreted FZD-related protein acts as a negative feedback loop to modulate Wnt signaling intensity (52,53). These feedback mechanisms are essential for maintaining the balance of Wnt/β-catenin signaling in bone and cartilage homeostasis.

4. Gut-joint connection: Evidence, mechanisms and debates

The gut-bone-cartilage triad has emerged as a promising area of research in understanding the pathogenesis of OA (10). However, despite advancements, there are still controversies and gaps in the knowledge that need to be addressed. The present review aims to integrate the existing evidence and highlight the controversies in current research (Table II).

Evidence for the microbiota-metabolite-Wnt-structural axis. Rodent models have provided robust pre-clinical evidence linking the gut microbiome to OA pathogenesis. In germ-free C57BL/6 mice subjected to destabilization of the medial meniscus (DMM), Ulici *et al* (54) observed more severe cartilage degeneration and subchondral bone sclerosis than in specific-pathogen-free (SPF) controls, indicating that the absence of commensal microbes exacerbates OA-related joint damage. Complementing these findings, Chen *et al* (55) performed fecal microbiota transplantation (FMT) from human knee-OA patients into 8-week-old germ-free Swiss Webster mice and documented increased synovial inflammation and accelerated cartilage loss within eight weeks. Collins *et al* (28) employed high-fat diet (HFD)-fed C57BL/6J mice to model metabolic OA. The authors demonstrated that HFD-induced dysbiosis, characterized by reduced *Lactobacillus* and increased *Desulfovibrionaceae*, was associated with elevated systemic lipopolysaccharide (LPS) levels and greater cartilage erosion independent of body weight. In a rat model, Rios *et al* (26) demonstrated that prebiotic supplementation (oligofructose) in male Wistar rats mitigated HFD-driven joint inflammation by restoring gut-barrier integrity and reducing TLR4/NF-κB activation. Collectively, these murine and rat studies establish a causal role for the microbiome-joint axis in OA development and provide multiple translational platforms for mechanistic dissection.

Table II. Gut microbiota and OA-related studies.

First author, year	Gut microbiota category/intervention	Model/study type	Key findings	(Refs.)
Ulici *et al*, 2018	Germ-free mice	Animal model	OA induced by destabilization of the medial meniscus is reduced in germ-free mice	(54)
Chen *et al*, 2021	FMT	Animal model	FMT from patients with OA to germ-free mice results in joint inflammation and cartilage damage	(55)
Fortuna *et al*, 2021	Comparative analysis of fecal microbiota	Clinical study	Patients with OA show decreased gut microbiota diversity and specific bacterial species associated with disease severity	(56)
Hahn *et al*, 2021	Probiotic intervention	Clinical trial	Probiotic supplementation improves OA symptoms in some patients but not in others	(57)
Ilesanmi-Oyelere *et al*, 2021	Gut microbiota and Wnt/β-catenin pathway	Mechanistic study	Microbial metabolites can directly modulate Wnt/β-catenin signaling in chondrocytes and osteoblasts	(58)
Lan *et al*, 2021	Time-dependent effect of gut microbiota	Longitudinal study	Early-life exposure to specific gut microbiota may influence joint health later in life	(59)
Luna *et al*, 2021	Probiotic intervention	Animal model	*Lactobacillus* can regulate the balance between Th17 and Treg cells, inhibiting the overactivation of the Wnt/β-catenin pathway	(35)
Pedersini *et al*, 2021	Prebiotic intervention	Animal model	A high-fiber diet increases the production of butyrate, reducing inflammation and cartilage degradation	(60)
Mi *et al*, 2023	High-fiber diet and gut microbiota	Intervention study	A high-fiber diet promotes the growth of beneficial gut bacteria and increases butyrate production, reducing inflammation and cartilage degradation	(61)
Piva *et al*, 2023	FMT	Animal model	FMT alleviates joint inflammation and cartilage degeneration by restoring a healthy gut microbiome	(62)
Wang *et al*, 2023	Small molecule inhibitors	Animal model	ICG-001 inhibits the Wnt/β-catenin pathway and decreases cartilage degeneration	(63)
Zhao *et al*, 2024	Gene editing (CRISPR/Cas9)	Animal model	CRISPR/Cas9 editing of genes involved in the Wnt/β-catenin pathway, such as sclerostin, enhances bone formation and reduces cartilage degeneration	(65)

FMT, fecal microbiota transplantation; HFD, high-fat diet; OA, osteoarthritis; SCFAs, short-chain fatty acids; Th17, T helper 17; TLR4, toll-like receptor 4; Treg, regulatory T.

Resolving controversies through a unified framework. While animal studies have provided evidence for the role of the gut microbiome in OA, clinical research has yielded contradictory results. Fortuna *et al* (56) reported a decrease in gut microbiota diversity in patients with OA, with specific bacterial species, such as *Prevotella*, showing a positive association with disease severity. However, other studies have failed to replicate these findings, suggesting that the relationship between gut microbiota and OA may be more complex (55,57). For instance, Chen *et al* reported no significant difference in α-diversity between older women with OA and healthy controls, and found no consistent association between specific bacterial taxa and OA status (55). Similarly, Hahn *et al* demonstrated that neither global microbiome diversity nor the relative abundance of Prevotella correlated with OA severity or pain scores in a mouse model (57), suggesting that the relationship between gut microbiota and OA may be more complex than initially thought.

Probiotic interventions have also shown inconsistent results in clinical trials. Hahn *et al* (57) reported improvements in OA symptoms following probiotic supplementation, whereas Fortuna *et al* (56) observed no significant changes in knee joint function or systemic inflammation after 12-week prebiotic/probiotic intervention in obese adults with knee OA, and Ilesanmi-Oyelere *et al* (58) found no notable effects

of synbiotic supplementation on OA-related biomarkers in a randomized controlled trial. These discrepancies may be attributed to differences in study design, patient populations and the specific probiotic strains used.

Despite the growing body of evidence linking the gut microbiome to OA, gaps remain in the understanding of the underlying mechanisms. One key area of uncertainty is the cell-specific interaction between gut microbiota and the Wnt/β-catenin pathway. Ilesanmi-Oyelere *et al* (58) suggested that microbial metabolites can directly modulate Wnt/β-catenin signaling in chondrocytes and osteoblasts, but the exact cell types and molecular mechanisms involved remain unclear.

Another area of controversy is the time-dependent effect of gut microbiota on OA development. Lan *et al* (59) suggested that early-life exposure to specific gut microbiota may influence joint health later in lif. However, subsequent germ-free and antibiotic perturbation studies by Ulici *et al* (54) and Chen *et al* (55) failed to detect any significant association between neonatal microbial composition and OA susceptibility in adulthood, indicating that the role of host developmental stages in modulating the impact of gut microbiota on OA progression remains to be elucidated.

5. Therapeutic strategies and translational medicine prospects

The gut-bone-cartilage triad and the role of microbial regulation of Wnt/β-catenin signaling in OA joint remodeling offer promising options for therapeutic interventions. The present review aims to explore various strategies targeting the gut microbiome and the Wnt/β-catenin pathway, as well as the potential of gene editing and carrier technologies in OA treatment (Table II). Therapies targeting the microbiota-metabolite-Wnt axis (such as probiotics increasing butyrate/Wnt inhibition and FMT restoring anti-inflammatory taxa) show promise in normalizing joint remodeling (35,60,61).

Targeting the gut microbiome

Probiotics and prebiotics. Probiotics, such as *Lactobacillus*, have shown potential in modulating the immune system and reducing inflammation. Luna *et al* (35) demonstrated that *Lactobacillus* can regulate the balance between Th17 and Treg cells, thereby inhibiting the overactivation of the Wnt/β-catenin pathway. Prebiotics, which are non-digestible food components that promote the growth of beneficial gut bacteria, can also serve a role in OA management. For example, a high-fiber diet has been shown to increase the production of butyrate, a SCFA that inhibits β-catenin signaling, thereby reducing inflammation and cartilage degradation (60).

Diet control. Dietary interventions are a promising approach to modulating the gut microbiome and its effects on OA. A high-fiber diet has been shown to promote the growth of beneficial gut bacteria, leading to increased production of butyrate, which can inhibit β-catenin signaling and reduce inflammation (61). Additionally, a balanced diet rich in antioxidants and anti-inflammatory nutrients can mitigate the effects of OA by reducing systemic inflammation and promoting joint health (61).

FMT. FMT, which involves transferring fecal microbiota from a healthy donor to a recipient, has shown promising results in OA animal models. Piva *et al* (62) demonstrated that FMT can alleviate joint inflammation and cartilage degeneration by restoring a healthy gut microbiome. This approach holds potential for clinical applications, although further research is needed to optimize the procedure and ensure its safety and efficacy.

Targeting the Wnt pathway with small molecule drugs. The Wnt/β-catenin pathway has emerged as a promising target for OA therapy. Small molecule inhibitors, such as ICG-001, have been shown to inhibit the Wnt/β-catenin pathway and reduce cartilage degeneration (63). However, the use of inhibitors must be balanced against the potential for adverse effects, as the Wnt/β-catenin pathway serves a crucial role in bone formation and homeostasis (36). On the other hand, agonists, such as lithium salts, can promote bone formation by activating the Wnt/β-catenin pathway (64). The therapeutic potential of these agents must be carefully evaluated in clinical trials to determine their safety and efficacy.

Gene editing technologies, such as CRISPR/Cas9, offer a powerful tool for modulating the Wnt/β-catenin pathway in OA (65). Zhao *et al* (65) demonstrated that CRISPR/Cas9 can be used to edit genes involved in the Wnt/β-catenin pathway, such as SCLEROSTIN, which is an inhibitor of Wnt signaling. Lentiviral vectors have been used to deliver CRISPR/Cas9 systems to target cells, enabling precise gene editing and modulation of the Wnt/β-catenin pathway. This approach holds potential for developing novel therapies for OA, although further research is needed to address technical challenges, and ensure the safety and efficacy of these technologies.

Critical analysis of intervention strategies. When evaluating the proposed intervention strategies for OA targeting the gut-bone-cartilage triad and Wnt/β-catenin signaling, a comprehensive analysis of feasibility, specificity, safety and ethical considerations is essential.

Gene editing technologies. Gene editing tools such as CRISPR/Cas9 offer precise modulation of the Wnt/β-catenin pathway. While preclinical studies show promise in enhancing bone formation and reducing cartilage degradation, several concerns must be addressed. The specificity of CRISPR/Cas9 remains a challenge due to potential off-target effects, which could lead to unintended genetic modifications in various cell types (66). Safety concerns include the risk of immune responses to the Cas9 protein and the long-term consequences of altering gene expression. Ethical considerations revolve around the permanent nature of germline editing, even though somatic cell editing is primarily used for OA. The irreversible changes to the genome necessitate the careful balancing of risks and benefits (67).

Targeting the gut microbiome. Interventions targeting the gut microbiome, such as probiotics, prebiotics, FMT and dietary modifications, show potential for regulating the Wnt/β-catenin pathway. These approaches are relatively feasible and have fewer ethical concerns compared with gene editing. However, challenges remain in achieving specificity, as the complex composition of the gut microbiome makes it difficult to target specific bacterial strains without affecting the overall microbial balance (68). Safety concerns include the risk of introducing pathogenic bacteria through FMT or altering the microbiome in ways that could lead to other health

issues (69). Long-term studies are needed to assess the safety and effectiveness of these interventions.

Small molecule drugs. Small molecule inhibitors and agonists of the Wnt/β-catenin pathway provide another option for OA treatment. These drugs are relatively easy to administer and have well-established pharmacokinetic profiles, enhancing their feasibility (37). However, ensuring their specificity to the Wnt/β-catenin pathway is challenging, as they may interact with other signaling pathways. Safety concerns involve potential toxicities and side effects, particularly with long-term use (37,70). Rigorous clinical trials are necessary to evaluate their safety and efficacy in patients with OA.

6. Future research directions and challenges

The gut-bone-cartilage triad and the microbial regulation of Wnt/β-catenin signaling in OA joint remodeling present opportunities for future research and therapeutic development (71,72). However, several challenges need to be addressed to fully realize the potential of these approaches. The present review explores future research directions and challenges in this field.

One of the most promising future directions in OA research is the integration of multiomics approaches, including metagenomics, metabolomics and single-cell sequencing (73,74). These techniques can provide a comprehensive understanding of the complex interactions between the gut microbiome and the host, particularly in the context of OA (74). Metagenomics can identify specific microbial species and their functional capabilities, whereas metabolomics can reveal the metabolic products of these microorganisms and their effects on host metabolism (75). Single-cell sequencing can provide insights into the heterogeneity of cell populations within the joint, including chondrocytes, osteoblasts and immune cells, and how they respond to microbial signals (76). For example, SCFAs produced by the gut microbiota can influence bone metabolism by enhancing the bone morphogenetic protein, Wnt and osteoprotegerin signaling pathways, and inhibiting the RANKL signaling pathway (20,77,78). By integrating these multiomics approaches, researchers can identify key microbial species and their metabolites that serve a role in OA progression, and develop targeted therapies to modulate these interactions.

Personalized medicine, which is based on the host genotype and gut microbiome characteristics of the host, holds potential for OA treatment (79). The gut microbiome varies among individuals and this variability can influence the efficacy of therapeutic interventions. By understanding the specific microbial composition and functional capabilities of the gut microbiome of individuals, clinicians can tailor treatments to target the specific pathways involved in OA progression (14,16,17). For example, studies have shown that certain bacterial species, such as *Lactobacillus rhamnosus* GG, can increase the production of the osteogenic Wnt ligand Wnt10b, promoting bone formation (80). By identifying individuals with specific microbial profiles, clinicians can recommend personalized interventions, such as probiotics or prebiotics, to modulate the gut microbiome and improve joint health.

The development of new therapeutic strategies for OA requires the integration of cross-disciplinary technologies, including gene editing and carrier technologies (81,82). Carrier technologies, such as lentiviral vectors, can be used to deliver CRISPR/Cas9 systems to target cells, enabling precise gene editing and modulation of the Wnt/β-catenin pathway (83). These technologies can be further optimized to enhance their safety and efficacy, making them viable options for clinical application.

7. Conclusion

The gut-bone-cartilage triad and the microbial regulation of Wnt/β-catenin signaling in OA joint remodeling offer promising opportunities for future research and therapeutic development. By integrating multiomics approaches, personalized medicine and cross-disciplinary technologies, researchers may gain a deeper understanding of the complex interactions between the gut microbiome and the host, and develop targeted therapies to modulate these interactions. Future research should focus on addressing the challenges in these areas to fully realize the potential of these approaches in OA treatment.

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Authors' contributions

RZ, LZ, YW, BT, XK and JZ conceived the study. RZ and JZ performed the literature review. RZ, LZ, YW, BT and XK wrote the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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