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Review

Gut microbiota and obesity-associated osteoarthritis

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SUMMARY

Obesity is a well-known primary risk factor for osteoarthritis (OA). In recent decades, the biomechanics-based theoretical paradigm for the pathogenesis of obesity-associated OA has been gradually but fundamentally modified. This modification is a result of accumulating evidence that biological factors also contribute to the etiology of the disease. The gut microbiota is a complicated ecosystem that profoundly influences the health of the host and can be modulated by the combined effects of environmental stimuli and genetic factors. Recently, enteric dysbacteriosis has been identified as a causal factor in the initiation and propagation of obesity-associated OA in animal models. Gut microbes and their components, microbe-associated lipid metabolites, and OA interact at both systemic and local levels through mechanisms that involve interplay with the innate immune system. However, the demonstration of causality in humans will require further studies. Nonetheless, probiotics, prebiotics, dietary habits and exercise, which aid the restoration of a healthy microbial community, are potential therapeutic approaches in the treatment of obesity-associated OA.

Introduction

Osteoarthritis (OA), which is the most prevalent arthritic disease and one of the leading causes of disability, is no longer considered as a degenerative illness of the cartilage but as a disorder of the whole joint with a heterogeneous and multifaceted etiology[1]. Obesity is a predisposing risk factor in OA initiation and perpetuation[2,3]. The pathophysiological mechanisms that underpin this close link have not been fully elucidated, but microbial causes of gut origin have been proposed.

The human body is not a self-sufficient and isolated unit, but a diverse and dynamic ecosystem. The intestinal canal is an excellent culture medium harboring approximately 10^{14} microorganisms, which contains microbial genetic information that represents an extension of the host's metagenomes and, thereby, influences the individual's health status[4,5]. In turn, the gut microbiome can be shaped by the combined effects of environmental stimuli and genetic factors[6]. The crosstalk among the environment, the gut microbiota and the host is a fundamental determinant of metabolic and immune physiology or pathology[7,8]. Interference of the delicate balance of homeostatic mechanisms caused by nutrient overload, microbial agents or immune dysfunction underlies many diseases[9,10]. Links have been demonstrated between dysbiosis of the gut microbiota and rheumatoid arthritis (RA) in animal models and humans[11]. Furthermore, the involvement of the gut microbiota in obesity-associated OA is being elucidated.

Hence, we review the key findings on the association between obesity and OA in a historical context and summarize the evidence that gut microbes, their components, and microbe-associated lipid metabolites contribute mechanistically to the etiology and pathogenesis of obesity-associated OA (Fig. 1). Additionally, we review the potential therapeutic approaches for gut microbial ecosystem reshaping in the prevention and treatment of OA.

Obesity and OA

The concept that OA is a wear-and-tear form of arthritis resulting from years of long, hard use has been proposed for

Abbreviations: OA, osteoarthritis; RA, rheumatoid arthritis; MetS, metabolic syndrome; HFD, high-fat diet; LPS, lipopolysaccharides; PGN, peptidoglycan; FFAs, free fatty acids; PRRs, pattern recognition receptors; TLRs, Toll-like receptors; NLRs, NOD-like receptors; PGN-PS, peptidoglycan–polysaccharide.

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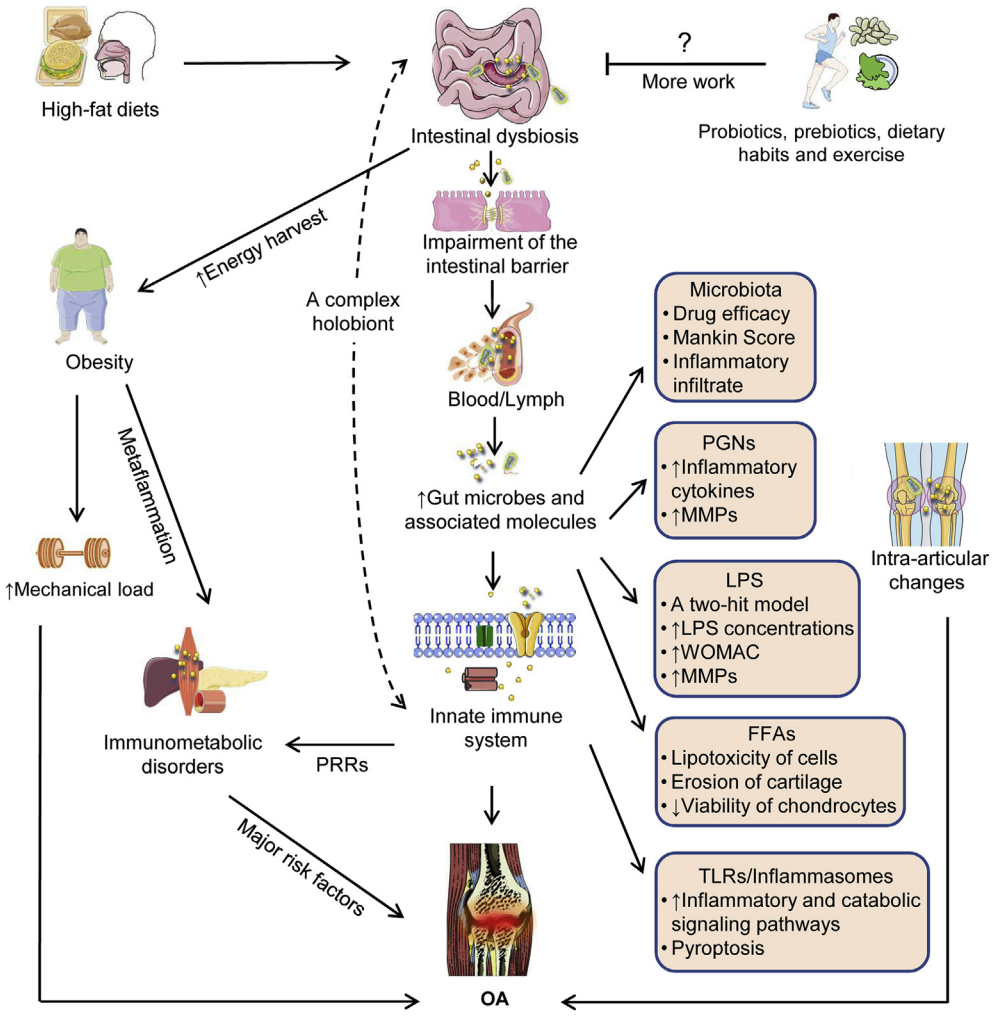

Fig. 1. A schematic illustration of the proposed mechanisms underlying the gut microbiome–osteoarthritis (OA) axis, and potential therapeutic approaches involving altering the microbiota composition. Abbreviations: LPS, lipopolysaccharides; PGNs, peptidoglycans; FFAs, free fatty acids; PRRs, pattern recognition receptors; TLRs, Toll-like receptors; MMPs, matrix metalloproteases; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

decades[12]. However, obesity significantly increases the risk of developing OA in nonweight-bearing joints, such as hand and temporomandibular joints, thereby indicating that obesity influences OA in a nonmechanical manner[2,3]. However, metabolic and mechanical factors are inextricably interwoven in weight-bearing joints. Thus, demonstrating the net effects of these factors without reciprocal interference *in vivo* is difficult. Nonetheless, some animal studies with ingenious designs demonstrated that body fat instead of body mass was highly correlated with the radiographic and symptomatic severities of knee OA (KOA) caused by a high-fat diet (HFD) or sucrose diet[13–15]. Metabolic disturbance due to nutrient overload is a comorbidity factor in OA-related osteophyte formation and cartilage degeneration that is independent of weight[16]. In addition to systemic factors, the locally hypertrophic infrapatellar fat pad is involved in cartilage degradation by secreting proinflammatory cytokines in obese mice[17]. However, a study performed by superimposing energy-dense diets on a tail-suspension mouse model found that infrapatellar fat pad inflammation and chondrocyte apoptosis were the results of metabolic stresses caused by an HFD alone, and the surface irregularity of articular cartilage and osteophyte formation resulted from both metabolic stresses and mechanical load[18]. An animal study using an *in vivo* tibial loading model indicated that severe adiposity and systemic inflammation aggravated cartilage damage induced by mechanical load[19]. Collectively, these results support the determinative role of these biological contributions in OA etiology. Nonetheless, mechanical effects may be important in some cases.

The delineation of OA into distinguishable phenotypes on the basis of etiological underpinnings has attracted considerable interest. An OA subtype called metabolic OA displays a unique OA trajectory characterized by its major causative metabolic factors[1]. The convergence of research into OA and metabolic syndrome (MetS) has yielded considerable information about their bidirectional effects. Epidemiological and experimental studies indicated the increased incidence of OA in patients with MetS[13,20]. A large-scale cohort study provided solid evidence that the accumulation of MetS components (e.g., central obesity, hypertension, high triglyceride levels and impaired fasting glucose) and their clustering significantly increased the risk of KOA occurrence and progression[21]. A study of obese mice further suggested that improved glucose tolerance and the disrupted coexpression of inflammatory cytokines delayed the progression of structural damage in OA without lowering the inflammatory cytokine levels[15]. Moreover, OA is associated with the increased prevalence of MetS and its components, particularly in young individuals[22]. Regardless of some controversial findings[23,24], the bona fide association between MetS

and OA phenotypic outcomes is generally accepted, as this link persists after the body weight or body mass index is adjusted[22,25]. Metabolic OA has even been proposed as a new criterion for the definition of MetS, which is supported by shared pathogenic mechanisms, such as inflammation, in the etiologies of MetS and OA[26].

Persistent inflammation is less pronounced in OA than in prototypical RA[27]. This situation is reminiscent of the low-level subacute inflammation that occurs in obesity. Accumulating evidence suggests that obesity provides a permissive inflammatory setting in OA pathophysiology. The altered plasma levels of human C-reactive protein, which is a well-established biomarker for systemic inflammation, can be evoked by metabolic stresses and used as a prognostic biomarker for the estimation of individual susceptibility to developing OA later in life[28]. Obesity also triggers a locally dynamic inflammatory response guided by predominant infiltration of proinflammatory M1-polarized macrophages in the OA synovium prior to cartilage degradation[29]. Some proinflammatory cytokines and adipokines produced by adipocytes are highly involved in OA pathogenesis[30,31]. A preclinical study found that improved metabolic inflammation substantially mitigated OA deterioration elicited by an HFD[28]. All of these data indicate the causative role of metabolic inflammation.

To summarize briefly, the link between obesity and OA onset and progression is well-established, and MetS and metabolic inflammation are considered as major hidden risk factors that provide unifying mechanisms underlying this association.

Gut microbiota and immunometabolic disorder regulation

The interfaces between metabolism and immunity exist at multiple levels within a complex network and have important implications for physiological homeostasis[7–10]. Gut microbes and microbe-associated molecules may be present in the intricate network involved in the pathogenesis and potentiation of immunometabolic disorders, such as MetS and metabolic inflammation.

Gut microbiota

Large-scale alterations in the gut microbiota, especially in the proportional representation of *Bacteroidetes* and *Firmicutes*, in leptin-deficient obese mice[32] and the reverse changes during weight loss in obese individuals[33] suggest that microbiome configurations are correlated with host energy balance. A seminal study found that the colonization of germ-free mice with gut microbiota harvested from the cecum of conventionally raised donors induced a significant increase in epididymal fat weight and total body fat content even with decreased chow consumption[34]. The overgrowth of a specific taxa, such as endotoxin-producing *Enterobacter*, has been identified as an etiological factor rather than an epiphenomenon in obesity[35].

A series of studies found that a Western diet-mediated gut microbiota was an instigator of MetS by activating multiple mechanisms or pathways in various organs and tissues[36]. The modulation of MetS-associated phylotypes of the gut microbiota attenuates metabolic deterioration in mice fed an HFD[37]. Specific taxonomic changes, such as the decreased abundance of *Akkermansia muciniphila*, in a holistic bacterial community result in adipose tissue inflammation and systemic dysmetabolism[38]. A study of dietary intervention in obese human subjects highlighted the importance of restoring the gut microbiota in the amelioration of chronic inflammation[39].

These data provide evidence that an altered gut microbiota plays a robust causal role in the development of obesity and immunometabolic disorders.

Components from gut microbes and microbe-associated lipid metabolites

A number of leading theories about the role of the components of gut microbes and microbe-associated lipid metabolites as key molecules in relaying and transferring signals from the gut to systemic tissues have been proposed[40–42]. These molecules are likely involved in the emergence and persistence of immunometabolic disorders.

Lipopolysaccharide (LPS), which is a major component of the outer membranes of Gram-negative bacteria, can provoke vigorous and generalized proinflammatory responses in infected hosts[40,43]. The increased metabolic concentrations of plasma LPS (by two-to three-fold) due to microbiota dysbiosis and impairment of the intestinal epithelium barrier caused by an HFD are defined as metabolic endotoxemia, which can serve as a sufficient molecular mechanism for the initiation of obesity and hyperinsulinemia via an inflammation-mediated pathway[40]. Meanwhile, the process of uptake and trafficking of gut-derived LPS is a coherent mechanism for the hypertrophy of adipose tissues because it can facilitate lipoprotein transcytosis through the endothelial barrier and endocytosis in adipocytes[44]. Gut-derived LPS can augment adipose macrophage accumulation and skew the polarization of alternatively activated M2 macrophages toward proinflammatory M1 phenotypes[43].

Peptidoglycan (PGN) is also a component of bacterial cell walls. Bacterial PGNs derived from the intestinal microbiota can penetrate internal sites and induce immune and inflammatory responses[45]. Specific PGN motifs can enhance the cytotoxicity of adipocytes by stimulating cell-autonomous lipolysis, which drives hyperlipidemia and systemic inflammation[41]. In addition to adipocytes, other types of metabolic cells, such as hepatocytes, can be activated by the mimetics of bacterial PGN and cause considerable whole-body insulin resistance[46].

Free fatty acids (FFAs) are released from adipocytes during triglyceride lipolysis and can be utilized by various tissues. An expanded adipose tissue mass can accelerate FFA efflux into the bloodstream[42]. FFAs are also bioactive molecules that link obesity and metabolic diseases by mechanisms involving the activation of oxidative stress and innate immune pathways[42]. Imbalanced microbial populations are associated with the considerably increased expression of key genes associated with FFA synthesis, FFA transport and immune regulation in the liver[47]. Altered serum FFA profiles are related to specific gut microbial signatures, including imbalanced populations of *Akkermansia* and *Lactobacillus*[48].

Innate immunity

The effects of the gut microbiota on host infection/inflammation mainly rely on pattern recognition receptors (PRRs), particularly the Toll-like receptors (TLRs) and NOD-like receptors (NLRs)[7,8]. In addition to their classical role in detecting pathogens and inducing innate immune responses, PRRs are emerging as key players in host metabolism programming. TLR4, a well-characterized membrane receptor, can be activated by both classical microorganism-derived toxins, such as LPS and PGNs, and endogenous metabolic cues, such as FFAs[49,50]. This receptor also plays a major role in linking increased dietary consumption of lipids, body fat accumulation and intestinal dysbacteriosis with metabolic inflammation and insulin resistance[49,50]. NLR proteins, which are cytosolic PRRs, are essential components of the inflammasome. This large, multimolecular immune complex assembles upon the recognition of infection or pathogens[51,52]. Recently, the NLRP3 inflammasome has been identified as a remote control for MetS by modulating the prevalence of

colitogenic species of intestinal microflora and the influx of bacterial TLR agonists into portal circulation[53,54].

The gut microbiota and the innate immune system can work as a complex holobiont; the innate immune system can shape the gut microbiota, and the gut microbiota has immune-activating functions[55,56]. Most perturbations in the microbiome or innate immune system can result in a new equilibrium for the pathogenesis of metabolic diseases[56]. This idea was further validated by the finding that genetic modification of the NLRP3 inflammasome or TLR5 induced impaired glucose metabolism, which was closely related to an altered microbiota structure[53,57,58]. Alterations in microbial community structure, elevation of TLR ligand levels and overexpression of TLRs were also observed in mice and humans with obesity or metabolic disorders[58].

Dysbacteriosis and OA

The concept that gut microbiota correlates with musculoskeletal health has been recognized for >60 years[59]. Previous studies on animal models and humans revealed the role of the microbiota in the onset, severity and progression of RA[60]. Although the importance of intestinal dysbiosis in either triggering or driving autoimmunity related to RA has been proposed[11], the mechanism underlying the gut microbiome–joint axis remains unclear. Evidence from animal studies indicates that the gut microbiota is also involved in the etiology of OA. Work on the gut microbiome–OA connection will provide a basis for the discovery of novel therapeutics for patients with chronic inflammatory arthritis.

Gut microbiota

The evidence for the efficacy of oral chondroitin sulfate in OA treatment is contentious and inconsistent[61]. A hypothesis paper proposed that the relative abundance of *A. muciniphila*, a commensal gut bacterium, might determine the contribution of chondroitin sulfate to the amelioration or aggravation of OA[62]. An animal study indicated that the altered abundance of the gut microbes *Lactobacillus* spp. and *Methanobrevibacter* spp. was associated with the Mankin scores of articular cartilage[14]. *Lactobacillus casei* can enhance the mitigative effects of type II collagen/glucosamine on OA treatment by downregulating the inflammatory responses of articular tissues in mice[63]. In revolutionary initial research, Schott *et al.* provided direct evidence that obesity-associated OA was an inflammatory ailment driven by obesity-related gut dysbiosis[64]. They found that reversal of a proinflammatory shift in the obese murine gut microbiota, through the prebiotic manipulation of specific microbial species, particularly *Bifidobacterium pseudolongum*, could reduce inflammatory profiles in the colon and circulation, thereby preserving the articular cartilage and essentially rescuing OA[64]. Similar to a previous study showing that the intestinal epigenome and even gene expression were reprogrammed by an obesity-associated gut microbiome[65], this study indicated that alterations in the obesogenic diet-conditioned microbiota changed the colonic gene expression patterns associated with the support of intestinal cell types related to epithelial proliferation and barrier function; thus, endotoxin leakage and macrophage infiltration into the synovium were reduced[64]. The therapeutic modification of dysbalanced microbial populations characterized by a MetS-like phenotype in TLR5 knockout mice can alleviate the OA cartilage pathology and subchondral bone morphology[19]. This finding further indicates the role of a person's enterotype in the development of metabolic OA.

A considerable number of both intracellular and extracellular bacteria were observed in the synovial tissues of patients with OA, which was associated with a substantial quantity of inflammatory infiltrate[66]. However, the exact source of these organisms is difficult to identify because many species are normal commensal residents both in the intestinal tract and skin[66]. It seems reasonable to propose the gut as the source of these organisms because impaired gut permeability and mucosal competence have been observed in patients with arthritis[66,67], and some living bacteria could be transferred from the gut to the joints/enthesis through the circulatory or lymphatic system[68].

Components from gut microbes and microbe-associated lipid metabolites

A hypothesis article proposed the pivotal role of metabolic endotoxemia in cross-sectional associations among gut dysbiosis, systemic inflammation and articular damage in obesity-induced OA[69]. However, another hypothesis article proposed that an increased serum endotoxin load was insufficient for OA onset and progression but exerted adjuvant effects on the process. A two-hit model of OA pathogenesis was formulated, wherein an initial proinflammatory innate immune response triggered by LPS was the first hit. Structural damage in a joint resulted from the second hit, which involved coexisting complementary mechanisms, such as inflammasome activation or assembly by the fragmented matrices of joint tissues that synergistically activated innate immunity[70]. Reliably quantifying LPS has been a challenge for years because some LPS inhibitors combine with LPS and form complexes that mask detection in biospecimens[71,72]. Nonetheless, an increased serum LPS concentration was previously detected in obese mice with OA[14]. A study also optimized the methodology of LPS quantification, thereby confirming that LPS placed a burden in both synovial fluid and serum samples of patients with OA[72]. Synovial LPS concentrations were correlated with macrophage activation, osteophyte severity, joint space narrowing severity and the total Western Ontario and McMaster Universities OA Index score in the knee[72]. LPS can also induce the secretion of matrix metalloproteases and components of the innate immune response in cultured chondrocytes[73] and accelerate the matrix degradation of articular cartilage explants[74]. These studies strongly support the pathogenic role of LPS in the perpetuation of OA.

Although not specific to patients with OA, peptidoglycan–polysaccharide (PGN-PS) complexes were detected in cells in the synovial sublining layer of OA-afflicted joints[75]. PGN-PS complexes were also isolated successfully from human feces and ileostomy fluids. The arthritogenic properties of PGN-PS complexes were further proven by the adjuvant-induced arthritis model[76]. Bacterial PGNs were present in some immune cells, including macrophages and dendritic cells, in the synovia of patients with OA. The different cellular phenotypes coexpressed costimulatory molecules that were involved in antigen presentation and produced cytokines contributing to the inflammatory internal environments in joints[77]. Several *in vitro* studies indicated the direct stimulatory effects of bacterial PGNs on synovial fibroblasts obtained from patients with OA and showed that bacterial PGNs induced the expression of matrix metalloproteases and proinflammatory cytokines[78]. All of these results suggest that the intra-articular PGNs are involved in triggering or exacerbating OA progression.

The serum and synovial fluid lipidomic profiles are sensitive biomarkers of the radiographic stage of obesity-associated OA[79]. Some metabolites related to FFA metabolism in the synovial fluid, such as myristic acid, oleic acid and lanosterol, increased with the structural deterioration of OA[80]. Pathological concentrations of oleate could reduce the viability of articular chondrocytes through apoptosis[81]. The accumulation of ectopic lipids was observed in articular cartilage in joints afflicted with OA, and total fatty acids in general and arachidonic acid in particular closely correlated with

the erosion severity of the cartilage surface[82]. The lipotoxic effects induced by dyslipidemia in dominant cells within synovial tissues, including adipocytes and macrophages, worsened synovitis in patients with OA and MetS[83]. The exertion of FFA-induced lipotoxicity in chondrocytes correlated with the amount of cellular FFAs, which were originally sequestered within lipid droplets[81]. Thus, FFAs may play an important role in OA pathophysiology.

Innate immunity

The complex and intricate interplay between the innate immune system and the intestinal microbiota plays a role in immunometabolic disorders[8,56,58] and has been recognized as a causal factor in the biological basis of metabolic OA[19,26,28,29]. In addition, overexpression of TLR2 and TLR4 has been observed in the lesions of OA articular cartilage[84]. The treatment of chondrocytes obtained from OA patients with PGN and LPS activated TLR2-mediated inflammatory and catabolic signaling pathways[84]. These results indicate the direct pathogenic role of non-immunocytes, which operate via the same mechanisms as canonical innate immune responses in OA. The activated synovial fibroblasts in patients with OA are also part of the innate immune system due to the activation of their outer membrane protein, TLR2, with PGN stimulation[78]. The oral administration of resveratrol partly rescued the joint architecture disorganization in obesity-related OA by suppressing the TLR4-mediated inflammatory signaling pathways in the cartilage[85]. However, MetS-like disorders elicited by TLR5 deletion did not aggravate load-induced cartilage damage in mice[19]. There are a number of possibilities to explain this. In particular, the extent of metabolic changes is insufficient to cause damage, the effects of metabolic factors are time-dependent and require time to manifest, and TLR5 itself may be involved in OA progression.

Increasing evidence has indicated that the NLRP3 inflammasome is a novel biomarker for OA diagnosis and monitoring[86]. The high correlation between NLRP3 protein expression and pro-oxidant enzyme levels in the synovial membranes of patients with KOA suggested the possibility that the inflammasome was activated by oxidative stress in OA progression[87]. Inhibition of the expression of the NLRP3 inflammasome or its components, such as pro-caspase-1, contributed to the amelioration of OA progression[51,88]. In addition to the NLRP3 inflammasome, the NLRP1 inflammasome showed upregulated expression in the synovia of the joints of patients with OA[51,87]. NLRP1 and NLRP3 inflammasomes also mediated inflammation and pyroptosis induced by LPS in fibroblast-like synoviocytes obtained from patients with OA[51]. These data strongly indicate the important role of inflammasomes in OA pathology and progression. Intriguingly, some exogenous and endogenous stimuli, including LPS and oxidative stress, which activate inflammasomes in OA progression, overlap with common pathogenic factors in obesity. However, whether these inflammasomes can be activated in the context of obesity contributing to OA development needs further investigation.

Therapeutics

Considering the continuously increasing global prevalence of obesity, novel preventive and therapeutic approaches for realizing symptomatic and structural relief of obesity-associated OA are greatly needed. Probiotics, prebiotics, nutritional supplements, dietary habits and exercise may influence the gut microbiome–OA interlinkage. Thus, these methods are considered as potential therapeutic approaches in the treatment of obesity-associated OA.

Probiotics and prebiotics, which are safe and effective dietary substances that can be used for elaborating microbial communities[89], are plausible therapeutic options for obesity-associated OA. A randomized double-blind clinical trial proposed that commercial probiotic *L. casei Shirota* exhibited beneficial effects on the treatment outcomes of knee joints afflicted with OA[90]. Supplementation with prebiotic fiber in the form of oligofructose could reverse the detrimental effects of fat-enriched diets on gut microbial communities by increasing the abundance of beneficial *Bifidobacteria* at the expense of numerous proinflammatory microbes, while inducing a considerable and consistent reduction in metabolic inflammation. It protected the joints of patients with OA against articular cartilage degeneration[64]. Green-lipped mussel extract, a dietary supplement, is efficient in reducing OA symptoms, and its therapeutic efficacy is likely correlated with a decrease in *Clostridia* spp., which are potent modulators of colonic Th17 and $CD4^+$ regulatory T cells, in the microbiota[91].

The structures and functionalities of microbial communities are strongly related to diet[36,37]. Some data have verified that dietary fats, especially saturated fatty acids, exert toxic effects on the etiologies of OA and the proinflammatory profiles of microbial communities might be a hidden causal factor underlying these effects[64,92]. Conversely, high intake of dietary fiber and polyunsaturated fatty acids or a high ratio between polyunsaturated fatty acids and saturated fatty acids was associated with the alleviation of the symptoms and joint structures of obesity-associated OA and reduced the risk of the illness[93–95]. Although the role of the gut microbiota still needs to be further explored, dietary habits provide a potential path toward the regulation of OA progression.

Although evidence from clinical trials on the effectiveness of exercise or physical activity for OA in individuals with obesity is limited, some intervention studies, which were not restricted to patients with obesity, had many recruited subjects that were overweight or obese, and the results confirmed the beneficial therapeutic effects of exercise on obesity-associated OA to some extent[96–98]. An experimental study in obese mice showed that wheel running exerted protective rather than damaging effects on OA[15]. The integrated therapeutic approaches of exercise and dietary weight loss induce considerable improvements in knee pain and mobility performance in adults with obesity, compared with a single intervention[99,100]. In addition, exercise considerably contributes to the modification of obese gut microbiota[101–103]. Several specific microbiota taxa, such as *Lactobacillus* and *Bifidobacterium*, which can be positively regulated by exercise[102,104], also have potential value in OA treatment[63,64]. Metabolic endotoxemia is also lower in active individuals than in those with sedentary lifestyles[105]. Nonetheless, given the varying degrees of obesity in patients with OA and the pleiotropic effects of exercise involving mechanical and biological effects, the context-dependent roles of exercise should be further explored. Whether exercise presents favorable effects on OA by regulating the gut microbiota should be clarified.

Conclusion and future perspectives

The association between obesity and OA has been well established. Researchers have only recently begun to appreciate aberrant intestinal microbiota as a causal factor in the genesis and perpetuation of obesity-associated OA in animal models. However, the demonstration of the causality in humans will require further research. Microbiota-associated molecules affect the etiopathology of OA at both systemic and local levels by mechanisms involving innate immune activation. Given that many factors potentially contribute to immunometabolic disorders, at what point and to what extent microbiota-mediated factors play a major role in OA pathogenesis remains to be elucidated. In addition, further mechanistic studies are still required to provide a deep understanding of the interactions between the microbiota and the host either locally in the intestine or peripherally in the joint tissues. Probiotics and

prebiotics, dietary habits, and exercise may influence the gut microbiome–OA interlinkage and are considered as potential therapeutic approaches in the treatment of obesity-associated OA. Some oral nutritional supplements, such as green-lipped mussel extract, which have symptom-modulating effects in OA, although no consensus has been reached about the mechanism of action, may act by modulating the gut microbiome. The exploration of approaches for restoring a healthy microbiota, especially increasing the amount of specific commensal microbiota that antagonize proinflammatory microbes and maintain the intestinal mucosa barrier, is an important future direction for OA treatment.

Author contributions

All authors contributed substantially to drafting the article or revising it critically for important intellectual content. All authors approved the final version for submission.

Conflict of interest

None of the authors have competing interests to disclose. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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