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News & Views

The gut microbiome-joint axis in osteoarthritis

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Osteoarthritis (OA), the most common joint disorder, was reported to affect 7% of the global population, and the number of people with OA has increased by almost 50% from 1990 to 2019 [1]. OA can occur in almost any moveable joint; however, the most commonly affected joints are the knee, hip, and hand. Pain, swelling, and stiffness are the most common clinical symptoms, which often lead to functional limitation and poor quality of life. With the ongoing process of population aging and an increasing incidence of obesity worldwide, OA will become a greater burden on society.

Although tremendous efforts have been made to control this disease, there is no effective treatment for OA yet. At present, pain control and function improvement for the purpose of increasing the patient's quality of life is still the main goal of disease management. With regard to analgesic medication, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are the most commonly used drugs; however, their adverse effects are of great concern [2,3]. Arthroplasty surgery has a high chance of relieving symptoms and improving the physical function and quality of life for end-stage OA patients, but it is a costly procedure and involves a considerable level of risk. Around 0.5%–1% of patients die within 3 months after arthroplasty surgery, and the risk of post-surgical venous thromboembolism over a 12-month period was elevated by nearly 6-fold versus patients with similar OA severity who did not undergo surgery [4]. Thus, identifying novel pathogenic pathways, especially modifiable ones, is urgently needed for OA, and findings will provide new therapeutic targets for OA.

Over recent decades, several studies have demonstrated that gut microbial dysbiosis can cause inflammatory disorders and immune dysregulation [5,6]. The gut microbiome generates pro-inflammatory compounds including lipopolysaccharides (LPS), which is an important outer membrane component of gram-negative bacteria. The gut microbiome is also responsible for producing bacterial metabolites with inflammation-modulatory properties such as short-chain fatty acids (SCFAs), bile acids (BAs) as well as tryptophan-derived aryl hydrocarbon receptor (AhR) ligands[7]. Since inflammation is related to OA, these findings led to speculation that the gut microbiome could play a role in the pathogenesis of OA. We aimed to summarize relevant studies relating to the microbiome and OA and discuss the potential gut microbiota-joint axis in OA with the purpose of providing insights into the biological mechanisms of the gut microbiome for OA.

As a large microbial ecosystem, trillions of microbial cells are housed in the human gastrointestinal tract. Therefore, the gut microbiome has been deemed a virtual endocrine organ, which produces a range of compounds that are involved in various physiological processes, such as interacting with the host's innate immune system and triggering immune responses at local and distant sites. Although the pathogenesis of OA has not been thoroughly elucidated, the existing evidence has suggested that inflammation and immune disorders are commonly involved in the structural damage of cartilage and joint pain. Gut microbiome dysbiosis represents an imbalanced state of the composition and function of intestinal microbes. Gut microbiome dysbiosis can result in leaky gut mucosa, leading to an increase in the blood level of LPS and triggering systemic low-grade inflammation. Increased serum LPS was reported to be associated with OA development and LPS itself could induce degradation of cartilage matrix via nuclear factor kappa-B (NF-κB) activation (Supplementary Text 1 online). In addition, gut microbiome dysbiosis may cause dysregulation of the metabolites, which were reported to drive the cross-talk between the host and its microbiome, as well as their respective functions. The SCFAs, which are the primary end products of bacterial fermentation from fibers, can reduce the production of pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), thus alleviating matrix metalloproteinases-13 (MMP-13) production and cartilage damage (Supplementary Text 2 online). The BAs, especially secondary BAs derived from bacterial metabolism of liver BAs produced from cholesterol (involved in the digestion of dietary lipids), were found to act as dynamic signaling molecules via the G protein-coupled BA receptor and the farnesoid X receptor, so as to modulate the host's inflammation and immunological function. BAs could retard NLRP3

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inflammasome activation through BA receptors, which may reduce reactive oxygen species production and lower catabolic changes in tissues of the joint (Supplementary Text 3 online). Tryptophan is an essential aromatic amino acid that can be directly converted into AhR ligands by the gut microbiome (e.g., *Lactobacillus* spp. and *Peptostreptococcus russellii*), which has a profound impact on inflammatory responses. AhR ligands were reported to be able to downregulate IL-17 level, which is highly involved in joint degeneration and tissue senescence of OA. Furthermore, tryptophan metabolites such as indole-derivatives, e.g., indoxyl-3-sulfate, indole-3-propionic acid and indole-3-aldehyde, could activate AHR signaling in astrocytes and suppress central nervous system inflammation, and may contribute to neuropathic pain in OA (Supplementary Text 4 online).

A number of animal studies have demonstrated a link between the gut microbiome and OA (Table 1). First, differences in the relative abundance of a number of Operational Taxonomic Units, which refers to a group of closely related sequences, of gut microbiota were noted between specific pathogen-free mice with high versus low maximum articular cartilage structure scores, suggesting that factors related to the gut microbiota could promote the development of OA after joint injury [8]. Second, transplanting fecal samples from OA patients with metabolic syndrome to germ-free mice increased gut permeability (i.e., higher plasma LPS level), endotoxemia and systemic low-grade inflammation (i.e., plasma concentrations of IL-1β, IL-6, and macrophage inflammatory protein 1-α (MIP-1α)) and lead to aggravated severity of OA induced by meniscal ligamentous/injury surgery. Alterations of *Ruminococcaceae*, *Faecalibaterium*, and *Fusobacterium* exhibited consistent associations with both the inflammatory biomarker and histological OA severity in mice [9]. Third, in the mice that received destabilized medial meniscus surgery, the antibiotic-induced intestinal microbiota dysbiosis reduced the serum level of LPS and down-regulated the inflammatory response, such as suppression of the levels of TNF-α and IL-6, leading to decreased MMP-13 expression

Table 1
Published studies relating to microbiota and osteoarthritis.

Year	Study population/ experimental animals	Design	Sample size	OA type	Findings	Conclusion
2018	Mice	Animal study	43	DMM model	Differences in relative abundance of a number of operational taxonomic units of gut microbiota were noted between SPF mice with high vs low maximum articular cartilage structure scores	Factors related to the gut microbiota promote the development of OA after joint injury
2019	Rotterdam study and Lifelines-DEEP study	Cross-sectional study (level of evidence: 4)	1427 + 867[a]	OA-related knee pain	Higher relative abundance of *Streptococcus* species is associated with increased OA related knee pain	Microbiome is a possible therapeutic target for OA related knee pain
2020	Mice and hospital based study	Animal study and case-control study (level of evidence: 3b)	42/20[b]	MLI model + knee OA	A greater abundance of *Fusobacterium* and *Faecalibaterium* and lesser abundance of *Ruminococcaceae* in transplanted mice were consistently correlated with OA severity and systemic biomarkers concentrations	Direct gut microbiome-OA connection exists
2020	Mice	Animal study	54	DMM model	Antibiotic-induced intestinal microbiota dysbiosis reduced the serum level of lipopolysaccharide and the inflammatory response	Gut microbiome dysbiosis alleviates the progression of OA
2021	UK twins study	Case-control study (level of evidence: 3b)	114	Unspecified OA	*Bifidobacterium longum* and *Faecalibacterium prausnitzii* were decreased, while *Clostridium* spp. was increased in the OA patients	Significant alterations in the gut microbial composition and function were observed in OA
2021	Hospital based study	Case-control study (level of evidence: 3b)	182	Overweight knee OA	7 optimal microbial biomarkers in genus levels as a panel, including *Gemmiger*, *Klebsiella*, *Akkermansia*, *Bacteroides*, *Prevotella*, *Alistipes*, and *Parabacteroides*, to build the random forest model, and achieved an 83.36% area under the curve of receiver operating characteristic	Crucial microbial biomarkers that may contribute to overweight OA individuals were discovered and validated
2021	Xiangya osteoarthritis study	Cross-sectional study (level of clinical evidence: 4)	1388	Symptomatic hand OA	Higher relative abundance of the genera *Bilophila* and *Desulfovibrio* as well as lower relative abundance of the genus *Roseburia* was associated with symptomatic hand OA	Alterations in the composition of the gut microbiome were observed in symptomatic hand OA
2022	Johnston county osteoarthritis study and mice	Case-control study (level of clinical evidence: 3b) and animal study	92/31[c]	Obese hand plus knee OA + germ-free mice	There were no significant differences in α- or β-diversity or genus level composition between OA patients and controls, but mice transplanted with patient or control microbiota exhibited a significant difference in α-diversity and β-diversity	Increased intestinal permeability allowing for greater absorption of lipopolysaccharide, rather than a dysbiotic microbiota, may contribute to the development of OA associated with obesity

DMM, destabilized medial meniscus; SPF, specific pathogen free; OA, osteoarthritis; MLI, meniscal/ligamentous injury.
[a] The numbers of participants in the discovery and validation studies were 1427 and 867, respectively.
[b] The numbers of mouse and participants were 42 and 20, respectively.
[c] The numbers of participants and mouse were 92 and 31, respectively.

and improvement of OA. This study revealed a relationship between inflammatory response and gut microbiota in OA [10].

Several human studies have also found that gut microbiome dysbiosis was associated with OA at different joint sites (Table 1). First, two cross-sectional studies using data collected from large-sample community-based observational studies demonstrated significant associations between the gut microbiome and prevalent symptomatic OA. Results from the Rotterdam study (n = 1427) reported a significant difference in the gut microbiome composition between participants with and without OA-related knee pain and a higher relative abundance of *Streptococcus* species was associated with increased OA-related knee pain [11]. The findings of the association between a higher relative abundance of *Streptococcus* species and OA-related knee pain were validated in an independent cohort (i.e., Lifelines-DEEP study (n = 867)) [11]. Results from the Xiangya OA (XO) study, a community-based longitudinal study of the natural history and risk factors of OA in a rural area of China, showed that higher relative abundance of the genera *Bilophila* and *Desulfovibrio* whereas lower relative abundance of the genus *Roseburia* was associated with prevalent symptomatic hand OA [12]. Second, one case-control study identified seven optimal microbial genera biomarkers, including *Gemmiger*, *Klebsiella*, *Akkermansia*, *Bacteroides*, *Prevotella*, *Alistipes*, and *Parabacteroides*, to distinguish overweight knee OA patients (n = 86) and overweight normal people (n = 96) [13], while another case-control study observed that microbial species of *Bifidobacterium longum* and *Faecalibacterium prausnitzii* were decreased but *Clostridium* spp. was increased in the OA patients (n = 57) compared with healthy controls (n = 57) [14]. In contrast, one case-control study reported no significant differences in either α-diversity (i.e., the number and distribution of taxa expected within a single group) or β-diversity (i.e., the similarity in organismal composition between groups) or genus level composition of gut microbiota between obese patients with both hand OA and knee OA (n = 59) and healthy controls (n = 33); however, they found that patients had higher serum LPS compared to controls, and mice transplanted with cases' or controls' microbiota exhibited a significant difference in α-diversity and β-diversity. Thus, they concluded that there is a role of gut microbiota in OA, increased intestinal permeability allowing for higher levels of serum LPS may contribute to the development of OA associated with obesity [15].

Although previous studies have suggested a potential role for microbiome contribution to OA, several limitations and challenges of microbiome research in OA should be acknowledged. First, most of the previous studies have relied on the 16S rRNA amplicon sequencing method to profile microbial communities in human beings. Due to the limited genetic information provided by the 16S rRNA amplicon sequencing method, this approach is unable to pinpoint specific microbial species and strains. Thus, the 16S rRNA amplicon sequencing method is not powerful enough to differentiate closely related species and cannot distinguish specific species which may play a role in knee, hip, or hand OA. Moreover, the technology is largely confined to the taxonomic scope to bacteria and archaea. As such, it cannot provide potentially informative signals on eukaryal and viral members of the gut flora, which may also have an impact on OA. The whole-genome shotgun metagenomic sequencing method provides robust estimates of microbial community composition and diversity by untargeted sequencing of all microbial genomes. This approach can provide detailed functional annotations of microbial communities with the species-level resolution for the entire milieu of gut microbes (i.e., bacteria, fungi, and viruses). Once this technology becomes more affordable, future studies may utilize metagenomic shotgun sequencing with superior algorithms to gain an in-depth understanding of the gut microbiome, so as to clarify the microbe-microbe interactions on the risk of OA and improve the gut microbiome-joint axis in OA. Second, cross-sectional studies preclude the unequivocal establishment of a causal relationship between the gut microbiome and OA because the temporal sequence between these two factors cannot be delineated. Meanwhile, case-control studies with small sample sizes may lack statistical power to identify possibly related microbiome taxa to incident OA. In addition, the possible fluctuations in the microbiome make it more challenging to interpret the results from the related studies. Therefore, prospective cohort studies with large sample sizes that allow the investigators to identify incident OA cases and characterize the microbiome in a longitudinal manner are of utmost importance. Third, previous human studies did not identify consistent alterations of specific microbial taxa in the OA population. Thus, generalizing the findings from a single population to other populations should be cautious because the characteristics affecting the gut microbiome may vary greatly in different populations, and results generated from one study should be validated in other populations. Fourth, future research should elaborate on how the microbiome and metabolites related to microbes associate with the occurrence and progression of OA by utilizing multi-omics data and more sophisticated computational analysis techniques. Finally, findings on relation of the gut microbiome to OA in humans are often based on observational studies; thus, the relationship can be affected by potential bias, including unmeasured confounders, misclassification of both the microbiome and OA outcome, as well as selection bias, and does not easily translate into causal links. On the other hand, the majority of microbiome-related animal studies examined the modulation effects at the genus or species level, and only specific strains of a given species were found to be clinically effective. Thus, results from the animal studies using precise interventions and robust preclinical models collaborating with the findings generated from the observational studies in humans are needed to help understand the biological mechanisms of the gut-joint axis in OA.

China is the highest populated country in the world, with 1.4 billion people. With the rapid aging of the population and increased prevalence of obesity, it is anticipated that the burden of OA will become a formidable challenge for the health systems in China. With limited resources, it is time to gear OA research toward patient-centered outcomes, with a particular focus on symptomatic OA or joint pain and its sequelae. To fill in this knowledge gap, we, the investigators mainly at Xiangya Hospital, launched a prospective longitudinal OA study, i.e., the Xiangya Osteoarthritis (XO) study, in a rural area of China (NCT04033757) to describe the natural history of radiographic and symptomatic OA covering multiple joints (i.e., tibiofemoral, patellofemoral, hip, hand, foot and lumbar joints), and to examine a set of putative risk factors (e.g., microbiome and microbiome-related compounds) for the risk of incident and progressive radiographic and symptomatic OA covering multiple joints. Specifically, participants from the XO study received radiographic and ultrasound examinations for multi joints at baseline and each follow-up visits [12,16]. This study also collected fasting blood, urine, stool, saliva and plaque samples for biochemical and genomic tests. On-going studies, such as the "associations of gut microbiome and related metabolites with osteoarthritis in human combining with validation research and poetical mechanistic investigations in vitro and ex vivo" using data from the XO study, are expected to offer deeper insights on the gut microbiome-joint axis in OA.

In summary, gut microbiome dysbiosis can lead to the dysregulation of various compounds and functions, systematic inflammation and immune disorder, which are associated with both joint pain and structural damage of cartilage in OA. Thus, we speculate that the compounds of gut microbiome could play key roles in the hypothesis of the gut-joint axis in OA. Although previous studies have suggested microbiome may play a potential role in OA, future studies require thoughtful and thorough planning to form

the research question, to collect data with robust and reproducible technologies, and to aim the specific population; the results could guide the investigators to develop the novel therapeutic strategies for OA.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary materials

Supplementary materials to this news & views can be found online at https://doi.org/10.1016/j.scib.2023.03.024.

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