Microbiome Question Q5: Does the gut microbiome play a role in modulating innate or adaptive immunity of the host that could interact with osteoarthritis?

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Response/Recommendation: Yes, the available preclinical studies demonstrate a possible correlation between a poor gut microbiome and development or progression of osteoarthritis.

Level of Evidence: High

Delegate Vote: Agree: %, Disagree: %, Abstain: %

Rationale:
Osteoarthritis (OA) is a chronic, degenerative joint disease characterized by cartilage loss, subchondral bone remodeling, synovitis, and pain, positioning it as the leading cause of disability worldwide. In 2021, an estimated 607 million people (≈7.7% of the global population) were affected by OA, suffering from substantial disability. The prevalence of OA is projected to rise further with increased age and obesity afflicted populations (1). Dysbiosis is a poorly defined term that refers to an adverse composition or function of the host microbiome. Dysbiosis of the gut microbiome disrupts homeostatic interactions between microorganisms and the host and has been linked to systemic inflammation and immune dysregulation (2). Emerging evidence suggests that dysbiosis of the gut microbiome may contribute to pathophysiology of OA through altered immune and metabolic signaling via a putative "gut–joint axis." (3) Accordingly, we will evaluate whether dysbiosis of the gut mirobiome plays a role in the development and progression of OA in preclinical models.

Gut joint axis

Dysbiosis of the gut microbiome is characterized by alteration in the taxonomic composition of the gut microbiota, often resulting in reduced microbial diversity (2). Dysbiosis of the gut microbiome commonly leads to decreases in the abundance of gut microbe-derived metabolites such as the short-chain fatty acid (SCFA) and increases in lipopolysaccharides (LPS) (4). Loss of SCFA signaling (via GPR43, GPR109A) can expression of claudins, occludin, and zonula occludens-1 by gut endothelial cells, reducing tight junctions and thereby causing increased intestinal permeability (5, 6). A more permeable gut lining then allows for translocation of microbial products such as LPS from the gut into the systemic circulation (7). These changes initiate coordinated alterations in innate and adaptive immune pathways that may influence joint tissues and progression of OA (8).

Innate immune system

Intestinal epithelial cells (IECs) actively participate in innate immunity. An adverse composition of the gut microbiota can result in reduced abundance of SCFA, and increased abundance of microbial-associated molecular patterns (MAMPs) that activate Toll-like receptors (TLRs) and NOD-like receptors

(NLRs) on IECs, triggering NF-κB–mediated secretion of IL-1β, IL-6, TNF-α, and chemokines into the systemic circulation (9). Additionally, changes in gut permeability can permit systemic dissemination of MAMPs, including LPS, which binds TLR4 on monocytes, macrophages, and dendritic cells, to include pro-inflammatory cytokine production at locations remote from the gut. This chronic low-grade activation of the innate immune system promotes macrophage polarization toward an M1-like phenotype, increasing TNF-α, IL-6, and inducible nitric oxide synthase expression. Systemically primed monocytes may traffic to synovial tissues, contributing to synovitis (6, 10-12). Dysbiosis may also activate complement pathways and alter innate lymphoid cell (ILC3) signaling, further amplifying systemic inflammation (8, 13, 14).

Adaptive immune system

Microbial metabolites can regulate T cell differentiation. Short chain fatty acid and tryptophan-derived indoles activate GPR43 and aryl hydrocarbon receptor (AhR) signaling, promoting transcription of forkhead box P3 (FoxP3) and supporting regulatory T cell (Treg) differentiation (15, 16). Gut microbiota-derived metabolites regulate the balance between regulatory T cells and pro-inflammatory Th17 cells (17). **Th17 cells secrete IL-17, a cytokine that drives pro-inflammatory mediator production, matrix metalloproteinase activity, and RANKL-dependent bone resorption** (18). Dendritic cell programming under enhanced TLR stimulation further reinforces Th17 differentiation over Treg induction, and activated T cells generated in gut-associated lymphoid tissue may enter the systemic circulation and contribute to inflammatory amplification within joint tissues (19)

Preclinical studies supporting the link between gut dysbiosis and OA

Germ free mice studies

Ulici et al. (20) investigated the role of the gut microbiome in post-traumatic osteoarthritis using germ-free (GF) mice subjected to destabilization of the medial meniscus (DMM). Compared with specific pathogen-free controls, GF mice experienced significantly reduced cartilage degeneration, lower OARSI scores, and decreased osteophyte formation despite identical injury. **Huang et al. (21)** examined whether the gut microbiota from human donors with metabolic syndrome and OA could influence OA progression by transplanting fecal microbiota from donors into germ-free mice prior to meniscal/ligamentous injury. Germ-free mice without colonization developed minimal OA, whereas mice colonized with donor microbiota exhibited significantly worsened cartilage damage, increased synovial inflammation, elevated systemic inflammatory markers, and greater intestinal permeability.

Guss and colleagues showed that antibiotic-induced disruption of the gut microbiome could reduce the severity of load-induced joint degeneration (22).

Gut dysbiosis and OA correlations

A systematic review by Chisari et al. (23), evaluated preclinical models investigating the relationship between diet-induced impairment of the gut microbiome and progression of osteoarthritis. Across multiple rodent studies, high-fat or high-sugar diets were shown to induce alterations in gut microbiota composition, including an increased Firmicutes/Bacteroidetes ratio, reduced microbial diversity, impaired intestinal barrier integrity, and elevated circulating lipopolysaccharide (LPS) levels. These microbiota shifts were consistently associated with increased synovial inflammation, higher histologic scores, and greater cartilage degradation. Collectively, these findings support a correlation between diet-induced alterations to the gut microbiome and severity of OA in preclinical models.

In a study by Collins et al (24) , lipodystrophic mice were used to examine gut microbiota–cartilage associations independent of adiposity and diet. While high-fat diet reduced microbial diversity and altered the Bacteroidetes:Firmicutes ratio, systemic LPS levels were not associated with cartilage damage. Multivariable analysis identified nine bacterial genera independently associated with Modified Mankin histologic scores, including positive associations (Rikenella, Kingella) and negative associations (e.g., Paraprevotella, Blautia, Dorea). These findings support a microbiome–cartilage axis in osteoarthritis that is independent of obesity and systemic endotoxemia. Moreover, a systematic review by Marchese et al. (3) showed a decrease in OA was positively correlated with a higher level of diversity in the composition of the gut flora.

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