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Abstract

The role of the gutl microbiome within a "gut-joint" axis is increasingly studied in osteoarthritis. The gut microbiome, particularly via its role in low-grade systemic inflammation, could be involved in joint destruction and osteoarthritic pain. Its mechanisms of action in osteoarthritis remain complex, with on the one hand a direct action of intestinal dysbiosis on osteoarthritis involving systemic inflammation, and on the other hand an indirect effect via the promotion of metabolic syndrome and obesity. The published works in mice have mainly focused on the role of the intestinal microbiota in joint destruction in metabolic models of osteoarthritis. In humans, works have focused on indirect markers of the gut microbiota, such as lipopolysaccharide, or metabolites, such as tryptophan-and related metabolites. Also, intestinal dysbiosis could be one of the explanatory factors of osteoarthritic pain. A better understanding of the role of the gut microbiom in osteoarthritis in humans and from experimental models could lead to new therapeutic insights in osteoarthritis.

Key Words: Osteoarthritis, gut microbiome, dysbiosis, metabolic syndrome, inflammation, joint destruction, pain

1. What is gut microbiome ?

Gut microbiome is a complex ecosystem including all commensal unicellular species of digestive tract. It is composed of 10^{13} cells, which is as many as the number of cells in the whole human body, and corresponds to a weight of 1 to 2 kilograms [1]. The gut microbiome is building up gradually after birth to reach an adult status around 2 years old [2]. It can be influenced by various factors such as diet, environment, genetics, medication, immune system, sex and age [3-7]. The gut microbiome is composed of more than 2000 different species, including bacteria (divided into four main phyla: *Firmicutes, Bacteroidetes, Actinobacteria*, and *Proteobacteria*), viruses, fungi, and archaea [8,9]. As a result, it is composed of numerous metabolites produced directly by microorganisms or by the transformation of molecules derived from the environment (i.e. food) and the host. The gut microbiome plays a fundamental role in the homeostasis of the organism: it is involved in digestion through fermentation of non-digestible food residues, assimilation of nutrients, hydrolysis of polysaccharides, vitamins synthesis (K, B12 and B8), absorption of fatty acids, and indirect effects through the metabolites, and finally the functions of the central nervous system and the immune system [10].

2. How to study gut microbiome?

For many years, the analysis of the gut microbiome has been limited by the fact that most of its microorganisms are not cultivable. Actually, only 30% of the dominant species can be cultured *in vitro* by conventional methods. The development of high-throughput sequencing techniques and metagenomics analyses now allows a more precise study of the gut microbiome [11]. Metagenomics, in particular, is a reference method for genetic analysis of complex environments. It relies on the sequencing of the genome of multiple microorganisms belonging to different species in a given environment at a given time. It differs from classical genomics, which consists of sequencing a single microorganism's genome. A typical metagenomic analysis will determine the composition and diversity of a microbiome, and the abundance of the different species. There are two main methods for metagenomic studies used in gut microbiome: global metagenomics by direct sequencing of total DNA, and targeted metagenomics by 16S RNA gene sequencing [12]. The 16S RNA gene sequencing method is based on the amplification and the sequencing of the 16S ribosomal RNA gene present in all bacteria. By comparing obtained sequences with a reference database, it is possible to identify the bacteria and their relative abundance. The metagenomic technique known as "shotgun", more complex and expensive, consists of sequencing the total DNA present in the sample. After reassembling the genomes and/or comparing them with reference databases, it is possible to obtain a precise taxonomic composition of the studied microbiomes and have a comprehensive overview of the functions driven by the gut microbiome [13].

Another way of understanding gut microbiome functions is to measure its metabolites, i.e. the products of microbial metabolism. Those metabolites may be derived directly from microorganisms,

environmental substrates (especially food residues), and different interactions with the host. Among the most studied metabolites of gut microbiome, we can cite:

- Metabolites of tryptophan. Tryptophan is an essential amino acid present in food, which is a precursor of a multitude of bioactive compounds. Tryptophan can be metabolized by some members of the gut microbiota into indole derivatives. These molecules activate the AhR *(aryl hydrocarbon receptor*), on intestinal immune and epithelial cells with a key role in intestinal homeostasis *via* induction of IL-22 and antimicrobial peptides production. Tryptophan is also metabolized by host cells toward the serotonin and IDO (indoleamine 2,3-dioxygenase) pathways. Indeed more than 80% of serotonin (also called 5-hydroxytryptamine) is produced in the digestive tract under the influence of gut microbiome [15]. The IDO pathway leads to the production of kynurenin and its derivatives, which have an important role in various metabolic, neurological and immune pathways.
- Short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate, which are produced by the fermentation of non-digestible polysaccharides, and mostly present in fibers. SCFAs are mostly produced by anaerobic bacteria belonging to *Firmicutes* taxa. SCFAs play an important role in metabolism and immunity regulation with anti-inflammatory and immunoregulatory actions [16].
- Bile acids, especially in their conjugated form have an important role for bacterial proliferation and inflammatory regulation in gut microbiome.

Al these metabolites can be detected and quantified in feces or circulating blood. They are conditioned by microorganism's abundance, gut microbiome activity and interactions with the host. The concentration in circulating blood also reflects intestinal permeability, a major factor influencing the systemic impact of the intestinal microbiota.

Some markers are used to assess intestinal permeability indirectly:

- The serum lipopolysaccharide (LPS) level, also known as endotoxin, is a component of extracellular membrane of gram-negative bacteria. However, its quantification is complex and can be done indirectly.
- Zonulin is a protein that plays a role in the regulation of enterocyte permeability and whose serum level reflects the permeability of the intestinal barrier.

3. Dysbiosis and inflammation

The ecosystem composing the gut microbiome is characterized by a balance between each microorganism and with the host cells. The alteration of gut microbiota composition and functions and its dialog with the host, sometimes called "dysbiosis", is implicated in metabolic diseases such as obesity or metabolic syndrome [16] but also in autoimmune and/or auto-inflammatory diseases such as inflammatory bowel diseases (Crohn's disease, ulcerative colitis), rheumatoid arthritis or spondyloarthritis. Some of these dysbiosis-associated diseases exhibit local and systemic low-grade

inflammation mediated by different mechanisms. These mechanisms may include the proliferation of certain pro-inflammatory species (such as *Proteobacteria*) or the depletion of anti-inflammatory species (such as some members of the *Firmicutes*). Such imbalances lead to a characteristic signature of the gut microbiome associated with some diseases such as obesity and type 2 diabetes [17]. Inflammation related to intestinal dysbiosis can be mediated by different metabolites such as SCFAs. For example, decreased butyrate production is associated with the activation of neutrophils and macrophages [18]. On the one hand, some tryptophan metabolites may have a pro-inflammatory role, in particular through the activation of the IDO (indolamine 2,3 dioxygenase) pathway and the excessive kynurenin production [12]. On the other hand, microbiota-derived tryptophan metabolites may also have anti-inflammatory effects. LPS, during its systemic circulation, can also cause activation of innate immunity through the binding to different receptors expressed by macrophages such as the Toll-like receptor 4 (TLR4) complex, which also includes the MD-2 protein and the CD14 receptor. Furthermore, some inflammatory states are associated with an increased intestinal permeability illustrated by an increase of serum level of zonulin. Increased intestinal permeability allows greater passage of pro-inflammatory metabolites or LPS into the systemic circulation and translocation of bacteria or bacterial fragments into the bloodstream [19].

4. Experimental models in osteoarthritis

The role of gut microbiome is increasingly being studied, with the idea that a "gut-joint" axis is involved in the pathophysiology of osteoarthritis (OA) [20] (**Figure 1**). The difficulty is to determine whether there is a direct relationship between a specific intestinal dysbiosis and OA or whether dysbiosis is related to OA through obesity and metabolic diseases, which are themselves risk factors for OA [21,22]. Nevertheless, there is an accumulation of evidence on the role of intestinal dysbiosis in both human and animal models of OA. Several mice models have been particularly interested in the role of diet, obesity and metabolic syndrome in OA. Schott et *al.* showed an alteration of the gut microbiome in a mice model of high-fat diet-induced obesity. This alteration was associated with a loss of diversity, a significant decrease of certain species such as *Bifidobacteria* and an increase in the abundance of pro-inflammatory species. In these obese mice subjected to the destabilization of the medial meniscus (DMM) responsible for post-traumatic OA, the administration of the prebiotic oligofructose drastically reduced cartilage destruction. This effect of oligofructose appears to be mediated by the mitigation of intestinal microbiota alterations, as well as by a decrease in systemic inflammation mediated by Tumor Necrosis Factor (TNF) and LPS in the bloodstream [23]. Furthermore, Guss et *al.* have demonstrated an association between an altered gut microbiome, the blood level of pro-inflammatory cytokines and joint destruction in the DMM and high-fat diet obese mice model [24]. On the other hand, Collins et *al.* showed, based on a mouse model of high fat/high sucrose diet-induced obesity, an increase in systemic and joint fluid LPS level, associated with increased joint destruction [33]. In this study, there was an association between the excess of some species such as *Lactobacillus spp* and *Methanobrevibacter spp* and the histological severity of OA as measured using the Mankin score [25]. The action of gut microbiome on joint destruction in OA is also supported by several recent works. Huang et *al.* performed

fecal microbiota transplantation from healthy subjects or from patients with metabolic syndrome to mice subjected to DMM. Fecal transplantation from patients with metabolic syndrome was associated with a more severe OA and an increased intra-articular and systemic inflammation. Gut microbiota alterations characterized by an increased abundance of *Fusobacterium* and *Faecalibacterium and* decreased abundance of *Ruminococcaceae was* also found in these mice compared to mice transplanted with healthy subjects' microbiota [26]. In another way, Ulici *et al*. highlighted the structural role of the microbiota in OA independently of obesity. In fact, using the DMM mouse model of OA again, joint progression was less important in axenic mice (mice living in a sterile environment, without microbiota) than in controls, illustrating the critical role of microbiota in the promotion of joint alteration [27].

5. Gut microbiome and human osteoarthritis

Several studies have shown a link between human OA and gut microbiota-related metabolites or biomarkers such as LPS. Loef et *al.* demonstrated in a cohort of 5,328 patients with knee or hand OA an association between post-prandial serum concentration of plasma fatty acids and structural damages in men (at the knees and hands) [28]. Other studies have also highlighted the disturbances of tryptophan metabolites in OA. Based on a transcriptomic and metabolomic study, Huang et *al.* showed a significant decrease in serum tryptophan concentration in 12 OA patients compared to 20 healthy volunteers [29].

With regard to LPS, Huang et *al.* found a positive association between blood or synovial LPS levels and joint destruction in 24 patients with knee OA, as well as an association between the level of LPS binding protein (LPB) in the synovial fluid and pain intensity [30]. Similarly, Daghstani et *al.* showed an association between blood or synovial fluid soluble CD14 level, an indirect marker of TLR4 activation by LPS, and pain in 184 patients with knee OA [31]. Correlations were also found with radiographic progression. These two studies highlighted the role of LPS and these receptors in structural progression and pain in OA.

Little work has been done on direct analyses of the bacterial composition of the intestinal microbiota in patients with OA. The most striking study, involving 1,444 patients with knee or hip OA, identified a specific signature of the gut microbiome associated with pain with a correlation between the WOMAC pain score and the abundance of some pro-inflammatory species such as the *Streptococcus genus* [32].

Moreover, the phenomenon of bacterial translocation could also play a role in OA. The DNA of certain bacteria present in gut microbiome has been found in cartilage, which is usually recognized as a sterile tissue since it is not vascularized. This presence suggest that metabolites and bacterial fragments derived from gut microbiote may reach joint. Likewise, Dunn et *al*. studied 42 patients with knee OA, 67 patients with hip OA and 20 controls. Using a ribosomal 16S RNA approach, they showed a specific microbial signature in the cartilage of OA patients with an increased proportion of gram-negative constituents, such as the *Betaproteobacteria* family [33].

6. Therapeutic Perspectives

The gut microbiome could be an interesting therapeutic target in OA [34]. Modifications of the gut microbiome, beyond hypocaloric diet and weight loss, with the use of pro and prebiotics, has already been the subject of several studies. Oral administration of *Streptoccocus thermophilus* in 80 patients in a randomized, double-blind, placebo-controlled study has been associated with a diminution of knee osteoarthritis progression measured by serums biomarker and WOMAC score [35]. In addition, the use of *Lactobacillus casei Shirota,* in a randomized, double-blind, placebo-controlled clinical trial in 537 patients, showed a significant decrease of the WOMAC score and pain after 6 months in the treated active group [36]. These results are enthusiastic, but such studies deserve confirmation before recommending these probiotics in clinical practice. In this respect, none of these probiotics are included in the current recommendations established by scientific societies. Diets enriched in dietary fibers have also been studied in non-interventional cohorts, and have shown a relationship between fiber intake, particularly at more than 25 grams per day, and the reduction of pain in osteoarthritis [37,38], possibly via the production of SCFAs. The consumption of a prebiotic such as oligofructose could be a new potential avenue of investigation in metabolic OA, as shown by studies conducted in animals [23]. The potential value of manipulation of the intestinal microbiota by antibiotics in OA has also been studied, in particular with doxycycline but without significant improvement [39]. Restoration of the intestinal barrier could also be an interesting therapeutic approach. Physical activity, which is an integral part of the treatment of OA, could also act by directly modifying the intestinal microbiota [40]. Despite a modest efficacy, symptomatic slow-acting drugs for OA (SYSADOA) (i.e., glucosamine or chondroitin sulfate) could act on the symptoms of OA by modifying the intestinal microbiota [41]. Finally, fecal transplantation in OA is not currently being considered until now.

7. Conclusion

Experimental and human data are accumulating to implicate intestinal dysbiosis both in the structural alterations and the pain characterizing OA **(Table 1).** The action of the gut microbiome in OA is complex and most certainly involves a loss of diversity and alterations in the abundances of everal microbial taxa. Additional factors related to the gut microbiome could also be involved in OA. Among these factors are diet, metabolites, LPS production, alteration of the intestinal barrier, or bacterial translocation. The exact role and contribution of each of these factors remain uncertain, and it is not easy to discriminate obesity-related from OA-related microbiota alterations, as these two diseases are often associated. There are also potential links between dysbiosis and osteoarthritic pain reinforced by the action of the gut microbiome on the central nervous system. The association of pain and dysbiosis should open up interesting therapeutic prospects at a time when we are in dire need of new treatments, both symptomatic and structure-modulatory.

Species	Abondance	Expermiment	Publications
Mice model			
Bifidobacteria	Decreased	Gut microbiome alteration in obesity mice model induced by high fat diet	Schott et al. 2018
Lactobacillus spp	Increased	Associated with more important histological severity in post-traumatic osteoarthritis (DMM) in obesity mice model with high fat diet	Collins et al. 2015
Methanobrevibacter spp	Increased		
Fusobacterium	Increased	Association with increased histological severity in fecal transplantation of gut microbiome from patients with metabolic syndrome in mice model of post traumatic osteoarthritis by DMM	Huang et al. 2020
Faecalibacterium	Increased		
Ruminococcaceae	Decreased		
Human model			
Streptococcus	Increased	Association with a higher WOMAC pain score study of 1444 patients with hip osteoarthritis and knee osteoarthritis	Boer et al. 2019
Betaproteobacteria	Increased	Alteration of the microbial signature of cartilage in 67 patients with hip osteoarthritis, 42 patients with hip osteoarthritis and 20 controls.	Dunn et al. 2020

Table 1: Summary table of the different microbial species involved in osteoarthritis

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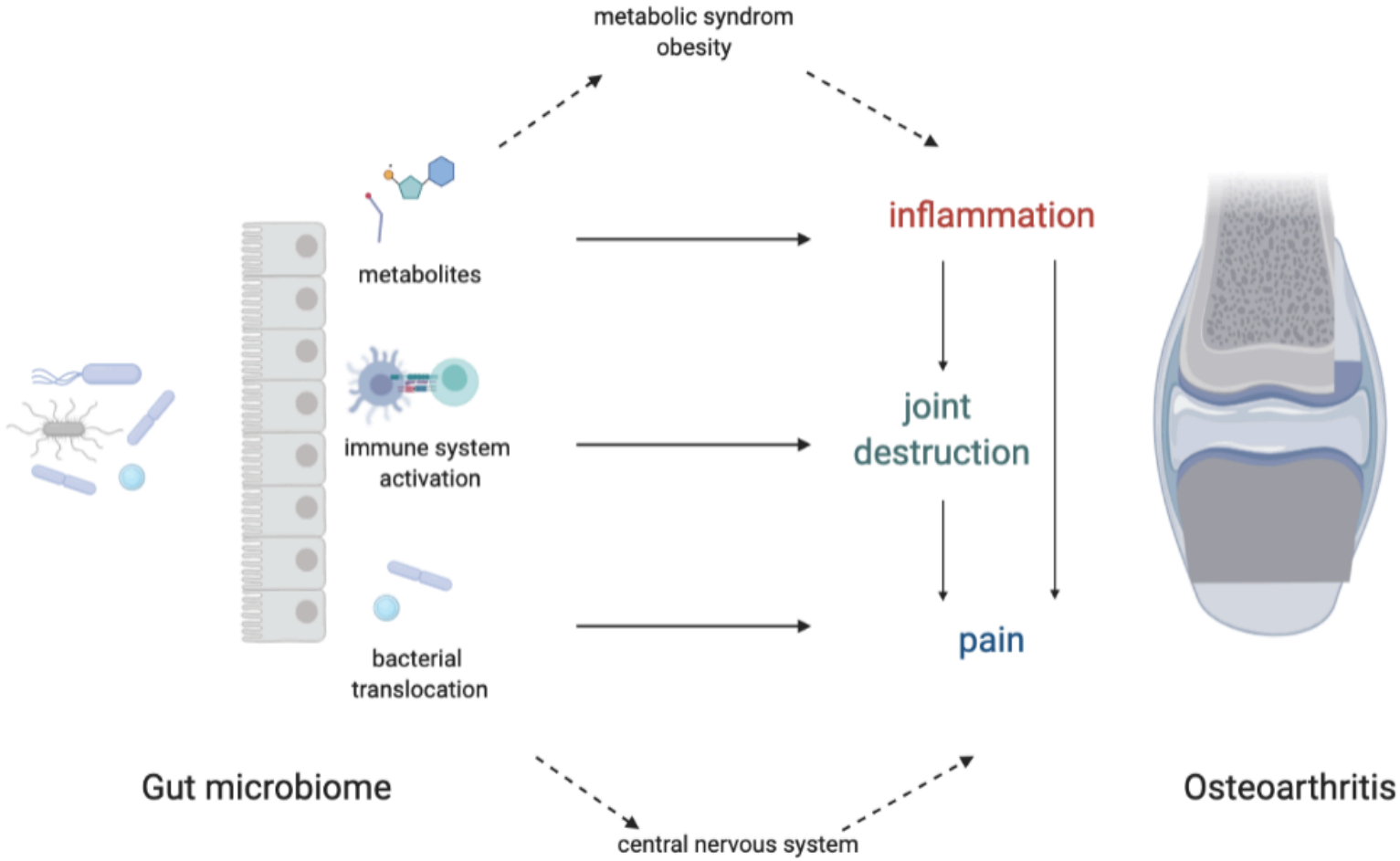

Figure 1 Summary table of the role of gut microbiome in osteoarthritis