Gut-disc axis: A cause of intervertebral disc degeneration and low back pain?

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Abstract

Purpose Low back pain (LBP), a widely prevalent and costly disease around the world, is mainly caused by intervertebral disc (IVD) degeneration (IDD). Although numerous factors may trigger this degenerative process, microbiome dysbiosis has recently been implicated as one of the likely causes. However, the exact relationship between the microbiome and IDD is not well understood. This review summarizes the potential mechanisms and discusses microbiome dysbiosis’s possible influence on IDD and LBP.

Methods Prospective literature review.

Results Alterations in microbiome composition and host responses to the microbiota causing pathological bone development and involution, led to the concept of gut-bone marrow axis and gut-bone axis. Moreover, the concept of the gut-disc axis was also proposed to explain the microbiome’s role in IDD and LBP. According to the existing evidence, the microbiome could be an important factor for inducing and aggravating IDD through changing or regulating the outside and inside micro-environment of the IVD. Three potential mechanisms by which the gut microbiota can induce IVD and cause LBP are: (1) translocation of the bacteria across the gut epithelial barrier and into the IVD, (2) regulation of the mucosal and systemic immune system, and (3) regulation of nutrient absorption and metabolites formation at the gut epithelium and its diffusion into the IVD. Furthermore, to investigate whether IVD is initiated by pathogenic bacteria and establish the correlation between the presence of certain microbial groups with the disease in question, microbiome diversity analysis based on 16S rRNA data can be used to characterise stool/blood microbiota from IVD patients.

Conclusion Future studies on microbiome, fungi and viruses in IDD is necessary to revolutionize our thinking about their possible role in the development of IVD diseases. Furthermore, we believe that inflammation inhibition and interruption of amplification of cascade reaction in IVD by targeting the gut and IVD microbiome is worthwhile for the treatment of IDD and LBP.

Level of Evidence I Diagnostic: individual cross-sectional studies with the consistently applied reference standard and blinding.

Keywords Low back pain · Intervertebral disc degeneration · Microbiome · Metabolites · Inflammation

Introduction

Low back pain (LBP) is a leading cause of disability worldwide affecting millions of people in their day-to-day activities [1]. There are many potential causes of LBP, including mechanical stress, age, genetic factors, but intervertebral disc (IVD) degeneration (IDD) is regarded as one of the most likely causes [2]. One of the major concerns around IDD is [3], however the exact cause and nature of such inflammation are not clearly understood. One of the putative triggers of inflammation has been hypothesized to be
infection of the IVDs by skin bacteria, especially *P. acnes* [4, 5]. Intriguingly, alterations in the microbiome (microbes in and on the human body) composition in the gastrointestinal system, skin and mouth are associated with the regulation of inflammation and autoimmunity in many other diseases, like rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, septic arthritis and other infectious diseases [6–11]. However, it is not yet clear if such microbial changes play any role in IDD. The existing evidence strongly indicates that changes in the microbiome composition and associated metabolites might play a key role in the regulation and management of LBP in patients with IDD.

**Human microbiome and IDD**

The human microbiome is rapidly emerging as an important player in regulating our health and diseases owing to advances in sequence-based detection methods. Strategies such as metataxonomics are being used as a targeted approach to sequence 16S rRNA genes (encoding bacteria’s ribosomal subunits that include both conserved and variable regions) via probes or primers to detect and identify bacteria, and specify a phylum, a group, a genus or even a species [12]. Further understanding of the microbiome in terms of functional genes can be done using metagenomics that can analyse the composition, function and variations of the microbiome [13]. Compared to 16S rRNA gene sequencing, metagenomic sequencing could allow deeper characterization of microorganism complexity and could identify a more accurate definition at the species level. The shotgun metagenomics could help in building a comprehensive description of the microbiome community [14].

Besides maintaining a stable microbial diversity, which in turn affects the characteristics of the host, microbiome can also affect the host phenotypes by secreting several microbial metabolites. Metabolomics can easily identify these markers and strengthen the early detection of diseases [15].

Recently, Rajasekaran et al. evaluated 24 lumbar IVDs and reported that the composition of the microbiome in healthy IVDs differed from those in the degenerated IVDs and herniated IVDs [16]. The study found *Firmicutes, Actinobacteria* and *Saccharopolyspora* to be abundant in normal IVD samples, which were related to the intestinal barrier function and antibacterial protection. On the other hand, few common human pathogens such as *Bacillus coagulans* and *Bacillus clausii* were detected in degenerate and herniated IVDs that have been implicated in spondylodiscitis, fracture, joint infections, meningitis and endocarditis. Based on the functional analysis, the microbiome can be distinguished as “good” or “bad” microbials. For instance, *Saccharopolyspora*, defined as “good microbiota” was found in healthy IVDs which produces macrolide antibiotics effectively against most gram-positive bacteria and some gram-negative bacteria. Some “bad” bacteria, which were found in higher abundance in degenerated and herniated IVDs, like *Pseudomonas veronii, Pseudomonas stutzeri, Streptococcus anginosus* that can cause sub-clinical infection and inflammatory response inducing IVDs degeneration. Microbiome dysbiosis, an imbalance between “good” and “bad” microbiota can be influenced by various environmental factors, including diet, diseases, genetic makeup of the host and medical intervention. This disrupts the diversity of the gut microorganisms by regulating the numbers of bacterial communities [17, 18]. However, the mechanisms by which “good” bacteria protect the IVD tissues, and “bad” bacteria damage the IVD are still unclear and require further investigation.

This study also challenges the dogma associated with IVD sterility. The presence of 58 overlapping bacterial species between the intervertebral IVDs and gut, 29 between IVD and skin suggests that IVD microbiome may talk to the gut microbiome, the gut microbiome may infiltrate into the IVD environment and play a key role in the development of IDD. Findings from this study provided evidence for us to further dwell into the phenomenon of IVD dysbiosis which could be an important cause of inflammation and IVD degeneration. In this regard, *P. acnes* has been identified as the most frequently isolated anaerobic microbe and has a great association with the vertebral osteomyelitis in bone and joint infection diseases [19]. Moreover, studies in animal models and humans have shown that a persistent imbalance of microbial community could regulate the secretion of inflammatory cytokines TNF-α, IL-1β and PGE-2. Interestingly, these inflammatory molecules have been reported to correlate with IDD. Taken together, all these strongly indicate that there are a variety of environmental factors that could induce dysbiosis by modifying the gut immune system and enhancing inflammation. Moreover, these changes could have far-researching influences as seen in degenerative spinal diseases and bone dysfunctions.

**Dysbiosis, IVD degeneration and low back pain**

Alterations in microbiome composition and host responses to the microbiota causing pathological bone development and involution [20, 21], led to the concept of gut-bone marrow axis [22, 23] and gut-bone axis [21]. Following the report by Rajasekaran et al., a similar concept of gut-disc axis has emerged that may play a key role in IDD and low back pain [16]. We explain below the cross-talks between gut microbiome and three different tissue types, and how they might be implicated in low back pain.
**Gut-bone marrow axis**

Gut dysbiosis has been found to enhance barrier permeability and increase intestinal inflammation in animal models of arthritis, diabetes and obesity [24–26]. Changes of gut microbiota induce the low-grade inflammation through enhancing the resolution of some specific inflammatory factors like short-chain fatty acids (SCFAs), which are generated by fermentation of complex carbohydrates, or promoting the leakage of bacterial products such as LPS (lipopolysaccharide) [27]. This low-grade inflammation can regulate the gut epithelial barrier by changing the expression of myeloid differentiation primary response gene 88 (MyD88) [28]. Besides, gut bacteria can also influence peripheral immune cells, bone marrow haematopoietic stem and progenitor cells (BM HSPCs). This is clearly demonstrated by the fact that germ-free mice have reduced numbers of myeloid progenitors in BM [29]. Moreover, researchers found the rag1-deficient mice have lower numbers of HSPCs and this effect could be reversed through faecal transplantation from wild-type mice [30]. Gut microbiome has shown the capability of changing HSPC differentiation through destroying BM function in obesity [31]. Furthermore, human spine has 26 vertebral bodies, and each consists of a typical bone marrow niche. They are another rich source of immune cells and gut dysbiosis can cause aberrant immune cell formation from the spinal bone marrows, just like the bone marrows in the hindlimbs. This is another root of systemic inflammation and may indirectly lead to back pain [32]. Therefore, the existence of gut-bone marrow axis can help us to understand the function of microbiome on distant organs.

**Gut-bone axis**

Gut hormones secreted from enteroendocrine cells following nutrient ingestion via food intake modulate metabolic processes including glucose homeostasis and food intake, and several of these gut hormones are involved in the regulation of the energy-demanding processes of bone remodelling [33]. Food is a source of nutrients which could be taken up by gut enteroendocrine cell to secrete gut hormones which are involved in the regulation of the energy-demanding process of bone remodelling. Biomarkers of bone turnover reduce slowly after diet consumption with substantially larger influences observed on bone resorption, compared with bone formation [34]. After diet intake, enteroendocrine cells in the gut secrete cytokines and hormones that regulate different metabolic processes [35]. For example, SCFAs can modify the musculoskeletal system by regulating the bone cells [21]. Gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are gut secreted hormones responsible for the amplification of insulin secretion, which in turn can stimulate insulin-mediated increases in bone formation [36]. Moreover, knockout of the GIP receptor in mice resulted in decreased bone mineral density (BMD) (3.7% decrease in total BMD at five months of age compared to wild type) bone strength, and a decrease in markers of bone formation, alkaline phosphatase and osteocalcin [37]. Much research has proved that the changeable level of BMD has a positive relationship with low back pain. [38, 39] Understanding the pathophysiology and physiology of the gut-bone axis may identify new therapeutic candidates for bone disorders and back pain.

**Gut-disc axis**

IVD is complex fibrocartilaginous joints that are generally referred to as the largest avascular structures in the human body. The blood vessels in the IVD exist only in the longitudinal ligaments and the outer layers of the annulus fibrosus. However, there is neovascularization when disc herniates into the epidural space, physical damage and fracture or a local inflammation on the disc and endplates. Thus, the infiltration of blood vessels into the degenerating disc will also be detected [37]. Gut microbes alter the intestinal microbial environment, fostering the production of various signalling molecules, immune cells and metabolites that may benefit bone. We hypothesize the microbial effects on the IVD mainly through the bloodstream. These metabolites and biological molecules produced by the gut microbiome reach distance tissue and cause a local pathological change.

According to the existing evidence, we believe that microbiome could be an important factor for inducing and aggravating IDD through changing or regulating the outside and inside microenvironment of the IVD. Figure 1 illustrates the three potential mechanisms by which the gut microbiota can induce IVD and cause LBP: (1) translocation of the bacteria across the gut epithelial barrier and into the IVD, (2) regulation of the mucosal and systemic immune system and (3) regulation of nutrient absorption and metabolites formation at the gut epithelium and its diffusion into the IVD.

**Translocation of the bacteria across the gut epithelial barrier and into IVDs**

Growing evidence support that low-grade inflammation associated with microbiome dysbiosis is an essential factor for the onset of musculoskeletal diseases, like rheumatoid arthritis [38, 39]. Taking cues from this, it’s likely that the microbiome dysbiosis in the gut and IVD could be related to the IDD and herniation, and possibly LBP.

A healthy IVD microenvironment is very similar to the central nervous system (CNS). CNS is regarded as an immune-privileged, where blood–brain barrier (BBB) and blood–spinal cord barrier separate the CNS from any systemic inflammatory states to maintain homeostasis within...
this specialized, vulnerable organ [40]. The blood–disc barrier keeps the IVD immune-privileged and protects it from systemic infection. The blood–disc barrier keeps the IVD separated from other potential inflammation, but it also blocks the immune surveillance (playing the role of sentry) started by our body’s immune system on the inner of disc. Immune cell cannot get timely feedback from the inner microenvironment of disc, which causes the worse inflammatory reaction. So it is the lack of IVD immune surveillance and hypoxic conditions that foster ideal conditions for the reproduction of anaerobic bacteria within the IVD upon invasion [41]. Furthermore, intestinal inflammation can promote intestinal permeability allowing more bacteria to cross the epithelial barrier [42]. Though most of the translocated bacteria are killed quickly by the immune system, a few bacteria can enter and survive while evading the immune response [43]. These bacteria arrive near the IVD and recruit more inflammatory cells (e.g. T cells, B cells, dendritic cells and macrophages) via release of pro-inflammatory factors (e.g. IL-6 and TNFα) [44]. Inflammatory cellular infiltration causes blood vessels to grow into the IVDs, which destroys the IVD’s appropriate anaerobic
environment. Additionally, abnormal mechanical loads and continuous microscopic injuries may also induce irreversible IVD damage and microfractures formation. A broken IVD provides an ideal place for the reproduction and growth of bacteria that evade humoral and cellular immunity, as well as diffusion of harmful microbiome metabolites. Microfractures also allow the immune cells to enter the IVD, which further aggravates IVD damage.

Bacterial invasion into the broken IVDs stimulates the IVD cells to secret inflammatory cytokines, e.g. IL-1α/β, IL-17, TNF-α and IL-6. At the same time, these cytokines destroy the IVD extracellular matrix (ECM) by promoting aggrecan and collagen degradation. A series of chain reactions started by these cytokines results in chemokine production, which further damages the ECM [45]. Such inflammation inside the IVD also induces an imbalance in anabolic and catabolic responses by IVD cells, resulting in IDD, herniation and discogenic back pain. Moreover, the release of inflammatory molecules secreted by damaged IVDs and activation of macrophages, T and B cells, mast cells and neutrophils further amplify the inflammatory cascade and thereby IDD. Bacterial translocation into the IVDs can also lead to activation of these immune cells by the release of lipopolysaccharide (LPS) and cause persistent pain. Such inflammation also results in increased innervation into degenerate IVDs that amplifies pain and transmit the pain signal to peripheral afferent nerve fibres located in dorsal root ganglia (DRG) and brain [46].

Regulation of the mucosal and systemic immune system

IDD has been proven to be correlated with abnormal production of pro-inflammatory factors by IVD cells (nucleus pulposus cells and annulus fibrosus cells) themselves, as well as immune cells, e.g. neutrophils, T cells and macrophages [45]. These molecules trigger a series of pathogenic and inflammatory reactions in IVD, which can activate senescence, apoptosis and autophagy and cause IDD [47, 48].

Gut microbiota communicates with the human immune system in a reciprocal manner [49, 50]. It has been reported that in a germ-free mouse model, the absence of gut microbiota produces an immature mucosal immune system and reduces proper immune signalling [51]. Immune system also regulates the localization and composition of microbiome [52]. Besides, communication with different niche-specific microbiomes is very important to develop and enhance the function of the immune system. When there is a gut dysbiosis, weakening of the epithelial barrier promotes increased permeability resulting in increased contact between the intestinal microbiota and the mucosal immune system [53, 54]. This excessive contact causes a massive influx of activated immune cells. These cells release vast quantities of pro-inflammatory cytokines (e.g. IL-6 and TNFα) into the bloodstream and regulate bone metabolism. These inflammatory cytokines and activated immune cells can migrate and gather near IVDs and induce IDD by modulating bone resorption and remodelling [45, 55].

Notably, the migration of immune cells into the IVD stimulates the IVD cells to generate neurogenic factors, e.g. brain-derive neurotrophic factor (BDNF) and nerve growth factor (NGF) [45, 56, 57]. This induces the appearance of nociceptive nerve fibres in the IVD as well as dorsal root ganglion (DRG). In addition, immune cells cause an elevated expression of pain-associated cation channels in the DRG due to the creation of an inflammatory milieu. In fact, DRG stimulation is used as a treatment strategy for chronic LBP [58].

Regulation of nutrient absorption and metabolites at the gut epithelium

A layer of mucus cover on the gastrointestinal epithelium forms a physical and firm barrier to prevent the invasion of pathogens in our gut [54]. Goblet cells produce mucins (MUC) continuously in normal physiological circumstances; however, gut toxins, inflammatory cytokines, microbiome and microbial metabolites modify this process positively or negatively [59]. Some inflammatory molecules like TNFα, IL-1β and IL-6 are the main regulators of mucin exocytosis and synthesis [60]. It has been known that IL-6 promotes the expression of the secreted gel-forming mucins (MUC5AC, MUC2, MUC6 and MUC5B) [61–63]. The prominent secreted gel-forming mucin in the small and large intestine is Mucin2 (MUC2). MUC2 is an important protective barrier against external pathogens, and it has diverse functions in intestinal homeostasis [64]. The mucus layer serves as an energy provider for gut microbiome. Moreover, it also serves as a matrix for commensal microbiome colonization and attachment, which prevents pathogenic bacteria from growing/binding within the mucus [65]. Currently, the capability of microbiota to degrade MUC2 has been thought of as a pathogenicity factor. Pathogens, including enterotoxigenic E. coli, could degrade MUC2 mucin through different mechanisms [66, 67]. Besides, acute intestinal infection induces rapid mucus secretion, which may aid in eliminating pathogens. Cross talk between the intestinal microbiota and mucus layer contributes to the regulated production of mucin by goblet cells [68]. Moreover, goblet cells are heavily influenced by interactions with the immune system. The epithelial barrier could be influenced or impaired by the damaged goblet cell, synthesis dysregulation and altered post-translational modifications when immune system changes in our gut [69]. The impaired epithelial barrier results in translocation of bacteria and their toxic metabolites. Cell wall components like endotoxin/LPS, microbiome metabolites, such as SCFAs/D-lactate and inflammatory factors produced

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by immune cells infiltrate into bloodstream and induce long-distance inflammation in the IVD [70]. For instance, SCFAs are fermented by the bacteria in the gut where they provide energy to epithelial cells and promote the activity of immune cells [71, 72]. SCFAs have emerged as key regulatory metabolites produced by the gut microbiota.

Although many studies have evaluated the effects of prebiotic consumption on bone resorption or osteoclast formation, our understanding of how gut microbes communicate with IVD remains ill-defined [73]. The degenerative disc is accompanied by vertebral bone remodelling, including bony endplate thickening and osteophyte formation [74]. Calcification of the IVD has been correlated with osteoblast formation [75]. Animal research showed reduced osteoblast numbers in C57BL/6 mice and osteoporotic mice following propionate and butyrate treatment. SCFAs promote the differentiation of naïve CD4+ cells into Tregs resided preferentially on the endosteal surfaces of bone [76]; Tregs could promote osteoblast differentiation and suppress osteoclastogenesis [77, 78], moreover, it is also required for parathyroid hormone-stimulated (PTH-stimulated) bone formation [79]. Besides, SCFAs have direct effects on inhibition of bone resorption or osteoclast formation either via activation of G Protein-Coupled Receptors (GPCR) or through histone deacetylase (HDAC) inhibition. Moreover, the appearance of calcium deposits in the disc and expression of the extracellular calcium-sensing receptor (CaSR) are closely related to the GPCR in the degenerated discs [80], which means that the diffusion of gut-derived SCFAs into the IVDs can therefore lead to calcification and IDD. SCFAs can also induce pro-inflammatory phenotypes of immune cells in the IVD and lead to the pathogenesis of neuropathic pain.

**Taxonomic characteristics of gut microbiota in patients with IVD**

The toxaemic factor hypothesis has been proposed for the relationship between microbiome dysbiosis and degenerative disease. This hypothesis assumed that the overgrowth of gram-negative bacteria in the intestines leads to an increase in toxic metabolites that enter the circulation and ultimately promote inflammation [81]. To investigate whether IVD is initiated by pathogenic bacteria and establish the correlation between the presence of certain microbial groups with the disease in question [75], taxonomic characteristics of stool/blood microbiota from IVD patients can be performed using microbiome diversity analysis based on 16S rRNA data. 16S rRNA gene sequencing is the most commonly used method of microbiome diversity analysis [74] that aims to identify the composition of the microbial (bacterial) group in the biological samples. Microbiome diversity analysis includes alpha diversity and beta diversity analysis. Alpha diversity is used to measure how many microbial species exist in a single sample and the proportion of each species. Beta diversity aims to measure the similarity of the composition of the microbiome across different samples [76]. LEfSe (linear discriminant analysis effect size) analysis is frequently used to analyse differences in the microbiome and find the biomarkers [77]. PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) [78] helps us to predict the functional composition of a metagenome using marker gene data and a database of reference genomes.

**Future directions**

Findings by Rajasekaran et al. will lead to a paradigm shift and help us gain greater insight into the role of human microbiome in the pathophysiological changes of IDD. But it still has limitations with respect to sample size and challenges to avoid the cross-contamination of air pollutants and blood-borne bacteria while collecting IVD tissues. Moreover, this study only detected the existence of bacteria in IVDs. It has been shown that there is a large diversity of both eukaryotic viruses and prokaryotic phages in healthy humans [82]. Besides, human blood, which like IVD tissues was thought to be sterile in healthy conditions, has been detected to contain fungi and viruses [83]. We strongly believe that recognition of the effects of microbiome on IDD will broaden our horizons about microbial ecology in the gut and IVD in LBP patients. Future studies on fungi and viruses in IDD are necessary to revolutionize our thinking about their possible role in the development of IVD diseases. Furthermore, we believe that inflammation inhibition and interruption of amplification of cascade reaction in IVD by targeting gut and IVD microbiome are worthwhile for the treatment of IDD and LBP.

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