

Review

Pathological Relationship between Intestinal Flora and Osteoarthritis and Intervention Mechanism of Chinese Medicine*

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ABSTRACT Chinese medicine (CM) has a good clinical effect on osteoarthritis (OA), but the mechanism is not very clear. Evidence-based medicine researches have shown that intestinal flora plays a role in the pathogenesis and succession of OA. Intestinal flora affects the efficacy of CM, and CM can affect the balance of intestinal flora. This paper focuses on the relationship between intestinal flora, intestinal microenvironment, brain-gut axis, metabolic immunity and OA, and preliminarily expound the significance of intestinal flora in the pathogenesis of OA and the mechanism of CM intervention. The above discussion will be of great significance in the prevention and treatment of OA by CM from the perspective of intestinal flora.

KEYWORDS osteoarthritis, intestinal flora, pathogenesis, treatment, mechanism of Chinese medicine

Osteoarthritis (OA) is not only a common chronic disease among middle-aged and elderly, but also the main source of disability in elderly in developing countries. OA related medical problems and medical expenses increased sharply. Thus, ensuring the effective treatment and prevention of OA has become the major public health problem. Furthermore, the pathogenesis of OA is unclear.^(1,2) In recent years, studies have found that intestinal flora is closely related to the occurrence and development of certain diseases,^(3,4) including the development of OA, causing acute or chronic symptoms.⁽⁵⁾ Yet, the role of intestinal flora in OA between the development of succession characteristics and the interaction with the host, as well as their drug effects are unclear. In this paper, the role of intestinal flora in OA pathogenesis are discussed, which will provide the reference for further study on the prevention and treatment of OA from the perspective of targeting intestinal flora.

Intestinal flora structure and metabolites dynamically change accompanied by their host's age, diet structure and intestinal environment. Intestinal flora plays an important role as a "metabolite filter" in human dietary structure and oral drugs. These intestinal microecology, metabolites and corresponding brain-intestinal axis and signal pathways are closely related to the occurrence and development of bone and joint diseases. In recent years, high-throughput sequencing techniques, such as macrogenomics, 16s RNA genomics,

and metanomics have been used to analyze the composition of intestinal flora, further confirming that an imbalance of intestinal flora and changes in metabolites are closely related to the occurrence of OA. CM has a good clinical effect on osteoarthritis, yet, the mechanism is still unclear. Intestinal flora affects the efficacy of CM, and the CM can also affect the balance of intestinal flora. Therefore, it is of great significance to elaborate the prevention and treatment of OA by CM from the perspective of intestinal flora.

Relationship between Intestinal Flora, Intestinal Microenvironment and OA

The stable environment formed by intestinal flora, intestinal flora metabolites (short-chain fatty acids, inorganic salts, etc.) and the intestinal mucosal immune system is called

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intestinal microenvironment.^(6,7) An increasing number of studies have shown that the intestinal microenvironment dominated by intestinal flora remains stable and the body will keep healthy. Otherwise, the body is susceptible to a disease state, which is closely related to the intestinal microenvironment in a variety of diseases.^(8,9) Studies have found that there is a potential cross-sectional association between inflammation, intestinal microflora and knee joint injury. Studies on the polymorphism of intestinal microflora in mice with diet-induced OA have found that OA is associated with a reduction of *bacteroidetes* and *brucellosis* bacteria.^(10,11) The mechanisms of intestinal flora-intestinal microenvironment-OA can be summarized as follows: the mechanisms of intestinal flora-intestinal microenvironment-OA can be summarized as two aspects, namely: on the one hand, intestinal flora regulate nutrient absorption and endothelial cells of the intestinal immune system; on the other hand, microorganism and bacterial molecular metabolites translocate across the endothelial barrier and enter systemic circulation.⁽¹²⁾ Therefore, it is of great significance to explore the relationship between intestinal flora, the intestinal microenvironment and OA. What is worthy of noting is that the specific network and drug regulation mechanisms have not been elucidated and require further research.

Relationship between Intestinal Flora, Brain and OA

Investigating the brain-gut axis is an emerging discipline which is generated by the intersection of brain science and gastrointestinal related fields. The connection between the intestinal flora and the brain affects the immunity, metabolism, nervous system and behavior. After the establishment of communication between the intestinal flora and brain, mutual regulations are carried out through signals of nervous system, neuroendocrine and nerve immunity.^(13,14) Intestinal flora can affect chronic degenerative diseases through the gut-brain network. Therefore, intestinal flora is closely related to OA. Generally speaking, based on the theories of gut-brain axis, gut-brain peptides, gut-brain interactions and CM theories of Shen (Kidney)-bone marrow generation and Gan (Liver)-tendon blood storage, the intestinal flora interacts with each other and influences each other via the gut-brain network and two-way regulation.^(15,16) In addition, gastrointestinal

activity also effects the sensation, emotion and behavior of the central nervous system.^(17,18)

Brain-intestinal peptide, which is the material basis of the brain-intestinal related network, is one kind of secretory substance mainly involved in the gut-brain related network. Histamine, serotonin, substance P, corticotrophin releasing factor, and other related factors, work together in the brain and related networks, with some neurotransmitters or peptide hormone transferring between the central nervous system and enteric nervous system. Overview, the brain is closely links to the bowel, and the body via the brain-gut axis and neuroendocrine network to establish a two-way loop between gastrointestinal function of brain gut interaction, which is closely related to a variety of joint degenerative disease.^(19,20)

Relationship between Intestinal Flora, Metabolic Immunity and OA

Intestinal flora is closely related to immune diseases, degenerative diseases and metabolic diseases, which is of great significance for rational, safe, and effective drug treatments.^(21,22) The intestinal microbiome has been shown to have an influence on the immune system. New mechanisms have been discovered by which changes in the microbiome can increase the risk of autoimmune diseases.^(23,24) Given the unsatisfactory results of current therapies, new approaches are needed to treat OA. With the discovery of the microbiome contributes to the production of inflammatory cytokines and the application of emerging sequencing technologies, it is clear that intestinal flora, acting as an environmental factor, plays an important role in the pathogenesis of OA.^(25,26)

Bacterial lipopolysaccharide is the main component of bacterial endotoxin. Relevant studies have shown that lipopolysaccharide can induce and mediate inflammatory processes.^(27,28) However, the mechanism of lipopolysaccharide causes local inflammatory reactions and the consequently affects chondrocyte degeneration is still unclear. Moreover, the effects on bone formation are also unclear.^(29,30) Inflammation associated with cartilage degeneration, is mainly caused by bacterial lipopolysaccharide related inflammatory cytokines, including interleukin (IL)-1, IL-6 and activation factor ligands (RANKL). Yet, how bacteria lipopolysaccharide mediates the production of these factors by cartilage is unclear. Despite the

relevant researches are scarce both at domestic and international academic sector, the research of the axis of intestinal flora-metabolic immunity-OA may provide a new clue for the clinical treatment of OA.^(31,32)

Relationship between Intestinal Flora, Signal Pathways and OA

Studies have found that disorders of intestinal flora are closely related to toll-like receptors (TLRs). The employ of a toll-like receptor 4 (TLR4) monoclonal antibody can improve the microflora diversity in an ulcerative colitis rat model. This suggests that TLR4 may play a bidirectional regulatory role, both affecting the occurrence of ulcerative colitis and the changes in the intestinal flora of ulcerative colitis patients.^(33,34) Studies have found that the myeloid differentiation primary response gene 88 (MyD88)-dependent TLR/nuclear factor kappa-B signal transduction pathway are involved in both pulmonary and intestinal immune regulation in a rat model of intestinal flora imbalance.⁽³⁵⁾ TLR recognition of bacterial lipopolysaccharides plays an inflammatory role mainly through a MyD88-dependent signaling mechanism, and thereby mediates an inflammatory response.^(36,37) Inflammatory factors generated by bacterial lipopolysaccharides play a role in inhibiting chondrocyte degeneration through TLR signal pathway, yet, the specific mechanism is still unclear.^(38,39) Current research on the role of intestinal flora on OA pathogenesis and the effect of drugs is one research hotspot.

At present, it is a hot and difficult point to research the pathogenesis of OA and the way of drug action mode from the perspective of intestinal flora. TLRs can recognize bacterial lipopolysaccharides, thereby inducing the secretion of proinflammatory cytokines, and then play a corresponding signal pathway, thereby inducing the occurrence and development of OA. Engaging in research in this area will help to elucidate the pathogenesis of OA and provide a new therapeutic avenues for the targeted prevention and control by CM.

Mechanisms of CM to Treat OA through Regulating Gut Microflora

The oral administration of CM is widely used in clinical practice. Oral administration is the main route of administration for traditional medicine compounds, as their main chemical composition can be directly

absorbed into the human digestive tract. In the digestive tract, part of the chemical composition in the form of a prototype or metabolites can be absorbed into the blood, and then via the blood circulation reach to the target organs. However, because of the existence of abundant intestinal microorganisms in the intestinal tract, there is an interaction between intestinal microorganisms and CM: on one hand, intestinal flora has an impact on the metabolism and absorption of CM; on the other hand, oral CM affects the balance of intestinal microorganisms.^(40,41) The interaction mechanism between CM and intestinal microorganism is shown as follows.

Research shows that CM compounds can adjust the dynamic balance of intestinal microecology through the proliferation of probiotic bacteria. CM compounds can enhance acclimatization resistance, by changing the structure of the active ingredients, degrading the toxic ingredients, and influencing each other mutual adjustment.^(42,43) In addition, intestinal flora has a metabolic effect on CM. Some effective components of CM must be first metabolized by intestinal flora before they can be absorbed and used by the body to produce therapeutic effects.^(44,45) With the advance studies on human intestinal flora, considering intestinal flora as a direct or indirect therapeutic target, pharmacological approaches utilizing intestinal flora interventions are the basis of "treatment through bacteria". This is also an important breakthrough and research direction in the treatment of diseases. In clinical practice, traditional medicine has special advantages in the prevention and treatment of bone and joint diseases due to its unique mechanism of action, despite this mechanism still remaining unclear. Therefore, it is a direction worthy of further research to explore the mechanism of CM compounds to treat OA through their activity on intestinal flora.

Summary and Prospect

With the advance of modern research, especially since the explosion in interest on intestinal microflora, researchers have found that intestinal microflora is closely related to the occurrence and development of bone and joint diseases. By reviewing how intestinal flora affects OA, the regulation of intestinal flora and the intervention of CM, what can be found is that intestinal flora acts as an environmental stimulus and plays an important role in the pathogenesis of OA. Therapeutic

strategies for the regulation of intestinal flora have great prospects, especially via the application of CM. Future studies on intestinal flora should focus on exploring whether there are specific pathogens which mediate the pathogenesis of OA and how signal transduction pathways influence the host. The discovery of specific pathogens can be used for the early diagnosis and prognosis of OA. Therefore, future advance studies are essential on intestinal flora research which investigate clear therapeutic targets for the treatment of OA using a CM approach. CM provides a good framework to treat OA much better. Future strategies could employ CM to target intestinal microflora in a precise way, in order to relieve the symptoms and improve the quality of life for KOA patients. In this way, CM could be used both for standard, and precision treatment of KOA.

In summary, this paper discusses the association between intestinal flora and OA by investigating the role of intestinal flora. This paper clarifies that intestinal flora is an important factor in the diagnosis and intervention of OA, which will provide new research avenues for the prevention and treatment of OA. Based on previous research and the overall concept of CM, we believe that intestinal flora, as an important part of the human body, should also play an important role in disease diagnosis and prevention. What is worth of thinking is whether it is possible to improve the diagnostic criteria of OA by studying the relationship between the CM constitution theory and intestinal flora. The promising therapeutic target is to influence the intestinal flora of patients through CM compounds, and thereby intervene the disease, so as to provide a basic theoretical basis for the research of CM. In the future, studies on intestinal flora and OA are worth of exploring.

Conflicts of Interest

There are no conflicts of interest to declare.

Author Contributions

Lu M and Zhou Q designed the article structure. Lu FG and Wang HX guided the writing of content. Wu YR and Kuang GY wrote the manuscript. All authors provided edits to the manuscript.

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