Editorial

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The Role of Microbiome Alterations in the Pathogenesis of Ankylosing Spondylitis: Insights and Implications for Future Therapies

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Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory disease predominantly affecting the axial skeleton, with an increasing body of evidence suggesting that the gut microbiome plays a critical role in disease onset and progression. This article reviews recent research on the gut microbiome in AS, exploring how dysbiosis and microbial dysregulation may influence immune responses, inflammation, and the development of axial spondyloarthritis. We discuss potential therapeutic strategies targeting the microbiome, including probiotics, prebiotics, and fecal microbiota transplantation, which may offer novel treatment avenues for AS patients. Additionally, the review addresses challenges and future directions in microbiome-based interventions.

Keywords: Ankylosing spondylitis • Gut microbiome • Dysbiosis • Immune modulation • Microbial therapies • Spondyloarthritis • Probiotics • Prebiotics

Introduction

Ankylosing spondylitis (AS) is a chronic, inflammatory autoimmune disorder primarily affecting the axial skeleton, particularly the sacroiliac joints and spine. It is characterized by progressive stiffness and fusion of the spine, leading to disability and significantly reducing the quality of life in affected individuals. AS is part of a group of diseases known as spondyloarthropathies, which share certain genetic and environmental factors. One of the most significant genetic risk factors for AS is the presence of the HLA-B27 gene, but it is not sufficient by itself to cause the disease, indicating that other factors, particularly environmental ones, play a key role in disease onset and progression. Among the potential environmental triggers, recent research has focused on the gut microbiome and its influence on immune system function. The human microbiome is a complex ecosystem of microorganisms, including bacteria, fungi, viruses, and archaea, residing in various parts of the body, with the gut microbiome being the most studied. The gut microbiota is involved in regulating immune system development, maintaining gut homeostasis, and protecting against pathogens. Alterations in the microbiome, known as dysbiosis, have been implicated in a variety of autoimmune diseases, including AS. This growing body of research suggests that dysbiosis may not only contribute to the pathogenesis of AS but could also represent a target for future therapeutic strategies. This paper aims to explore the role of microbiome alterations in the pathogenesis of AS, discussing the latest insights and the implications of these findings for future therapeutic approaches [1-3].

Discussion

The Microbiome and Immune Regulation

The human microbiome, particularly the gut microbiota, has a crucial role in modulating the immune system. It does so through a variety of mechanisms, including the induction of

tolerance to harmless antigens, the stimulation of antimicrobial immune responses, and the regulation of systemic inflammation. These interactions are largely mediated through the gut-associated lymphoid tissue (GALT), which communicates with peripheral immune cells. In health, the microbiome maintains a balanced relationship with the host immune system, ensuring immune homeostasis. However, disturbances in this balance, such as those caused by dysbiosis, can lead to abnormal immune activation and chronic inflammation, key features in the pathogenesis of autoimmune diseases like AS. Several studies have linked specific changes in the gut microbiota to autoimmune diseases. In the case of AS, the most prominent connection is between the gut microbiome and the HLA-B27 genotype, a major genetic risk factor for the disease. Research has shown that individuals with AS have a distinct microbiome composition compared to healthy controls. These differences may contribute to the initiation and exacerbation of AS through mechanisms like increased intestinal permeability, molecular mimicry, and modulation of local immune responses [4].

Dysbiosis in Ankylosing Spondylitis

Dysbiosis, or the imbalance in microbial communities, is a key feature in the pathogenesis of AS. Studies have consistently shown that patients with AS exhibit specific microbiome alterations, particularly an increase in the abundance of pro-inflammatory bacteria and a decrease in anti-inflammatory microbial species. For example, an overrepresentation of certain types of Enterobacteriaceae, such as Klebsiella pneumoniae, has been found in the gut microbiota of AS patients. Klebsiella has been implicated in triggering autoimmune responses in genetically predisposed individuals, particularly those with the HLA-B27 allele. This pathogen is thought to induce a molecular mimicry mechanism, where its antigens resemble those found in the body's tissues, leading to the activation of self-reactive T cells and promoting chronic inflammation. In addition to Klebsiella, other studies have identified alterations in microbial diversity and a reduction in beneficial microbes like Faecalibacterium prausnitzii, a species known for its anti-inflammatory properties. These changes may disrupt the regulatory balance of immune responses, promoting inflammation and contributing to the pathogenesis of AS. Moreover, there is evidence that the gut-bone axis, a concept describing the interaction between gut microbiota and bone metabolism, plays a role in AS. Dysbiosis could influence bone remodeling by affecting the immune cells responsible for bone resorption and formation, thus exacerbating the disease's musculoskeletal manifestations [5].

Intestinal Permeability and Inflammation

Intestinal permeability, often referred to as "leaky gut," is another critical factor linking the microbiome to the pathogenesis of AS. In a healthy individual, the intestinal barrier functions as a selective gate, controlling the passage of nutrients and preventing the entry of harmful substances into the bloodstream. In patients with AS, however, there is evidence of increased intestinal permeability, allowing the translocation of microbial products, such as lipopolysaccharides (LPS), into the bloodstream. These microbial products can trigger systemic inflammation by activating immune cells, such as macrophages and dendritic cells, through pattern recognition receptors like toll-like receptors (TLRs). This process exacerbates inflammation in both the gut and joints, contributing to the characteristic symptoms of AS [6]. The role of intestinal permeability in AS is further supported by studies showing that the use of probiotics or other interventions aimed at restoring gut barrier function can lead to improvements in disease activity. These findings suggest that addressing gut health may be a viable therapeutic strategy in AS.

The Role of the Gut-Joint Axis

The gut-joint axis refers to the communication between the gut microbiota and the joints, with both systems influencing each other in a bidirectional manner. This interaction has been increasingly recognized in the pathogenesis of autoimmune diseases like AS. As mentioned earlier, microbial products, such as LPS, can enter the bloodstream through an impaired intestinal barrier and reach distant organs, including the joints. Once in the joints, these products can activate local immune cells, promoting inflammation and contributing to the development of arthritis. Moreover, the gut microbiota can influence the production of specific cytokines and immune cells, including Th17 cells, which play a pivotal role in the inflammation seen in AS. Th17 cells, which are known to be activated by certain microbiota-derived signals, contribute to joint inflammation by producing pro-inflammatory cytokines such as IL-17. The role of Th17 cells in AS is well-documented, and their activation appears to be heavily influenced by the gut microbiota. Therefore, interventions that target the microbiome may have the potential to modulate the Th17 response and reduce inflammation in AS patients [7].

Therapeutic Implications: Microbiome-Based Approaches

The growing understanding of the role of the microbiome in AS has led to the exploration of microbiome-based therapeutic strategies. These strategies aim to restore the balance of the microbiota, enhance gut barrier

function, and modulate immune responses. Probiotics, prebiotics, and fecal microbiota transplantation (FMT) are some of the most promising approaches being investigated. Probiotics are live microorganisms that confer health benefits to the host when administered in adequate amounts. Several studies have demonstrated that probiotics can help restore microbial diversity and reduce inflammation in autoimmune diseases, including AS. For example, Lactobacillus and Bifidobacterium strains have shown potential in modulating the immune system and reducing disease activity in AS patients. Similarly, prebiotics, which are non-digestible food components that promote the growth of beneficial microbes, may help improve gut health and reduce inflammation in AS. Fecal microbiota transplantation (FMT) is another novel approach under investigation. FMT involves transferring fecal material from a healthy donor to a recipient, with the goal of restoring a healthy microbiome. Preliminary studies have shown that FMT can improve gut microbiome diversity and reduce disease activity in patients with inflammatory bowel diseases (IBD), and there is growing interest in applying this approach to AS.

Conclusion

Ankylosing spondylitis is a complex autoimmune disorder with a multifactorial etiology, involving genetic predisposition, environmental triggers, and immune dysregulation. Emerging evidence points to the gut microbiome as a critical player in the pathogenesis of AS, with dysbiosis potentially driving immune system dysfunction and chronic inflammation. Key mechanisms through which the microbiome influences AS include increased intestinal permeability, molecular mimicry, and the activation of Th17 cells. These insights provide new opportunities for developing microbiome-based therapies, such as probiotics, prebiotics, and fecal microbiota transplantation, which could complement existing treatments and potentially offer disease-modifying effects. While the evidence linking the microbiome to AS is compelling, much more research is needed to fully elucidate the specific microbial signatures associated with disease progression and to optimize microbiome-based therapeutic interventions. Furthermore, the complexity of the gut microbiota and its interaction with host genetics, environmental factors, and immune responses presents a significant challenge. Nonetheless, the growing recognition of the microbiome's role in AS holds promise for the development of novel, targeted therapies that could improve patient outcomes and quality of life.

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