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J Rheumatol 2018;94;36-39
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The Role of the Microbiome in Gut and Joint Inflammation in Psoriatic Arthritis and Spondyloarthritis

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ABSTRACT. Spondyloarthritis (SpA) encompasses a group of diseases characterized by an inflammatory arthritis involving both joints and entheses. However, extraarticular symptoms constitute a large element of the pathology and should not be underestimated. Microscopic gut inflammation is observed in 50% of patients with SpA and has been linked to disease activity, underscoring the effect of gut inflammation in SpA. In this review, we discuss the influence of gut microbiota on SpA pathogenesis. A change in microbiota composition has been linked to the development of various inflammatory arthritis, and dysbiosis is a potential factor in the pathogenesis of multiple inflammatory diseases. In this context, several groups have reported the modulatory effects of gut microbiota-derived metabolites on the effect of immune cells. The gut mucosa is populated by several types of regulatory T cells, but also some specialized unconventional innate-like T cells. These cells are predominantly found at mucosal and epithelial barrier sites, where they serve an essential role in modulating host-microbial interplay. Apart from the close association between the composition of the microbiota and inflammatory diseases, the therapeutic value of dysbiosis needs further investigation, and the identification of a causal inflammatory pathway between gut dysbiosis and musculoskeletal inflammation could revolutionize the therapeutic approach in SpA. (J Rheumatol Suppl. 2018 June; 94:36–9; doi:10.3899/jrheum.180135)

Key Indexing Terms:
- GRAPPA
- MICROBIOME
- SPONDYLOARTHRITIS

The Gut: Gateway to Joint Inflammation in Spondyloarthritis

Spondyloarthritis (SpA) consists of a group of chronic inflammatory diseases that primarily affect the musculoskeletal system and share common clinical features, genetic susceptibility, and pathophysiological mechanisms. These diseases include axial spondyloarthritis, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), some juvenile forms, reactive arthritis, and inflammatory bowel disease (IBD)-associated arthritis. SpA affects up to 1% of Western society, and its prominent clinical features include inflammatory stiffness, swelling, and/or loss of function of the axial skeleton (spine and sacroiliac joints) and/or peripheral joints, which may lead to irreversible structural and functional impairments and decreased quality of life. Patients with SpA frequently develop extraarticular manifestations such as acute anterior uveitis, psoriasis, and IBD.

Over the past 3 decades, our group has played a leading role in the examination of gut-joint disease in patients with SpA. We found that about 50% of SpA patients without gastrointestinal symptoms demonstrate microscopic signs of intestinal inflammation. Overall, 6.5% of these patients with SpA evolved to Crohn disease in 5 years’ time, but this fraction reached 20% of patients in the subset with chronic microscopic gut inflammation. Interestingly, the presence of microscopic gut inflammation was also linked to early disease onset, high disease activity, and the presence of bone marrow edema in sacroiliac joints. This finding underscores the potential effect of gut inflammation on the extent...
of disease in patients with SpA. Conversely, patients with IBD commonly develop joint inflammation with features of SpA\(^1\). The mechanism by which gut inflammation affects joint disease has been a longstanding area of research, but is still not well understood. Particularly, it is far from clear how gut microbiota influence SpA pathogenesis.

The human gut harbors a tremendously diverse microbial community, including the microbiota that modulate many physiological processes during homeostasis. The contribution of gut microbiota to the development of gut and joint disease is apparent from multiple experimental animal models, including HLA-B27 transgenic rats\(^2\) and SKG mice\(^8\). These models mimic gut and joint involvement in human SpA. Interestingly, these models do not develop SpA-like symptoms under germ-free conditions.

The microbiota, however, have been linked to the development of both chronic gut inflammation\(^9\) and arthritic pathologies\(^10,11\) when its composition is disturbed in animal models.

Dysbiosis, a change in microbial diversity and community composition, has gained much attention as a potential causal or contributing agent to many chronic inflammatory diseases, including IBD and SpA. Important immune- and barrier-modulating functions of the intestinal microbiota are attributed to the fermentation of dietary fibers into short-chain fatty acids (acetate, propionate, and butyrate). In Crohn disease, butyrate-producing bacteria, such as members of the cluster IV and XIVa Clostridia, which are known to steer regulatory T cell (Treg) functionality and to help maintain barrier integrity, are underrepresented\(^9\). Beyond butyrate, other metabolites, and antigens associated with Clostridium cluster IV and XIVa have gut barrier-protective effects. There is also evidence that gut microbiota-derived metabolites may modulate immunity by affecting innate-like T cell functions.

Data have shown a reduction of Faecalibacterium prausnitzii, which belongs to the cluster IV Clostridia, in stool samples of patients of SpA\(^12\). Moreover, we observed a significant correlation between the abundance of the genus Dialister in ileal and colon biopsies and the Ankylosing Spondylitis Disease Activity Score, a validated measure of disease activity that is widely used in axial SpA\(^13\). Other researchers have also found associations between the mucus-degrading Ruminococcus gnavus and Bath Ankylosing Spondylitis Disease Activity Index in AS stool samples\(^14,15\).

Collectively, microbial alterations are associated with clinical readouts of inflammation, which suggests the possibility of a connection between dysbiosis and disease status, although it is not firmly established.

**Microbial-responsive T Cells in the Intestine: Regulators of Gut and Joint Inflammation?**

Genome-wide association studies in both SpA and IBD have revealed polymorphisms in signaling pathways implicated in disease development, such as the interleukin 23 (IL-23) pathway\(^1\). This was strikingly shown in the SKG model, which carries a ZAP70 mutation, altering T cell receptor (TCR) signaling that depends on the IL-23/IL-17 pathway for development of gut and joint pathology\(^16,17\). These mice only show SpA-like disease (enthesitis and ileitis) when injected with β(1,3)-glucan, a microbial component\(^16\), but not when kept in germ-free conditions\(^8\). Further, tumor necrosis factor (TNF), a proinflammatory cytokine, is one of the most important cytokines involved in SpA and IBD pathogenesis, as proven by the success of anti-TNF therapy in both diseases\(^18\) and the development of Crohn-like ileitis, sacroiliitis, and enthesis in a TNF-overexpressing mouse model (TNF\(^\text{AARE}^+\))\(^19\). Recently, it was shown that germ-free TNF\(^\text{AARE}^+/−\) mice do not develop Crohn-like ileitis, TNF\(^\text{AARE}^+/−\)-associated dysbiosis is actively contributing to ileitis development, but its effect on enthesitis and arthritis is currently unknown\(^20\). Thus, aberrations in both pathways might result in an altered immune response to mucosal bacteria and their products, leading to disease initiation and progression.

The gut immune system harbors a number of regulatory cells, of which the CD4+CD25+FOXP3+ Tregs are the most studied population. Tregs are very important in maintaining peripheral tolerance and preventing exaggerated immune responses to physiologic environmental entities\(^21\). Next to Tregs, the gut mucosa is populated by several highly specialized, unconventional T cells with potent immune-modulatory properties that can also respond to gut microbiota either directly or indirectly. Innate-like T cells, such as invariant natural killer T cells (iNKT), mucosal-associated invariant T (MAIT) cells\(^22\), and γ-δ T cells\(^21\), are predominantly found at mucosal and epithelial barrier sites where they serve an essential role in modulating host-microbial interplay. These cells can release a broad spectrum of Th1-related cytokines (e.g., interferon-γ and TNF), Th2 (e.g., IL-4 and IL-10), or Th17 (e.g., IL-17 and IL-22) upon TCR activation, but also upon TCR-independent stimulation and act as a “bridge” between innate and adaptive immune responses. iNKT and MAIT cells both express a semi-invariant TCR that shows antigen restriction toward nonpolymorphic MHC-like molecules (CD1d and MR1, respectively) and that respond to microbial-derived products\(^22\). iNKT cells recognize bacterial-derived glycolipid molecules, whereas MAIT cells can be activated by vitamin B2 (riboflavin) metabolites, which are end products of bacterial and yeast biosynthetic pathways. These innate-like immune cells display plasticity; they can be skewed from an immune-protective role toward a predominant proinflammatory IL-17 profile in response to uncontrolled IL-23 signaling events\(^23\). The alteration in cellular phenotype could be mediated either directly or indirectly by chronic inflammation, by an aberrant Treg crosstalk, or by altered...
microbial-derived signals. There is some evidence from mouse studies that innate-like T cells are functionally skewed with altered features compared to steady state\textsuperscript{19,24}. However, whether these processes also occur in humans and whether there are regional differences according to the site of inflammation remains to be determined.

**Is the Intestinal Microbiota a Potential Target for SpA?**

Dysbiosis in inflammatory diseases such as SpA is poorly understood. The plasticity of the dysbiosis will determine whether correcting dysbiosis has therapeutic applications. In this context, 2 distinct hypotheses have been proposed to explain the relationship between microbiota and disease association\textsuperscript{25}. The first involves a unidirectional model in which dysbiosis occurs early in life (e.g., influenced by early-life antibiotic exposure, delivery mode, breastfeeding, etc.) with subsequent alterations in the mucosal immune system development. This leads to a permanent alteration in microbiota composition and immune polarization in adult life. Such a scenario has been described in mice lacking lymphotixin αβ, which affects the formation of gut-associated lymphoid tissue in the neonatal period and leads to the colonization and expansion of segmented filamentous bacteria that ultimately drive IL-17–mediated autoimmunity\textsuperscript{26}. The second model suggests a more reversible balance between microbiota composition, gene susceptibility, and immune activation that is compatible with the therapeutic application of microbiota as a target.

In the context of PsA and SpA, there is evidence for both unidirectional and multidirectional models. For example, breastfeeding was reported to protect against the development of AS\textsuperscript{27}, which could be an indirect link with its effect on microbiota composition. In addition, HLA-B27 may lead to changes in gut microbiota composition\textsuperscript{28}. In psoriasis, a differential relationship exists between microbiota and disease in adult versus neonatal life\textsuperscript{29}. In human PsA, profound changes in microbiota have been described\textsuperscript{30}. Whether similar shifts in microbiota occur in all different forms of SpA is not clear\textsuperscript{31}. Further, whether the gut is the only involved barrier site is equally unclear in view of data on lung microbiota\textsuperscript{31} and other rheumatic diseases such as rheumatoid arthritis\textsuperscript{32,33}.

The contribution of dysbiosis to inflammatory disease opens perspectives for the development of novel therapies aimed at restoring homeostatic microbial ecological communities. The concept of ecosystem restoration follows the idea that a dysregulated microbiota can be restored by the transfer of specific microbial consortia or even full microbial ecosystems [fecal microbiota transplantation (FMT)] from a healthy donor to a diseased individual. FMT is highly effective in restoring microbial complexity as a treatment for healthy donor to a diseased individual. FMT is highly effective in restoring microbial complexity as a treatment for recurrent *Clostridium difficile* infections in humans\textsuperscript{34} and for the restoration of rumen function in ruminants\textsuperscript{35}. The success of ecosystem restoration in several diseases may be a key to better understanding the precise effect of microbial changes on SpA disease initiation and progression, especially in analyzing the potential use of microbial supplementation as a therapeutic choice for patients with SpA.

Collectively, the data highlight that much more needs to be understood about the complex interrelration between genetics, environment, and inflammation, including regional and time-dependent effects. Further, the role of microbiota in educating and altering the functionality of local immune cells and its role in the development of SpA needs further research.

**REFERENCES**


