Intestinal Microbiota, HLA-B27, and Spondyloarthritis

Dangerous Liaisons

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KEYWORDS

• Spondyloarthritis • HLA-B27 • Microbiota • Innate mucosal immunity

KEY POINTS

- Spondyloarthritis (SpA) is a rheumatic disease commonly associated with extra-articular features, such as gut inflammation.
- Gut microbial changes have been detected in patients with SpA.
- Alterations in mucosal immunity potentially driven by HLA-B27 and microbiome interactions could potentially underly SpA disease development.

INTESTINAL MICROBIOTA IN SPONDYLOARTHRITIS: GOOD, BAD, AND UGLY

The human gut harbors a tremendously diverse microbial community that correlates with and even modulates many health-related processes. Disruption of this ecological equilibrium leads to dysbiosis, which is involved in a growing list of diseases, particularly inflammatory and autoimmune disease. Intriguingly, spondyloarthritis (SpA) patients frequently develop extra-articular manifestations, such as acute anterior uveitis, psoriasis, and inflammatory bowel disease (IBD). Moreover, microscopic signs of intestinal inflammation were observed in 50% of patients with SpA without gastrointestinal symptoms,[1] from which a fraction develops Crohn disease (CD) over time.[1,2] The presence of microscopic gut inflammation has been linked to early onset disease, high disease activity, and degree of bone marrow edema in sacroiliac joints.[3,4] Conversely, patients with

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IBD commonly develop joint inflammation with features of SpA.[5] Thus, there is an unclear relationship between joint and gut inflammation in SpA disease.

Experiments done on animal models of SpA provide compelling evidence for the involvement of indigenous microbiota in the disease. Rats transgenic for HLA-B27, a well-known risk factor for SpA (discussed later), develop SpA-like disease when exposed to specific pathogen-free enteric bacteria but not when raised under germ-free conditions.[6] A gut microbiota dysbiosis has been reported in HLA-B27 rats with notably an increase of *Akkermansia muciniphila* and *Bacteroides vulgatus*.[7,8] Both of these bacteria have mucolytic activity, which facilitates the access and the invasion of the gut epithelium by other microorganisms that may contribute to distant joint inflammation. Similarly, in the ankylosing enthesopathy model, mice do not develop joint disease in germ-free conditions.[9] Under conventional microbial conditions, SKG mice spontaneously develop chronic autoimmune arthritis. In contrast, under specific pathogen-free conditions, only the injection of curdlan (a major component of bacterial and yeast cell walls) can provoke severe arthritis, ileitis resembling CD, and unilateral uveitis.[10,11]

Gut dysbiosis has been demonstrated in several SpA subtypes (**Table 1**). It is challenging to compare and identify a simple, common dysbiosis detected in SpA studies. Several factors can explain these differences: the technology used to access the microbiome diversity, the level of taxonomic identification, the functional complementation and redundancy (proteins from different bacteria can achieve the same functions), patient characteristics (eg, diet, geography, medications, disease duration, or genotype), and the nature of the samples analyzed (feces or biopsies). In studies analyzing fecal samples, the microbial diversity observed was reduced in patients with SpA compared with healthy control subjects (see **Table 1**). Two studies analyzed (ileal/colonic) biopsies as starting material. Intriguingly, in both studies, a higher microbial diversity was observed in patients with SpA. Of note (functional) dysbiosis in the gut microbiome of patients with IBD has also been extensively reported (see **Table 1**; for extended details we refer to recent reviews[12,13]).

Two bacterial genus/species have been proposed as a marker of disease activity in axial SpA. Breban and colleagues[14] evidenced an increase of the species *Ruminococcus gnavus* abundance in patient feces compared with healthy control subjects. This species is also positively correlated with disease activity in patients having a history of IBD. *R gnavus* display a mucolytic activity, and this ability may contribute to trigger or maintain inflammation. Tito and colleagues[15] evidenced a strong association between the intestinal inflammation status and the mucosal microbiota profile of patients with SpA. Furthermore, the authors highlighted a positive correlation between the abundance of the bacterial genus *Dialister* with the Ankylosing Spondylitis Disease Activity Score. Manasson and colleagues[16] reported that *Dialister* bacteria was independently enriched in reactive arthritis patients with sacroiliitis and those with uveitis. Wen and colleagues,[17] also demonstrated dysbiosis between axial SpA and healthy control subjects analyzing shotgun sequencing data from feces. The authors reported an increase of abundance of the bacterial class Actinobacteria in ankylosing spondylitis compared with healthy control subjects. Actinobacteria are able to modify proteins by ubiquitination, targeting the proteins for degradation by proteasomes.[18] The authors proposed that Actinobacteria may activate the nuclear factor-κB pathway via the ubiquitination of the inhibitor molecule IκB inducing the accumulation of inflammatory factors in patients with ankylosing spondylitis.

Despite the identification of promising candidates and linking gut to joint inflammation, no single organism has been identified as inducing SpA or IBD. In both diseases, it is still not known if the gut microbiota is involved in the initiation of the disease or is a

Table 1
Overview of microbiome studies in patients with SpA

Reference	Disease	Technology	Sample	Number of Participants	Alpha-Diversity Compared with Healthy Control Subjects	Increased Compared with Healthy Control Subjects	Decreased Compared with Healthy Control Subjects	Interaction with Disease Parameter
Scher et al,[55] 2015	Psoriatic arthritis	16S rRNA amplicon seq	Feces	16 (+17 control subjects)	Decreased diversity		*p_Verrucomicrobia*, *c_Verrucomicrobiae*, *c_Clostridia*, *o_Verrucomicrobiales*, *g_Pseudobutyrivibrio*, *g_Akkermansia*, *g_Ruminococcus*	
Manasson et al,[16] 2018	Reactive arthritis	16S rRNA amplicon seq	Feces	30 (+32 control subjects)	No significant difference	*g_Ewinia*, *g_Pseudomonas*		Bacteria candidate (unranked) TM7, *p_Firmicutes*, *c_Clostridia*, *c_Fusobacteria*, *o_Fusobacteriales*, *g_Dialister*, *g_Erwinia*, *g_Campylobacter*
Breban et al,[14] 2017	SpA	16S rRNA amplicon seq	Feces	49 (+18 control subjects) + validation: 38 (+51 control subjects)	Decreased diversity	*f_Coriobacteriaceaea*, *g_ Coprococcus*, *g_Ruminococcus*, *s_Bifidobacterium longum*, *s_Blautia pruducta*, *s_Ruminococcus gnavus*		*s_Ruminococcus gnavus*

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Table 1
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Reference	Disease	Technology	Sample	Number of Participants	Alpha-Diversity Compared with Healthy Control Subjects	Increased Compared with Healthy Control Subjects	Decreased Compared with Healthy Control Subjects	Interaction with Disease Parameter
Tito et al,[15] 2017	Axial SpA	16S rRNA amplicon seq	Ileal and colonic biopsies	27 (+15 control subjects)	Trend to increased diversity (specially for patients with acute gut inflammation)			*g_Dialister*
Costello et al,[56] 2015	AS	16S rRNA amplicon seq	Ileal biopsies	9 (+9 control subjects)	Increased diversity	*f_Bocteroidaceoe*[a], *f_Rikenelloceae*[a], *f_Lachnospiraceae*[a], *f_Ruminococcaceae*[a], *f_Porphyromonadaceae*[a]	*f_Actinomycetaceae*[a], *f_Gemellaceae*[a], *f_Streptococcoceae*[a], *f_Veillonellaceae*[a], *f_ Prevotellaceae*[a]	
Stoll et al,[57] 2018	SpA (mainly AS)	16S rRNA amplicon seq	Feces	11 (+10 control subjects)	ND		*s_Faecalibacterium prausnitzii* A2-165	
Wen et al,[17] 2017	AS	Shotgun seq	Feces	73 (+83 control subjects) + validation: 24 (+31 control subjects)	Decreased diversity	*g_Collinsella*, *g_Neisseria*, *g_Bifidobacterium*, *g_Rothia*, *g_ Actinomyces*	*g_Entrobacter*, *g_Citrobacter*, *g_Fusobacterium*, *s_Prevotella meloninogenica*, *s_Prevotella copri*, *s_Prevotella* sp C561	

Halfvarson et al,[58] 2017	IBD	16S rRNA amplicon seq	Feces	109 (+9 control subjects)	*o_Alteromonadales*, *s_Alistipes massiliensis*	*f_Ruminococcaceae*, *f_Lactospiraceae*, *g_Coprococcus*, *g_Ruminococcus*, *g_Methano-brevibacter*, *s_Faecalibacterium prausnitzii*, *s_Prevotella copri*
Lloyd-Price et al,[59] 2019	IBD	16S rRNA amplicon seq + Shotgun seq	Feces + ileal and rectal biopsies	105 (+27 control subjects)	s_*Prevotella copri*, s_*Bacteroides fragilis*, s_*Escherichia coli*, s_*Klebsiella pneumonia*[b]	s_*Faecalibacterium prausnitzii*, s_*Bacteroides uniformis*, s_*Eubacterium rectale*, s_*Alistipes putredinis*[b]

Taxonomic abbreviations: phylum (p), class (c), order (o), family (f), genus (g), species (s).

Abbreviations: AS, ankylosing spondylitis; ND, not determined.

[a] No multiple test correction (q-value).

[b] Here are only represented the 4 most dysbiotic species out of 87 in total.

Data from Refs.[14–17,55–59]

consequence of the disease development. Moreover, other microorganisms within the microbial communities may play a role in SpA disease, such as fungi, virus, or protist. Additionally, a specific combination of genetic, microbiota, and other environmental factors can be involved and contribute to the disease. Evidence indicates that gut dysbiosis-induced intestinal inflammation leads to a compromised intestinal barrier in patients with SpA.[19] This could lead to translocation of bacterial components, some of which may traffic to the joints causing local inflammation.[20] Alternatively, intestinal T cells and macrophages, primed by the dysbiotic microbiota, might travel to the joints where they induce inflammation in the synovium.[21]

These observations suggest that restoring immune homeostasis in the gut by modulating the microbiota is a promising therapeutic strategy for targeting remote sites of inflammation, such as articular joints in rheumatic disorders. One of the treatment options is the use of probiotics. A noncontrolled pilot study found a positive effect of supplementing a probiotic consisting of a mixture of *Lactobacillus acidophilus* and *Lactobacillus salivarius* to patients with SpA with quiescent ulcerative colitis.[22] In this study, significant reductions were noted in two disease activity indices: Bath Ankylosing Spondylitis Functional Index and Visual Analogue Scale scores. However, other studies failed to document significant beneficial effects of probiotics. As an alternative to probiotic treatment, the use of fecal microbiota transplants may be explored to restore the microbiota equilibrium. More research and clinical testing are needed to fully explore the use and efficacy of microbiome-tailored approaches in the treatment of SpA pathology.

INNATE(-LIKE) LYMPHOCYTE RESPONSES IN THE GUT: SENSORS OF INTESTINAL DYSBIOSIS IN SPONDYLOARTHRITIS?

The human gut mucosal immune system has largely evolved to maintain an essentially symbiotic relationship with a complex microbial community. Commensal microbiota plays a key role in the development and maturation of the host immune system, in this way indirectly leading to protection against the deleterious effect of pathogenic microorganisms.[23] The size of the intestinal immune system is substantial (about 70%–80% of all the immune cells are found in the gut wall) and a diverse and mostly unique composition of cell subsets are present even early in life as recently underscored by advanced high-dimensional cytometric analyses of human gut biopsies.[24,25]

The understanding of the innate immune responses involved in the protection of tissue homeostasis and the immune response to infection at mucosal surfaces has evolved over the last years, but many questions remain on the tight regulation of multiple cellular interactions. Although resident mononuclear phagocytes (mainly macrophages and dendritic cells) are key inducers of primary immune responses, a clear separation of adaptive and innate immunity in the intestinal milieu is more challenging to define because also highly differentiated lymphocytes seem to possess innate-like immune cell functions. An essential first layer of host defense against pathogens is the epithelial layer, in which absorptive enterocytes, mucus-producing goblet cells, enteroendocrine cells and Paneth cells (predominantly found in the small intestine), and particular T-cell subsets are present. The latter, the so-called intraepithelial lymphocytes, include cells from the T-cell receptor (TCR) $\alpha\beta$+ and TCR$\gamma\delta$+ lineages, comprise a considerable fraction of the total body's T cells, and play a key role in host (innate) immune responses (extensively reviewed in[26]). Scattered throughout the lamina propria or organized in tissue-specific lymphoid structures, such as Peyer patches, isolated lymphoid follicles, and cryptopatches, other innate(-like) intestinal lymphocytes are found.[27] These include TCR$\gamma\delta$+ T cells, more recently identified

populations of innate lymphoid cells (ILC), invariant natural killer T cells (iNKT), and mucosal associated invariant T (MAIT) cells (reviewed in[28,29]).

ILCs form a rare population of (lineage negative) lymphoid cells lacking rearranged antigen-specific receptors, which are found in blood circulation but predominantly present in mucosal areas. ILCs include natural killer cells with cytotoxic properties and non-cytotoxic "helper-like" ILCs, which express the interleukin-7 receptor (CD127).[30] The activity of ILCs is shaped by multiple tissue-specific signals, including nutrients, microbial factors, and cytokines and therefore they are important players in (gut) tissue homeostasis and inflammation.[30] iNKT and MAIT cells are classified as unconventional T cells (to which also subsets of γδ and CD1a and CD1b restricted T cells belong) and both express a semi-invariant TCR and show antigen restriction toward nonpolymorphic MHC-like molecules (CD1d and MR1 respectively) by which they can respond to microbial-derived products. iNKT cells recognize bacterial-derived glycolipid molecules, whereas MAIT cells are activated by vitamin B_2 (riboflavin) metabolites, such as ribityllumazines and pyrimidines. Many vitamin biosynthetic pathways are unique to bacteria and yeast organisms, suggesting that MAIT cells recognize these ligands to detect microbial infections. iNKT and MAIT cells can also be activated independently of their TCR stimulation, mainly by cytokine-mediated signaling events.[31] Similar to the classic delineation of T-helper subsets, ILC, iNKT, and MAIT cells have been categorized into distinct subsets based on shared transcription factors and cytokine signatures including: ILC1/iNKT1/MAIT1 cells expressing the transcription factor T-bet and producing interferon-γ, ILC2/iNKT2 regulated by GATA3 and secreting interleukin (IL)-5 and IL-13, and finally ILC3/iNKT17/MAIT17 cells characterized by the key Th17-related transcription factor RORγt and IL-17 and IL-22 expression.[32–34] Of note, it is at the moment unclear whether a subpopulation of MAIT2 cells exists, but MAIT cells expressing high levels of IL-13 have been described recently.[35] This classification holds true to some extent (being also less clear for human-derived cells) because they show a general plasticity *in vivo* and the existence of discrete functional compartments within the known subsets have been reported.[35,36]

Strong evidence suggests that host-microbial interactions play a key role in the development and function of these lymphoid cells. From experiments with germ-free and antibiotic-treated mice, it is clear that ILC, iNKT, and MAIT cells experience maturation in the gut mucosal surfaces.[10,37,38] ILC diversity seems maintained on encounter with microbiota, by epigenetic mechanisms of ILC specification.[36,39] Furthermore, it was recently shown rather unexpectedly that commensal microbiota-derived metabolites can even control the development of thymic MAIT cells in mice, in a process where a MAIT ligand (5-OP-RU: 5-[2-oxopropylideneamino]-6-d-ribitylaminouracil) is able to travel from mucosal surfaces to the thymus, there being presented by MR1 expressing cells.[40] In this regard, one might speculate that gut dysbiosis as observed in patients with SpA could have significant immunologic effects potentially contributing to SpA pathology. This might be especially relevant in the context of an aberrant IL-23/IL-17 (type 3) immunity strongly associated with SpA disease.[31,41] Indeed, several studies have highlighted that MAIT, ILC, γδ, and iNKT cells, of which some express Rorγt, can act as major contributors to IL-17-mediated pathology in SpA joints.[42–45] Whether local gut interactions between these immune cells and microbiota might potentially contribute to SpA pathology warrants further investigation.[31]

HLA-B27 AND THE MICROBIOTA: THE NEW KID ON THE BLOCK?

It has been known for a long time that the MHC class I gene HLA-B27 is an important genetic risk factor for the development of SpA, still its exact contribution to the disease

development remains enigmatic. Given the potential role for microbiota in the pathogenesis of SpA as described, it is plausible to hypothesize that HLA-B27 might affect the composition of the microbial community in susceptible patients. From a teleologic perspective, the major histocompatibility complex is easily the most polymorphic set of genes in the human species. Some have proposed that this diversity helps to reduce the chance that any single infectious agent would eliminate the human race. If so, it is logical to believe that HLA molecules would present bacterial antigens such that one's HLA type would impact the ecosystem that constitutes the gut microbiota. Experimental evidence supports this hypothesis. Using samples obtained during colonoscopy on healthy individuals, Asquith and colleagues[46] reported that the gut microbiome of HLA-B27-positive individuals differed from those with other HLA types. This study also supports the contention that the change in the microbiota is primary rather than secondary to a change in intestinal mucosa. The same study also demonstrated that HLA-DRB1, which predisposes to rheumatoid arthritis, likewise has an effect to shape the microbiota.[46] Other publications on sprue,[47] diabetes,[48] and CD[48] have also reported that HLA molecules affect the composition of the microbiota.

The simplest hypothesis to explain the mechanism of this effect of HLA is to cite its known function in antigen presentation. The diversity of HLA results in differential immunity to specific bacteria, which in turn skews the composition of the microbiota. A seminal study by Paun and colleagues[48] indicates that the antibody immune responses to specific commensal bacteria are impacted by one's HLA alleles. With regard to HLA-B27 specifically one might assume this is linked to particular changes in adaptive CD8 T-cell responses. Although this idea was abandoned for some time with the notion that $CD8^+$ T cells are not essential for joint and gut disease manifestations in a B27 transgenic rat model,[49] several recent reports have resurrected the potential importance of $CD8^+$ T cells in human SpA disease.[50–52] Studies directly linking B27-$CD8^+$ T cells responses to alterations in intestinal microbiota are therefore of interest. It is possible that this is not the only mechanism by which HLA-B27 impacts the microbiota. For example, in HLA-B27 transgenic rats, antimicrobial peptides are increased in the gut before the onset of bowel or joint inflammation.[7] Because HLA-B27 tends to misfold,[53] some evidence indicates that it activates the unfolded protein response, which in turn could affect the synthesis of antimicrobial peptides and thus alter the microbiota. In addition, this could underlie alterations in type 3 responses observed in SpA,[54] affecting intestinal antimicrobial responses. In this regard, a further understanding of the mechanisms by which HLA-B27 alters gut microbiota could lead to strategies to suppress or even prevent SpA pathology.

CONCLUDING REMARKS

The precise relationship between intestinal changes and joint inflammation as observed in patients with SpA is still ill defined but it is clear from clinical and experimental data that underlying genetic predisposing factors (eg, HLA-B27) and/or environmental factors (microbiota) might play a key role herein. Future research approaches including in-depth (paired) microbial and immune cell profiling of gut tissue samples from patients with SpA and control individuals will shed further light on this matter. Moreover, this will lead to better knowledge regarding the presence of specialized immune subsets in the SpA gut mucosae and potentially their role in antimicrobial responses. Unraveling the underlying cellular and molecular pathways in SpA disease models will help to clarify the precise nature of the relationship among microbiota, mucosal, and HLA-B27-mediated immunity and their complex contribution to gut and joint pathology.

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DISCLOSURE

The authors have nothing to declare.

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