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The Microbiome in Psoriasis and Psoriatic Arthritis: Joints

Jose U. Scher

ABSTRACT. The microbiome is a known and established immunomodulator of many inflammatory disorders, including psoriasis and psoriatic arthritis. Microbes co-evolved with their human hosts and provide them with nutritional, metabolic, and immunologic support. An accumulating body of evidence has revealed that psoriatic diseases are characterized by a state of intestinal dysbiosis, which has been linked to a decrease in beneficial commensals and fatty acids. This has been shown in both animal models and human samples, and multiple studies have addressed the physiological and potentially pathogenic role of intestinal and cutaneous microbes in human health and disease. In this review, we discuss state-of-the-art literature in the field of the microbiome in psoriatic diseases that was presented during the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2017 annual meeting, with a special emphasis on synovio-entheseal inflammation. A better understanding of these microbe-host interactions can lead to novel diagnostic and therapeutic targets. (*J Rheumatol Suppl.* 2018 June;94:32–5; doi:10.3899/jrheum.180134)

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For millennia, microbes have co-evolved with their human hosts, populating most mucosal sites. These microorganisms are fundamental to their host's physiology and help maintain immune and metabolic homeostasis. An accumulating body of literature has established the mechanisms that underlie the crosstalk between the microbiome-mucosal interface and the downstream host immune response. However, the precise molecular signaling that directs this microbial influence in disease pathogenesis is emerging and continues to be a central research area in the fields of inflammation, oncology, and autoimmunity.

Joshua Lederberg defined and described the microbiome as “the ecological communities of commensal, symbiotic, and pathogenic microorganisms (including their genes) that literally share our body space”¹. While adults carry 2–3

pounds of bacteria at any given moment, the genes within the human microbiome astoundingly outnumber the host's genetic contribution 100-fold². These populations, with niche-specific characteristics, inhabit the upper and lower respiratory tract, skin, upper gastrointestinal tract, and female genital tract. However, the largest proportion of human microorganisms resides in the lower gastrointestinal tract, which is home to hundreds of bacterial, viral, and fungal species that form a complex and dynamic ecosystem³.

The microbial colonization of the gut begins at birth with vaginal- or cutaneous-derived bacteria, depending on delivery mode⁴. These populations vary significantly, and the intestine's final composition depends on many factors, including host genetics, milk and food types, maternal microbiota, and exposure to antibiotics and other insults⁵.

After the first year of life (when solid food is introduced), the human microbiome begins to maintain its overall structure over time and becomes robust and resilient^{2,6}. However, when this equilibrium is perturbed, a dysbiotic process can serve as a triggering factor for the initiation and perpetuation of many inflammatory arthritides, including rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA)⁷. This process has been studied and validated over the last 2 decades in animal models of these disorders, where specific perturbations in the microbiome's composition can result in downstream inflammatory events at mucosal surfaces, ultimately leading to systemic disease in susceptible hosts⁵. Multiple cells residing in the intestinal lamina propria appear to be important in translating dysbiosis into local and distal proinflammatory programs, including

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dendritic cells, Th17 cells, plasma cells, innate lymphoid cells, γ - δ T cells, and several others⁸. Several mechanisms have been proposed through which microbiome community perturbations may direct the immune response, including altered epithelial and mucosal permeability, loss of immune tolerance to components of commensals, and trafficking of effector immune cells into the synovium.

Intestinal Microbiome in PsA and SpA: From Models to Humans

The clinical and biological connection between SpA, PsA, and gut inflammation is well established. As a group, SpA-spectrum diseases share a genetic predisposition (i.e., HLA-B27); effector immune cells in their pathogenesis (Th17 cells and other type-17 cells); and clinical manifestations around peripheral and axial arthritis, psoriasis, and intestinal inflammation. The reason certain specific phenotypes are expressed in particular individuals at the expense of other phenotypes has remained one of the leading enigmas in the field. What is more certain is the well-established connection between the development of synovio-entheseal inflammation and psoriasis in the context of clinical (and subclinical) gut inflammation (and vice versa). This is best exemplified by the so-called “enteroarthropathies,” in which intestinal infectious agents trigger distal disease.

This is indeed the case in reactive arthritis (ReA), where bacterial gut pathogens cause joint inflammation in genetically predisposed patients⁹. Moreover, about 20% of patients with ReA go on to develop ankylosing spondylitis (AS). A similar pattern of gut-joint axis pathology is evidenced in Whipple disease and jejunoileal bypass arthritis^{10,11}. Intriguingly, over 50% of patients with SpA and PsA have subclinical gut inflammation, supporting the involvement of mucosal inflammation in the pathogenesis of these diseases^{12,13}.

Similarly, there is an intimate and reciprocal connection between gut and joint inflammation in inflammatory bowel disease (IBD), in which peripheral arthritis occurs in up to 25% of patients¹⁴. Spine involvement, particularly asymptomatic sacroiliitis, is even more frequent, with fully manifested AS developing in up to 1 in 10 patients with IBD.

Animal models of SpA and PsA (i.e., HLA-B27 transgenic rats and SKG mice) do not develop SpA-like disease when raised under germ-free conditions (cages voided of microorganisms). It is only when exposed to specific members of the enteric community that these animals develop the phenotype (peripheral arthritis, SpA, psoriasiform skin disease, and Crohn-like ileitis), supporting the hypothesis that gut microbiota is indeed necessary for the initiation of disease^{15,16}. However, the mechanism by which this occurs is still a matter of intense research. Certainly, the role of Type-17 cells and the interleukin (IL)-23/IL-17 axis appears to play a central role^{17,18,19} because these cells are essential in the initiation and maintenance of gut inflammation in

IBD²⁰. Similarly, the high expression of IL-17 can be found in the synovial fluids of SpA, while increased circulating Th17 cells have also been reported²¹.

To date, there have been few comprehensive studies of intestinal inflammation characterization in humans with SpA spectrum disease and PsA. Classic work by Mielants, *et al* initially found an increased intestinal permeability in patients with RA, SpA, and IBD²². More recent, Ciccia, *et al* found that more than half of patients with PsA have subclinical gut inflammation and increased levels of Th17 as well as Th9 cells²³. Similarly, only a handful of studies have characterized the link between PsA and the microbiome. Two studies have assessed the cutaneous microbiota composition in patients with psoriasis, with somehow divergent findings. However, both Gao, *et al* and Fahlén, *et al* found that psoriatic plaques have a significantly lower abundance of *Propionibacterium spp.*^{24,25}. This is of interest because PsA develops in up to one-third of patients with psoriasis, making the skin microbiome a potential biomarker (and target) for the development of synovio-entheseal inflammation.

Our group described the intestinal microbiome in both patients with psoriasis and PsA compared to healthy controls and found that, while both psoriasis and PsA groups showed decreased abundance of the *Coprococcus* genus compared to healthy controls, the PsA group was further characterized by significantly lower levels of the *Akkermansia* and *Ruminococcus* genera. This suggests a continuum in the loss of diversity that may potentially correlate with the natural history of disease²⁶. Curiously, studies in IBD also implicate these genera, with a decreased abundance of *Ruminococcus* and *Akkermansia* in both ulcerative colitis and Crohn disease²⁷. Further, we found that this intestinal dysbiosis in patients with PsA correlates with decreased levels of medium-chain fatty acids (MCFA) in the intestinal luminal content, which are known to be beneficial for the maintenance of gut epithelial health²⁸. These may also represent potentially modifiable biological factors in the progression from psoriasis to PsA²⁶. Although this is still a nascent field, recent work on human SpA²⁹, IBD-arthritis³⁰, and ReA³¹ points toward a common gut dysbiotic process that underlies these inflammatory arthritides.

Strategies to Restore Intestinal Homeostasis

There are multiple potential ways to alter the intestinal microbial community in an attempt to restore gut health and downstream immune responses in psoriatic disease. The strategies range from dietary habit changes to modifying the bioactive molecules that are produced by bacterial strains. Although there is some evidence for a potential clinical benefit of weight loss in psoriasis and PsA^{32,33}, the data remain nonexistent for microbial ecosystem therapeutics through fecal microbiota transplant. This is not the case in IBD, where many studies have shown significant positive results in the treatment of colitis^{34,35,36}, supporting an

argument that these interventions could at least theoretically be applied to the treatment of psoriatic disease.

The involvement of the microbiome in humans has been studied for several decades and is familiar to the rheumatology community. The advent of large, parallel sequencing technologies and dramatic advances in the understanding of mucosal immunology have provided a more precise knowledge of the microbe-host cross-talk in physiology and inflammatory disease. How and why microorganisms and their components influence immune homeostasis and the downstream activation of proinflammatory events in autoimmunity is a matter of intense research. Similarly, the application of this basic knowledge in the clinical setting and as potential therapeutic targets is offering new opportunities for the treatment and prevention of psoriatic disease and related conditions.

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