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The role of the gut and microbes in the pathogenesis of spondyloarthritis

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A B S T R A C T

The intestinal microbiota is firmly implicated not only in the pathogenesis of inflammatory bowel disease (IBD) but increasingly also in the development of inflammation at extraintestinal tissue sites. Significant clinical, genetic, immunological, and microbiological overlap exists between IBD and spondyloarthritis (SpA), which indicates that pathophysiological mechanisms are shared between these diseases and may center on the intestinal microbiota. Recently, culture-independent techniques have enabled the microbiota in health and disease to be described in increasing detail. Moreover, functional studies have identified myriad host effector and regulatory pathways that shape or are shaped by this microbial community. We consider the complex relationship between SpA pathogenesis and gut microbes, with a discussion of how manipulation of the gut microbiota itself may be a promising future target for SpA therapy.

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Introduction

The potential of the human microbiota to redefine our understanding of spondyloarthritic diseases or spondyloarthritides (SpAs) is discussed within this review. We begin with an overview of the microbiota, moving to potential relationships between the intestinal microbiota and SpA pathogenesis as this has been a major and ongoing focus of research efforts. This discussion includes consideration of different inflammatory pathways that may intersect with an altered gut microbiota, a phenomenon termed "dysbiosis". We further consider how extraintestinal translocation of intestinal microbes or microbial products may contribute to SpA-related disease, in addition to microbiota-related immune pathways that may link gut and joint pathology. Finally, we review therapeutic manipulation of the microbiota and future research directions for both clinicians and basic scientists. The authors acknowledge the valuable contributions of many to this field, especially those that could not be cited in this review due to space constraints.

The human microbiome

The past decade has seen the advent of high-throughput sequencing approaches to characterize the human microbiota in increasing detail. The human body provides a plethora of habitats for the colonization of trillions of microbes. This is manifest in the high degree of inter-site variation in the community structure of microbiota. For instance, anaerobic Firmicutes/Bacteroidetes spp. dominate the intestine, whereas Actinobacteria and Proteobacteria spp. are found in high abundance on the skin [1]. Indeed, even individual teeth may have a distinct microbial community structure [2]. It is also evident that there is considerable interindividual variation in the microbiota at least at the species level. However, despite this species diversity, it appears that there is an aggregate selection towards species with similar functional gene profile at specific tissue sites [1].

The microbiota is rapidly acquired post partum and persists in a state of flux for the first few years of life. A myriad of factors influence the early structure of the microbiota including delivery method, parenteral nutrition, early infection, and antibiotic use in infancy. As the first few years of life represent a critical window of microbial exposure and immune education of the host, it is therefore feasible (albeit unproven) that early changes to the microbiota may be relevant to the pathogenesis of SpA-related diseases, despite their adult onset.

By roughly 3 years of age, the microbiota appears to stabilize, more closely resembling that of an adult. Nonetheless, this stability is relative. For instance, consumption of a strongly plant- or animal-based diet by human subjects can lead to changes within the microbiota within 24 h, although reversion to a pre-diet community structure is observed within days of returning to a "normal" dietary intake [3]. Following antibiotic treatment, the microbiota is also rapidly impacted, but returns to a pre-antibiotic state consistent with the idea of ecological memory. The intrinsic stability of the microbiota remains an ongoing area of research, but it is possible that a failure to return to a "normal" gut ecosystem following a disturbance of the microbiota in SpA-susceptible individuals may be functionally relevant to disease pathogenesis.

The definition of what constitutes a "normal" gut microbiome, however, is far from resolved. Recently, many efforts are undertaken to study the composition and function of the human gut microbiome as a new strategy to understand IBD. The European MetaHIT consortium identified three different metagenomes from fecal samples from four European countries [4]. These so-called enterotypes were not nation or gender specific. Each enterotype had a dominant bacterial genus: enterotype 1 was dominated by the genus *Bacteroides*, enterotype 2 by *Prevotella*, and enterotype 3 by *Ruminococcus*. These enterotypes appeared to be functionally different and showed differences in substrate fermentation [4]. However, this concept has not been confirmed by others, such as the National Institutes of Health Human Microbiome Project.

Links between SpA and bowel disease

SpA refers to a group of clinically and genetically related disorders, whose entities include ankylosing spondylitis (AS), psoriatic arthritis (PsA), juvenile SpA, reactive arthritis (ReA), and inflammatory