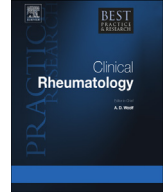




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2

The intestinal microbiome in human disease and how it relates to arthritis and spondyloarthritis



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Humans and microbes have developed a symbiotic relationship over time, and alterations in this symbiotic relationship have been linked to several immune mediated diseases such as inflammatory bowel disease, type 1 diabetes and spondyloarthropathies. Improvements in sequencing technologies, coupled with a renaissance in 16S rRNA gene based community profiling, have enabled the characterization of microbiomes throughout the body including the gut. Improved characterization and understanding of the human gut microbiome means the gut flora is progressively being explored as a target for novel therapies including probiotics and faecal microbiota transplants. These innovative therapies are increasingly used for patients with debilitating conditions where conventional treatments have failed. This review discusses the current understanding of the interplay between host genetics and the gut microbiome in the pathogenesis of spondyloarthropathies, and how this may relate to potential therapies for these conditions.

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Introduction

It has long been hypothesized that most human diseases arise because of interactions between host and environmental factors, including the microbiome. There are ten fold more bacteria in and on our

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bodies than the total of our own cells, with the human intestine containing ~100 trillion bacteria. Our microbial communities are not passive bystanders, and we are only just beginning to appreciate the influence our microbial residents have on our overall health. Interrogation of our microbial communities using classical microbiology techniques offered a restricted view of these communities, allowing us to only see what we could grow in isolation. However, recent advances in sequencing technologies have greatly facilitated the systematic and comprehensive interrogation of the microbiome, and in turn, the elucidation of its role in human health and disease.

Dynamics of the gut microbiome

It is estimated that 29% of all microbes that live in and on the human body reside in the gut. The human gut microbiome contains a dynamic and vast array of microbes that are essential to health as well as providing important metabolic capabilities. Until recently, comprehensive studies of this type of microbial community has been difficult and limited due to classical analysis techniques [1,2], notably the limited capacity to profile bacterial populations using culture based methods. The application of molecular techniques, particularly sequencing, has shown the remarkable amount of diversity in the human gut, exceeding all previously held beliefs. Originally, the dominant species in the gut was thought to be *Escherichia coli*, as pathogen detection was the primary aim and normal flora was disregarded and considered inconsequential. Sequencing based methods have shown, in contrast to classical culture, a far greater diversity of bacteria living in our gut [2,3], and profiled them quantitatively with much greater accuracy. This has provided researchers with the tools required to examine microbial communities in health and in many diseases where it has been long suspected that the microbiome interacts with the host to causing disease. This has been of particular value in investigation of the gut's role in metabolism, pathogen resistance, as well as the body's immune response and role in driving immune-mediated diseases.

Studies comparing the gut microbiota of lean and obese twins have shed light on the importance of intestinal microbes and how a change in microbiome composition can affect food metabolism in the gut [3–5]. Turnbaugh et al. showed that even with a similar genetic make-up, obese twins had substantial differences in the composition and diversity of their gut flora with a dominance of Gram-positive bacteria from the phylum Firmicutes, compared with discordant or lean twins [3]. This shift in gut flora composition altered how food was broken down and metabolised in the gut, leading to increased body mass index, adiposity and obesity [3,4,6]. This demonstrates that shifts in the intestinal microbiome have potential functional consequences on the health of the individual [7]. To distinguish whether the changes observed in the human twins played a causative role in their obesity, faecal samples from four twin pairs were transplanted into germ free mice [8]. The authors found that the Firmicutes phylum that dominated the microbial communities in the obese twin, lead to obesity in the germ-free mice. In contrast, *Bacteroides* dominated the microbial communities in the lean twin, and kept the germ-free mice lean.

Whilst it is not surprising that diet can change the intestinal microbial community, it is only in recent years that these changes have been shown to influence the tendency to develop inflammatory disease. Maslowski, Vieira et al., 2009 showed that a lower intake of fibre from complex plant polysaccharides adversely affects the makeup of the intestinal microbiota, which leads to less production of immunomodulatory products in particular short-chain fatty acids (SCFA) [9]. These SCFA are produced by the phylum Bacteroidetes, so a shift in the flora from predominantly Bacteroidetes to Firmicutes due to a more western diet with less fibre, reduces the amount of SCFA secreted. The effect SCFA has on the immune response was investigated in a mouse strain deficient in single G protein–coupled receptor, GPR43 [9]. Mice lacking GPR43 failed to suppress inflammation in models of colitis, arthritis and asthma, as did germ-free wild-type mice also lacking SCFA. Wild type mice raised in non-germ-free conditions were able to suppress inflammation. This suggests that diet-induced reduction in faecal SCFA leads to a reduced ability to suppress a variety of inflammatory conditions. Fascinatingly, genetic studies have now demonstrated association of multiple GPRs with human diseases, notably with ankylosing spondylitis (AS), providing evidence for a role of this mechanism in disease pathogenesis [10].

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