The Microbiome’s Effect on Psoriatic Arthritis

Epidemiological evidence points to an intimate relationship between intestinal inflammation and joint inflammation, such as psoriatic arthritis.

The microbiome — the trillions of microbes found in the body — has become a subject of increasing interest in the etiology of inflammatory immune-mediated diseases. The microbiome has been correlated with metabolic, neoplastic and autoimmune diseases, including obesity, diabetes mellitus, gastrointestinal cancer, rheumatoid arthritis, lupus, and psoriasis. Much of the original research on the microbiome in autoimmunity was first reported on inflammatory bowel disease. Strong epidemiologic evidence suggests that there is an intimate relationship between intestinal inflammation and joint inflammation in spondyloarthropathies, including psoriatic arthritis.

Research into the role that microbiota in the gut might play in the human immune system started in the late 1990s. The microbiome of the gut, also known as the gut flora, has been shown to influence autoimmune diseases, including inflammatory disorders. A poor mix of microbes (dysbiosis) in the gut may also aggravate the immune system and induce inflammation.

The revolution of high-throughput microbial DNA sequencing has advanced the knowledge and understanding of mucosal immunity and how it relates to gut microbiota. "In fact, it is now well established that the intestinal microbiota shape the immune system and mediate homeostasis in healthy states or promote inflammation when dysbiosis occurs," state authors led by Jose Scher, M.D., of New York University School of Medicine, New York, in a recent review of the microbiome in inflammatory arthritis and human rheumatic diseases.

The intestinal microbiome also appears to affect distant sites, including the joints, through immunomodulation. Research suggests that common immune-mediated inflammatory pathways seen in the “skin-joint-gut axis” in psoriatic arthritis are induced or at least mediated by the microbiome.

Dr. Scher and colleagues recently characterized the diversity and taxonomic relative abundance of the gut microbiota in patients with never-treated, recent-onset psoriatic arthritis. Using high-throughput sequencing, they compared the composition of gut microbiota in 16 patients with psoriatic arthritis, 25 patients with psoriasis of the skin, and 17 healthy, matched controls. They also assessed samples for the presence and levels of fecal and serum secretory IgA, proinflammatory proteins, and fatty acids.

They found that the gut microbiota in patients with psoriatic arthritis and psoriasis was less diverse as compared to that of the healthy controls. The psoriatic arthritis and psoriasis patients had a lower relative abundance of multiple intestinal bacteria, and those samples from psoriatic arthritis patients had a lower abundance of what are considered to be beneficial bacteria.

The researchers noted that the gut microbiota profile in psoriatic arthritis was similar to that in patients with inflammatory bowel disease. Changes in specific inflammatory proteins in the psoriatic arthritis patients were distinct from that in patients with skin psoriasis and healthy controls. The dysbiosis in the psoriatic arthritis patients correlated with decreased levels of both medium-chain fatty acids and RANKL in the intestinal lumen. This suggests that microbiome changes are linked to alterations in mucosal integrity and dissemination of systemic inflammation, they state.

In addition, the gut microbiota profile in patients with psoriasis was between that of psoriatic arthritis patients and that of the controls, leading the researchers to suggest that there is a continuum in disappearing intestinal microorganisms through the natural history of the disease.

Microbiome Targeting Strategies

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Microbiome Targeting Strategies

Since the microbiome has been implicated in inflammatory responses, researchers have attempted to modulate the composition of gut flora or their byproducts to stop inflammation. These attempts range from fecal microbial transplantation to restore a "healthy" intestinal microbiome to the use of agents such as probiotics, prebiotics, specific microbiome-derived metabolites, or molecular targets.

Fecal microbial transplantation has proven highly effective, and in some cases has even cured, patients with antibiotic-resistant Clostridium difficile infections. This treatment has been used in autoimmune diseases, most notably in inflammatory bowel disease, with some promising results in small studies.

Future clinical trials of fecal microbial transplantation that also include immune effects will determine whether this approach can be adapted to treat psoriatic arthritis. In a new review, Dr. Scher and colleagues suggest that the potential immune-modulating effects of fecal microbial transplantation in rheumatic diseases should first be attempted in previously untreated patients with new onset disease or in those with advanced disease who are not responding to any other therapy.

Another strategy relies on incorporating agents based on live organisms to modify the composition of the microbiome. Animal studies show amelioration of inflammatory bowel disease by either Bacteroides fragilis or a cocktail of Clostridia. Other studies show a beneficial effect of Lactobacillus strains in collagen-induced arthritis. These studies are all small and only show modest, if any, effects.

Still other researchers have used molecules with immunomodulating properties, including polysaccharides, structural proteins, and short-chain fatty acids, that show some potential as treatments for inflammatory bowel disease and other systemic autoimmune disorders. Multiple pharmaceutical companies have microbiota-based approaches in the pipeline for inflammatory and autoimmune disease in both preclinical studies and clinical trials.

What’s more, the microbiome may be found to be involved in pharmacokinetcis of oral disease-modifying anti-rheumatic drugs or serve as a predictor of drug response. Therefore, it may also be used for therapeutic purposes in autoimmunity and rheumatic diseases. Ultimately, researchers are looking to answer "whether we can successfully target the microbiome for therapeutic purposes in autoimmune and rheumatic diseases," state Dr. Scher and colleagues.

References:
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