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The role of the gastrointestinal tract in the pathogenesis of rheumatic diseases

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A B S T R A C T

Dysregulation of the intestinal epithelial barrier in genetically susceptible individuals may lead to both intestinal and extra-intestinal autoimmune disorders. There is emerging literature on the role of microbiota changes in the pathogenesis of systemic rheumatic diseases such as rheumatoid arthritis, spondyloarthropathies, and connective tissue diseases. Although the role of the gastrointestinal tract in the pathogenesis of spondyloarthropathies is well defined and many studies underline the importance of gastrointestinal inflammation in modulating local and systemic inflammation, the data are inconclusive regarding the effect of dysbiosis on rheumatoid arthritis and connective tissue diseases. This review aims to summarize current data on the role of the gastrointestinal involvement and intestinal microbiota in the pathogenesis of systemic rheumatic disease.

Introduction

The gastrointestinal tract regulates the trafficking of macromolecules between the environment and the host through an epithelial barrier mechanism [1]. The intestinal epithelial barrier, together with the gut-associated lymphoid tissue and neuroendocrine network, plays a fundamental role in controlling the equilibrium between tolerance and immunity to non-self-antigens [1]. Dysregulation of this organ in genetically susceptible individuals may lead to both intestinal and extraintestinal

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autoimmune disorders [1]. The gastrointestinal tract is colonized by many trillions of microbes that represent the so-called microbiota [2]. These microorganisms are not mere bystanders because they play metabolic, trophic, and protective roles and participate in normal human development and homeostasis [2]. The perturbation of this interaction results in dysbiosis that in turn may influence the susceptibility of the host to many immune-mediated diseases. There is emerging literature on the role of microbiota changes in the pathogenesis of systemic autoimmune disease such as type 1 diabetes, celiac disease, ankylosing spondylitis (AS), and rheumatoid arthritis (RA). This review aims to summarize the current data on the role of the gastrointestinal involvement and intestinal microbiota in the pathogenesis of systemic rheumatic disease.

Rheumatoid arthritis

RA is a chronic autoimmune inflammatory disorder affecting 0.5–1% of the population [3]. Although the cause of RA remains elusive, it has been demonstrated that in genetically predisposed subjects carrying the (Human Leukocyte Antigen) HLA–DRB1*04 cluster, environmental factors such as the oral and gut microbiota may lead to the abnormal activation of the innate and adaptive immunity, which involve cellular and humoral immune responses [4]. This activation leads to the formation of autoantibodies [rheumatoid factors (RF) and antibodies against citrullinated peptides/proteins (ACPA)] and invasion of T cells and B cells into the synovium [4] (Fig. 1). Loss of intestinal integrity and increased intestinal permeability have been demonstrated in RA patients, particularly those receiving non steroid anti-inflammatory drugs (NSAIDs) and those with active joint disease [5–7]. Alteration of intestinal permeability may facilitate antigenic absorption and contribute to the persistence of the disease; however, more studies are required to further clarify this specific issue.

Gastrointestinal microbiota in rheumatoid arthritis patients

Many studies have asserted the role of gastrointestinal microbiota in the pathogenesis of RA. This is suggested by the evidence that the oral bacteria *Porphyromonas gingivalis* (PG) is capable of inducing the local production of citrullinated protein [8]. PG is a leading pathogen of chronic periodontitis [9] and produces a unique bacterial enzyme, PG peptidyl-arginine deiminase (PPAD), which has the ability to convert arginine residues in proteins to citrulline [8]. Because protein citrullination alters the protein structure, PPAD may be involved in the alteration of the host signaling network and immune evasion (Fig. 1).

Unlike in the case of the oral microbiome, conflicting data emerge from the studies of the intestinal microbiome in animal models of RA and in humans. Data from murine studies support the role of microbiota in influencing arthritis susceptibility. Liu X et al. [10] performed 16S rRNA sequencing to characterize the gut microbiota of DBA1 mice that did or did not develop collagen-induced arthritis and demonstrated marked and significant divergence in the distribution of microbiota after arthritis induction. Mice susceptible to collagen-induced arthritis (CIA) showed enriched operational taxonomic units (OTUs) affiliated with the genus *Lactobacillus* prior to arthritis onset. With disease development, the abundance of OTUs affiliated with the families *Bacteroidaceae*, *Lachnospiraceae*, and S24-7 significantly increased in CIA-susceptible mice. Notably, germ-free mice conventionalized with the microbiota from CIA-susceptible mice showed a higher frequency of arthritis induction than those conventionalized with the microbiota from CIA-resistant mice. In this study, the serum concentration of interleukin (IL)-17 and the proportions of $CD8^{+}$T cells and Th17 lymphocytes in the spleen were significantly higher in the susceptible group. Using genetic approaches, Block et al. [11] demonstrated that gut microbiota regulates arthritis through follicular helper T (Tfh) cells, which are defective in antibiotic-treated mice, but not Th17 cells. In particular, the authors investigated the contribution of Th17 and Tfh cells in the induction of arthritis in a K/BxN autoimmune arthritis model that is dependent on segmented filamentous bacteria for the induction of the autoimmune phenotype. The authors particularly studied how microbiota modulates the differentiation of Th17 and Tfh cells. Using genetic approaches, they demonstrated that IL-17 is dispensable for arthritis and that antibiotic treatment inhibits disease in IL-17-deficient animals; this suggests that the gut microbiota regulates arthritis independent of Th17 cells. In contrast, conditional deletion of *Bcl6* in T cells blocked Tfh cell

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