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Review Article

Studying the Link between Rheumatoid Arthritis and Gut Dysbiosis: A Mini Review

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Rheumatoid arthritis (RA) is an autoimmune disease that affects the joints and may lead to disability. Recent advances have allowed us to study the human gut microbiota in great details. Numerous studies have shown that changes in gut microbiota may be playing a critical role in the pathogenesis of RA. In this review we summarize human and animal studies which show evidence that gut microbiota is directly affecting not only the development of RA but also its progression. In this review we also show evidence on how altering gut microbiota could be used as a treatment for RA.

1. Introduction

Rheumatoid arthritis (RA) is one of the most common types of arthritis, with prevalence of 0.5-1% in the populations of Europe and North America [1]. RA primarily affects the lining of synovial joints particularly the small diarthrodial joints of hands and feet [2, 3]. RA being a chronic autoimmune disease affects women three times more than men and occurs mostly in the fifth decade of life [1]. The mean age at diagnosis is 54.1 ± 12.0 years, while the median in population is 58 with males being younger at diagnosis [4–6]. Global trends have also shown that between 1990 and 2017 the prevalence of RA has increased by 7.4% (95% CI 5.3–9.4%) and the incidence by 8.2% (95% CI 5.9–10.5%) [7]. The pathogenesis of RA involves numerous cells of both innate and adaptive immune system [8]. How these cells interact together in the synovium is complex process; however T lymphocytes (T cells) and macrophages are thought to be the most integral components of RA [8, 9].

RA is known to be caused by interaction of both genetic and environmental factors. RA has been classically known to be a disease of type III hypersensitivity reaction involving autoimmune antibodies called Rheumatoid factors (RF) [10]. RF was thought to be the initiator of the disease, although now we know that some level of RF may be found even in individuals with no RA. Other autoantibodies have also been indicated to play a part in the pathogenesis of RA including anti-citrullinated protein antibodies (ACPAs), anti-peptidyl arginine deiminase-4 (anti-PAD-4), anti-carbamylated protein antibodies (anti-CarP), and anti-glucose-6-phosphate isomerase (anti-GPI) [11–13]. Twin studies have also shown that genetic inheritability may be playing a part in the development of RA, with one study showing the inheritability to be as high as 65% [14]. A study from Taiwan showed that relative risk of developing RA increased with a positive family history of RA [15]. Some research have also shown that multiple environmental, behavioral, and lifestyle factors like decaffeinated coffee drinking, smoking, periodontal disease, lower educational level, alcohol use, and obesity may lead to increased risk of developing RA [16–18].

Multiple studies have shown that levels of antibodies involved in the pathogenesis of RA are elevated long before the onset of RA symptoms [19]. One prospective study following healthy patients showed that patients developed increased RF levels even before the clinical onset of RA [20].

The fact that these antibodies are present before the onset of RA symptoms raises question of what the starting

point of formation of these antibodies is and which environmental, behavioral, and lifestyle factors may be playing the most significant role.

2. Aims and Objectives

The aim and objective of this review is to highlight the role of gut dysbiosis in the development and progression of RA, and how treatments targeting gut dysbiosis may provide a beneficial treatment modality. With this review we believe more focus can be brought on the role of gut microbiota in RA and help direct prospective studies.

3. Gut Microbiota

In recent years there has been a great interest among researchers on the study of gut microbiota and its effect on human diseases. Various successful studies on the changes in gut microbiota and consequent disease development has encouraged researchers to study the effect of gut dysbiosis on the development of autoimmune diseases even more [21, 22].

Numerous clinical studies have been performed to explore how the gut microbiota is affected in RA. When comparted to healthy individuals, the gut microbiota of individuals with RA have been shown to have reduction in bacteria belonging to the Bifidobacertium and Bacteroides family, with an increase the species of the genus Prevotella [23, 24].

Scher et al. performed sequencing of 16S gene on 114 fecal DNA samples, 44 of these samples were from patients with new onset RA. Results from this study showed that compared to healthy individuals, the samples from new onset RA patients had an increase in Prevotella and decrease in Bacteroides subgroup [25]. Similar studies performed by Alpizar-Rodriguez et al. and Vaahtovuo et al. showed that individuals with preclinical RA had increased levels of Prevotella and decreased levels of Bacteroides subgroup, the genera Bifidobacterium and Eubacterium rectale–Clostridium coccoides [26, 27].

Looking at other microbial species, a study in China showed that RA patients had increased Ligilactobacillus salivarius in the intestines, in saliva, and on the teeth, while Haemophilus species were decreased in these sites. However, only in the first year following the commencement of RA was the amount of Prevotella in the stomach increased. The scientists demonstrated that the dysbiosis seen in RA patients partially improved after receiving treatment with disease-modifying medicines [28]. Same study showed that the gut of RA patients was enriched with a large cluster of bacteria, including Gordonibacter pamelaeae, Clostridium asparagiforme, Eggerthella lenta, and Lachnospiraceae, as well as smaller clusters containing strains such Bifidobacterium dentium and Ruminococcus lactaris. Another study from China showed that RA patients had more fecal Lactobacillus species than healthy controls [29].

Gut microbiota is also significantly different among RA patients undergoing and those not undergoing any treatment. Gut microbiota of patients not undergoing any treatment contains severe abnormalities, whereas the group undergoing treatment shows restoration of normal gut microbiota [30].

These differences give evidence that gut microbiota might be playing a significant role in the pathogenesis of RA. This evidence is further supported by animal studies.

4. Animal Studies

Maeda et al. evaluated immune response in germ-free arthritis-prone SKG mice by inoculating fecal samples from RA patients and healthy controls into them. Firstly, analyzing the fecal sample from RA patients showed that there was increase in Prevotella copri in their intestinal microbiota compared to healthy controls. Secondly, the SKG mice that were given microbiota from RA patients had an increase in intestinal T helper 17 (Th17) cells and developed severe arthritis [31].

The pathogenesis that causes the raise in Th17 cells has been reported in studies. Gut epithelial cells create a physical barrier that precisely regulates antigen trafficking though paracellular routes. However, the onset of gut dysbiosis causes production of zonulin that may compromise the integrity of the barrier created by gut epithelium, leading to the disassembly of tight junction proteins [32–34]. Increased epithelial permeability caused by abnormal intestinal barrier function may let microbial fragments and products into the lamina propria and subepithelial space [35]. These chemicals will activate proinflammatory T cells, such as T helper 1 (Th1) and T helper 17 (Th17) cells, upon attaching to certain antigen-presenting cell receptors. This activation causes B cells to develop into plasma cells that produce autoantibodies. These gut-primed immune cells can move to different organs and tissues [36, 37]. After reaching their target organs and tissues, these immune cells and their byproducts will trigger macrophage activation and production of proinflammatory cytokines [38].

A unique study was performed by Jubair et al. whereof they induced collagen-induced arthritis (CIA) in mice by immunization with type II collagen (CII) and studying the resulting immune responses and arthritis. The results showed that there was significant early dysbiosis in the CIA, which then continued to progress. By use of broad-spectrum antibiotics, the gut microbiota in these mice was depleted. This depletion of gut microbiota reduced the severity of arthritis by ~40% and also resulted in reduction of important serum inflammatory cytokines Tumor necrosis factor alpha (TNF-α), Interleukin 1 beta (IL-1β), Interferon gamma (IFN-γ), and Interleukin 6 (IL-6) [39]. IL-1β and TNF-α are the main proinflammatory cytokines released by macrophages that result in the disastrous effects of RA. These cytokines cause the adjacent articular cartilage's chondrocytes and synovial fibroblasts to release enzymes that break down collagen and proteoglycans, causing tissue to degrade [40, 41]. Hence, regulation of these cytokines is essential for control of RA.

5. Treatment of RA Using Gut Microbiota

Since these studies suggest gut microbiota plays a part in the pathogenesis of RA, we can hypothesize that improving or altering gut microbiota could be used as a management option

for RA patients. One way this could be achieved is by using probiotics. Probiotics is the use of live microorganisms to get a health benefit to the host [42]. The efficacy of probiotics has been proven in mice studies. Inoculation of Clostridium, an indigenous intestinal microbiota, increased the number of T regulatory cells (T (regs)) [43]. T (regs) are involved in down regulating inflammation, and their inoculation could reduce RA severity by suppressing inflammation. Oral administration of microbiota Lactobacillus casei in CIA rats decreased the levels of proinflammatory cytokines. Along with this, Lactobacillus casei treated rats also showed normal histopathology without any typical sign of RA such as synovial infiltration, pannus formation, cartilage, and bone destruction [44]. A study to see the effect of probiotic Bifidobacteria in cases of ulcerative colitis, an inflammatory disease, showed that Bifidobacteria induced the production of IL-10, which is an anti-inflammatory cytokine [45].

Similar improvements with the use of probiotics were also seen in human studies. A randomized, double-blind, placebo-controlled, parallel-design, clinical pilot trial was conducted by Mandel et al., 44 RA patients were randomly assigned to receive either Bacillus coagulans or a placebo. The treatment arm of the study reported improvement in pain assessment scores compared to the placebo group [46]. In a similar randomized double-blind clinical study, 46 females with RA were given capsules containing Lactobacillus casei or a placebo. The treatment showed decrease in the levels of serum high-sensitivity C-reactive protein (hs-CRP) and fewer counts of tender and swollen joints [47].

6. Discussion

Although it is challenging to establish a direct connection between gut dysbiosis and the risk of rheumatic diseases from case-control studies and cross-sectional research, experimental evidence suggests that gut dysbiosis may influence systemic immune responses, reduce tolerance, and result in autoimmunity [48].

Numerous studies show that there is an increase in Prevotella and decrease in Bacteroides species in the gut of patients with RA. Some studies have also demonstrated that these changes in gut microbiota occur even before clinical onset of RA. These results are very valuable since the current laboratory tests that are recommended for RA include, erythrocyte sedimentation rate (ESR) and CRP which provide information on the acute phase response which lack sensitivity and specificity [49]. More sensitive and specific laboratory tests for diagnosis of RA are the autoantibodies RF and anti-CCP [50]. But the problem remains that these autoantibodies are elevated in other autoimmune disease and healthy people as well [19]. Due to these reasons, evaluation of gut microbiota could serve as a more specific diagnostic tool.

The main limitation that remains in the literature on this topic is the use of human controls. As mentioned in this review, RA has several environmental, behavioral, and lifestyle risk factors. A growing body of research indicates that RA is a complex disease that depends on the combination of genetic and environmental factors [21].

7. Conclusion

As it has been shown in this review, gut microbiota seems to be playing a major role in the development and progression of RA. We believe our understanding of how gut microbiota worsens or improves RA could be a very powerful diagnostic and therapeutic tool. The most important role of gut microbiota in RA for our benefit will be utilizing it to prevent and treat RA. Despite the huge number of studies already available on the role of gut dysbiosis in RA, there is lack of more longitudinal clinical studies to see the effects of using pro and prebiotics that specifically increase the number of protective bacteria and reduce the proinflammatory bacteria.

The great technological advances that we have made in recent years has allowed us to explore the gut microbiota to great extent and change our approach from considering microbiota as commensals to understanding that they play a major role in immune homeostasis. We believe these advances need to be used for our benefit. Exploring the world of microbiota might provide us with valuable information and management plans on varies diseases, especially autoimmune diseases.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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