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The Microbiome: a Revolution in Treatment for Rheumatic Diseases?

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Abstract
Purpose of Review The microbiome is the term that describes the microbial ecosystem that cohabits an organism such as humans. The microbiome has been implicated in a long list of immune-mediated diseases which include rheumatoid arthritis, ankylosing spondylitis, and even gout. The mechanisms to account for this effect are multiple. The clinical implications from observations on the microbiome and disease are broad.
Recent Findings A growing number of microbiota constituents such as *Prevotella copri*, *Porphyromonas gingivalis*, and *Collinsella* have been correlated or causally related to rheumatic disease. The microbiome has a marked effect on the immune system. Our understanding of immune pathways modulated by the microbiota such as the induction of T helper 17 (Th17) cells and secretory immunoglobulin A (IgA) responses to segmented filamentous bacteria continues to expand. In addition to the gut microbiome, bacterial communities of other sites such as the mouth, lung, and skin have also been associated with the pathogenesis of rheumatic diseases.
Summary Strategies to alter the microbiome or to alter the immune activation from the microbiome might play a role in the future therapy for rheumatic diseases.

Keywords Microbiome · Ankylosing spondylitis · Rheumatoid arthritis · Psoriatic arthritis · Mucosal immunity

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Introduction

The list of diseases influenced by the microbiome is growing rapidly. This tally includes atherosclerosis [1], diabetes [2], obesity [3], starvation [4], Crohn's disease [5], ulcerative colitis [5], irritable bowel syndrome [6], necrotizing enterocolitis [7], chronic fatigue syndrome [8], overactive bladder syndrome [9], multiple sclerosis [10], uveitis [9], autism [11], fatty liver [12], various cancers [13], asthma [14], and many other diseases in which the immune system has been implicated. Within the practice of rheumatology, systemic lupus erythematosus [15], rheumatoid arthritis [1617••], ankylosing spondylitis [18], psoriatic arthritis [19], Behcet's disease [20], enteropathic arthritis [21•], scleroderma [22•], and even gout [23] are affected by the microbiome. Thus, it behooves every rheumatologist to have some familiarity with this rapidly emerging area. The bulk of the microbiome resides within the intestines. The American Society of Microbiology now has an annual art competition in which the rules demand that the drawing is created by bacteria (http://www.microbeworld.org/backend-submitted-news/2132-announcing-asm-s-agar-art-2016-winners). If bacteria can create art, surely they can affect immune-mediated disease.

What Is the Microbiome?

The microbiome is a term first suggested by Joshua Lederberg [24]. It describes all the microbial life that coexists in an ecosystem such as the human body. Bacteria comprise the bulk of the microbiome, but viruses, yeast, protozoans, and even helminths can also contribute. The NIH recognized the emerging importance of the microbiome when it initiated the Human Microbiome Project in 2007 to characterize the bacteria that inhabit the human body [25]. Europe has a similar project called Meta Hit. The rapid reduction in the cost of next generation sequencing has enabled this characterization to make substantial progress. The New York Museum of Natural History has featured the microbiome in a dedicated exhibit, and Amsterdam now has an entire museum dedicated solely to appreciating the microbiome.

The human microbiome includes approximately 50 trillion bacteria which live primarily in anaerobic conditions in the bowel [26]. This equates to about 1 bacteria for every living cell. On a genetic level, there are about 150 bacterial genes in the human body for every mammalian gene [27]. These organisms provide vital functions. They are the major source or regulator of serotonin [28]. They synthesize much of the vitamin K in the body [29]. As discussed below, these bacteria educate the immune system.

Understanding the Bowel as an Organ in the Immune System

Although many would not list the bowel as a part of the immune system, others would argue that it is the largest organ in the immune system. The major immunoglobulin produced by the bowel and its mucosa is immunoglobulin A (IgA). While serum levels of IgA are just a fraction of serum levels of immunoglobulin G (IgG), actually more IgA is synthesized than IgG [30]. The half-life of IgA is much shorter due to its excretion through the bowel. Bacteria in the lumen of the intestine have minimal contact with the immune system since mucus forms an effective barrier. However, some bacteria are adherent to the epithelium of the intestine and these are more likely to trigger an immune response. In a seminal cell paper in 2014, Palm and colleagues showed that patients with inflammatory bowel disease have more IgA-coated bacteria in their bowel compared to healthy controls [31••]. Furthermore, transferring the IgA-coated bacteria alone to a germ-free mouse was sufficient to induce histological change in the recipient's colon [31••].

Mice which are raised in a germ-free environment have an immune system which is poorly developed (reviewed in [32]). A germ-free environment requires that the mice be delivered by Cesarian section and that all food is sterilized before the mice are allowed to ingest it. Many lymphocyte subsets are influenced by gut bacteria. For example, a variety of *Clostridia* [33] and *Helicobacter pylori* [34] induce regulatory T cells that express Fox P3. Polysaccharide A from *Bacteroides fragilis* alone is sufficient to induce an increase in Fox P3-positive cells [35]. T cells that synthesize interleukin-17, so called T helper 17 (TH17) cells, are induced locally in mice by exposure to segmented filamentous bacteria (SFB) [36]. The K/BxN arthritis model is induced by an immune response to glucose 6 phosphate isomerase. This arthritis model is ameliorated in germ-free mice and worsened when germ-free mice are switched into a specific pathogen-free living environment [36]. The K/BxN model is one of the several models of joint disease with reduced joint swelling in germ-free conditions. Other models which are improved include inflammation induced by the absence of the IL-1 receptor antagonist [37] and inflammation induced by a mutation in ZAP-70 [38], which is a T cell signaling molecule. The model of spondyloarthritis in rats induced by the expression of human leukocyte antigen (HLA)-B27 and beta$_2$ macroglobulin is also ameliorated by germ-free conditions [39]. One of the few models not improved by the absence of bacteria is adjuvant arthritis [40], a model in which joint disease is induced in rats by immunization with killed mycobacteria in mineral oil. A potential explanation for this observation is that the model itself already incorporates bacterial cell wall such that additional effects from bacteria in the gut are obviated.

Work is continuing to establish whether specific gut microbes or microbial products may impact the function of other immune cells, many of which are known to be impacted by the intestinal microbiota, including intraepithelial lymphocytes [41], plasmablasts [42], follicular helper T cells [43••], and innate lymphoid cells (reviewed in [44]).

The impact of the intestine on the immune response is not limited to the bowel itself because lymphocytes migrate from the bowel to distant sites. For example, by studying mice whose cells express a pigment that changes color after photoactivation, Morton and colleagues [45] could show movement of lymphocytes from the intestine to the spleen and to a variety of lymph nodes. McAleer and colleagues [46] have shown that the immune response to a fungus in the lung is influenced by microbiota on the bowel including SFB.

Rheumatic Diseases and the Intestinal Microbiome

Implicating the gut microbiome in the pathogenesis of a disease often starts by demonstrating that the microbiome differs in those affected by a disease compared to healthy controls. Such an analysis does not provide a mechanism, and many studies have not completely excluded the effects from medications. In some instances such as inflammatory bowel diseases, a shift in the microbiome in theory could result from the

local inflammation rather than act as the cause of the inflammation. Nonetheless, comparing the microbiome between those with a disease and those who are healthy but age and gender matched is an appropriate strategy to determine if the microbiome might be causally related to the disease. Such an approach has been used to implicate the microbiome in the pathogenesis of rheumatoid arthritis (RA) [16, 17••], ankylosing spondylitis [18], psoriatic arthritis [19], and scleroderma [22•]. Even when the same disease is studied, not all studies have implicated the same bacteria. For example, *Prevotella copri* was disproportionately increased in one study on RA [16]. A different genus of *Prevotella*, *Prevotella histicola*, suppresses inflammation in the collagen-induced arthritis model [47]. Another study on RA implicated *Collinsella* and other relatively rare species [48]. The latter study showed further that *Collinsella* could be transferred to germ-free mice with resultant exacerbation of joint disease in the model of collagen-induced arthritis [48]. Studies on patients may differ in terms of exclusionary criteria such as medications or recent use of antibiotics; they also may differ in terms of the site from which the microbiome was sampled. For example, results based on an ileal biopsy might differ from results based on feces which in turn might differ from sampling from rectal mucosa. A major study on RA from China [17••] showed some overlapping changes in oral and gut microbiota. This study further showed that treatment of the underlying disease resulted in a trend to make the microbiome more similar to that of healthy controls. Finally, studies on new onset disease might give very different results from study on disease once it is well established.

Much of the interest in the microbiome in RA has focused on an organism known as *Porphyromonas gingivalis* [49]. This is because *P. gingivalis* is unique among bacteria due to its expression of peptidyl arginine deiminase, the enzyme that converts arginine to citrulline. Therefore, *P. gingivalis* could generate cyclic citrullinated peptides which are generally regarded as the critical antigen in RA. Colonization of mice with *P. gingivalis* worsens collagen-induced arthritis [50]. Several studies have correlated the extent of gingivitis, the detection of *P. gingivalis*, or antibodies reactive to this microbe with the development of RA (reviewed in [51]); however, some studies have been unable to make these correlations. One study based on intestinal biopsies from patients with ankylosing spondylitis found an increase in *Dialister*, an organism also commonly found in gingival mucosa [21•]. The microbiome of saliva is altered in Behcet's disease [20]. In addition to the mouth and especially gingival mucosa as being potentially related to the pathogenesis of RA, some have implicated the microbiome of the lung in this disease [52]. Bacteria in the skin might play a causal role in psoriasis [53]. The urethral tract including the prostate is a suspected source of bacteria that has been causally implicated in reactive arthritis and ankylosing spondylitis [54].

The contribution of the microbiome to systemic lupus erythematosus is most likely through the virome based on an extrapolation that toll-like receptor 7 (TLR7) is important in the pathogenesis of lupus [55]. TLR7 recognizes single-stranded RNA as could be derived from a virus. Furthermore, an interferon response which is classically induced by a virus is now established in many patients with lupus [56]. Although viruses would intuitively be most linked to lupus, one study reported that SFB and other intestinal bacteria increase the titer of antinuclear antibodies [15].

The microbiome would seem to be an unlikely contributor to crystal-induced arthritis such as gout. However, studies in mice indicate that the subcutaneous injection of uric acid crystals induces very little inflammation unless a bacterial cofactor such as endotoxin is injected as well [57]. The absence of receptors for bacterial products such as TLR2 or TLR4 also inhibits the inflammatory response to urate [58].

HLA Molecules Shape the Microbiome

HLA alleles have been implicated in the causation of most immune-mediated diseases. Many speculate that the uniquely extensive polymorphism of the HLA system helps to protect a species from extinction from a microbial pathogen. HLA molecules have been recognized in several studies as a genetic factor which shapes the microbiome. Our own studies in transgenic rats showed that either HLA-B7 or HLA-B27 altered the microbiome in these rodents [59, 60]. A study in transgenic mice showed the mice which express HLA-DR 0401 differ in their gut microbiome compared to mice which express the closely related HLA-DR 0402 [61]. A human study showed that the DQ2-positive infants with a first-degree relative affected by celiac disease have a fecal microbiome that differs from controls [62]. Although it is logical to hypothesize that these differences result from differences in the immune response controlled by HLA, such a mechanism has never been conclusively demonstrated.

The Mechanism by Which the Microbiome Affects the Inflammatory Response

The mechanism by which the microbiome affects inflammation is potentially multifactorial. Since lymphoid subsets such as Tregs and Th17 cells are implicated in immune-mediated diseases, any effect on these subsets could in turn affect susceptibility to the disease in question. Adjuvants are required in most models of autoimmunity. Most adjuvants are microbial products which can activate antigen-presenting cells through an effect on TLRs or NLRs. Accordingly, a shift in the microbiome might correlate with a differential activation of the innate immune system. As discussed above, a unique

mechanism could be an enzymatic effect of the bacteria to generate an autoantigen such as a citrullinated peptide.

Antigenic mimicry is an accepted cause of autoimmunity in rheumatic fever [63] as well as in Guillain-Barre syndrome [64]. The culprits are beta hemolytic streptococci and campylobacter, respectively. In a mouse model of uveitis reliant on a transgenic mouse whose T cell receptors recognize an antigen derived from the retina, Horai and colleagues showed that the gut microbiome was critical by reducing disease severity in germ-free mice or in mice treated with broad spectrum oral antibiotics [65•]. Although the evidence strongly pointed toward mimicry, the investigators could not identify the specific microbe responsible for this effect. Mimicry has been implicated in the response to an autoantigen in the ZAP-70 model [66•] and suggested in a survey of the microbiome in patients in China with RA [17••].

Bacteria which alter the intestinal mucosal barrier or the epithelium can increase bowel permeability resulting in translocation of bacteria from the intestine to distant sites. A recent study showed that about one third of patients with Crohn's disease have bacterial DNA detectable in their blood [67]. Patients with reactive arthritis secondary to organisms such as *Salmonella* or *Yersinia* have DNA from those organisms detectable in affected joints [68, 69]. Histology has demonstrated that bacterial cell is common in synovium from patients with RA and present to a much smaller extent in patients with osteoarthritis [70]. Bacterial DNA from organisms found in the mouth is present in the joint of patients with RA and psoriatic arthritis [71]. Inflammation within a joint space could increase vascular permeability and thus make the accumulation of bacterial products a secondary phenomenon. However, the phlogistic effects of bacterial cell wall would argue that their presence within the joint is a causal factor in disease. In addition, our own unpublished data in the HLA-B27+ rat model would suggest that specific bacteria accumulate in joints indicating that the presence of bacterial products is not a nonspecific effect from increased vascular permeability.

Extrapolations to Clinical Practice

To date, manipulating the microbiome has had the greatest success in the treatment of *Clostridium difficile* colitis [72]. Fecal transplants [73], probiotics [74], and diets are actively being studied as treatments for a variety of diseases. Although a specific change in the microbiome has not been firmly linked with a human disease with few possible exceptions, a number of clinical caveats can be suggested from observations to date. For example, diet clearly has a marked influence on the microbiome [75]. Therefore, patients who report that a change in diet affects the activity of their disease might be noticing a consequence from an alteration in the microbiome. Second, it is likely that most if not all medications are metabolized in part by the gut microbiome. Even if not metabolized by the microbiome, activity of the medication could be affected by an indirect effect of the microbiome. Established examples include acetaminophen [76] and monoclonal antibodies used for cancer immunotherapy [77]. Finally, mouse studies clearly show that the exposure to the microbiome during infancy continues to affect the immune system later in life [78]. Accordingly, a delivery by Cesarian section might influence health many years after birth. Similarly, breast feeding affects which bacteria colonize the gut. A recent study found that patients with ankylosing spondylitis have been breast fed less often than controls [79•].

Conclusions

Certainly, the most direct "success" from microbiome research would be to discover that a specific bacterium results in a specific disease and then eliminate, reduce, or disarm that bacterium so that disease is unlikely to develop. In most instances, the science is not so far advanced to allow this, although it is worth noting that the incidence of rheumatic fever has been dramatically reduced and fecal transplants are an effective option to treat colitis induced by *C. difficile*. As we proceed to untangle the various complex contributions of microbiota to both health and disease, it is possible to mitigate the effects of the microbiome without identifying the causally related organism. For example, since sulfasalazine protects the intestinal epithelium from injury, we speculate that some of the benefit from sulfasalazine might result from its ability to improve bowel permeability and thus reduce the wide spread distribution of bacterial products. A siRNA to SMAD7 is being studied for Crohn's disease; its activities include reducing the bowel permeability associated with this disorder [80]. Possibly, the benefit of doxycycline in RA relates to its alteration of the microbiome. TLR antagonists or drugs that block the intracellular pathways activated by the microbiome are actively being studied for inflammatory diseases [81].

The effect of the germ-free state on several animal models of arthritis is quite marked, suggesting that the relative contribution of the microbiome is great. However, germ-free studies rarely distinguish between a nonspecific effect on the immune response and a specific effect on a causally related organism. Still the cataloging of the human microbiome began less than a decade ago. The potential from this endeavor seems vast.

Key Points

– An altered or "dysbiotic" microbiota is reported in several rheumatic diseases including RA, AS, PsA, and systemic sclerosis.

- Translocation of microbial products or migration of microbially primed immune cells to distinct sites (for example from gut to joint) may represent a relevant pathogenic mechanism.
- The microbiome is an attractive therapeutic target since it is amenable to manipulation through interventions such as diet, probiotics, fecal transplantation, or antibiotics.
- Therapy of disease induced by the microbiome could include an approach such as reduction in bowel permeability that did not depend on which specific bacteria induce disease.

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Compliance with Ethical Standards

Conflict of Interest JTR reports research collaboration for OpenBiome, consultancy for Abbvie, consultancy for Santen, speaking for Mallinckrodt, consultancy for Gilead, speaking for Janssen, consultancy for Genentech, consultancy for Allergan, grants from Alcon Research Institute, consultancy for Portage, consultancy for Topivert, consultancy for Mitotech, and consultancy for Xoma, outside the submitted work. MJA declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and were in compliance with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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•• Of major importance

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