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## Microbiome in Inflammatory Arthritis and Human Rheumatic Diseases

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### INTRODUCTION

Ever since its modern conception as a medical discipline, the study of microorganisms has paralleled the many technological advances in microbiology. In the 17<sup>th</sup> century, the inventor of the microscope, Antony van Leeuwenhoek, was also the first to describe – in the plaque of his own gums- the millions of microorganisms (or “*animalcules*”) that reside within us. It is that multitude of microbes populating most human body cavities and surfaces, including its genetic and enzymatic composition, what defines our microbiome<sup>1</sup>.

For centuries, the role of the microbiome as potential determinant of health and disease has been rather ignored. This has been true in most fields of human research, but particularly so in autoimmune and rheumatic conditions. The reasons are multifactorial. Chief among those was the advent of the Koch’s postulates in the late 1800’s, which exerted a profound influence on how investigators thought about causality in Medicine<sup>2</sup>. Unbeknownst at the time, however, was the fact that asymptomatic carriers are a common feature of many infectious diseases and that several microorganisms are fastidious in nature with complex nutritional requirements in order to grow. The latter fundamentally prevented the study of bacteria within the context of a dynamic biological community, the role of commensal taxa, the downstream molecular events and the resulting immune interactions between microorganisms and their host.

Consequently, only the prevalent microbiologic techniques were utilized in the past to characterize unique agents capable of triggering clinical rheumatic syndromes. Over time, the search led to correlative studies of specific bacteria and viruses in the etiopathogenesis of these disorders, most notably of rheumatoid arthritis (RA), psoriasis (PsO), inflammatory bowel disease (IBD), and the related spondyloarthritis (SpA), including ankylosing spondylitis (AS) and reactive arthritis (ReA).

The revolution of culture-independent, high-throughput microbial DNA sequencing, in parallel with the resurgence and further understanding of mucosal immunity, has

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exponentially advanced our knowledge of the interplay between our microbes and ourselves. That profound, bidirectional interaction and its consequences in physiology and disease have led to a whole new field of research. Despite the relative novelty of the *Human Microbiome* as a discipline, a substantial body of evidence has accumulated addressing its potential involvement in the pathogenesis of rheumatic disease<sup>3</sup>. Here, we will critically review the available data in animal and human studies, focusing on the role of intestinal microbiome in RA, PsA, and SpA. The role of the microbiome in autoimmunity and other rheumatic diseases has been reviewed elsewhere and is beyond the scope of this manuscript<sup>4,5</sup>. We include a description of the prospects of microbiome manipulation for therapeutic purposes and conclude by delineating challenges and opportunities in the field.

### Human Microbiome and Mucosal Immunity in Physiology and Disease

With the advent of massively parallel sequencing technologies and ever more sophisticated multi-omics methodologies, the human microbiome is now better understood in both its composition and functionality. It is now recognized that over 100 trillion cells inhabiting our human bodies are rather prokaryotic in nature. At any given time, we carry 3–6 pounds of bacteria that contain roughly 3 million protein coding genes<sup>6</sup>. We have also come to realize that different biological niches are populated by unique microbial consortia that can only survive under certain nutritional conditions. For example, the intestinal microbiome is entirely differentiated from that of the skin or the genitourinary tract<sup>7</sup>. And this is in part related to the various metabolic functions that derive from our own physiological needs. In fact, our intestinal microbes (represented by more than 1000 different species) have co-evolved in a mutually beneficial manner and provide the enzymatic machinery to help us degrade complex polysaccharides from the diet and extract essential vitamins and amino acids required for our evolutionary success. As a result, this new knowledge all but challenged our understanding of the *self*, leading to the notion that we should consider human beings as supraorganisms<sup>8</sup>.

This evolutionary process of co-adaptation between intestinal microbiome and host immune responses is now increasingly appreciated. In fact, it is now well established that the intestinal microbiota shapes the immune system and modulates homeostasis in healthy states or promotes inflammation when dysbiosis occurs<sup>9</sup>.

In order to keep this massive antigenic load compartmentalized in the intestinal lumen, mammals have developed multiple protective mechanisms. These include a physico-chemical barrier composed by a mucus layer, antimicrobial proteins and secretory IgA (sIgA) that keep the microbiota away from epithelial cells. Evading bacteria encounter tightly adherent intestinal epithelial cells, a mechanical barrier containing sensors of pathogen-associated molecular patterns (PAMPs) [i.e. toll-like receptors (TLRs)] and a variety of antibacterial molecules. The innate immune cells, most notably macrophages and dendritic cells (DCs), continuously sense the lumen and survey for detrimental antigens<sup>10</sup>. Ultimately, antigens are presented by MHC II molecules and interact with B- or T-cell receptors to induce adaptive immune responses. Depending on the microbial antigen, a specific cytokine milieu is then generated to influence a specific type of CD4+ T cell differentiation. While T helper 1 (Th1) cells develop in response to intracellular pathogens

and produce IFN $\gamma$ , both Th2 and Th17 cells are stimulated by extracellular microorganisms (producing IL-4 and IL-17, respectively). Regulatory T cells (Tregs), by contrast, actively prevent these pro-inflammatory properties via generation of anti-inflammatory cytokines such as IL-10. This fine homeostatic equilibrium is required to maintain a state of basal "physiological inflammation" in the lamina propria<sup>11</sup>.

With this in mind, the NIH Human Microbiome Project was launched<sup>12</sup> to address two central questions: 1) Is there a core human microbiome?, and 2) Do perturbations in the microbiome composition and/or its metabolites correlate with human disease states? Concomitantly, the DNA sequencing and multi-omics technological revolution has provided the necessary scientific tools<sup>13,14</sup>. Most analytical approaches in human studies have utilized novel bioinformatics tools coupled with parallel DNA sequencing platforms to: 1) describe the taxonomic relative abundance of bacterial species in a given sample (taking advantage of 16s rRNA gene amplification) and/or 2) better understand the overall functional enzymatic potential of a microbiome of interest (using whole-genome shotgun sequencing for metagenomics analysis). This has been complemented at times by the use of metabolomics [measuring the actual content of bacterial metabolites, such as short- and medium-chain fatty acids (SCFAs, MCFAs)], proteomics and metatranscriptomics<sup>15</sup>. These methods evaluate the possibility that associations with disease states may rather be dependent on the presence of certain bacterial components or by-products, and not necessarily the microorganism *per se*. Multiple examples of microbiome correlations with metabolic, neoplastic and autoimmune diseases have now been reported, including those in obesity and diabetes<sup>16,17</sup>, gastrointestinal cancer<sup>18</sup>, atherosclerosis<sup>19</sup> and psoriasis<sup>20</sup>. As expected, many of the original contributions to the field in autoimmunity were originated in the IBD literature. Noticeably, IBD patients reveal a dysbiotic process characterized by decreased intestinal (beneficial) microbiota diversity<sup>21,22</sup> and increase in enterobacteria<sup>23</sup>.

### Perspectives on the role of intestinal microbiome in Rheumatology

Long before the study of the microbiome became technically possible, the suggestion that intestinal microorganisms were involved in autoimmunity leading to clinical inflammatory arthritides had long been proposed. At the dawn of the 20<sup>th</sup> century, Carl Warden suggested in his "*toxemic factor hypothesis*" that overabundant gram-negative anaerobes in the intestinal canal produced of a noxious substance that, once absorbed, was responsible for RA development<sup>24</sup>. Modern microbiologic reports cemented the notion that gut-infecting (or colonizing) bacteria could induce distal arthritis. Several of the spondyloarthropathies, most notably IBD-related arthritis, ReA and axial SpA are clear examples of this. Other arthritides rarely seen currently are perhaps even more relevant as proof-of-principle that intestinal dysbiosis can lead to distal synovial inflammation. This is the case of Whipple's disease, in which the mere presence of *Tropheryma whipplei* is necessary – although not always sufficient – for the development of articular compromise<sup>25</sup>. Even more intriguing is an arthritic syndrome triggered in many instances by jejunoileal-bypass surgery. This disruption of the normal gastrointestinal anatomy, and consequently of its populating microbial communities, often led to bacterial overgrowth and antibody production that ultimately promoted synovial inflammation (and a pathognomonic form of dermatitis)<sup>26</sup>.

As a result, multiple attempts to alter the composition of intestinal bacteria have led to several therapeutic regimens in inflammatory arthritis. A classic example is illustrated by sulfasalazine, a drug rationally designed to combine a sulfa antibiotic with a salicylate through an azo-bond<sup>27,28</sup>, ultimately was deemed a disease-modifying anti-rheumatic drug (DMARD) and FDA-approved for the treatment of RA, IBD and AS. Other medications with antibiotic properties (hydroxychloroquine and tetracyclines) have also been included in the therapeutic armamentarium of RA.

### Rheumatoid Arthritis

Evidence that RA follows the epidemiology of an infectious vector is both intriguing and debated. In fact, only skeletal remains from Amerindians show erosive changes reminiscent of RA, a finding not seen in European or Asian archaeological sites<sup>29</sup>. In line with this, an increased prevalence of RA has been reported in several American Indian and Alaska Native populations (e.g., up to 8% in the case of Chippewa Indians). Prior attempts have also implicated bacterial triggers in the pathogenesis of RA<sup>30,31</sup>. Several studies –reviewed extensively elsewhere<sup>32</sup>– have pointed towards periodontitis and the oral microbiota (e.g., *P. gingivalis*) as the inciting factor<sup>33,34</sup>. Although *P. gingivalis* represents a relevant taxon given its intrinsic capability to citrullinate peptides through the enzyme peptidyl arginine deiminase (PAD), it is possible that periodontal inflammation *per se* elicited by a variety of microorganisms (including *Prevotella* and *Leptotrichia* species) contribute to disease development<sup>35,36</sup>. Another possibility is that the distal airways represent the actual site of citrullination, perhaps as a consequence of environmental insults (i.e., smoking) and/or microbial challenges. This is largely based on work by Deane et. al., who described the presence of small airway inflammation and anti-citrullinated peptide antibodies (ACPAs) in RA sputa<sup>37,38</sup> and data from Klareskog group who identified shared immunological citrullinated targets in joints and lungs of patients with RA<sup>39,40</sup>. Recent epidemiologic studies also suggest a correlation between gastrointestinal and urinary infections and decreased risk of RA<sup>41</sup>, indicating the possibility of disease development in response to intestinal microbiota perturbation.

There is an abundant body of literature addressing the role of the microbiome in inflammatory arthritis (Table 1). In fact, multiple animal models have established a biological connection between the presence of microbiota and development of synovitis. Kohashi et al. demonstrated that adjuvant-induced arthritis in rats only developed under germ-free (GF) conditions (within isolators voided of all microorganisms). Conventionally raised animals, however, displayed only a mild phenotype, suggesting a potential modulatory immune effect for the microbiome. This same group further reported a protective role of certain Gram-negative enterobacteria (*E. coli* and *Bacteroides* species) when introduced into otherwise GF arthritis-susceptible rats<sup>42,43</sup>. Collagen-induced arthritis (CIA) is also modulated by bacteria or its components, since only GF animals develop disease after intradermal injection of native type II collagen<sup>44</sup>. Furthermore, bacterial-derived lipopolysaccharide (LPS) by itself is also capable of potentiating CIA in mice<sup>45</sup>. Similarly, in the streptococcal cell wall-induced rat arthritis model, the presence of gut microbiota renders animals resistant to joint inflammation<sup>46</sup>.

Most recently, investigators have utilized novel approaches in order to define the exposure of an animal to the gut microbiota and the downstream immune response. In the so-called gnotobiotic experiments, specifically characterized taxa are incorporated into GF (or antibiotic treated) animals and the biologic events are described both *in vivo* and *ex vivo*. There are several noteworthy examples. First is the IL-1 receptor-antagonist knock-out (Il1rn<sup>-/-</sup>) mouse, which develops a spontaneous autoimmune T-cell-mediated arthritis when raised under conventional cages. While GF animals do not get arthritic, *Lactobacillus bifidus*-monocolonized Il1rn<sup>-/-</sup> mice develop high incidence of severe joint disease, in a Th17 and TLR4 dependent manner<sup>47</sup>.

Other studies have made use of gnotobiotic tools. The K/BxN T-cell receptor transgenic model is caused by T-cell-driven production of autoantibodies against glucose-6-phosphate isomerase. Inflammatory arthritis is also mitigated in GF animals, mostly due to a deficiency of Th17 cells in both the lamina propria and the periphery. Introduction of the commensal segmented filamentous bacteria (SFB) is sufficient for development of disease phenotype. Conversely, antibiotic use strongly hampers inflammatory arthritis in K/BxN mice<sup>48</sup>. This is of high relevance since, for the first time, specific intestinal commensals demonstrated the ability to drive adaptive T-cell differentiation locally, followed by systemic disease at distal sites. While this remains a matter of intense mechanistic research, lamina propria Th17 proliferation in physiological states requires the activation of local DCs to produce polarizing cytokines<sup>49</sup> and the ability of T-cell receptor (TCR) to specifically recognize commensal intestinal bacterial antigens<sup>50</sup>.

Taken together, these findings suggest that perturbations in intestinal microbiota composition may suffice for the triggering of arthritis in a variety of experimental murine models. Potentially joint protective (or deleterious) properties, however, might also depend on host genetic and gender background<sup>51</sup>. Arthritis-susceptible (HLA DRB1\*0401) transgenic mice, for example, show alterations in intestinal microbiota composition and increase in gut permeability when compared to arthritis-resistant controls<sup>52</sup>.

Despite these advances in understanding the intestinal-joint biologic connection, human data has been scarce (Table 2). Toivanen et al, initially characterized intestinal flora in patients with RA using gas-liquid chromatography (GLC), and found that levels of several anaerobic bacteria accounted for most differences between RA and controls (although GLC technology cannot discriminate directionality)<sup>53</sup>. Utilizing low-throughput hybridization, another study revealed lower levels of the *Bacteroides-Porphyromonas-Prevotella* bacterial group in early RA patients compared to non-arthritic controls<sup>54</sup>. Although of interest, the lack of PCR-primer specificity rendered these findings virtually impossible to interpret at the lower taxonomic levels.

Most recently, our group characterized the intestinal microbiome of new-onset, DMARD/steroid-naïve RA (NORA) patients with the use of 16s rRNA and whole-genome shotgun (WGS) sequencing. Compared to chronic RA, PsA patients and healthy controls, the NORA cohort had a significantly higher abundance of *Prevotella copri*<sup>55</sup>. This observation is intriguing because most other studies have shown that *Prevotella* prevalence is typically low in healthy individuals (with the exception of some aboriginal populations). The reasons for

this remain unclear, but it is possible that it relates to either dietary factors (as fiber consuming subjects -and children in particular- have very high levels of intestinal *Prevotella*<sup>56</sup>), geographic variability or a combination. The relationship between fiber intake and RA incidence, however, is yet to be studied. Several other findings were considered of interest. First, increases in *Prevotella* correlated with a reduction in reportedly beneficial microbes (i.e., *Bacteroides*) in NORA subjects. Interestingly, the relative abundance *P. copri* inversely correlated with the presence of ‘shared-epitope’ genes, suggesting that the human intestinal microbiome composition could also be partially dependent on the host genome. Second, there were significant differences between the metagenomes of the cohorts. Functionally, although not yet fully studied, these variations may be relevant as predictors of treatment response. This relates to the fact that dihydrofolate (DHF) reductase is high in metagenome samples rich in *Bacteroides*, potentially serving as a competitor to host DHF reductase for MTX binding and metabolism. If so, an increase in DHF reductase-high microbiota in RA subjects (i.e., *Bacteroides* overabundant) may help explain, at least partially, why only some RA patients respond adequately to oral MTX. Finally, colonization of mice revealed the ability of *P. copri* to dominate the intestinal microbiota, and resulted in an increased sensitivity to DSS colitis, a model for IBD. Other investigators have addressed the potential for local and systemic pro-inflammatory properties of the genus *Prevotella*, including its role in DSS colitis and osteomyelitis<sup>57,58</sup>.

Taken together, these studies reveal a potential role for the gut microbiome in the pathogenesis of RA. However, they remain mostly correlative, and not necessarily representing causation. Further validating human studies and mechanistic approaches in gnotobiotic mice are required to rigorously evaluate downstream RA immune events in response to local microbial perturbation.

### Spondyloarthritis and Psoriatic Arthritis

Unlike RA, the existence of SpA has been documented for centuries, its prevalence is significantly higher in Caucasoid populations, clinical manifestations are much more heterogeneous in nature, genes (particularly HLA-B27) have a relatively larger effect in disease incidence, and there is a prominent role for pro-inflammatory Th17 cells and its signature cytokine, IL-17. The epidemiologic relationship between intestinal microorganisms, gut inflammation and SpA is perhaps even more remarkable. This is supported by the established role of infectious diarrhea in the pathogenesis of ReA, and the association between IBD and AS and PsA (mostly in the axial forms)<sup>59,60,61</sup>.

This heterogeneity is also evident in the many, but yet imperfect, animal models of SpA (Table 1). Several examples are elemental as proof-of-principle that the microbiome is a significant contributor to disease. Pivotal studies first described spontaneous inflammatory SpA-like disease in transgenic rats expressing HLA-B27 and multiple copies of human beta-2 microglobulin. The phenotype is characterized by sacroiliitis, peripheral arthritis, psoriasiform skin inflammation and colitis<sup>62</sup>. When these rats are raised under GF conditions, however, they fail to develop inflammatory intestinal or peripheral joint disease<sup>63</sup>. In contrast, HLA-B27 rats colonized with various commensal *Bacteroides* species ultimately develop inflammation, suggesting that the presence of specific taxa is sufficient



for disease initiation and propagation<sup>64</sup>. The mechanism by which this occurs remains elusive, but it is likely to be mediated by a combination of HLA-B27 misfolding and activation of intestinal and circulating Th17 cells, in an IL-23 dependent manner<sup>65,66</sup>. The directionality of this gene-microbiome interaction is a matter of intense research. A recent study compared the intestinal microbial composition of HLA-B27 transgenic rats (prior to disease development) and wild-type controls, revealing an increase in *Prevotella spp.* and a decrease in *Rikenellaceae* and *Akkermansia* in the transgenic animals<sup>67</sup>. It is plausible therefore that, as in RA-like disease, microbiota alterations are rather a consequence of host genetic predisposition or perhaps a superimposed requirement for activation of downstream immunologic events in susceptible animals.

Work performed in other models has also shed light into the requirement of gut bacteria for SpA inflammation. The ANKENT mouse model spontaneously develops progressive enthesitis and ankylosis. The disease is also HLA-B27 dependent and triggered by commensals<sup>68</sup>. In the SKG model, mice develop SpA-like disease after systemic injection of  $\beta$ -glucan, a major component of bacterial and yeast cell walls<sup>69</sup>. Furthermore, the incidence and severity of arthritis and ileitis in SKG mice were dependent on the presence of host microbiota and downstream production of IL-23-dependant IL-17/IL-22<sup>70</sup>. Mice overexpressing IL-23 through minicircle DNA technology develop enthesitis and osteoproliferation by activation of enthesial resident T cells<sup>71</sup>. Taken together, these experiments strongly support a model in which a genetically predisposed host reacts to a dysbiotic process by altering the immune balance in the lamina propria towards a pro-inflammatory state dominated by IL-23 production and activation of  $\gamma\delta$ T-cells capable of amplifying the response through cytokines such as IL-17 and TNF $\alpha$ . This process ultimately leads to both local and systemic clinical repercussions in the form of colitis, psoriasis, enthesitis and arthritis.

As discussed, AS and PsA patients are at increased risk for the development of clinical IBD. Intriguingly, even a larger proportion of them have microscopic subclinical gut inflammation, characterized by increased infiltrate of IL-22 and IL-23 producing cells<sup>72-75</sup>. Very few studies described the intestinal microbiome in these disorders (Table 2). Using denaturing gradient gel electrophoresis, Stebbings et al. found a higher prevalence of sulfate-reducing bacteria in AS patients<sup>76</sup>. Another study demonstrated a distinct gut microbial signature in AS utilizing 16S sequencing<sup>77</sup>. AS patients had a higher prevalence of several bacterial families in the terminal ileum (e.g., *Lachnospiraceae* and *Prevotellaceae*), and a concomitant decrease in *Ruminococcaceae* and *Rikenellaceae* families compared to healthy controls. In children with enthesitis-related arthritis, the relative abundance of *Faecalibacterium prausnitzii* was significantly lower than healthy controls<sup>78</sup>. Our group also defined the intestinal microbiome of PsA patients compared to psoriasis and healthy controls. While both PsO and PsA groups showed decreased *Coprococcus*, the PsA group was further characterized by significantly lower levels of *Akkermansia* and *Ruminococcus*, suggesting a chronological loss of diversity that may potentially correlate with the natural history of disease<sup>79</sup>. Curiously, studies in IBD revealed a similar reduction of *Ruminococcaceae* family and *Akkermansia* genus. This state of intestinal dysbiosis in PsA patients correlated with decreased levels of both medium-chain

fatty acids (MCFAs) and RANKL in the intestinal lumen, suggesting that microbiome perturbations are linked to alterations in mucosal integrity and perhaps dissemination of systemic inflammation.

Many novel findings in the IBD literature, including the role of the intestinal virome in Crohn's- and ulcerative colitis-specific dysbiosis<sup>80</sup> and the colitogenic properties of sIgA-coated human bacteria<sup>81</sup>, may also prove highly relevant to SpA and/or PsA and further advance our knowledge of their pathogenesis.

## INTESTINAL MICROBIOME TARGETING STRATEGIES

Therapies targeting intestinal bacteria have been part of the anti-rheumatic strategy for many decades. However, broad antibiotic drugs have not demonstrated efficacy. Despite indirect evidence that certain classes of antibacterials may hypothetically modulate the risk for RA and juvenile arthritis<sup>82</sup>, this approach is currently unsubstantiated. First, the notion that certain classes of antibiotics target microorganisms based on Gram-stain properties has become outdated. This is based on multiple culture-independent studies showing far-reaching taxonomic changes with drugs previously thought to be bacteriostatic against just a few microorganisms<sup>83</sup>. Moreover, indiscriminate use of antibiotics at early age could potentially determine the fate of various conditions, including obesity and even autoimmune disorders<sup>41,82,84</sup>.

Most recently, numerous groups are currently attempting to modulate bacterial composition or its byproducts to abrogate inflammatory responses. The various methods now being utilized range from ecosystem-level interventions to single-target approaches, including individual species or their metabolites<sup>85</sup>.

Fecal microbial transplantation (FMT) is utilized in an attempt to restore a “healthy” intestinal microbiome in a recipient, utilizing the full bacterial community from a close donor. For decades, FMT has proven highly effective (an even curative) in antibiotic-resistant *Clostridium difficile* infectious colitis<sup>86</sup>. Despite striking results, the use of this technique presents its own array of challenges, including how to define a healthy microbiome and who to consider an appropriate donor. Nevertheless, FMT has already been applied to autoimmune diseases, most notably in IBD. The results-although based on relatively small samples-remain promising as in some series, patients respond favorably to FMT<sup>87</sup>. Well-designed clinical studies, paired with phenotypic characterization of taxonomy and immune effects are still needed to understand whether this approach could eventually be adapted for the treatment of RA, PsA or SpA.

More specific approaches are also being employed. The strategy relies on incorporating agents based on single-strain live organisms or a defined bacterial consortium leading to an FMT-independent modification of the host microbiome composition. Several animal studies have successfully treated autoimmune manifestations with this methodology; including amelioration of IBD by either *Bacteroides fragilis*<sup>88</sup> or a cocktail of *Clostridia*<sup>89</sup> through induction of colonic Treg cells. This is in contrast to the pro-colitogenic and pro-arthritis effects of *Bacteroides* in the HLA-B27 transgenic rats<sup>64</sup> and the detrimental role of *Lactobacillus* in adjuvant-induced rat arthritis and joint inflammation in the *Il1rn*<sup>-/-</sup>



mice<sup>42,47,90</sup>. Other studies, however, have shown a beneficial effect of *Lactobacillus* strains in CIA<sup>91</sup>. Still, there is scarce evidence that probiotics have therapeutic value RA. Studies conducted so far are rather small and usually with modest or no effect<sup>92–94</sup>.

Other sophisticated approaches are rather exploiting bacterial-derived bioactive effectors. Several efforts utilize molecules with immune-modulating properties, including polysaccharides, structural proteins, and SCFAs, with some showing evidence as potential treatments for IBD and other systemic autoimmune disorders<sup>88,95–98</sup>. Nevertheless, the effectiveness of these compounds, tolerability and long-term properties are yet to be elucidated.

## CONCLUSIONS

The vastness of the human intestinal microbiome is increasingly being recognized. Its overwhelming diversity, resilience and functional potential have transformed the way we now view physiology and disease. Rapidly accumulating evidence indicates the existence of an intricate symbiosis between the microbiome and its harboring host. In order to take full advantage of the essential byproducts generated by this bioreactor, humans have evolved to actively tolerate this constant and massive antigenic load within the intestinal lumen through a state of low-grade inflammation. However, perturbations in the relative composition of commensals can alter the immune homeostasis of the lamina propria and elicit aberrant systemic responses. Animal models of inflammatory arthritis have considerably advanced our mechanistic understanding of the dysbiotic process in connection with the key cellular responses and downstream immune events. Given the presence of a pre-clinical phase in many autoimmune diseases (i.e., autoantibodies preceding clinically evident inflammation), the microbiome could hypothetically contribute casually through a variety of mechanisms. A state of dysbiosis could lead to a specific adaptive immunodifferentiation of effector cells (e.g., SFB-dependent Th17 cell activation), the provision of neoantigens (i.e., *P. gingivalis*-driven citrullination of peptides and generation of ACPAs) and/or serve as co-stimulatory signals (e.g., in the presence of potentially arthritogenic ACPAs, disease could only be triggered through a “second event”, driven by bacterial components and consequent cellular immune response). As more human microbiome studies become available, many questions will require rigorous exploration. These include: the directionality of the dysbiotic process (i.e., Are microbiome alterations actual inciting events in the autoimmune process or rather a consequence of ecological adaptation to inflammatory milieu?); the specificity of commensal antigen recognition by T-cells; the timing of microbial perturbation in the different phases of disease (i.e., pre-clinical, early and chronic) and the contribution of communities in other body niches such as the periodontal and lung (in RA) and the skin (in PsA); the relationship between the microbiome and metabolome to immunosuppressive drugs (i.e., Could the microbiome be involved in pharmacokinetics of oral DMARDs and/or serve as predictor to drug response?). Ultimately, the answer to many of these questions will largely depend on whether we can successfully target the microbiome for therapeutic purposes in autoimmune and rheumatic diseases.

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Table 1

Murine models of RA-like and SpA-like disease known to be modulated by intestinal microbiome or bacterial-derived metabolites

Animal	Manipulation	Phenotype	Germ-Free effect	Taxa/Molecule involved	Ref.
Rat	Adjuvant-Induced Arthritis	RA-like synovitis	Arthritis	<i>E. Coli</i> <i>Bacteroides spp</i>	42,43
Rat	Collagen-Induced Arthritis	RA-like synovitis	Arthritis	Type II collagen LPS	44,45
Rat	Streptococcal Cell Wall-Induced Arthritis	RA-like synovitis	Arthritis	<i>S. pyogenes</i> cell wall	46
Mouse	IL-1 Receptor-Antagonist k.o.	RA-like synovitis	No Arthritis	Lactobacillus bifidus	47
Mouse	K/BxN Transgenic	RA-like synovitis	No Arthritis	SFB	48
Rat	HLA-B27/β2 Tg	Colitis, psoriasis and arthritis	No Disease	<i>Bacteroides spp</i>	62-63
Mouse	HLA-B27/ANKENT	Enthesitis and ankylosis	No Disease	<i>Bacteroides/Enterococcus spp</i> ; <i>Veillonella/Staphylococcus spp</i> (LPS suppresses enthesitis)	68
Mouse	SKG (ZAP-70 single-point mutation)	Arthritis, psoriasisiform lesions and colitis	No Disease	β-glucan Gut commensals	69-70

**Table 2**

Human rheumatic diseases associated with altered intestinal microbiome

Human Rheumatic Disease	Technology employed	Taxa/Molecule implicated	Ref.
Early Rheumatoid Arthritis	Gas-liquid chromatography (GLC)	Anaerobic bacteria	53
Early Rheumatoid Arthritis	16S rRNA hybridization, and DNA-staining	↓ <i>Bifidobacteria</i> ↓ <i>Bacteroides-Porphyromonas-Prevotella</i>	54
New-Onset Rheumatoid Arthritis	16S rRNA gene and WGS sequencing	↑ <i>Prevotella copri</i> ↓ <i>Bacteroidetes</i>	55
Ankylosing spondylitis	Denaturing gradient gel electrophoresis (DGGE)	↑Sulfate-reducing bacteria	76
Ankylosing spondylitis	16S rRNA gene sequencing	↑ <i>Lachnospiraceae</i> and <i>Prevotellaceae</i> ↓ <i>Ruminococcaceae</i> and <i>Rikenellaceae</i>	77
Juvenile Idiopathic Arthritis (enthesitis-related arthritis, ERA)	16S rRNA gene sequencing	↓ <i>Faecalibacterium prausnitzii</i>	78
New-Onset Psoriatic Arthritis	16S rRNA gene sequencing	↓ <i>Akkermansia</i> and <i>Ruminococcus</i> ↓ <i>Medium-chain fatty acids (MCFAs)</i> ↓ <i>Intestinal RANKL</i>	79