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Microbiota mediated mucosal inflammation in arthritis

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Abstract

Mucosal surfaces are a unique symbiotic environment between a host and a vast and diverse ecology of microbes. These microbes have great immunomodulatory potential with respect to the host organism. Indeed, the mucosal immune system strikes a delicate balance between tolerance of commensal organisms and overt inflammation to ward off pathogens. Disruptions of the microbial ecology at mucosal surfaces has been described in a vast number of different human disease processes including many forms of arthritis, and the resulting implications are still being understood to their fullest. Here we will review the current state of knowledge in microbe-host interactions as it relates to the development of arthritis through bacterial translocation, bacterial metabolite production, education of the immune response, and molecular mimicry.

Keywords

Microbiome; mucosal immunity; rheumatoid arthritis; spondyloarthritis

1. Introduction

Commensal microorganisms exist in complex and diverse communities lining barrier surfaces of the human body. Population disturbances in these communities, often termed dysbiosis, have been associated with many human diseases, including many forms of arthritis[1–5], with expansions and reductions of specific taxa found in different forms of disease. For examples, *Prevotella copri* has been associated with new onset rheumatoid arthritis (RA)[1], and expansion of these bacteria has been noted in the period of time preceding RA development[5], while *Ruminococcus gnavus* and *Dialester* are associated with patients with axial spondyloarthritis (axSpA) particularly those with bowel inflammation[2,3].

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Declaration of Competing Interest

None.

Dysbiosis is also seen in rodent models of arthritis, and administration of broad-spectrum antibiotics in these models ameliorates disease, indicating that the disease process may be microbe-dependent[6–8]. Further understanding of the microbial-mucosal interactions that occur in the development of the different forms of arthritis may provide insights into the mechanisms that underlie these diseases.

Exploration of a few key mechanisms in this review will illustrate the multiple ways by which microbes can alter mucosal immunity and predispose the host to arthritis. Note, that much of the information herein will focus on bacterial-stimulation of immune responses, as there is limited information regarding the role of viruses and fungi at barrier surfaces in the development of arthritis, although the field is rapidly evolving.

2. Mechanisms by which bacteria and host interact

Bacteria use surface proteins, carbohydrates, and lipids in order to communicate with each other, a concept known as quorum sensing, as well as survive within their host. Gram-positive organisms often communicate with each other utilizing a two-component system of a peptide signal that activates a kinase to phosphorylate a response protein in order to communicate with other bacteria. Gram-negative organisms often utilize acylated homoserine lactones for the same purpose. Additionally, bacterial surface molecules such as bacteriocins and Type VI secretion system effectors can be used to ward off other bacteria that may invade their niche while other molecules like LuxI/LuxR in *Pseudomonas aeruginosa* are used to gain entrance into a niches that would be advantageous for them to inhabit[9]. One such niche, where some bacterial species gain a competitive advantage, is the mucus layer closest to the host epithelia. Species such as *Bacteroides thetaiotamicron*, a common human commensal, are capable of utilizing mucin glycans as an energy source when dietary sources are sparse[10], while others like *P. aeruginosa* travel along and through mucin scaffolds[11]. Other commensal organisms such as *Bacteroides fragilis* coat themselves in host immunoglobulin A (IgA) in order to gain access to novel niches in different mucosal layers[12].

While bacteria have adapted mechanisms to live within the host ecosystem, the host itself is not a bystander in this process, but instead actively participates in maintaining balance with commensals through an array of mechanisms. The innate immune system plays a pivotal role in sensing bacteria through toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLR), and neutrophil extracellular traps (NETs). The adaptive immune system also plays an important role with both T cells and B cells playing large parts in the sensing and recognition of commensal organisms. Understanding how these immune pathways sense and regulate microbial populations during host health allows one to comprehend how these processes contribute to immune education and potential mechanisms for arthritis development.

2.1 Innate Immune System

The innate immune system is of critical importance to the maintenance of homeostasis with microbiota. Recognition of broad pathogen-associated molecular patterns (PAMPs) is of utmost importance, as it would be physiologically impossible to mount a rapid adaptive

immune response against such a varied group of micro-organisms. These PAMPs are a group of highly conserved antigens (protein, lipids, polysaccharides, and nucleic acid in origin) among microbes that make it easy for the host to recognize self from non-self. They are recognized by Toll-like receptors (TLRs) that are found on the surface of many immune and non-immune cell types, which are found commonly at barrier tissue sites. Example PAMP-TLR pairs include lipopolysaccharide and TLR4 and single-stranded RNA and TLR7 and TLR8. Signaling through TLRs occurs through the MyD88 and TRIF dependent pathways, and ultimately results in the activation of NFkB, which translocates into the nucleus of the cell and incites the transcription and production of pro-inflammatory cytokines such as interferons[13]. Intriguingly, this innate sensing pathway is also important in linking adaptive immune responses. Selective deficiency of MyD88 in CD4+ T cells results in poor follicular helper T cell development in the gut and anti-bacterial IgA responses leading to intestinal dysbiosis and increased susceptibility to chemically induced colitis[14]. Thus, TLR signaling is fundamental for innate protection against pathogens as well as maintenance of microbial homeostasis and mucosal immunity.

There are additional mechanisms by which the host's innate immune system is able to recognize intracellular pathogens. When PAMPs or other danger-associated molecular patterns (DAMPS) like cytosolic double-stranded DNA are present inside of a host cell, NLRs are able to signal and incite a response from the inflammasome. The inflammasome is composed of NOD proteins, which sense components of microbes found intracellularly. For examples, NOD1 recognizes γ-glutamyl diaminopimelic acid, a Gram-negative derived peptidoglycan breakdown product, and NOD2 recognizes muramyl dipeptide, another component of bacteria-derived peptidoglycan. When these NOD domains bind their cognate antigen, homodimerization of NOD proteins occurs. The amino-terminal domain of these proteins, known as the caspase recruitment domain (CARD), recruits the kinase receptor-interacting serine/threonine-protein kinase 2 (RIP2), which leads to downstream activation of NFkB. Another family of NLRs contains pyrin domains instead of CARD domains. Dimerization of these proteins leads to the cleavage of pro-caspase 1 into active caspase 1 followed by cleavage of pro-IL-1β or pro-IL-18 into their active forms[15]. Alternatively, non-canonical inflammasome activation, which occurs in the setting of Gram negative bacteria, is triggered by the production of caspase-11 in the context of NLR activation. This pathway leads to the production of gasdermin D, resulting in plasma membrane pore formation and cell death. Interestingly, neutrophils are sensitive to this type of inflammasome activation, although they are resistant to canonical inflammasome cell death. This can directly lead to the production of NETs in the context of Gram negative bacteria interacting with neutrophils[16].

Neutrophils are highly responsive to innate signals from PAMPs and DAMPs and contribute to the maintenance of barrier tissues through rapid and pro-inflammatory responses to pathogens or breaches of the barrier. By forming NETs, which are combinations of neutrophil DNA, oxidative granules, neutrophil elastase, peptidyl arginine deiminase (PAD) and myeloperoxidase, neutrophils provide a potent cytotoxic response against bacteria[17]. The formation of NETs, as discussed later, is increasingly appreciated in the development of multiple autoimmune and arthritic conditions.

Innate lymphoid cells (ILCs) are a unique and rare population of tissue-resident, often in barrier tissues, lymphocytes that participate in sensing of commensal organisms and link adaptive responses. These cells, while originating from the common lymphoid progenitor, do not carry B or T cell receptors or maintain the ability to undergo receptor gene recombination. They however maintain a range of effector functions that are highly similar to T helper cells, and are able to maintain the balance with intestinal microbes through these functions. ILC1 cells, which are the innate counterparts to Th1 cells, secrete IFNγ in response to IL-12, IL-15, and IL-18 in the milieu. This function helps the ILC1s to aid in the clearance of intracellular bacteria and viruses. ILC2s are comparable to Th2 cells, are most abundant in the lung and abdominal fat, and secrete cytokines such as IL-5, IL-9, and IL-13[18,19]. This allows for ILC2s to be highly functional in the clearance of parasites, especially helminths[20]. ILC3 cells are analogous to Th17 cells, and produce IL-22 and IL-17, important cytokines for barrier integrity, after stimulation with IL-23 and IL-1β. In the human intestine, ILC1 and ILC3 populations predominate, and may exist as a continuum between the two phenotypes[19,21]. Furthermore, intestinal ILC3s connect adaptive immune mechanisms through regulating follicular helper T cells in gut-associated lymphoid tissues and thereby affecting B cell affinity maturation in germinal centers[22]. Therefore, the absence of a competent ILC3 response has the potential to modulate mucosal antibody responses to commensal organisms as well as impair barrier function.

2.2 Adaptive Immune System

Adaptive immunity is also highly involved in the response to commensal organisms and provides a more targeted response to certain taxa in ways that would be outside of the scope of the innate immune system. Immune cells patrol the lamina propria of the intestine and other mucosal sites and gather in Peyer's Patches, which are lymphoid structures that arise in the small intestine and, to a lesser extent, in the colon. Similar tertiary structures exist in other mucosal tissues; for example, bronchus-associated lymphoid tissue (BALT) in the lungs. The patrolling cells are then able to drain to the mesenteric lymph nodes and re-enter the general circulation.

At the intestinal epithelium, microbial antigens are sampled through three methods: (1) dendritic cells protrude cellular dendrites between epithelial cells into the intestinal lumen in response to bacteria-produced metabolites, thereby directly sampling luminal contents[23]; (2) goblet-cell associated passages (GAPs) form following release of mucin, allowing microbial crossing of the epithelium, where dendritic cells and other mononuclear phagocytes capture these microbes[24]; and (3) transcytosis through microfold (M) cells forming the epithelial layer of Peyer's patches. After mononuclear phagocytes capture microbes, they travel to the nearest lymphoid structure (Peyer's patch or mesenteric lymph node) where they influence adaptive immune responses. Interestingly, the intestinal location of dendritic cell antigen sampling and drainage to lymph nodes highly influences polarization of T cells. Sampling and drainage to proximal small intestinal lymph nodes promotes a tolerogenic T cell response while more distal sampling and draining lymph nodes results in inflammatory T cell responses[25]. In the draining lymphoid structures of mucosal surfaces, not only are T cells polarized and matured, but also B cells mature and produce IgA for transcytosis across the mucosal epithelium.

While T cells develop receptors (TCRs) against commensal organisms, microbiota are able to influence the polarization of T helper cell populations. Classically, segmented filamentous bacteria (SFB) in mice have been well described to induce T helper 17 (Th17) cell differentiation through SFB adhesion to epithelial cells, triggering release of serum amyloid A proteins and endocytosis of SFB antigens, which stimulate Th17 cell differentiation[26,27]. Many other studies have described influences upon T cell differentiation in response to discrete intestinal microbes[28], but most microbes seem to incite the expansion of regulatory T (Treg) cells through the production of metabolites like short chain fatty acids (SCFA). Butyrate, a common SCFA, has been shown to be able to directly influence Treg differentiation *in vitro* through its ability to inhibit histone deacetylation. In vivo studies supported this data, demonstrating that mice dosed with broad spectrum antibiotics and oral butyrate displayed an increase in peripheral Tregs[29]. Studies in germ-free mice have demonstrated a relative lack of CD4+ T cells, with Th1 and Th17 subsets being depleted more heavily than Tregs, compared to microbially colonized mice; subsequent colonization of germ-free mice leads to a widespread increase in T helper and Treg population and functionality[30]. Furthermore mice deficient in TLR9, which lack the ability to sense commensal DNA through CpG oligodeoxynucleotide motifs, have significantly decreased intestinal Tregs[31]. In aggregate, these findings suggest that microbes are integral in the maintenance and specific regulation of CD4 T cell differentiation into subsets. The host must maintain a competent T cell response in order to maintain the balance with intestinal microbiota; these delicate balances can be easily perturbed in the case of intestinal dysbiosis.

B cells also play a major role in the sensing and maintenance of intestinal homeostasis and responses to commensal organisms. B cells are largely divided into two groups: B1 and B2 cells. B1 cells are derived from the pleuroperitoneal cavity in mice but not in humans. They are thought to be mildly autoreactive and therefore more suited to traffic to the intestine, where they secrete broadly-reactive IgA[32]. B2 cells are bone-marrow derived in both mice and humans, and undergo stringent development in order to maintain competent and non-autoreactive B cell receptor (BCR) specificity. These B cells are also able to traffic to GALT such as the Peyer's Patches, and there secrete IgA that is targeted specifically against microbes. Interestingly, emerging evidence suggests that the lines between these two populations may be more blurred than originally thought. B2 cells are able to exhibit a B1-like phenotype when they are forced to transgenically express a BCR that is associated with B1 cells[33]. This indicates that these populations may differentiate based on BCR specificity.

IgA is secreted at high rates along the intestinal tract via T-independent and T dependent processes, and commonly coats resident bacteria. The T-cell independent process occurs largely at the small intestinal mucosa. The IgA secreted from this process is generally low affinity and does not target any specific commensal taxa, but rather broadly coats a variety of commensal organisms in a highly polyreactive manner. In stark contrast, T-dependent IgA is more commonly secreted at the colonic mucosa. This IgA is far more antigen-specific, and has undergone affinity maturation in local Peyer's Patch germinal centers[34,35]. While it is physiologically normal for organisms to be coated in IgA, excess coating can signal increased host immune surveillance or bacteria that may be expanding into a novel niche.

When M cells transcytose microbial antigens, they first enter the subepithelial dome (SED) of the Peyer' patch. In the SED, T cells promote B cell proliferation without a germinal center based on B cell receptor (BCR) affinity to its antigen. B cells with low-affinity BCRs reside in this space and produce IgA without further maturation in a germinal center. However, when either greater amounts of antigen or a cognate B cell with high-affinity are present in the SED, the B cell will mobilize into the Peyer's patch germinal center, resulting in affinity maturation of B cells[36]. In this way, mucosal immunity is regulated through both the presence of antigens and BCR affinity.

3. Mechanisms by which bacteria can affect arthritis development

As described above, there are multiple ways by which the host immune system can sense and respond to the commensal organisms that colonize mucosal surfaces. This is physiologically imperative, as the firewall between microbes and self must be maintained in order for the host to remain healthy. However, this balance is delicate and once perturbed, may result in a range of disease and possibly arthritis. We will now explore multiple hypotheses for mechanisms by which microorganisms can affect the host in a way that incites arthritis development: bacterial translocation, bacterial metabolite secretion, mucosal immune cell dysregulation, and cross-reactive epitopes.

3.1 Bacterial Translocation Hypothesis

Under physiologic conditions, the mucosal epithelium and associated products act as a barrier between the human body and the outside world. However, there are many types of perturbations that can lead to a breakdown of this barrier. Intestinal barrier dysfunction has been described in axSpA; patients have decreased tight junctions formed between intestinal epithelial cells, leading to fluid and bacteria being able to aberrantly access the host[37]. Similarly, *P. gingivalis* has been demonstrated to lead to the breakdown of intestinal gut tight junctions in murine models of RA[38]. Some have described increased intestinal permeability for microbes as a cause for disease, terming this the "leaky gut hypothesis." While this is a popular hypothesis among the lay population, there have been few studies that have demonstrated how translocation of bacteria across a barrier contributes to arthritis development. Conceptually, increased epithelial permeability allows for the entry of microbes into a normally protected environment. Live bacteria and pieces of bacteria can gain entry into the circulation and thereby traffic to distal tissues. Several issues arise when this occurs. Bacteria as well as pieces of bacteria are potently immunogenic through the response of TLRs, NLRs, and recognition by cognate B and T cells as described above. Bacterial trafficking to distal tissues like the joint, therefore, can incite powerful immune responses that can lead to downstream tissue damage.

One well-known example of bacteria inciting arthritic disease is in the case of reactive arthritis, a type of SpA that results in acute asymmetrical joint damage post-infection with a genitourinary or gastrointestinal pathogen. In this case, bacterial antigen and nucleic acid translocation to joint spaces by innate immune cells incites a powerful and rapid inflammatory response that leads to joint destruction[39]. Multiple different bacteria have been shown to traffic to joint spaces and to incite reactive arthritis, but common organisms

include *Chlamydia trachomatis*, *Campylobacter, Salmonella, Shigella,* and *Yersinia* species. The full mechanism by which reactive arthritis develops is still unclear, but there are several interesting points that can inform our understanding of the condition as a whole. Firstly, the bacteria associated with reactive arthritis are intracellular pathogens. This suggests a potential mechanism by which bacterial antigens are subsequently found it the joint space: phagocytic cells engulf these bacteria and translocate them as they circulate within the host. Phagocytic digestion of the bacteria would lead to the presence of bacterial DNA and antigens that would be expelled into the joint upon the death of the phagocytic cell. There is also a potential genetic effect, as reactive arthritis is associated with the MHC class I molecule HLA B27, which is prone to misfolding in the endoplasmic reticulum and activating the unfolded protein response. In the setting of HLA B27 and the unfolded protein response, intracellular pathogens like *Salmonella* have altered intracellular localization that improve their survival and replication[40]. Such findings suggest mechanisms by which genetics and microbes operate in concert to allow increased bacterial access to the host and transfer to sites where they initiate inflammation.

Lyme arthritis is another arthritic disease whose pathogenesis is affected by the trafficking of bacteria to joint spaces. In Lyme arthritis, *Borrelia burgdorferi* and its antigens have been detected in the joint spaces and cartilaginous tissues around the joints. While the true mechanism of Lyme arthritis pathogenesis is still unclear, the presence of bacterial antigens in the joint space likely plays a key role. This hypothesis is supported by the murine model of disease in which young mice are inoculated with *Borrelia burgdorferi*. Five days after infection, bacteria are present within the joint leading to inflammatory cell infiltrate followed by joint destruction[41]. In addition to an innate immune response, there are several adaptive immune responses to *B. burgdorferi* in the joint space. *B. burgdorferi*-specific Th1 cells have been identified in the joint space of infected mice[42,43]. Additionally, adaptive immunity is required to resolve *B. burgdorferi* infection in the joint, as Rag-deficient mice display an increased bacterial burden in the joint. Transfer of both B and T cells into Rag-deficient mice reduces arthritis severity, but transferring only T cells worsens disease in these mice[44]. These findings indicate that an aggressive immune response to bacteria and bacterial antigens in the joint potentiates disease. While T cells are important for the resolution of active infection, it appears that they may also play an active role in the development of arthritis in murine models of Lyme arthritis.

The association between bacterial translocation to the joint space extends beyond the known bacteria associated arthritic diseases. In the case of RA, Pianta et al. demonstrated that *Prevotella* bacterial DNA can be detected in the joint space and synovial fluid of patients with new-onset RA[45]. However, Asquith et al. identified bacterial DNA in multiple tissues including the joints from rats with and without the HLA-B27/β2m transgene that predisposes them to spondyloarthritis[46], a finding that suggests that the mere presence of bacterial DNA in the joint is not sufficient for arthritis. Yet in both studies, controls to eliminate environmental contaminants were lacking.

3.2 Bacterially derived metabolite hypothesis

Bacterial metabolism results in the generation of products (metabolites) that affect themselves and the other bacteria around them. These molecules can be secreted in order to participate in quorum sensing or to better establish a niche within the host mucosa. However, these metabolites, similar to bacterial surface antigens, also have the potential to affect the host immune system, and do so in varied ways. Albeit only two classes of metabolites, short chain fatty acids and indoles, are discussed below, this is a rapidly expanding field with numerous pathways and mechanisms yet to be elucidated.

Short chain fatty acids (SCFAs) are one class of bacterial metabolites with immunomodulatory properties. These metabolites, most commonly acetate, butyrate, and propionate, are generated from anaerobic fermentation of dietary fibers in the gut[47]. Bacteroidetes, an abundant Gram-negative phylum in the intestine, primarily generates acetate and propionate; Firmicutes, an abundant Gram-positive phylum in the intestine, generates butyrate[48]. SCFAs function in the host to maintain epithelial barrier integrity[49] and modulate adaptive immunity. Mice fed a diet supplemented with SCFAs had increased FoxP3+ Tregs in the colon[50] and increased IL-10 production by T cells[51], which are hypothesized to be mediated by SCFAs acting as histone deacetylase inhibitors[50]. In murine collagen-induced arthritis, butyrate-induced expansion of Tregs resulted in reduced arthritis severity[52]. Furthermore, these metabolites modulate B cell metabolism that promotes antibody responses and plasma cell generation[53], adding another potential mechanism to affect arthritis development. Finally, Lucas et al. demonstrated that SCFAs can regulate bone mass, protecting from bone loss in arthritis[54]. When viewed through the lens of dysbiosis in arthritis, the loss of butyrate-producing Firmicutes, observed in the HLA-B27/β2m transgenic rat models of SpA, accompanies an increase in arthritic severity[55]. Taken together, SCFAs seem to be protective from the development of arthritis.

Indoles are another bacteria-derived metabolite with significant immunomodulatory activities. They are derived from bacterial metabolism of dietary tryptophan and signal through the aryl hydrocarbon receptor (AhR). Although host metabolism of tryptophan by the enzyme indoleamine 2,3-dioxygenase (IDO) to generate kynurenine has been shown to be anti-inflammatory[56,57], there are remote reports of indole having an arthritogenic effect in animal models of arthritis[58]. Bacteria generate an array of indole-containing structures, and their signaling through the AhR has a multitude of downstream effects. Indole derivatives such as 2-(1'H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) can induce Tregs directly as well as indirectly through DCs' support of FoxP3 Tregs in the experimental autoimmune encephalomyelitis (EAE) model, rednering mice proected from disease[59]. Indole-3-lactic acid (ILA) induces immunoregulatory CD4+CD8αα+ intraepithelial lymphocytes that promote oral tolerance to dietary antigens[60]. Along with studies demonstrating a protective role of AhR signaling during diseases like EAE, and the fact that many indoles are natural ligands of AhR, it has been assumed that indoles are anti-inflammatory[61]. However, two lines of data argue that this is not the case for indole itself or RA: First, the oxidized and sulfated form of indole (indoxyl sulfate) has been shown to promote EAE through the differentiation of Th17 cells[62]; and second, specific T cell AhR deficiency, and not myeloid cell deficiency, protected mice from CIA[63]. Interestingly, and

also of relevance to RA, AhR signaling in B cells can alter downstream antibody glycosylation patterns as well as cell-fate decisions[64], and antibody glycosylation patterns can alter the pathogenicity of the antibody[65,66]. These data highlight the complexity of this field: The effects of one indole-containing compound cannot be extrapolated to all compounds in this metabolic class nor it cannot be extrapolated to all tissues or disease states.

3.3 Mucosal Immune Dysregulation Hypothesis

As noted in prior sections, microbiota and their products result in education of the mucosal immune response. Thus, changes in microbial ecology, as have been described in all forms of arthritis[1–8,55,67,68], have the potential to alter immune cell populations and functions. Indeed, altered populations and functions of immune cells at mucosal sites have been linked to both human arthritis and animal models. Several animal models including K/BxN, collagen-induced arthritis, SKG, and HLA-B27/β2m transgenic rat have indicated microbial influences on Th17 cell differentiation as a requirement for arthritis development[6,7,55,69,70]. In the K/BxN model of spontaneous murine inflammatory arthritis, germ-free housing conditions attenuates disease due to a lack of Th17 cells. Colonization with SFB resulted in Th17 cell development as well as arthritis[69]. In a more translational study, Viladomiu et al. isolated expanded IgA-coated *E. coli* from individuals with Crohn's disease-associated axSpA and gavaged into K/BxN mice. The presence of these bacteria worsened arthritic disease in these mice in a Th17-dependent manner[71]. Similarly, in the collagen-induced arthritis murine model of inflammatory arthritis dysbiosis is linked with the development of Th17 immune responses in the intestine. Depletion of the microbiota with broad-spectrum antibiotics reduced the Th17 responses and affected pathogenic antibody development, particularly when antibiotics were given at the time of booster immunization[6]. These data suggested differential effects of the microbiome in modulating adaptive immunity during different stages of arthritis development.

Like T and B cells, ILCs also are modulated in response to commensal organisms, and because of their effects on adaptive immunity, have the potential to alter the development of arthritis. ILC population disturbances have been described in the circulation and intestinal tissues of patients with SpA[72], and in the case of psoriatic arthritis, expanded ILC3s in the circulation correlate with disease activity[73]. Given the role of ILC3 cells in barrier integrity and mucosal immune development, changes in their function may have substantial influences on the development of arthritis, although the precise ways in which they do so have yet to be identified.

Bacterial-host immune interactions at another mucosal site, the periodontium, has been implicated in RA pathogenesis, especially supported by the link between RA and periodontal disease. *Porphyromonas gingivalis*, which can cause periodontal disease, expresses a peptidyl-arginine deiminase (PAD) that is able to generate citrullinated antigens[74] and theoretically, but not proven, stimulate the generation of antibodies to citrullinated-protein antigens (ACPA) that are pathognomonic of RA. In murine inflammatory arthritis in which mice were transgenic for the shared epitope HLA-DRβ1, brushing of the gingiva with *P. gingivalis* followed by induction of CIA incited Th17

responses, ACPA generation, and increased disease severity compared to mice without *P. gingivalis* colonization[75]. In another line of study, patients with periodontitis were noted to have a similar citrullinated antigens compared to the RA joint. *Aggregatibacter actinomycetemcomitans* (*Aa*) was identified in the periodontal space to secrete leukotoxin A that stimulated hypercitrullination by neutrophil PADs and release of cirullinated antigens that could be detected by serum ACPA from RA patients. Antibodies both to *Aa* and to this leukotoxin were enriched in patients with RA[76], providing another intriguing link between microbes and disease development.

Furthermore, microbes are able to induce NETs at mucosal surfaces, best studied in the lung in the setting of RA. During NETosis myeloperoxidase triggers translocation of serine proteases to the nucleus where histones are cleaved; PAD4 also mobilizes to the nucleus, citrullinating histones. This intracellular material is extruded into the extracellular matrix, and often contains the microbial products that initially stimulated the reaction. Altered NETosis, whether formation or clearance by macrophages, has been associated with RA, and even suggested as one mechanism for stimulating ACPA production[77,78]. Thus, while NETosis can be helpful for pathogen clearance and the resolution of infection[17], it can provide a source of autoantigens to which autoantibodies may develop in the right genetic context.

3.4 Cross-reactive epitope hypothesis

Given the presence of specific HLA DR4 and B27 associations with RA and AS, respectively, an arthritogenic peptide produced by microbes has been sought. Certainly, this is the case in in the development of Lyme arthritis. Crowley et al. discovered an increase in autoreactivity against apolipoprotein B-100[79] as well as matrix metalloproteinase-10[80] in patients with Lyme arthritis. Similarly, Pianta et al. described robust T-cell reactivity against annexin A2 in patients with Lyme arthritis[81]. Although a specific cross-reactive antigen has yet to be defined in RA, several lines of evidence suggest that a microbial antigen may trigger autoantibody responses key for this disease. Typically, mucosal IgA+ B cells mature into antibody-producing plasmablasts that enter the general circulation and eventually home back to the mucosa; however, the percentage of this class of B cells in circulation is rarely above 10%. Interestingly, rates of circulating IgA+ plasmablasts are significantly increased to nearly 40% in the preclinical period of RA[82], where autoimmunity is present but clinical evidence of disease is absent, suggesting that mucosal antigens (microbes) are stimulating this expansion. In further support of this, many ACPA are of the IgA isotype, and are found in sputa of individuals at-risk for developing RA[83]. It is conceivable that sequence homology between bacterial antigens and host proteins could result in antibody cross-reactivity[84], and through B cells processes of epitope spreading and affinity maturation, could result in a microbially stimulated antibody becoming more specific for a host antigen.

Similarly, there is evidence for a role of molecular mimicry in SpA. The MHC class I molecule HLA B27 is a risk factor for axial SpA, and bacterial dysbiosis is associated with the presence of this gene in the absence of disease[68]. While most individuals with this gene will not develop SpA, some will in the presence of specific bacterial infections, resulting in reactive arthritis and leading a cross-reactive epitope hypothesis in this disease. In support of

a bacterial-stimulus for disease, B27 transgenic rats will not develop arthritis in a germ-free environment[85]. Yet it is unclear if the lack of disease is due to the lack of immune development as discussed above, or due to the lack of a specific microbial antigen. In the clinically related disease uveitis, which can often co-occur with SpA, there are animal model data to suggest a cross-reactive T cell epitope. Mice transgenic for TCR recognition of a retinal epitope were unable to develop disease in a microbe-poor environment. Disease could still be triggered in the transgenic mice in the absence of the self-antigen because intestinal bacteria were sufficient to active the autoreactive T cells[86]. Although these data do not directly demonstrate antigen cross-reactivity, they are supportive of such a hypothesis.

4. Conclusion

Commensal organisms have a great capacity to affect the physiology of their host. Microbes have been implicated in the development of myriad diseases, and the list continues to grow. When thinking about the role of microbes in stimulating the development of arthritic disease, it is important to not forget the role of community effect. These microbes, much like humans, exist in vast and diverse communities, and much of their biological programming functions within the context of this community. Therefore, community effects on the host could have much more powerful outcomes than the actions of just an isolated microbe.

There are many ways by which microbes can stimulate a breach of immunological tolerance, as they live in such close proximity to us, and the balance between physiology and pathophysiology is so delicate. The mucosal immune system does a extraordinary job of promoting tolerance to helpful microbes while keeping at bay pathogens and other threats. However, when this system breaks down the consequences can be vast. Similarities between microbial antigens and self-antigens can lead to a breach of tolerance that leads to the development of autoantibodies and autoreactive T cells. If bacteria can aberrantly gain entry into the host, they can traffic to distal tissue sites and incite widespread inflammation leading to tissue damage. The metabolites that they secrete as a mechanism of biosynthesis and energy generation can lead to immunomodulatory effects on other bacteria and the host in which they reside. And importantly, inflammation at the mucosal surface can have vast and complicated implications for both mucosal immune system dysregulation as well as effects on the bacterial communities living at the surface. It has been well described that in a variety of diseases, including arthritis, the diversity of bacteria at the intestinal is altered. We do not yet understand the full consequences of this loss of diversity, but it seems that it is foreboding in the context of autoimmune disease development.

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Research Agenda

- The link between specific microbial dysbiosis and arthritic diseases lacks mechanistic understanding of how these particular microbes lead to disease.
- The role of mucosal immunity in the development of joint inflammation remains to be elucidated.

Practice Points

- In spite of changes in microbial ecology associated with arthritis, no data support the use of antibiotics, probiotics, or supplements to alter the microbiome.
- Intestinal inflammation is associated with spondyloarthritis and should be assessed symptomatically.

In rheumatoid arthritis, there is a strong association with oral and pulmonary diseases, for which this group of patients should be evaluated.