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Do Bugs Control Our Fate? The Influence of the Microbiome on Autoimmunity

Irene Fung · Jackie P.-D. Garrett · Anupama Shahane · Mildred Kwan

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Abstract Autoimmune disease has traditionally been thought to be due to the impact of environmental factors on genetically susceptible individuals causing immune dysregulation and loss of tolerance. However, recent literature has highlighted the importance of the microbiome, (a collective genome of microorganisms in a given niche) in immune homeostasis. Increasingly, it has been recognized that disruptions in the commensal microflora may lead to immune dysfunction and autoimmunity. This review summarizes recent studies investigating the interplay between the microbiome and immune-mediated organ-specific diseases. In particular, we review new findings on the role of the microbiome in inflammatory bowel disease, celiac disease, psoriasis, rheumatoid arthritis, type I diabetes, and multiple sclerosis.

Keywords Microbiome · Microbiota · Inflammatory bowel disease · Colitis · Crohn's disease · Ulcerative colitis · Celiac disease · Psoriasis · Multiple sclerosis · Encephalitis · Rheumatoid arthritis · Diabetes · Autoimmunity

I. Fung · J. P.-D. Garrett
Division of Allergy and Immunology,
Children's Hospital of Philadelphia,
Philadelphia, PA, USA

A. Shahane
Division of Rheumatology, Department of Internal Medicine,
Philadelphia, PA, USA

I. Fung · J. P.-D. Garrett · A. Shahane · M. Kwan
Perelman School of Medicine, University of Pennsylvania,
Philadelphia, PA, USA

M. Kwan (✉)
Allergy & Immunology, Perelman School of Medicine,
University of Pennsylvania, Penn Medicine at Valley Forge,
1001 Chesterbrook Boulevard,
Berwyn, PA 19312, USA
e-mail: mildred.kwan@uphs.upenn.edu

Introduction

Humans have long been known to harbor a great number of microorganisms in the gut, oral cavity, and on the skin. It is notable that ~10^{14} total organisms, composed of ~1000 distinct species [1, 2••, 3, 4••] inhabit the human gut [1, 2••, 3, 4••, 5•]. This genetic catalog of microbial species within a defined environment is referred to as a microbiome. More recently, the impact of the microbiome has been found to significantly impact human disease development [5•]. It has become clear that humans fall into enterotypes: balanced symbiotic states of microbiota defined by characteristic populations of bacterial species and the genes they encode [5•, 6]. In addition, composition of the microbiome is influenced by numerous factors including diet [4••, 5•, 7, 8], antibiotics [1, 6, 8], microbe-microbe interactions [9], host genetics [7, 10], and others (e.g. oxygen tension [9]). Changes in these factors can cause microbiome disruption, otherwise known as dysbiosis.

The advent of massive parallel sequencing technology has allowed for genetic evaluation of the microbiome, including commensal bacteria that previously were unidentifiable through traditional culture techniques. Additionally, the use of gnotobiotic mice, in which the presence and composition of the microbial composition is experimentally manipulated, has allowed for evaluation of specific microorganisms that may affect immune development. In particular, germ-free (GF) mouse experiments have led to great discoveries in autoimmune disease pathogenesis [5•, 11]. In this article, we review the interaction of the microbiome with the immune system and how disruption of this interaction may lead to autoimmune disease.

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The Microbiome and Mucosal Immunity

The host mucosal immune system, particularly in the gut, works to protect the host from commensals and influences the make-up of the microbiome. After birth, the neonatal gut is colonized with maternal bacteria and ultimately forms a stable microbiotic profile. The mucosal immune system inhibits the entrance of intestinal bacteria through multiple mechanisms that include the epithelial barrier (e.g. mucus, tight junctions) [1, 3, 5•, 12], antimicrobial peptides [1, 3, 5•, 11, 12], mucosal IgA [1, 3, 5•, 12], and innate and adaptive immunity [1, 3, 5•, 12]. However, the containment of intestinal bacteria can be perturbed by environmental factors such as chemicals, tissue injury (e.g. ischemia), and pathogenic infection [1]. Defects in mucosal immunity allow bacteria to penetrate the epithelial barrier and induce inflammatory responses. If these defects or immune responses are not regulated, chronic inflammation can occur leading to a shift in the gut microbiome, often to a less diverse population of colonizing bacteria [9].

Conversely, microbiota directly influence normal mucosal immune system development. GF mice have underdeveloped Peyer's patches, mesenteric lymph nodes, and splenic white pulp [2••, 3, 5•, 9, 11, 12] as well as defective formation of intestinal lymphoid follicles [1, 9] and decreased numbers of intestinal lymphocytes [2••, 5•, 9, 11, 12]. These deficiencies can largely be corrected with the introduction of specific bacterial mixes, some single species, or bacterial products [9]. Microbiota also influence T cell subpopulations at steady state. Th17 cells, usually abundant in the gut, are absent in GF mice [2••, 5•, 6, 11, 12] but can be restored with introduction of segmented filamentous bacteria (SFB) [1–3, 5•, 9, 11–13]. T regulatory cells (Tregs) are also decreased in the large intestine of GF mice [5•, 6, 12], although are proportionately increased in the small intestine [4, 12]. Tregs can be induced by commensal bacteria such as *Bacteroides infantis* (B), *Bacteroides fragilis* (in particular by polysaccharide A (PSA) [2••, 3, 4••, 11, 12], and by specific Clostridial mixes (clusters XIVa and IV) [4••, 6]. Finally, reduced levels of IgA [2••, 3, 6, 12, 13] and IgG [2••] are observed in the gut of GF mice, suggesting a role for microbiota in specific antibody production.

Inflammatory Bowel Disease

Implicated Signaling Pathways and the Microbiome

Inflammatory bowel disease (IBD) is a chronic, relapsing inflammatory disease characterized by mucosal damage in genetically susceptible hosts. There are two main subtypes: Crohn's disease (CD), which is distinguished by transmural inflammation, and ulcerative colitis (UC), which is localized to the superficial layers of the colon. IBD incidence has increased dramatically in recent years in Westernized countries. Associated environmental changes in lifestyle, diet, antibiotic use, and hygiene may alter GI microbiota [14]. As described below, recent studies suggest that innate immune susceptibility and microbiota influence on the immune system are interdependent variables for IBD development.

Pattern recognition receptors (PRRs) recognize characteristic microbial molecular products and then stimulate innate immune responses. Two families of PRRs implicated in IBD pathogenesis are Toll-like receptors (TLRs), and nucleotide oligomerization domain (NOD) receptors. There are 11 known human TLRs, some which exist on the cell surface and others on endosomes. As a group they recognize a diverse array of bacterial, viral and fungal and endogenous patterns. Recently, abnormal TLR4 signaling in the mouse was found to induce spontaneous colitis as early as at 8 weeks of age, compared to controls [15].

Nucleotide-binding domain, leucine-rich repeat (NLR) proteins, including NOD receptors, are cytoplasmic proteins that regulate inflammation and apoptosis. In particular, NOD2 binds bacterial muramyl dipeptide (MDP) and regulates TLR sensitivity as well as potentiates NF-kB and IL-1β processing. NOD2 polymorphisms are associated with Crohn's disease susceptibility [16] and recent studies suggest how NOD2 may be implicated. First, intestinal immune cells chronically exposed to commensal bacteria develop tolerance for these microbes, and do not secrete cytokines upon NOD2 stimulation, unlike their peripheral counterparts [17]. Second, multivariate analysis of IBD patients using NOD2 and ATG16L1 genotyping and 16SrRNA microbiota sequencing showed association between IBD-susceptibility polymorphisms and altered microbiome [18]. ATG16L1 is required for autophagy, a defense mechanism against bacteria. NOD1 and NOD2 recruits ATG16L1 to the bacterial entry site for autophagy [19], and NOD2 and ATG16L1 risk alleles are associated with decreased antimicrobial secretion from Paneth cells[18]. In addition, recent demonstration that NOD2-deficient weaning mice have altered microbial community structure suggests that NOD2 influences microbial composition early on in development [20].

Inflammasomes are large multi-protein platforms that mediate secretion of pro-inflammatory cytokines. The NLRP3 inflammasome consists of NLRP3, a linker apoptosis-associated speck-like protein containing CARD (ASC), and caspase-1. Via activated caspase-1, the NLRP3 inflammasome cleaves pro-IL-1 and pro-Il-18 into their active counterparts. The NLRP6 inflammasome has a similar structure, and cleaves pro-IL-18 to produce active IL-18. As reviewed in [21] , inflammasome signaling in intestinal epithelial cells shape gut microbiota, and this in turn may lead to IBD pathogenesis. Mice deficient in NLRP3, ASC,

or caspase-1 are highly susceptible to chemically-induced colitis [22]. Possible mechanisms include increased epithelial permeability, systemic infiltration of commensal bacterial, and increased inflammation at the colon [22, 23]. Similarly, mice deficient in NLRP6 inflammasome components have altered GI microbiota and a shift towards a pro-inflammatory state and colitis [24].

Role of Commensal Gut Bacteria and Dysbiosis in IBD

As shown by three recent studies, there are diverse mechanisms in which commensal microbiota may confer immune protection against IBD development. First, early microbial exposure are directly associated with invariant NK cells (iNKT) numbers. GF mice given colitis accumulated iNKTs in the colonic lamina propria, which was associated with increased morbidity. Although introduction of microbiota in adult mice had no effect, neonatal exposure to conventional microbiota abrogated iNKT accumulation and reduced subsequent susceptibility to colitis [25]. Second, MDP ligation of NOD2 in human FOXP3+ Tregs was shown to mediate cell protection from Fas-mediated apoptosis [26]. This demonstrated the importance of NOD2 activation for Treg survival in the Fas-ligand-rich environment of IBD. In a third study, CD patients with unaffected NOD2 upregulated β-defensin and LL-37 mRNA in a manner dependent upon bacterial genomic fragment concentration [27].

Benefits conferred by the microbiome suggest that replacement of commensal flora may be therapeutic. Indeed, probiotic strains reduce inflammation in the UC and colitis mouse models [28–30], and this is shown to occur through a NOD2-dependent pathway, and with induction of local IL-10 production [29, 30]. However, a randomized double-blind placebo-controlled trial with *Lactobacillus acidophilus* La-5 *and Bifidobacterium animalis* subsp showed no significant benefit for maintaining remission one year after treatment [31]. Moreover, a recent Cochrane review of probiotics for UC treatment reached no definite conclusion regarding the efficacy of this treatment from the 4 studies identified [32].

Shifts in microbiome composition seen in dysbiosis may drive the chronic inflammation seen in IBD. Several studies support this notion: gut bacteria is required in animal models to initiate inflammation, fecal stream diversion produces clinical CD remission in humans, and increased mucosal bacterial load is seen in IBD patients (reviewed in [33••]). However, identification of a culprit species has been difficult. For example, using 16SrRNA analysis, increased *Enterobacteriaceae* was found in CD patients compared to controls [33••]. However, *Enterobacteriaceae* were not proportionally increased at sites of inflammation as expected if these organisms caused disease. In mouse model studies of colitis, while one recent study showed that *Enterobacteriaceae* numbers are associated with colitis [34], another study demonstrated that *Enterobacteriaceae* colonization did not induce disease [35].

Although identification of a culprit bacterial species remains elusive, identification of microbiota may still be useful for IBD diagnosis. A recent group was able to distinguish pediatric CD from UC patients by identifying differing taxa in fecal samples [36], while a second group found a significant decrease in oral microbiome diversity in pediatric CD patients compared to healthy controls [37].

If host immune-gut microbiome interactions are implicated in dysbiosis and subsequent IBD development, it follows that antibiotic therapy targeting pathogenic microbes could be an effective treatment modality. In support of this, a recent systematic review showed significantly increased remission rates in patients with CD and UC treated with antibiotics compared to controls [38••]. However, there was moderate heterogeneity of these results which reflected diverse types and combinations of antibiotic treatments. For perianal fistula, 3 trials (123 patients) demonstrated that ciprofloxacin or metronidazole use led to significant reduction in fistula drainage (R=0.8; 95 % CI 0.66–0.98) [38••]. Although changes in microbiota were not directly analyzed before and after treatment, this analysis suggests that accurate targeting of pathogenic bacteria, without sacrifice of commensal bacteria, could be effective for IBD management.

Genetic studies of spondyloarthropathies (SpA), notably IBD- associated arthritis and reactive arthritis, provide strong evidence of the role of intestinal microbes in inflammatory arthritis pathogenesis. The role of HLA-B27 in SpA is well-established, and animal studies show that HLA-B27 transgenic rats raised in a GF environment did not develop peripheral inflammatory arthropathy [39]. Studies demonstrate an effect of HLA-B27 on normal human microbial flora as well as host response to microbial exposure [40].

Celiac Disease

Celiac disease is a systemic immune mediated disorder elicited by reactivity to ingested gluten and prolamines from wheat, rye, barley and, sometimes, oats. The altered Th1 and innate response in Celiac disease lead to pathological changes in the gut, including infiltrating lymphocytes, villous atrophy, and extra-intestinal manifestations. The main treatment modality is a gluten free diet (GFD), but in many cases patients have continuing nutritional deficiencies and systemic disease. There is a strong genetic component with expression of HLA-DQ2 or HLA-DQ8 alleles in >90 % of patients and >70 % concordance in monozygotic twins. This suggests that environmental factors, perhaps through dysbiosis, also influence the development of disease.

Multiple studies have demonstrated disruptions in the microbiota of celiac patients with a shift towards healthy microbiota when patients are on a GFD. In general, it has been found that gram positive bacteria (*Firmicutes*) are decreased and gram negative bacteria (*Bacteroides*, *E. coli*) are increased in celiac duodenal and fecal samples (reviewed in [41•]). However, the studies do not all agree on changes in microbiota [41•, 42••]. A recent study indicated that *Bacteroides* was decreased in celiac susceptible infants and that delayed introduction of gluten could decrease incidence of disease [42••]. In addition, changes in the metabolome (the full complement of metabolites in an organism) were suggested to be a marker of loss of tolerance [42••]. Studies examining the effects of a GFD on healthy adults also have demonstrated the influence of diet on the microbiome. GFD caused reductions in healthy bacteria (Bifidobacterium, *B. longus*, Lactobacillus) with an increase in unhealthy bacteria (*E. coli*, Enterobacteriaceae). Additionally, the altered microbiota from these individuals caused reduced secretion of pro-inflammatory cytokines TNF-α, IFN-γ, and IL-8 and a decrease in anti-inflammatory cytokine IL-10 from peripheral blood mononuclear cells *in vitro* [43•, 44].

Type 1 Diabetes Mellitus

Type 1 Diabetes (T1D) is a chronic multisystem disease characterized by progressive destruction of the pancreatic beta cells [45]. The resulting lack of insulin secretion impacts fat, protein and carbohydrate metabolism.

Genetic background plays a role in susceptibility to T1D as demonstrated by susceptibility HLA polymorphisms HLA-DR3 and HLA-DR4 [46••]. However, as the concordance in monozygotic twin siblings of those with T1D is only 50 % [47], environmental factors must play a role. The role of microorganism exposure in T1D pathogenesis was first identified in animal models of T1D, including the non-obese diabetic (NOD) mouse strain and BioBreeding diabetes-prone (BB-DP) rats. These studies demonstrate that prevention of diabetes can be achieved through neonatal exposure to microbes and their by-products, including mycobacteria [48], persistent LCMV [49], bacterial antigens [50] and specific vaccines[51].

Initially, it was shown that GF environments increased the risk of T1D and that the presence of bacteria protected against T1D development [52, 53]. Myeloid differentiation factor 88 (MyD88) is an adaptor protein downstream of multiple PRRs which recognize invading microbes. MyD88 knockout NOD mice were protected from T1D, but almost all GF MyD88$^{-/-}$ NOD mice developed T1D. However, colonization of the MyD88 KO NOD mice with 6 strains of bacteria reduced incidence of T1D [52]. Further studies identified specific bacteria or bacterial products which determine T1D development [46••]. For example, monoculture of NOD female mice with *Bacillus cereus* delayed the onset of diabetes [54]. Second, SFB presence in female NOD mice protected from diabetes development, although this did not affect onset of insulitis [55]. Finally, lactobacillus johnsonii N62 may also delay the onset of T1D, by influencing intestinal integrity [56].

The intestinal microbiota influences nutrition, and this also has a role in T1D pathogenesis [57]. Gliadin, a glycoprotein implicated in the intestinal damage of celiac disease, has been studied in terms of T1D pathogenesis. Results are conflicting. Funda et al. found that both NOD mice fed gluten free (GFD) and gluten enriched (GED) diets developed diabetes at a significantly lower rate than mice fed a standard diet, with those on GFD having the lowest rate of diabetes [58]. Possible mechanisms for disease induction include increased intestinal permeability due to inflammation [59], increased T cell activation leading to beta cell apoptosis [60] and Treg suppression [61].

Human studies have demonstrated taxonomic differences in the intestinal microbiome of subjects with T1D. Using 16 S RNA to examine microbiome taxonomy, one study found that as infants approached toddlerhood, children who developed T1D had a decrease in intestinal microbiota diversity and a higher proportion of the Bacteroidetes phyla [62•]. In contrast, those who did not develop T1D had higher proportion of the *Firmicutes* phyla and retained a stable microbiota diversity [62•]. In addition, Brown et al. found *Actinobacteria*, *Bacteroidetes*, and *Proteobacteria* were higher in T1D cases while *Firmicutes*, *Fusobacteria*, *Tenericutes*, and *Verrucomicrobia* were higher in controls subjects [63].

The importance of the microbiota in T1D pathogenesis is now a target for disease management. The PRODIA study, currently ongoing in Finland, is investigating if probiotics can decrease autoantibodies in children with genetic susceptibility to T1D [64].

Psoriasis

Role of Commensal Skin Bacteria and Dysbiosis in Cutaneous Disease

Although most microbiome research has focused on the gut, the skin has a unique microbiome with clinical consequences as well. Current genomic methods have discovered a microbiome with greater diversity than anticipated from traditional culture techniques. Using these approaches, most skin bacteria are derived from four phyla: *Actinobacteria*, *Firmicutes*, *Bacteroidetes*, and *Proteobacteria*. The factors that influence the composition of bacteria on the skin

include: 1.) skin site (i.e. moist (*Staphylococcus*, *Corynebacterium*), dry (Gram negative organisms) or sebaceous (*Propionibacterium* spp.); 2.) host factors (age, sex); and 3.) environment (occupation, cosmetics, antibiotic use). Additionally, fungi (e.g. *Malassezia* spp.) and *Demodex* mites are also considered part of normal skin flora. As in the gut, the interaction of the host skin immune response and the skin microbiota serve to counterbalance and modulate each other allowing for appropriate defense against pathogenic microorganisms (reviewed in [65•]).

Psoriasis is a skin disease that results in disruption of cutaneous immune responses. Using culture based methods, differences in bacteria in psoriatic lesions and uninvolved skin have previously been observed (reviewed in [66]). Utilizing skin swabs and genomic techniques, one study showed that *Firmicutes* were increased and *Actinobacteria* were decreased in psoriatic lesions compared with uninvolved and healthy skin. Another study showed that *Propionibacterium* spp. were decreased in lesional skin while uninvolved skin from psoriatic patients harbored intermediate numbers compared to skin from healthy controls that had the highest abundance of *Propionibacterium* [67]. A third study showed decreases in *Actinobacteria* and *Propionibacteria* as well as a higher ratio of *Streptococcus*:*Propionibacteria* in skin biopsies of psoriatic lesions. In addition, *Staphylococci* was decreased in lesional skin while *Proteobacteria* was more abundant than previously reported [66]. These differences may be due to different sampling techniques used (swab vs biopsy) as well as sites sampled (e.g. dry vs sebaceous). Other studies looking at fungi of the microbiome have essentially determined that there are no differences between psoriatic lesions and uninvolved skin or skin from healthy controls [68, 69].

Multiple Sclerosis

Multiple sclerosis is a progressive neurological disease characterized by CNS inflammation, focal demyelination, and axonal and neuronal perikaryal injury [70].

Investigation of MS immunopathogenesis has been greatly enabled by animal models, in particular that of the mouse experimental autoimmune encephalomyelitis (EAE) model. This model has demonstrated how commensal gut flora activates CNS auto-reactive T cells, which recruit autoantibody-producing B cells [71]. GF mice developed significantly attenuated EAE with lower levels of pro-inflammatory IFN-γ and IL-17A and had increased CD4+CD25+Foxp3+ Treg cells compared to their conventionally colonized counterparts [72]. Colonization of GF mice with SFB, known to induce Th17 cells in the gut, restored disease [72] .

Recent evidence suggests that specific commensal species and GF conditions lead to different clinical outcomes in EAE. Probiotic lactobacilli (and oral antibiotics) suppressed EAE onset by IL-10 production [73–75] and via CD1d expressing CD5+ regulatory B cells [74, 75]. Further, it was demonstrated that *B. fragilis* conferred resistance to EAE in a PSA-dependent manner [76].

As aforementioned, it has been suggested that inflammasome signaling shapes gut microbiota and thereby impacts IBD development. [21]. Recently, NLRP3 and ASC have been found to also play a critical role in EAE progression [77, 78], likely through production of caspase-1-dependent cytokines which influence Th1 and Th17 development.

It has been argued that viruses are members of the microbiome, and that their dysbiosis is implicated in multiple sclerosis [79•]. Herpes viruses, known to cause acute meningoencephalits and myelitis, can exist in humans chronically and are associated with MS (reviewed in [79•]). Similarly, human endogenous retroviruses (ERVs) are significantly associated with neuroinflammation. ERVs integrate within the host genome, and may modulate host response and MS pathogenesis [79•]. However, association does not mean causation [80•], and more research is needed to elucidate the role of viruses in multiple sclerosis pathogenesis.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune inflammatory arthritis of unknown etiology. Disease may be due to the interplay between host and environmental factors. Host genetics in RA has been studied extensively. The most significant association concerns an epitope in the third hypervariable region of HLA-DRB1, known as the "shared epitope". Also, twin studies have shown higher concordance of RA in monozygotic twins (12–15 %) compared to dizygotic twins (3.5 %) [81]. Although genetic predisposition is an important susceptibility factor, environmental factors likely play a significant role in RA etiopathogenesis.

Infection has been implicated in RA, with *Proteus mirabilis*, *Porphyromonas gingivalis*, *Escherichia coli*, and Epstein-Barr virus infection proposed, although conclusive evidence is lacking. Emerging data suggests that the role of microorganisms is not directly pathogenic, but is indirect due to immune alteration.

Role of Commensal Oral Bacteria and Dysbiosis in RA

The oral mucosa has a unique microbiome that is influenced by oral niche, host factors, and exogenous microorganisms. Dysbiosis of the oral microbiome may allow otherwise beneficial commensals to cause disease [82], and it has been noted that diversity of the oral microbiota increases in oral disease [83]. The association between RA and inflammatory

oral disorder is of great interest. First, *Porphyromonas gingivalis*, a common cause of periodontitis, in conjunction with smoking, is one proposed etiologic link between periodontal disease and RA [84]. *P. gingivalis* expresses peptidyl arginine deiminase (PADI) which converts C-terminal arginine to citrulline. Citrullination of bacterial and potentially human proteins by PADI may expose hidden epitopes leading to loss of tolerance in genetically susceptible individuals. Resulting autoimmune responses alongside endogenous citrullination is thought to produce anti-citrullinated peptide/protein antibodies (ACPA). In fact, a direct correlation between ACPA antibodies and *P. gingivalis* lipopolysaccharide specific antibodies has been noted in RA patients and up to 20 % of unaffected first-degree relatives, with higher levels compared to controls [85, 86].

Dysbiosis can increase pathobionts, which are commensals that cause disease with host change. This produces Th17 skewing, activating local inflammatory cascades with tissue damage and clinical disease [87, 88•]. In predisposed individuals, this local immune response may result in systemic autoimmunity [89] with auto-reactive Th17 cells and B cell activation with autoantibody production. Migration of autoreactive lymphocytes to synovial tissue further potentiates local inflammation with pannus formation and joint damage [90].

Studies involving GF animal models support the role of microbiota in immune homeostasis. GF rats developed severe arthritis in an adjuvant-induced arthritis model while conventionally raised rats developed mild disease at low incidence [91]. Gnotobiotic animal studies have shown rapid onset of severe inflammatory arthritis in IL-1 receptor antagonist-deficient (IL-1rn$^{-/-}$) mice. When raised under GF conditions, IL-1rn$^{-/-}$ mice do not develop disease, but *Lactobacillus bifidus* introduction restored the development of arthritis [89]. In the K/BxN T-cell receptor transgenic arthritis mouse model, GF animals had reduced disease due to decreased peripheral Th17 cells. Introduction of SFB resulted in disease onset which could be inhibited by SFB-targeted antibiotic treatment. Another study showed differences in the fecal microbiome of transgenic mice with RA susceptible HLA-DRB1*0401 compared to resistant DRB1*0402. Specifically, female *0401 mice had significantly different microbiota than *0402 females and this lead to increased gut permeability and Th17-type cytokine transcripts in the former [92•]. Results suggest that interactions between gut commensals and host gender and genetic background influence susceptibility to disease.

Role of Antibiotics in the Treatment of RA

Emerging discoveries regarding the role of the microbiome suggest that antibiotics may be effective for RA by protecting against dysbiosis. In keeping with this, tetracyclines such as minocycline and doxycycline have been shown to reduce collagenase activity in animal models [93]. Moreover, a 2003 meta-analysis showed that tetracycline use was associated with significant reduction in disease compared to control patients [94]. More recently, a randomized placebo-controlled trial evaluating the efficacy of roxithromycin showed improvement in ACR 20, ACR 50 and ACR 70 responses in treated patients compared to controls [95]. Roxithromycin efficacy in RA is thought occur via inhibition of pro-inflammatory cytokines production by T cells and macrophages [96].

Conclusions

The recent explosion in microbiome studies highlights the role of commensal bacteria in maintaining immune homeostasis. Factors that affect the balance between the immune system and composition of microbiota lead to dysbiosis, and produce loss of tolerance and subsequent autoimmune disease. Currently, there is data implicating microbiota in proinflammatory responses in animal models for IBD, RA, T1D, and MS. In celiac disease and psoriasis, disruptions in the microbiome have been noted, but there is less data indicating a direct role for commensals in disease pathogenesis as of yet. This is an exciting time in microbiome research as we seek to define its possible roles in autoimmune disease induction, progression, maintenance, and therapy.

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- •• Of major importance

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