Cellular Immunology 339 (2019) 59–67

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Modulation of autoimmune arthritis by environmental 'hygiene' and commensal microbiota

David Langan[a,c], Eugene Y. Kim[a,d], Kamal D. Moudgil[a,b,c,*]

[a] Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore, MD 21201, United States
[b] Department of Medicine, Division of Rheumatology, University of Maryland School of Medicine, Baltimore, MD 21201, United States
[c] Baltimore VA Medical Center, Baltimore, MD 21201, United States
[d] Department of Biomedical Sciences, Washington State University, Spokane, WA 99224, United States

ARTICLE INFO

Keywords:
Autoimmunity
Arthritis
Aryl hydrocarbon receptor
Hygiene hypothesis
Indoles
Microbiota
Microbiome
Metabolites
Natural products
Probiotics
Prebiotics
Rheumatoid arthritis
Short-chain fatty acids
Th17/Treg balance
Tryptophan

ABSTRACT

Observations in patients with autoimmune diseases and studies in animal models of autoimmunity have revealed that external environmental factors including exposure to microbes and the state of the host gut microbiota can influence susceptibility to autoimmunity and subsequent disease development. Mechanisms underlying these outcomes continue to be elucidated. These include deviation of the cytokine response and imbalance between pathogenic versus regulatory T cell subsets. Furthermore, specific commensal organisms are associated with enhanced severity of arthritis in susceptible individuals, while exposure to certain microbes or helminths can afford protection against this disease. In addition, the role of metabolites (e.g., short-chain fatty acids, tryptophan catabolites), produced either by the microbes themselves or from their action on dietary products, in modulation of arthritis is increasingly being realized. In this context, re-setting of the microbial dysbiosis in RA using prebiotics, probiotics, or fecal microbial transplant is emerging as a promising approach for the prevention and treatment of arthritis. It is hoped that advances in defining the interplay between gut microbiota, dietary products, and bioactive metabolites would help in the development of therapeutic regimen customized for the needs of individual patients in the near future.

1. Introduction

Rheumatoid arthritis (RA) is one of the most common chronic autoimmune diseases, with an estimated global prevalence varying from 0.24 to 1 per cent in different countries [1,2]. Although, the highest reported prevalence of RA is in western, post-industrial nations, the burden of this disease is rapidly increasing in developing nations [3–5]. The exact etiology of this disease remains unknown, but genetics, sex, age, smoking, and infection are among the factors that influence RA susceptibility [6–8]. Synovitis (inflammation of the synovial lining of the joints) is often preceded years earlier by the appearance of serum biomarkers such as anti-cyclic citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF) [7]. Genome-wide association studies have identified certain HLA-DRB1 alleles and the shared epitope (SE), as well as PTPRC (protein tyrosine phosphatase, receptor type C) and PTPN22 (protein tyrosine phosphatase, non-receptor type 22) as genetic risk factors for RA [9–11]. Besides genetics, other factors are involved in the onset and progression of RA [9,12,13]. The monozygotic twin concordance for RA varies from 15 to 30% in studies from different countries, which is lower compared to 35%–45% for certain other autoimmune disorders [14–16]. The concordance rate of RA in monozygotic twins is about 4 times higher than that for dizygotic twins [16]. The sibling recurrence risk rate reported for RA is generally low, about 8% when accounting for the total population prevalence, compared to that for other common autoimmune diseases [17]. These statistics point towards the importance of environmental factors in RA pathogenesis

Abbreviations: AA, Adjuvant arthritis; AhR, Aryl hydrocarbon receptor; BCTD, Bhsp65 C-terminal determinants; Bhsp65, Mycobacterial heat-shock protein 65; CIA, Collagen-induced arthritis; CV, Conventional; EAE, Experimental autoimmune encephalomyelitis; GF, Germ-free; Hsp, Heat-shock protein; IBD, Inflammatory bowel disease (IBD); LAB, Lactic acid bacteria; MS, Multiple sclerosis; RA, Rheumatoid arthritis; SCFA, Short chain fatty acids; SPF, Specific pathogen free; TCDD, Tetrachlorodibenzodioxin; T1D, Type 1 diabetes; Th17, T heper 17; Treg, T regulatory; Trp-C, Tryptophan catabolites

* Corresponding author at: Department of Microbiology and Immunology, University of Maryland School of Medicine, 685 W. Baltimore Street, HSF-1, Suite-380, Baltimore, MD 21201, United States.
E-mail address: kmoudgil@som.umaryland.edu (K.D. Moudgil).

https://doi.org/10.1016/j.cellimm.2018.12.005
Received 30 November 2018; Received in revised form 9 December 2018; Accepted 9 December 2018
Available online 10 December 2018
0008-8749/

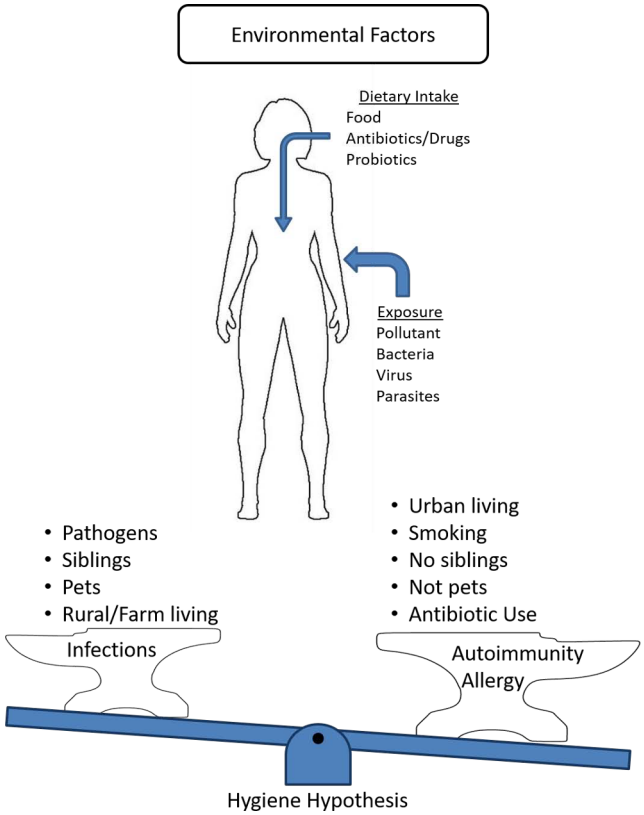

Fig. 1. The 'Hygiene hypothesis' proposes an imbalance in the host immune response (e.g., Th1 versus Th2; Th17/Treg) to various environmental agents and pathogens such that the host is rendered more prone to allergies and autoimmunity, while retaining the ability to fight effectively against certain infectious pathogens.

[18,19].

Industrialization continues to alter our environment in ways that have had unexpected deleterious implications on human health. The World Health Organization (WHO) has emphasized upon the likely contribution of these changes to the increasing prevalence of many chronic non-communicable diseases (NCDs), including RA [168,22]. Indeed, pollutants, pathogens, dietary factors, and the complexity of an individual's microbiome have been linked to increased risk of certain chronic NCDs (Fig. 1) [8,20–24]. The idea of an environmental impact on RA susceptibility and severity was proposed several decades ago [25]. However until recently, direct mechanisms linking the environment to the risk of RA development remained largely speculative and correlative, as it was not known why certain environmental factors would break immune tolerance and trigger or worsen the disease. There are now examples of toxins such as 2,3,7,8-tetrachlorodibenzodioxin (TCDD) found in air pollutants and cigarette smoke, which exacerbate the RA-associated inflammatory process in the synovial tissue of the joints [26]. Also, correlations between microbiome composition and dietary habits of RA patients are being elucidated [27]. The fact that numerous experimentally-induced animal models of RA are based on injection of a microbial product (e.g., complete Freund's adjuvant) [28,29]. and that relative "cleanliness" of the animal housing facility can modify disease severity [30], the impact of environmental "hygiene" and the microbiome on disease development is increasingly being appreciated [31,32]. In this review, we first introduce the "Hygiene hypothesis" of autoimmune pathogenesis, and then present a summary of the early work connecting autoimmune disorders to microbial factors, followed by more recent studies in the last decade or so on the influence of the microbiome on RA pathogenesis.

2. 'Hygiene hypothesis'

2.1. Origin of the 'Hygiene hypothesis' and expansion of its scope to include autoimmune diseases

The 'Hygiene hypothesis' was initially proposed to explain the epidemiological finding that there was an increase in the incidence of atopy in industrialized nations, when compared with developing countries [31,33,34]. Atopy, a term derived from Greek word atopos meaning "out of the way," is used medically to define a genetic predisposition to develop type I hypersensitivity (allergic illnesses such as asthma, rhinitis, and dermatitis) mediated by immunoglobulin E (IgE) and other related mediators [35]. The hypothesis was developed by Strachan after he observed that children without siblings were more likely to develop hay fever [36], and that there was an inverse correlation between household size and the incidence of hay fever [37]. It was suggested that the increased exposure to microbes during early childhood, as a result of having other siblings, protected these children from immune hypersensitivities. Since then, the scope of the Hygiene hypothesis has been expanded to include helminthic parasites and commensal organisms (microbiota), as well as autoimmune diseases such as type 1 diabetes (T1D) and multiple sclerosis (MS) [31,38,39]. There is compelling evidence that exposure to certain microbes and helminths could be beneficial in ameliorating immune-mediated diseases such as allergies and autoimmune diseases (Table 1, Figs. 1 and 2) [40]. Relatively recent epidemiological studies seem to support the Hygiene hypothesis. For example, children in Central Europe growing up on farms [41] and those exposed to pets, farm animals, and residing in rural areas of Eastern Europe [42] showed reduced risk of developing asthma. Additionally, a study in the US showed that both food allergy and asthma were reduced in children raised with a greater number of siblings; however, the incidence of skin infection and respiratory syncytial virus infection was increased [43], suggesting that exposure to certain microbes can exacerbate, while that to others can reduce immune-related disorders. Protection from inflammatory bowel disease (IBD) was also shown to be a result of spending early childhood on a farm [44]. Interestingly, an epidemiological study conducted in South Africa suggested that childhood exposure to helminthic infection is associated with reduced incidence of IBD [45]. In order to further examine the relationship between environmental biodiversity, human commensal microbiota and allergic diseases, a study was conducted to examine skin biodiversity between healthy and atopic patients [46]. From that study, it was concluded that healthy patients had higher environmental biodiversity in their surroundings as well as higher genetic diversity of gammaproteobacteria (one of the classes of bacteria of the phylum Proteobacteria, which contains gram negative bacteria) on their skin. Furthermore, IL-10 expression in peripheral blood mononuclear cells (PBMC) was positively correlated with a specific gammaproteobacterial genus, *Acinetobacter*, in healthy individuals compared to atopic individuals. Recently, it has been shown that infection of a RA patient with *Aggregatibacter actinomycetemcomitans* triggered disease symptoms as well as ACPA production, both of which were significantly reduced upon effective antibiotic therapy [47]. The association of this bacteria with ACPA production is attributed to its toxin, named leukotoxin A, which facilitates global hypercitrullination in neutrophils.This study provided a direct evidence for infection-induced autoimmunity in RA.

2.2. Support for the 'Hygiene hypothesis' from studies in various experimental models of autoimmunity

Our laboratory's foray into studying the potential role of "hygiene" in modulating the susceptibility to adjuvant arthritis (AA) in rats was initiated by a finding that Fischer 344 (F344) rats manifested differential clinical profiles of AA induction and severity depending on whether they were bred and maintained in a specific pathogen free

Table 1
The impact of exposure to microbes or helminths on disease susceptibility and severity in animal models of autoimmunity.

Response	Diseases	Mechanisms	Reference
Immune response to Hsps	RA	Spontaneous T cell response to BCTD of Bhsp65 can protect against AA in CV F344 rats	[30]
	MS, T1D, and IBD	Oral treatment with Bhsp65-expressing *L. lactis* promotes Treg induction	[121–123]
Immune tolerance	Allergy and IBD	GF environment increases iNKT cells which exacerbate oxazolone-induced colitis and OVA-induced allergic asthma	[51]
	T1D	TLR and MyD88 adaptor function is necessary for commensal bacteria-mediated resistance to T1D in NOD mice	[54]
	Allergy, IBD, T1D, RA, and MS	Healthy probiotic species has been used to protect against OVA-induced asthma, spontaneous/DSS-induced colitis, spontaneous T1D, CIA, and MOG-induced EAE. Typically, the mechanisms of immunoregulation involve decreasing proinflammatory cytokines such as TNF-α and IFN-γ, but increasing IL-10 and TGF-β	[126–132]
	IBD and MS	PSA from *Bacteroides fragilis* can protect against infectious colitis by increasing IL-10-producing CD4+ T cells, and against EAE by inducing IL-10-secreting FoxP3+ Tregs	[165,166]
	Allergy, IBD, and arthritis	*Bifidobacterium* and *Bacteroides* produce acetate and propionate that bind to Gpr43 expressed on granulocytes, and can suppress colitis, K/BxN arthritis, and OVA-induced asthma	[138]
	Allergy	Endotoxin tolerance from exposure to farm dust can protect against dust mite-induced asthma by reducing IL-5 and IL-13, and it requires A20 (DUB enzyme) to be expressed in lung epithelial cells	[167]
	Allergy, T1D, RA, and MS	Nematodes, trematodes, and a protozoan parasite have been used to treat OVA- and house dust mite-induced asthma, anaphylaxis, CIA, spontaneous arthritis in MRL/lpr mice, T1D, and EAE. While most typical mechanisms involve increasing FoxP3$^+$ Tregs and elevating TGF-β levels, some parasites can increase IL-10-producing T or B cells. Components of parasites such as egg antigen or excretory-secretory products can elicit Tregs, increase IL-5 and IL-33, or induce Th2 skewing	[20,63–79]

(SPF) versus a conventional (CV) facility [30]. Specifically, CV F344 rats were relatively resistant to AA, whereas SPF F344 rats were susceptible to AA with over 70% incidence rate and disease scores of intermediate severity. Our findings corroborated those of earlier studies that had identified a similar trend between the disease incidence and the type of housing facility in which animals were raised [48,49]. We suggested that this difference was due to the higher exposure of rats to microbes in the CV facility relative to a SPF or a germ-free (GF) facility. In order to examine this proposition, we performed two different sets of experiments. First, we transferred the SPF F344 rats into the CV environment for at least 3–4 weeks and observed whether this was sufficient to confer significant resistance to AA. Interestingly, such a transfer rendered the SPF F344 rats resistant to AA. Next, we transferred SPF F344 rats into the CV facility, but also regularly fed them with neomycin in water or acidified water for 4 weeks. We observed that F344 rats that received regular water were resistant to AA, while F344 rats that were fed either neomycin or acidified water remained susceptible to AA at levels similar to that of SPF F344 rats. These results supported the idea that a higher microbial burden in CV F344 rats compared to SPF F344 rats suppressed the development and severity of AA.

Similarly, in the collagen-induced arthritis (CIA) model, Dark Agouti rats in a GF facility develop more severe disease than those in a CV facility [50]. Furthermore, commensal organisms or external microbes have been shown to be protective in animal models of IBD [51,52], and T1D [53,54] as well as in a rat experimental autoimmune encephalomyelitis (EAE) model of human multiple sclerosis [55]. Interestingly, a study in GF rats concluded that colonizing rats with gram-negative bacteria before inducing AA resulted in milder disease development, whereas colonizing them with gram-positive bacteria resulted in relatively severe disease [56]. This observation was possibly a result

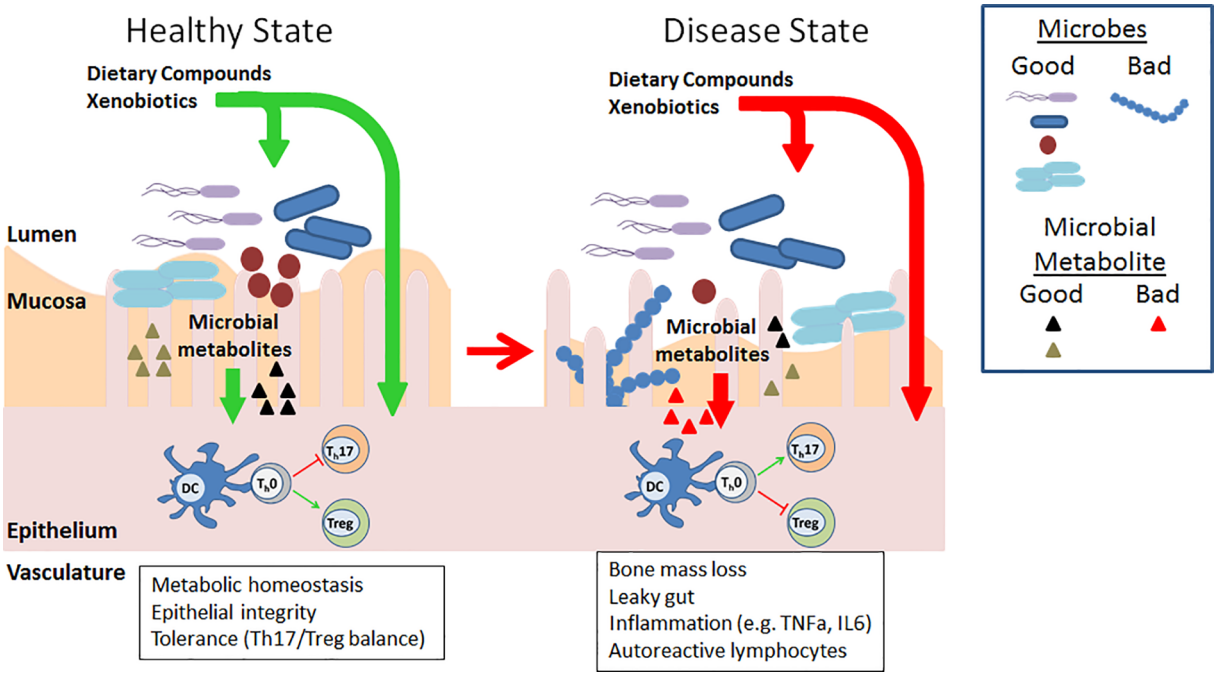

Fig. 2. The impact of dietary and other exogenous compounds on the maintenance of health, regulation of the host immune system through specific metabolites, and homeostasis of the host microbiome. Perturbation of microbial composition and the metabolites generated either by them and/or from their dietary substrates may result in chronic inflammation locally and at peripheral sites (e.g., the joints).

of effector responses induced by gram-specific cell wall components. However, the fact that most probiotics are gram-positive lactic acid bacteria (LAB), including *Lactobacillus* and *Bifidobacterium*, suggests that this association cannot be attributed to gram-specific cell wall components alone. Based on above observations, there are suggestions that deliberate exposure to microbes or specific adjuvants can be used to induce protection against some autoimmune diseases, for example T1D [53]. However, unlike above examples, a reverse pattern of disease modulation, namely induction or aggravation of autoimmunity by exposure to microbes, including housing in a CV environment compared to GF conditions, has also been observed in animal models of ankylosing spondylitis (HLA-B27 transgenic rats) [57], iodine-induced thyroiditis in NOD-H2^{h4} mice [58], experimental autoimmune thyroiditis in rats [59], EAE in mice transgenic for T cell receptor specific for myelin-basic protein [60], and Pristane-induced arthritis in mice [61]. Mechanisms involved in triggering autoimmunity include, but are not limited to, breakdown of immune tolerance, molecular mimicry, and production of pro-inflammatory cytokines [30,62].

2.3. The role of helminthic and other parasites in the modulation of autoimmunity

Parasites induce a strong T helper 2 (Th2) cell response and eosinophilia, and they have been shown to enhance immunoregulation in not just Th1-mediated autoimmune diseases, but also in Th2-mediated allergies [63]. Parasites that ameliorate disease in animal models of autoimmunity and allergy include nematodes such as *Heligmosomoides polygyrus*, *Nippostrongylus brasiliensis*, and *Litomosoides sigmodontis*; trematodes such as *Schistosoma mansoni*, *Schistosoma japonicum*, and *Fasciola hepatica*; and protozoan *Trypanosoma brucei*. Several helminthic and other parasites have been tested for their therapeutic effects in various diseases using animal models, including ovalbumin-induced (OVA)/house dust mite-induced asthma [63,64], anaphylaxis [65], CIA [20,66,67], spontaneous arthritis in MRL/lpr mice [68], T1D [69–72], and EAE [73] (Table 1). While the most typical mechanism of protection by these parasites involves increasing FoxP3$^+$ Treg and elevating TGF-β levels, some parasites can increase IL-10-producing T or B cells [63]. Interestingly, IL-5 has also been shown to induce Foxp3+ Treg [73], which further reinforces the connection between parasites and induction of Treg. Instead of whole parasites, certain components of parasites such as egg antigen [74,75] or excretory-secretory products [76–79] have been used as therapeutic agents. These components elicit similar immunoregulatory mechanisms as mentioned above, but also involve increasing IL-5 and IL-33 to promote eosinophilia [77] and Th2 skewing [78]. However, not all parasites assist in down-modulating allergy or autoimmunity. For example, the rat tapeworm *Hymenolepis diminuta* was shown to aggravate arthritis in K/BxN model by increasing complement component C5a and mast cell activation [80].

3. Role of the gut microbiome and the gut-associated immune responses in RA pathogenesis

After the generation of gnotobiotic and GF animals in the middle of the 20th century, it became apparent that the bacteria in and around us influence the development of our immune system in ways not previously anticipated [81]. Later, Joshua Lederberg emphasized that our understanding of the microbiome's role in many facets of health and disease had been all but ignored [82]. In the following years, numerous studies examined the correlations between the microbiome composition and autoimmunity, as highlighted by studies in MS and RA [83–85]. However, many of the earlier studies were limited to correlations alone, without much elaboration of the underlying mechanisms. Nevertheless, it has become clear that the dysbiosis observed in RA and some other autoimmune diseases needs to be re-set (Fig. 2), and this can be achieved via multiple approaches such as prebiotic diets, probiotics, antimicrobial interventions, and fecal microbiota transplants [85–87].

3.1. Mechanisms to explain the association of gut microbiota with RA and other autoimmune diseases

Certain microbial species are present more often or in higher amounts in the microbiome of RA patients relative to healthy individuals. These include *Porphyromonas gingivalis* and *Prevotella copri* [88–90]. The species *P. gingivalis* of the phylum Bacteroidetes is the only bacteria of the human microbiome known to produce citrullinated proteins, a result of harboring the enzyme peptidyl arginine deiminase (PAD), which can convert an arginine residue in a protein into citrulline (post-translational modification)[91]. Strains of *P. gingivalis* are shown to exacerbate the severity of CIA [92]; however, not all strains increased arthritis severity when given prior to onset of the disease. Another species of the Bacteroidetes phylum, *P. copri*, has also been linked to human RA. When fecal samples from RA patients harboring dysregulated *P. copri* numbers were administered to SGK mice (=zeta-chain (TCR) associated protein kinase; mutation 1, Shimon Sakaguchi mice), their Th17 numbers increased along with arthritis severity [93]. Members of the genus *Prevotella* may influence bone loss by regulating the levels of short-chain fatty acids (SCFAs) that mediate osteoclastogenesis in the host [94]. Another member of the genus *Prevotella*, *Prevotella histicola*, has been shown to inhibit the development of CIA in humanized, HLA-DQ8-bearing mice. This effect was mediated primarily through modulation of the Th17/Treg balance via CD103+ dendritic cells (DCs) and myeloid suppressors, but without affecting innate pathways involving Toll-like receptors (TLRs) [95].

Furthermore, the T cells exhibit plasticity and under certain conditions can convert from disease-regulating Treg into Th17. Such Th17 cells were found to be pathogenic, at least in CIA [96]. Certain gut microbiota also stimulate IL-1β production and assist in the development of Th17 cells [97]. Therefore, it is not surprising that in some autoimmune models, the gut microbiota seem to play a critical role in their pathogenesis (Fig. 2). For example, Dan Littman and colleagues showed that the presence of segmented-filamentous bacteria (SFB) in mice increased the expression of inflammatory genes and drove the differentiation of Th17 cells relative to non-colonized mice [98]. These findings have been corroborated, and SFB has been shown to exacerbate disease in the K/BxN model (of arthritis) and EAE [99,100]. It has been suggested that SFB drives Th17 differentiation through flagellin-mediated TLR5 activation of dendritic cells (DCs) in the gut [101]. However, the relevance of this finding to human RA is not yet fully clear because humans appear to be colonized with SFB only during early childhood [102]. In addition, this phenomenon may not apply to every Th17/Treg-mediated autoimmune disease as SFB has been shown to protect against T1D in NOD mice despite enhanced Th17 cells present in the gut [103]. Interestingly, the TLR5-binding site may be conserved in other commensals of the human gut such as *Clostridium sporogenes* [104], but it is not yet clear if there is a direct correlation between this particular species of the gram-positive genus *Clostridium* and RA. However, an abundance of *Clostridiaceae* has been reported in both RA and IBD-associated arthropathy [105].

The host regulates the microbiome, and vice versa. From the host side, this dynamic relationship is partially mediated via pattern recognition receptors (PRRs) such as the TLRs in a MyD88 (myeloid differentiation primary response 88)-dependent manner, as shown in commensal bacteria-mediated resistance to T1D in NOD mice [54]. It is likely that this immune pathway and others might regulate the immune events prior to the onset of RA as well as during the disease course, in part as a result of immune cells that undergo differentiation and activation in the gut [106]. However, the precise mechanisms by which the microbiome regulates this process has not yet been fully defined. Recently, it was shown that the gut microbiota of K/BxN mice, a model of spontaneous autoimmune arthritis, influences disease by regulating the migration and activity of T follicular helper (Tfh) cells in the Peyer's patches [107]. This arthritis model is often used to study antibody-mediated mechanisms of autoimmune arthritis. A contrasting but

significant role of gut commensals in autoimmunity is highlighted by the activation of autoreactive T cells by a crossreactive antigen derived from gut microbiota, leading to the development of autoimmune uveitis [108,109]. This study also revealed that potentially autoreactive T cells can be primed in the gut, but mediate their effector function at a peripheral site (the eye), as discussed below in reference to the pathogenesis of autoimmune arthritis as well.

Interestingly, studies have shown that targeting the alpha4beta7 (α4β7) gut-homing integrin can ameliorate arthritis in certain autoimmune arthritis models [110,111]. For example, the efficacy of AM80 (a synthetic retinoid that is an agonist for retinoic acid receptor-α (RARα)) in ameliorating CIA was attributed to retaining of the T cells in the gut and preventing systemic trafficking of Tfh and Th17 cells, in part by regulating α4β7 expression [110]. Also, the targeting of α4β7 with inhibitors was shown to protect against CIA [111]. Other studies have revealed that certain natural compounds mediate their effect against arthritis in part by regulating the balance of Th17 vs Treg cells in the gut-associated lymphoid tissue (GALT) [112,113]. Interestingly, the relative percentage of $\alpha4\beta7^+$ T cells, particularly the Treg fraction in this population, in the synovial tissue of RA patients has been found to be significantly higher than that in their peripheral blood or synovial fluid [114]. This was attributed to C-C chemokine receptor type 2 (CCR2)-mediated recruitment of $\alpha4\beta7^+$ T cells to the inflamed tissue. However, the integrin α4β7 is recognized by mucosal vascular addressin cell adhesion molecule-1 (MADCAM-1), and MADCAM-1 in at least one study was reported to be expressed in the bone marrow tissue adjacent to subchondral bone of the joint [115]. Therefore, additional factors might be involved in the preferential migration of these cells into the joints.

Recently a study in RA showed that individuals possessing the PTPN22 risk allele have higher incidence of harboring DNA from *Mycobacterium paratuberculosis* (MAP) [116,117]. This again brings up the potential association of mycobacterial infection or of mounting of a T cell response to heat-shock protein (Hsp) of microbial origin, with developing autoimmunity. However, immune response to Hsps may also have a protective effect against arthritis. As discussed above, we showed that response to Hsp65 may partially explain the disparate susceptibility trends of SPF F344 vs CV F344 to AA [30]. In that study, we examined the T cell responses to the T cell determinant region 177-191 (B177) of 65 kDa mycobacterial heat shock protein (Bhsp65), which represents the pathogenic epitope of that antigen. Also tested was the T cell response to Bhsp65 C-terminal determinants (BCTD), which we have previously shown to be associated with recovery from AA [29]. Splenocytes isolated from CV F344 rats raised weak, but significant proliferative responses to BCTD when compared with SPF F344 splenocytes, without any differences in the response to B177 or control antigen (hen egg lysozyme (HEL)) (Table 1). In addition, the adoptive transfer into SPF F344 rats of BCTD-restimulated splenocytes of CV F344 prior to AA induction conferred resistance in recipient rats. Interestingly, antibody responses to hsp65 appeared to also depend on the presence of commensal gut flora [118]. In this regard, hsp60 from microflora identified in the appendix and large intestine can stimulate the differentiation of naïve T cells into $Foxp3^+$ Treg cells [119]. Indeed, certain gut microbes may drive proliferation of both conventional T cells and $Foxp3^+$ T cells since long-term antibiotic treatment prevents their activation [120]. Immune response to Hsps has been exploited for therapeutic purposes. For example, genetically-engineered *Lactococcus lactis* that expresses Bhsp65 and assists in the expansion of Treg has been used to decrease disease severity in experimental models of MS [121], T1D [122], and IBD [123].

4. Probiotics for health maintenance and regulation of autoimmunity

Understanding the complex relationship between the host and the microbiome may also enable disease modulation in RA using probiotic species [124,125]. Some of the microorganisms that have been used to treat diseases in animal models of allergy and autoimmunity are typically "healthy" commensal species such as *Lactobacillus*, *Bifidobacteria*, *Bacteroides*, and *Escherichia coli Nissle 1917* (Fig. 2). These bacteria have been shown to induce protection against OVA-induced asthma [126], spontaneous/DSS-induced colitis [127,128], T1D [129,130], CIA [131], and EAE [132]. Typically, the mechanisms of immunoregulation involve a decrease in pro-inflammatory cytokines such as TNF-α and IFN-γ, but an increase in immunosuppressive cytokines such as IL-10 and TGF-β. There is some controversy over probiotic benefit in humans due in part to the lack of long-term survival of the probiotic in the gut after being consumed. The harsh environment of the stomach combined with poor dietary habits may make an individual's gut unsuitable for many probiotic species, but currently efforts are being made to address probiotic viability issues [124]. It has now been shown that strain-specific characteristics such as the expression of different cell wall components may influence probiotic potencies [133]. Of different strains of *P. freudenreichii* cultured with human PBMCs, the strains with specific surface proteins (SlpB and SlpE) induced the highest IL-10 levels and reduced TNF-α and IFN-γ [134]. This strain-specific phenotype was believed to be the result of the ability of the probiotic to bind closely to the cell monolayer layer, allowing for increased uptake of microbial metabolites that are potentially immunoregulatory in nature. A recent study revealed inter-individual differences among people in terms of successful colonization, or resistance to it, of gastrointestinal mucosa by the probiotic (live bacterial strain) as well as its impact on the gut microbiome and local gene expression [135]. These disparate outcomes were determined in part by the baseline host-intrinsic factors and microbiome. Furthermore, the above-mentioned differences were not reflected in the fecal presence of the probiotic, which was comparable among individuals. Interestingly, unlike humans, mice were inherently resistant to colonization by the probiotics, which was driven by the gut microbiome [135]. Another study examined the effects of antibiotics treatment on colonization of gastrointestinal mucosa by the probiotics as well as subsequent reconstitution of gut microbiome and local gene expression profiles in people [136]. Antibiotic treatment was found to enhance such colonization, but probiotic treatment following antibiotic therapy interfered with recovery of the gut microbiome and transcriptional program to its original baseline levels. However, these deficits could be compensated by autologous fecal microbiome transplantation [136]. Furthermore, the above-mentioned enhancement of probiotic colonization following antibiotic treatment was much more marked in humans than in mice [136]. The sections below highlight some microbe-derived metabolites with immunoregulatory properties, whose production by "healthy" commensals and probiotics could explain how they contribute to ensuring homeostasis.

5. Microbiota-derived metabolites and their impact on autoimmune pathogenesis

5.1. Short-chain fatty acid (SCFA)-metabolizers and SCFAs

Much of the probiotic research has been focused on understanding the benefits of a few classes of bacteria capable of producing lactic acid and SCFAs (e.g., acetate, propionate, and butyrate) [124]. Indeed, numerous clinical and preclinical studies show that SCFA-producing probiotic strains improve disease outcome [84]. For example, supplementing *Lactobacillus helveticus* was recently shown to protect mice against CIA [137]. Additionally, *Bifidobacterium* and *Bacteroides* produce SCFAs such as acetate and propionate from the fermentation of carbohydrates. These metabolites bind to the G-coupled protein receptor 43 (Gpr43) expressed on granulocytes to suppress diseases such as colitis, arthritis in the K/BxN model, and OVA-induced asthma [94,138]. However, the mechanism of reduction in inflammation imparted by increasing SCFAs may be dependent on the major cell type or process driving the disease in a particular autoimmune model [139],

and occasionally unexpected outcomes may be noted. For example, oral supplementation of SCFA ameliorated EAE and CIA, which represent predominantly T cell-driven diseases, whereas similar treatment worsened arthritis in the K/BxN serum (antibody)-induced arthritis model [139]. In an effort to expand on the scope of the influence of the microbial metabolome on RA, researchers have begun studying other metabolites known to be produced by the microbiome and elucidating their cross-talk with various immune pathways.

5.2. Tryptophan (Trp)-metabolizers and Trp derivatives

It has been reported that endogenous metabolism of tryptophan is perturbed in RA [140–142]. Mice in a CV facility showed considerable difference in tryptophan metabolism, when compared to mice raised in a GF facility [143]. This observation in animals raises the possibility that the microbiome may contribute to the increased endogenous host tryptophan metabolism observed in RA, as mentioned above. In addition to production of SCFAs described above, certain commensal and probiotic species including *Lactobacillus* and *Bifidobacterium* species also produce tryptophan-derivatives that bind the aryl hydrocarbon receptor (AhR) [124,125,144]. The AhR was originally studied in the context of toxicology and oncology with regard to the effects of TCDD [145,146]. It is now evident that AhR can interact with several endogenous ligands as well as numerous exogenous ligands that are present in the environment. Interestingly, a recent study showed that SCFAs, especially butyrate, enhanced the responsiveness of human Caco-2 cells to microbe-derived AhR ligands [119,120]. This implies cross-talk between the immune pathways involved in the signaling of these different metabolites. However, it has yet to be shown whether increasing SCFAs enhances AhR responsiveness in vivo, and whether this might be a relevant mechanism explaining the outcomes of SCFA treatment studies.

Microbe-derived tryptophan-derivatives are enzymatically produced in a few pathways with indole, indole-3-aldehyde (IAld), or indole-3-propionate (I3P) being some of the major compounds produced. There are several additional intermediates that have varying affinity and agonistic activity for the AhR pathway [144,147]. *Clostridium sporogenes* produces I3P, an agonist for the pregnane X receptor (PXR), which can protect against IBD in animals by reducing the expression of TNF-α by enterocytes and improving the tight junction barrier [148]. It was also shown using a *Citrobacter rodentium* colitis model that I3P administration increased the number of IL-17A$^+$ intraepithelial leukocytes [149]. Whether this compound (i.e., I3P) has physiological relevance in RA remains to be shown, but it appears to regulate disease-relevant pathways through the PXR. The concentration of these tryptophan-derivatives may be tightly controlled by tryptophan availability [150]. Interestingly, endogenous tryptophan metabolism is also altered in CIA [151]. Although microbial tryptophan metabolism may play a role in the development of RA and disease in animal models of RA, causation has yet to be directly studied. In an autoimmune model of MS, it was shown that microbe-derived tryptophan metabolites mediate disease in an AhR-dependent manner [152]. Indirubin, derived from the Indigo plant (*Indigo naturalis*) and used in a Chinese herbal medicine for leukemia treatment [153], is also produced by gut bacteria from the metabolism of tryptophan. Indirubin was shown to reduce IL-6 and IL-8 in response to TNF-α stimulation of ex vivo-cultured RA fibroblast-like synoviocytes (RA-FLS), and this effect was partially dependent on mitogen-activated protein kinases (MAPK) signaling and activation of P21-activated kinase 1 (PAK1) [154].

5.3. Other microbe-derived immunoregulatory metabolites that influence arthritis

Various AhR ligands may exert pleiotropic effects on the immune system, as observed in the case of EAE [155,156]. The AhR-mediated effects on EAE are specific to the immune state during which the receptor is engaged, with protection mediated through dendritic cells and T cells [157]. AhR signaling supports retinoic acid production by DCs in addition to the differentiation of Foxp3$^+$ Treg. The metabolite 1,4-dihydroxy-2-naphthoic acid (DHNA), only known to be produced by *Propionibacterium freudenreichii* and *Lactobacillus casei LP1*, is an AhR ligand [158,159]. These bacteria and DHNA can be found in cheese, with L. casei being investigated as a probiotic therapy for RA [84]. Vitamin K2 is a class of menaquinones (MK) that vary in chain length, of which MK5-12 is produced by the microbiome. Interestingly, DHNA can be converted to MK by the gut microbiota. Plant-derived MK4 has been tested in CIA as well as clinical studies, and microbiome-derived MK7 has been tested in a clinical trial; treatment with MK4/MK7 led to reduced levels of general inflammatory markers, namely C-reactive protein and matrix metaolloproteinase-3 as well as disease activity score-28 (DAS28) [160–162]. In addition to producing MKs, tryptophan-derivatives, and SCFAs, several species of Lactobacillus and Bifidobacterium can also generate the neurotransmitter γ-aminobutyric acid (GABA) [163], another anti-arthritic metabolite. Inflammation in CIA was downregulated in mice given GABA [164]. Since whole live probiotics may have unwanted side effects as well, bacterial products such as polysaccharide A (PSA) from *Bacteroides fragilis* has been tested and shown to protect against infectious colitis by increasing IL-10-producing CD4+ T cells [165], and against EAE by inducing IL-10 secreting FoxP3+ Treg [166]. In another study on IBD and RA, an increase in gut microbial tyrosine degradation pathways was found in IBD-associated arthropathy [105].

6. Concluding remarks

It is evident that both external (foreign) and internal (commensals) microbial agents and helminthic parasites can modify the onset and progression of autoimmunity in genetically susceptible individuals.

As the population in the United States ages and more countries industrialize, the burden of RA and other autoimmune diseases is likely to grow. Therefore, finding new ways to limit the exposure to environmental risk factors and to ensure a healthy homeostatic state of microbiome-host relationship is critical for preventing or delaying the onset of autoimmunity as well as reducing the progression and flare-up of the disease process in RA and other autoimmune diseases. In parallel, personal and public health measures to implement appropriate cultural and life-style changes would be required to curb the increasing prevalence of autoimmune diseases.

Declaration

The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Declaration of interest

None.

Acknowledgements

This work was supported in part by grants (to KDM) from the National Institutes of Health, Bethesda, MD (R01 AT 004321) and the United States (U.S.) Department of Veterans Affairs [Biomedical Laboratory Research and Development Service] (VA Merit Review Award 5 I01 BX002424). We thank Rakeshchandra Reddy Meka, Steven Dudics, and Shivaprasad H. Venkatesha for helpful discussions. We also thank Carol Fowler and Tom Bowen for help with the VA Research Facilities. This material is the result of work supported in part with resources and the use of facilities at the VA Maryland Health Care System, Baltimore, Maryland.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cellimm.2018.12.005.

References

[1] A. Gibofsky, Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis, Am. J. Manag. Care 18 (13 Suppl) (2012) S295–S302.
[2] M. Cross, et al., The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study, Ann. Rheum. Dis. 73 (7) (2014) 1316–1322.
[3] Y. Alamanos, A.A. Drosos, Epidemiology of adult rheumatoid arthritis, Autoimmun. Rev. 4 (3) (2005) 130–136.
[4] I. Rudan, et al., Prevalence of rheumatoid arthritis in low- and middle-income countries: a systematic review and analysis, J. Glob. Health 5 (1) (2015) 010409.
[5] J. van den Hoek, et al., Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study, Rheumatol. Int. 37 (4) (2017) 487–493.
[6] S. Rantapaa-Dahlqvist, What happens before the onset of rheumatoid arthritis? Curr. Opin. Rheumatol. 21 (3) (2009) 272–278.
[7] A. Kleyer, et al., Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies, Ann. Rheum. Dis. 73 (5) (2014) 854–860.
[8] V. Taneja, Arthritis susceptibility and the gut microbiome, FEBS Lett. 588 (22) (2014) 4244–4249.
[9] A.B. Begovich, et al., A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis, Am. J. Hum. Genet. 75 (2) (2004) 330–337.
[10] J. Holoshitz, The rheumatoid arthritis HLA-DRB1 shared epitope, Curr. Opin. Rheumatol. 22 (3) (2010) 293–298.
[11] A.M. Walsh, et al., Integrative genomic deconvolution of rheumatoid arthritis GWAS loci into gene and cell type associations, Genome Biol. 17 (2016) 79.
[12] K. Sakurai, et al., HLA-DRB1 shared epitope alleles and disease activity are correlated with reduced T cell receptor repertoire diversity in CD4+ T cells in rheumatoid arthritis, J. Rheumatol. 45 (7) (2018) 905–914.
[13] K. Yamamoto, et al., Genetics of rheumatoid arthritis in Asia–present and future, Nat. Rev. Rheumatol. 11 (6) (2015) 375–379.
[14] G.S. Cooper, F.W. Miller, J.P. Pandey, The role of genetic factors in autoimmune disease: implications for environmental research, Environ. Health Perspect. 107 (Suppl. 5) (1999) 693–700.
[15] C.M. Deighton, et al., Contribution of inherited factors to rheumatoid arthritis, Ann. Rheum. Dis. 51 (2) (1992) 182–185.
[16] A.J. Silman, et al., Twin concordance rates for rheumatoid arthritis: results from a nationwide study, Br. J. Rheumatol. 32 (10) (1993) 903–907.
[17] T.J. Vyse, J.A. Todd, Genetic analysis of autoimmune disease, Cell 85 (3) (1996) 311–318.
[18] D.P. Bogdanos, et al., Twin studies in autoimmune disease: genetics, gender and environment, J. Autoimmun. 38 (2–3) (2012) J156–J169.
[19] T. Frisell, S. Saevarsdottir, J. Askling, Family history of rheumatoid arthritis: an old concept with new developments, Nat. Rev. Rheumatol. 12 (6) (2016) 335–343.
[20] Y. Osada, et al., Schistosoma mansoni infection reduces severity of collagen-induced arthritis via down-regulation of pro-inflammatory mediators, Int. J. Parasitol. 39 (4) (2009) 457–464.
[21] D. Statovci, et al., The Impact of Western Diet and Nutrients on the Microbiota and Immune Response at Mucosal Interfaces, Front. Immunol. 8 (2017) 838.
[22] P. Vineis, S. Stringhini, M. Porta, The environmental roots of non-communicable diseases (NCDs) and the epigenetic impacts of globalization, Environ. Res. 133 (2014) 424–430.
[23] J. Vaahtovuo, et al., Fecal microbiota in early rheumatoid arthritis, J. Rheumatol. 35 (8) (2008) 1500–1505.
[24] L. Padyukov, et al., A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis, Arthritis Rheum. 50 (10) (2004) 3085–3092.
[25] S. Cobb, W. Bauer, I. Whiting, Environmental factors in rheumatoid arthritis: a study of the relationship between the onset and exacerbations of arthritis and the emotional or environmental factors, Ann. Rheum. Dis. 1 (4) (1939) 364–365.
[26] S. Kobayashi, et al., A role for the aryl hydrocarbon receptor and the dioxin TCDD in rheumatoid arthritis, Rheumatology (Oxford) 47 (9) (2008) 1317–1322.
[27] P. Toivanen, Normal intestinal microbiota in the aetiopathogenesis of rheumatoid arthritis, Ann. Rheum. Dis. 62 (9) (2003) 807–811.
[28] E.F. Rosloniec, et al., Collagen-induced arthritis, Curr. Protoc. Immunol. (2010) Chapter 15: p. Unit 15 5 1–25.
[29] K.D. Moudgil, et al., Diversification of T cell responses to carboxy-terminal determinants within the 65-kD heat-shock protein is involved in regulation of autoimmune arthritis, J. Exp. Med. 185 (7) (1997) 1307–1316.
[30] K.D. Moudgil, et al., Environmental modulation of autoimmune arthritis involves the spontaneous microbial induction of T cell responses to regulatory determinants within heat shock protein 65, J. Immunol. 166 (6) (2001) 4237–4243.
[31] L.T. Stiemsma, et al., The hygiene hypothesis: current perspectives and future therapies, Immunotargets Ther 4 (2015) 143–157.
[32] T. Van de Wiele, et al., How the microbiota shapes rheumatic diseases, Nat. Rev. Rheumatol. 12 (7) (2016) 398–411.
[33] A. Sheikh, D.P. Strachan, The hygiene theory: fact or fiction? Curr. Opin. Otolaryngol. Head Neck Surg. 12 (3) (2004) 232–236.
[34] B. Schaub, R. Lauener, E. von Mutius, The many faces of the hygiene hypothesis, J. Allergy Clin. Immunol. 117 (5) (2006) 969–977 quiz 978.
[35] H.G. Rapaport, Clemens von Pirquet and allergy, Ann. Allergy 31 (10) (1973) 467–475.
[36] D.P. Strachan, Hay fever, hygiene, and household size, BMJ 299 (6710) (1989) 1259–1260.
[37] D.P. Strachan, E.M. Taylor, R.G. Carpenter, Family structure, neonatal infection, and hay fever in adolescence, Arch. Dis. Child. 74 (5) (1996) 422–426.
[38] H. Okada, et al., The 'hygiene hypothesis' for autoimmune and allergic diseases: an update, Clin. Exp. Immunol. 160 (1) (2010) 1–9.
[39] J.F. Bach, The effect of infections on susceptibility to autoimmune and allergic diseases, N. Engl. J. Med. 347 (12) (2002) 911–920.
[40] G.A. Rook, et al., Mycobacteria and other environmental organisms as immunomodulators for immunoregulatory disorders, Springer Semin. Immunopathol. 25 (3–4) (2004) 237–255.
[41] M.J. Ege, et al., Exposure to environmental microorganisms and childhood asthma, N. Engl. J. Med. 364 (8) (2011) 701–709.
[42] M.S. Kramer, et al., The low prevalence of allergic disease in Eastern Europe: are risk factors consistent with the hygiene hypothesis? Clin. Exp. Allergy 39 (5) (2009) 708–716.
[43] R.S. Gupta, et al., Hygiene factors associated with childhood food allergy and asthma, Allergy Asthma Proc. 37 (6) (2016) 140–146.
[44] S. Timm, et al., Place of upbringing in early childhood as related to inflammatory bowel diseases in adulthood: a population-based cohort study in Northern Europe, Eur. J. Epidemiol. 29 (6) (2014) 429–437.
[45] K.M. Chu, et al., Childhood helminth exposure is protective against inflammatory bowel disease: a case control study in South Africa, Inflamm. Bowel Dis. 19 (3) (2013) 614–620.
[46] I. Hanski, et al., Environmental biodiversity, human microbiota, and allergy are interrelated, Proc. Natl. Acad. Sci. U.S.A. 109 (21) (2012) 8334–8339.
[47] A. Mukherjee, et al., Rheumatoid arthritis-associated autoimmunity due to aggregatibacter actinomycetemcomitans and its resolution with antibiotic therapy, Front. Immunol. 9 (2018) 2352.
[48] O. Kohashi, et al., Susceptibility to adjuvant-induced arthritis among germfree, specific-pathogen-free, and conventional rats, Infect. Immun. 26 (3) (1979) 791–794.
[49] A.G. van de Langerijt, et al., Susceptibility to adjuvant arthritis: relative importance of adrenal activity and bacterial flora, Clin. Exp. Immunol. 97 (1) (1994) 33–38.
[50] M.A. Breban, et al., Influence of the bacterial flora on collagen-induced arthritis in susceptible and resistant strains of rats, Clin. Exp. Rheumatol. 11 (1) (1993) 61–64.
[51] T. Olszak, et al., Microbial exposure during early life has persistent effects on natural killer T cell function, Science 336 (6080) (2012) 489–493.
[52] S. Rakoff-Nahoum, et al., Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis, Cell 118 (2) (2004) 229–241.
[53] B. Singh, A. Rabinovitch, Influence of microbial agents on the development and prevention of autoimmune diabetes, Autoimmunity 15 (3) (1993) 209–213.
[54] L. Wen, et al., Innate immunity and intestinal microbiota in the development of Type 1 diabetes, Nature 455 (7216) (2008) 1109–1113.
[55] S.F. Zorzella, et al., Resistance to experimental autoimmune encephalomyelitis development in Lewis rats from a conventional animal facility, Mem. Inst. Oswaldo Cruz 102 (8) (2007) 931–936.
[56] O. Kohashi, et al., Reverse effect of gram-positive bacteria vs. gram-negative bacteria on adjuvant-induced arthritis in germfree rats, Microbiol. Immunol. 29 (6) (1985) 487–497.
[57] J.D. Taurog, et al., The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats, J. Exp. Med. 180 (6) (1994) 2359–2364.
[58] N.R. Rose, et al., The role of iodine in autoimmune thyroiditis, Crit. Rev. Immunol. 17 (5–6) (1997) 511–517.
[59] W.J. Penhale, P.R. Young, The influence of the normal microbial flora on the susceptibility of rats to experimental autoimmune thyroiditis, Clin. Exp. Immunol. 72 (2) (1988) 288–292.
[60] J. Goverman, et al., Transgenic mice that express a myelin basic protein-specific T cell receptor develop spontaneous autoimmunity, Cell 72 (4) (1993) 551–560.
[61] S.J. Thompson, C.J. Elson, Susceptibility to pristane-induced arthritis is altered with changes in bowel flora, Immunol. Lett. 36 (2) (1993) 227–231.
[62] N.R. Rose, The role of infection in the pathogenesis of autoimmune disease, Semin. Immunol. 10 (1) (1998) 5–13.
[63] M.S. Wilson, et al., Suppression of allergic airway inflammation by helminth-induced regulatory T cells, J. Exp. Med. 202 (9) (2005) 1199–1212.
[64] K. Kitagaki, et al., Intestinal helminths protect in a murine model of asthma, J. Immunol. 177 (3) (2006) 1628–1635.
[65] N.E. Mangan, et al., Helminth infection protects mice from anaphylaxis via IL-10-producing B cells, J. Immunol. 173 (10) (2004) 6346–6356.
[66] X. Song, et al., Impact of Schistosoma japonicum infection on collagen-induced arthritis in DBA/1 mice: a murine model of human rheumatoid arthritis, PLoS One 6 (8) (2011) e23453.
[67] L. Mattsson, et al., Parasite-mediated down-regulation of collagen-induced arthritis (CIA) in DA rats, Clin. Exp. Immunol. 122 (3) (2000) 477–483.
[68] M.C. Salinas-Carmona, et al., Spontaneous arthritis in MRL/lpr mice is aggravated by Staphylococcus aureus and ameliorated by Nippostrongylus brasiliensis infections, Autoimmunity 42 (1) (2009) 25–32.
[69] Q. Liu, et al., Helminth infection can reduce insulitis and type 1 diabetes through CD25- and IL-10-independent mechanisms, Infect. Immun. 77 (12) (2009) 5347–5358.

[70] P.K. Mishra, et al., Prevention of type 1 diabetes through infection with an intestinal nematode parasite requires IL-10 in the absence of a Th2-type response, Mucosal Immunol. 6 (2) (2013) 297–308.
[71] M.P. Hubner, J.T. Stocker, E. Mitre, Inhibition of type 1 diabetes in filaria-infected non-obese diabetic mice is associated with a T helper type 2 shift and induction of FoxP3+ regulatory T cells, Immunology 127 (4) (2009) 512–522.
[72] M.P. Hubner, et al., Helminth protection against autoimmune diabetes in non-obese diabetic mice is independent of a type 2 immune shift and requires TGF-beta, J. Immunol. 188 (2) (2012) 559–568.
[73] G.T. Tran, et al., Interleukin-5 mediates parasite-induced protection against experimental autoimmune encephalomyelitis: association with induction of antigen-specific CD4(+)CD25(+) T regulatory cells, Front. Immunol. 8 (2017) 1453.
[74] P. Zaccone, et al., Schistosoma mansoni egg antigens induce Treg that participate in diabetes prevention in NOD mice, Eur. J. Immunol. 39 (4) (2009) 1098–1107.
[75] M.M. Eissa, et al., Anti-arthritic activity of Schistosoma mansoni and Trichinella spiralis derived-antigens in adjuvant arthritis in rats: role of FOXP3+ Treg cells, PLoS One 11 (11) (2016) e0165916.
[76] J.R. Grainger, et al., Helminth secretions induce de novo T cell Foxp3 expression and regulatory function through the TGF-beta pathway, J. Exp. Med. 207 (11) (2010) 2331–2341.
[77] C.M. Finlay, et al., Helminth products protect against autoimmunity via innate type 2 cytokines IL-5 and IL-33, which promote Eosinophilia, J. Immunol. 196 (2) (2016) 703–714.
[78] A.N. Peon, et al., Helminth products potently modulate experimental autoimmune encephalomyelitis by downregulating neuroinflammation and promoting a suppressive microenvironment, Mediators Inflamm. 2017 (2017) 8494572.
[79] I.B. McInnes, et al., A novel therapeutic approach targeting articular inflammation using the filarial nematode-derived phosphorylcholine-containing glycoprotein ES-62, J. Immunol. 171 (4) (2003) 2127–2133.
[80] R. Graepel, et al., Murine autoimmune arthritis is exaggerated by infection with the rat tapeworm, *Hymenolepis diminuta*, Int. J. Parasitol. 43 (7) (2013) 593–601.
[81] H.A. Gordon, L. Pesti, The gnotobiotic animal as a tool in the study of host microbial relationships, Bacteriol. Rev. 35 (4) (1971) 390–429.
[82] J. Lederberg, A.T. McCray, 'Ome sweet 'omics – a genealogical treasury of words, Scientist 15 (7) (2001) 8.
[83] B.L. Cantarel, et al., Gut microbiota in multiple sclerosis: possible influence of immunomodulators, J. Invest. Med. 63 (5) (2015) 729–734.
[84] X. Wu, et al., Molecular insight into gut microbiota and rheumatoid arthritis, Int. J. Mol. Sci. 17 (3) (2016) 431.
[85] B. Balakrishnan, V. Taneja, Microbial modulation of the gut microbiome for treating autoimmune diseases, Expert Rev. Gastroenterol. Hepatol. (2018) 1–12.
[86] E.A. Eloe-Fadrosh, et al., Functional dynamics of the gut microbiome in elderly people during probiotic consumption, MBio 6 (2) (2015).
[87] P.L. Hibberd, et al., No evidence of harms of probiotic Lactobacillus rhamnosus GG ATCC 53103 in healthy elderly-a phase I open label study to assess safety, tolerability and cytokine responses, PLoS ONE 9 (12) (2014) e113456.
[88] A. Pianta, et al., Evidence of the immune relevance of prevotella copri, a gut microbe, in patients with rheumatoid arthritis, Arthritis Rheumatol. 69 (5) (2017) 964–975.
[89] J.U. Scher, et al., Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis, Elife 2 (2013) e01202.
[90] J.U. Scher, S.B. Abramson, Periodontal disease, Porphyromonas gingivalis, and rheumatoid arthritis: what triggers autoimmunity and clinical disease? Arthritis Res. Ther. 15 (5) (2013) 122.
[91] P. Mangat, et al., Bacterial and human peptidylarginine deiminases: targets for inhibiting the autoimmune response in rheumatoid arthritis? Arthritis Res. Ther. 12 (3) (2010) 209.
[92] H. Jung, et al., Arthritic role of Porphyromonas gingivalis in collagen-induced arthritis mice, PLoS One 12 (11) (2017) e0188698.
[93] Y. Maeda, et al., Dysbiosis contributes to arthritis development via activation of autoreactive T cells in the intestine, Arthritis Rheumatol. 68 (11) (2016) 2646–2661.
[94] S. Lucas, et al., Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss, Nat. Commun. 9 (1) (2018) 55.
[95] E.V. Marietta, et al., Suppression of inflammatory arthritis by human gut-derived prevotella histicola in humanized mice, Arthritis Rheumatol 68 (12) (2016) 2878–2888.
[96] N. Komatsu, et al., Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis, Nat. Med. 20 (1) (2014) 62–68.
[97] M.H. Shaw, et al., Microbiota-induced IL-1beta, but not IL-6, is critical for the development of steady-state TH17 cells in the intestine, J. Exp. Med. 209 (2) (2012) 251–258.
[98] I.I. Ivanov, et al., Induction of intestinal Th17 cells by segmented filamentous bacteria, Cell 139 (3) (2009) 485–498.
[99] H.J. Wu, et al., Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells, Immunity 32 (6) (2010) 815–827.
[100] Y.K. Lee, et al., Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis, Proc. Natl. Acad. Sci. U.S.A. 108 (Suppl. 1) (2011) 4615–4622.
[101] H. Liu, et al., TLR5 mediates CD172alpha(+) intestinal lamina propria dendritic cell induction of Th17 cells, Sci. Rep. 6 (2016) 22040.
[102] Y. Yin, et al., Comparative analysis of the distribution of segmented filamentous bacteria in humans, mice and chickens, ISME J. 7 (3) (2013) 615–621.
[103] M.A. Kriegel, et al., Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in nonobese diabetic mice, Proc. Natl. Acad. Sci. U.S.A. 108 (28) (2011) 11548–11553.
[104] T. Prakash, et al., Complete genome sequences of rat and mouse segmented filamentous bacteria, a potent inducer of th17 cell differentiation, Cell Host Microbe 10 (3) (2011) 273–284.
[105] D.A. Muniz Pedrogo, et al., An increased abundance of clostridiaceae characterizes arthritis in inflammatory bowel disease and rheumatoid arthritis: a cross-sectional study, Inflamm. Bowel Dis. (2018).
[106] C.D. Buckley, H.M. McGettrick, Leukocyte trafficking between stromal compartments: lessons from rheumatoid arthritis, Nat. Rev. Rheumatol. (2018).
[107] F. Teng, et al., Gut microbiota drive autoimmune arthritis by promoting differentiation and migration of Peyer's patch T follicular helper cells, Immunity 44 (4) (2016) 875–888.
[108] R. Horai, et al., Microbiota-dependent activation of an autoreactive T cell receptor provokes autoimmunity in an immunologically privileged site, Immunity 43 (2) (2015) 343–353.
[109] C.R. Zarate-Blades, et al., Gut microbiota as a source of a surrogate antigen that triggers autoimmunity in an immune privileged site, Gut Microbes 8 (1) (2017) 59–66.
[110] D. Naskar, et al., Synthetic retinoid AM80 ameliorates lung and arthritic autoimmune responses by inhibiting T follicular helper and Th17 cell responses, J. Immunol. 198 (5) (2017) 1855–1864.
[111] Y.Z. Xu, et al., Orally available and efficacious alpha4beta1/alpha4beta7 integrin inhibitors, Bioorg. Med. Chem. Lett. 23 (15) (2013) 4370–4373.
[112] B. Tong, et al., Norisoboldine ameliorates collagen-induced arthritis through regulating the balance between Th17 and regulatory T cells in gut-associated lymphoid tissues, Toxicol. Appl. Pharmacol. 282 (1) (2015) 90–99.
[113] B. Tong, et al., Sinomenine suppresses collagen-induced arthritis by reciprocal modulation of regulatory T cells and Th17 cells in gut-associated lymphoid tissues, Mol. Immunol. 65 (1) (2015) 94–103.
[114] A.I. Lazarovits, J. Karsh, Differential expression in rheumatoid synovium and synovial fluid of alpha 4 beta 7 integrin. A novel receptor for fibronectin and vascular cell adhesion molecule-1, J. Immunol. 151 (11) (1993) 6482–6489.
[115] E. Jimenez-Boj, et al., Interaction between synovial inflammatory tissue and bone marrow in rheumatoid arthritis, J. Immunol. 175 (4) (2005) 2579–2588.
[116] R.C. Sharp, S.A. Beg, S.A. Naser, Polymorphisms in protein tyrosine phosphatase non-receptor type 2 and 22 (PTPN2/22) are linked to hyper-proliferative t-cells and susceptibility to mycobacteria in rheumatoid arthritis, Front. Cell. Infect. Microbiol. 8 (2018) 11.
[117] H. Shoda, et al., Immune responses to Mycobacterial heat shock protein 70 accompany self-reactivity to human BiP in rheumatoid arthritis, Sci. Rep. 6 (2016) 22486.
[118] J. Bjork, et al., Role of the bowel flora for development of immunity to hsp 65 and arthritis in three experimental models, Scand. J. Immunol. 40 (6) (1994) 648–652.
[119] R. Ohue, et al., Bacterial heat shock protein 60, GroEL, can induce the conversion of naive T cells into a CD4 CD25(+) Foxp3-expressing phenotype, J. Innate Immun. 3 (6) (2011) 605–613.
[120] S. Cording, et al., Commensal microbiota drive proliferation of conventional and Foxp3(+) regulatory CD4(+) T cells in mesenteric lymph nodes and Peyer's patches, Eur. J. Microbiol. Immunol. (Bp) 3 (1) (2013) 1–10.
[121] R.M. Rezende, et al., Hsp65-producing Lactococcus lactis prevents experimental autoimmune encephalomyelitis in mice by inducing CD4+LAP+ regulatory T cells, J. Autoimmun. 40 (2013) 45–57.
[122] Y. Ma, et al., Oral administration of recombinant Lactococcus lactis expressing HSP65 and tandemly repeated P277 reduces the incidence of type I diabetes in non-obese diabetic mice, PLoS One 9 (8) (2014) e105701.
[123] A.C. Gomes-Santos, et al., Hsp65-producing lactococcus lactis prevents inflammatory intestinal disease in mice by IL-10- and TLR2-dependent pathways, Front. Immunol. 8 (2017) 30.
[124] S.M. Aqaeinezhad Rudbane, et al., The efficacy of probiotic supplementation in rheumatoid arthritis: a meta-analysis of randomized, controlled trials, Inflammopharmacology 26 (1) (2018) 67–76.
[125] A.T. Mohammed, et al., The therapeutic effect of probiotics on rheumatoid arthritis: a systematic review and meta-analysis of randomized control trials, Clin. Rheumatol. 36 (12) (2017) 2697–2707.
[126] A. Lyons, et al., Bacterial strain-specific induction of Foxp3+ T regulatory cells is protective in murine allergy models, Clin. Exp. Allergy 40 (5) (2010) 811–819.
[127] M. Schultz, et al., Lactobacillus plantarum 299V in the treatment and prevention of spontaneous colitis in interleukin-10-deficient mice, Inflamm. Bowel Dis. 8 (2) (2002) 71–80.
[128] N.S. Nanda Kumar, et al., Probiotic administration alters the gut flora and attenuates colitis in mice administered dextran sodium sulfate, J. Gastroenterol. Hepatol. 23 (12) (2008) 1834–1839.
[129] F. Calcinaro, et al., Oral probiotic administration induces interleukin-10 production and prevents spontaneous autoimmune diabetes in the non-obese diabetic mouse, Diabetologia 48 (8) (2005) 1565–1575.
[130] R. Valladares, et al., Lactobacillus johnsonii N6.2 mitigates the development of type 1 diabetes in BB-DP rats, PLoS One 5 (5) (2010) e10507.
[131] J.S. So, et al., Lactobacillus casei potentiates induction of oral tolerance in experimental arthritis, Mol. Immunol. 46 (1) (2008) 172–180.
[132] T. Secher, et al., Oral administration of the probiotic strain Escherichia coli Nissle 1917 reduces susceptibility to neuroinflammation and repairs experimental autoimmune encephalomyelitis-induced intestinal barrier dysfunction, Front. Immunol. 8 (2017) 1096.
[133] L.V. McFarland, C.T. Evans, E.J.C. Goldstein, Strain-specificity and disease-specificity of probiotic efficacy: a systematic review and meta-analysis, Front. Med. (Lausanne) 5 (2018) 124.
[134] S.M. Deutsch, et al., Identification of proteins involved in the anti-inflammatory

properties of Propionibacterium freudenreichii by means of a multi-strain study, Sci. Rep. 7 (2017) 46409.
[135] N. Zmora, et al., Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features, Cell 174 (6) (2018) 1388–1405 e21.
[136] J. Suez, et al., Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT, Cell 174 (6) (2018) 1406–1423 e16.
[137] M. Yamashita, et al., Preventive effect of Lactobacillus helveticus SBT2171 on collagen-induced arthritis in mice, Front. Microbiol. 8 (2017) 1159.
[138] K.M. Maslowski, et al., Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43, Nature 461 (7268) (2009) 1282–1286.
[139] M. Mizuno, et al., The dual role of short fatty acid chains in the pathogenesis of autoimmune disease models, PLoS One 12 (2) (2017) e0173032.
[140] K. Schroecksnadel, et al., Increased degradation of tryptophan in blood of patients with rheumatoid arthritis, J. Rheumatol. 30 (9) (2003) 1935–1939.
[141] K. Schroecksnadel, et al., Tryptophan degradation increases with stage in patients with rheumatoid arthritis, Clin. Rheumatol. 25 (3) (2006) 334–337.
[142] J.H. Flinn, et al., Excretion of tryptophan metabolites by patients with rheumatoid arthritis, Arthritis Rheum. 7 (1964) 201–210.
[143] W.R. Wikoff, et al., Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites, Proc. Natl. Acad. Sci. U.S.A. 106 (10) (2009) 3698–3703.
[144] H.M. Roager, T.R. Licht, Microbial tryptophan catabolites in health and disease, Nat. Commun. 9 (1) (2018) 3294.
[145] J.A. Zack, R.R. Suskind, The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident, J. Occup. Med. 22 (1) (1980) 11–14.
[146] S. Safe, S.O. Lee, U.H. Jin, Role of the aryl hydrocarbon receptor in carcinogenesis and potential as a drug target, Toxicol. Sci. 135 (1) (2013) 1–16.
[147] T. Zelante, et al., Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22, Immunity 39 (2) (2013) 372–385.
[148] M. Venkatesh, et al., Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and Toll-like receptor 4, Immunity 41 (2) (2014) 296–310.
[149] Pablo A. Romagnoli, G.K. Shenk, Quynh-Mai Pham, Leigh Maher, Kamal Mohan Khanna, Commensal metabolite indol-3-propionic acid promotes gut barrier function by regulating IL-22 production during intestinal inflammatory conditions, J. Immunol. (2016) 196(1).
[150] J.L. Botsford, R.D. Demoss, Escherichia coli tryptophanase in the enteric environment, J. Bacteriol. 109 (1) (1972) 74–80.
[151] L. Kolodziej, Systemic metabolism of tryptophan and its catabolites, kynurenine and 3-HAA, in mice with inflammatory arthritis, Gene 512 (1) (2013) 23–27.
[152] V. Rothhammer, et al., Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor, Nat. Med. 22 (6) (2016) 586–597.
[153] R. Hoessel, et al., Indirubin, the active constituent of a Chinese antileukaemia medicine, inhibits cyclin-dependent kinases, Nat. Cell Biol. 1 (1) (1999) 60–67.
[154] M. Huang, et al., Indirubin inhibits the migration, invasion, and activation of fibroblast-like synoviocytes from rheumatoid arthritis patients, Inflamm. Res. 66 (5) (2017) 433–440.
[155] F.J. Quintana, et al., Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor, Nature 453 (7191) (2008) 65–71.
[156] M. Veldhoen, et al., The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins, Nature 453 (7191) (2008) 106–109.
[157] J.H. Duarte, et al., Differential influences of the aryl hydrocarbon receptor on Th17 mediated responses in vitro and in vivo, PLoS One 8 (11) (2013) e79819.
[158] K. Isawa, et al., Isolation and identification of a new bifidogenic growth stimulator produced by Propionibacterium freudenreichii ET-3, Biosci. Biotechnol. Biochem. 66 (3) (2002) 679–681.
[159] J.E. Kang, T.J. Kim, G.S. Moon, A novel lactobacillus casei lp1 producing 1,4-dihydroxy-2-naphthoic acid, a bifidogenic growth stimulator, Prev. Nutr. Food Sci. 20 (1) (2015) 78–81.
[160] M.S. Abdel-Rahman, E.A. Alkady, S. Ahmed, Menaquinone-7 as a novel pharmacological therapy in the treatment of rheumatoid arthritis: a clinical study, Eur. J. Pharmacol. 15 (761) (2015) 273–278.
[161] H. Okamoto, et al., Anti-arthritis effects of vitamin K(2) (menaquinone-4)–a new potential therapeutic strategy for rheumatoid arthritis, FEBS J. 274 (17) (2007) 4588–4594.
[162] K. Ebina, et al., Vitamin K2 administration is associated with decreased disease activity in patients with rheumatoid arthritis, Mod. Rheumatol. 23 (5) (2013) 1001–1007.
[163] D.M. Linares, et al., Lactic acid bacteria and bifidobacteria with potential to design natural biofunctional health-promoting dairy foods, Front. Microbiol. 8 (2017) 846.
[164] J. Tian, et al., Oral GABA treatment downregulates inflammatory responses in a mouse model of rheumatoid arthritis, Autoimmunity 44 (6) (2010) 465–470.
[165] S.K. Mazmanian, J.L. Round, D.L. Kasper, A microbial symbiosis factor prevents intestinal inflammatory disease, Nature 453 (7195) (2008) 620–625.
[166] J. Ochoa-Reparaz, et al., A polysaccharide from the human commensal Bacteroides fragilis protects against CNS demyelinating disease, Mucosal Immunol. 3 (5) (2010) 487–495.
[167] M.J. Schuijs, et al., Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells, Science 349 (6252) (2015) 1106–1110.
[168] WHO, Geneva: WHO, 2013 [27 May 2013], Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020, in: Follow-up to the Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases, Sixty-Sixth World Health Assembly, Document # WHA66.10.