CHAPTER TWO

Friend or foe? *Lactobacillus* in the context of autoimmune disease

Rebecca L. Fine[a,b], Derek L. Mubiru[a,c], Martin A. Kriegel[a,*]
[a]Department of Immunobiology, Yale School of Medicine, New Haven, CT, United States
[b]Yale New Haven Hospital, New Haven, CT, United States
[c]Department of Molecular, Cellular and Developmental Biology, Yale University, New Haven, CT, United States
*Corresponding author: e-mail address: martin.kriegel@yale.edu

Contents

1. Introduction: Influences on host-microbiota interactions in autoimmunity 30
   1.1 The genus *Lactobacillus* 32
2. Lactobacilli in autoimmune and neurologic diseases 34
3. *Lactobacillus johnsonii* and *L. reuteri* as paradigms 35
4. The gut barrier as a decisive factor for translocation of enterococci and lactobacilli 38
5. The influence of diet on *L. reuteri* growth and translocation 44
6. A variety of metabolites of *L. reuteri* influence host health 45
7. Conclusion: Strain-specific effects of lactobacilli have implications for translational medicine 47

Acknowledgments 49
Declaration of interest 49
References 49

Abstract

Over the last decade, the interplay between the gut microbiota, the consortium of intestinal microbes that colonizes intestinal mucosal barriers, and its host immune system has been increasingly better understood. Disruption of the delicate balance between beneficial and pathogenic commensals, known as dysbiosis, contributes to a variety of chronic immunologic and metabolic diseases. Complicating this paradigm are bacterial strains that can operate paradoxically both as instigators and attenuators of inflammatory responses, depending on host background. Here, we review the role of several strains in the genus *Lactobacillus* within the context of autoimmune and other chronic disorders with a predominant focus on *L. reuteri*. While strains within this species have been shown to provide immune health benefits, they have also been demonstrated to act as a pathobiont in autoimmune-prone hosts. Beneficial functions in healthy hosts include competing with pathogenic microbes, promoting regulatory T cell development, and protecting the integrity of the gut barrier. On the other hand, certain strains can also break through a dysfunctional gut barrier, colonize internal tissues

Advances in Immunology, Volume 146
ISSN 0065-2776
https://doi.org/10.1016/bs.ai.2020.02.002

such as the spleen or liver and promote inflammatory responses in host tissues that lead to autoimmune disease. This review summarizes the manifold roles that these commensals play in the context of health and disease.

1. Introduction: Influences on host-microbiota interactions in autoimmunity

The human gut is home to trillions of commensal bacteria spanning thousands of species that are increasingly better delineated (Almeida et al., 2019; Nayfach, Shi, Seshadri, Pollard, & Kyrpides, 2019; Pasolli et al., 2019). The collection of these bacteria, the gut microbiota, has co-evolved with the host and environment to create a mutually beneficial state. These microbes provide nutrients and facilitate maturation of the host immune system by antigenic stimulation and by providing metabolic genes and pathways extrinsic to the human genome. Within healthy individuals, this ecosystem maintains a delicate equilibrium: a shift in the relative or absolute abundance of one or several bacterial taxa can result in intestinal dysbiosis. This imbalance among commensal microbes can disrupt normal immunomodulatory functions, triggering local as well as systemic inflammation. These maladaptive processes can create a milieu that leads to autoimmune disease. Although these observations might tempt one to categorize commensal species as either beneficial or harmful, in many circumstances they lie on a spectrum of mutualism and parasitism. What determines whether a bacterium is helpful or harmful is the ecosystem in which the bacteria live and is significantly influenced by host factors and genetic background.

Commensal microbes are influenced by the recent evolutionary history of the host background, shifts in nutrients, and other metabolic and immunologic processes, including those related to systemic infections. For example, an enrichment in *Prevotella* among other gut commensals of children from the west African country Burkina Faso was linked to metabolic benefits and protection from inflammation and noninfectious colonic diseases, possibly because the microbiota co-evolved with the polysaccharide-rich diet of these individuals (De Filippo et al., 2010). In European populations, enrichment of *Prevotella copri* was shown to improve glucose metabolism and increase the potential to ferment complex polysaccharides (Kovatcheva-Datchary et al., 2015). In contrast, in American subjects, *P. copri* was associated with the development of early-onset rheumatoid arthritis (RA), and

in gnotobiotic mice, was colitogenic and inflammatory, inducing synovitis and promoting peripheral Th17 cell expansion (Dehner, Fine, & Kriegel, 2019; Maeda et al., 2016; Scher et al., 2013). The geographic, ethnic, cultural and genetic disparities between African, European and American subjects underscores the importance of host background and environment in determining how a commensal species will operate within its host. In addition, strain differences likely contribute further to the heterogeneity of host effects (De Filippis et al., 2019; Tett et al., 2019). Thus, gut commensals cannot be easily classified in a binary fashion, as the contributions each species make may be highly context- and strain-dependent.

Within the context of autoimmune diseases, otherwise beneficial microbes promote autoimmunity through a variety of mechanisms (Ruff & Kriegel, 2015). One increasingly appreciated molecular mechanism is cross-reactivity of homologous components within the bacteria with host proteins targeted in autoimmune patients (Gil-Cruz et al., 2019; Greiling et al., 2018; Ruff et al., 2019; Ruff & Kriegel, 2015). Although rare, the most obvious scenario represents bacterial orthologs of autoantigens that exist within the human microbiota. Specifically, commensal orthologs of the autoantigen and RNA binding protein Ro60 have been identified. Ro60 is a primordial self-antigen targeted by T and B cells of patients with the autoimmune disease systemic lupus erythematosus (SLE). Mice colonized with the commensal *Bacteroides thetaiotaomicron* containing such a Ro60 ortholog spontaneously develop systemic anti-human Ro60-directed T and B cell responses. These responses have also been identified in lupus patients who carry a defined set of Ro60 ortholog-expressing mucosal and skin commensals within their microbiomes (Greiling et al., 2018). Autoimmunity can also occur through autoantigen-specific T cells and autoantibodies cross-reacting with homologous epitopes within non-orthologous proteins of gut bacteria. For example, the abundant plasma protein β_2-glycoprotein I is a major target in patients with antiphospholipid syndrome (APS), an autoimmune clotting disorder. Mimotopes of well-defined T and B cell autoepitopes are expressed within proteins of the common human colonic commensal *Roseburia intestinalis* (Ruff et al., 2019). *R. intestinalis* mimotopes were shown to cross-react with autoantigen-reactive $CD4^+$ T cells and pathogenic monoclonal antibodies derived from APS patients. Furthermore, oral gavage with *R. intestinalis* induced APS-related autoimmune pathologies in genetically susceptible mice, supporting a role for *R. intestinalis* in inciting autoimmunity in this setting (Ruff et al., 2019). In contrast, *R. intestinalis* likely plays a protective

role in gut inflammation through butyrate production. *R. intestinalis* was one of the taxa found to be significantly decreased in patients with Crohn's disease or ulcerative colitis (Vich Vila et al., 2018). In a mouse model of colitis, *R. intestinalis* supplementation had therapeutic benefit evidenced by a reduction in colon shortening, intestinal mucosal epithelial injury, and mucosal lymphocyte infiltration, changes attributed to increased regulatory T cell (T_{reg}) numbers and anti-inflammatory cytokines (Shen et al., 2018). In addition, butyrate-producing *R. intestinalis* was shown to confer protection against experimental atherosclerosis (Kasahara et al., 2018). These examples underscore the complexity of the contribution of specific gut commensals to health and immunity. Host genetics, diet, and metabolism serve as modifying factors for the gut microbiota that then influence health and disease via various mechanisms such as through metabolites or antigens. Additional examples within lactobacilli are discussed next in more depth.

1.1 The genus *Lactobacillus*

One of the most influential communities within the host microbiome is comprised of representatives of the genus *Lactobacillus*, which colonizes the mouth, gastrointestinal and genital tracts of humans and many vertebrates (Walter, 2008). The genus includes over 200 gram-positive, aerotolerant or anaerobic species that are diverse in niche, metabolism and immunologic effects on host. Lactobacilli carry out fermentation of lactose into lactic acid and are thus valued for food production and as probiotics. Many species within the genus are classified as "Generally Recognized As Safe" (GRAS) (Salvetti, Torriani, & Felis, 2012). Two representative species, *L. reuteri* and *L. johnsonii*, co-evolved with the host and have developed factors that enable them to persist in the gut. In particular, *L. reuteri* adapted to human hosts by reductive evolution but to rodent hosts by developing a large pan-genome. Through evolutionary selection, these lactobacilli grow optimally at 37 °C in vertebrates, and possess enzymes to combat oxidative stress (e.g., methionine sulfoxide reductase B) and resistance to low pH and defensins (e.g., D-alanine-D-alanyl carrier protein ligase), as well as IgA proteases that enable degradation of host immunoglobulins (Di Rienzi et al., 2018; Duar et al., 2017; Walter, 2008). *Lactobacillus* species *L. iners*, *L. crispatus*, *L. jensenii* and *L. gasseri* are predominant in the human vaginal microbiome (Anderson et al., 2014; Duar et al., 2017; Mendes-Soares, Suzuki, Hickey, & Forney, 2014), where they adhere specifically to vaginal

epithelium cells, lower environmental pH, and protect against pathogens by providing a mechanical barrier and producing antibacterial compounds (Macklaim, Gloor, Anukam, Cribby, & Reid, 2011; Molenaar, Singer, & Ouburg, 2018). Furthermore, lactobacilli are found in the breast milk of humans and are increased in neonates during breastfeeding but are decreased in the GI tracts of humans later in life when compared to rodents (Sinkiewicz & Ljunggren, 2009).

Within the gut, different *Lactobacillus* species have beneficial effects on gut barrier integrity and microbial community health. Various *Lactobacillus* strains including those of *L. acidophilus*, *L. casei*, *L. rhamnosus*, and *L. plantarum* increase tight junction protein expression in the intestinal epithelium and upregulate mucin protein expression, which strengthens the barrier and reduces translocation of pathogenic bacteria. For example, co-culturing intestinal epithelial cells with *L. rhamnosus* prevents high sugar media-induced gut permeability in *Drosophila* (Pereira, Malik, Nostro, Mahler, & Musselman, 2018). Similarly, *L. johnsonii* and *L. reuteri* were shown to ameliorate pathogen-induced loss of transepithelial electrical resistance in vitro (Liu et al., 2015). Furthermore, *Lactobacillus* strains produce bacteriocins such as reuterin and brevicin 925A, which carry direct antimicrobial effects against pathogens (La Fata, Weber, & Mohajeri, 2018).

The impact of lactobacilli on biologic processes within the host is altered in response to changes in their ecosystem. In mice challenged with *Campylobacter jejuni* infection, prophylactic or therapeutic application of *L. johnsonii* ameliorated secretion of pro-inflammatory mediators such as interleukin-6, monocyte chemoattractant protein-1 (also known as CCL2), TNFα and nitric oxide, by influencing adaptive immune cells within the gut. Interestingly, *L. johnsonii* treatment induced T_{reg} expansion in the presence of *C. jejuni* infection, but not when applied alone (Bereswill et al., 2017). Furthermore, changes in host immune responses in turn lead to altered microbial functions of lactobacilli. For example, mice defective in sensing microbiota-derived ATP expand T follicular helper cells and produce enhanced secretory IgA (sIgA). These mice have increased sIgA coating of *L. reuteri* and overall greater ratios of Firmicutes to Bacteroidetes associated with obesity. Oral gavage of wild-type mice with sIgA-coated lactobacilli resulted in altered glucose homeostasis and fat deposition (Perruzza et al., 2019). Finally, lactobacilli may also influence the efficacy of therapeutic drugs. The effects of the chemotherapeutic agent cyclophosphamide are enhanced by *L. johnsonii*, *L. murinus*, and an *Enterococcus* strain (*E. hirae*), suggesting that certain lactobacilli affect

anticancer efficacy, possibly by reducing T_{reg} cells and stimulating cognate antitumor cytotoxic T lymphocyte responses (Daillere et al., 2016). Although taxa within the genus *Lactobacillus* are beneficial in a variety of ways, certain strains can also turn into pathobionts in the environment of a predisposed host.

2. Lactobacilli in autoimmune and neurologic diseases

The variable effects of lactobacilli on autoimmune diseases highlights their dual role as symbiont and pathobionts depending on the context. *L. rhamnosus* and *L. reuteri* have been studied in the context of probiotic use in infants prone to type 1 diabetes and the former was associated with reduced progression to islet autoimmunity (Vatanen et al., 2018). *L. johnsonii*- but not *L. reuteri*-fed rats susceptible to type 1 diabetes developed less diabetes together with decreased pro-inflammatory cytokines and higher levels of the gut barrier strengthening tight junction protein claudin (Valladares et al., 2010). The same strain N6.2 was linked with protective Th17 cells in this rat model and with decreased indoleamine 2,3-dioxygenase (IDO) expression, thereby altering kynurenine:tryptophan ratios (Lau et al., 2011; Valladares et al., 2013). Similar alterations in plasma metabolites have been found in a double-blind, randomized control trial of healthy human subjects taking this *Lactobacillus* strain as a probiotic (Marcial et al., 2017). In this setting, however, an increase in Th1 cells with only a trend in Th17 cells was noted in the peripheral blood of the study subjects.

In patients with RA, data suggested a functional improvement in those treated with probiotic oral capsules containing *L. rhamnosus* and *L. reuteri* compared to placebo (Pineda Mde et al., 2011). On the other hand, *L. salivarius* was enriched in fecal, dental and salivary samples from a cohort of RA patients in a large Chinese metagenomics study (X. Zhang et al., 2015). Lastly, the autoantigenic target PDC-E2 (pyruvate dehydrogenase subunit) in primary biliary cirrhosis contains a cross-reactive motif that is present in *L. delbrueckii* (Bogdanos et al., 2005). Thus, systemic, non-gut inflammatory diseases may be worsened by lactobacilli, while in a healthy host, lactobacilli may be beneficial by downregulating inflammation within the gastrointestinal environment.

Lactobacilli also impact the progression of non-gut conditions such as depression through metabolite secretion, abnormal signaling, and

translocation (Main & Minter, 2017). The vagal nerve innervates the GI tract, responding to inflammatory mediators or metabolites, and relaying signals to the central nervous system. Mice colonized with *L. rhamnosus* have modulated GABA receptor expression patterns in the brain and decreased depressive symptoms, a finding that was not observed in vagotomized mice (Bravo et al., 2011). *L. reuteri* is among other bacteria that can metabolize tryptophan to an agonist of the aryl hydrocarbon receptor (AhR). *L. reuteri*-derived indoles that can activate AhR have been shown to not only ameliorate colitis and metabolic syndrome but also modulate astrocyte activity and suppress CNS inflammation in multiple sclerosis (Lamas et al., 2016; Natividad et al., 2018; Rothhammer et al., 2016). Furthermore, *L. murinus* or *L. reuteri* supplementation in models of high salt-induced experimental autoimmune encephalitis ameliorated disease through reduction in Th17 cells (Wilck et al., 2017). On the other hand, some metabolic effects of *Lactobacillus* spp. can exacerbate disease. *Lactobacillus*, among other taxa, are relatively increased in the GI tracts of patients suffering from Parkinson's disease (Minato et al., 2017; Petrov et al., 2017). Certain strains carrying the enzyme tyrosine decarboxylase may increase the levodopa requirement for Parkinson's disease patients by increasing the conversion of levodopa to dopamine (van Kessel et al., 2019).

3. *Lactobacillus johnsonii* and *L. reuteri* as paradigms

As introduced above, *L. johnsonii* and *L. reuteri* are two related gut-associated autochthonous species that have co-evolved with the host and have complex relationships with the host immune system. While both species are generally beneficial, individual strains can also incite inflammation through the induction of immune cell responses and weakening of the gut barrier. *L. johnsonii* has been shown to protect against liver injury by inducing cytokines that enhance mucosal barrier function and promote recruitment of regulatory dendritic cells to the liver via IL-22 secreted by gut innate lymphoid cells type 3 (ILC3) (Nakamoto et al., 2017).

L. johnsonii can also skew T cell differentiation toward the Th17 lineage, which is protective in certain situations, such as Th1/2-biased autoimmune diseases like type 1 diabetes (T1D) (Lau et al., 2011), similar to Th17-inducing segmented filamentous bacteria in T1D-prone animals in the absence of MyD88 (Burrows, Volchkov, Kobayashi, & Chervonsky, 2015; Kriegel et al., 2011; Yurkovetskiy et al., 2013). The Th17-biased

immune response mediated by *L. johnsonii* differs from other species of lactobacilli such as *L. reuteri* or *L. murinus*. Th17 skewing and protective effects were not seen with *L. reuteri*-fed type 1 diabetes-prone mice. Instead, studies on other autoimmune diseases support Th17 cell-reducing effects by certain *Lactobacillus* strains. *L. murinus* and *L. reuteri* loads were reduced in mice fed a high-salt diet with subsequent expansion of Th17 cells, and supplementation with either of these species prevented salt-sensitive hypertension and experimental autoimmune encephalitis (EAE) by reducing Th17 cells through tryptophan metabolism to indoles (Wilck et al., 2017). These studies underscore the pathogenic versus protective role of Th17 induction and heterogeneity of disease outcomes depending on host predisposition and commensal species.

L. reuteri partly protects against autoimmunity by promoting T_{reg} cell differentiation, thereby enhancing immune regulation. *L. reuteri* metabolic production of indoles under a tryptophan-rich diet induces regulatory intraepithelial lymphocytes via AhR-mediated downregulation of the transcription factor ThPOK in $CD4^+$ T cells (Cervantes-Barragan et al., 2017). In scurfy mice, introduction of *L. reuteri* attenuated multiorgan inflammation induced by $Foxp3^+$ T_{reg} deficiencies and improved survival (He et al., 2017). A follow up study from the same group found that *L. reuteri* supplementation reduced Th1/Th17 cells, restored gut microbial diversity, and ameliorated the development of EAE (He et al., 2019). Patients suffering from inflammatory bowel disease also experienced significant anti-inflammatory effects via expansion of T_{reg} cells after consuming a probiotic yogurt containing certain *L. reuteri* and *L. rhamnosus* strains (Lorea Baroja, Kirjavainen, Hekmat, & Reid, 2007). Furthermore, a mix of probiotic *Lactobacillus* strains improves lupus-like disease in the MRL/lpr model (Mu, Tavella, et al., 2017; Mu, Zhang, et al., 2017; Zhang, Liao, Sparks, & Luo, 2014), although *Lactobacillus* strains, in particular *L. reuteri*, are pathogenic in other lupus models (Luo et al., 2018; Zegarra-Ruiz et al., 2019). Fitting with a homeostatic role in the gut compared to the periphery, mice with colitis induced by immune checkpoint blockade exhibit a reduction in fecal *Lactobacillus* (Wang, Zheng, et al., 2019), as was the case in colitis exacerbated by dermatitis via skin-gut interactions (Kiyohara et al., 2019). In the setting of checkpoint inhibition (not dermatitis), *L. reuteri* administration prevented the development and progression of colitis, likely through reducing the effects of immune checkpoint blockade on ILC3 expansion (Wang, Zheng, et al., 2019). Similarly, *L. reuteri* has been shown to be protective in chemically (dextran sodium sulfate (DSS))-induced colitis.

L. reuteri administration before induction of colitis reduced inflammatory platelet- and leukocyte-endothelial interactions (Schreiber et al., 2009). Another mechanism suggests direct effects on the gut barrier. Two different *L. reuteri* strains ameliorated DSS-induced murine colitis in vivo by increasing mucus thickness (Ahl et al., 2016). In humans, rectal enemas with a probiotic *L. reuteri* strain ameliorated signs and symptoms of pediatric ulcerative colitis (Oliva et al., 2012).

Contrary to these immunoregulatory effects, however, is the ability of *L. reuteri* to enhance systemic TLR7 signals and promote plasmacytoid dendritic cell (pDC) recruitment to non-gut organs in a TLR7 overexpressing lupus model (Zegarra-Ruiz et al., 2019). The TLRs 3, 7, 8 and 9 are receptors expressed on the endosomal membrane of antigen-presenting cells and recognize nucleic acids that have entered the host cells. Activation of these TLRs in the endosomal compartment leads to a type I IFN response and the production of inflammatory cytokines. The stereotypic nature of the endosomal TLRs makes them prime candidates for activation by defined patterns of nucleic acids from commensal bacteria and viruses taken up in the gastrointestinal tract. For example, TLR3 sensing of *L. reuteri* dsRNA and other lactobacilli-derived dsRNA trigger IFN-β production in mice and alleviate chemically induced colitis in addition to exerting its expected antiviral effects (Kawashima et al., 2013; Lee & Ko, 2016). *L. reuteri* may thus induce an anti-inflammatory response inside the gut but inflammation systemically as shown in the TLR7-overexpressing lupus model (Zegarra-Ruiz et al., 2019). Systemic translocation of *L. reuteri* occurred in this model, which aggravates widespread inflammation in extraintestinal tissues (Zegarra-Ruiz et al., 2019). However, stimulation of TLR7 with oral or topical imiquimod leads to type I IFN induction in the gut with reduced chemically induced colitis in vivo (Sainathan et al., 2012). Moreover, enteric viruses induce TLR3/7-dependent IFN-β production that also leads to amelioration of gut inflammation, suggesting that this pathway exhibits locally protective effects during gut inflammation but predisposes to systemic inflammation under certain conditions (Yang et al., 2016; Zegarra-Ruiz et al., 2019). *L. johnsonii* similarly triggers upregulation of TLR7 and TLR9, inducing a type I IFN response in colonic epithelial cell line cultures and replenishing Paneth cells in vivo in autoimmune-prone animals (Kingma et al., 2011). Thus, the type I IFN pathway may act restoratively in the gut as opposed to its inflammatory effects in the periphery. TLR3/7 signals from the enteric virome may downregulate gut pathogen-triggered inflammation. This interaction could reflect an evolutionarily conserved pathway in which pro-inflammatory signals in the gut are dampened

while gut barrier leakiness is increased to fight systemic viral and other microbial infections. Allowing gut microbes to translocate into extraintestinal infected tissues will trigger type I IFN inflammatory responses and enhance antiviral activity, albeit at the same time risking non-gut autoimmunity in the periphery of predisposed hosts. Table 1 summarizes the differential effects of *L. reuteri* strains on gut and non-gut autoimmune diseases, respectively.

4. The gut barrier as a decisive factor for translocation of enterococci and lactobacilli

Translocation of bacteria and their metabolites across the gut barrier has been increasingly implicated in the development of inflammatory and metabolic diseases. Physiologic sampling of microbial communities leads to education of the gut immune system and oral tolerance (Fine, Manfredo Vieira, Gilmore, & Kriegel, 2019; Macpherson & Uhr, 2004). Depending on bacterial virulence patterns and host predisposition, however, bacteria may gain access to more distant sites beyond the mesenteric lymph nodes and induce systemic and organ-specific inflammatory immune responses that can lead to autoimmunity (Fine et al., 2019). In mice with a genetic predisposition to develop lupus-like autoimmunity, the gut pathobiont *Enterococcus gallinarum* translocates to the liver and secondary lymphoid organs, where it triggers humoral and cellular inflammation (Manfredo Vieira et al., 2018). It also leads to upregulation of autoantigens and endogenous retroviral antigens in the liver that are subsequently recognized by the host immune system during an autoimmune attack. Collectively, these processes lead to organ-specific (liver) and systemic autoimmunity culminating in autoimmune-related deaths. Treatment with antibiotics or targeting with a vaccine suppresses *E. gallinarum* translocation and growth in internal organs, thereby reducing mortality substantially (Manfredo Vieira et al., 2018). Another more innate immune-prone lupus model, TLR7 transgenic mice, exhibits translocation of *L. reuteri* and propagation of the TLR7-type I IFN axis as elaborated above (Zegarra-Ruiz et al., 2019). In addition, other studies have revealed that lactobacilli and enterococci are dominant translocating genera in predisposed hosts. Translocation of lactobacilli can be induced by psychological stressors as was shown in a murine social disruption model (Lafuse et al., 2017). Chemical stressors such as antibiotics also promote translocation of gut commensal bacteria across the colonic epithelial to the mesenteric lymph nodes, which is associated with gut inflammation

Table 1 Summary of mechanistic studies on *L. reuteri* in autoimmune disease models.

Autoimmune disease models (in reverse chronologic order)	*L. reuteri* strain/origin	Intervention/ predisposition	Study findings (related to *L. reuteri*)	Human associations	Reference (PMID)
Gut inflammation					
Checkpoint inhibitor-induced colitis	Probiotic *L. reuteri* ATCC PTA 6457 (human)	Daily gavage for 3 days	Enhanced susceptibility to colitis after anti-CTLA-4 and anti-PD-1 treatment was associated with reduced *Lactobacillus*. *L. reuteri* co-administration rescued mice from colitis development	N.D.	Wang, Zheng, et al. (2019) (31214189)
DSS-induced colitis	*L. reuteri* R2LC (rat), *L. reuteri* ATCC PTA 4659 (human breast milk)	Daily gavage for 14 days	Three percent DSS-induced colitis was significantly reduced by either strain and associated with reversal of adherent mucus depletion by DSS. One strain, R2LC, increased tight junction proteins in colonic crypts	N.D.	Ahl et al. (2016) (27096537)
DSS-induced colitis	*L. reuteri* CNCM I-5022 (murine) together with two other *Lactobacillus* strains	Gavage 3 ×/week for 3 weeks	*L. reuteri* together with an *L. murinus* and *L. taiwanensis* strain, isolated from the feces of wild-type mice due to AhR activity in culture supernatants, suppressed 2% DSS-induced colitis. Amelioration was AhR-dependent manner in a gnotobiotic host colonized with a microbiota from CARD9$^{-/-}$ mice that are hypersusceptible to colitis	Tryptophan and AhR activity was reduced in stool of IBD patients. Reduced AhR activity associated with a CARD9 risk allele	Lamas et al. (2016) (27158904)

Continued

Table 1 Summary of mechanistic studies on *L. reuteri* in autoimmune disease models.—cont'd

Autoimmune disease models (in reverse chronologic order)	*L. reuteri* strain/origin	Intervention/ predisposition	Study findings (related to *L. reuteri*)	Human associations	Reference (PMID)
TNBS-induced colitis	*L. reuteri* ATCC PTA 6457 (human), *L. reuteri* ATCC PTA 4659 (human breast milk)	Daily gavage for 7 days	*L. reuteri* suppressed acute colitis, which was dependent on a histidine decarboxylase gene and a histidine-containing diet. The anti-inflammatory effects were mediated by luminal conversion of L-histidine to histamine, which triggers histamine H2 receptors in the gut	N.D.	Gao et al. (2015) (26670383)
DSS-induced colitis	*L. reuteri* R2LC (rat), *L. reuteri* JCM 5869 (rat), *L. reuteri* ATCC PTA 4659 (human), *L. reuteri* ATCC 55730 (human)	Daily gavage for 17 days	Five percent DSS-induced colitis severity was significantly reduced by *L reuteri* pretreatment, which reduced P-selectin expression and abolished increased platelet- and leukocyte-endothelial cell interactions	N.D.	Schreiber et al. (2009) (19147805)
Systemic lupus or multiorgan autoimmunity					
TLR7 tg lupus-like disease, imiquimod-induced lupus	*L. reuteri* SP-C2-NAJ0070 (primary isolate from murine spleen)	Natural colonization of TLR7 tg mice in animal facility, monocolonization of germ-free mice treated with imiquimod	TLR7-driven systemic autoimmunity including lupus nephritis was aggravated by translocated *L. reuteri* but not *L. johnsonii*. *L. reuteri* enhanced plasmacytoid DC accumulations and type I interferon signatures in gut and non-gut tissues. *L. reuteri* monocolonization worsened gut barrier leakiness induced by imiquimod. Barrier leakiness, translocation, and autoimmunity could be prevented by a resistant starch diet that is fermented by Clostridiales and related taxa to SCFAs that tighten the gut barrier and inhibit *L. reuteri* growth	Lactobacilli including *L. reuteri* were enriched in a subset of SLE patients with concomitant reduction in SCFA-producing Clostridiales	Zegarra-Ruiz et al. (2019) (30581114)

MRL/lpr (Fas mutant) lupus model	*L. reuteri* CF48-3A together with other *Lactobacillus* strains	Antibiotic pretreatment followed by weekly gavages prior to onset of disease	Pretreatment with a mixture of five Lactobacilli reduced signs of lupus nephritis and gut barrier leakiness in female and castrated male, but not sex hormone-intact male mice. Clinical improvements were associated with increased T_{reg} versus Th17 cell populations	N.D.	Mu, Zhang, et al. (2017) (28697806)
Scurfy (Foxp3 mutant, T_{reg}-deficient) mice prone to multiorgan inflammation	*L. reuteri* DSM 17938 (human breast milk)	Daily oral gavage for 1–2 weeks	Liver and lung inflammation was ameliorated by *L. reuteri* gavage via restoration of purine metabolism and Th1/Th2 balance. Effects were mediated via the adenosine A2A receptor triggered by *L. reuteri*-derived inosine	N.D.	He et al. (2017) (27994068)
Neuroinflammation					
Experimental autoimmune encephalomyelitis	*L. reuteri* DSM 17938 (human breast milk)	Daily oral gavage for 20 days	*L. reuteri* treatment reduced inflammatory cells in spinal cord, peripheral Th1/Th17 cells and plasma cytokines IFN-γ/IL-17, and restored gut microbial diversity in EAE mice	N.D.	He et al. (2019) (30899262)
Experimental autoimmune encephalomyelitis	*L. reuteri* (murine isolate) and *L. murinus*	Daily gavage starting at 10–12 weeks of age with/without a high-salt diet	A high-salt diet worsened EAE and spinal cord Th17 accumulation, which was ameliorated by *L. reuteri* or *L. murinus* administration. Salt-sensitive hypertension was similarly affected by these strains	A high-salt challenge in healthy subjects increased blood pressure and Th17 cells. This intervention reduced *Lactobacillus* species in those subjects colonized at baseline	Wilck et al. (2017) (29143823)

Continued

Table 1 Summary of mechanistic studies on *L. reuteri* in autoimmune disease models.—cont'd

Autoimmune disease models (in reverse chronologic order)	*L. reuteri* strain/origin	Intervention/ predisposition	Study findings (related to *L. reuteri*)	Human associations	Reference (PMID)
Experimental autoimmune encephalomyelitis	Naturally colonizing murine *L. reuteri* (and other tryptophan-metabolizing microbiota) as determined by quantitative PCR	Daily feeding of a tryptophan-depleted diet (with/without tryptophan supplementation) and antibiotics starting day 22 after induction of EAE	Type I interferon signaling in astrocytes induced aryl hydrocarbon receptor expression, which mediated beneficial effects via tryptophan metabolites from the microbiota. Ampicillin-sensitive, vancomycin-resistant microbiota, in particular *L. reuteri*, provided indoles that limit neuroinflammation in the brain through this pathway	Indole derivatives were decreased in the serum of MS patients and AhR-transcriptional target CYP1B1 was decreased in MS brain tissue	Rothhammer et al. (2016) (27158906)

Abbreviations: AhR, aryl hydrocarbon receptor; SCFAs, short-chain fatty acids; EAE, experimental autoimmune encephalitis; DSS, dextran sodium sulfate; IBD, inflammatory bowel disease; MRL, Murphy Roths Large; MS, multiple sclerosis; N.D., not determined; TLR7, Toll-like receptor 7; tg, transgenic; TNBS, trinitrobenzene sulfonic acid.
Studies on primary isolates of *L. reuteri* and interventional studies using *L. reuteri* products as a therapy that altered outcomes are summarized in this table. Studies are listed in reverse chronologic order for each autoimmune disease category.

(Knoop, McDonald, Kulkarni, & Newberry, 2016). Interestingly, only those oral antibiotics that promote gut commensal translocation predispose hosts to increased inflammation in vivo, and a single dose of most antibiotics tested was sufficient for bacterial translocation (Knoop et al., 2016). Furthermore, systemic administration of antibiotics, in this case ceftriaxone, disrupts mucosal homeostasis and facilitates the translocation of enterococci and lactobacilli into systemic tissues (Chakraborty et al., 2018). Thus, both oral and systemic administration of certain antibiotics can facilitate translocation of lactobacilli and enterococci across the gut barrier.

Gut barrier integrity is also weakened by innate signals during chemotherapy or by inflammatory states promoted by TNFα, lipopolysaccharides and other innate triggers of pattern recognition receptors such as TLRs (Fine et al., 2019). Using the TLR7 transgenic mice again as a paradigm, TLR7 signaling aggravated by *L. reuteri* but not *L. johnsonii* promotes gut leakiness, facilitating translocation of both species of lactobacilli (Zegarra-Ruiz et al., 2019). Given that *L. reuteri* but not *L. johnsonii* promoted systemic autoimmunity in this setting, species-specific effects on the host differ despite the shared feature of various lactobacilli translocating to internal tissues. TLR7-dependent gut leakiness occurred not only in transgenic mice under specific pathogen-free conditions but also in wild-type germ-free mice treated with the TLR7 agonist imiquimod. Thus, there are host factors (e.g., TLR7 overexpression) predisposing to gut bacterial translocation that include innocuous bystanders (*L. johnsonii*) as well as pathobionts (*L. reuteri*) that aggravate leakiness and systemic inflammation in a vicious cycle. Species and strain differences likely account for the diverse effects of lactobacilli in health and disease, which was specifically shown for different outcomes in lupus-prone hosts.

In human patients with SLE, *Lactobacillus* species including *L. reuteri* were enriched in a subset of patients who carried a decreased abundance of Clostridiales and other taxa capable of producing short-chain fatty acids (SCFAs) (Zegarra-Ruiz et al., 2019). In addition to a dysbiotic gut with an imbalance of lactobacilli versus Clostridiales, patients with SLE were also shown to carry Lactobacillales DNA in the blood stream (Ogunrinde et al., 2019; Zegarra-Ruiz et al., 2019), suggesting lactobacilli may also translocate in humans to tissues. Consistent with this notion, *Lactobacillus* signals are detectable in human livers besides enterococci (Manfredo Vieira et al., 2018). The loss of Clostridiales and other SCFA producers in the subset of SLE patients with lactobacilli enrichment in the stool further suggests a functional link leading to dysbiosis. Indeed, in the TLR7 transgenic model, SCFAs, which are produced via fermentation of dietary resistant starch,

exhibit protective effects via tightening of the gut barrier and growth-inhibitory effects on *L. reuteri* (Zegarra-Ruiz et al., 2019). Bacterial translocation, therefore, occurs in the setting of a weakened gut barrier that depends on environmental factors such as a poor diet and host genetic background.

5. The influence of diet on *L. reuteri* growth and translocation

Diet can alter the composition of the gut microbiome and affect barrier function; in particular, dietary fiber strengthens the gut barrier (Schroeder et al., 2018). Mice fed a Western diet have altered gut microbial composition and increased penetrability of the mucosal layer compared to mice fed a control chow diet. In these mice, barrier defects were prevented via administration of the fiber inulin and whole microbiota transplants from chow-fed mice, suggesting that maintenance of a certain bacterial community structure is crucial for proper mucus production and function (Schroeder et al., 2018). Moreover, in gnotobiotic mice colonized with a fully sequenced synthetic human gut microbiota, deprivation of dietary fiber forced gut microbes to adopt host-secreted mucus glycoproteins as a nutrient source, a plausible mechanism for the observed compromise of the mucosal layer (Desai et al., 2016). In a mouse model predisposed to autoimmune encephalomyelitis, early dietary supplementation with non-fermentable fiber prevented autoimmunity in adult life by altering gut microbial composition and function (Berer et al., 2018). This fiber diet led to increased production of long-chain fatty acids and a shift to Th2 immune responses as opposed to pathogenic Th1/17 responses. Furthermore, in the aforementioned study of TLR7-dependent lupus-like disease, administration of a diet high in resistant starch strengthened the gut barrier by increasing the abundance of Clostridiales and other SCFA-producing families that are known to ferment resistant starch, thereby reducing the growth and translocation of *L. reuteri* (Zegarra-Ruiz et al., 2019).

While the mechanism of growth inhibition of *L. reuteri* is unclear, recent work by Oh and colleagues point to a lytic phage within *L. reuteri* (and other lactic acid bacteria) that is inducible by high fructose or SCFAs that are produced during high fiber fermentation (Oh et al., 2019). The indirect influence of fibers on phages via SCFAs might therefore promote killing of *L. reuteri* and prevent translocation in addition to providing barrier strengthening effects. The microbiota is also capable of inducing expression of endogenous retrovirus (ERV) proteins which incite host immune responses (Virgin, 2014; Young, Mavrommatis, & Kassiotis, 2014).

In immunodeficient mice, the emergence of endogenous murine leukemia viruses occurs spontaneously but is contingent on the presence of microbial triggers from the gut microbiota (Young et al., 2012). Additionally, gut pathobiont translocation to the liver induces hepatic ERV gp70 in genetically predisposed animals, leading to the overproduction of anti-ERV immune complexes that contribute to systemic autoimmunity (Manfredo Vieira et al., 2018). Viruses within host cells (ERVs within eukaryotic and phages within bacterial cells) can thus either promote or ameliorate host-microbiota interactions.

6. A variety of metabolites of *L. reuteri* influence host health

In addition to directly inducing host effects in tissues after translocation, bacteria in the gut also alter the immune system distantly via secreted metabolites. *L. reuteri* promotes gut homeostasis through modulating arginine and tryptophan metabolism. Among a variety of metabolites, *L. reuteri* is best known to produce reuterin, which has antimicrobial activity and thereby likely shapes the gut microbial communities in its own niche. This and other metabolic products have recently been reviewed in more depth (Mu, Tavella, & Luo, 2018). *L. reuteri* also converts the amino acid arginine to L-ornithine, which stimulates tryptophan metabolism in gut epithelial cells by upregulating the enzyme indoleamine 2,3-dioxygenase 1 (IDO1). Products of tryptophan metabolism such as kynurenines bind aryl hydrocarbon receptors and induce Rorγt^+ IL-22^+ ILC3 cells (Qi et al., 2019). Under abundant tryptophan availability, *L. reuteri* but not *L. johnsonii* expands and degrades tryptophan into AhR ligands indole-3-aldehyde, leading to IL-22 transcription (Zelante et al., 2013). Depending on the local environment and context, IL-22 will be detrimental or beneficial for host health (Nakamoto et al., 2017; Tsai et al., 2017).

Gut microbiota including *L. reuteri* also regulate T_{reg} differentiation and expansion via different mechanisms (Livingston, Loach, Wilson, Tannock, & Baird, 2010; Tang et al., 2015). *L. reuteri* induced production of IL-10, IL-2 and TGF-β by murine dendritic cells as well as expansion of $Foxp3^+$ cells in the MLN and spleen. Furthermore, inosine metabolite production by *L. reuteri* restored homeostasis in T_{reg} cell deficient mice. This T_{reg}-independent effect was mediated through adenosine A_{2A} receptors, thereby inhibiting Th1/Th2 expansion and reducing multiorgan inflammation (He et al., 2017). Activation of adenosine A_{2A} receptors has pleiotropic effects including enhanced T_{reg} expansion and activity as well as inhibition

of effector T cell (T_{eff}) and natural killer cell activity (Ohta & Sitkovsky, 2014). Interestingly, under certain conditions, inosine may also promote T_{eff} proliferation and T cell-mediated tumor killing in vitro. This effect was observed in low glucose settings, indicating the variable effects on T_{regs} and T_{eff} depending on nutrient concentrations in microenvironment (Wang, Gnanaprakasam, et al., 2019). Finally, metabolite distribution may matter with regards to host effects. Increased inosine absorption was shown to be promoted via *L. reuteri*-based lengthening of intestinal villi and by modulating the gut microbiota composition (He et al., 2017).

L. reuteri-dependent conversion of histamine to L-histidine is another well-established strain-dependent metabolic process that aids colonic motility (Chen et al., 2019; Mu et al., 2018). This pathway was likely selected due to co-evolutionary anti-parasitic and prokinetic effects with benefits for the host. In addition, histamine-producing *L. reuteri* suppresses chronic intestinal inflammation and colorectal carcinogenesis in mice by reducing the activity of cancer-associated cytokines (Gao et al., 2017, 2015). *L. reuteri* mutants incapable of producing histamine were unable to exhibit such protective effects in these studies. Given the importance of histamine in mediating symptoms in allergic disease, certain *L. reuteri* strains may play also a disease-promoting role in atopy, which remains to be tested. Secretion of other yet to be determined metabolites of *L. reuteri* may instead be responsible for pro-inflammatory responses in predisposed hosts by aggravating pDC-derived IFNα systemically (Zegarra-Ruiz et al., 2019). Future studies need to elucidate the entire spectrum of microbial metabolites secreted by *L. reuteri*. The effects on the immune system will likely be determined by histamine versus interferonogenic metabolite secretion depending on strain-level differences, location of *L. reuteri* within the host, and the sensitivity of host cells to these metabolites.

Lastly, communication with the nervous system is also mediated by *L. reuteri* and its metabolites. Remarkably, *L. reuteri* affects vagus nerve mediated oxytocin signaling in autism-spectrum disorders (Buffington et al., 2016; Sgritta et al., 2019). High-fat diet-induced shifts in the gut microbial composition of maternal mice affects the oxytocin levels, ventral tegmental area plasticity, and social behavior of their offspring. Treatment with *L. reuteri* corrects social deficits in the offspring of mice fed a high-fat diet. In oxytocin receptor-deficient mice, *L. reuteri* treatment does not rescue offspring from exhibiting social deficits. These findings indicate that *L. reuteri* improves synaptic plasticity through metabolites in a vagus nerve- and oxytocin-dependent manner (Buffington et al., 2016; Sgritta et al., 2019).

7. Conclusion: Strain-specific effects of lactobacilli have implications for translational medicine

Gut commensals and lactobacilli in particular have complex effects on the host depending on bacterial strain-level attributes, host genetics, and environmental factors (Fig. 1). Diet, medication, and other environmental

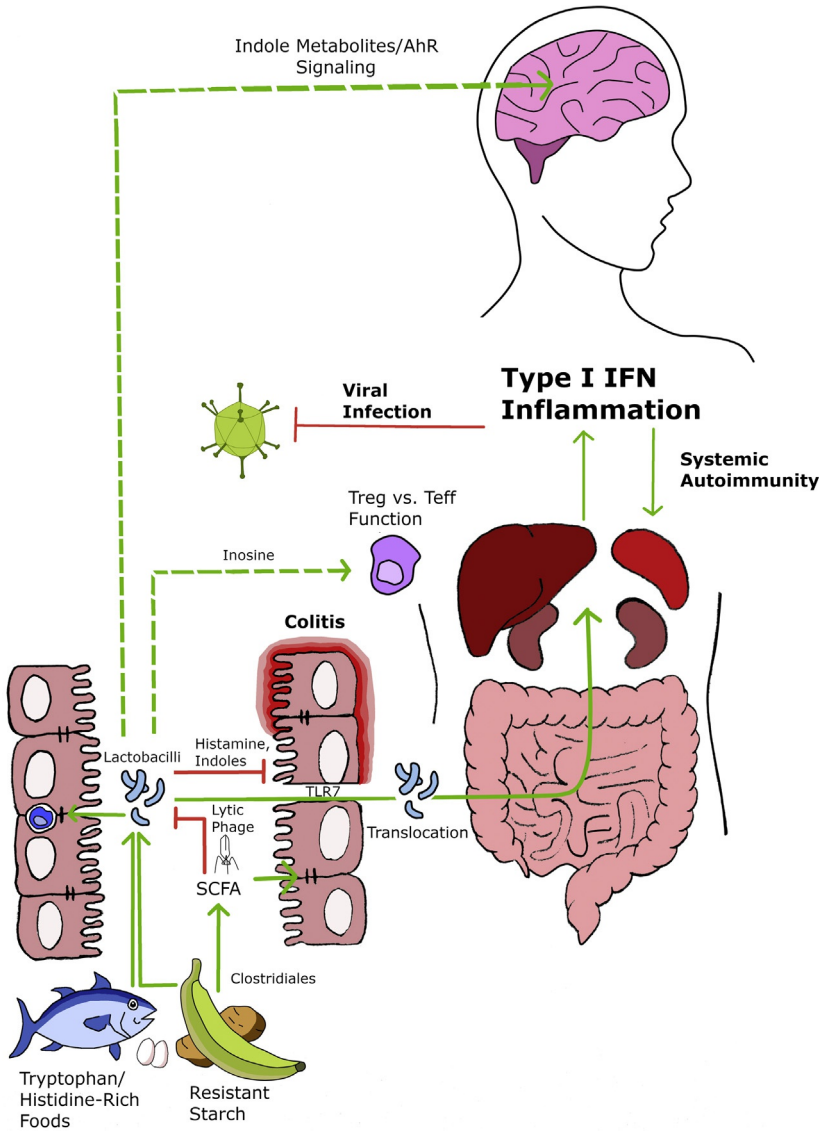

Fig. 1 See legend on next page.

influences have profound effects on these commensal bacteria and thereby on the pathogenesis of immune-mediated diseases. Lactobacilli influence not only the host directly but also other microbiota within the same regional niche, which in turn affects the integrity of the intestinal mucosal barrier as well as immune signaling pathways and functions, respectively. Emerging areas of research are how translocation of live microbiota and its metabolites influence immune mechanisms in the periphery and the relationship between individual strains and its bacteriophages in health and disease.

As more studies dissect the multiple ways in which lactobacilli interact with host cells, strain- and niche-specific differences will become clearer. Within the gut microbiome, there is no straight-forward distinction between "friend and foe," which was exemplified by *Lactobacillus* species under different host and environmental contexts as reviewed here. This paradigm supports the need to a personalized health care approach

Fig. 1 The importance of local versus peripheral effects of *Lactobacillus* spp. within predisposed hosts. Different gut bacterial strains within a species, exemplified here by *L. reuteri*, may exert local and distant pro-inflammatory or protective effects depending on the host background and environment. Some strains translocate across the gut barrier and secrete metabolites that promote TLR7-mediated type I IFN production and systemic inflammation affecting various non-gut organs (shown are liver, spleen, and kidneys) (Zegarra-Ruiz et al., 2019). Others affect astrocytes via metabolites triggering aryl hydrocarbon receptors that are upregulated by type I IFN (Rothhammer et al., 2016). Collectively, these processes may worsen systemic lupus erythematosus but ameliorate multiple sclerosis and viral infections (He et al., 2019; Wilck et al., 2017; Yang et al., 2016; Zegarra-Ruiz et al., 2019). Other strains secrete histamine in the gut which can dampen colonic inflammation (Gao et al., 2017, 2015). *L. reuteri* also increases inosine levels in the host, thereby contributing to immune homeostasis in the gut, normalizing T_{eff} balances and inhibiting autoimmunity induced by T_{reg} deficiency (He et al., 2017). In addition, the effects of *L. reuteri* on the vagus nerve via oxytocin signals (not shown) improve behavioral abnormalities due to social deficits (Buffington et al., 2016; Sgritta et al., 2019). A variety of environmental factors alter these host-microbiota interactions. For instance, dietary influences as well as infection by bacteriophages may alter the outcomes of systemic host effects (Oh et al., 2019; Schroeder et al., 2018). Resistant starch (equivalent to the type of starch in raw potatoes or green bananas) is metabolized by Clostridiales and functionally related taxa to SCFAs that in turn can induce lytic bacteriophages in *L. reuteri* (Oh et al., 2019; Zegarra-Ruiz et al., 2019). Additionally, tryptophan- and histidine-rich diets (for instance, found in tuna or eggs) allow *L. reuteri* strains to metabolize these substrates to indoles and histamine, respectively. These metabolites mediate local and systemic host effects, i.e., amelioration of gut or brain inflammation (Cervantes-Barragan et al., 2017; Gao et al., 2015; Rothhammer et al., 2016). Specifically, *L. reuteri*-derived indole derivatives were shown to induce gut intraepithelial $CD4^+$ $CD8\alpha\alpha^+$ T cells with immunoregulatory capacity (depicted as a blue cell between two epithelial cells) (Cervantes-Barragan et al., 2017). Further details and additional references are provided in the main text.

in order to developing new therapies centered around the human microbiome. Further research will need to delineate the implications for human health in individual subjects, including the potential danger of taking unrestricted probiotics that contain certain *Lactobacillus* strains. They may promote immune disease in a predisposed host or cause even frank bacteremia in critically ill patients (Yelin et al., 2019; Zegarra-Ruiz et al., 2019). More generally, unrestricted use of probiotics cannot be recommended in light of the varied effects of the gut microbiota on predisposed subjects. Instead, recommendations tailored to patient subsets based on their gut microbiota and genetic background are most likely the safest and most efficacious way forward.

Acknowledgments

We would like to thank William Ruff for editing sections on autoimmunity and Daniel Zegarra-Ruiz for discussions on diet-microbiota interactions that are represented in this review. Work discussed in this review was supported by grants from the National Institutes of Health (NIH) (K08AI095318, R01AI118855, T32AI07019, T32DK007017-39), the O'Brien Center at Yale (NIH P30DK079310), the Yale Rheumatic Diseases Research Core (NIH P30 AR053495), the Yale Liver Center (NIH P30 DK34989), the Women's Health Research at Yale, the Arthritis National Research Foundation, the Arthritis Foundation, the Lupus Research Institute, and the Lupus Foundation of America.

Declaration of interest

M.A.K. received salary, consulting fees, honoraria, and research funds from Roche, Bristol-Meyers Squibb, AbbVie, and Cell Applications and is an employee of Roche. M.A.K. holds an international patent on the use of antibiotics and commensal vaccination to treat autoimmunity and received royalties. The remaining authors have declared that no conflict of interest exists.

References

Ahl, D., Liu, H., Schreiber, O., Roos, S., Phillipson, M., & Holm, L. (2016). *Lactobacillus reuteri* increases mucus thickness and ameliorates dextran sulphate sodium-induced colitis in mice. *Acta Physiologica (Oxford, England)*, *217*(4), 300–310. https://doi.org/10.1111/apha.12695.

Almeida, A., Mitchell, A. L., Boland, M., Forster, S. C., Gloor, G. B., Tarkowska, A., et al. (2019). A new genomic blueprint of the human gut microbiota. *Nature*, *568*(7753), 499–504. https://doi.org/10.1038/s41586-019-0965-1.

Anderson, A. C., Sanunu, M., Schneider, C., Clad, A., Karygianni, L., Hellwig, E., et al. (2014). Rapid species-level identification of vaginal and oral lactobacilli using MALDI-TOF MS analysis and 16S rDNA sequencing. *BMC Microbiology*, *14*, 312. https://doi.org/10.1186/s12866-014-0312-5.

Berer, K., Martinez, I., Walker, A., Kunkel, B., Schmitt-Kopplin, P., Walter, J., et al. (2018). Dietary non-fermentable fiber prevents autoimmune neurological disease by changing gut metabolic and immune status. *Scientific Reports*, *8*(1), 10431. https://doi.org/10.1038/s41598-018-28839-3.

Bereswill, S., Ekmekciu, I., Escher, U., Fiebiger, U., Stingl, K., & Heimesaat, M. M. (2017). *Lactobacillus johnsonii* ameliorates intestinal, extra-intestinal and systemic pro-inflammatory immune responses following murine *Campylobacter jejuni* infection. *Scientific Reports*, 7(1), 2138. https://doi.org/10.1038/s41598-017-02436-2.

Bogdanos, D. P., Baum, H., Okamoto, M., Montalto, P., Sharma, U. C., Rigopoulou, E. I., et al. (2005). Primary biliary cirrhosis is characterized by IgG3 antibodies cross-reactive with the major mitochondrial autoepitope and its Lactobacillus mimic. *Hepatology*, *42*(2), 458–465. https://doi.org/10.1002/hep.20788.

Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., et al. (2011). Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(38), 16050–16055. https://doi.org/10.1073/pnas.1102999108.

Buffington, S. A., Di Prisco, G. V., Auchtung, T. A., Ajami, N. J., Petrosino, J. F., & Costa-Mattioli, M. (2016). Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell*, *165*(7), 1762–1775. https://doi.org/10.1016/j.cell.2016.06.001.

Burrows, M. P., Volchkov, P., Kobayashi, K. S., & Chervonsky, A. V. (2015). Microbiota regulates type 1 diabetes through Toll-like receptors. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(32), 9973–9977. https://doi.org/10.1073/pnas.1508740112.

Cervantes-Barragan, L., Chai, J. N., Tianero, M. D., Di Luccia, B., Ahern, P. P., Merriman, J., et al. (2017). *Lactobacillus reuteri* induces gut intraepithelial CD4(+) CD8alphaalpha(+) T cells. *Science*, *357*(6353), 806–810. https://doi.org/10.1126/science.aah5825.

Chakraborty, R., Lam, V., Kommineni, S., Stromich, J., Hayward, M., Kristich, C. J., et al. (2018). Ceftriaxone administration disrupts intestinal homeostasis, mediating non-inflammatory proliferation and dissemination of commensal enterococci. *Infection and Immunity*, *86*(12), e00674–e00718. https://doi.org/10.1128/IAI.00674-18.

Chen, H., Nwe, P. K., Yang, Y., Rosen, C. E., Bielecka, A. A., Kuchroo, M., et al. (2019). A forward chemical genetic screen reveals gut microbiota metabolites that modulate host physiology. *Cell*, *177*(5), 1217–1231.e1218. https://doi.org/10.1016/j.cell.2019.03.036.

Daillere, R., Vetizou, M., Waldschmitt, N., Yamazaki, T., Isnard, C., Poirier-Colame, V., et al. (2016). *Enterococcus hirae* and *Barnesiella intestinihominis* facilitate cyclophosphamide-induced therapeutic immunomodulatory effects. *Immunity*, *45*(4), 931–943. https://doi.org/10.1016/j.immuni.2016.09.009.

De Filippis, F., Pasolli, E., Tett, A., Tarallo, S., Naccarati, A., De Angelis, M., et al. (2019). Distinct genetic and functional traits of human intestinal *Prevotella copri* strains are associated with different habitual diets. *Cell Host & Microbe*, *25*(3), 444–453.e443. https://doi.org/10.1016/j.chom.2019.01.004.

De Filippo, C., Cavalieri, D., Di Paola, M., Ramazzotti, M., Poullet, J. B., Massart, S., et al. (2010). Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(33), 14691–14696. https://doi.org/10.1073/pnas.1005963107.

Dehner, C., Fine, R., & Kriegel, M. A. (2019). The microbiome in systemic autoimmune disease: Mechanistic insights from recent studies. *Current Opinion in Rheumatology*, *31*(2), 201–207. https://doi.org/10.1097/BOR.0000000000000574.

Desai, M. S., Seekatz, A. M., Koropatkin, N. M., Kamada, N., Hickey, C. A., Wolter, M., et al. (2016). A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell*, *167*(5), 1339–1353, e1321. https://doi.org/10.1016/j.cell.2016.10.043.

Di Rienzi, S. C., Jacobson, J., Kennedy, E. A., Bell, M. E., Shi, Q., Waters, J. L., et al. (2018). Resilience of small intestinal beneficial bacteria to the toxicity of soybean oil fatty acids. *eLife*, 7, e32581. https://doi.org/10.7554/eLife.32581.

Duar, R. M., Lin, X. B., Zheng, J., Martino, M. E., Grenier, T., Perez-Munoz, M. E., et al. (2017). Lifestyles in transition: Evolution and natural history of the genus Lactobacillus. *FEMS Microbiology Reviews*, *41*(Supp_1), S27–S48. https://doi.org/10.1093/femsre/fux030.

Fine, R. L., Manfredo Vieira, S., Gilmore, M. S., & Kriegel, M. A. (2019). Mechanisms and consequences of gut commensal translocation in chronic diseases. *Gut Microbes*, 1–14. https://doi.org/10.1080/19490976.2019.1629236. Epub ahead of print.

Gao, C., Ganesh, B. P., Shi, Z., Shah, R. R., Fultz, R., Major, A., et al. (2017). Gut microbe-mediated suppression of inflammation-associated colon carcinogenesis by luminal histamine production. *The American Journal of Pathology*, *187*(10), 2323–2336. https://doi.org/10.1016/j.ajpath.2017.06.011.

Gao, C., Major, A., Rendon, D., Lugo, M., Jackson, V., Shi, Z., et al. (2015). Histamine H2 receptor-mediated suppression of intestinal inflammation by probiotic *Lactobacillus reuteri*. *mBio*, *6*(6), e01358-01315. https://doi.org/10.1128/mBio.01358-15.

Gil-Cruz, C., Perez-Shibayama, C., De Martin, A., Ronchi, F., van der Borght, K., Niederer, R., et al. (2019). Microbiota-derived peptide mimics drive lethal inflammatory cardiomyopathy. *Science*, 366(6467), 881–886. https://doi.org/10.1126/science.aav3487.

Greiling, T., Dehner, C., Chen, X., Hughes, K., Iniguez, A., Boccitto, M., et al. (2018). Commensal orthologs of the human autoantigen Ro60 as triggers of autoimmunity in lupus. *Science Translational Medicine*, *10*(434), eaan2306. https://doi.org/10.1126/scitranslmed.aan2306.

He, B., Hoang, T. K., Tian, X., Taylor, C. M., Blanchard, E., Luo, M., et al. (2019). *Lactobacillus reuteri* reduces the severity of experimental autoimmune encephalomyelitis in mice by modulating gut microbiota. *Frontiers in Immunology*, *10*, 385. https://doi.org/10.3389/fimmu.2019.00385.

He, B., Hoang, T. K., Wang, T., Ferris, M., Taylor, C. M., Tian, X., et al. (2017). Resetting microbiota by *Lactobacillus reuteri* inhibits T reg deficiency-induced autoimmunity via adenosine A2A receptors. *The Journal of Experimental Medicine*, *214*(1), 107–123. https://doi.org/10.1084/jem.20160961.

Kasahara, K., Krautkramer, K. A., Org, E., Romano, K. A., Kerby, R. L., Vivas, E. I., et al. (2018). Interactions between *Roseburia intestinalis* and diet modulate atherogenesis in a murine model. *Nature Microbiology*, *3*(12), 1461–1471. https://doi.org/10.1038/s41564-018-0272-x.

Kawashima, T., Kosaka, A., Yan, H., Guo, Z., Uchiyama, R., Fukui, R., et al. (2013). Double-stranded RNA of intestinal commensal but not pathogenic bacteria triggers production of protective interferon-beta. *Immunity*, *38*(6), 1187–1197. https://doi.org/10.1016/j.immuni.2013.02.024.

Kingma, S. D., Li, N., Sun, F., Valladares, R. B., Neu, J., & Lorca, G. L. (2011). *Lactobacillus johnsonii* N6.2 stimulates the innate immune response through Toll-like receptor 9 in Caco-2 cells and increases intestinal crypt Paneth cell number in biobreeding diabetes-prone rats. *The Journal of Nutrition*, *141*(6), 1023–1028. https://doi.org/10.3945/jn.110.135517.

Kiyohara, H., Sujino, T., Teratani, T., Miyamoto, K., Arai, M. M., Nomura, E., et al. (2019). Toll-like receptor 7 agonist-induced dermatitis causes severe dextran sulfate sodium colitis by altering the gut microbiome and immune cells. *Cellular and Molecular Gastroenterology and Hepatology*, 7(1), 135–156. https://doi.org/10.1016/j.jcmgh.2018.09.010.

Knoop, K. A., McDonald, K. G., Kulkarni, D. H., & Newberry, R. D. (2016). Antibiotics promote inflammation through the translocation of native commensal colonic bacteria. *Gut*, *65*(7), 1100–1109. https://doi.org/10.1136/gutjnl-2014-309059.

Kovatcheva-Datchary, P., Nilsson, A., Akrami, R., Lee, Y. S., De Vadder, F., Arora, T., et al. (2015). Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of Prevotella. *Cell Metabolism*, *22*(6), 971–982. https://doi.org/10.1016/j.cmet.2015.10.001.

Kriegel, M. A., Sefik, E., Hill, J. A., Wu, H. J., Benoist, C., & Mathis, D. (2011). Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in non-obese diabetic mice. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(28), 11548–11553. https://doi.org/10.1073/pnas.1108924108.

La Fata, G., Weber, P., & Mohajeri, M. H. (2018). Probiotics and the gut immune system: Indirect regulation. *Probiotics and Antimicrobial Proteins*, *10*(1), 11–21. https://doi.org/10.1007/s12602-017-9322-6.

Lafuse, W. P., Gearinger, R., Fisher, S., Nealer, C., Mackos, A. R., & Bailey, M. T. (2017). Exposure to a social stressor induces translocation of commensal lactobacilli to the spleen and priming of the innate immune system. *Journal of Immunology*, *198*(6), 2383–2393. https://doi.org/10.4049/jimmunol.1601269.

Lamas, B., Richard, M. L., Leducq, V., Pham, H. P., Michel, M. L., Da Costa, G., et al. (2016). CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. *Nature Medicine*, *22*(6), 598–605. https://doi.org/10.1038/nm.4102.

Lau, K., Benitez, P., Ardissone, A., Wilson, T. D., Collins, E. L., Lorca, G., et al. (2011). Inhibition of type 1 diabetes correlated to a *Lactobacillus johnsonii* N6.2-mediated Th17 bias. *Journal of Immunology*, *186*(6), 3538–3546. https://doi.org/10.4049/jimmunol.1001864.

Lee, H., & Ko, G. (2016). Antiviral effect of vitamin A on norovirus infection via modulation of the gut microbiome. *Scientific Reports*, *6*, 25835. https://doi.org/10.1038/srep25835.

Liu, H. Y., Roos, S., Jonsson, H., Ahl, D., Dicksved, J., Lindberg, J. E., et al. (2015). Effects of *Lactobacillus johnsonii* and *Lactobacillus reuteri* on gut barrier function and heat shock proteins in intestinal porcine epithelial cells. *Physiological Reports*, *3*(4), e12355. https://doi.org/10.14814/phy2.12355.

Livingston, M., Loach, D., Wilson, M., Tannock, G. W., & Baird, M. (2010). Gut commensal *Lactobacillus reuteri* 100-23 stimulates an immunoregulatory response. *Immunology and Cell Biology*, *88*(1), 99–102. https://doi.org/10.1038/icb.2009.71.

Lorea Baroja, M., Kirjavainen, P. V., Hekmat, S., & Reid, G. (2007). Anti-inflammatory effects of probiotic yogurt in inflammatory bowel disease patients. *Clinical and Experimental Immunology*, *149*(3), 470–479. https://doi.org/10.1111/j.1365-2249.2007.03434.x.

Luo, X. M., Edwards, M. R., Mu, Q., Yu, Y., Vieson, M. D., Reilly, C. M., et al. (2018). Gut microbiota in human systemic lupus erythematosus and a mouse model of lupus. *Applied and Environmental Microbiology*, *84*(4), e02288-17. https://doi.org/10.1128/AEM.02288-17.

Macklaim, J. M., Gloor, G. B., Anukam, K. C., Cribby, S., & Reid, G. (2011). At the crossroads of vaginal health and disease, the genome sequence of *Lactobacillus iners* AB-1. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(Suppl. 1), 4688–4695. https://doi.org/10.1073/pnas.1000086107.

Macpherson, A. J., & Uhr, T. (2004). Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. *Science*, *303*(5664), 1662–1665. https://doi.org/10.1126/science.1091334.

Maeda, Y., Kurakawa, T., Umemoto, E., Motooka, D., Ito, Y., Gotoh, K., et al. (2016). Dysbiosis contributes to arthritis development via activation of autoreactive T cells in the intestine. *Arthritis & Rhematology*, *68*(11), 2646–2661. https://doi.org/10.1002/art.39783.

Main, B. S., & Minter, M. R. (2017). Microbial immuno-communication in neurodegenerative diseases. *Frontiers in Neuroscience*, *11*, 151. https://doi.org/10.3389/fnins.2017.00151.

Manfredo Vieira, S., Hiltensperger, M., Kumar, V., Zegarra-Ruiz, D., Dehner, C., Khan, N., et al. (2018). Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science*, *359*(6380), 1156–1161. https://doi.org/10.1126/science.aar7201.

Marcial, G. E., Ford, A. L., Haller, M. J., Gezan, S. A., Harrison, N. A., Cai, D., et al. (2017). *Lactobacillus johnsonii* N6.2 modulates the host immune responses: A double-blind, randomized trial in healthy adults. *Frontiers in Immunology*, *8*, 655. https://doi.org/10.3389/fimmu.2017.00655.

Mendes-Soares, H., Suzuki, H., Hickey, R. J., & Forney, L. J. (2014). Comparative functional genomics of Lactobacillus spp. reveals possible mechanisms for specialization of vaginal lactobacilli to their environment. *Journal of Bacteriology*, *196*(7), 1458–1470. https://doi.org/10.1128/JB.01439-13.

Minato, T., Maeda, T., Fujisawa, Y., Tsuji, H., Nomoto, K., Ohno, K., et al. (2017). Progression of Parkinson's disease is associated with gut dysbiosis: Two-year follow-up study. *PLoS One*, *12*(11), e0187307. https://doi.org/10.1371/journal.pone.0187307.

Molenaar, M. C., Singer, M., & Ouburg, S. (2018). The two-sided role of the vaginal microbiome in *Chlamydia trachomatis* and *Mycoplasma genitalium* pathogenesis. *Journal of Reproductive Immunology*, *130*, 11–17. https://doi.org/10.1016/j.jri.2018.08.006.

Mu, Q., Tavella, V. J., Kirby, J. L., Cecere, T. E., Chung, M., Lee, J., et al. (2017). Antibiotics ameliorate lupus-like symptoms in mice. *Scientific Reports*, 7(1), 13675. https://doi.org/10.1038/s41598-017-14223-0.

Mu, Q., Tavella, V. J., & Luo, X. M. (2018). Role of *Lactobacillus reuteri* in human health and diseases. *Frontiers in Microbiology*, *9*, 757. https://doi.org/10.3389/fmicb.2018.00757.

Mu, Q., Zhang, H., Liao, X., Lin, K., Liu, H., Edwards, M. R., et al. (2017). Control of lupus nephritis by changes of gut microbiota. *Microbiome*, *5*(1), 73. https://doi.org/10.1186/s40168-017-0300-8.

Nakamoto, N., Amiya, T., Aoki, R., Taniki, N., Koda, Y., Miyamoto, K., et al. (2017). Commensal Lactobacillus controls immune tolerance during acute liver injury in mice. *Cell Reports*, *21*(5), 1215–1226. https://doi.org/10.1016/j.celrep.2017.10.022.

Natividad, J. M., Agus, A., Planchais, J., Lamas, B., Jarry, A. C., Martin, R., et al. (2018). Impaired aryl hydrocarbon receptor ligand production by the gut microbiota is a key factor in metabolic syndrome. *Cell Metabolism*, *28*(5), 737–749, e734. https://doi.org/10.1016/j.cmet.2018.07.001.

Nayfach, S., Shi, Z. J., Seshadri, R., Pollard, K. S., & Kyrpides, N. C. (2019). New insights from uncultivated genomes of the global human gut microbiome. *Nature*, *568*(7753), 505–510. https://doi.org/10.1038/s41586-019-1058-x.

Ogunrinde, E., Zhou, Z., Luo, Z., Alekseyenko, A., Li, Q. Z., Macedo, D., et al. (2019). A link between plasma microbial translocation, microbiome, and autoantibody development in first-degree relatives of systemic lupus erythematosus patients. *Arthritis & Rhematology*, *71*(11), 1858–1868. https://doi.org/10.1002/art.40935.

Oh, J. H., Alexander, L. M., Pan, M., Schueler, K. L., Keller, M. P., Attie, A. D., et al. (2019). Dietary fructose and microbiota-derived short-chain fatty acids promote bacteriophage production in the gut symbiont *Lactobacillus reuteri*. *Cell Host & Microbe*, *25*(2), 273–284.e276. https://doi.org/10.1016/j.chom.2018.11.016.

Ohta, A., & Sitkovsky, M. (2014). Extracellular adenosine-mediated modulation of regulatory T cells. *Frontiers in Immunology*, *5*, 304. https://doi.org/10.3389/fimmu.2014.00304.

Oliva, S., Di Nardo, G., Ferrari, F., Mallardo, S., Rossi, P., Patrizi, G., et al. (2012). Randomised clinical trial: The effectiveness of *Lactobacillus reuteri* ATCC 55730 rectal enema in children with active distal ulcerative colitis. *Alimentary Pharmacology & Therapeutics*, *35*(3), 327–334. https://doi.org/10.1111/j.1365-2036.2011.04939.x.

Pasolli, E., Asnicar, F., Manara, S., Zolfo, M., Karcher, N., Armanini, F., et al. (2019). Extensive unexplored human microbiome diversity revealed by over 150, 000 genomes from metagenomes spanning age, geography, and lifestyle. *Cell*, *176*(3), 649–662.e620. https://doi.org/10.1016/j.cell.2019.01.001.

Pereira, M. T., Malik, M., Nostro, J. A., Mahler, G. J., & Musselman, L. P. (2018). Effect of dietary additives on intestinal permeability in both Drosophila and a human cell co-culture. *Disease Models & Mechanisms*, *11*(12), dmm034520. https://doi.org/10.1242/dmm.034520.

Perruzza, L., Strati, F., Gargari, G., D'Erchia, A. M., Fosso, B., Pesole, G., et al. (2019). Enrichment of intestinal Lactobacillus by enhanced secretory IgA coating alters glucose homeostasis in P2rx7(−/−) mice. *Scientific Reports*, *9*(1), 9315. https://doi.org/10.1038/s41598-019-45724-9.

Petrov, V. A., Saltykova, I. V., Zhukova, I. A., Alifirova, V. M., Zhukova, N. G., Dorofeeva, Y. B., et al. (2017). Analysis of gut microbiota in patients with Parkinson's disease. *Bulletin of Experimental Biology and Medicine*, *162*(6), 734–737. https://doi.org/10.1007/s10517-017-3700-7.

Pineda Mde, L., Thompson, S. F., Summers, K., de Leon, F., Pope, J., & Reid, G. (2011). A randomized, double-blinded, placebo-controlled pilot study of probiotics in active rheumatoid arthritis. *Medical Science Monitor*, *17*(6). CR347-354. https://doi.org/10.12659/msm.881808.

Qi, H., Li, Y., Yun, H., Zhang, T., Huang, Y., Zhou, J., et al. (2019). Lactobacillus maintains healthy gut mucosa by producing L-Ornithine. *Communications Biology*, *2*, 171. https://doi.org/10.1038/s42003-019-0424-4.

Rothhammer, V., Mascanfroni, I. D., Bunse, L., Takenaka, M. C., Kenison, J. E., Mayo, L., et al. (2016). Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nature Medicine*, *22*(6), 586–597. https://doi.org/10.1038/nm.4106.

Ruff, W. E., Dehner, C., Kim, W. J., Pagovich, O., Aguiar, C. L., Yu, A. T., et al. (2019). Pathogenic autoreactive T and B cells cross-react with mimotopes expressed by a common human gut commensal to trigger autoimmunity. *Cell Host & Microbe*, *26*(1), 100–113.e108. https://doi.org/10.1016/j.chom.2019.05.003.

Ruff, W. E., & Kriegel, M. A. (2015). Autoimmune host-microbiota interactions at barrier sites and beyond. *Trends in Molecular Medicine*, *21*(4), 233–244. https://doi.org/10.1016/j.molmed.2015.02.006.

Sainathan, S. K., Bishnupuri, K. S., Aden, K., Luo, Q., Houchen, C. W., Anant, S., et al. (2012). Toll-like receptor-7 ligand Imiquimod induces type I interferon and antimicrobial peptides to ameliorate dextran sodium sulfate-induced acute colitis. *Inflammatory Bowel Diseases*, *18*(5), 955–967. https://doi.org/10.1002/ibd.21867.

Salvetti, E., Torriani, S., & Felis, G. E. (2012). The genus Lactobacillus: A taxonomic update. *Probiotics and Antimicrobial Proteins*, *4*(4), 217–226. https://doi.org/10.1007/s12602-012-9117-8.

Scher, J. U., Sczesnak, A., Longman, R. S., Segata, N., Ubeda, C., Bielski, C., et al. (2013). Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis. *eLife, 2*, e01202. https://doi.org/10.7554/eLife.01202.

Schreiber, O., Petersson, J., Phillipson, M., Perry, M., Roos, S., & Holm, L. (2009). *Lactobacillus reuteri* prevents colitis by reducing P-selectin-associated leukocyte- and platelet-endothelial cell interactions. *American Journal of Physiology Gastrointestinal and Liver Physiology*, *296*(3), G534–G542. https://doi.org/10.1152/ajpgi.90470.2008.

Schroeder, B. O., Birchenough, G. M. H., Stahlman, M., Arike, L., Johansson, M. E. V., Hansson, G. C., et al. (2018). Bifidobacteria or fiber protects against diet-induced microbiota-mediated colonic mucus deterioration. *Cell Host & Microbe*, *23*(1), 27–40. e27. https://doi.org/10.1016/j.chom.2017.11.004.

Sgritta, M., Dooling, S. W., Buffington, S. A., Momin, E. N., Francis, M. B., Britton, R. A., et al. (2019). Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder. *Neuron*, *101*(2), 246–259.e246. https://doi.org/10.1016/j.neuron.2018.11.018.

Shen, Z., Zhu, C., Quan, Y., Yang, J., Yuan, W., Yang, Z., et al. (2018). Insights into *Roseburia intestinalis* which alleviates experimental colitis pathology by inducing anti-inflammatory responses. *Journal of Gastroenterology and Hepatology*, *33*(10), 1751–1760. https://doi.org/10.1111/jgh.14144.

Sinkiewicz, G., & Ljunggren, L. (2009). Occurrence of *Lactobacillus reuteri* in human breast milk. *Microbial Ecology in Health and Disease*, *20*(3), 122–126. https://doi.org/10.1080/08910600802341007.

Tang, C., Kamiya, T., Liu, Y., Kadoki, M., Kakuta, S., Oshima, K., et al. (2015). Inhibition of Dectin-1 signaling ameliorates colitis by inducing Lactobacillus-mediated regulatory T cell expansion in the intestine. *Cell Host & Microbe*, *18*(2), 183–197. https://doi.org/10.1016/j.chom.2015.07.003.

Tett, A., Huang, K. D., Asnicar, F., Fehlner-Peach, H., Pasolli, E., Karcher, N., et al. (2019). The *Prevotella copri* complex comprises four distinct clades underrepresented in westernized populations. *Cell Host & Microbe*, *26*(5), 666–679.e667. https://doi.org/10.1016/j.chom.2019.08.018.

Tsai, P. Y., Zhang, B., He, W. Q., Zha, J. M., Odenwald, M. A., Singh, G., et al. (2017). IL-22 upregulates epithelial claudin-2 to drive diarrhea and enteric pathogen clearance. *Cell Host & Microbe*, *21*(6), 671–681.e674. https://doi.org/10.1016/j.chom.2017.05.009.

Valladares, R., Bojilova, L., Potts, A. H., Cameron, E., Gardner, C., Lorca, G., et al. (2013). *Lactobacillus johnsonii* inhibits indoleamine 2,3-dioxygenase and alters tryptophan metabolite levels in BioBreeding rats. *The FASEB Journal*, *27*(4), 1711–1720. https://doi.org/10.1096/fj.12-223339.

Valladares, R., Sankar, D., Li, N., Williams, E., Lai, K. K., Abdelgeliel, A. S., et al. (2010). *Lactobacillus johnsonii* N6.2 mitigates the development of type 1 diabetes in BB-DP rats. *PLoS One*, *5*(5), e10507. https://doi.org/10.1371/journal.pone.0010507.

van Kessel, S. P., Frye, A. K., El-Gendy, A. O., Castejon, M., Keshavarzian, A., van Dijk, G., et al. (2019). Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease. *Nature Communications*, *10*(1), 310. https://doi.org/10.1038/s41467-019-08294-y.

Vatanen, T., Franzosa, E. A., Schwager, R., Tripathi, S., Arthur, T. D., Vehik, K., et al. (2018). The human gut microbiome in early-onset type 1 diabetes from the TEDDY study. *Nature*, *562*(7728), 589–594. https://doi.org/10.1038/s41586-018-0620-2.

Vich Vila, A., Imhann, F., Collij, V., Jankipersadsing, S. A., Gurry, T., Mujagic, Z., et al. (2018). Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. *Science Translational Medicine*, *10*(472), eaap8914. https://doi.org/10.1126/scitranslmed.aap8914.

Virgin, H. W. (2014). The virome in mammalian physiology and disease. *Cell*, *157*(1), 142–150. https://doi.org/10.1016/j.cell.2014.02.032.

Walter, J. (2008). Ecological role of lactobacilli in the gastrointestinal tract: Implications for fundamental and biomedical research. *Applied and Environmental Microbiology*, *74*(16), 4985–4996. https://doi.org/10.1128/AEM.00753-08.

Wang, T., Gnanaprakasam, J. N. R., Chen, X., Kang, S., Xu, X., Sun, H., et al. (2019). Inosine is an alternative carbon supply that supports effector T cell proliferation and antitumor function under glucose restriction. *bioRxiv*, 766642. https://doi.org/10.1101/766642.

Wang, T., Zheng, N., Luo, Q., Jiang, L., He, B., Yuan, X., et al. (2019). Probiotics *Lactobacillus reuteri* abrogates immune checkpoint blockade-associated colitis by inhibiting group 3 innate lymphoid cells. *Frontiers in Immunology*, *10*, 1235. https://doi.org/10.3389/fimmu.2019.01235.

Wilck, N., Matus, M. G., Kearney, S. M., Olesen, S. W., Forslund, K., Bartolomaeus, H., et al. (2017). Salt-responsive gut commensal modulates TH17 axis and disease. *Nature*, *551*(7682), 585–589. https://doi.org/10.1038/nature24628.

Yang, J. Y., Kim, M. S., Kim, E., Cheon, J. H., Lee, Y. S., Kim, Y., et al. (2016). Enteric viruses ameliorate gut inflammation via Toll-like receptor 3 and Toll-like receptor 7-mediated interferon-beta production. *Immunity*, *44*(4), 889–900. https://doi.org/10.1016/j.immuni.2016.03.009.

Yelin, I., Flett, K. B., Merakou, C., Mehrotra, P., Stam, J., Snesrud, E., et al. (2019). Genomic and epidemiological evidence of bacterial transmission from probiotic capsule to blood in ICU patients. *Nature Medicine*, *25*(11), 1728–1732. https://doi.org/10.1038/s41591-019-0626-9.

Young, G. R., Eksmond, U., Salcedo, R., Alexopoulou, L., Stoye, J. P., & Kassiotis, G. (2012). Resurrection of endogenous retroviruses in antibody-deficient mice. *Nature*, *491*(7426), 774–778. https://doi.org/10.1038/nature11599.

Young, G. R., Mavrommatis, B., & Kassiotis, G. (2014). Microarray analysis reveals global modulation of endogenous retroelement transcription by microbes. *Retrovirology*, *11*, 59. https://doi.org/10.1186/1742-4690-11-59.

Yurkovetskiy, L., Burrows, M., Khan, A. A., Graham, L., Volchkov, P., Becker, L., et al. (2013). Gender bias in autoimmunity is influenced by microbiota. *Immunity*, *39*(2), 400–412. https://doi.org/10.1016/j.immuni.2013.08.013.

Zegarra-Ruiz, D. F., El Beidaq, A., Iniguez, A. J., Lubrano Di Ricco, M., Manfredo Vieira, S., Ruff, W. E., et al. (2019). A diet-sensitive commensal Lactobacillus strain mediates TLR7-dependent systemic autoimmunity. *Cell Host & Microbe*, *25*(1), 113–127.e116. https://doi.org/10.1016/j.chom.2018.11.009.

Zelante, T., Iannitti, R. G., Cunha, C., De Luca, A., Giovannini, G., Pieraccini, G., et al. (2013). Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity*, *39*(2), 372–385. https://doi.org/10.1016/j.immuni.2013.08.003.

Zhang, H., Liao, X., Sparks, J. B., & Luo, X. M. (2014). Dynamics of gut microbiota in autoimmune lupus. *Applied and Environmental Microbiology*, *80*(24), 7551–7560. https://doi.org/10.1128/AEM.02676-14.

Zhang, X., Zhang, D., Jia, H., Feng, Q., Wang, D., Liang, D., et al. (2015). The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nature Medicine*, *21*(8), 895–905. https://doi.org/10.1038/nm.3914.