Title

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Journal

Current Environmental Health Reports, 3(3)

ISSN

2196-5412

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Publication Date

2016-09-01

DOI

10.1007/s40572-016-0100-5

Peer reviewed

HHS Public Access

Author manuscript

Curr Environ Health Rep. Author manuscript; available in PMC 2018 January 11.

Published in final edited form as:

Curr Environ Health Rep. 2016 September ; 3(3): 270–286. doi:10.1007/s40572-016-0100-5.

The Microbiota, Immunoregulation, and Mental Health: Implications for Public Health

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Conflict of Interest

Christopher A. Lowry, David G. Smith, Philip H. Siebler, Dominic Schmidt, Christopher E. Stamper, James E. Hassell Jr., Paula S. Yamashita, James H. Fox, Stefan O. Reber, Lisa A. Brenner, Andrew J. Hoisington, Teodor T. Postolache, Kerry A. Kinney, Dante Marciani, Mark Hernandez, Sian M.J. Hemmings, Stefanie Malan-Muller, Kenneth P. Wright, Rob Knight, Charles L. Raison, and Graham A.W. Rook report no conflicts of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Abstract

The hygiene or “Old Friends” hypothesis proposes that the epidemic of inflammatory disease in modern urban societies stems at least in part from reduced exposure to microbes that normally prime mammalian immunoregulatory circuits and suppress inappropriate inflammation. Such diseases include but are not limited to allergies and asthma; we and others have proposed that the markedly reduced exposure to these old friends in modern urban societies may also increase vulnerability to neurodevelopmental disorders and stress-related psychiatric disorders, such as anxiety and affective disorders, where data are emerging in support of inflammation as a risk factor. Here we review recent advances in our understanding of the potential for old friends, including environmental microbial inputs, to modify risk for inflammatory disease, with a focus on neurodevelopmental and psychiatric conditions. We highlight potential mechanisms, involving bacterially-derived metabolites, bacterial antigens, and helminthic antigens, through which these inputs promote immunoregulation. Though findings are encouraging, significant human subjects research is required to evaluate the potential impact of old friends, including environmental microbial inputs, on biological signatures and clinically meaningful mental health prevention and intervention outcomes.

Keywords

anxiety; depression; lactobacilli; microbiome; mycobacteria; posttraumatic stress disorder

Introduction

It is firmly established that inflammation can play a causative role in psychiatric disorders [reviewed in 1]. Here we summarize major points from the human data, but there is also a mass of animal data that falls outside the scope of this review. Raised levels of cytokines are found in the blood and cerebrospinal fluid (CSF) of a subset of cases of depression and psychosis [1-3], and raised expression is found in the brains of suicide victims [1]. Moreover depression is associated with polymorphisms of inflammatory cytokine genes [4], and the risk alleles tend to have inflammatory functions within the immune system [5]. The known environmental risk factors are also proinflammatory [6]. Recently, using non-invasive positron emission tomography (PET) scans, it has been possible to confirm that there is activation of microglia (tissue-resident macrophages in the central nervous system (CNS)) in depressed and in psychotic subjects [7;8]. Very direct evidence for the contributory role of inflammation comes from the observation that some patients become depressed when treated with IFN-alpha, an inflammatory cytokine [9]. Finally, antiinflammatory treatments such as inhibitors of cycloxygenase, or a neutralizing antibody to tumor necrosis factor (TNF) are therapeutic in those patients who have raised inflammatory biomarkers [10;11]. (The same subset tends to be resistant to conventional antidepressants [12]). Finally, it has been shown

in rodents and monkeys that inflammation occurring during pregnancy can lead to abnormalities of brain development and behavior that are reminiscent of autism or schizophrenia [13;14], while epidemiological findings suggest that the same is true in humans [15].

A second class of evidence that inflammation can play a causative role in psychiatric disorders comes from studies of the pathways that link peripheral inflammation to changes in CNS function [1]. Cytokines can 1) access the brain via the circumventricular organs where there is a reduced blood-brain barrier, 2) be transported into the brain by specific transport mechanisms, or 3) cause inflammatory changes in the cells of the blood-brain barrier [16]. Other signals are transmitted via the vagus nerve which, in response to inflammatory signals in the periphery, drives cytokine release in the CNS [16]. Peripheral inflammation also activates enzymes such as indoleamine 2,3-dioxygenase that convert tryptophan to N-formylkynurenine, which is then converted to kynurenine. Kynurenine is raised in the plasma of depressed suicide attempters [17], and, following entry into the brain, it is converted into several metabolites with potent neuropsychiatric effects [18]. Meanwhile peripheral TNF somehow drives brain microglia to secrete chemokine (C-C motif) ligand 2 (CCL2; also referred to as monocyte chemoattractant protein 1 (MCP1), which attracts monocytes into the brain [19].

Against this background we now consider how microbial exposures, including environmental microbial exposures, influence the regulation of our immune systems in the context of the effects of inflammation on CNS function.

The “Old Friends” hypothesis and mental health

The epidemic of inflammatory disease, including allergy and asthma, in modern urban societies is increasing dramatically, but underlying biological mechanisms are still unexplained. The hygiene or “Old Friends” hypothesis proposes that this epidemic is due at least in part to reduced exposure to environmental microorganisms that normally prime immunoregulatory circuits and suppress inappropriate inflammation [20]. We and others have proposed that reduced exposure to these old friends in modern urban societies may increase vulnerability to neurodevelopmental disorders (including autism spectrum disorder (ASD), schizophrenia), and stress-related psychiatric disorders such as anxiety and mood disorders [21-38]. Exaggerated inflammation is emerging as an important risk factor in all of these disorders [21-38]. Immunoregulation, measured as a balanced expansion of effector T cell (also called helper T (Th) cell) populations and regulatory T cells (Treg), is known to be driven by microbial signals. These signals originate mainly from organisms with which mammals co-evolved, including: 1) the symbiotic microbiota residing in the cutaneous and mucosal surfaces (e.g., surfaces of the upper airways, lungs, and gastrointestinal tract); 2) pathogens associated with the “Old Infections” (for example, helminths) that were present throughout life in evolving human hunter-gatherer populations; and 3) organisms from the natural environment with which humans were inevitably in daily contact through inhalation or ingestion (and so had to be tolerated by the immune system) [25]. Immunoregulation is thought to be compromised in developed countries because of reduced contact with these three categories of organisms that are necessary for regulation, in the same way that removal

of other reliably experienced developmental resources such as sunlight or vitamins cause a range of physiological problems [25]. Here we explore our rapidly expanding understanding of the potential role for compromised immunoregulation in allergies, neurodevelopmental disorders, and stress-related psychiatric disorders, and the diverse mechanisms through which exposure to the old friends may increase immunoregulation and suppress inappropriate inflammation.

Comorbidity of allergy, anxiety, and affective disorders

The hygiene hypothesis originated in epidemiologic studies of allergy. As originally envisaged by Strachan [39], the hygiene hypothesis proposed that lower incidence of infection in early childhood could be an explanation for the rapid rise in allergic diseases, such as asthma and hay fever, documented during the 20th century. Allergic or atopic disorders including allergic rhinitis, allergic asthma, eczema, and food allergies are prevalent and potentially disabling conditions [40]. These disorders are all increasing in prevalence in developed countries [40]. The “Old Friends” hypothesis was proposed to emphasize that we no longer believe that exposure to childhood infections or outright pathogens *per se* is beneficial but rather that lack of exposure to symbiotic organisms, as well as the “Old Infections”, is harmful [20]. Indeed, hygiene is important for prevention of serious infections. Epidemiological and clinical studies report a high incidence of anxiety and increased levels of emotional reactivity in individuals suffering from allergies [41-46]. This comorbidity is evidenced by the fact that the incidence of anxiety disorders among individuals with allergies is more than double with respect to the general population [41;44;47;48]. Moreover, studies in mice report that intranasal (i.n.) or aerosolized allergen exposure in sensitized animals results in the activation of limbic brain regions and anxiety-like behavioral responses [49;50]. While these studies have not quantified normalized antigenic exposures from airborne allergens, they suggest a strong association between allergy and anxiety disorders, consistent with a potential role for inadequate immunoregulation and exaggerated inflammation in both conditions.

Inadequate immunoregulation as a risk factor for neurodevelopmental and neuropsychiatric disorders

Results from animal models and clinical studies are consistent with the idea that inadequate immunoregulation increases risk for development of neurodevelopmental disorders, including ASD [51-54]. Elevated serum levels of the proinflammatory cytokine, interleukin (interleukin)-17A (IL-17A, produced by IL-17-expressing T cells, called Th17 cells, as well as a number of families of innate lymphoid cells (ILCs)) [55], have been noted in children with autism and were furthermore associated with symptom severity [53]. Th17 cells are involved in infection, autoimmunity, and inflammation, especially in skin or mucosal surfaces of the lungs and gut [56;57]. A Th17 bias may emerge during fetal development, as recent studies in mice have shown that maternal retinoic acid receptor–related orphan nuclear receptor γt (RORγt)–dependent Th17 cells and IL-17A mediate abnormal cortical development and an autism-like phenotype of offspring in a maternal immune activation model [51].

Importantly, for the thesis of this review, recent studies have demonstrated that the gut microbiota has the capacity to induce a specific population of Treg, the RORγt$^+$ subset of Treg [58;59]. Loss of RORγ$^+$ (there are two isoforms of RORγ, RORγt and RORγ) Tregs results in enhanced production of interleukin 17 (IL-17) and interferon-γ in the colons of otherwise unchallenged mice, and increases in chemically-induced colitis, indicating a decreased ability of colonic Tregs lacking RORγ to regulate inflammatory responses [58]. In germ-free mice, introduction of specific bacterial species are sufficient to increase RORγ$^+$ Tregs to levels observed in their conventionally raised specific pathogen-free counterparts [58]. Thus, Choi and colleagues [51] argue that therapeutic targeting of Th17 cells in vulnerable pregnant mothers may reduce the risk of bearing children with inflammation-dependent ASD-like phenotypes, and specific immunoregulatory bacteria have the ability to shift the balance of RORγ$^+$ T cells from a Th17 to a Treg bias. A window of vulnerability may coincide with a predicted window of time during the late second trimester and early third trimester associated with increased risk of autism following maternal infections [60], maternal exposures to stressors [61], and maternal exposures to environmental pollutants [62]. This time frame coincides with a critical window of Treg development in the fetus, including the emergence, seeding, and expansion of Treg populations and Th17 cells (from 12 weeks of gestation until early postnatal development, with some continued development out to 2 years of age) [63]. Together with the finding that maternal stress is associated with an infant microbiota with a biological signature of increased potential for inflammation [64], immunoregulatory or antiinflammatory approaches may have value for both prevention and treatment of ASD. Consistent with this hypothesis, treatment with the antiinflammatory flavonoid, luteolin, results in a significant improvement in functioning in children with ASD [65], in association with decreases in plasma concentrations of biomarkers of inflammation [66].

Alterations in T cell number and function have also consistently been detected in patients with schizophrenia [67]. Researchers have subsequently proposed that maternal immune activation, induced by intrauterine infection and additional factors, could facilitate the preferential generation of Th17 cells and subsequent priming of neuroinflammatory processes, ultimately contributing to the neuroprogression in schizophrenia [68]. A meta-analysis found that treatment with nonsteroidal antiinflammatory drugs (NSAID) could be a potential treatment strategy to reduce symptom severity in schizophrenia [69]. Recent non-human primate studies using 1st and 2nd trimester infection with a viral mimic of double stranded RNA have demonstrated behavioral abnormalities in offspring resembling both ASD and schizophrenia [70;71]. Further, abnormal neuronal dendritic formations were characterized in association with the behavioral changes observed in the non-human primate model of maternal immune activation [72], suggesting developmental changes in offspring associated with inadequate immunoregulation during pregnancy. Thus, an argument can be made supporting a role for inflammatory insults, particularly Th17-driven inflammation in the skin or mucosal surfaces of the lungs and gut, as risk factors for neurodevelopmental and neuropsychiatric disorders. Furthermore, an argument can be made that prophylactic exposure of the mother to Treg-promoting and Th17-reducing commensal or environmental bacteria may reduce that risk.

Inadequate immunoregulation as a risk factor for stress-related mental health disorders

Human and animal studies are consistent with the hypothesis that inadequate immunoregulation increases risk for development of stress-related psychiatric disorders [25;73;74]. That is, chronic low-grade inflammation (a potential consequence of chronic infection, psychosocial stress, trauma, exposure to environmental pollutants or toxins, autoimmune processes, chronic allergy) is associated with increased risk for mental disorders [75;76]. In prospective studies, high baseline plasma concentration of C-reactive protein (CRP; an acute-phase protein and pattern recognition receptor that is induced in response to inflammation), measured before deployment in military personnel, was associated with increased likelihood of posttraumatic stress disorder (PTSD) symptoms after deployment, suggesting that inflammation before trauma exposure may predispose individuals to PTSD symptoms [73]. Similar findings were evident in a gene expression study in soldiers pre- and post-deployment (Breen et al. 2015), where results indicated that genes involved in networks of innate immunity and interferon signalling are overexpressed in PTSD cases pre-deployment, suggesting causality (Breen et al., 2015). Furthermore, increased circulating levels of the proinflammatory cytokine IL-6 immediately following trauma exposure predict the later development of PTSD symptoms [77]. Although not confirmed in all studies, low-grade inflammation has been associated with PTSD, as indicated by elevated serum CRP, IL-1β, and IL-6 [78-80]. Moreover, patients with PTSD show enhanced spontaneous secretion of IL-1β, IL-6 and tumor necrosis factor (TNF) by isolated peripheral blood mononuclear cells, which correlates with symptom severity [81;82]. Consistent with these findings, subjects with PTSD also have higher risk for autoimmune disease, including inflammatory bowel disease and rheumatoid arthritis [83], while genome-wide association studies in PTSD cohorts have revealed association with *ANKRD55* [84], a gene associated with several autoimmune and inflammatory disorders, including multiple sclerosis [85;86], type 2 diabetes mellitus [87], celiac disease [88], and rheumatoid arthritis [89].

Similar findings have been documented for developing depressive symptoms. For example, a study of over 3,000 individuals showed that elevated baseline plasma CRP or IL-6 predicted cognitive symptoms of depression measured 12 years later [90]. Moreover, in a study published early in 2014, elevated plasma concentrations of IL-6 in 9-year old children predicted depressive symptoms measured at age 18 [91]. Therefore, it is reasonable that exposures to immunoregulatory or antiinflammatory bacteria may be useful for the prevention or treatment of symptoms of PTSD or major depression. Consistent with this hypothesis, the glucocorticoid antiinflammatory hydrocortisone decreases the risk of subsequent PTSD if administered immediately after trauma exposure [92]. Furthermore, treatment of depressed patients with standard antidepressants plus an antiinflammatory compound was reported to decrease depressive symptoms more than antidepressants with a placebo [11;93].

“Old Friends” with immunoregulatory potential

The previous paragraphs show how anxiety and affective disorders are comorbid with chronic inflammatory conditions, and are epidemiologically linked to persistent

inflammation, even in the absence of any clinically apparent inflammatory condition. The latter situation is evidence of failing immunoregulation. Similarly, we also described how failing immunoregulation during pregnancy, in animals and humans, can lead to neurodevelopmental problems in the fetus mediated by excessive inflammation. We now discuss, within each of the microbiological categories that constitute the old friends, the organisms that have been shown to have immunoregulatory properties that might be exploited for prevention of, or as therapies for, psychiatric conditions.

Commensal or mutualistic microorganisms with immunoregulatory potential

Much of the focus on the interface between the human microbiome and potential positive human health outcomes has been put on commensal or mutualistic organisms, particularly those associated with the gut microbiome. Two recent studies have shed light on the potential for commensal gut microorganisms to influence immunoregulatory circuits [58;59]. These two studies demonstrated that the gut microbiota induces expansion of a specific subset of cells, known as the RORγt$^+$ Treg in the lamina propria of the gastrointestinal tract. They then used chemical inhibitors and genetic manipulation to block the function of these Treg, and demonstrated that they have broad antiinflammatory effects in several models of colitis. They also noted that this cell type is severely depleted in germ-free or antibiotic-treated mice [58;59]. However, reconstituting the gut microbiota could restore expansion of these Treg. Importantly, oral administration of a single microbial species was sufficient to increase the frequency of RORγt$^+$ Treg within the colon of germ-free mice, in some cases to levels observed in specific-pathogen-free control mice, which have a typical microbiota. Commensal bacteria that increase RORγt$^+$ Treg include several species belonging to the phylum Firmicutes, a phylum with a large number of probiotic species, to include Clostridium histolyticum, C. ramosum, Enterococcus faecium, Lactobacillus casei, L. rhamnosus, and *Staphylococcus saprophyticus*. However, species from other phyla were also effective, including *Bifidobacterium breve* (Actinobacteria), *Bacteroides thetaiotaomicron* and *Parabacteroides johnsonii* (Bacteroidetes), *Fusobacterium mortiferum*, and *F. nucleatum* (Fusobacteria), and *Acinetobacteria lwoffi* (Proteobacteria). As mentioned above, loss of RORγ^+ Tregs results in enhanced production of colonic IL-17 and interferon-γ and increases in chemically-induced colitis, indicating a decreased ability of colonic Tregs lacking RORγ to regulate inflammatory responses [58]. Thus, commensal bacteria from diverse phyla have the capacity to induce Treg (Table 1). Many of these same probiotic species have been shown to have stress-protective and mental health benefits in rodent and human studies (Table 1). The mechanisms through which bacteria from such diverse phyla can induce immunoregulatory pathways are not clear, but a number of candidate mechanisms are discussed below.

"Old Infections" with immunoregulatory potential

A number of "Old Infections" can induce immunoregulation. For example, humans co-evolved with *Helicobacter pylori* for tens of thousands of years. *H. pylori* is found in higher abundance in rural Papua New Guineans [94] and was recently found in previously uncontacted Amazonian Amerindians [95], as well as in the 5300-year old Iceman [96]. *H. pylori* is potently immunoregulatory, and consequently has protective effects in allergy and chronic inflammatory disorders [97;98]. Additional "Old Infections" include hepatitis A

virus (HAV), *Toxoplasma gondii* (*T. gondii*), *Salmonella*, gut helminths and blood nematodes, and *Mycobacterium tuberculosis* [6;99]. A common feature of many of these "Old Infections" is that they bind the C-type lectin receptor, dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN; also referred to as cluster of differentiation 209 (CD209)) on dendritic cells (DC), in many cases using the receptor to gain entry into immune cells and subvert the host immune response [100-105]. Interactions between "Old Infections" and DC-SIGN can induce immunoregulatory responses [101;104], and the central feature of pathogens that can interact with DC-SIGN is that they cause chronic infections that can last a lifetime, persistence that is often dependent on a suppression of Th1 and concomitant shift to Th2 immunity [103].

Environmental microorganisms with immunoregulatory potential

In addition to commensal and mutualistic microorganisms and the "Old Infections", environmental microorganisms also induce immunoregulation following ingestion [106] or inhalation [107;108]. These organisms have been referred to as "pseudocommensals" because they would have been present in large numbers throughout mammalian evolution, even if they do not colonize the gut [20;109]. Our understanding of the "Old Friends" hypothesis has been informed by studies using heat-inactivated and viable environmental bacteria, particularly soil-derived bacteria belonging to the genus *Mycobacterium*, which can be viewed as a case study of the potential for environmental microorganisms to influence immunoregulatory circuits and prevent inflammatory disease [110]. While it has long been believed that mycobacteria are not normally present in the human microbiome or the built environment in developed countries, recent studies reveal that a broad spectrum of *Mycobacteria spp.* are systemic residents of operating metropolitan water distribution systems [111;112]. To what extent these and other microbes impact humans through common infrastructure exposures, however, remains unknown. Another recent study has defined the hidden 'non-tuberculous mycobacteriome', with approximately 50 prevalent and abundant mycobacterial operational taxonomic units, in the nostrils, buccal mucosa, oropharynx, and dental plaque of healthy subjects [113], a distribution that may reflect the environmental origin of these microorganisms. Together, (1) disruption of the commensal microbes, (2) a reduction in "Old Infections", and (3) diminished contact with immunoregulatory environmental microbes have the potential to increase vulnerability to allergic and inflammatory disorders, as well as mental health disorders, where chronic inflammation is emerging as an associated risk factor.

Diverse molecular mechanisms through which "Old Friends" induce antiinflammatory and immunoregulatory effects

Bacterially derived metabolites that induce immunoregulatory responses

Tryptophan and bacterially- and host-derived tryptophan metabolites—

Evidence suggests that commensal bacteria are important for the extraction, synthesis or absorption of some amino acids, including tryptophan. In particular, plasma tryptophan and N-acetyltryptophan concentrations in conventionally reared mice are 40% and 60% lower, respectively, compared to germ-free mice [114], suggesting that the gut microbiota plays an

important role in metabolism of tryptophan. A subset of enteric bacteria expresses tryptophanase, which converts tryptophan to indole, pyruvate, and ammonia. Meanwhile, it is becoming increasingly clear that tryptophan and diverse tryptophan metabolites (both bacterially-derived and host-derived) have immunomodulatory effects. Tryptophan influences proliferation of T cells by regulating passage through the gap 1 (G1) phase of the cell cycle [115]. Tryptophan depletion, secondary to activation of indoleamine-2,3-dioxygenase, regulates immune tolerance of the fetus and regulates immune responses in models of skin allograft rejection, tumor growth and autoimmune encephalomyelitis [116] and chemically-induced colitis [117]. The tryptophan metabolite melatonin induces Treg via actions on melatonin receptors (MT_1) [118]. Interactions between bacterially-driven and host-driven tryptophan metabolism are important for host defense. For example, $CD4^+$ T cells defend against certain pathogens, including *Chlamydia* and *Leishmania*, by starving the pathogens of tryptophan. In those cases, tryptophan starvation works well, since those pathogens are natural tryptophan auxotrophs (lack the ability to synthesize tryptophan). *Mycobacterium tuberculosis*, on the other hand, is capable of synthesizing tryptophan, and it is protected from this mechanism of host defense; a small molecule inhibitor of *M. tuberculosis* tryptophan synthesis turns *M. tuberculosis* into an auxotroph and restores the efficacy of host-mediated tryptophan depletion [119]. Perhaps just as important, even probiotic species such as *Lactobacillus* spp. are capable of tryptophan biosynthesis and metabolism and generate tryptophan metabolites that activate the aryl hydrocarbon receptor (Ahr), resulting in immunoregulation and mucosal protection from damage [120]. Immunoregulatory bacterially-derived tryptophan metabolites that serve as Ahr agonists include tryptamine, indol-3-acetaldehyde, indole-3-acetic acid, indole-3-aldehyde, and kynurenine [120]. Other bacterially derived tryptophan metabolites that interact with Ahr include indole, 3-methyl-indole, indoxyl sulfate, 6-formylindolo[3,2b] carbazole, and kynurenic acid [121]. Activation of Ahr can either induce functional Treg cells that suppress inflammation, or enhance Th17 cell differentiation and increase inflammation, depending on the specific nature of the agonist [122;123]. Specifically, Ahr induces $ROR\gamma t^+$ Tregs [124], consistent with studies discussed above demonstrating that specific species within the gut microbiota can induce $ROR\gamma t^+$ Tregs and mucosal immune tolerance [58;59]. Thus, the microbiota, acting via synthesis of tryptophan and generation of tryptophan metabolites that interact with Ahr, regulates both Treg and Th17 cell differentiation in a ligand-specific fashion, constituting a unique target for therapeutic immunomodulation.

Short chain fatty acids (SCFAs)—Short chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are produced by bacteria in the gut during fermentation of insoluble fiber from dietary plant matter [125]. SCFAs support the growth of probiotic *Bifidobacterium* and *Lactobacillus* species. Furthermore, SCFAs have antiinflammatory effects by regulating the release of cytokines and chemokines from immune cells [126-128]. Of particular importance, propionate and acetate can directly induce colonic Tregs and their suppressive capacity via activation of G protein coupled receptor (GPCR) 43, encoded by the free fatty acid receptor 2 gene (*Ffar2*) [129;130]. This is one of the primary routes by which *Clostridia* affect Treg populations [131]. Furthermore, butyrate, which is also a metabolite of *Clostridia* species, potentiates DCs to induce Treg through inhibition of histone deacetylase (HDAC) and may induce epigenetic changes [131].

Microbial molecules that induce immunoregulatory responses

A number of bacterial antigens have been identified that increase immunoregulatory circuits, predominantly by interactions with the pattern recognition receptor (PRR) DC-SIGN on DCs. DC-SIGN ligation interferes with toll-like receptor-mediated inflammatory responses, resulting in decreases in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, decreases in IL-6, TNF, and IL-12, concurrently with increases in IL-10 [101]. Activation of DC-SIGN in DCs may be a common mechanism through which bacterial antigens derived from the old friends bias T cell differentiation toward a Treg phenotype (Table 1). Examples of such molecules, together with their sources, receptors and mode of action are listed in Table 2.

Other immunoregulatory molecules from "Old Infections"—In addition to the heterogeneous group of molecules described above there is mounting interest in microbial products that imitate the Lewis^X trisaccharide motif (Figure 1).

Lewis-X$^+$lipopolysaccharide (LPS)—The lipopolysaccharide (LPS) Lewis (Le) antigens of *H. pylori* are able to bind DC-SIGN in gastric DCs and block Th1 development [103;104]. Conversely, Le$^-$ *H. pylori* induce strong Th1 responses [103;104]. Although the specific mechanisms are not clear, *H. pylori* potently drives Treg responses [98].

Helminthic parasite antigens—The Lewis-X$^+$ soluble egg antigen (SEA) from the helminthic parasite *Shistosoma mansoni* binds DC-SIGN and induces expansion of Th2 and Treg responses [103;132]. Sole Th2 antiinflammatory immunomodulators apparently emerged when metazoan parasites invaded vertebrates. Indeed, Th2 immunity may have been developed as a repair response to tissue and organ damage resulting from inflammatory processes directed towards relatively large parasites like helminths [133]. Hence, to prevent an inflammatory Th1 immunity, parasitic helminths produced compounds that mimic those that the host makes to avert inflammatory responses that would interfere with tissue healing or cause fetal rejection in mammals; agents that besides inducing Th2, inhibit, but do not abrogate, Th1 immunity [134]. The main family of helminth-derived immunomodulators contains as a pharmacophore the sugar fucose (Fuc); these immunomodulators, which are glycans, structurally and functionally imitate the Lewis^X trisaccharide motif, like lacto-N-fucopentaose III (LNFPIII), a Lewis^X-containing immunomodulatory glycan found in human milk [135;136] and SEA from *S. mansoni* (Fig. 1 A,B). The sugar Fuc is rare in both vertebrates and bacteria and is involved in ontogenesis and some immunological functions, like acting as a Th2 immune modulator. The success of the immunological mimicry developed by helminths is shown by the long-term relationship between the parasite and its host. Fucosylated glycans exert their sole Th2 immune modulatory effects by binding to DC-SIGN, which binds oligosaccharides carrying either mannosyl or fucosyl residues [137]. Any inflammation induced by parasite infection must be tightly regulated and evidence suggests that this function is mediated by induction of Treg by diverse parasites [138].

Membranous cells (M cells) transfer intact gut microorganisms from the bronchopulmonary and intestinal lumens and present them to antigen presenting cells

In order for bacterial antigens, such as the glycans described above, to influence DC function and induce immunoregulatory responses, it is necessary for the bacteria to have direct contact with antigen presenting cells, raising the question of how bacteria in the airways or gastrointestinal tract come into direct contact with these cells. Antigen presenting cells, e.g. alveolar macrophages and $CD11c^+$ DCs, are common in the airways [139], but host mechanisms also ensure that microorganisms in both the airways and gastrointestinal tract can be transferred from the airway or gastrointestinal tract lumen into the body for presentation to antigen-presenting cells. This function is performed in part by microfold or membranous cells (M cells), which are found in both the airways and gastrointestinal tract. M cells in the airways have been documented as entry sites for *M. tuberculosis* in mice [140]. Similar reports have been made for M cell recognition of mycobacteria in the gastrointestinal tract. Regarding studies involving oral inoculation with mycobacteria, Fujimura wrote that in "1-hour post-inoculated specimens, bacteria were found adhering specifically to M cells, and the microfolds of the M cells were seen to stretch like tentacles toward the bacteria and to catch them." [141]. Mycobacteria are translocated into M cells, and are subsequently presented to mucosal macrophages and DCs [141]. Although we have focused primarily on the mucosal membranes of the airways and gastrointestinal tract, evidence suggests an important dialogue between the skin microbiota and immune function as well, which should be explored further [142-144].

Antiinflammatory and immunoregulatory interventions

Anti-inflammatory agents such as inhibitors of cycloxygenase, or a neutralizing antibody to TNF are significantly therapeutic in those patients who have raised inflammatory biomarkers [10;11]. Can we therefore exploit the anti-inflammatory properties of immunoregulation-inducing microorganisms? Extensive investigation of animal models has shown that administration of immunoregulatory probiotics and some other manipulations of the microbiota have profound effects on the development and function of the brain. This work has been reviewed recently and will not be described here [145;146], though examples where microbial agents were used in therapeutic models are given in Table 1. Human studies are rare, but there is direct evidence that large doses of probiotics can modulate the human brain. Women were given a milk product fermented with a complex mixture of probiotics twice daily for 4 weeks [147]. Magnetic resonance imaging was used before and after the intervention to measure resting brain activity and the brain response to images of emotional faces. Compared to subjects who had not taken the probiotic, changes in the intrinsic activity of resting brain and in the emotional response were demonstrated [147]. In another randomized, double-blind, placebo-controlled study it was found that when normal volunteers consumed a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) for 30 days, anxiolytic effects were detected by several validated questionnaires [148]. In a very recent study, *Clostridium butyricum* or placebo were administered orally every morning and evening from 2 weeks before laryngectomy. Hamilton anxiety scores of placebo recipients increased as the surgery approached, but these scores decreased in those taking the probiotic [149]. Finally, recent studies in humans

demonstrate that administration of the immunoregulatory probiotic, *Lactobacillus casei*, for 8 weeks reduced gastrointestinal symptoms and decreased perceived stress in medical students preparing for a standardized exam [150].

However, as we make clear in this review, orally ingested probiotics are not the only possible approach. An environmental soil saprophyte already known to induce Treg in mice [24] was tried as an immunotherapeutic in a human cancer trial [151]. While there was no prolongation of survival it was noted that immunotherapy recipients had improved cognitive functioning and emotional health [151]. More recently the same organism, administered subcutaneously as a killed preparation, has been tested in an animal model where exposure to chronic psychosocial stress induces expansion of *Helicobacter* spp. [152], pathobionts, that are known to induce colitis in individuals with inadequate immunoregulation [153;154]. Pre-immunisation with the environmental saprophyte blocked stress-induced colitis, blocked stress-induced exaggeration of chemically-induced colitis, and reduced anxiety-related behaviors in stressed mice. Remarkably, these effects were dependent upon the induction of Treg [152].

Conclusions

Exaggerated inflammation is emerging as a risk factor for neurodevelopmental and neuropsychiatric disorders, such as ASD and schizophrenia, and stress-related psychiatric disorders, including PTSD and major depression. Antiinflammatory interventions have shown some promise in treating these conditions. Meanwhile, there is increasing evidence that the microbiota associated with mucosal membranes in the airways and gastrointestinal tract have potential for antiinflammatory and long-term immunoregulatory effects on the host immune system. Thus, bioimmunomodulatory approaches hold promise for the prevention and treatment of these disorders. Here we have highlighted the potential mechanisms through which the microbiota, including microbial inputs from the environment, may elicit antiinflammatory and immunoregulatory responses. The evidence suggests that both bacterial metabolites and bacterial and helminthic antigens have potential for antiinflammatory and immunoregulatory effects that may have value in the prevention and/or treatment of neurodevelopmental, neuropsychiatric, and stress-related mental health disorders.

Acknowledgments

Effort undertaken during the preparation of this review was sponsored by the Department of the Navy, Office of Naval Research Multidisciplinary University Research Initiative (MURI) Award, Award No. N00014-15-1-2809.

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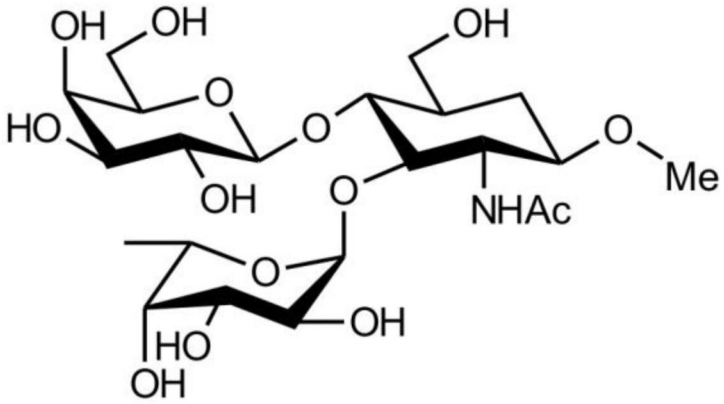
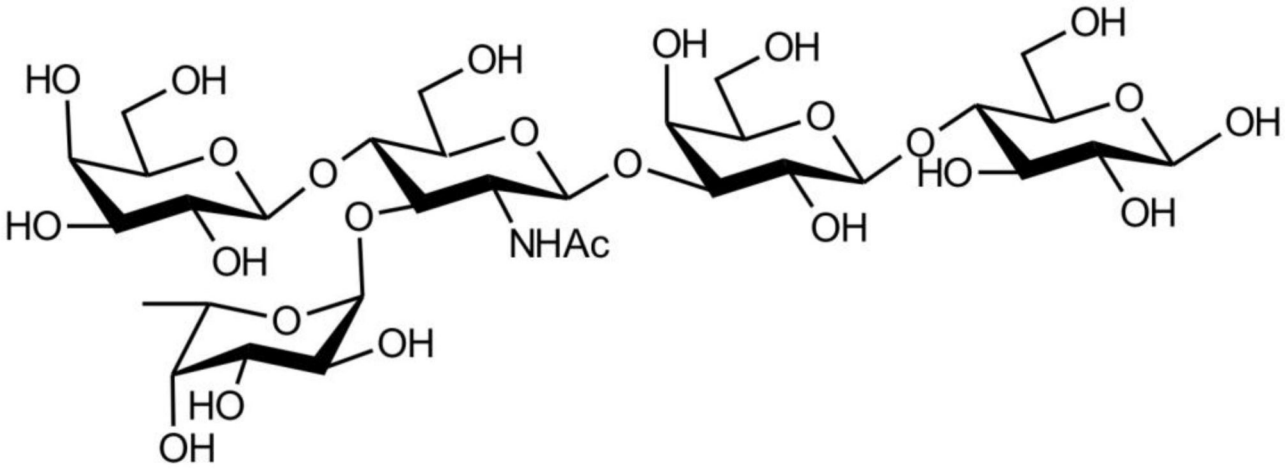


A. Lewis X trisaccharide



B. Lacto-N-fucopentaose III (LNFPIII)

Figure 1.
Structures of the Lewis^X trisaccharide motif and its helminth-derived analogue lacto-n-fucopentaose III (LNFPIII).

Table 1
Immunoregulatory microorganisms with beneficial effects in mental health studies

Phylum/ Microorganism	Model	Environmental Sources	Mental health relevant findings	Immunoregulation
Actinobacteria				
Mycobacterium vaccae	Human	Environmental saprophyte (soil, mud, water, grasses, decaying organic matter) [155-161]	Increased cognitive function, decreased pain in patients with advanced non-small-cell lung cancer [151]	↑DCreg [162]
	Mouse		Activation of brain serotonergic systems and antidepressant-like behavioral effects [163]; decreased anxiety/increased cognitive function [164]	↑Treg [110]
			Promotion of proactive behavioral responses to psychosocial stress; prevention of stress-induced colitis and stress-induced exaggeration of chemically-induced colitis; reduction of anxiety-like behavior in stressed mice [152]	
Bifidobacterium breve	Mouse	Human commensal	Increased cognitive function [165]; decreased anxiety-related behaviors [166]	↑*Rorγ*+ Helios^{-} Treg [58]
Bifidobacterium infantis	Rat	Human commensal	Reversal of depressive-like behavior following maternal separation [167]	↑Treg [168]
Bifidobacterium longum	Human	Human commensal	Decreased anxiety and depressive symptoms in healthy volunteers (administered with *L. helveticus*) [148;169]	
	Mouse		Decreased-colitis associated anxiety [170;171]; increased cognitive function (1714) [165]; decreased stress, anxiety- and depression-related behaviors [166]	↑Treg and functional Treg responses [172]
Bacteroidetes				
Bacteroides fragilis	Mouse	Human commensal	Developmental protection from some of the behavioral symptoms associated with Autism Spectrum Disorder [54]	↑Treg [173]
Firmicutes				
Clostridium butyricum	Human	Endospore-forming soil bacterium	Anxiolytic effects [149]	
Enterococcus faecium	Mouse	Human commensal, wetlands [174]	Increased brain antioxidant markers [175]	

Phylum/ Microorganism	Model	Environmental Sources	Mental health relevant findings	Immunoregulation
Lactobacillus casei	Human	Human commensal, fermented foods [176]	Improvement in anxiety symptoms in patients with chronic fatigue syndrome [177]; improved mood [178]	↑*Rorγ*+ Helios⁻ Treg [58]
			Decreased perceived stress in medical students preparing for a nationwide exam [150]	
Lactobacillus fermentum	Rat	Human commensal, raw vegetables [179], fermented foods [176;180]	Decreased anxiety and inhibition of antibiotic-induced cognitive impairment [181]	↑Treg [182]
Lactobacillus helveticus	Human	Fermented foods [176]	Decreased anxiety and depressive symptoms in healthy volunteers (administered with *B. longum*) [148;169]; increased cognitive function (IDCC3801) [183]	
	Rat		Improved cognitive function, decreased anxiety-related behavior [184]; prevention of stress-induced cognitive impairment and anxiety- and depressive-like responses [185]	
	Mouse		Decreased anxiety-related behavior [186]; improved cognitive function, decreased anxiety-related behavior (administered with *L. rhamnosus*) [187;188]	↑Treg (with *L. rhamnosus* [189]
Lactobacillus pentosus	Mouse	Fermented foods [176]	Improved cognitive function [190]	
Lactobacillus reuteri	Human	Human commensal, fermented foods [176]	Increased workplace healthiness [191]	↑Treg [192]
Lactobacillus rhamnosus	Mouse	Human commensal, fermented foods [176]	Vagus nerve dependent alterations in GABA receptor mRNA expression in brain, reduced anxiety- and depression-related behavior[193]; improved cognitive function, decreased anxiety-related behavior (administered with *L. helveticus*) [187;188]	↑*Rorγ*+ Helios⁻ Treg [58]; ↑Treg (with *L. helveticus*) [189]

Immunoregulatory probiotics that induce Rorγ^{+}Helios^{-} Tregs, but have not been tested in the context of mental health, *F. mortiferum, A. lwoffii, L. casei, E. faecium, F. nucleatum, P. johnsonii, L. rhamnosus, C. histolyticum, B. thetaiotaomicron, S. saprophyticus, C. ramosum* [58].

Adapted from Hoisington et al. [31], with permission.

Table 2
Microbial molecules that induced immunoregulatory responses

Molecule	Source	Receptor	Actions
Polysaccharide A (PSA)	*Bacteroides fragilis*	Unclear in mice, DC-SIGN on human DC [194]	Expands Treg population [195]
Surface layer protein A (SlpA)	*Lactobacillus acidophilus*	DC-SIGN	More IL-10 and less IL-12 p70 [196]
Mannose-capped lipoarabinomannan	*Mycobacterium tuberculosis*	mannose receptor (MR), dectin-2, DC-SIGN, TLR2 [101;197;198]	Expansion of Treg through a prostaglandin E2-dependent mechanism [199]
60 kDa chaperonin-1 (Cpn60.1); Heat shock 60 kDa protein (Hsp60)	*M. tuberculosis* & homologous molecules from microbiota [200]	DC-SIGN, TLR2 and others?	Expand Treg [201-204]
DnaK; also known as Hsp70, GroP, GrpF, Seg	*M. tuberculosis* & homologous molecules from microbiota	DC-SIGN and others? [200]	Drive immunoregulatory pathways? [204]
Glyceraldehyde-3 phosphate dehydrogenase (GAPDH)	Mycobacteria and homologous molecules from microbiota [205]	DC-SIGN [200]	Reduce proinflammatory cytokines and chemokines [206]
Lipoarabinomannan carrier protein LprG	*M. tuberculosis*	DC-SIGN [200]	Binds to triacylated glycolipids and increases their agonist activity at TLR2 [101;207]
Lewis-X^+ lipopolysaccharide (LPS)	*Helicobacter pylori*	DC-SIGN [103;104]	Drives Treg responses [98].
Lewis-X^+ soluble egg antigen (SEA)	*Schistosoma mansoni*	DC-SIGN [137]	Drive expansion of Th2 and Treg responses [103;132]