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Evolutionary Aspects of Diverse Microbial Exposures and Mental Health: Focus on "Old Friends" and Stress Resilience

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Abstract

The prevalence of inflammatory disease conditions, including allergies, asthma, and autoimmune disorders, increased during the latter half of the twentieth century, as societies transitioned from rural to urban lifestyles. A number of hypotheses have been put forward to explain the increasing prevalence of inflammatory disease in modern urban societies, including the hygiene hypothesis and the "Old Friends" hypothesis. In 2008, Rook and Lowry proposed, based on the evidence that increased inflammation was a risk factor for stress-related psychiatric disorders, that the hygiene hypothesis or "Old Friends" hypothesis may be relevant to psychiatric disorders. Since then, it has become more clear that chronic low-grade inflammation is a risk factor for stress-related psychiatric disorders, including anxiety disorders, mood disorders, and trauma- and stressor-related disorders, such as posttraumatic stress disorder (PTSD). Evidence now indicates that persons raised in modern urban environments without daily contact with pets, relative to persons raised in rural environments in proximity to farm animals, respond with

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greater systemic inflammation to psychosocial stress. Here we consider the possibility that increased inflammation in persons living in modern urban environments is due to a failure of immunoregulation, i.e., a balanced expression of regulatory and effector T cells, which is known to be dependent on microbial signals. We highlight evidence that microbial signals that can drive immunoregulation arise from phylogenetically diverse taxa but are strain specific. Finally, we highlight *Mycobacterium vaccae* NCTC 11659, a soil-derived bacterium with anti-inflammatory and immunoregulatory properties, as a case study of how single strains of bacteria might be used in a psychoneuroimmunologic approach for prevention and treatment of stress-related psychiatric disorders.

Keywords

Anxiety; Darwinian medicine; Depression; Gut-brain axis; Hygiene hypothesis; Microbiome; Microbiota; Microbiota-gut-brain axis; Old friends; Posttraumatic stress disorder

1 Introduction

In this chapter, we focus on the potential role of exposures to diverse microbial environments in promotion of stress resilience, particularly in the context of prevention and treatment of stress-related psychiatric disorders, including anxiety disorders, mood disorders, and trauma- and stressor-related disorders such as posttraumatic stress disorder (PTSD) (American Psychiatric Association 2013). One approach to prevention of stress-related mental health disorders is to *identify modifiable risk factors* (Insel and Scolnick 2006). In this review, we outline evidence supporting the hypothesis that: (1) inappropriate inflammation is a risk factor for the development and persistence of symptoms of stress-related psychiatric disorders; and (2) exposures to diverse microbial environments, including non-pathogenic bacteria found in nature, can induce anti-inflammatory and immunoregulatory responses and thus regulate the inflammatory response to day-to-day stressors and traumatic events, in turn promoting resilience to stress. A failure of immunoregulation, which is defined as a balanced expression of regulatory T cells (Treg) and effector T cells, may be involved in contributing to an overreactive inflammatory stress response thus predisposing individuals to the development of stress-related psychiatric disorders (Langgartner et al. 2018), particularly in urban environments with reduced exposures to diverse microbial environments (Böbel et al. 2018). Promoting stress resilience by increasing contact with microbial “Old Friends,” i.e., microorganisms with anti-inflammatory and immunoregulatory properties, may provide an alternative strategy for prevention and treatment of stress-related psychiatric disorders.

2 Global Incidence and Prevalence of Common Mental Health Disorders

Common mental health disorders include anxiety disorders, depressive disorders, and trauma- and stressor-related disorders, such as PTSD that are classified in ICD-10 as: “neurotic, stress-related and somatoform disorders” and “mood disorders” (Patel and Kleinman 2003; World Health Organization 1992; National Collaborating Centre for Mental Health (UK) 2011). Anxiety and mood disorders are the most prevalent forms of

common mental health disorders and substantially contribute to the global burden of disease (Whiteford et al. 2013). The World Health Organization surveyed mental health conditions in 2015 and found an estimated 3.6% of the global population was suffering from anxiety disorders and 4.4% of the global population was suffering from depression, with women being more likely to be affected by these disorders than men (World Health Organization 2017). Depression is ranked as the single largest contributor to global disability while anxiety disorders are ranked as the sixth largest contributor to global disability (World Health Organization 2017). Subsequent to the onset of the COVID-19 pandemic, the global prevalence and burden of anxiety and mood disorders has increased further, particularly among young persons, and again with a stronger impact on females (Santomauro et al. 2021).

While previously classified as an anxiety disorder, and thus included among the common mental health disorders, PTSD is now classified in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) as a trauma- and stressor-related disorder (American Psychiatric Association 2013). PTSD is particularly prevalent among military Veterans. Since October of 2001, approximately 2.7 million U.S. troops have been deployed in recent conflicts (Wenger et al. 2018). Findings suggest that approximately 20% of returning service members meet criteria for PTSD or associated mental health conditions (Tanielian et al. 2008). In the USA, many Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans are resistant to engaging in conventional mental health treatments (Kim et al. 2010; Kim et al. 2010), highlighting the importance of exploring alternative interventions (Williams et al. 2011). Moreover, a substantial proportion of individuals are not significantly helped by traditional treatments. Non-response rates in outcome studies for PTSD are often as high as 50% (Schottenbauer et al. 2008). Similar non-response rates have been described in non-military populations (Stein et al. 2006, 2009).

3 A Need for more Effective Therapies with a More Rapid Onset of Action

First-line psychotherapies for generalized anxiety disorder (GAD), as one example of an anxiety disorder, include cognitive behavioral therapy (CBT), cognitive therapy (CT), and applied relaxation, while first-line pharmacotherapies for GAD include selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) (Anxiety and Depression Association of America 2015). Meanwhile, first-line psychotherapies for major depressive disorder include psychotherapy, including CBT, interpersonal psychotherapy (IPT), and problem-solving therapy (PST), while first-line pharmacotherapies for major depressive disorder include SSRIs, SNRIs, bupropion, mirtazapine, and a number of newer agents (Anxiety and Depression Association of America 2020). However, several limitations affect the efficacy and feasibility of these treatments. These limitations include, but are not limited to, delayed onset of action, adverse effects that impair quality of life, relapse risk upon withdrawal, and non-adherence (Andrews et al. 2011; Freedman 2010; Li et al. 2012; Lin et al. 1995; Mathew et al. 2012; Papakostas and Fava 2009; Rush et al. 2006b).

First-line therapies for the treatment of PTSD are evidence-based cognitive behavioral psychotherapies, for example, CBT and eye movement desensitization and reprocessing

(EMDR) (Resick et al. 2017; Department of Veterans Affairs DoD 2017; American Psychological Association 2017; Watkins et al. 2018). These interventions are effective in reducing PTSD symptoms; however, not all persons respond with complete recovery (Steenkamp et al. 2020). For example, approximately two-thirds of US Veterans who complete these treatments continue to meet diagnostic criteria for PTSD (Steenkamp et al. 2020; Stein et al. 2006, 2009) and there are high dropout rates from first-line psychotherapies for PTSD (Kehle-Forbes et al. 2016; Steenkamp et al. 2020).

First-line pharmacotherapies for PTSD include SSRIs (Martin et al. 2021). Unfortunately, pharmacotherapies also have important shortcomings. Indeed, only about half of patients respond to SSRIs and more than a third of SSRI-treated patients fail to respond, do not reach full remission, or even develop SSRI resistance (Bernardy and Friedman 2015; Golden et al. 2002; Rush et al. 2006a; Kemp et al. 2008). Furthermore, most patients who initially respond to SSRI treatment fail to maintain therapeutic gains over time. In particular, Veterans affected by PTSD are generally resistant to SSRI therapy (Schnurr et al. 2007; Prigerson et al. 2001; Friedman et al. 2007).

4 A Need for Approaches to Increasing Stress Resilience: Strategies for Prevention of Common Mental Health Disorders

While it is important to pursue novel, fast acting interventions, including pharmacological interventions, for treatment of stress-related psychiatric disorders, there is also a need for novel approaches to *prevention* of these common mental health disorders (Insel and Scolnick 2006). When considering approaches to prevention of stress-related psychiatric disorders, one could argue that a reasonable strategy would be to target risk factors for these disorders, focusing on modifiable risk factors (Fig. 1). One factor that seems to increase risk of developing stress-related psychiatric disorders is chronic low-grade inflammation (Rohleder 2014). In the next section, we briefly consider the evidence that inappropriate or excessive inflammation is a risk factor for development of stress-related psychiatric disorders.

5 Inflammation as a Risk Factor for Common Mental Disorders

Increasing evidence suggests that inflammation plays an important role in determining risk of development of stress-related psychiatric disorders, including anxiety disorders, mood disorders, and trauma- and stressor-related disorders such as PTSD. A connection between increases in cytokine activation, low-grade background inflammation, and stress-related psychiatric disorders has been observed in numerous studies implying a role for chronic low-grade inflammation in both the risk of development of stress-related psychiatric disorders and the persistence of symptoms (Capuron and Dantzer 2003; Dantzer et al. 1998, 1999; Miller and Raison 2016; Michopoulos et al. 2017; Flux and Lowry 2023; Rohleder 2014).

5.1 Inflammation as a Risk Factor for Anxiety Disorders

Anxiety disorders such as GAD, panic disorder (PD), and phobias (agoraphobia, social phobia, etc.) have been shown to be associated with chronic low-grade inflammation. For example, heightened proinflammatory markers, such as C-reactive protein (CRP), have been

demonstrated in individuals diagnosed with anxiety disorders (Michopoulos et al. 2017; Vogelzangs et al. 2013; Copeland et al. 2012; Bankier et al. 2008). Other studies have found increased circulating proinflammatory cytokines, such as tumor necrosis factor (TNF), interleukin (IL) 1 beta, and IL-6 among individuals diagnosed with GAD and PD (Vieira et al. 2010; Hoge et al. 2009; Michopoulos et al. 2017; Brambilla et al. 1994; Zou et al. 2020). In line with these findings, there have been reports of high incidences of anxiety disorders and increased levels of emotional reactivity in individuals with inflammatory disease, including asthma, allergies, and autoimmune disorders (Lowry et al. 2016; Stanhope et al. 2022; von Mutius and Vercelli 2010; von Mutius et al. 1994). The weight of evidence is consistent with the hypothesis that inappropriate inflammation plays a role in determining risk of anxiety disorders (Haroon et al. 2012; Michopoulos et al. 2017).

Interestingly, lower levels of interferon gamma (IFNγ), a proinflammatory cytokine, have been found in both GAD and PD patients (Tukel et al. 2012; Vieira et al. 2010). Decreased IFNγ secretion from isolated peripheral blood mononuclear cells (PBMCs) from GAD patients could reflect decreased exposures to diverse microbial environments. For example, administration of the soil-derived bacterium, *Mycobacterium vaccae* NCTC 11659, or the type strain of *M. vaccae*, *M. vaccae* ATCC 15483, increases IFNγ and Th1 signaling in mice (Gong et al. 2020; Lahey et al. 2016; Smith et al. 2020; Zhang et al. 2016). Meanwhile, in humans, immunization with *Mycobacterium vaccae* NCTC 11659 increases IFNγ responses of PBMCs to subsequent antigen challenge up to a month following treatment (von Reyn et al. 2017). Interestingly, IFNγ expression, possibly arising from meningeal T cells then acting on both microglia and neurons in the brain, is necessary for social behavior (Filiano et al. 2016).

Consistent with a potential dysregulation of immunoregulation in individuals with anxiety disorders, lower phytohemagglutinin (PHA)-stimulated secretion of anti-inflammatory cytokines, including IL-2, IL-4, and IL-10 from isolated PBMCs have been documented in GAD patients (Vieira et al. 2010). Consistent with these findings, Hou et al. 2017 reported decreased circulating concentrations of IL-10, as well as higher TNF/IL-10 and TNF/IL-4 ratios (Hou et al. 2017). Altogether, data are consistent with the hypothesis that persons with a diagnosis of GAD have dysregulation of immunoregulation.

5.2 Inflammation as a Risk Factor for Mood Disorders

Among the common mental health disorders, the strongest case can be made for a role for inappropriate inflammation as a risk factor for development of mood disorders. This has been reviewed extensively elsewhere (Capuron and Dantzer 2003; Dantzer et al. 1998, 1999; Miller and Raison 2016; Michopoulos et al. 2017; Flux and Lowry 2023) and thus will not be reviewed in detail here.

Evidence supports impaired immunoregulation in persons with a diagnosis of mood disorders. Previous studies have demonstrated lower percentages of Treg in association with lower serum concentrations of the anti-inflammatory cytokines IL-10 and transforming growth factor beta 1 (TGFβ-1) in persons with major depressive disorder (Grosse et al. 2016; Li et al. 2010; Chen et al. 2011; Snijders et al. 2016) and increases in percentages of Treg following treatment (Grosse et al. 2016).

Based on the weight of existing evidence, induction of Treg has been proposed as one novel intervention for treatment of major depressive disorder, at least in the subset of patients with inflammatory MDD (Ellul et al. 2018).

5.3 Inflammation as a Risk Factor for Trauma and Stressor-Related Disorders

As mentioned above, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) recategorized PTSD into a new classification of "Trauma- and Stressor-Related Disorders." In this revision of the DSM, the main diagnostic criterion of this class requires a previous exposure to a traumatic or stressful event (American Psychiatric Association; 2013). The DSM-5 describes clusters of specific behavioral symptoms that accompany PTSD including "re-experiencing," "avoidance," "negative alterations in cognitions and mood," and "hypervigilance" (Reber et al. 2016; American Psychiatric Association 2013). PTSD affects 10–30% of individuals who have experienced a traumatic event (VanElzakker et al. 2014) with the greatest likelihood of PTSD occurring due to traumas involving interpersonal violence such as forms of assault, rape, or abuse (Yehuda and LeDoux 2007). According to the National Center for PTSD, about 6% of the population will experience PTSD at some point in their lives (National Center for PTSD 2022). About 8% of women develop PTSD sometime in their lives compared with about 4% of men (National Center for PTSD 2022). Approximately 60% of men and 50% of women experience at least one traumatic event throughout their lifetime (National Center for PTSD 2022). This suggests that there is an underlying vulnerability to developing PTSD that affects a percentage of the population.

Not everyone develops PTSD following a traumatic event; individual variability based on genetic, epigenetic, and environmental factors contributes to how susceptible an individual is to developing trauma- and stressor-related disorders (Reber et al. 2016; American Psychiatric Association 2013). While PTSD places a significant burden on the individual and society at large due to negative social and psychiatric consequences, it is also correlated with negative somatic consequences including autoimmune disorders, metabolic syndrome, pulmonary disease, and cardiovascular diseases that may be due to underlying mechanisms of low-grade systemic inflammation (Babson et al. 2015; Dennis et al. 2016; Lindqvist et al. 2014; Speer et al. 2018; Wolff et al. 2011). A transdiagnostic meta-analysis (i.e., a meta-analysis that quantitatively integrates the literature on the relationship of inflammatory biomarkers to trauma exposure and related symptomatology) found that trauma exposure was associated with increased circulating CRP and circulating proinflammatory cytokines, including IL-1β, IL-6, and TNF (Tursich et al. 2014), suggesting that trauma exposure may be causal for chronic low-grade inflammation. Conversely, studies indicate that increased biomarkers of inflammation, including increased circulating CRP concentrations, predict future risk of developing PTSD (Eraly et al. 2014; Schultebraucks et al. 2020). Finally, persons with a diagnosis of PTSD have a higher risk of developing an autoimmune disorder. Specifically, Veterans diagnosed with PTSD have a significantly higher risk for diagnosis with any of the autoimmune disorders alone or in combination (i.e., thyroiditis, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, and lupus) considered individually compared with Veterans with no psychiatric disorders (O'Donovan et al. 2014). This is suggestive of a broad failure of immunoregulation and an inability to suppress

inappropriate inflammation in Veterans with a diagnosis of PTSD. Consistent with these findings, those with a PTSD diagnosis have a decreased proportion of peripheral Treg cells (Sommershof et al. 2009), and Treg abundance can be increased following successful treatment using narrative exposure therapy (NET) (Morath et al. 2014).

Recent studies have demonstrated that persons with a diagnosis of PTSD, relative to healthy controls, have elevated circulating concentrations of lipopolysaccharide (LPS) and lipopolysaccharide-binding protein (LBP) (Voigt et al. 2022). LPS is a component of the outer membrane of gram-negative bacteria, while LBP is induced by prolonged elevation of LPS and is considered a biological marker of "leaky gut," a condition where bacteria and other microorganisms within the lumen of the gut can translocate across the gut mucosa into the body and systemic circulation. Together, these data are consistent with the hypothesis that PTSD is associated with a dysregulated microbiome-gut-brain axis (Hemmings et al. 2017; Loupy and Lowry 2019; Malan-Muller et al. 2018, 2022) and that comprehensive therapy would benefit from stabilizing the dysregulated microbiome and gut mucosal barrier.

6 The Increasing Incidence and Prevalence of Inflammatory Disease in Modern Urban Societies

In 2002, Jean-François Bach published an article in the *New England Journal of Medicine* reporting an alarming increase in the incidence of immune disorders in the 50-year period from 1950–2000 (Bach 2002). Included were increases in autoimmune disorders, including Crohn's disease (a form of inflammatory bowel disease (IBD), multiple sclerosis, and type 1 diabetes, as well as asthma, citing data from a number of contemporary original research articles (Pugliatti et al. 2001; Tuomilehto et al. 1999; Dubois et al. 1998; Farrokhyar et al. 2001). These historical trends are consistent with a gradient of the incidence of asthma and atopy based on rural vs. urban living, with, for example, the Amish (who maintain traditional farming practices, including use of large animals for farm work) having the lowest prevalence, Swiss farmers (who have adopted modern farming practices, including the use of tractors instead of animals for farm work) having intermediate levels of prevalence, and Swiss non-farmers having the highest prevalence (Holbreich et al. 2012). These differences have persisted in subsequent studies and mechanistic studies point toward an important role of innate immune signaling, leading the authors to conclude "These findings suggest that in the Amish, intense and presumably sustained exposure to microbes activates innate pathways that shape and calibrate downstream immune responses" (Stein et al. 2016).

7 Urban vs. Rural Upbringing and Mental Health

Although there are many potential confounds, meta-analysis suggests that individuals living in urban areas have an increased risk of developing any psychiatric disorder, and specifically an anxiety disorder or a mood disorder, relative to individuals living in rural areas (Peen et al. 2010; Stamper et al. 2016). This relationship led Böbel et al. (2018) to conduct a study to determine if differences were evident in inflammatory immune responses to a psychosocial stress exposure (the Trier Social Stress Test (TSST)) in healthy young persons that were either: (1) raised on a farm with farm animals for the first 15 years of life; or

(2) raised in a city in the absence of daily contact with animals. The two groups did not differ in early life or perceived life stress. However, even though rural participants reported higher levels of anxiety before and after the TSST, urban participants responded with greater stress-induced increases in circulating PBMCs and prolonged increases in circulating IL-6, a proinflammatory cytokine. These data are consistent with the hypothesis that not only does the transition to an urban lifestyle involve increased risk of immune disorders, such as allergic asthma, but that it also involves increased risk of stress-related psychiatric disorders in which psychosocial stress and exaggerated inflammation are thought to be important risk factors (Rohleder 2014).

8 Hypothetical Frameworks Highlighting the Importance of Exposures to Diverse Microbial Environments to Mental Health

A number of hypotheses have been put forward to explain the increasing incidence and prevalence of inflammatory disease in modern urban societies. These include the hygiene hypothesis (Strachan 1989, 2000), the “Farm Effect” (von Mutius 2022), the biodiversity hypothesis (von Hertzen et al. 2011; Haahtela 2022), the disappearing microbiota hypothesis (Blaser and Falkow 2009; Blaser 2015), and the “Old Friends” hypothesis (Rook et al. 2004). What all of these hypotheses share, however, is that they propose, in one manner or another, that reduced exposures to diverse microbial ecosystems are responsible for increases in noncommunicable diseases in modern urban environments. Here we will briefly describe each of these hypotheses in turn, then focus on the “Old Friends” hypothesis, the context in which the most research has been done to evaluate the role of diverse microbial exposures in promotion of stress resilience and mental health.

8.1 The Hygiene Hypothesis

Initially, the term “hygiene hypothesis” was based on observations made by David Strachan, then at the London School of Hygiene and Tropical Medicine, in which a decrease in hay fever was observed in children with multiple older siblings in first world countries (Strachan 1989). This led Strachan to the conclusion that an excess of hygiene and decreases in childhood illness exposures were the causes of the increase in hay fever seen in first world countries (Strachan 1989; Rook and Lowry 2022; Rook et al. 2014a). Media and journalists latched onto this phrase as it was a simplistic concept that determined our excess cleanliness was the cause of our allergies and autoimmune disorders (Rook and Lowry 2022). While hay fever was not a new concept and was first described in the tenth century by Abu Bakr Al-Razi who called it “rose fever,” a connection between wealth, urbanization, and hay fever was observed in the nineteenth century by Dr. Charles Blackley (1873; Azizi 2010; Bungy et al. 1996). Blackley noticed that hay fever was more prevalent in wealthy and urbanized people compared to common people who did not live in the city (Blackley 1873; Rook and Lowry 2022). With this connection and Strachan’s suggestion that allergic diseases were prevented by infections in early childhood, the hygiene hypothesis was developed and initially focused on allergic disorders without taking into consideration humanity’s evolutionary history and dependence on microorganisms during the hunter-gatherer phase (Rook and Lowry 2022). These early childhood infections, which were largely not present during the hunter-gatherer phase of human evolution, are known as *crowd infections*, which

became prevalent during urbanization. Crowd infections either elicit immunity or kill the host, which is why they cannot persist in hunter-gatherer groups but are common in urban environments. Crowd infections are not protective against chronic inflammatory disorders and instead have been shown to worsen them. Hygienic practices have been shown to decrease rates of crowd infections, as repeatedly emphasized by public health agencies during the COVID-19 pandemic, and thus a focus on negative consequences of hygiene, as proposed in the hygiene hypothesis, is somewhat misleading from the perspective of public health.

8.2 The "Farm Effect"

Subsequent studies demonstrated that rural upbringing confers protection against allergic asthma (von Mutius 2022). The protective effect of rural upbringing against allergic asthma is so highly replicated, it is referred to as simply the "Farm Effect" (von Mutius 2022; Genuneit 2012).

8.3 The Biodiversity Hypothesis

The biodiversity hypothesis states that current deficits in the exposure to natural environments and microbial diversity of individuals living in Westernized civilizations have unintended adverse health consequences (von Hertzen et al. 2011; Haahtela 2022; von Hertzen et al. 2015). Lack of exposure to microbial biodiversity especially during early development causes a deficiency in immunoregulatory circuits and leads to increased risk of developing allergic asthma later in life (von Hertzen et al. 2011, 2015; Haahtela 2022).

8.4 The Disappearing Microbiota Hypothesis

The disappearing microbiota hypothesis (Blaser and Falkow 2009; Blaser 2015) postulates that the important factor in increasing prevalence of modern allergic and metabolic diseases might not be decreased exposures to environmental microorganisms but instead could reflect the loss of ancestral microorganisms through vertical transfer, i.e., from one generation to the next, which in turn affects human physiology and disease risk. Notable losses include *Helicobacter pylori*, and losses of microbiota due to antibiotic use.

8.5 The "Old Friends" Hypothesis

The "Old Friends" hypothesis was formulated by Professor Graham Rook and colleagues in 2004 as a revision of the hygiene hypothesis (Rook et al. 2004). It provides a useful hypothetical framework for explaining the increases in inflammatory diseases in modern urban societies, in part because it highlights the importance of immunoregulation, indicated by a balanced expansion of regulatory T cells (Treg) and effector T cell populations, which are known to be driven by microbial signals. It is also useful in that it takes the focus away from hygiene (i.e., the idea that we are "too clean"), particularly at a time when personal hygiene is important to avoid transmission of communicable disease, including COVID-19, and instead emphasizes the importance of exposures to diverse microbial environments with microbial signals that can drive immunoregulation. Immunoregulation is driven mainly by organisms with which mammals co-evolved, including: (1) the commensal microbiota, which have been altered by the Western lifestyle, including a diet that is commonly low

in microbiota-accessible carbohydrates (Sonnenburg and Sonnenburg 2014; von Hertzen et al. 2015); (2) pathogens associated with the "old infections" that were present throughout life in evolving human hunter-gatherer populations (Atherton and Blaser 2009); and (3) organisms from the natural environment with which humans were inevitably in daily contact with (and, consequently, had to be tolerated by the immune system) (Rook et al. 2014a). Immunoregulation is thought to be compromised in modern high-income settings due to reduced contact with these three categories of organisms (Rook et al. 2014a; Ohnmacht et al. 2015; Sefik et al. 2015). Failure of immunoregulation, attributable to reduced exposure to the microbial environment within which the mammalian immune system evolved, is thought to be one factor contributing to recent increases in stress-related and chronic inflammatory disorders in high-income countries (Sonnenburg and Sonnenburg 2014; Atherton and Blaser 2009; Rook et al. 2014a). Finally, and directly relevant to the thesis of this chapter, data from both preclinical and clinical studies are consistent with the hypothesis that inadequate immunoregulation also increases risk for development of stress-related psychiatric disorders (Raison et al. 2010; Rook et al. 2013, 2014a; Rook and Lowry 2008), an idea first put forward by Rook and Lowry in 2008 (Rook and Lowry 2008). Figure 2 illustrates the three categories of "Old Friends," while Fig. 3 illustrates potential mechanisms underlying induction of immunoregulation by microbial signals.

8.5.1 The Phylogenetically Broad But Strain-Specific Nature of Microorganisms That Induce Immunoregulation—

Commensal microbes are initially transmitted by mothers and other family members and play an important role in the development of mammalian organ systems including the gut, immune system, and brain (Rook et al. 2014a, b). Germ-free mice have severely deficient numbers of regulatory T cells (Ohnmacht et al. 2015; Sefik et al. 2015). The immunoregulatory potential of single strains of bacteria is highlighted by the fact that inoculation of germ-free mice with single strains of bacteria is sufficient to restore percentages of Rorγ^+ Helios$^-$ Treg (a distinct population of Tregs in the mouse colon that constrains inflammatory responses) to levels found in specified pathogen-free (SPF) mice. This induction mapped to a broad, but specific, array of individual bacterial species, meaning that bacteria from widely different phyla were capable of inducing these immunoregulatory effects, but that the effects were strain-specific. We have yet to understand the "code" that enables one bacterial strain to induce immunoregulatory responses, while other closely related strains cannot do so. This remains an important objective for future studies.

Given that we do not yet understand fully what enables specific strains of bacteria to drive immunoregulation, a reasonable strategy might be to promote high diversity of the gut microbiota, in hopes that one or more strains could provide the bacterial signals that drive immunoregulation. A number of physiological variables and lifestyle factors that are positively or negatively associated with diversity of the gut microbiota have recently been identified (Manor et al. 2020).

8.5.2 Immunoregulatory Strategies for Prevention of Stress-Related Psychiatric Disorders: Soil-Derived *Mycobacterium vaccae* NCTC 11659 as a Case Study—

Ellul and colleagues recently proposed a path toward induction of Treg to

promote psychoneuroimmune resilience with the intention of developing an immunotherapy approach to treatment of major depressive disorder. The strategy proposed involves use of low-dose interleukin 2 (IL-2), which induces Treg and inhibits inflammatory Th17 lymphocytes (Ellul et al. 2018). Another approach might be use of bacterial strains that have demonstrated anti-inflammatory and immunoregulatory effects (for recent review, see Sterrett et al. 2022; Flux and Lowry 2020, 2023; Loupy and Lowry 2019; Lowry et al. 2016).

We have been studying the potential of one such bacterial strain, *M. vaccae* NCTC 11659, in rodent models in order to test the hypothesis that this strain has potential as an intervention for prevention and treatment of stress-related psychiatric disorders. Although not yet tested in clinical trials for stress-related psychiatric disorders, it has been studied in numerous clinical trials for other conditions (for review, see Amoroso et al. 2021). *M. vaccae* NCTC 11659 induces regulatory T cells in mice and rats and has shown particular promise for promotion of stress resilience effects in a number of stress models, consistent with prevention of a PTSD-like syndrome (Table 1).

9 Conclusions

Interventions that increase immunoregulation and attenuate chronic low-grade inflammation have potential for prevention and/or treatment of stress-related psychiatric disorders in which a failure of immunoregulation and the resulting chronic low-grade inflammation are recognized as risk factors. Increased exposure to immunoregulatory “Old Friends” may provide a novel and promising strategy to promote stress resilience for the purposes of prevention and treatment of stress-related psychiatric disorders, including anxiety disorders, mood disorders, and trauma- and stressor-related disorders, such as PTSD.

10 Future Directions

Although evidence strongly supports the hypothesis that exposures to “Old Friends” can promote stress resilience, the mechanisms involved are not completely understood, particularly in the context of the microbiome-gut-brain axis signaling mechanisms. Thus, future studies should identify mechanisms involved, which will facilitate development of novel interventions.

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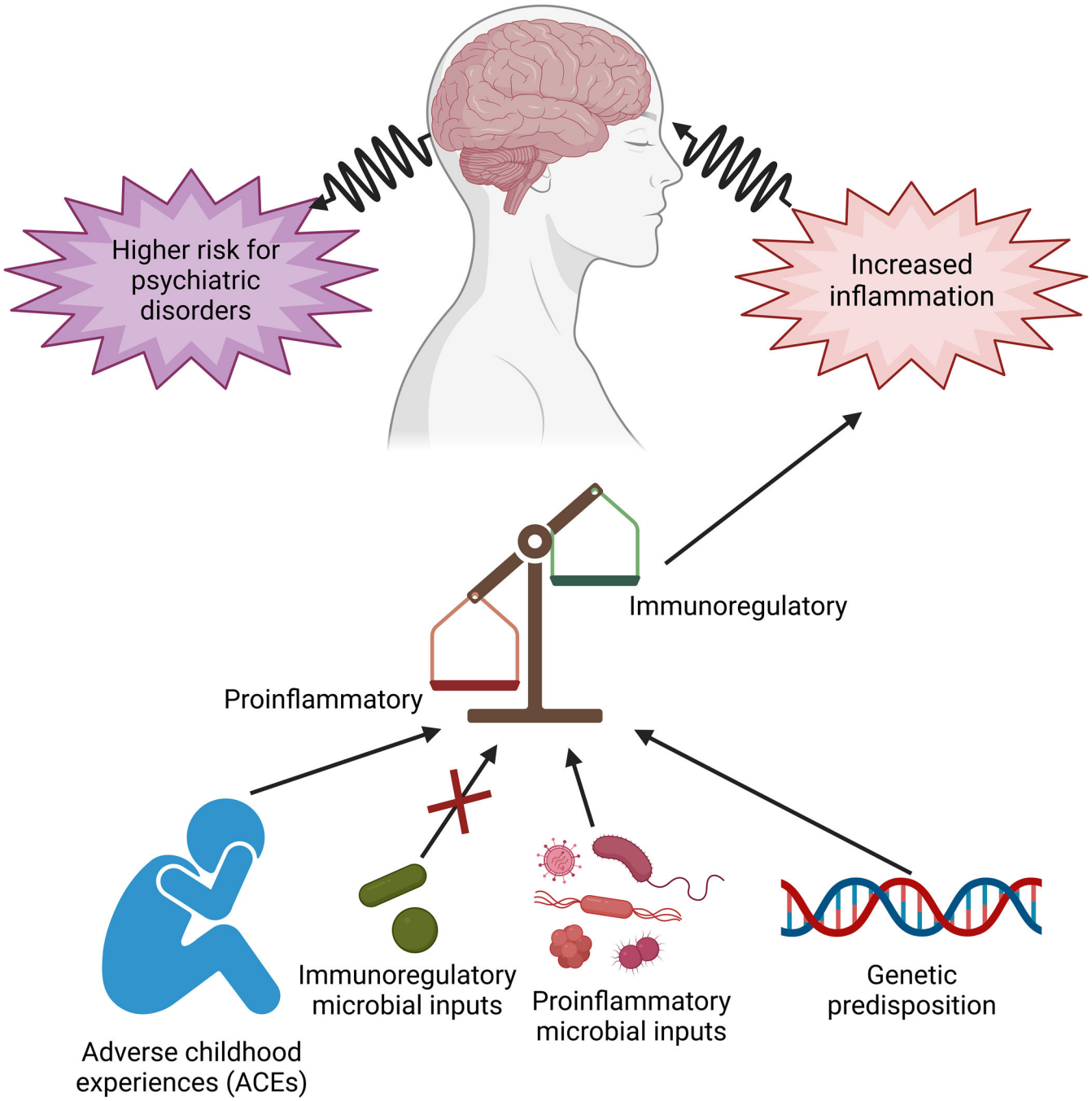

Fig. 1.

Risk factors for stress-related psychiatric disorders include: (1) genetic predisposition; and (2) environmental influences, including adverse childhood experiences (ACEs), and exposures to diverse microbial inputs. Microbial inputs can be either proinflammatory or anti-inflammatory/immunoregulatory (i.e., resulting in a balanced expression of regulatory T cells (Treg) and effector T cells). A failure of immunoregulation can lead to chronic low-grade inflammation and increased risk of stress-related psychiatric disorders. Figure created with biorender.com

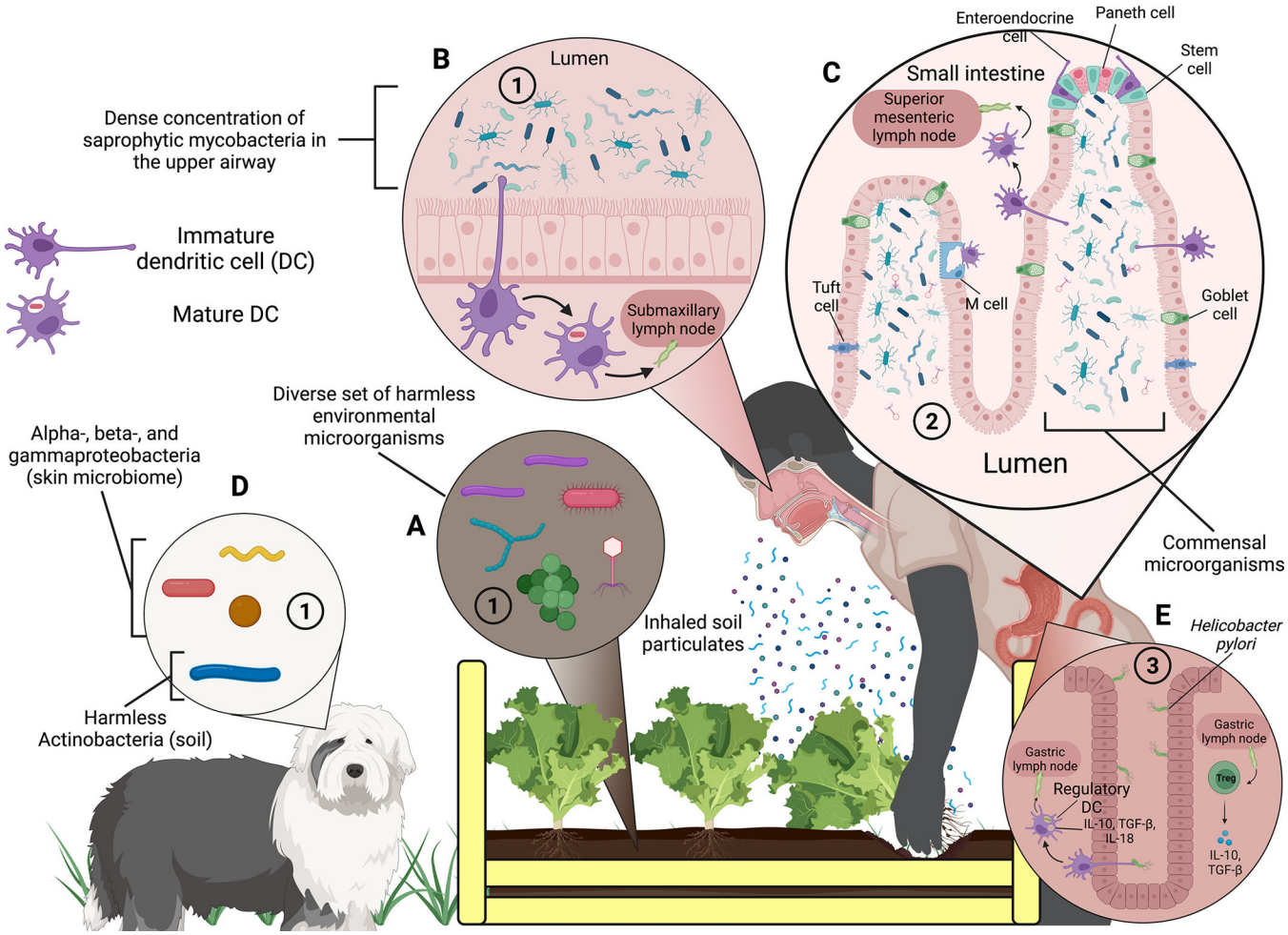

Fig. 2.

Potential sources of the three categories of "Old Friends" and how they interact with the immune system to induce anti-inflammatory and immunoregulatory effects. The three categories of "Old Friends" are: (1) harmless environmental microorganisms found in mud, untreated water, and fermenting vegetable material that have been depleted during the transition from a rural to an urban lifestyle; (2) organisms that form part of the co-evolved human microbiota (including commensal microorganisms); and (3) "Old Infections," i.e., infections present in early man that usually do not sterilize or kill the host and that have also been depleted since urbanization. (**A**) The soil in this diagram depicts a diverse set of microorganisms that live within it, an environment that is rare to find in an urban environment compared to a rural one, thus depicting the first category of "Old Friends." Here, a person harvesting lettuce they have grown is agitating the soil enough to form soil particulates that they eventually breathe in, exposing themselves to "Old Friends." (**B**) One broad subset of soil microbes, Actinobacteria, are commonly found in the upper airway, depicted by mycobacteria from the genus *Mycobacterium* being inhaled into the nasal cavity (Macovei et al. 2015; Kim et al. 2022). Dendritic cells "sample" the contents of the nasal lumen by extending pseudopods that allow the cell to phagocytize a bacterium. The dendritic cell will then digest it and $CD103^{+}$, $CCR7^{+}$ dendritic cells migrate to a

nearby lymph node via a lymphatic vessel to present processed antigens of the bacterium to lymphocytes. (**C**) Dendritic cell sampling is a common theme of the innate immune system – in the lumen of the small intestine, home to part of the gut microbiome, dendritic cells undergo a similar process of phagocytizing microorganisms in the lumen, digesting them, and ultimately presenting the processed antigens to lymphocytes. Unlike in the upper airway, dendritic cells in the small intestine mostly sample microorganisms that form part of the co-evolved human microbiota – the second category of "Old Friends." The commensal microbes in the small intestine are especially influenced by whether a person was raised in an urban/rural environment as well as diet. (**D**) Animals that humans are in close contact with, such as dogs, can also influence the composition of the human microbiota. Commensal microbes from a dog's skin microbiome can be transferred to a person's skin, where they can colonize to form part of the person's skin microbiome (Song et al. 2013); further, dogs can expose their owners to "Old Friends" by bringing microbes found in mud and untreated water into the house. (**E**) The last category of "Old Friends" is depicted by *Helicobacter pylori* infecting the epithelial cells of the stomach. Unlike a regular infection that produces a robust inflammatory response, if *H. pylori* is tolerated by the dendritic cells and lymphocytes of the immune system, then an anti-inflammatory and immunoregulatory response (i.e., characterized by a balanced expression of regulatory and effector T cells) arises instead (Arnold et al. 2012; Lundgren et al. 2005). Abbreviations: DC, dendritic cell; IL, interleukin; TGF-β, transforming growth factor beta; Treg, regulatory T cell. Not to scale. Figure created with biorender.com

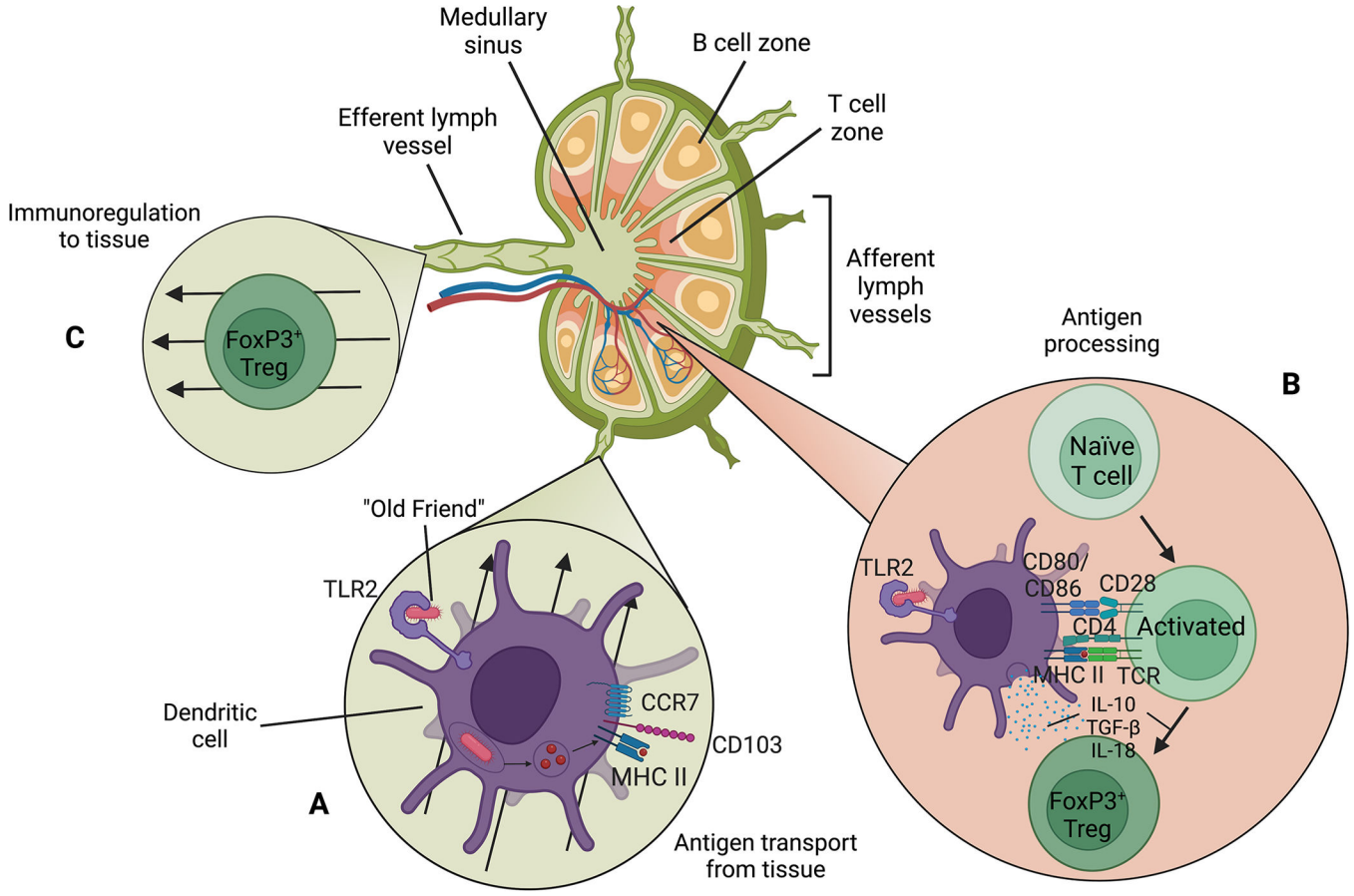

Fig. 3.

A dendritic cell transports a phagocytized “Old Friend” to a lymph node and presents it to naïve T cells, resulting in differentiation of naïve T cells into regulatory T cells. (**A**) A mature CD103^{+}, CCR7^{+} dendritic cell migrates to a lymph node via an afferent lymph vessel. An “Old Friend” is bound to TLR2 and is ultimately phagocytized and bound to MHC II for presentation to a lymphocyte. (**B**) Activation of a naïve T cell in the presence of IL-10, TGF-β, and IL-18 secreted from a dendritic cell results in differentiation of the naïve T cell to a FoxP3^{+} regulatory T cell. (**C**) A FoxP3^{+} regulatory T cell migrates from the lymph node to tissue via an efferent lymph vessel. Abbreviations: CCR, C-C chemokine receptor; CD, cluster of differentiation; IL, interleukin; MHC, major histocompatibility complex; TCR, T cell receptor; TGF-β, transforming growth factor beta; TLR, toll-like receptor; Treg, regulatory T cell. Not to scale. Figure created with biorender.com

Table 1

PTSD-relevant findings following immunization with Mycobacterium vaccae NCTC 11659

PTSD symptom based on DSM-5	**Effects of *M. vaccae* NCTC 11659 in rodent models**
Intrusions	N.A.
Avoidance (avoiding people, situations, circumstances resembling or associated with the event)	Decreased stress-induced anxiety-like defensive behavioral responses (avoidance) (Amoroso et al. 2019a, b; Frank et al. 2018; Reber et al. 2016; Loupy et al. 2021) Promotion of proactive behavioral responses to stress (Amoroso et al. 2019a, b; Frank et al. 2018; Reber et al. 2016; Loupy et al. 2021)
Negative alterations in mood and cognition	Antidepressant-like behavioral effects (Lowry et al. 2007; Siebler et al. 2018) Prevention of surgery-induced microglial priming (Fonken et al. 2018; Frank et al. 2018; Frank et al. 2019) and cognitive impairment (Fonken et al. 2018)
Alterations in arousal or reactivity (hypervigilance for threat, exaggerated startle response, irritability, difficulty concentrating, sleep problems)	Enhanced fear extinction in fear-potentiated startle (Fox et al. 2017; Hassell et al. 2019; Loupy et al. 2019) Enhanced fear extinction in models of stress-induced exaggeration of cued fear paradigms (Hassell 2019) Prevention of stress-induced cortical hyperarousal (Bowers et al. 2019) Prevention of stress-induced sleep and behavioral impairments (Bowers et al. 2021)