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Review

Microbial Translocation Disorders: Assigning an Etiology to Idiopathic Illnesses

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Abstract: Gut microbes are immunologically tolerated in the gastrointestinal tract but trigger aggressive immune responses upon translocation across the gut barrier. Although oral tolerance, a physiological process that dampens immune responses to food proteins and commensal microbiota, remains poorly defined, significant progress was made during and after the Human Immunodeficiency Virus epidemic in the 1980s and the discovery of regulatory T cells in 1995. Additional insight was gained after the discoveries of innate lymphoid cells in 2008 and the functional elucidation of mucosal mast cells. Prior to the historical discovery of human pathogens, the etiologies of most human diseases were considered unknown. The same was true about many genetic disorders prior to the Human Genome Project. Here, we hypothesize that many of the remaining idiopathic conditions, including autoimmune, fibroproliferative, and neuropsychiatric diseases as well as some cancers, can be considered microbial translocation disorders triggered by the host immune responses to extraintestinal gut microbes and/or their constituent parts. In addition to microbial translocation, we also discuss potential interventions for intestinal barrier rehabilitation, including antibodies against tumor necrosis factor-like ligand 1A and membrane lipid replacement supplements.

Keywords: disorders of unknown etiology; microbial translocaton; microbiome; immunity; gut barrier

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1. Introduction

Biological barriers, comprised primarily of epithelial and endothelial cells, separate the body compartments from each other and protect tissues and organs from external chemical, biological, and physical agents. Similarly, biological barriers, such as the blood-brain barrier (BBB) maintain the homeostasis of biomolecular transport into tissues and organs [1]. Although there are several biological barriers in the human body, here we focus primarily on the intestinal epithelial barrier that separates the luminal prokaryotes from eukaryotic host cells.

In the gastrointestinal (GI) system, gut barrier function is highly dependent on the integrity of intestinal epithelial cell (IEC) plasma membranes and the presence of tight junction (TJs) molecules that bind IECs tightly to each other. In addition, the adequate functioning of intestinal barriers requires an intact, gut-associated lymphoid tissue (GALT),

that is comprised of B and T lymphocytes, macrophages, dendritic cells as well innate lymphoid cells (ILCs), that along with IECs can recognize gut antigens and bacteria [2]. Under pathological circumstances, damaged TJs and plasma membranes contribute to barrier dysfunction and microbial passage into host tissues [3].

Microbial translocation (MT) the term used throughout this article, refers to the "escape" of intestinal microorganisms or toxins into the host systemic circulation by passing through the intestinal barrier and lamina propria, reaching mesenteric lymph nodes and the circulatory system [4,5].

Different translocation pathways across the gut barrier have been described as paracellular or transcellular. The former facilitates the transport of solutes and nutrients, while the latter promotes the translocation of cells and particles, including granulocytes, microbes, and microbial components [4]. Such translocation can also involve specific cell types. For example, antigen processing by GALT requires transcytosis of microbes and toxins through the intestinal membranous (M) cells [5].

From a host perspective, the plasma membrane participates actively in immune defenses and contributes to microbiota tolerance by externalizing phosphatidylserine (PS), a global immunosuppressive marker [6]. Indeed, due to their short, 3–5 days lifespan, IECs can externalize PS en masse, extending tolerance to the gut microbial community [7]. Some gut microbes, including *E. coli*, contribute to the tolerogenic intestinal milieu by externalizing PS on their own surfaces, suppressing host immunity [8,9].

From the microbiota perspective, host tolerance can be promoted by increasing the levels of interleukin 10 (IL-10), a tolerogenic cytokine that upregulates regulatory T cells (T regs), dampening host immune responses to commensals [10,11]. For example, *Faecalibacterium prausnitzii* (*F. prausnitzii*), can induce host dendritic cells (DCs) to release IL-10 and other tolerogenic molecules, thus participating actively in the immune acceptance of gut flora [12]. Moreover, natural killer cells (NKCs) can promote gut tolerance by releasing interferon γ (IFN-γ), a cytokine that can convert tryptophan to kynurenine, causing upregulation of the key tolerogenic enzyme indoleamine 2,3-dioxygenase (IDO). In return, kynurenine can bind with aryl hydrocarbon receptor (AhR), suppressing immune responses to commensals [13–16].

The 1995 discovery of Tregs, an IL-2-expressing subgroup of T helper cells (Th), has contributed to a better understanding of the molecular underpinnings of oral and gut immune tolerance [17]. Mucosal mast cells (MCs) suppress T regs in the presence of gut pathogens, triggering the opposite drive, activation of effector T cells, and immunogenicity [18]. The relationship between Tregs and MCs maintains gut homeostasis by upholding the careful balance between commensal acceptance and pathogen rejection.

In addition, the finding that group-3 innate lymphoid cells (ILC3s) release IL-2, a Treg-activating cytokine, emphasizes further the molecular intricacies of gut immune tolerance [19] (Figure 1). Furthermore, the finding that IL-10, a primarily anti-inflammatory cytokine, enhances IL-2 secretion and suppresses proinflammatory IL-17, has shed additional light on the cellular and molecular underpinnings of the intestinal tolerogenic milieu [20,21]. Together, these novel findings have contributed to a better understanding of gut barrier homeostasis and MT.

While increased immune tolerance can promote MT, an excessively immunogenic environment can be equally detrimental. For example, inflammatory bowel diseases (IBD), such as Chron's disease or ulcerative colitis, has been associated with increased MT as evidenced by the elevated levels of translocation markers, such as lipopolysaccharide-binding protein (LBP) and soluble CD14 (sCD14), that have been reported in this pathology [22,23].

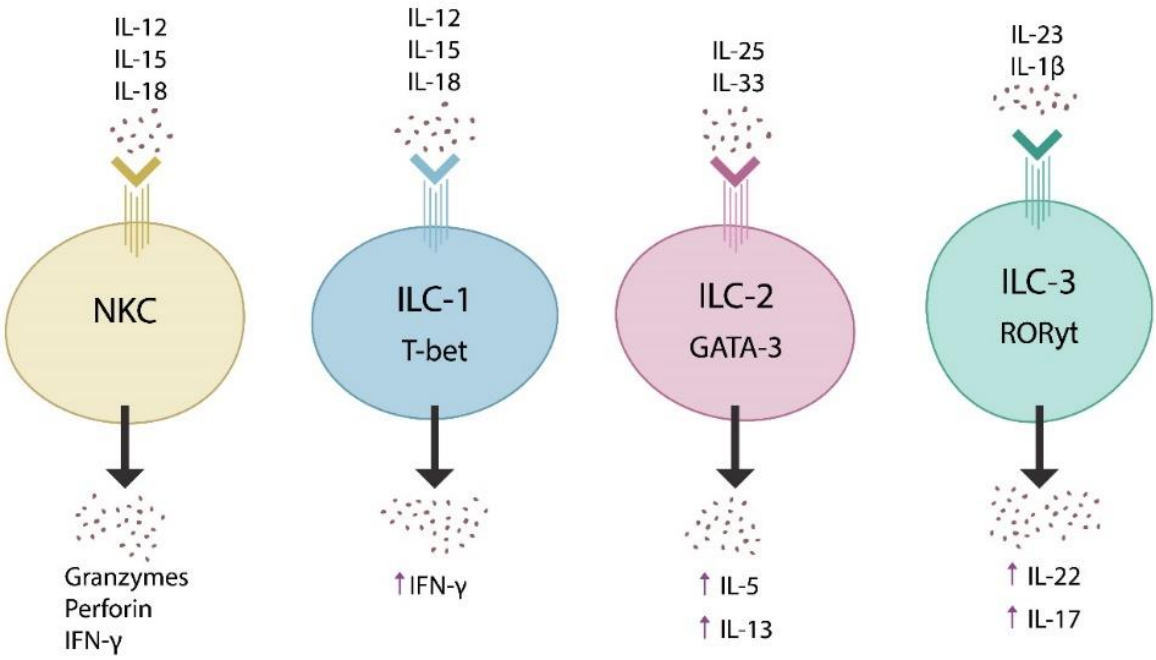

Figure 1. Innate lymphoid cells are comprised of NKCs and innate lymphoid cells types 1, 2, and 3 (ILC1, ILC2, and ILC3). These cells are activated by various cytokines (**top**), release other cytokines (**bottom**), and express transcription factors, including T-bet, GATA-3, and RORγt. When dysregulated, these lymphoid systems may trigger autoimmunity, fibrotic and neuropsychiatric illnesses.

Numerous pathogens, including Human Immunodeficiency Virus (HIV), promote self-tolerance by exploiting the host tolerogenic systems, including PS, IL-2, IL-10, or IDO, and in the process facilitating MT and toxin passage [24]. Indeed, MT was poorly defined prior to the arrival of HIV, a virus capable of increasing intestinal permeability by depleting IL-22, the guardian of gut barrier function (Figure 2) [25–29].

In addition to HIV, several other pathogens can hijack the molecular pathways of intestinal tolerance, promoting MT. For example, bacteria and viruses can amplify infectivity by generating IL-10 orthologues or increasing IL-10 itself, inducing self-tolerance and averting host defenses [30,31]. Another mechanism utilized by enveloped viruses to induce tolerance is apoptotic mimicry, a Trojan horse maneuver of PS externalization to facilitate viral uptake by the phagocytes [32].

In 2002, a new family member of tumor necrosis factor α (TNFα) was discovered, the TNF-like cytokine 1A (TL1A) that over the past two decades has revolutionized the field of MT and very likely other disorders of uncertain etiology [33]. TL1A, a T cell co-stimulator, is a ligand of death receptor 3 (DR3) and participates actively in the pathogenesis of many cancers as well as other autoimmune, fibroproliferative diseases and neuropsychiatric disorders, including schizophrenia [34–37]. Indeed, anti-TL1A antibodies, currently in Phase 2 trials for ulcerative colitis, may prove beneficial for several idiopathic diseases [38–40] (NCT02840721).

Transcellular MT, a process of microbial passage through the IECs or M cells, is highly dependent on the integrity of the membrane lipid bilayer and its repair capacity [41]. Conversely, the replacement of damaged membrane lipids with undamaged glycerolphospholipids (GPL), using dietary supplements can repair cell membranes, lowering MT. Here, we propose that the concomitant treatment with TL1A antibody and membrane lipid replacement supplements may be a superior approach to achieve gut barrier repair than each modality applied individually [41].

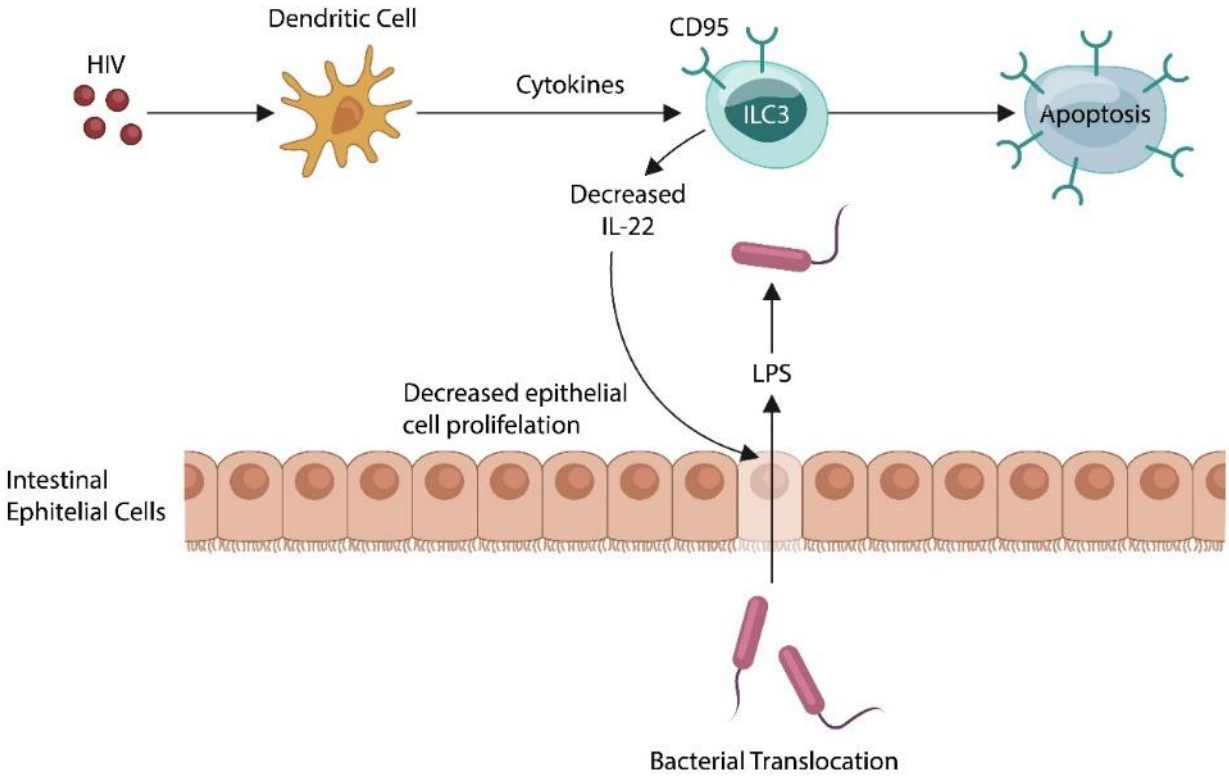

Figure 2. HIV induces apoptotic loss of ILC3, lowering IL22, the guardian of the gut barrier. This, in turn, promotes the translocation of intestinal microbes and their molecules into the systemic circulation. Activated host immunity maintains a state of low-grade inflammation that characterizes many diseases of uncertain etiology.

2. The Microbiome and Innate Lymphoid Cells

The Human Microbiome Project, initiated in 2007, revealed that the microbial organ is comprised of more than 2000 bacterial species, belonging to 12 different phyla, more than 90% of which are related to *Proteobacteria*, *Firmicutes*, *Actinobacteria*, or *Bacteroidetes species* [42–44]. Aside from prokaryotic microbes, the gut microbiome also contains yeasts, fungi, and viruses that influence the barrier function by releasing signaling molecules and metabolites as well as by direct interaction with IECs [45,46]. For example, the human gastrointestinal (GI) tract virome (viral microbiome) contains a variety of RNA and DNA viruses, most of which are bacteriophages (phages) or bacteria-infecting viruses, that regulate the microbiome composition as well as the permeability of gut barrier [47]. In addition, phages can be disseminated throughout the body by the circulatory system and can interact directly with human cells [48,49]. Moreover, as phages ingress into microbial cells by lysing the cell wall, they often release microbial fragments, such as muramyl peptides, lipoteichoic acids, or LPS, triggering responses related to gut pathology [50].

Discovered in 2008, innate lymphoid cells (ILCs) are mucosa-anchored non-T, non-B lymphocytes, consisting of natural killer cells (NKCs) and ILC1, ILC2, and ILC3 cells [51]. These systems play a pivotal role in maintaining the homeostasis of the gut barrier, intestinal tolerance, and nutrient transport [52,53]. Unlike the B and T lymphocytes which express specific antigen receptors, ILCs respond to transcription factors and synthesize cytokines [54,55] (Figure 1). For example, ILC3 express retinoic acid receptor-related nuclear receptor γt (RORγt), are activated by IL-23 and IL-1β, while they release IL-22 and IL-17, cytokines involved in the integrity of the gut barrier as well as the blood-brain barrier (BBB) (Figure 1) [56,57].

MT was poorly defined prior to the HIV epidemic but was extensively studied in the context of this virus which was known for activating the immune system and increasing gut barrier permeability [58–60]. Indeed, HIV triggers ILC3 apoptosis, lowering IL-22, which in return alters the intestinal barrier, promoting MT [61] (Figure 2).

Under physiological conditions, IL-22, acts as a guardian of gut barrier function, while IL-17 is known for initiating inflammation and recruiting neutrophils, and clearing invading pathogens [62]. Dysfunctional IL-17 may trigger chronic inflammation, a characteristic of several disorders of unclear or unknown etiologies, including autoimmune diseases, pathological fibrosis, and neuropsychiatric disorders, such as schizophrenia [63–65]. Maintaining an appropriate balance between the tolerogenic IL-22 and proinflammatory IL-17 is necessary for enabling GALT to distinguish between gut commensals and pathogens [66]. For example, GALT dyshomeostasis, due to dysfunctional ILC3 and an impaired Tregs/Th17 ratio, was demonstrated to trigger food allergies and IBD [67–69].

Abundantly expressed in the intestinal mucosa, ILCs protect the gut barrier by releasing IFN-γ, a cytokine that activates tryptophan metabolism, promoting tolerance via kynurenine and IDO. On the other hand, the dysfunctional release of IFN-γ by NKCs or ILC1, may lead to pathological fibrosis, major depressive disorder (MDD), and systemic lupus erythematosus (SLE), further connecting ILCs with the disorders of uncertain etiology [70–72] (Figure 1). Indeed, impaired ILC2 and dysfunctional release of IL-5 and IL-13 were demonstrated in MDD and suicidal behavior, linking neuropathology to this lymphoid system. Along this line, a recent study has connected dysfunctional ILCs with the loss of *Alloprevotella rava* (*A. rava*), *a*, a salivary microbe whose absence was associated with suicidality [73,74]. Moreover, IL-5 and IL-13 have been known for their role in eliminating *Helicobacter pylori* (*H. pylori*), a pathogen previously implicated in MDD [75,76].

Taken together, these data show that ILCs are essential for maintaining the homeostasis of the intestinal barrier and the immune acceptance of gut microbes. Conversely, dysfunctional ILCs can trigger barrier dysfunction and MT, predisposing patients to disorders of uncertain etiology [77,78].

2.1. The Mast Cells of Intestinal Mucosa

The human gut harbors the largest body population of MCs, a system associated with ILCs, that regulates the gut barrier function and integrity [79]. Conversely, dysfunctional MCs with aberrant tryptase release were demonstrated in IBD, a disorder associated with systemic pathology and MT [80].

MCs have been known historically for their role in histamine release and allergic reactions however, these cells also participate in several other physiological and pathological processes, including immunity, inflammation, emotional regulation, olfaction, and cognition [81]. For example, Mastocytosis is a rare disease characterized by an increased number of MCs and a clinical picture marked by abdominal pain, enlarged lymph nodes as well as neuropathology, such as depression, anxiety, and cognitive disorders [82–84].

Cerebral MCs reside inside the BBB, including the thalamus, hypothalamus, and leptomeninges where they maintain CNS homeostasis by signaling with astrocytes, microglia, and endothelial cells (ECs) [85]. Regardless of their location, MCs respond to infection by forming extracellular traps (ET), also referred to as ETosis, or pathogen elimination by externalizing antimicrobial peptides (AMPs) and nuclear DNA [86]. ETosis may account for the elevated cell-free DNA (cfDNA) documented in many disorders of uncertain etiology, including autoimmunity, cancer, pulmonary fibrosis, and schizophrenia [87–91]. In this regard, as cfDNA and ETs have been associated with gut barrier breakdown and MCs may be the drivers of MT pathology [92].

Human MCs share some common characteristics with neurons as they are long living and capable of producing neurotransmitters, such as acetylcholine (ACh), gamma-aminobutyric acid (GABA), histamine, and serotonin (5-HT), suggesting their important role in maintaining CNS homeostasis [93]. Indeed, brain resident MCs produce approximately 50% of the CNS histamine, a biogenic amine implicated in the pathogenesis of schizophrenia, Parkinson's disease (PD), and sleep disorders [94,95]. While neuronal histamine is produced in the hypothalamic tubero-mamillary nucleus, MCs are associated with meningeal vessels. Indeed, the dysfunctional release of histamine has been linked to migraine headaches [96]. Moreover, as histamine modulates the sleep-wake cycle, learning, and memory, dysfunctional histaminergic signaling may trigger certain neuropathology, including schizophrenia [97–99]. Indeed, histamine 3 (H3) receptor antagonists are currently in schizophrenia clinical trials [100].

Aside from schizophrenia, histamine has been found to be involved in other neuropsychiatric conditions, including Tourette's syndrome, delirium, and postoperative cognitive impairment [101–103]. Moreover, histamine was demonstrated to activate microglia, suggesting that the dysfunctional release of this biogenic amine may trigger the elimination of healthy neurons and synapses by aberrant microglia [104–106].

Earlier studies have demonstrated that HIV can "hide" in MCs, utilizing them as reservoirs and thus preventing complete viral eradication. Since a subcategory of MCs can express chymase, an alternative SARS-CoV-2 entry portal, MCs may harbor this virus, maintaining a latent source of infection that could account for some cases of Long-COVID [107,108]. Interestingly, MCs express a viable renin angiotensin system (RAS), including angiotensin II (ANG II), a peptide implicated in the pathogenesis of several idiopathic diseases, including pulmonary fibrosis, autoimmune diseases, and neurodegenerative disorders [109–111].

Taken together, these data connect MCs with intestinal barrier disruption and MT, suggesting their involvement in the pathogenesis of idiopathic disorders.

2.2. Pathogen-Induced Genomic Disruption

Numerous studies have linked idiopathic disorders with both genomic damage and dysfunctional DNA damage repair (DDR) systems. However, this line of research is rarely considered when the etiopathogenesis of these conditions is discussed [112–117]. The COVID-19 pandemic has drawn the attention of researchers and clinicians to DNA damage as the SARS-CoV-2 virus can directly and indirectly alter the human genome [118,119]. This could be significant as the SARS-CoV-2 virus may exhibit bacteriophage behavior and trigger pathology similar to the *E. coli*-released colibactin, including IBD, colorectal carcinoma (CRC), and new onset psychosis [120,121].

Another gut commensal, *Morganella morganii* (*M. morganii*) was found to damage the host DNA by releasing indolimine, a recently identified genotoxic molecule [122]. Indeed, earlier studies have implicated *E. coli* and *M. morganii* in schizophrenia, further connecting dysfunctional DNA with disorders of uncertain etiology [123]. Moreover, colibactin and indolimine were demonstrated to increase the permeability of the gut barrier, facilitating MT, which likely promotes the pathogenesis of idiopathic illnesses [121,124–127]. On the other hand, MCs-released histamine, an established protector of DNA, was demonstrated to prevent physical and chemical genomic damage, while antihistaminic drugs may cause DNA insults [128,129]. This places MCs at the center of DDR, emphasizing the adaptive role of these cells in reversing genomic damage and promoting neuroplasticity. Indeed, an MC activator, IL-10 was associated with mild genotoxicity and enhanced DDR response, suggesting that limited genomic damage may be adaptive [130,131]. In this regard, novel studies have reported that mild to moderate DNA damage promotes DDR-mediated neuroplasticity, while extensive (beyond repair) genomic disruption triggers neuronal death, and eventually neurodegenerative disorders [132,133]. We feel that these observations are significant as dysfunctional MCs and IL-10 signaling have been implicated in psychiatric and neurocognitive disorders [134,135]. Interestingly, recent studies have found that

neuronal DNA can differ from cell to cell, a phenomenon known as somatic mosaicism, and this condition may drive the pathogenesis of some neuropsychiatric disorders [136,137].

3. Autoimmune Disease as an MTD Phenomenon

Under physiological conditions, microbes and/or microbial components have been detected in many host tissues, including the circulatory system and the CNS [138,139]. Pathologically, microbial antigens, such as LPS, have been demonstrated in Alzheimer's disease (AD) brains, cardiovascular disease (CVD), diabetes, and some cancers, suggesting that these conditions could be reconceptualized as microbial translocation disorders (MTDs) [140–143]. In addition, several autoimmune diseases, including SLE, were associated with MT, further linking these disorders to a dysfunctional GI tract barrier. Indeed, preclinical studies have implicated *Enterococcus gallinarum* (*E. gallinarum*) in SLE, and reports indicate that the elimination of this bacterium by the antibiotic treatment could alleviate many autoimmune effects [144,145].

3.1. MT in Neuropsychiatric Disorders

Microorganisms, including *E. coli* and *H. pylori*, express antigens resembling human glutamate receptors, suggesting that N-methyl-D-aspartate (NMDA) autoantibodies, documented in cases of schizophrenia, could be conventional immunoglobulins directed at translocated microbial proteins [146,147].

Bacteroides species and *Pseudomonas fluorescens* were shown to generate γ-aminobutyric acid (GABA), a neurotransmitter associated with neuropsychiatric pathology, including anxiety, schizophrenia, and epilepsy, and thus linking these conditions to MTDs [148,149]. For example, anti-GABA-B receptor encephalitis, an autoimmune disease mediated by antibodies against this protein, could be the result of translocated GABA-producing microbes [150]. Interestingly, autoantibodies against GABA-A receptor α1 were detected in patients with schizophrenia, further connecting neuropsychiatric conditions with MTDs [151].

Lactobacillus plantarum, *Bacillus subtilis*, and *E. coli* were demonstrated to synthesize acetylcholine (ACh) and express nicotinic or muscarinic receptors, and these can elicit the respective antibodies upon translocation [152,153]. For example, autoantibodies against cholinergic receptors, documented in myasthenia gravis, and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), may be conventional antibodies against translocated ACh-expressing microbes [154–156].

Furthermore, metabotropic glutamate receptors subtype 2 (mGluR2), an entry portal of both SARS-CoV-2 and rabies virus (RABV), suggests that "autoantibodies" against the virus/receptor complex may be conventional immunoglobulins against known pathogens [157,158]. Moreover, mGluR2 autoantibodies, documented in infections of *Mycoplasma* and Herpes viruses, may represent antibodies directed at these pathogens [159].

3.2. MT in Sleep Disorders and Neuropathy

Preclinical studies have reported that gut microbiota regulate neurological signaling associated with neuropathy and neuropathic pain, linking this disorder of unclear etiology to MT [160,161]. In addition, as histamine contributes to wakefulness, and several microbial species release histamine, insomnia may be linked to the translocation of histamine-releasing microbes, such as *M. morganii* [162–164]. Indeed, dysfunctional histamine signaling has been documented in infections of *Trypanosoma brucei brucei*, the etiologic agent of African sleeping sickness, suggesting that molecular mimicry with histaminergic receptors may drive this pathology [165]. Moreover, preclinical studies have linked intestinal dysbiosis to a dysfunctional sleep/wake cycle, further connecting insomnia with the GI tract microbes [166]. Interestingly, the hypnotic properties of microbial peptidoglycans and lipoteichoic acid (cell wall components of Gram-positive bacteria) have been known for decades [165,167]. For example, the sleep-promoting effects of a bacterial cell wall molecule, muramyl peptide, discovered in the 1970s, connects the microbiome with sleep [165].

Translocated muramyl peptide or lipoteichoic acid have been demonstrated to act as pathogen-associated molecular patterns (PAMPs) and trigger the release of IL1β and tumor necrosis factor alpha (TNFα), molecules that are involved in both sleep and autoimmune disorders [167–169]. Indeed, IL1β or TNFα antagonists, which are established rheumatoid arthritis (RA) treatments, were demonstrated to possess hypnotic properties, further linking insomnia to autoimmune inflammation [170,171]. Moreover, as muramyl peptide or lipoteichoic acid are bacteriophage entry portals, sleep disturbances may be associated with anti-phage antibodies [172–174]. Furthermore, the presence of influenza-induced narcolepsy, an autoimmune disease marked by autoantibodies against orexin-producing neurons, suggests that antiviral antibodies may cross-react with human proteins [175,176]. Moreover, encephalitis lethargica and post-viral parkinsonism have been associated with influenza virus cross-reactivity with basal ganglia proteins, suggesting that this virus in some instances may blend into the gut virome and remain in the body for longer periods of time [177,178]. Furthermore, microbe-generated N-formyl methionine-containing peptides were found to activate mammalian formyl peptide receptors (FPR), which are molecules involved in neuroinflammation and neurodegeneration, indicating their potential microbial involvement in these pathologies [179–182].

3.3. MT in Movement and Fatiguing Disorders

Yersinia enterocolitica and some *E. coli* species have been shown to express norepinephrine (NE) and dopamine (DA) receptors. Therefore, anti-dopamine D2 receptor (D2R) antibodies and antibodies against β adrenergic receptors (documented in movement disorders and ME/CFS respectively) may be directed at translocated NE and DA-generating microbes [183–185]. Furthermore, several gut species, including *E. coli* and *Salmonella*, express CpxA, a bacterial serotonin receptor that can trigger, upon translocation, antibodies against host serotonin (5HT), as demonstrated in fibromyalgia and panic disorder [186–188] (Table 1).

Table 1. Gut microbes and viruses (column I) express biomolecules resembling human proteins (column II). When microbes translocate into the systemic circulation, the host mounts an antibody response against these antigens that can be misconstrued as autoantibodies (column III), resulting in human pathology (column IV).

Bacteria/Virus	Microbe Proteins	Host Antibody	Pathology	References
E. coli/H. pylori	NMDA	Anti-NMDA Ab	Schizophrenia	[146,147]
Bacteroides; *Pseudomonas fluorescens*	GABA-A GABA-B	Anti-GABA-A α1/anti-GABA-B	Schizophrenia; Epilepsy; MDD	[148,149]
Lactobacillus plantarum/ *E. coli*	Ach; nicotinic and muscarinic receptors	Anti-Ach receptor Ab	Myasthenia Gravis; ME/CFS	[154–156]
SARS-CoV-2/RABV	mGluR2	Anti-mGluR2 antibody	Paraneoplastic syndromes	[157,158]
E. coli; *Yersinia enterocolitica*	Norepinephrine and dopamine receptors	Anti-D2R Ab; Anti-adrenergic receptors β Ab	Tic disorder; ME/CFS	[183–185]
Gram + microbes	Lipoteichoic acid; muramyl peptide	Systemic Translocation	Sleep disorders	[165–167]
E. coli/Salmonella	CpXA serotonin receptor	Anti- CpxR Ab	Fibromyalgia; panic disorder	[186–188]
E. coli and other bacteria	N-formyl methionine	neutrophil activation	Rheumatoid arthritis (RA)	[179–181]
Influenza	Orexin neurons	Anti-orexin neurons Ab	Narcolepsy	[175,176]

Taken together, the line between conventional antibodies and autoantibodies has become blurred, especially after the discovery of the microbiome and MT, suggesting that many autoimmune disorders could, in fact, be reconceptualized as MTD.

4. Fibroproliferative Diseases Such as MTDs

Fibroproliferative diseases are idiopathic conditions associated with increased worldwide morbidity and mortality as well as a lack of effective therapies. They affect many organs, including the intestine, liver, kidney, heart, and lung, and are characterized by pathological scar formation [189]. Indeed, fibrogenesis is a physiological or pathological response to chemical, mechanical, or immune insults in which the healing process involves fibroblast-mediated reorganization of the extracellular matrix (ECM) [190,191]. Dysfunctional healing with excessive fibroblast activation and overproduction of ECM is believed to drive pathological fibrosis. In addition, fibroblast growth factors are established participants in gut barrier integrity and loss of fibroblast growth factor 9 (FGF9) has been associated with pulmonary fibrosis, further linking this pathology to MTD [192–194].

Transforming growth factor-β (TGF-β), a tolerogenic cytokine and master regulator of gut microbiota, was demonstrated to promote fibrosis by abnormally activating ILCs, Th17, NKCs, and B lymphocytes [195–198]. In addition, a subset of IL-10-producing NKCs was reported to promote fibrosis, an action independent of the elimination of defective cells [199,200]. Moreover, ILC2-released IL-13 was shown to drive collagen deposition, indicating that dysfunctional ILCs may promote pathological fibrosis [201] (Figure 1). Furthermore, microbiota-generated curli amyloid fibrils were reported to disrupt ILC3, IL-17, and IL-22, promoting both autoimmunity and intestinal fibrosis, highlighting the interconnectedness of these pathologies [202–205].

A variety of gut viruses and microbial species can drive excessive fibrosis as they express the integrin motif or arginine-glycine-aspartate (RGD), known for binding integrins αvβ6 and αvβ8, highlighting a mechanism of pathological fibroproliferation [206,207]. Interestingly, integrin αvβ6 is an activator of TGF-β, liking integrins to the master regulator of gut microbiota [208].

Considering the above data together, translocated microbes may have the ability to drive the pathogenesis of fibroproliferative disorders by disrupting the function of NKCs and ILCs. At the molecular level, ECM proliferation may be triggered by microbe-disrupted integrins and fibroblast growth factors.

5. Neuropathology as MTDs

Several recent studies have reported new onset psychosis after SARS-CoV-2 infection or even after the administration of mRNA vaccines, connecting viral antigens with this neuropsychiatric pathology [209–214]. As SARS-CoV-2 disrupts the intestinal barrier and tryptophan absorption, it enables MT and secondary bacterial infections. These observations have reawakened the interest in the infectious hypothesis of neuropsychiatric illness entertained by many researchers and clinicians both at present and in the past. For example, Emil Kraepelin hinted at the microbiome when hypothesizing that under pathological circumstances microbes from various body compartments could migrate into the brain and trigger neuropathology [215]. Along this line of thought, IBD and CRC, conditions characterized by increased intestinal permeability and MT appear to validate Kraepelin's migration model [216–218]. The same can be stated about psychosis induced by urinary tract infections (UTI), a destabilizing condition in patients with psychiatric illness [219–221] (next subsection). Moreover, Kraepelin's paradigm appears to be validated by the link between maternal influenza and offspring with schizophrenia, or childhood viral enteritis, and the development of psychiatric illness later in life [222–225]. Furthermore, the finding that some gut microbes express tryptophan decarboxylase and can synthesize endogenous hallucinogens, such as tryptamine or N, N-dimethyltryptamine (DMT), further suggests support for Kraepelin's hypothesis of microbe-mediated neuropathology [226,227]. Indeed, new onset psychosis associated with COVID-19 may be explained by the selective

upregulation of tryptophan decarboxylase-expressing gut microbes, such as *M. morganii*, a bacterium previously implicated in schizophrenia [123].

The 2001 discovery of trace amine-associated receptors (TAARs), proteins that can sense minute amounts of tryptamine, further substantiates Kraepelin's hypothesis [228]. The recent finding that microbial metabolite 4-ethylphenyl sulfate (4EPS) disrupts oligodendrocyte maturation in multiple sclerosis (MS), has further connected the microbiome to this neuropathology [229–231]. Furthermore, in other studies, several gut microbial species were demonstrated to trigger celiac disease by synthesizing gliadin-mimicking peptides, molecules capable of altering the TJ protein, zonulin [232,233]. This appears to be significant as the systemic translocation of these microbes and their zonulin-like antigens may lead to the generation of anti-gliandin antibodies, further linking the microbiome to autoimmunity [234]. Interestingly, elevated IgA anti-gliadin antibodies were found in patients with schizophrenia, connecting this disorder to dysfunctional biological barriers [235].

Urinary Tract Microbiome and MTDs

Urinary tract infections (UTIs) are common conditions that affect over 150 million people worldwide each year [236,237]. UTI-associated bladder carcinoma is a serious complication connected to microbial genotoxins, including colibactin and indolimines secreted by *E. coli* and *M. morganii* respectively [238]. In addition, UTIs are often associated with acute psychosis or psychotic decompensation in stable patients with psychiatric illness [239–241]. Along this line, a novel study has taken a fresh look at the connection between UTI and psychosis, emphasizing the role of the previously underappreciated bladder microbiome [221,242]. A recent study, found that a large number of UTI patients were hospitalized with new onset psychosis or psychotic decompensation, suggesting a link between psychopathology and uropathogenic bacteria [239–242]. For example, UTI-associated *E. coli* and *M. morganii*, were found to activate local and CNS MCs, leading to excessive histamine release and exacerbation of both cystitis and psychosis [243–247]. Indeed, schizophrenia with negative symptoms, was associated with UTI caused by *M. morganii*, *Hafnei alvei*, *Pseudomonas aeruginosa*, *Pseudomonas putida*, and *Klebsiella pneumoniae*, further connecting the bladder microbiome with neuropathologies [248–250].

The urinary bladder expresses numerous receptors, including serotonergic 5-HT7 (5-HT7Rs) and 5-HT4Rs. These receptors are also present in the brain and were previously implicated in schizophrenia [251–254]. Despite the bladder's anti-bacterial defenses, including the urothelial barrier, AMP-containing mucus, local ILCs, and MCs, uropathogenic bacteria can overcome these barriers by upregulating IL-10 [255]. Recent studies have found that IL-10 could also account for the absence of long-lasting antibodies in UTIs, and the frequent recurrences found in patients [236,256–258]. Moreover, dysfunctional ILCs were associated with both UTI and schizophrenia, connecting immunity to both pathologies [259,260]. Furthermore, dysfunctional MCs and histamine signaling have been documented in interstitial cystitis and psychosis, highlighting the key role of these cells in disorders of unclear etiology [261–263].

6. GI Tract Cancer as MTD

The microbiome can be related to cancer development through the induction of inflammation, as well as the production of toxins, in both cases creating favorable niche environments for tumor development.

Genotoxic molecules released by some intestinal microbial species have been shown to activate bacteriophages (phage) embedded in commensals' DNA. Similarly, phages can eliminate susceptible microbes and increase the abundance of virus-resilient microorganisms, such as tryptophan carboxylase-expressing bacteria that synthesize endogenous serotonergic hallucinogens [264,265]. In addition, some strains of *E. coli* inhibit DNA mismatch repair proteins by synthesizing colibactin, a tumor-promoting toxin. Colibactin-associated IBD and CRC are more prevalent in patients with schizophrenia compared to the general population, linking this disorder to both DNA damage and MT [266–269]. The standard histopathological detection of gut inflammation is specified by the presence of inflammatory infiltrates. However, low-grade inflammation may be a much more common occurrence, defined by the elevated systemic expression of proinflammatory cytokines in the absence of the inflammatory infiltrate aggregates. Low-grade inflammation can be casually related to dietary habits, microbiome dysregulation, or both [270,271]. Thus, aside from genomic damage, some *E. coli* species have been known for maintaining a state of low-grade inflammation that can predispose patients to cancer [267]. The cancer risk is further increased by the inflammation caused by a colibactin-disrupted gut barrier and MT [266,268].

Alteration of the human gut phageome, especially bacteriophages infecting *Fusobacterium nucleatum* (*F. nucleatum*), *Peptacetobacter hiranonis*, and *Parvimonas micra*, has been associated with CRC, emphasizing the likely viral etiology of this type of tumor [272].

F. nucleatum is a common oral microbe which can reach the colon, accelerating the progression of CRC. *F. nucleatum* can cause transient bacteremia triggered by chewing, daily hygiene, or dental procedures, indicating several pathways for contributing to tumorigenesis [273]. Aside from *Fusobacterium*, *Bacteriodes fragilis*, especially via its *B. fragilis* toxin (BFT) can trigger chronic intestinal inflammation, predisposing to CRC [274]. The common microbial strains linked to CRC are *Bacteroides fragilis*, *Escherichia coli*, *Enterococcus faecalis* and *Streptococcus gallolyticus.* Other species identified in CRC patients' tumor and fecal samples include *F. nucleatum*, *Parvimonas*, *Peptostreptococcus*, *Porphyromonas* and *Prevotella* [275].

Indeed, previous studies have connected *F. nucleatum* with carcinogenesis as well as the pathogenesis of poorly understood disorders, including CVD, preeclampsia, AD, and autoimmune disorders. These observations further link various microbes to these pathologies [273].

A growing body of evidence has shown that the SARS-CoV-2 virus can thrive in GI tract reservoirs, likely blending into the gut virome [274,275].

Indeed, as some gut microbes express angiotensin converting enzyme 2 (ACE-2), the SARS-CoV-2 cell membrane entry portal, they may harbor the virus, possibly accounting for some, if not many of the symptoms of long COVID [276]. It remains to be seen if a higher occurrence of GI-related oncogenesis will be positively correlated with Long-COVID

Microbe-induced, genomic damage can also reactivate dormant viruses, including herpes simplex virus type 1 (HSV1) and Epstein-Barr virus (EBV), pathogens previously associated with schizophrenia as well as with various malignancies [277–280]. Indeed, EBV is a well-characterized oncovirus associated with several cancers, including CRC [281]. In addition, novel studies have connected phages and fungi to CRC, indicating the possible multi-kingdom etiology of this tumor [282,283].

7. Interventions

In two previous studies, we have discussed several strategies for gut barrier restoration and these therapeutic approaches will not be repeated here in more detail [284,285]. Table 2. summarizes these interventions. In this article, we will focus primarily on the TL1A antibody, currently known as PF-06480605, as well as on membrane lipid replacement therapy (MLR) [286] (287A).

Table 2. Quick reminder of gut barrier restoration strategies.

Compound	Action Mechanism	References
Navitoclax; Fistein; Quercetin; Dasatinib	Senotherapeutics (eliminate senescent cells or delete senescence markers)	[287]
Glycyrrhizin (glycyrrhizic acid); Gabexate mesylate; Monoclonal antibody.	HMGB1 inhibitors	[288,289]
Hu5F9; TTI-621	CD47 inhibitors	[290]
SCFAs; N-butanol extracts of Morinda citrifolia; milk fat globule membranes (MFGM); β-glucan	Anti-inflammatory (gut barrier)	[291,292]
Rhodobacter sphaeroides LPS; myeloid differentiation factor 2 (MD-2)	TLR4 antagonist	[293]
Niclosamide; ANO6 inhibitors	TMEM16F inhibitor	[294]
Membrane Lipid Replacement	Glycerophospholipids	[295]

7.1. PF-06480605 as a Senolytic

Antibody PF-06480605 is currently in phase 2a clinical trials for ulcerative colitis (NCT02840721). This monoclonal antibody inhibits TL1A, lowering innate and adaptive immunity as well as the fibrotic pathways [296] (Figure 3). TL1A, a T cell co-stimulator, is encoded by the TNFSF15 gene and binds to DR3, encoded by the TNFRSF25 gene [297]. In addition to being a T cell co-stimulator, TL1A/DR3 signaling can activate many cell types, including fibroblasts, ILC2 and ILC3, cancer cells, and macrophages/microglia. DR3 is abundantly expressed in the brain and has been implicated in the pathogenesis of several neuropsychiatric disorders and neurodegenerative diseases [298–300].

The TL1A and TNFSF15 gene have been involved in premature endothelial cell (EC) senescence, a cellular program of proliferation arrest with active metabolism and a detrimental, barrier-disrupting secretome, the senescence-associated secretory phenotype (SASP) [301,302].

Premature EC senescence and SASP have been associated with neuropsychiatric illness and pulmonary fibrosis, while in cancer, senescence can induce both tumorigenesis or tumor suppression [303–305]. Aside from T cells, TL1A also co-stimulates ILC2 and ILC3, promoting the release of IL-5, IL-13, IL-22, and IL-17, cytokines associated with premature cellular senescence. This suggests that PF-06480605 may possess senolytic properties [306–310].

7.2. Membrane Lipid Replacement Therapy

Cellular senescence, a term coined by Hayflick, denotes the arrest of cellular proliferation despite the presence of adequate nutrients and growth factors in the medium [311]. Due to their exit from the cell cycle, senescent cells may not undergo malignant transformation however, the long-term SASP presence in the microenvironment can promote tumorigenesis [312].

Senescent cells upregulate intracellular iron, often leading to plasma membrane damage by lipid peroxidation, a phenomenon we previously identified as ferosenescence [313]. In opposition to ferroptosis which is a nonapoptotic form of cell death, ferrosenescent cells remain alive and are characterized by upregulated cytosolic iron and damaged plasma membranes. In this regard, ferrosenescence bridges the gap between cellular senescence and senescence-associated lipid pathology (SALP) [314].

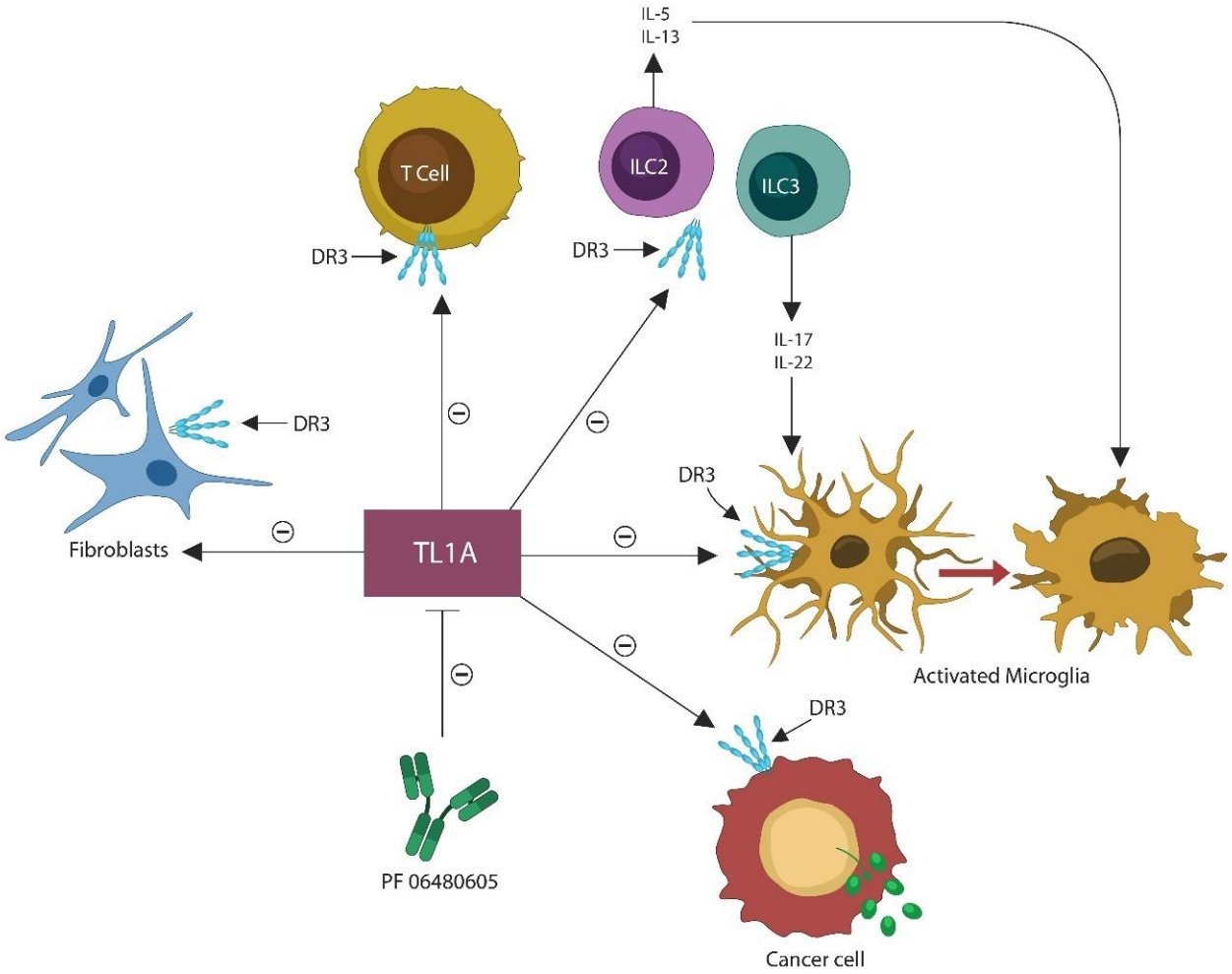

Figure 3. TL1A, a T cell co-stimulator, also stimulates other DR3-expressing cells, including ILC2, ILC3, fibroblasts, cancer cells, and microphages, including the brain macrophages, and microglia. This places TL1A at the center of the disorders of uncertain etiology, while its inhibition likely diminishes this pathology. Activated microglia often engages in the elimination of viable neurons, contributing to neurodegeneration. Anti-TL1A antibody, PF-06480605 blocks TL1A, inhibiting the stimulatory effect on these systems, and thus decreasing the incidence of idiopathic disorders.

In addition, ferrosenescence is reversible, which is in line with the novel findings, showing that cellular senescence can be reversed by inhibiting 3-phosphoinositide-dependent protein kinase 1 (PDK1) [315,316].

Since PS, a glycerophospholipid, was demonstrated to maintain PDK1 in an inactive conformation, the efficacy of membrane lipid replacement therapy is likely based, in part, on PDK1-reversed cellular senescence (Figure 4) [317]. Therefore, membrane phospholipid supplementation with natural glycerolphospholipids and PDK1 inhibition, could lower the detrimental effects of PDK1 in cancer (especially breast and CRC), schizophrenia, excessive fibrosis, and autoimmune inflammation [318–321].

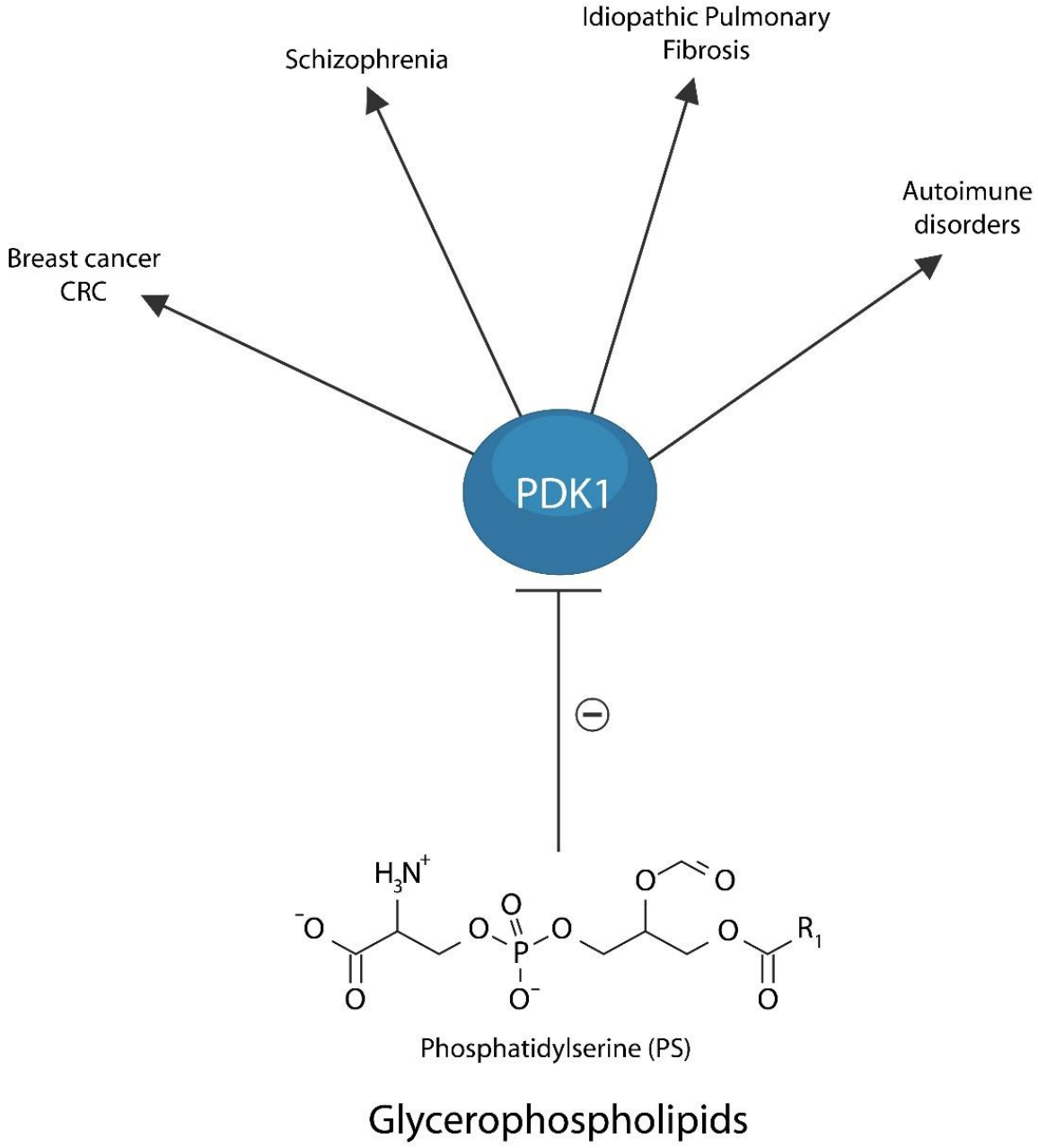

Figure 4. Membrane Lipid Replacement therapy with dietary glycerophospholipids maintains PDK1 in an inactive conformation, preventing its detrimental action in breast cancer and CRC, neuropsychiatric illness, including schizophrenia, pulmonary fibrosis, and autoimmune disorders. This model suggests that membrane lipid replacement therapy is likely beneficial for disorders of unclear etiology.

Membrane lipid replacement is also important in maintaining cell membrane integrity and function and appropriate membrane barriers (287A). In patients with a variety of diseases and disorders, including idiopathic diseases and those involving MT, membrane lipid replacement improved neurological, GI, and other symptoms, without any adverse effects, suggesting that other idiopathic diseases would also benefit from its use [285,286].

7.3. Challenges and Limitations

The observations presented here on the microbiome and idiopathic diseases are mostly based on retrospective longitudinal cohorts. Some of these cohorts may not have been sufficiently large to investigate in detail the host-pathogen interactions. For example,

lack of specimens or inability to link clinical records to the retrospective data (or both) comprises interpretative limitations and challenges. As such additional, studies based on prospective population cohorts are necessary for elucidating the complete role of gut microbial community in systemic disorders.

There is a growing body of literature on specific host-microbe interactions that are (of course) measurable, however, the MTD impact would be more likely akin to a network effect, involving different types, strengths, and microbes acting synergistically across biological thresholds. Unpicking this experimentally remains challenging. Moreover, a common underlying biological mechanism for MTDs does not equate to common clinical treatments, as these are likely to emerge on a disease-specific basis.

For this reason, what we hope to accomplish here is to raise the awareness of researchers and clinicians to a neglected pathology highlighted by HIV and COVID-19, that may account for many insufficiently understood illnesses.

8. Conclusions

Immunological tolerance vs. immunogenicity comprises a homeostatic continuum necessary for the immune acceptance of gut commensals and rejection of pathogens. This continuum is part of a larger adaptive system that ensures the perpetuation of species by extending immune tolerance to the microbiome, food, and fetal proteins.

Dietary tryptophan and microbial organ contribute to the biosynthesis of kynurenine and IDO, tolerogenic biomolecules capable of inhibiting immune system activation in response to selective foreign proteins, including food, microbiota, and the fetus. Disruption of tryptophan degradation and loss of beneficial commensals can break immune tolerance, triggering immunogenicity against beneficial gut flora as observed in IBD.

Disruption of the intestinal barrier promotes MT and subsequent immune activation in response to "escaped" microbes as tolerance is not extended outside the GI tract. Indeed, host responses to translocated microorganisms likely contribute to the pathogenesis of idiopathic illnesses, including autoimmune, fibroproliferative, malignant, and neuropsychiatric conditions as well as ME/CFS, fibromyalgia, and Gulf War Syndromes (GWSs). As these disorders are marked by premature cellular senescence, a defense mechanism against iron-induced membrane damage, restoring lipid homeostasis and repairing plasma membrane damage may reverse barrier dysfunction.

Several gut barrier rehabilitation strategies have been described and here we have focused on TL1A antibody and membrane lipid replacement. PF-06480605 and PDK1 inhibitors likely restore the homeostasis of plasma membranes, reversing ferrosenescence and rescuing IECs from ferroptosis, while membrane lipid replacement repairs and restores membrane barrier and other functions and reduces a variety of symptoms associated with loss of barrier function.

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