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Review

Long COVID and the Neuroendocrinology of Microbial Translocation Outside the GI Tract: Some Treatment Strategies

Adonis Sfera [1,2,*], Carolina Osorio [3], Sabine Hazan [4], Zisis Kozlakidis [5], Jose Campo Maldonado [6], Carlos Manuel Zapata-Martín del Campo [7], Jonathan J. Anton [8], Leah Rahman [9], Christina V. Andronescu [10] and Garth L. Nicolson [11]

1 Patton State Hospital, San Bernardino, CA 92407, USA
2 Department of Psychiatry, University of California, Riverside, CA 92521, USA
3 Department of Psychiatry, Loma Linda University, Loma Linda, CA 92354, USA
4 ProgenomaBiome, Ventura, CA 93003, USA
5 International Agency for Research on Cancer World Health Organization, 69372 Lyon, France
6 Department of Medicine, The University of Texas Rio Grande Valley, Edinburg, TX 78539, USA
7 Instituto Nacional de Cardiología and in Ignacio Chávez, Mexico City 14080, Mexico
8 Department of Biology, California Baptist University, Riverside, CA 92521, USA
9 Department of Neuroscience, University of Oregon, Eugene, OR 97402, USA
10 Medical Anthropology Department, Stanford University, Stanford, CA 94305, USA
11 Department of Molecular Pathology, The Institute for Molecular Medicine, Huntington Beach, CA 92647, USA
* Correspondence: adonis.sfera@dsh.ca.gov

Abstract: Similar to previous pandemics, COVID-19 has been succeeded by well-documented post-infectious sequelae, including chronic fatigue, cough, shortness of breath, myalgia, and concentration difficulties, which may last 5 to 12 weeks or longer after the acute phase of illness. Both the psychological stress of SARS-CoV-2 infection and being diagnosed with COVID-19 can upregulate cortisol, a stress hormone that disrupts the efferocytosis effectors, macrophages, and natural killer cells, leading to the excessive accumulation of senescent cells and disruption of biological barriers. This has been well-established in cancer patients who often experience unrelenting fatigue as well as gut and blood–brain barrier dysfunction upon treatment with senescence-inducing radiation or chemotherapy. In our previous research from 2020 and 2021, we linked COVID-19 to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) via angiotensin II upregulation, premature endothelial senescence, intestinal barrier dysfunction, and microbial translocation from the gastrointestinal tract into the systemic circulation. In 2021 and 2022, these hypotheses were validated and SARS-CoV-2-induced cellular senescence as well as microbial translocation were documented in both acute SARS-CoV-2 infection, long COVID, and ME/CFS, connecting intestinal barrier dysfunction to disabling fatigue and specific infectious events. The purpose of this narrative review is to summarize what is currently known about host immune responses to translocated gut microbes and how these responses relate to fatiguing illnesses, including long COVID. To accomplish this goal, we examine the role of intestinal and blood–brain barriers in long COVID and other illnesses typified by chronic fatigue, with a special emphasis on commensal microbes functioning as viral reservoirs. Furthermore, we discuss the role of SARS-CoV-2/Mycoplasma coinfection in dysfunctional efferocytosis, emphasizing some potential novel treatment strategies, including the use of senotherapeutic drugs, HMGB1 inhibitors, Toll-like receptor 4 (TLR4) blockers, and membrane lipid replacement.

Keywords: cortisol; HMGB1; microbial translocation; SARS-CoV-2

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1. Introduction

In the post-pandemic era, residual or long COVID-19 sequelae have been gradually emerging as many patients experience prolonged fatigue, cough, shortness of breath, myalgia, and problems with concentration long after the acute illness phase [1]. From a biological

pathway perspective, as both SARS-CoV-2 infection and the associated psychological stress upregulate cortisol, the function of macrophages and natural killer (NK) cells may be impaired, disrupting the clearance of senescent, damaged, or virus-infected cells. This may lead to biological barrier dysfunction and chronic fatigue, phenomena well-documented in cancer survivors treated with cellular senescence-inducing chemotherapy or radiation [2–5].

At the molecular level, upregulated cortisol lowers the expression of *claudin-1* (CLDN1), an intestinal tight junction protein, facilitating microbial translocation outside of the gastrointestinal (GI) tract [6]. In the central nervous system (CNS), *P-glycoprotein* (P-gp), a cortisol substrate, functions as a gatekeeper of the blood–brain barrier (BBB), likely accounting for hypercortisolemia-increased barrier permeability [7–9]. Interestingly, in the GI tract, gut microbiota and lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria, regulate P-gp, connecting this protein to microbial translocation [10,11].

Recent studies have found a direct relationship between circulating levels of cortisol and premature cellular senescence, a phenotype characterized by permanent cell cycle arrest, active metabolism, and a detrimental secretome [12]. The accumulation of senescent cells was found to be associated not only with organismal aging but also with chronic fatigue, pain, and depression, documented in cancer survivors [2]. On the other hand, enhanced elimination of senescent cells via senotherapeutics can correct barrier dysfunction, lowering fatigue [13–15].

NK cells and macrophages can execute the phagocytic engulfment (efferocytosis) of damaged or dead cells, including malignant, virus-infected, and senescent cells. Dysfunctional efferocytosis has been associated with biological barrier disruption, inflammatory bowel disease (IBD), and a constellation of symptoms reminiscent of long COVID and other fatiguing illnesses [16–21]. Indeed, NK cell dysfunction is one of the most consistent findings in long COVID-19, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), Gulf War illnesses (GWI), and fibromyalgia (FM), linking these pathologies to dysfunctional efferocytosis [22–27]. Moreover, NK cells had been previously linked to fatigue-associated thyroid, adrenal, hypothalamic, and pituitary disorders, thus connecting these neuroendocrine -related pathologies with dysfunctional immunity [28–32]. Furthermore, NK cells express estrogen, prolactin, and cortisol receptors as well as a functional renin-angiotensin-system (RAS), rendering them sensitive to hormonal fluctuations [33–35]. NK cells are capable of paracrine signaling and they secrete biomolecules, including *perforin*, *granzyme B*, and the *high mobility group box 1 protein* (HMGB1) that can facilitate the elimination of damaged, senescent, and/or malignant cells [36–38].

Microbial translocation markers, such as LPS, lipopolysaccharide binding protein (LPB), soluble *CD14* (sCD14), and HMGB1, were found to be elevated in long COVID, highlighting the role of dysfunctional gut barrier in this condition [30–41]. Indeed, accumulation of senescent cells has been associated with HMGB1 spillover into the extracellular space where it can act as an inflammagen and barrier disruptor [42–46]. Therefore, upregulated HMGB1, documented in ME/CFS, FM, and GWI, and COVID-19, directly links dysfunctional efferocytosis to chronic fatigue [47–50]. For example, gut HMGB1 disrupts the barrier tight junctions and is considered a biomarker of inflammatory bowel disease (IBD), a condition associated with both fatigue and increased GI tract permeability. This may explain certain SARS-CoV-2 bacteriophage-like properties as this virus can likely penetrate the microbial cell walls [51–57].

In this article, we will take a closer look at the role of dysfunctional NK cells and efferocytosis in long COVID and other fatiguing illnesses. We also discuss the comorbidity of *Mycoplasma* species and SARS-CoV-2 as well as their coinfection, barrier rehabilitation via senotherapeutic drugs, HMGB1 inhibitors, Toll-like receptor 4 (TLR-4) blockers and membrane lipid replacement (MLR).

2. Efferocytosis and Biological Barriers

Each day billions of cells throughout the body undergo apoptosis and are removed by professional phagocytes, macrophages, monocytes, and neutrophils as well as non-

professional phagocytes, including the intestinal epithelial cells (IECs) and the M2 microglia in the BBB [58–60]. Professional and non-professional phagocytes are assisted by NK cells that can eliminate defective and pathogen-infected cells without prior sensitization [61–63]. NK cells maintain the integrity of BBB and the intestinal barrier as they can promptly clear damaged cells, preventing inflammation and barrier disruption [64,65]. To accomplish this, NK cells perforate the membrane of targeted cells by releasing HMGB1, perforin, and granzyme, triggering apoptosis by Ca2+ influx [66,67]. Upregulated cytosolic Ca2+ is known to activate *TMEM16F,* an enzyme that flips phosphatidylserine (PS) to the outer leaflet of the cell membrane, providing a distress signal, that attracts immune cells, promoting phagocytosis [68]. Exposed PS (ePS) comprises an "eat me" or "fuse with me" signal that can lead to either cell death or syncytia formation, depending on the degree of cell membrane damage [69]. For example, less damaged cells can fuse with each other for protection, a phenomenon documented in in many tissues, including the CNS [70] (Figure 1). Several studies have demonstrated that senescent and cancer cells can avoid elimination by expressing CD47, a "don't eat me" signal, that inhibits phagocytosis [71–73].

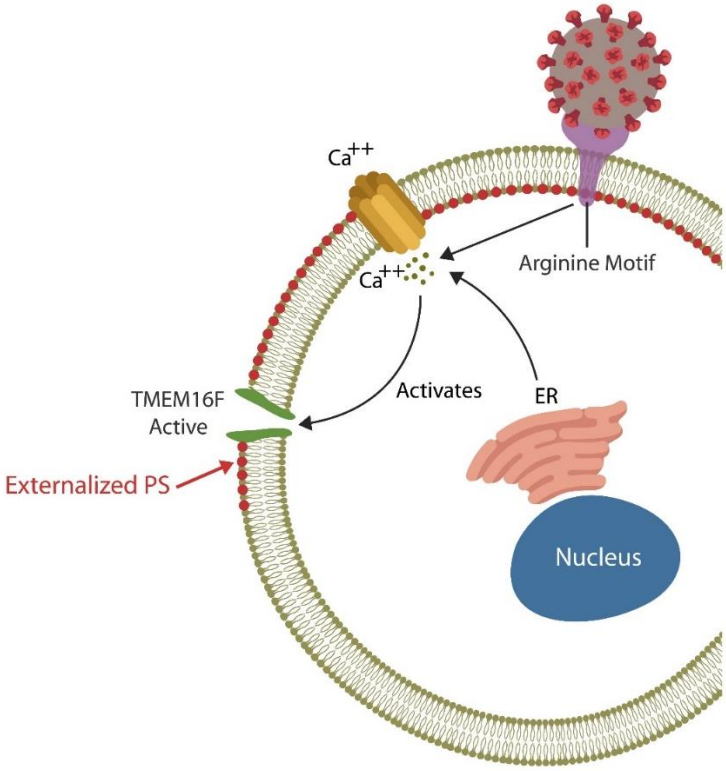

Figure 1. The SARS-CoV-2 receptor binding site (RBS) contains a double arginine insert (PRRA) or arginine motif, that perforates the cell membrane, triggering Ca2+ influx from both the endoplasmic reticulum (ER) and the extracellular compartment. Upregulated cytosolic Ca2+ activates TMEN16F, externalizing phosphatidylserine (ePS), an "eat me" or "fuse me" signal that leads to cell death (if the damage is irreparable) or cell–cell fusion (if the cell can be repaired). Cell–cell fusion or syncytia formation induces premature cellular senescence, disrupting biological barriers. The virus benefits from ePS as this comprises a global immunosuppressive signal, allowing its undetected entry into host cells.

2.1. Blood–Brain Barrier

The BBB, a highly regulated interface between the circulatory system and the CNS, consists of cerebral endothelial cells (ECs) that regulate the inward and outward movement of molecules and ions into the CNS [74]. BBB disruption enables viral entry into the brain along with inflammatory cells, and/or deleterious molecules that can trigger infection. Indeed, members of at least 11 viral families, including the human immunodeficiency

virus-1 (HIV-1), T-cell leukemia virus, lymphocytic choriomeningitis virus, West Nile virus, and others, can enter the brain, causing encephalitis [75–77].

COVID-19-mediated accumulation of senescent ECs compromises the BBB, allowing viral and microbial access to the CNS [78]. In contrast, enhanced elimination of senescent cells via senolytic drugs decreases COVID-19 mortality in rodents, highlighting the role of senescent cells in BBB dysfunction [79,80]. In addition, the S protein of the SARS-CoV-2 virus was demonstrated to directly bind bacterial LPS, outlining a virus-mediated mechanism of endotoxin entry into the CNS [40–81]. LPS-induced neuroinflammation has been associated with microglial fusion and multinucleation, generating highly phagocytic phenotypes that can cause collateral damage by eliminating viable neurons [82,83]. Indeed, long COVID has been associated with LPS-activated microglia (M1 phenotype), neuroinflammation and neuronal death [82–85]. On the other hand, the M2 microglial phenotype has been shown to repair the damage, protecting the neurons [58].

2.2. Intestinal Barrier

Many viruses, including SARS-CoV-2, enhance infectivity by usurping both the physiological cell–cell fusion and efferocytosis, disrupting biological barriers [75,86]. For example, the SARS-CoV-2 virus thrives in infected cells and likely inhibits their clearance, causing inflammation and barrier dysfunction [87]. In addition, SARS-CoV-2 promotes pathological cell–cell fusion and syncytia formation by generating cell membrane pores via the PRRA (proline-arginine-arginine-alanine) motif situated at the furin-cleavage site (FCS). This system is reminiscent of microbial twin arginine translocation pathway, a pore-forming mechanism implicated in bacterial virulence [88–90]. Moreover, SARS-CoV-2 fusion with Mycoplasma, an arginine dependent microorganism, may explain the high comorbidity of these very different infections [91]. Cell membrane pores lead to ePS, a global immunosuppressive signal, that helps the virus exploit host defenses [92]. The subsequent, syncytia formation can then induce premature cellular senescence and the release of senescence-associated secretory phenotype (SASP), a pathological secretome that disrupts endothelial barriers by promoting premature ECs senescence, a phenotype documented in both ME/CFS and COVID-19 [42,93–95].

Senescence-induced pathological syncytia can trigger lymphopenia by cell-in-cell phenomena, elimination of viable lymphocytes, including NK cells, a frequent finding in ME/CFS [96–98]. In addition, as cellular senescence upregulates HMGB1, it may further predispose to fatiguing disorders [44,47–49,99–102].

In the GI tract, IECs comprise a single layer of tightly linked columnar cells that are short-lived and need to be replaced every 4 to 5 days to maintain an adequate barrier function [103]. Moreover, IECs acting as non-professional phagocytes, can engulf the translocating microbes and/or antigens, preventing microbial translocation outside the GI tract [104]. However, accumulation of uncleared, defective IECs can trigger inflammation, predisposing to IBD and other illnesses marked by dysfunctional barrier [105]. Macrophages, intestinal NK cells, and Paneth cells contribute to barrier integrity by promptly removing damaged IECs, thus averting necrosis and inflammation-mediated pathology [21,106–108]. Interestingly, IECs were demonstrated to produce cortisol, a steroid hormone that lowers the expression of CLDN1 that in return increases intestinal permeability [109–111].

The role of ANG II: COVID-19-upregulated *angiotensin II* (ANG II) can disrupt efferocytosis inducing ECs senescence and vascular barrier dysfunction via *angiotensin II type 1 receptors* (AT-1Rs) which can enhance both cortisol and HMGB1 production, [112,113] (Figure 2).

Increased cytosolic ANG II disrupts the function of NK cells and, as these cells express a viable RAS, including ACE-2, the virus may directly infect these immune cells [114,115]. In the CNS, ANG II disrupts the BBB via AT1 receptors; in contrast, Losartan, an AT1 antagonist, can repair this and the intestinal biological barrier [116,117].

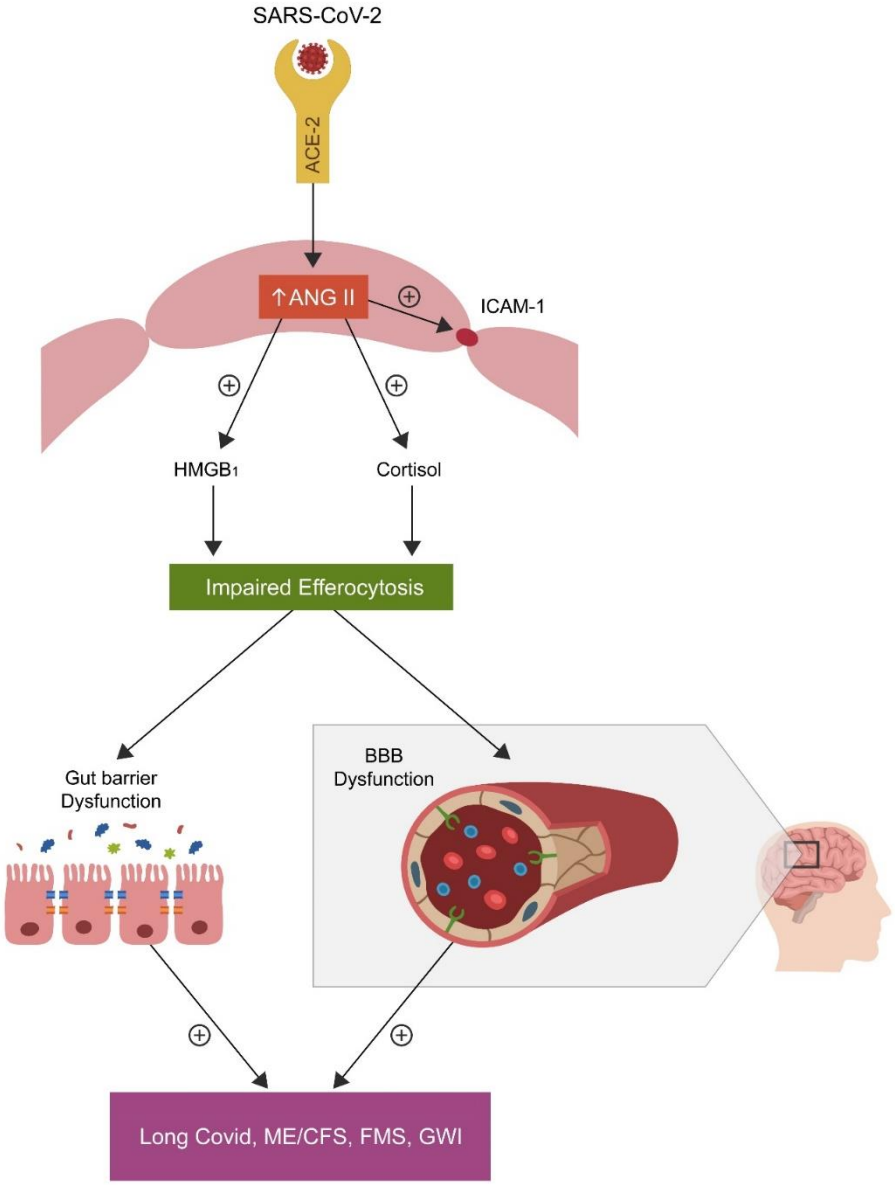

Figure 2. SARS-CoV-2 attachment to ACE-2, blocks this enzyme, causing angiotensin II (ANG II) accumulation by inhibiting its hydrolysis. Upregulated ANG II, increases both cortisol and HMGB1, disrupting the efferocytosis of senescent cells. Accumulation of senescent cells triggers inflammation and biological barrier disruption, a common pathology found not only in the disorders marked by chronic fatigue but also in neuropsychiatric and autoimmune diseases.

3. Biological Barriers and Chronic Fatigue

In previous research (2020 and 2021), we linked COVID-19 to ME/CFS via ANG II, endothelial senescence, intestinal barrier dysfunction, and microbial translocation from the GI tract into host systemic circulation [118,119]. Subsequently, these notions were validated by various groups and virus-induced cellular senescence as well as microbial translocation were documented in both acute COVID-19 illness and long COVID, linking intestinal barrier dysfunction to chronic fatigue [120–127]. Indeed, abnormal intestinal permeability has been documented in GWI, COVID-19 and FM, connecting these conditions to microbial translocation [127–129]. Aside from fatiguing illnesses, increased microbial migration outside the GI tract has also been demonstrated in autoimmune disorders, cancers, and neuropsychiatric conditions, including schizophrenia and Alzheimer's disease (AD) [130–134].

Numerous gut microbes express proteins that are identical or similar to those of the human host, eliciting antibodies upon translocation that could be misconstrued as autoantibodies. For example, several intestinal microbial species express *QseC*, an adrenergic receptor, indicating that antibodies against translocated QseC could trigger human pathology [135]. Indeed, autoantibodies against *β1 adrenergic receptors* were found in patients with ME/CFS as well as in certain cardiovascular diseases, linking these conditions to microbial translocation [136,137]. In addition, bacteria and archaea synthesize acetylcholine (ACh) and express nicotinic or muscarinic receptors that can elicit antibodies upon translocation, blurring the distinction between autoimmunity and immune reactions to gut microbes at extra-intestinal locations [138]. For example, antimuscarinic autoantibodies, documented in ME/CFS, may represent antibodies against translocating microbes expressing ACh receptors [139]. Indeed, ACh receptor autoantibodies, markers of myasthenia gravis and Lambert–Eaton syndrome, have also been documented in *Mycoplasma pneumoniae* and influenza, suggesting that, rather than autoantibodies, these could be conventional antibodies against translocated pathogens [140–144]. *Mycoplasma* infection has also been associated with autoantibodies against *N-methyl-D-aspartate* (NMDA) receptors, markers of neuropsychiatric disorders, including schizophrenia, connecting this illness to gut microbes [145,146]. Furthermore, microbiota-expressing *metabotropic glutamate receptors subtype 2* (mGluR2), linked to both SARS-CoV-2 and Rabies (RABV) viruses, may elicit antibodies rather than autoantibodies, further blurring the border between immunity and autoimmunity [147,148]. For example, mGluR2 autoantibodies, documented in paraneoplastic syndrome as well as in Mycoplasma and Herpes virus infection, may be conventional immunoglobulins against translocated microbes [149–151]. Together this data raises an important question: are antibodies against translocated microbial proteins being misidentified as autoantibodies [152,153]?

The human gut microbiome is composed of bacteria, yeasts, fungi, and viruses, an ecosystem in which microbes can inhibit some viral pathogens, while promoting others [154,155]. Most gut viruses are bacteriophages (bacteria-infecting viruses); however, others including SARS-CoV-2, may display bacteriophage-like properties and enter selective microbes, including the cell wall-deficient *Mycoplasmas* [156–158]. In addition, angiotensin converting enzyme-2 (ACE-2), the SARS-CoV-2 entry portal, is expressed by some gut microbes, indicating that the SARS-CoV-2 virus may enter some microbiota, potentially utilizing them as reservoirs [22]. Indeed, long COVID was found to reactivate Epstein–Barr virus (EBV), suggesting that translocating microbes, containing SARS-CoV-2, could play a key role in maintaining a state of latent infection [159].

When thinking about this problem, studying the microbiome may allow us to reconceptualize some autoimmune disorders as conventional immunity against translocating microbes or their antigens, a model that has already been proposed in the etiopathogenesis of systemic lupus erythematosus (SLE) [160,161]. This is significant as methotrexate, a drug often prescribed to patients with autoimmune disorders, can increase intestinal permeability, further facilitating microbial translocation, while at the same time, lowering host immune defenses that oppose these agents [162–164].

4. Rethinking *Mycoplasma*

Mycoplasmas, members of the Mollicutes class of bacteria, are among the simplest and smallest known self-replicating microorganisms [165]. Their genomes, containing about 400–600 genes, are comprised of either a single stranded RNA or a double stranded DNA nucleic acid. *Mycoplasmas* can be commensal or pathogenic, the former dwelling superficially, for example in the oral cavity, while the latter inside host cells [166,167]. Like SARS-CoV-2, some *Mycoplasma* species release immune modulators and proinflammatory cytokines that can disrupt host immunity or cause hyperinflammatory reactions ("cytokine storms") [168–171]. In addition, some *Mycoplasma species* synthesize *arginine deaminase* (ADI), an enzyme that can further disrupt host immunity [172,173].

The infection with SARS-CoV-2 virus results in variable patient outcomes, ranging from few or no symptoms, in some individuals, to critical illness and death in a small number of patients. As viral infections are often accompanied by secondary bacterial contagion, coinfection may contribute to the majority of unfavorable outcomes. Indeed, *Mycoplasma* comorbidity has been associated with poor COVID-19 prognosis, while epidemiological studies show up to 47% comorbidity between SARS-CoV-2 and *Mycoplasma* [174–180]. In addition, like SARS-CoV-2, *Mycoplasma* infections have been associated with BBB dysfunction and IBD, connecting this cell wall-deficient bacterium to biological barrier dysfunction [181–183].

Coinfection with *Mycoplasma species* has been demonstrated in other viral illnesses, including HIV-1, HHV-6, and various influenza strains as well as in some fatiguing illnesses and cancers. This suggests that *Mycoplasma* may thrive in defective cells and probably induce further cellular damage by disrupting efferocytosis [184–187]. There are also significant overlaps in the clinical picture, laboratory, and imaging studies between SARS-CoV-2 and *Mycoplasma* infections, further complicating the differential diagnosis [188–190]. Moreover, diagnostic tests, including *Mycoplasma species* serology, culture, and even nucleic acid amplification, such as PCR, are marked by numerous limitations [191–193]. In this regard, false-positive and -negative COVID-19 serological test results have been reported in many patients with *Mycoplasma pneumoniae* infection, highlighting the limitation of these assays [194,195]. The next generation sequencing by shot gun methodology appears promising for differentiating *Mycoplasma* from SARS-CoV-2 and may have a place in the diagnosis of long COVID [196]. However, leukopenia, lymphocytopenia, thrombocytopenia, and thromboembolism were documented in both SARS-CoV-2 and *Mycoplasma* infections, further highlighting their intertwined etiopathogenesis [197–200]. Furthermore, certain anti-microbial treatments, such as azithromycin or tetracyclines, were found beneficial for both *Mycoplasma* and COVID-19, further suggesting a likely silent partnership between these quite different infections [201,202].

Several *Mycoplasma* species express the integrin motif, Arg-Gly-Asp, or RGD, a cell attachment sequence that connects these pathogens to the host extracellular matrix (ECM) proteins, including *integrins, laminins, and fibronectin* (FBN) [169,203–206]. A recent milestone in COVID-19 pathogenesis was the revelation that SARS-CoV-2 receptor binding site (RBS) contains an RGD motif that could facilitate viral entry in host cells [207–209]. Since both SARS-CoV-2 and *Mycoplasma species* bind FBN and express the RGD motif, they may fuse with each other, engendering a combined pathology [206,209,210]. In addition, it has been established that *Mycoplasma fermentans incognitus* strain stimulates tissue plasminogen activator (tPA) which converts plasminogen to plasmin, a protein that, like furin, can cleave the SARS-CoV-2 S antigen at the S1/S2 site, triggering pathological cell–cell fusion [211–213]. Elevated plasmin and plasminogen levels are common findings in severe COVID-19 illness as well as in patients with various chronic diseases, including hypertension, diabetes, and cardiovascular diseases. This may account for an unfavorable COVID-19 prognosis in patients with these disorders [214,215]. Moreover, SARS-CoV-2 may benefit from its association with *Mycoplasma* as this bacterium can directly block host immunoglobulins, protecting the virus [216,217]. This finding may be significant, as COVID-19 vaccines may be less effective in patients infected with *Mycoplasma*.

Do Mycoplasma and COVID-19 Comprise a Binary Biological Weapon?

The pathogenic Mycoplasma fermentans incognitus strain, or Lo's Mycoplasma, was patented by Shyh-Ching Lo in 1993 (Patent Number 5,242,820) and several scientists and clinicians have linked this pathogen to over 45% of GWI cases [218]. *This connection was never ruled out, even though Shyh-Ching Lo published in 2000 that there was no serological connection between Mycoplasma fermentans and GWI. However, serological detection of Mycoplasma fermentans is fraught with difficulties that even Lo admits, and his study may have been marred by potential conflict of interest* [219]. *Indeed, significant fractions of ME/CFS and FM cases have been associated with Mycoplasma fermentans infections as well as those of other Mycoplasma*

species, indicating that this pathogen may be involved in various chronic illnesses [220–222]. Thus, the association of long COVID with Mycoplasma infections may establish this bacterial pathogen as a common coinfection in most fatiguing illnesses [175,223]. Moreover, Mycoplasma infections are associated with increased susceptibility to SLE, a condition also associated with excessive fatigue, linking this microorganism to other illnesses marked by exhaustion [224–226]. This could be important, because SLE has been associated with microbial translocation from various niches, possibly linking this autoimmune disease to Mycoplasma colonization [160,175]. Furthermore, lipid-associated membrane proteins (LAMPs) of Mycoplasma fermentans and Mycoplasma hominis have been shown to increase cortisol secretion, further connecting this bacterium to biological barrier dysfunction and chronic fatigue [227]. In 1995, the Institute for Genome Research in Rockville, Maryland completed the nucleotide sequencing of the Mycoplasma genitalium genome, opening the way for the manipulation of this pathogen [228]. Indeed, in 2010, a completely synthetic Mycoplasma mycoides JCVI-syn1.0. was created in the laboratory, contributing further to the potential weaponization of this pathogen [229]. In this regard, Mycoplasma/virus combinations appear suitable for the development of binary biological weapons comprised of independent microorganisms that are considered safe to handle separately, but lethal when mixed, as documented by several studies, including the US Airforce Counterproliferation Center Future Warfare Series No. 53 from 2010 Institute for Molecular Medicine (https://apps.dtic.mil/sti/pdfs/ADA556597.pdf, accessed on 29 September 2022) [230,231]. HIV-1 and Mycoplasma fermentans could be an example of this combination. Since SARS-CoV-2/Mycoplasma comorbidity predicts poor COVID-19 prognosis, it is possible that these infections could be further developed as binary biological weapons [232]. Indeed, the SARS-CoV-2 virus is highly contagious and should only be studied in biosafety level 3 (BSL3) laboratories; therefore, the larger scientific community cannot easily study this pathogen or its combinations [233]. Indeed, a microbial cofactor in COVID-19 disease cannot be ruled out, especially since most Mycoplasma species lack reliable antibody tests and are often associated with false-positive COVID-19 serology [193–195]. Moreover, given the possibility of Mycoplasma symbiosis and partnership with other pathogens, including Trichomonas vaginalis, influenza, and HIV, it might be tempting to create a SARS-CoV-2/Mycoplasma coinfection partnership similar to that found in HIV-1 [234–236].

Like SARS viruses, *Mycoplasma species* can also disrupt biological barriers, enabling microbial translocation into host tissues, including the brain. This pathology overlaps with "disorders of unknown etiology" that affect multiple organs and exacerbate many preexistent chronic conditions. Since both *Mycoplasmas* and SARS-CoV-2 induce symptoms that are difficult to connect to a specific etiology, they may be ideal candidates for the development of possible binary biological weapons.

5. Interventions

In our previous article on ME/CFS, we introduced some novel treatment strategies for barrier dysfunction, including senotherapeutics, short chain fatty acids (SCFAs), milk fat globule membranes (MFGM), β-glucan, and fecal microbial transplantation (FMT) [118]. Here, after a short discussion of some senotherapeutic strategies, we introduce HMGB1 inhibitors, TLR4 antagonists, and MLR.

5.1. Senotherapeutic Strategies

Senescent cells play a key role in organismal aging, while efferocytosis maintains the homeostasis of biological barriers by clearing senescent or damaged cells. Unchecked accumulation of senescent cells can spread the premature aging phenotype to the neighboring healthy cells via SASP paracrine signaling.

Senotherapeutic agents can be divided into senolytics and senomorphics, the former selectively eliminate senescent cells, while the later delete the senescent markers p16INK4a and p21CIP1, restoring the cells to pre-senescent status [237,238]. Here, we introduce a third senotherapeutic category, efferocytosis enhancers comprised of: syncytia inhibitors and

blockers of negative efferocytosis regulators. The former subcategory includes TMEM16F inhibitors, while the later contains inhibitors of anti-efferocytotic receptors.

5.2. TMEM16F Inhibitors

Include drugs like Niclosamide, a widely used anthelmintic agent that inhibits PS externalization, averting both viral fusion with host cells and pathological cell–cell fusion [239,240].

5.3. Negative Efferocytosis Regulator Blockers

Senescent and cancer cells can avert elimination by expressing CD47, a "don't eat me" marker that inhibits the key efferocytosis driver, *MER tyrosine kinase* (MERTK), thus blocking the clearance of damaged cells [240–243]. The recently designed CD47 inhibitors, including Hu5F9 and TTI-621, facilitate efferocytosis by blocking the expression of "do not eat me" signals, [244]. These compounds are currently in phase I and II clinical trials, respectively, and are anticipated to receive approval for anticancer indications (NCT04996004 and NCT02216409).

5.4. HMGB1 Antagonists

In the intracellular compartment, HMGB1 acts as a transcription factor that can facilitate the expression of many genes, including those involved in inflammation and immune responses [245]. Hyperacetylation of HMGB1 causes translocation of this protein from the nucleus into the cytosol where it can act as a danger associated molecular pattern (DAMP), or alarmin [246]. From the cytosol, HMGB1 can be released into the extracellular compartment by disintegrating cells or by secretion from lymphocytes, including NK cells. Extracellular HMGB1 has been associated with illnesses that have fatigue as a major symptom, such as rheumatoid arthritis, atherosclerosis, and certain cancers [245]. HMGB1 attaches to several receptors, including TLR4 and the receptor for advanced glycation end-products (RAGE). Binding to these receptors induces premature cellular senescence in many cell types, including ECs and the result is disruption of endothelial barrier [247–251]. In the GI tract, dysfunctional HMGB1 signaling with RAGE and TLR4, promotes IBD, chronic pain, and the illnesses FM, ME/CFS, long COVID, and GWI (in animal models of this disease) [252–258].

HMGB1 antagonists are likely beneficial for fatigue-related disorders via anti-inflammatory and pro-efferocytotic properties. These agents include:

Glycyrrhizin (glycyrrhizic acid), a HMGB1 inhibitor and a traditional medicine, extract from the *Glycyrrhiza glabra* plant, possesses anti-inflammatory, antioxidant, and antimicrobial properties, suggesting it could be beneficial for patients with chronic fatigue [259].

Gabexate mesylate is a synthetic protease inhibitor that blocks HMGB1. This inhibitor showed promising results in preclinical studies, especially for the treatment of neuropathic pain and gut barrier dysfunction [260,261].

Anti-HMGB1 monoclonal antibodies, highly specific antibodies that have been studied for the treatment of several CNS diseases, including stroke, traumatic brain injury (TBI), Parkinson's disease, epilepsy, and AD, suggesting potentially beneficial results for ME/CFS and similar illnesses [262].

DNA and DNA-like oligonucleotide duplexes, nucleic acids that have been studied in rodents for their anti-inflammatory properties, suggesting a potential role in illnesses marked by inflammation and chronic fatigue [245].

Peptide (HBP08) is a novel pharmacological agent that targets chronic inflammation and fatigue, suggesting that it could be developed as a potential therapy for ME/CFS [263].

N-butanol extracts of *Morinda citrifolia,* that were found to lower intestinal inflammation, and pain in animal models, suggesting that such extracts could be developed for the treatment of chronic fatigue [264–266].

5.5. TLR4 Antagonists

TLR4 is a sensor for HMGB1 and LPS, molecules implicated in chronic fatigue, pain, and depression [267]. In addition, TLR4 alters efferocytosis and exacerbates *Mycoplasma* infections, suggesting that biological barriers could be enhanced by inhibiting this protein [268,269] (Table 1). Several TLR4 antagonists are in development as potential therapeutics for IBD, including:

Rhodobacter sphaeroides LPS, a non-toxic molecule that competes with the toxic LPS of Gram-negative bacteria, suggesting a potential benefit as an inhibitor of intestinal barrier disruption [270].

Eritoran (E5564), a synthetic anti-LPS molecule that is considered a second generation TLR4 inhibitor; it has a long duration of action and superior inhibitory properties [271].

TAK-242 is a TLR 4 signaling inhibitor that prevents LPS-induced muscle wasting in mice and probably influences fatigue in humans [272].

Table 1. Biological barrier enhancers.

Interventions	Mechanism	References
Senolytic agents	Selective elimination of senescent cells	[237]
Senpmorphic agents	Delete senescent markers	[238]
TMEM16F inhibitors	Block PS externalization	[239,240]
CD47 inhibitors	Promote efferocytosis	[244]
HMGB1 antagonists	Inhibit RAGE and TLR4 signaling	[245,246]
TLR4 antagonists	Promote efferocytosis	[270]
MLR	Replace oxidated membrane lipids	[273,274]

5.6. Membrane Lipid Replacement (MLR)

SARS-CoV-2-induced cellular senescence causes a phenotype typified by upregulated cytosolic iron which predisposes cells to phospholipid peroxidation of their unsaturated cell membrane glycerolphospholipids and causes ferroptosis [273,274]. Ferroptosis is an iron-induced form of programmed cell death caused by the unchecked accumulation of oxidized lipids in the absence of glutathione peroxidase 4 (GPX4) [275]. Oxidized lipids act as foreign molecules that activate host PRR, triggering chronic inflammation, neuropathic pain, depression, and neurodegeneration [276–278]. Rescue from ferroptotic cell death can be achieved by lowering intracellular iron, increasing GPX4, or replacing cell membrane oxidized lipids. As the SARS-CoV-2 virus upregulates intracellular iron by hijacking host lysosomes and ferritinophagy (ferritin autophagy), restoring cellular iron homeostasis would require lysosomal rehabilitation, a currently unavailable modality. This is illustrated by the paucity of effective treatments for lysosomal disorders [279]. In addition, ferroptotic pores enhance lipid peroxidation by Ca2+ influx, further lowering GPX4 concentrations [280,281]. Therefore, once activated, ferroptotic cell death takes on a life of its own by initiating a vicious circle of body fat "rusting" and cell death [282]. In addition, enhanced lipid peroxidation and ferroptosis have been associated with ME/CFS, FM, GWI, chronic pain, and neuropsychiatric disorders [283–287]. Interestingly, excess glucocorticoids and ANG II, predispose patients to ferroptosis, while ferroptosis-disintegrating cells release HMGB1, linking this type of programed cell death to biological barrier dysfunction [288–290].

Natural membrane phospholipid supplementation with fructooligosaccharide-protected glycerolphospholipids, containing unsaturated fatty acids, was demonstrated to safely restore the homeostasis of biological barriers, limiting microbial translocation [291]. The aim of MLR is substitution of ferroptosis-prone polyunsaturated ether phospholipids (PUFA-ePLs) and oxidized lipids with healthy unsaturated glycerolphospholipids [292,293] (Table 1).

6. Discussion

The concept of microbial translocation as a key mechanism of chronic systemic immune activation, and disease was studied extensively in the HIV infection, a condition associated with chronic fatigue and increased prevalence of ME/CFS [294,295]. COVID-19, like HIV, causes intestinal barrier disruption, impaired efferocytosis, and accumulation of senescent, apoptotic, and necrotic cells that were previously associated with dysfunctional immune responses [296,297]. Indeed, the newly discovered innate lymphoid cells 3 (ILC3) that release interleukin 22 (IL22), a protector of intestinal barrier, have been implicated in both COVID-19 and HIV, linking dysfunctional mucosal immunity to these viral infections [298,299]. As loss of IL22 was associated with premature cellular senescence, this mechanism may account for the dysfunctional efferocytosis and gut barrier dysfunction in long COVID [300]. Moreover, both IL22 and IL10 protect gut mucosal immunity and act on the same receptors, loss of these cytokines may trigger the pathogenesis of long COVID and ME/CFS [301,302]. These findings are in line not only with our earlier hypothesis but also with the results novel studies that have connected dysfunctional efferocytosis with fatiguing illnesses, including FM, ME/CFS, and GWIs [303–305].

7. Conclusions

At the cellular level, life is made possible by cell membranes that separate the intracellular from extracellular compartments and intracellular membranes that separate various organelles from the cell cytoplasm [292]. At the tissue and organismal levels, the gut barrier, comprised of a single layer of epithelial cells, separates luminal prokaryotes from host eukaryotic cells. Although during the development and early life, a limited amount of microbial translocation is thought to help "educate" the immune system to distinguish "self" from "non-self" antigens, later in life gut microbes are immunologically tolerated only in the GI tract.

Weakening of biological barriers and microbial translocation into the systemic circulation, can result in the development of various pathologies, including premature cellular senescence, redox dysfunction, autoimmunity, and elevated inflammatory markers that can be manifested clinically in a variety of forms, such as long COVID, ME/CFS, FMS, GWI, IBD, and even some neuropsychiatric disorders [293]. Ferroptotic signatures, found in these illnesses "of unknown etiology", point to lipid pathologies, a modifiable risk factor, that may be reversed via novel, strategies, including enhanced clearance of senescent cells, MLR, HMGB1 inhibitors, and TLR4 receptor blockers.

This research connects long COVID to other fatiguing illnesses, including FM, ME/CFS, and GWIs, emphasizing the role of microbial translocation outside the GI tract as the driver of these pathologies. In contrast, correcting the barrier function could ameliorate clinical symptoms as demonstrated in GWIs [293].

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