



# Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome

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Edited by Maureen R. Hanson, Cornell University, Ithaca, NY, and accepted by Editorial Board Member Philippa Marrack June 25, 2021 (received for review February 28, 2021)

Although most patients recover from acute COVID-19, some experience postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection (PASC). One subgroup of PASC is a syndrome called “long COVID-19,” reminiscent of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). ME/CFS is a debilitating condition, often triggered by viral and bacterial infections, leading to years-long debilitating symptoms including profound fatigue, postexertional malaise, unrefreshing sleep, cognitive deficits, and orthostatic intolerance. Some are skeptical that either ME/CFS or long COVID-19 involves underlying biological abnormalities. However, in this review, we summarize the evidence that people with acute COVID-19 and with ME/CFS have biological abnormalities including redox imbalance, systemic inflammation and neuroinflammation, an impaired ability to generate adenosine triphosphate, and a general hypometabolic state. These phenomena have not yet been well studied in people with long COVID-19, and each of them has been reported in other diseases as well, particularly neurological diseases. We also examine the bidirectional relationship between redox imbalance, inflammation, energy metabolic deficits, and a hypometabolic state. We speculate as to what may be causing these abnormalities. Thus, understanding the molecular underpinnings of both PASC and ME/CFS may lead to the development of novel therapeutics.

COVID-19 | chronic fatigue syndrome | myalgic encephalomyelitis | redox | mitochondria

Acute COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can be a severe and even fatal disease. Beyond the acute illness, some survivors of COVID-19, even those who are only moderately ill during the acute infection, experience postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection (PASC). They report persisting, debilitating symptoms that last for months (1). In some people, these symptoms may be secondary to COVID-19–induced damage to the lung (hypoxia) and heart (reduced cardiac output) (2), skeletal muscle (3), kidneys (abnormal acid-base or fluid balance), or brain (small infarcts or hemorrhages) (4). However, some of these PASC patients, without apparent organ damage, also have persisting, debilitating symptoms (an illness called “long COVID-19”) that are similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (5).

ME/CFS is a complex, multisystem disorder leading to debilitating symptoms including profound fatigue, postexertional malaise, unrefreshing sleep, cognitive deficits, and orthostatic intolerance. The US Centers for Disease Control and Prevention and the US National Academy of Medicine estimate that 836,000 to 2.5 million people have ME/CFS in the United States alone (6). Many cases occur following what appears to be a common, infectious-like illness. However, diagnostic tests are rarely performed to document the responsible infectious agents. Postinfectious fatigue syndromes also follow in the wake of well-documented acute infections with multiple viruses, bacteria, and even parasites (5).

In this review, we speculate that the symptoms of both long COVID-19 and ME/CFS may stem from redox imbalance—which in turn, is linked to inflammation and energy metabolic defects.

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Author contributions: B.D.P., M.D.L., A.L.K., and S.H.S. analyzed data and wrote the paper.

The authors declare no competing interest.

This article is a PNAS Direct Submission. M.R.H. is a guest editor invited by the Editorial Board.

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This article contains supporting information online at <https://www.pnas.org/lookup/suppl/doi:10.1073/pnas.2024358118/-/DCSupplemental>.

Published August 16, 2021.

## Redox Imbalance Occurs in Both COVID-19 and ME/CFS

**Oxidative and Nitrosative Stress.** Oxidative and nitrosative stress have been reported in both acute COVID-19 and ME/CFS. Oxidative stress involves imbalance between reactive oxygen species (ROS) and antioxidant defense mechanisms. Nitrosative stress is characterized by excess reactive nitrogen species (RNS), such as peroxynitrite ( $\text{ONOO}^-$ ), generated by reaction of nitric oxide (NO) with superoxide anions ( $\text{O}_2^{\cdot-}$ ). NO has important physiological functions (including vasodilation and neurotransmission). However, increased RNS with excessive NO production can be at least as damaging as ROS and also can directly attack several antioxidant enzymes, including catalase (7). Thus, oxidative stress and nitrosative stress are linked bidirectionally.

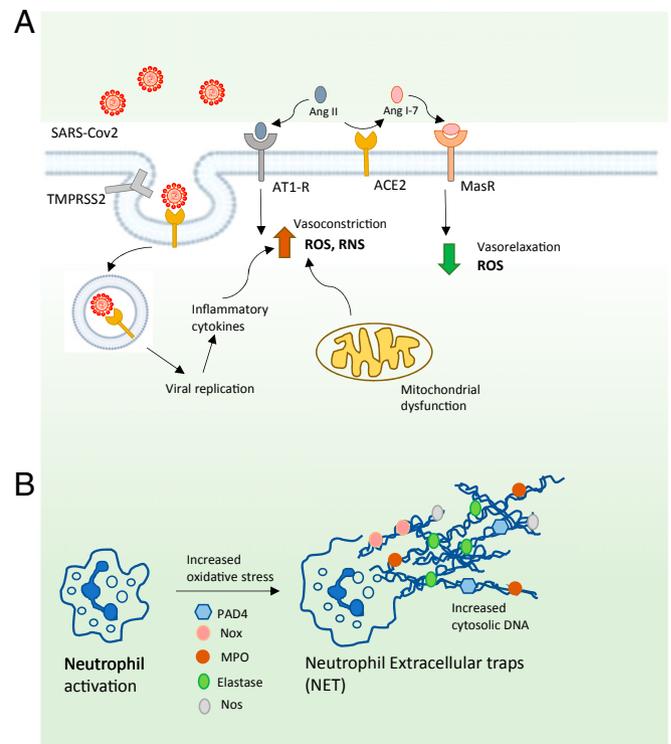
Like NO, ROS mediates physiologic cellular signaling and defense against pathogens. However, excessive ROS, when not adequately countered by antioxidants, damage cellular components including proteins, lipids, and DNA (8, 9).

**Redox Imbalance in Acute COVID-19.** Multiple examples of redox dysregulation have been reported in acute COVID-19, as is typical of many viral infections (10, 11). Overall levels of serum thiols are decreased in the serum of COVID-19 patients (12). As depicted in Fig. 1A, COVID-19 induces redox imbalance, in part because SARS-CoV-2 uses the angiotensin converting enzyme 2 (ACE2) receptor to enter cells (13, 14). This leads to accumulation of  $\text{O}_2^{\cdot-}$  as well as ROS and RNS by inducing mitochondrial dysfunction and production of proinflammatory cytokines (15).

In a computational study, binding affinity was significantly impaired when the disulfide bonds of both ACE2 and SARS-CoV-2 spike protein, which binds ACE2, were reduced to thiol groups (16). The spike protein has 40 cysteine residues, some of which contribute to the stability of interaction with the ACE2 receptor on the host (17). Analysis of the crystal structure of the spike protein with the ACE2 receptor revealed that the Cys480–Cys488 pair of the spike protein participates directly in binding to the ACE2 (18, 19). Similarly, certain cysteine residues on the ACE2 protein of the host play key roles in the interaction between the two proteins. A disulfide bond between Cys133 and Cys141 is present at the dimer interface, which has been linked to susceptibility to COVID-19 (17). Cattle and swine have a leucine residue at position 133 and are resistant to SARS-CoV-2.

Elderly subjects are more vulnerable to severe COVID-19. A linear oxidation of the plasma cysteine/cystine redox state over the entire age span and that of reduced glutathione/oxidized glutathione (GSH/GSSG) occur after ~45 y (20). The age-dependent decrease in thiol/disulfide ratio of extracellular fluids could modulate interaction of CoV-2 with the host cell in the airways. This redox-modulated binding is expected to affect the risk of severe infection in an age-dependent manner (21). Similarly, low levels of the antioxidant enzyme, alveolar Type II cell superoxide dismutase 3 (SOD3), in the lungs of the elderly correlate with severity of COVID-19 (12).

**Redox Imbalance in ME/CFS.** In people with ME/CFS, there are multiple biomarkers of oxidative stress: reduced levels of antioxidants (22); decreased levels of  $\alpha$ -tocopherol (23); increased levels of peroxides and superoxide that correlate with severity of symptoms (24); increased levels of isoprostanes, both at rest and after exercise (25); and reduced levels of thiobarbituric acid reactive substances and malondialdehyde levels, as well as reduced ascorbic acid and glutathione levels (26–30). These markers of redox imbalance also



**Fig. 1. Oxidative stress in COVID-19. (A) The ACE2 pathway.** SARS-CoV-2 infects cells harboring ACE2 and the protein transmembrane protease, serine 2 (TMPRSS2); together, these molecules prime the viral spike protein S, facilitating its entry by endocytosis. ACE2 converts angiotensin II (Ang II) to angiotensin 1 to 7 (Ang 1–7). This decreases ACE2 and elevates Ang II, which acts through the angiotensin 1 receptors (AT1-Rs), causing accumulation of superoxide radicals ( $\text{O}_2^{\cdot-}$ ) leading to hypertension and inhibition of vasodilation. Ang 1–7 binds the G-protein-coupled Mas receptor MasR, mediates vasorelaxation, and decreases  $\text{O}_2^{\cdot-}$  production. SARS-CoV-2 induces formation of reactive oxygen radicals (ROS) and RNS by eliciting mitochondrial dysfunction and production of proinflammatory cytokines. **(B) The NETs.** NETs are web-like structures extruded from activated neutrophils, comprising proteins assembled on a scaffold of decondensed chromatin, which target invading pathogens. The component proteins include oxidative and proinflammatory enzymes such as NADPH oxidase (Nox), neutrophil elastase, myeloperoxidase (MPO), NOS, and peptidyl arginine deiminase 4 (PAD4), which deaminates arginine to citrulline, resulting in the formation of citrullinated proteins (such as histone H3, causing its dissociation from DNA). Excessive accumulation of NETs causes inflammation and damage in COVID-19.

correlate with severity of symptoms (24, 31, 32). Brain magnetic resonance spectroscopy (MRS) reveals elevated levels of ventricular lactic acid consistent with oxidative stress (33–35).

When compared with healthy control subjects, people with ME/CFS also have multiple biomarkers of nitrosative stress: increased inducible nitric oxide synthase (NOS) with consequent increased NO, peroxynitrite, and nitrate, particularly following exercise (36, 37).

Immune responses to oxidized fatty acids (oleic, palmitic, and myristic acids) and markers of lipid peroxidation (such as malondialdehyde, acetylcholine, S-farnesyl-L-cysteine, and several NO-modified amino acids) also are significantly greater in ME/CFS patients as compared with controls (38, 39).

Metabolomic studies in plasma from ME/CFS subjects are consistent with these findings, revealing altered plasma levels of choline, carnitine, and complex lipid metabolites—consistent with oxidative stress and mitochondrial dysfunction (40–43).

## Elevated Levels of Prooxidants in COVID-19 and ME/CFS

As summarized in Table 1, increased levels of prooxidants have been reported in both acute COVID-19 and ME/CFS.

**Dysregulated Heme and Iron Homeostasis.** Increased levels of free iron in cells (44) and increased ferritin levels (45) both can cause oxidative damage (44). Iron stored in heme molecules is degraded via the bilirubin pathway, an important component of antioxidant defense (46, 47). Evidence of dysregulated heme and iron homeostasis has been reported in acute COVID-19 and ME/CFS (Table 1).

**Homocysteine.** Elevated levels of the amino acid homocysteine, seen in both acute COVID-19 and ME/CFS (Table 1), cause increased oxidative stress and are a risk factor for various cardiovascular diseases and dementia. Elevated homocysteine levels may indicate suboptimal activities of reverse transsulfuration enzymes or dysregulation of their cofactors and/or regulators (44, 48, 49).

**Neutrophil Extracellular Traps.** Neutrophils attack invading pathogens by forming neutrophil extracellular traps (NETs) and generating both ROS and RNS (50–53) (Fig. 1B). Abnormalities of

neutrophil biology have been reported in both acute COVID-19 and ME/CFS (Table 1).

**Abnormal Metabolism Involving the Gaseous Signaling Molecules NO and Hydrogen Sulfide.** The major gaseous signaling molecules include NO, carbon monoxide, and hydrogen sulfide (H<sub>2</sub>S). They play key roles in the regulation of blood pressure, inflammation, and neurotransmission (54, 55). Under physiological conditions, both NO and H<sub>2</sub>S have anti-inflammatory effects (48, 56). However, both deficient and excess production of these gaseous signaling molecules can create brain pathology, immune dysfunction, and redox imbalance (56, 57).

**NO.** NOS2 is significantly up-regulated in patients with severe and critical COVID-19 (58). There is evidence of nitrosative stress and disordered NO metabolism in people with ME/CFS (38). Levels of NO are higher in ME/CFS patients, which can accelerate nitrosative stress (27). Citrulline, a product of arginine metabolism by NOS, also is increased in ME/CFS (59).

**H<sub>2</sub>S.** Normal H<sub>2</sub>S metabolism protects against inflammation and redox imbalance (48, 60, 61). One of the modes by which H<sub>2</sub>S functions is by a posttranslational modification termed persulfidation or sulphydration (48, 62), which prevents irreversible oxidation of

**Table 1. Redox-related alterations shared by both COVID-19 and ME/CFS**

Redox-related alteration	COVID-19	ME/CFS
Iron and heme metabolism	Hyperferritinemia (171–174) Elevated bilirubin levels (175) Decreased bilirubin (176)	Decreased serum transferrin, elevated heme (26, 43)
Homocysteine	Increased blood levels (177, 178)	Increased cerebrospinal fluid levels (179)
Elevated superoxide levels	Negative correlation between decreased SOD3 in lungs of elderly patients with COVID-19 and disease severity (12)	Decreased expression and activity of SOD (27, 180)
Neutrophil response	In severe disease, elevated numbers of neutrophils and a high neutrophil to lymphocyte ratio; high ratio positively correlated with mortality (90, 120, 181); NETs observed	Neutropenia and a reduced oxidative burst (182), possibly secondary to an initially aggressive neutrophil response, had led to neutrophil exhaustion, similar to lymphocyte exhaustion seen (182)
NO	NOS2 is significantly up-regulated in patients with severe disease (58)	High levels of NO (27, 38); citrulline, a product of arginine metabolism by NOS, also increased (59)
H <sub>2</sub> S	Survivors have higher serum levels of H <sub>2</sub> S and higher numbers of circulating lymphocytes (70), perhaps because H <sub>2</sub> S stimulates T cell proliferation (71)	Dysregulation of H <sub>2</sub> S may play a role in ME/CFS (73) H <sub>2</sub> S can induce a torpor-like state in mice (74) No studies yet of H <sub>2</sub> S regulation in humans
Tryptophan metabolites	Decreased tryptophan, serotonin, and indolepyruvate levels and increased kynurenine, kynurenic acid, picolinic acid, and nicotinic acid (183) NAD metabolome depressed in SARS-CoV-2-infected cells and patient samples, and levels of NAD biosynthetic enzymes also are elevated in SARS-CoV-2-infected cells, possibly as a compensatory mechanism (184)	Nicotinamide phosphoribosyl transferase levels altered in peripheral blood mononuclear cells from ME/CFS patients (129)
Glutathione	Low blood levels of GSH in severe disease (185); severity of COVID-19 linked to decreased levels of vitamin D (185, 186)	Low GSH levels in the cortex of the brain and plasma (33, 187) Decreased SOD, catalase, glutathione peroxidase, and glutathione reductase activities in erythrocytes (27)
Cysteine	Cysteine levels decreased in serum, while levels of oxidized cysteine are higher (183) Cystine and methionine (methionine sulfoxide) increased (183)	Low levels of cystine, the oxidized form of cysteine, and increased levels of cystine and methionine (methionine sulfoxide) in the peripheral blood mononuclear cells of people with ME/CFS (188)
Selenium	Selenium levels low (189) and negatively correlated with recovery (189–191)	Unstudied
Vitamin C/ascorbate	Low plasma levels (192)	Low plasma levels (31, 193)
NAD metabolism	Nicotinamide phosphoribosyl transferase and nicotinamide riboside kinase increased (194)	Nicotinamide phosphoribosyl transferase levels increased (97)
Vitamin E levels	Low serum levels in pregnant women (195)	Decreasing serum levels correlate with severity of symptoms and levels increase in remissions (23, 196) Also, decreased levels in pediatric cases (193)

proteins (63, 64). H<sub>2</sub>S metabolism is disrupted in Alzheimer's disease, Parkinson's disease, and Huntington's disease and also, during aging (63, 65–67). H<sub>2</sub>S inhibits tau-phosphorylation, which may explain, in part, its role in protecting against Alzheimer's disease (68, 69).

Dysregulated H<sub>2</sub>S metabolism has been reported in acute COVID-19. Survivors reportedly exhibit higher serum levels of H<sub>2</sub>S and higher numbers of circulating lymphocytes (70); H<sub>2</sub>S stimulates T cell proliferation (71). Indeed, exogenous H<sub>2</sub>S therapy may be beneficial in mild to moderate COVID-19 disease (72).

Dysregulation of H<sub>2</sub>S may play a role in ME/CFS since the gas can affect adenosine triphosphate (ATP) production from oxidative phosphorylation (73). H<sub>2</sub>S can induce a torpor-like state in mice (74). However, studies of H<sub>2</sub>S regulation in people with ME/CFS have not yet been reported.

**Altered Levels of Tryptophan Metabolites.** Tryptophan serves as a precursor for nicotinamide adenine dinucleotide (NAD<sup>+</sup>) biosynthesis, making it important in redox balance. Abnormalities in the pathways by which tryptophan is transformed into serotonin or kynurenine pathway metabolites (75) have been reported in both acute COVID-19 and ME/CFS (Table 1), and can cause both oxidative stress and excitotoxicity (27).

### Reduced Levels of Small Molecule Antioxidants in Acute COVID-19 and ME/CFS

As summarized in Table 1, decreased levels of antioxidants have been reported in both acute COVID-19 and ME/CFS. Foremost among these small molecules is glutathione, which helps modulate immune activation (76, 77). Glutathione also enhances vitamin D metabolism (78) and vitamin D, in turn, reciprocally increases glutathione and decreases oxidative stress and levels of inflammatory cytokines and chemokines (79). The antioxidant small molecules also include cysteine, a semiessential amino acid synthesized endogenously via the reverse transsulfuration pathway (80) (*SI Appendix, Fig. S1*); selenium, an essential micronutrient incorporated into various selenoproteins which have antioxidant roles; vitamin C/ascorbate, which exerts antiviral and immunomodulatory effects (81) and vitamin E compounds, which have free radical scavenging and antiinflammatory activities (82).

### Impaired Energy Metabolism in COVID-19 and ME/CFS

**Impaired Energy Metabolism in Acute COVID-19.** Mitochondrial dysfunction has long been associated with fatigue (83), causes elevated oxidative stress, and could contribute to the symptoms of fatigue found in both acute COVID-19 and ME/CFS (84).

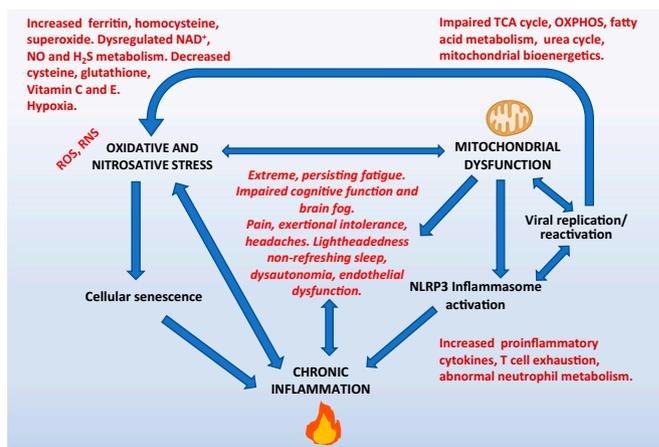
Mitochondrial dysfunction also has been linked to the pathogenesis of COVID-19. SARS-CoV-2 hijacks mitochondrial function and alters host metabolic pathways and immune response to facilitate pathogenesis. For instance, mitochondrial dysfunction triggered by SARS-CoV-2 causes accumulation of mitochondrial DNA (mtDNA) in the cytosol, leading to mtDNA-induced inflammasome activation and suppression of innate and adaptive immunity (85). The virus interferes with the RIG1-MAVS pathway to decrease type I interferon (IFN) production (86). SARS-CoV-2 infection of white blood cells leads to elevated glycolysis, increased mitochondrial reactive oxygen species (mtROS) production, and dysregulated mitochondrial bioenergetics (87, 88). In this study, the role of redox imbalance secondary to mitochondrial dysfunction in SARS-CoV-2 pathology was apparent; two potent antioxidants reduced viral load and proinflammatory cytokines. Elevated levels of lactate

dehydrogenase (LDH) were also reported in COVID-19 (89, 90), which could reflect mitochondrial dysfunction.

**Impaired Energy Metabolism in ME/CFS.** Metabolomic studies have reported evidence of impaired ATP production from oxygen, glucose, fatty acids, and amino acids in multiple cell types (41, 42, 91–94). Not just oxidative phosphorylation but also glycolysis—and possibly, the citric acid and urea cycles—are incriminated. In people with ME/CFS, there also is a more general hypometabolic state as previously proposed (73), characterized by depressed levels of most metabolites, as occurs in hibernating animals (41). Later, we speculate as to the cause of this hypometabolic state.

Both structural and functional mitochondrial abnormalities have been found in ME/CFS. Branching and fusion of mitochondrial cristae are observed in muscle biopsies of some patients (84). Although some studies have reported deletions of mtDNA genes, the most extensive controlled study using contemporary technology did not find mtDNA variants that correlated with susceptibility to ME/CFS—although it did find a correlation between specific haplogroups and mtDNA single-nucleotide polymorphisms and specific symptoms (95). Other reports have identified a deficit in Complex V (ATP synthase) activity of the electron transport chain (ETC) in lymphocytes, with a compensatory up-regulation of respiratory capacity (96, 97), and a decrease in mitochondrial membrane potential in CD8<sup>+</sup> T cells (98). Serum from ME/CFS patients reportedly contains a factor that induces mitochondrial fragmentation (99).

Clinical studies also indicate mitochondrial dysfunction. People with ME/CFS have significantly higher blood lactate levels after exercise as compared with controls, indicative of reduced oxidative phosphorylation and a switch to anaerobic glycolysis (100–102). Elevated lactate levels also have been reported in the ventricles of ME/CFS patient brains (33–35, 103). As in COVID-19, elevated serum LDH levels also are seen (104). LDH is a critically important enzyme in energy metabolism, catalyzing the bidirectional conversion of lactate to pyruvate and NAD<sup>+</sup> to reduced



**Fig. 2. The interactions between redox imbalance, mitochondrial dysfunction, chronic inflammation, and related symptoms. As explained in the text, redox imbalance, mitochondrial dysfunction, and inflammation are bidirectionally related to each other and may cause some of the symptoms of both long COVID-19 and ME/CFS. The bidirectional connections mean that an initial abnormality in one component can trigger abnormalities in other components and can precipitate a persistent, self-reinforcing pathological process.**

NAD<sup>+</sup> (NADH). Thus, an elevated level in the blood of subjects in a resting state could indicate a system struggling to generate energy. Alternatively, the elevated blood levels of LDH could indicate tissue destruction, such as occurs in malignancies or red blood cell hemolysis.

Finally, people with ME/CFS reportedly have significantly decreased levels of plasma coenzyme Q10 (CoQ10), whose levels correlate inversely with the degree of fatigue, impaired concentration and memory, and symptoms of autonomic dysfunction (105, 106). CoQ10/ubiquinone, a component of the ETC, can have both prooxidant and antioxidant effects, as well as anti-inflammatory effects (107).

The causes of mitochondrial dysfunction in people with ME/CFS remain speculative. Viral infection surely can cause impairment of mitochondrial structure (99) and function (97, 108), and impairment of mitochondrial function, in turn, encourages viral replication and T cell exhaustion (108). Immune activation, with the generation of proinflammatory cytokines, also can cause mitochondrial fragmentation, hyperpolarization of the mitochondrial membrane, and the generation of ROS (109).

### Connecting Redox Imbalance to Inflammation in COVID-19 and ME/CFS

**Connections between Inflammation and Redox Imbalance.** Systemic inflammation and neuroinflammation are seen in both acute COVID-19 and ME/CFS. Inflammation, in turn, is bidirectionally linked to redox imbalance (110); inflammation generates ROS and RNS, and redox imbalance causes cellular damage that evokes an inflammatory response, leading to vicious cycles (111, 112).

Glutathione plays a particularly important role in enabling and modulating the immune response (76). It is vital for proliferation of T lymphocytes; T cell activation, in turn, generates glutathione, which counters ROS levels and mediates a metabolic shift toward aerobic glycolysis and glutaminolysis (113)

Other connections between inflammation and redox imbalance exist as well. Higher interleukin-2 (IL-2) levels stimulate NO production (114, 115), and IL-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) stimulate cells to produce O<sub>2</sub><sup>•-</sup> (116, 117). Mitochondrial dysfunction also leads to increased proinflammatory responses and increased ROS levels.

**Inflammation in COVID-19 and Redox Imbalance.** The cytokine storm seen in severe cases of COVID-19 has been well characterized (118, 119). The nucleotide-binding oligomerization domain-like receptor containing pyrin domain 3 (NLRP3) inflammasome plays a key role in the effects of the cytokine storm; NLRP3, in turn, is activated by oxidative stress (118). Increased levels of the proinflammatory markers, C-reactive protein and IL-6, were associated with the disease (120).

Immunologic factors that correlated with more severe disease and higher mortality include neutrophilia, lymphocytopenia, low CD4<sup>+</sup> T cells, decreased C3, very low human leukocyte antigen D-related expression, and low numbers of CD19 lymphocytes and natural killer (NK) cells (121). In addition to these changes, COVID-19 is associated with inadequate Type I and Type III IFN responses and elevated chemokine expression (122–124). Finally, T cell exhaustion is commonly seen in COVID-19 and could be explained by low levels of glutathione (125).

**Inflammation in ME/CFS and Redox Imbalance.** The fatigue and cognitive deficits in people with ME/CFS are associated with neuroinflammation; positron emission tomography imaging reveals increased activation of microglia, astrocytes, and elevated

levels of cytokines in the brain and spinal cord (126, 127). Increased levels of various cytokines can trigger many of the symptoms of ME/CFS (and post-COVID-19 syndrome), as became clear in the 1980s when various cytokines were synthesized and used as treatments. For example, when IFN I- $\alpha$  is given as antiviral therapy, it induces persistent fatigue in patients with chronic hepatitis C virus infection (128).

In ME/CFS, the systemic circulation often contains elevated levels of inflammatory biomarkers—proinflammatory cytokines like IL-1 and TNF- $\alpha$  (106). Also, circulating lymphocytes often produce increased transcripts of these cytokines (129). Both COVID-19 and ME/CFS are associated with activation of the protein kinase R and 2- to 5A synthetase antiviral IFN response pathways (130–132).

People with ME/CFS often have increased numbers of CD8<sup>+</sup> T cells bearing activation antigens (133), although persistent T cell activation then may lead to exhaustion (134). Another characteristic finding in people with ME/CFS is impaired NK cell function (135). Redox imbalance leading to increased levels of L-kynurenine and lactate can impair NK cell function (136).

### Connecting Redox Imbalance, Inflammation, and Energy Metabolism

Viral infection triggers increased mitochondrial function and sometimes, mitochondrial damage. In either case, increased ROS are produced. ROS, in turn, damage mtDNA and proteins, including those comprising the ETC, causing a decrease in ATP production (137, 138). In COVID-19, damage to endothelial cells results in chronic inflammation, thrombosis, atherosclerosis, and lung injury. Endothelial mitochondria modulate these inflammatory pathways via redox signaling, involving mtROS. However, continued elevation of mtROS leads to senescence, promoting inflammation and chronic endothelial dysfunction, culminating in vicious cycles that involve ROS, inflammation, and mitochondrial dysfunction (139, 140).

A mode by which mitochondrial dysfunction causes inflammation is by activating the NLRP3 inflammasome in immune cells. The NLRP3 inflammasome participates in the processing and release of inflammatory cytokines, such as IL-1 $\beta$  and IL-18 (141). Damaged ROS-generating mitochondria can elicit persistent inflammation via NLRP3 inflammasome-dependent inflammatory pathways (142). Additionally, damaged mitochondria mount inflammatory responses by releasing mtDNA into the cytosol; the DNA and its purinergic components function as a damage-activated molecular pattern to trigger the innate immune system (143, 144). Finally, mitochondria also modulate both adaptive and innate immune responses (143, 145, 146). In COVID-19, a dysregulation of the innate immune system has been observed, causing aberrant engagement of antiviral signaling cascades, which facilitates evasion of the host immune system and which is linked to mitochondrial function as described earlier (85, 86, 147). Thus, infection and inflammation are intimately linked to energy metabolism and redox imbalance (Fig. 2).

### Hypometabolic State, the Cell Danger Response, and Integrated Stress Response

What might cause the hypometabolic state reported in ME/CFS? Dysregulated H<sub>2</sub>S production can induce a hypometabolic, torpor-like state in mice (73, 74). In addition, any of several stressors, including viral infection and oxidative stress, can trigger evolutionarily conserved protective responses that operate at the level of both the cell (the cell danger response) (148) and the whole organism (the integrated stress response, hibernation, and the state of dauer in *Caenorhabditis elegans*) (121, 149, 150). These protective responses generally are reversible when the stressor no longer is present. Since dysregulated H<sub>2</sub>S production can induce a hypometabolic, torpor-like state in mice

(74), H<sub>2</sub>S production may be one potential switch (73). Since protein translation consumes considerable ATP, a reduction in protein translation thereby makes ATP available for repair of injury and preservation of vital functions.

The hypometabolic state seen in ME/CFS (and that may be seen in PASC) could be secondary to a persisting stressor (such as redox imbalance or viral infection), or it could result from a defect in the “switch” that turns off the protective state. Abnormalities in purinergic signaling secondary to mitochondrial damage (151, 152) and mitochondrial dysfunction of any cause (153) are often associated with cellular and organism stress responses, and each has been linked to a wide variety of neurological disorders.

### Potential Redox-Based Therapeutics

Several therapies targeting redox imbalance already have been utilized or proposed for the treatment of disease. NO inhibits the replication of SARS-CoV-2 in vitro (154) and improves oxygenation in people with COVID-19 when administered by inhalation (155). Small studies of ubiquinol (156) and of a combination of NADH and CoQ10 (157) have reported clinical benefit. Many other potential treatments targeting redox imbalance also deserve consideration: for example, glutathione (and glutathione donors), N-acetyl cysteine, cysteamine, sulforaphane, ubiquinol, nicotinamide, melatonin, selenium, vitamin C, vitamin D, vitamin E, melatonin plus pentoxifylline, disulfiram, ebselen, and corticosteroids. In two cases of acute COVID-19, glutathione administered therapeutically counteracted dyspnea associated with COVID-19 pneumonia and reduced pulmonary inflammation (158).

In rodents, administering H<sub>2</sub>S donors reduced inflammation and oxidative stress and attenuated ventilator-induced lung injury as well as injury induced by pneumonia (159, 160). In addition, the H<sub>2</sub>S donor, GYY4137, suppressed replication of enveloped RNA viruses like SARS-CoV-2 (161–163). Additionally, the H<sub>2</sub>S donor, sodium hydrosulfide, inhibits platelet activation, NET formation, DNA, and ROS levels while decreasing SOD in the hyperhomocysteinemia (HHcy) group (164). Thus, treatment of acute COVID-19 with H<sub>2</sub>S donors may be efficacious (165).

A screen for inhibitors of the main protease of SARS-CoV-2 identified ebselen, an organoselenium compound, as a potential inhibitor for the protease, M<sup>Pro</sup> or NSP5, and a therapeutic agent for COVID-19 (166, 167).

In general, however, oral therapies directed at restoring redox balance have not produced dramatic improvements in conditions associated with redox imbalance (168). No single antioxidant can scavenge or neutralize the wide variety of ROS and RNS single-handedly. Hence, up-regulating pathways that counteract multiple abnormalities and bolster antioxidant defense and balance may be more beneficial. The timing of intervention may also be critical.

### Concluding Remarks

People with acute COVID-19 and people with ME/CFS share redox imbalance, systemic inflammation and neuroinflammation, impaired production of ATP and other abnormalities in common (Fig. 2), abnormalities that have bidirectional connections (169).

The syndrome of long COVID-19 that can develop in some COVID-19 survivors (people called “long haulers”) is very similar to ME/CFS, so it may well be that the group of abnormalities seen in acute COVID-19 and in ME/CFS also will be seen in long COVID-19. Presumably, redox abnormalities in COVID-19 are secondary to the infection with SARS-CoV-2. The same may be true among those ME/CFS patients whose illness began with an “infectious-like” illness.

Clearly, COVID-19-induced permanent damage to the lungs (chronic hypoxia), heart (congestive failure), and kidneys (fluid and acid-base abnormalities) could cause some of the persisting symptoms seen in long COVID-19. In both long COVID-19 and ME/CFS other symptoms (e.g., fatigue, brain fog) may be generated by neuroinflammation, reduced cerebral perfusion due to autonomic dysfunction, and autoantibodies directed at neural targets, as summarized elsewhere (170).

As many as 2.5 million people suffer from ME/CFS in the United States (6). The COVID-19 pandemic may generate a similar number of cases of long COVID-19 in the coming 1 to 2 y (5). It therefore is imperative that increased research be focused on both long COVID-19 and ME/CFS. Fortunately, the United States and several other countries have committed substantial funding to study chronic illnesses following COVID-19, one of which is long COVID-19. Two registries and associated biobanks of people with long COVID-19 and/or ME/CFS are available to aid research.\* We suggest that the study of the connections between redox imbalance, inflammation, and energy metabolism in long COVID-19 and in ME/CFS may lead to improvements in both new diagnostics and therapies.

**Data Availability.** There are no data underlying this work.

### Acknowledgments

This work was supported by Solve ME/CFS Initiative Grant 90089823 (to B.D.P.); the American Heart Association/Paul Allen Frontiers Group Project 19PABH134580006 (to B.D.P., S.H.S., and associates); US Public Health Service Grant 5U54AI138370 (to A.L.K.); and US Public Health Service Grant DA044123 (to S.H.S.). We acknowledge BioRender for the use of icons in figures and thank Julia Lemle for her artistic input in Fig. 2. A.L.K. thanks Jill Mazzetta for help in collecting pertinent literature. We thank the reviewers for several valuable suggestions.

\*They are the You + M.E. Registry (<https://youandmecovid.com/home>) and NIH (<https://searchmecfs.org/>).

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