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REVIEW

SARS-CoV-2 Infection Dysregulates Host Iron (Fe)-Redox Homeostasis (Fe-R-H): Role of Fe-Redox Regulators, Ferroptosis Inhibitors, Anticoagulants, and Iron-Chelators in COVID-19 Control

Sreus A.G. Naidu[a], Roger A. Clemens[b] and A. Satyanarayan Naidu[a]

[a]N-terminus Research Laboratory, Yorba Linda, CA, USA; [b]Department of International Regulatory Science, University of Southern California School of Pharmacy, Los Angeles, CA, USA

ABSTRACT

Severe imbalance in iron metabolism among SARS-CoV-2 infected patients is prominent in every symptomatic (mild, moderate to severe) clinical phase of COVID-19. *Phase-I – Hypoxia* correlates with reduced O_2 transport by erythrocytes, overexpression of HIF-1α, altered mitochondrial bioenergetics with host metabolic reprogramming (HMR). *Phase-II – Hyperferritinemia* results from an increased iron overload, which triggers a fulminant proinflammatory response – the acute cytokine release syndrome (CRS). Elevated cytokine levels (i.e. IL6, TNFα and CRP) strongly correlates with altered ferritin/TF ratios in COVID-19 patients. *Phase-III – Thromboembolism* is consequential to erythrocyte dysfunction with heme release, increased prothrombin time and elevated D-dimers, cumulatively linked to severe coagulopathies with life-threatening outcomes such as ARDS, and multi-organ failure. Taken together, Fe-R-H dysregulation is implicated in every symptomatic phase of COVID-19. Fe-R-H regulators such as lactoferrin (LF), hemoxygenase-1 (HO-1), erythropoietin (EPO) and hepcidin modulators are innate bio-replenishments that sequester iron, neutralize iron-mediated free radicals, reduce oxidative stress, and improve host defense by optimizing iron metabolism. Due to its pivotal role in 'cytokine storm', ferroptosis is a potential intervention target. Ferroptosis inhibitors such as ferrostatin-1, liproxstatin-1, quercetin, and melatonin could prevent mitochondrial lipid peroxidation, up-regulate antioxidant/GSH levels and abrogate iron overload-induced apoptosis through activation of Nrf2 and HO-1 signaling pathways. Iron chelators such as heparin, deferoxamine, caffeic acid, curcumin, α-lipoic acid, and phytic acid could protect against ferroptosis and restore mitochondrial function, iron-redox potential, and rebalance Fe-R-H status. Therefore, Fe-R-H restoration is a host biomarker-driven potential combat strategy for an effective clinical and post-recovery management of COVID-19.

KEYWORDS

COVID-19; ferroptosis inhibitors; Fe-R-H regulators; host metabolic reprogramming (HMR); iron chelators; iron-redox homeostasis (Fe-R-H)

CONTACT A. Satyanarayan Naidu asnaidu@nterminus.com 23659 Via del Rio, Yorba Linda, CA 92887, USA.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of the novel *coronavirus disease* (COVID-19) was isolated in the winter of 2019. On March 11, 2020, the World Health Organization (1) declared the COVID-19 outbreak a global pandemic (2). Based on the *W.H.O. Coronavirus (COVID) Dashboard* (as of Apr 19, 2022), this pandemic has so far recorded about 503 million confirmed cases and claimed 6.2 million deaths worldwide. Global campaigns for vaccination were rolled out faster than ever; however, the SARS-CoV-2 infections remain beyond control. Despite administration of 11.3 billion doses of vaccine to date, about 0.4 million cases of COVID-19 are reported every single day (W.H.O. 2022). The emergence of fast-spreading SARS-CoV-2 variants – *Alpha*-(B.1.1.7); *Beta*-(B.1.351); *Gamma*-(P.1) *Delta*-(B.1.617.2), *Mu*-(B.1.621) and *Omicron* (B.1.1.529) have already disrupted several vaccination and public health safety protocols (3). Unfortunately, there is no effective 'multivalent vaccine' yet that could provide immune protection against multiple SARS-CoV-2 variants. This global health crisis highlights the dire necessity for identification and characterization of specific antiviral intervention strategies that target highly conserved domains, which are less likely to mutate in the SARS-CoV-2 genome (4).

Available clinical data on the symptomatic manifestations of SARS-CoV-2 infection are extensive; however, the pathobiological spectrum and the host biomarker profiles during the sequential and progressive (asymptomatic, mild, moderate, severe to fatal) phases of COVID-19 remains elusive. During early stages of infection, the viral pathogen specifically targets the hematopoietic system and alters the '*iron (Fe)-redox homoeostasis* (Fe-R-H)' (5,6). Critical steps involved in the pathogenesis of COVID-19 include, that a genetically competent (virulent) SARS-CoV-2 virus: (1) infects and invades a susceptible host *via* specific cell surface receptors, (2) induces a '*host metabolic reprogramming* (HMR)' to ensure ready access to an active host cellular machinery for an uninterrupted viral replication, (3) inactivates the innate host defense arsenal to evade viral elimination, and (4) exits the infected host cell and repeats the viral propagation cycle for exponential growth and transmission (7). In accordance with its virulence spectrum and host susceptibility patterns, the clinical outcomes of SARS-CoV-2 infection are manifested into three major iron (Fe)-redox disruptive hematological conditions: (1) *Hypoxia/Hypoxemia*, an acute depletion of oxygen (O_2) transport in the blood (8,9); (2) *Hyperferritinemia*, an excess presence of iron storage protein, ferritin, in the blood (10,11); and (3) *Thromboembolism,* formation of blood clots with severe obstruction of veins, arteries and circulation (12,13).

Severe complications in COVID-19 patients such as *acute respiratory distress syndrome* (ARDS), *multiorgan dysfunction syndrome* (MODS), *Kawasaki-like disease*, are directly linked to local Fe-R-H disruption in damaged tissues and abnormal coagulation in blood vessels (14). Therefore, Fe-R-H dysregulation is a major risk factor and a common denominator in every sequential and progressive phase of SARS-CoV-2 infection (Figure 1).

This narrative review elucidates the defining role of Fe-R-H dysregulation in sequential and progressive phases of COVID-19 pathogenesis. An attempt has been made to describe the clinical outcomes of iron overload and O_2 depletion on *host metabolic*

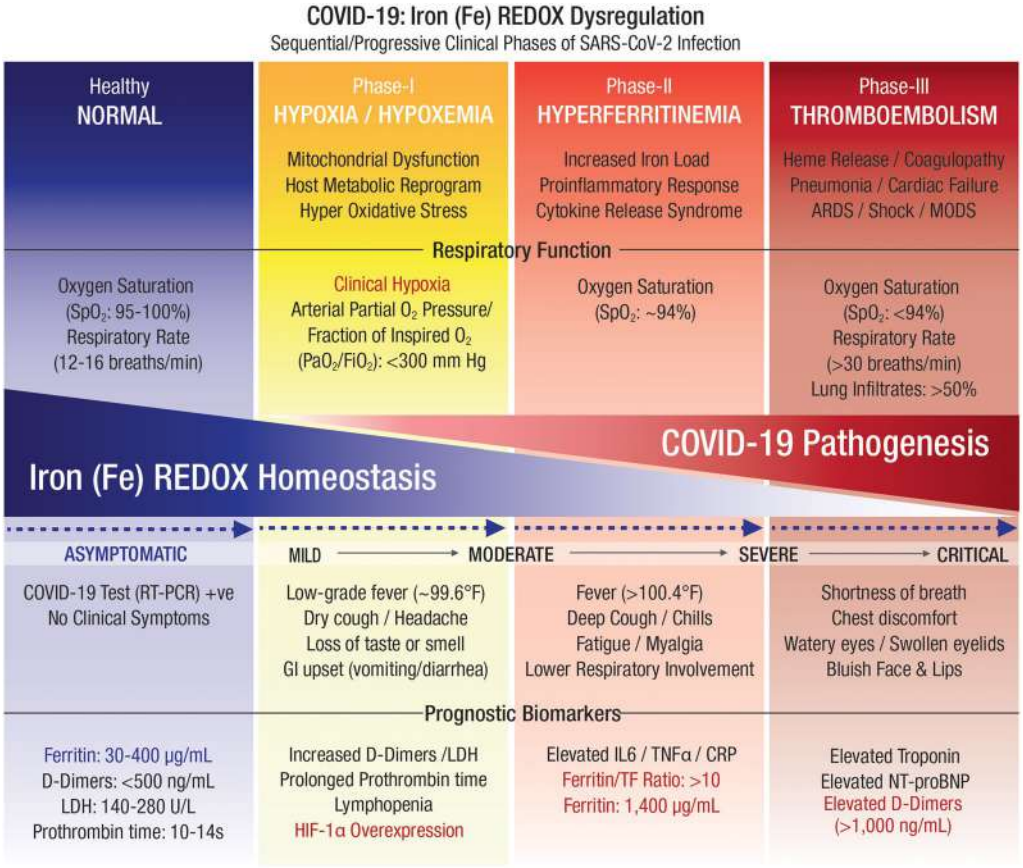

Figure 1. COVID-19: A severe dysregulation of iron (Fe)-redox homestasis (Fe-R-H). The pathobiological spectrum of SARS-CoV-2 infection suggests that COVID-19 is a clinical culmination of severe Fe-R-H dysregulation. Acute and progressive clinical imbalance in the iron metabolism of SARS.CoV-2 infected individuals is manifested in three symptomatic phases during the sequential development (mild, moderate to severe cases) of COVID-19. Phase-I – Hypoxia/Hypoxemia during the initial or mild stage of infection, leads to a distinct loss of taste (ageusia) and/or smell (anosmia). This early phase correlates with an overexpression of HIF-1α, which eventually alters mitochondrial function and sets the HMR. Phase-II – Hyperferritinemia resulting from an increased iron overload triggers proinflammatory responses that unleash an acute cytokine release syndrome (CRS). This clinical condition advances the COVID-19 patient from moderate to severe stage of the disease. During the CRS, elevation of specific cytokines (i.e. IL6, TNFα and CRP) strongly correlates with the altered ferritin/TF ratios in patients. Phase-III – Thromboembolism ensues as COVID-19 transits to the next level of life-threatening clinical state. Pneumonia with extreme lung infiltrates, RBC dysfunction with heme release contributes to severe coagulopathies and dire consequences including cardiac shock, ARDS with multi-organ failure. Elevated D-dimers and troponin serve as prognostic biomarkers to evaluate the severity of COVID-19 cases. Taken together, a severe imbalance in Fe-R-H plays a critical role in all three clinical phases of COVID-19 pathology.

reprogramming (HMR), mitochondrial dysfunction, and host energy metabolism, with cumulative effects on systemic manifestation of Fe-R-H-mediated hematological syndromes. Furthermore, specific biomarker signatures in response to HMR with implications in diagnostic, prognostic, and therapeutic management of COVID-19 have

been explained. Finally, a few potential Fe-R-H restoring strategies using Fe-redox regulators, ferroptosis inhibitors, and iron-chelators to relieve the symptomatic burden, reduce the disease severity and to improve the recovery of COVID-19 infected individuals has been discussed.

Iron and human physiology

Iron (Fe) is intimately linked to oxygen (O_2) and this metal element exists in two redox states: ferrous (Fe^{2+}) and ferric (Fe^{3+}), wherein both electron transitions regulate several fundamental cellular processes (15), including O_2 transport, energy metabolism, DNA/RNA synthesis, and cell survival as well as ferroptosis (16,17). The iron-containing non-enzymatic heme proteins such as *hemoglobin (Hb)* and *myoglobin (Mb)* are involved in transport and storage of O_2 in biological systems (18). As the primary protein in red blood cells (RBC), Hb represents about two-thirds of the body's iron. The enzymatic heme proteins, *cytochromes,* play a role in mitochondrial electron transport chain, and the iron-sulfur (Fe-S) cluster proteins, *oxidoreductases*, contribute to the cellular energy (ATP) production (19). The iron-based redox enzymes (i.e. *peroxidases, catalases, nitric oxide synthase, cyclooxygenase*) scavenge free radicals and protect cells from toxic reactive oxygen/nitrogen species (ROS/RNS). Other Fe-S cluster enzymes, such as *ribonucleotide reductases* (RNRs), *DNA polymerases* and *DNA helicases*, facilitate DNA synthesis and repair (20). Also, iron is involved in the synthesis of neuroglobin and neurotransmitters such as *dopamine, norepinephrine,* and *serotonin*, which are essential for cognitive function (21). Iron is stored by ferritin and transported in body fluids by iron-binding proteins *transferrin* (TF) and *lactoferrin* (LF) (22,23). Taken together, iron is a quintessential element in the genesis and evolution of life on our Blue Planet.

In human physiology, the dietary iron absorption is regulated in the GI tract *via* hepcidin from macrophages and eventually contributes to the surge in serum ferritin levels (24). Free iron compounds such as 'non-transferable bound iron' and 'labile plasma iron' accumulate in plasma and cells *via* saturated *iron-storage proteins* (ISPs) (25). Iron is potentially toxic due to its redox activity. Insufficient iron supply to erythroid cells, the major iron consumer in the body, leads to various forms of anemia. On the other hand, iron overload (hemochromatosis) may lead to tissue damage and diseases of liver, pancreas, and heart. Therefore, Fe-R-H is tightly regulated at the cellular and systemic level by *iron regulatory proteins* (IRP1, IRP2) and *hepcidin* (26). The *nuclear factor (erythroid-derived 2)-like 2* (Nrf2) *transcription factor* responds to oxidative/electrophilic stress and regulates several genes involved in iron metabolism, heme synthesis, Hb catabolism, iron storage, and iron export (27).

Iron (Fe)-redox-homeostasis (Fe-R-H)

Fe-R-H depends on the expression and activity of iron-carriers, iron-transporters, iron-regulators, and iron-storage proteins. *Divalent metal transporter 1* (DMT1) located in the intestinal enterocyte sequesters non-heme iron from the diet, and *ferroportin 1* (FPN1) exports iron into the circulation (28). Plasma TF and LF transport iron to various tissues and cells. After binding to *transferrin receptor 1* (TfR1), the complex

is endocytosed and release iron into the cytoplasm (29). Free iron is utilized either for metabolism, or sequestered by the cytosolic *ferritin*, as cellular iron reserve. Excess iron is exported from the cell *via* FPN1 and *hepcidin* (30). Intra-cellular IRPs modulate the expression of DMT1, TfR1, ferritin, and FPN1 *via* binding to the *iron-responsive element* (IRE) (31,32). The systemic Fe-R-H is mainly orchestrated by the *hepcidin/FPN1* axis.

Hepcidin/FPN1 axis

Both hepcidin and FPN1 collectively regulate the Fe-R-H in blood plasma (normal range: 10-30 μM range) (33,34). Hepcidin synthesis by hepatocytes is regulated by redox signals from the inflammatory cell cascade, physiological iron status, and erythropoietic drive (35). The proinflammatory cytokine, IL6, strongly activates hepcidin transcription *via* the JAK-STAT3 pathway. Hepcidin is released with feedback regulation in response to iron levels in plasma and tissue pool; accordingly, blocks any excess entry of iron into the circulation. Conversely, an erythropoietic drive could induce a negative feedback suppression of hepcidin release and increase iron availability for erythrocyte production (34).

Iron and viral pathology

Iron is crucial for both the host as well as the viral pathogen. Since iron plays a key role in the DNA/RNA synthesis and ATP generation, viruses rely on this metal element to replicate in host cells (36). Iron is essential for replication of several RNA viruses such as HCV, HIV and West Nile virus (37). Certain viral pathogens selectively infect the iron-acquiring cells or influence the cellular iron metabolism *via human hemochromatosis protein* (HFE) or *hepcidin* (36, 38). Iron also activates *nuclear factor kappa B* (NF-κB) *via* generating ROS (39).

Low intracellular iron levels are sufficient to support coronavirus (CoV) replication, whereas iron deficiency interferes with viral transcription, translation, assembly, and exocytosis (40). Iron is also an essential metallo-nutrient; however, its overload may lead to MODS (41). Pulmonary iron accumulation favors the progression of respiratory diseases like pulmonary fibrosis and ARDS (42). COVID-19 results in remarkably high ferritin levels, which represents a negative prognostic factor, due to a series of detrimental interferences on endothelium, coagulation, lungs *in primis*, and cells in multiple organs.

Fe-R-H dysregulation in COVID-19

During SARS-CoV-2 infection, free iron released into the circulation induces inflammation of alveolar macrophages and cause oxidative damage to the lungs (42). Increased iron load could increase blood viscosity with recurrent diffused micro/macro circulatory thrombosis and lead to high levels of D-dimers in COVID-19 patients. This could explain the cause of sudden deterioration and high case fatality rates (CFR) in some COVID-19 patients (43). Therefore, regulation and maintenance of systemic Fe-R-H is critical for the clinical management of COVID-19.

The Fe-R-H dysregulation could also trigger several clinical manifestations in COVID-19 patients including: i) decrease the functional Hb, ii) increase the cellular iron overload, iii) release free toxic heme into the circulation, iv) manifest hypoxemia and systemic hypoxia, v) reduce nitric oxide (NO•) synthesis, vi) activate coagulation pathway(s), vii) trigger ferroptosis with oxidative stress and lipoperoxidation, and viii) induce mitochondrial degeneration (8).

Hepcidin, the master regulator of Fe-R-H, is a clinical biomarker to assess the recovery of SARS-CoV-2 infection and an indicator to measure the efficacy of an anti-COVID intervention. Both local and systemic hepcidin levels could serve as a dynamic prognostic marker of disease progression (more the hepcidin, worse the disease) and treatment efficacy (in recovered individuals, hepcidin disappears in the serum when Fe-R-H is restored). In contrast, artificial attempts to block hepcidin expression with hepcidin antagonists could be detrimental for COVID-19 patients (14).

Metabolic status of a SARS-CoV-2 infected host, in particular, the diet, nutrition, age, sex, medical condition(s), lifestyle, and environmental factors, cumulatively govern the clinical manifestation of COVID-19 from asymptomatic, mild, moderate, severe to fatality outcomes (44). Interestingly, the Fe-R-H dysregulation and its associated physiological disorders or disease states continue for extended periods (for weeks or even months) in COVID-19 patients discharged as RT-PCR (SARS-CoV-2) negative survivors (45). These observations further emphasize the need to identify intricate pathophysiological mechanisms underlying the Fe-R-H dysregulation in COVID-19. It was also suggested that COVID-19 is a new hematological disease (46). Based on the consequential clinical manifestation of SARS-CoV-2 infection, the COVID-19 disease should be considered as an *Iron (Fe)-Redox Dysregulation (FeRD) Syndrome*.

Phase-I: COVID-19/hypoxia

During the initial encounter with SARS-CoV-2 viral pathogen, the host bioenergetic pathways diverge and converge at cellular redox level, based on iron status and O_2 availability of the infected individual. The ensuing '*host metabolic reprogram*' (HMR) determines the fate and responsive function(s) of the innate host defense in relation to the pathophysiological and metabolic outcomes of a COVID-19 patient (Figure 2).

Interaction of SARS-CoV-2 with the *angiotensin-converting enzyme 2* (ACE2) receptors on alveolar epithelia affects the *renin-angiotensin-aldosterone system* (RAAS), subsequently the blood pressure and lung function of the infected host (47). Beyond the classical pulmonary immune-hyperinflammation and ARDS, COVID-19 should be considered as a hypoxia-induced hematological syndrome (46), associated with Fe-R-H dysregulation and HMR.

SARS-CoV-2 could also initially invade both the central nervous system (CNS) and the peripheral nervous system (PNS) leading to early neurological symptoms and complications, such as anosmia (loss of smell), ageusia (loss of taste), encephalitis and Guillain-Barré syndrome (48). *Neuropilin-1* (NRP1) expressed in the CNS, significantly potentiates the entry of SARS-CoV-2 into the brain through trans-synaptic route *via* olfactory neurons or through damaged endothelium in the brain microvasculature (49,50).

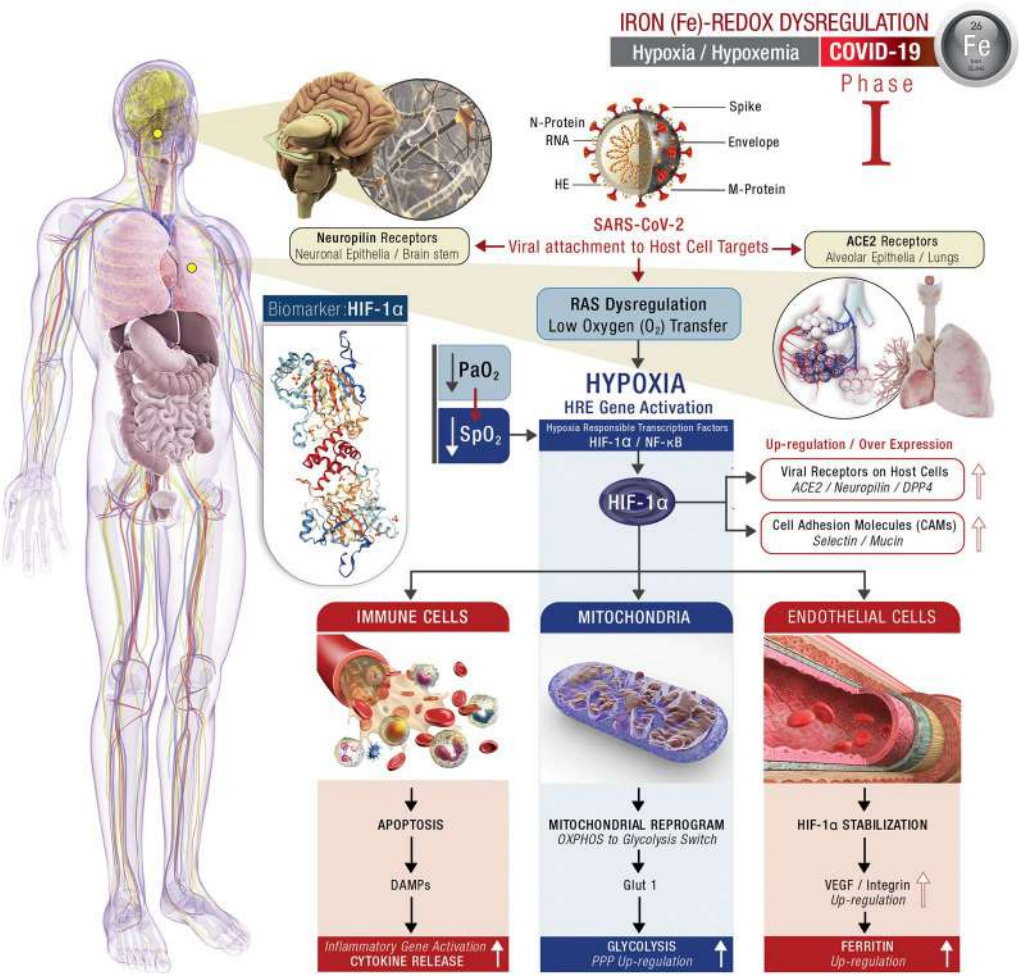

Figure 2. COVID-19/Phase-I: Hypoxia/Hypoxemia. SARS-CoV-2 binding to ACE2 on alveolar epithelia affects RAAS, subsequently the blood pressure and lung function of the infected host. Ensuing hypoxia, the reduced pO2 blocks OXPHOS/TCA cycle in mitochondria and activates anaerobic glycolysis. This shift in energy metabolism is regulated by different cellular systems, of which the HIF-1α is a critical trigger. Therefore, Phase-I COVID-19 is considered a hypoxia-induced blood disease, associated with Fe-R-H dysregulation and HMR. HIF-1α induced HMR affects the available energy reserves for immune function. Ultimately, HIF-1α could alter the host immune response, exacerbate the inflammation and cause tissue damage. SARS-CoV-2 could evade host innate immunity and sustain intracellular viral replication cycle by altering the mitochondrial dynamics by targeting the mitochondria-associated antiviral signaling (MAVS) pathways. HIF-1α may up-regulate VEGF to cause vascular leakage, damage epithelial barriers of alveoli and vascular endothelia. Phase-I Biomarker: HIF-1α (PDB 1H2N) is a heterodimeric transcription factor that regulates the activation of several genes responsive to cellular stress from hypoxia. As a key O_2 sensor and an adaptive hypoxic responder, HIF-1α plays a pivotal role in mitochondrial metabolism and HMR.

During early-phase of SAR-CoV-2 infection, the clinical onset of hypoxia/hypoxemia manifest as mild symptoms; however, up to 14% of such cases may become severe with dyspnea (shortness of breath), myalgia (muscle pain), tachypnea with a respiratory

frequency ≥ 30/min, hypoxemia with $SpO_2 \leq 93\%$, partial pressure of arterial O_2 to fraction of inspired O_2 ratio < 300 and/or pulmonary infiltrates involving more than 50% of lung parenchyma within 24 to 48 h (51). The progression of COVID-19 could be life-threating in 5% of cases (i.e. respiratory failure, septic shock and/or MODS) (52). Hypoxia is a pathobiological condition that exists at every developmental and progressive stages of the disease and a risk factor for high CFR in severe COVID-19 patients.

Effects of hypoxia-inducible factor (HIF) on COVID-19

Energy (as *adenosine triphosphate*, ATP) is vital for almost every cellular function in the body. Glycolysis and tricarboxylic acid cyle (TCA) are two exclusive bioenergetic pathways for ATP generation (53). These metabolic pathways are sensitive to nutrient availability and O_2 pressure (pO_2). This metabolic shift is regulated by different cellular systems, among which the HIF-1α is a decisive factor (54).

Hypoxia-inducible factor 1α

HIF-1α is a heterodimeric transcription factor that regulates the activation of several genes responsive to cellular stress from O_2 deficiency ('hypoxia'), which includes *erythropoietin* (EPO), *vascular endothelial growth factor* (VEGF), glycolytic enzymes, and glucose transporters (55). Macrophages and neutrophils express low level of HIF-1α under normal pO_2 in blood; however, during hypoxia, the HIF-1α is upregulated to enhance phagocytic activity for an effective host defense (56). CoVs use HIF-1α to exert anti-apoptotic effects on infected cells (57). SARS-CoV-2 could activate HIF-1α during hypoxemia and compromise innate host defense; thereby provide pathobiological advantage for viral propagation (58)

The viral interaction with susceptible host cells such as lung epithelia (alveolar type II cells) and capillary endothelium, could lead to inflammation and hypoxia with the induction of HIF-1α activity (59). Hypoxia and HIF-1α could either stimulate or inhibit cytokine-mediated inflammatory response. For example, the stabilized HIF-1α (*via* mtROS) may trigger or enhance 'cytokine storm', since the VEGF is transcriptionally upregulated by HIF-1α, and the endothelial cells initiate and develop severe COVID-19 (60). In severe COVID-19 cases, HIF-1α could trigger 'cytokine storm' through activation of immune cell cascade for proinflammatory cytokine release, up-regulate VEGF to cause vascular leakage, damage epithelial barriers of alveoli and vascular endothelia (58, 61).

SARS-CoV-2-induced mitochondrial dysfunction

The energy demand for an effective host response, especially during an acute inflammation such as 'cytokine storm', is contingent upon the active state of the immune cell cascade. Glycolysis is the major source of energy for neutrophils, dendritic cells (DCs) and macrophages (62). Activation of these immune cells by pro-inflammatory stimuli triggers a metabolic switch in favor of glycolysis (63). HIF-1α induced HMR affects the available energy reserves for immune function (64). Ultimately, HIF-1α also

may alter the host immune response, exacerbate the inflammation and cause tissue damage.

CoVs evade host innate immunity and sustain their intracellular replication cycle by altering the mitochondrial dynamics and targeting the *mitochondria-associated antiviral signaling* (MAVS) pathways (65). As a key O_2 sensor and an adaptive hypoxic responder, HIF-1α plays a pivotal role in altering mitochondrial function by inducing the synthesis of glycolytic enzymes *hexokinase 2*, *glucose-6-phosphate isomerase*, *triose-phosphate isomerase*, and *pyruvate kinase*. This mitochondrial dysfunction triggers HMR from the high energetic TCA cycle/OXPHOS to low energetic anaerobic glycolysis (66,67). After activation by *toll-like receptors* (TLRs) or pro-inflammatory cytokines, the immune cells also undergo similar switch in their mitochondrial metabolism. This altered metabolism is ensued after TLR4 activation and depends on the *phosphatidyl inositol 3'- kinase/AKT* pathway (68,69). After the HMR, any excess succinate is flushed out of the mitochondria into the cytosol. The inhibition of TCA cycle/OXPHOS is upregulated by HIF-1α through induction of *pyruvate dehydrogenase kinases* (70).

The HIF-1α stabilization in inflammatory cells depends on the ROS formation. The enhanced expression of this transcription factor increases the ROS levels (71). Mitochondria are major source of mtROS, potent inducers and stabilizers of HIF-1α (72). SARS-CoV-2-infected monocytes increase mtROS production. The mtROS-mediated stabilization of HIF-1α promotes SARS-CoV-2 replication and cytokine production in monocytes (73). HIF-1α also induces glycolysis and the consequent proinflammatory state of COVID-19 (74). SARS-CoV-2-infected monocytes express elevated levels of proinflammatory cytokines IL-6, IL-1β and TNF-α (73), resembling the 'cytokine storm' associated with lymphopenia in severe COVID-19 patients (75,76).

SARS-CoV-2-infected monocytes demonstrate altered oxidative metabolism, and down-regulation of proteins involved in the TCA cycle. Several intermediates of respiratory electron transport chain complexes are down-regulated in SARS-CoV-2-infected monocytes. The withdrawal of citrate from the TCA cycle is critical for lipid biosynthesis (77), which plays a major role in the viral assembly, especially in cross-linking the membrane components of SARS-CoV-2.

Phase-II: COVID-19/hyperferritinemia

SARS-CoV-2 infection induces the release of proinflammatory cytokines that stimulate synthesis of both ferritin and hepcidin, which are ultimate mediators of Fe-R-H dysregulation (17). Inflammation alters Fe-R-H as reflected by high iron content in reticuloendothelial cells and consequently high serum ferritin levels. If the iron-binding capacity of TF in the blood exceeds, free iron could be traced in the plasma in a redox-active state known as the *labile plasma iron* (LPI) that could form tissue damaging toxic free radicals (ROS/RNS) and cause subsequent fibrosis (78). Notably, a ferritin/TF ratio >10 predicts a five-fold higher risk of ICU admission and an eight-fold higher risk of the need for mechanical ventilation in COVID-19 patients (79). Excess iron load also generates ROS through Haber-Weiss reaction, which leads to oxidative stress, mitochondrial dysfunction and ferroptosis (80). Taken together, hyperferritinemia, cellular Fe-redox imbalance and iron dysregulation play a critical role in the pathogenesis of COVID-19 (81) (Figure 3).

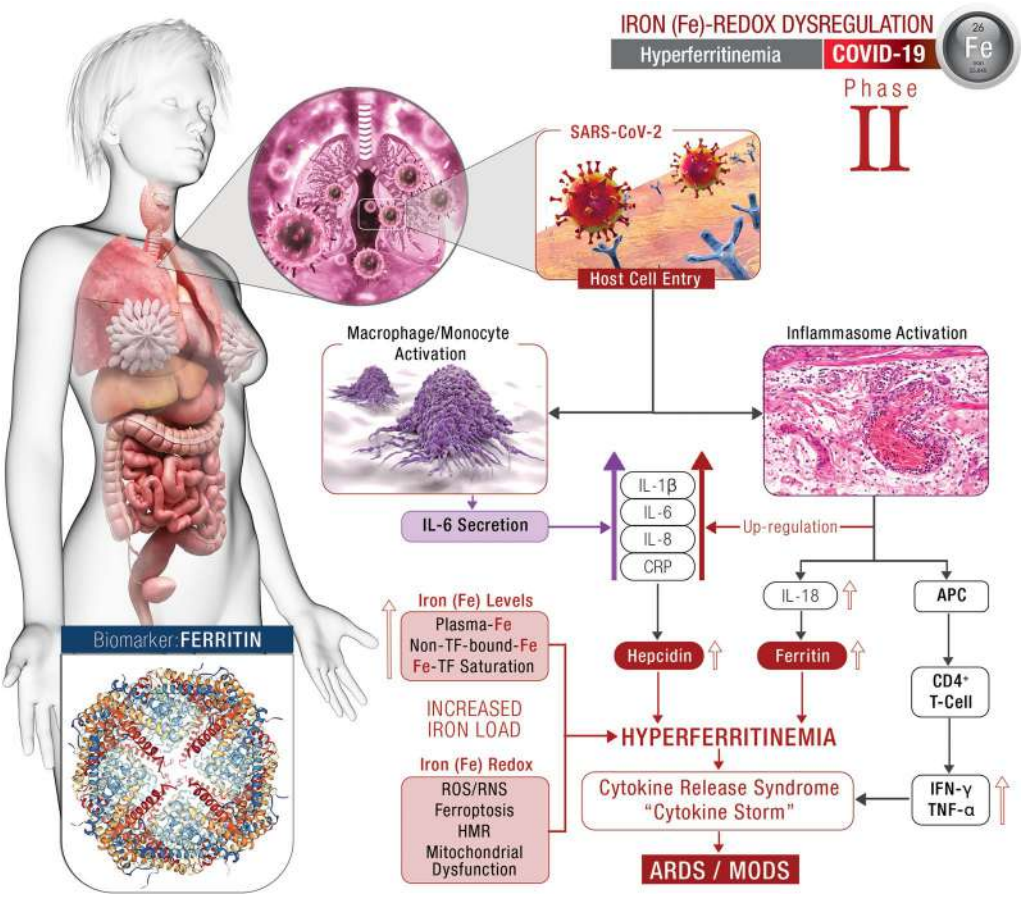

Figure 3. COVID-19/Phase-II: Hyperferritinemia. Hyperferritinemia, cellular redox imbalance and iron dysregulation play a critical role in the pathogenesis of COVID-19. Severe SARS-CoV-2 infections are characterized by a hyper-inflammatory state associated with elevated proinflammatory cytokines, which stimulate the synthesis of both ferritin and hepcidin, the ultimate mediators of Fe-R-H dysregulation. The altered Fe-R-H is reflected by high iron content in reticuloendothelial cells and elevated serum ferritin levels. When the iron-binding capacity of TF in the blood exceeds, free iron is traced in the plasma in redox-active state known as the labile plasma iron (LPI), which could form tissue damaging toxic free radicals. A ferritin/TF ratio >10 predicts a five-fold higher risk of ICU admission and an eight-fold higher risk of the need for mechanical ventilation in COVID-19 patients. An uncontrolled and dysfunctional immune response associated with macrophage activation leads to hyperferritinemia, and CRS (the 'cytokine storm'). CRS is characterized by the fulminant activation of large numbers of white blood cells that release inflammatory cytokines, eventually leading to MODS. Therefore, Phase-II COVID-19 is considered a broad spectrum hyperinflammatory disease, amplified by CRS. Phase-II Biomarker: Ferritin (PDB 4V6B) is a 474-kDa iron storage globular protein induced by stress signals such as hypoxia. Serum ferritin levels in the serum positively correlate with inflammatory cytokines and serve as a prognostic biomarker to estimate the COVID-19 disease spectrum and the severity of the cytokine storm. Elevated ferritin level (> 3000 ng/mL) in plasma is a prognostic marker for increased CFR in critically ill patients.

Hyperferritinemia and COVID-19

Severe COVID-19 infections are characterized by a hyper-inflammatory state associated with elevated inflammation markers such as ferritin, *C-reactive protein* (CRP), and

IL-6 (82,83). Ferritin, a 474-kDa major iron storage globular protein, maintains a large iron core in its cavity and exhibits ferroxidase activity (84). As an acute phase protein, ferritin expression is induced by stress signals such as hypoxia, iron overload and inflammation (85). Ferritin plays a major role in several Fe-redox pathways such as iron transport across membranes and Fe-R-H status.

Ferritin levels in 'non-severe' COVID-19 patients remain within a normal range (30–400 μg/L (86)); however, in hospitalized patients with severe COVID-19, ferritin is significantly elevated about 1.5 to 5.3 times (87). In hospitalized non-survivors, the ferritin levels measure at 1400 μg/L, about 3 to 4 times higher than the COVID-19 survivors. Furthermore, the proinflammatory cytokines, especially IL-6, are elevated in patients with severe COVID-19 (88). Several studies reported that both ferritin and IL-6 levels in plasma significantly elevate in non-survivors compared to discharged COVID-19 patients (82). Interestingly, the plasma levels of ferritin and IL-6 steadily decrease with gradual recovery from COVID-19 (10, 89). These findings suggest a strong link between hyperferritinemia and different inflammatory phases of SARS-CoV-2 infection. Therefore, ferritin is currently used as a prognostic biomarker to estimate the pathological spectrum and the severity of CRS in COVID-19 cases.

Hyperferritinemia and CRS—the 'cytokine storm'

Cytokine release syndrome (CRS), also known as the 'cytokine storm', is characterized by the fulminant activation of large numbers of white blood cells that release inflammatory cytokines including IL-1β and IL-6 (90). Cytokine profiles associated with the severity of COVID-19 also include elevated levels of IL-2, IL-7, *granulocyte colony stimulating factor* (GCSF), IFN-γ *inducible protein 10* (IP10), *monocyte chemoattractant protein 1* (MCP1), *macrophage inflammatory protein 1α* (MIP1α), and TNFα (91). This massive cytokine burst with elevated IL-6, clotting factors and fibrinogen could predispose the risk of thrombosis in COVID-19 patients (92).

During the CRS, rapidly released inflammatory cytokines stimulate hepatocytes, Kupffer cells, and macrophages, which all secrete ferritin (93). Uncontrolled and dysfunctional immune responses associated with macrophage activation, hyperferritinemia, and CRS ultimately leads to MODS (79). Such nonspecific acute phase response with elevated ferritin is an indicator of COVID-19 severity (86,87). Also, high ferritin level (>3000 ng/mL) in plasma serves as a prognostic biomarker for increased CFR in critically ill patients (94). Therefore, COVID-19 is also considered a broad spectrum hyper-inflammatory disease, amplified by the *cytokine release syndrome* (CRS) (91).

Ferroptosis and multi-organ failure in COVID-19

The cysteine-rich cytoplasmic tail of the CoV spike (S)-protein demonstrates a sequence homology with hepcidin (95). This hepcidin-like activity of SARS-CoV-2 could compromise the ability of RBC to transport O_2, increase the circulating/tissue levels of ferritin, which may cause serum iron deficiency and Hb depletion. The ensuing hyperferritinemia may lead to ferroptosis with high oxidative stress and lipoperoxidation. Ultimately, such condition could increase mitophagy, cellular apoptosis and tissue necrosis (96).

Free radicals could damage cellular lipids, nucleic acids, and proteins, with consequent oxidative stress that activate proinflammatory pathways. Furthermore, the iron-catalyzed oxidative damage of lipid membranes may trigger ferroptosis, the non-apoptotic cell death caused by Fe-R-H imbalance. Unlike apoptosis, ferroptosis is immunogenic that could ensue amplified cell death as well as set off a series of toxic reactions associated with inflammation (97). Ferroptosis-inducing factors could directly or indirectly affect *glutathione peroxidase* (Gpx) through different pathways, decrease antioxidant capacity, accumulate lipid peroxidation, and lead to oxidative cell death (59). Dependence on $NADPH/H^+$, polyunsaturated fatty acid metabolism, and the mevalonate and glutaminolytic metabolic pathways are implicated in this unique type of necrosis (98). The immunological consequences of ferroptosis could eliminate leukocyte subsets and compromise the immune function (99). Also, ferroptosis could affect the death of non-leukocytic cells and modulate different immune and inflammatory reactions by release and activation of different *damage-associated molecular patter*n (DAMP) signals (100). In general, ferroptosis is a form of inflammatory cell death associated with the release of DAMPs or lipid oxidation products during tissue injury (101). *Hemin*, but not biliverdin and bilirubin, promote erastin-induced ferroptosis (100). The iron-binding proteins TF and LF increase the iron intake and act as positive regulators of ferroptosis (102,103). The accumulation of oxidized phospholipids in myocardial and renal tissue from COVID-19 postmortem cases highlights ferroptosis, with severe ischemia–reperfusion injury, a detrimental factor in COVID-19 cardiac damage and MODS (104). Based on clinical observations and postmortem findings, ferroptosis may be an important cause of MODS in COVID-19 and is considered a new treatment target (105).

Fe-R-H dysregulation and COVID-19 severity

Fe-R-H has a robust correlation with the occurrence of severe COVID-19. Fe-redox determinations are specific and sensitive for the early prediction of disease severity in COVID-19 patients (106). Testing of serum ferritin and hepcidin levels could predict COVID-19 severity with 94.6% specificity, while parallel testing of serum ferritin and hepcidin show a sensitivity of 95.7% (82). Elevated levels of IL-6 and hyperferritinemia are suggested as red flags of systemic inflammation and poor prognosis in COVID-19 (107). The concentration of ferritin positively correlates with other inflammatory cytokines, such as IL-8, IL-10, CRP and TNF-α. Based on the logistic regression analysis, ferritin is an independent predictor of in-hospital mortality (108).

Phase-III: COVID-19/thromboembolism

During phase-III, the severe stage of COVID-19, *thromboembolism,* hematological parameters such as *anemia of inflammation* (AI), reduced numbers of peripheral blood lymphocytes and eosinophils with increased polymorphonuclear-to-lymphocyte ratios emerge as major risk factors (109,110). Altered iron metabolism, iron-restricted erythropoiesis due to hyper-inflammation are predisposing factors for AI (111,112). In tandem, AI with low Hb levels and hyperferritinemia potentially limits O_2 availability to tissues with detrimental outcomes in COVID-19 patients (113,114). This clinical

condition combined with hypoxia, also shows the signs of hemolysis with release of heme proteins and accumulation of free heme (115). The hemolysis-derived heme could initiate oxidative and inflammatory stress that may cause microvascular thrombosis, organ ischemia and MODS in severe COVID-19 cases (116,117).

Coagulopathy is a hallmark of iron toxicity and oxidized iron could modulate several pathways of coagulation cascade (118). SARS-CoV-2 could invade blood vessels, induce vascular damage, and activate systemic thrombotic events with severe to fatal coagulopathies in patients (119). Such coagulopathies are characterized by elevated procoagulant factors such as fibrinogen, along with high levels of D-dimers associated with increased CFR (82,120). The D-dimer dynamics reflect disease severity, and its level >1000 ng/mL is considered an independent risk factor for mortality in hospitalized COVID-19 patients (82) (Figure 4).

SARS-CoV-2 and hematopoietic responses

Severe COVID-19 patients demonstrate reduced erythrocyte turnover, low circulatory Hb levels (along with increased total bilirubin and ferritin serum concentrations) indicate disturbances in oxygen-binding capacity (121). Furthermore, the up-regulation of *erythroid precursor/progenitors* (EP/P) in peripheral blood together with hypoxia, anemia, and coagulopathies strongly correlates with COVID-19 severity and mortality outcomes (122). Accordingly, the SARS-CoV-2 may directly infect EP/P cells, trigger stress-induced erythropoiesis, impair the Fe-R-H homeostasis and aggravate the COVID-19 pathobiology. During erythropoiesis, the ACE2 expression is elevated in EP/P, which may increase the susceptibility of these erythroid cells to SARS-CoV-2 infection. Therefore, early EP/P (i.e. $CD34^{-}CD117^{+}CD71^{+}CD235a^{-}$) with high density of ACE2 receptors could serve as primary cell surface targets for SARS-CoV-2 infection. This host-pathogen interaction could facilitate circulatory spread of the virus and onset the hyper-inflammatory response in severe COVID-19 patients (123). When the SARS-CoV-2 viral particles are released from the infected EP/Ps, RBCs (and eventually from platelets), pose a major risk in manifesting thromboembolic/coagulopathic events in COVID-19 patients and vaccinated individuals (124). To date, thrombocytopenia and blood hypercoagulability are hallmark clinical manifestations in most of the phase-III COVID-19 critical patients.

SARS-CoV-2 interactions with hemoglobin (Hb)

Several clinical studies showed a strong association between SARS-CoV-2 infection and the host Hb status (125). In support of this observation: i) women are less susceptible to COVID-19, possibly due to their low Hb levels compared to males (126,127); ii) newborns delivered from COVID-19 positive mothers remain uninfected with SARS-CoV-2 (128), possibly due to the delayed Hb β-chain synthesis in neonates for a few weeks after birth (129); and iii) the number of COVID-19 cases reported from certain territories in Mediterranean region are extremely low, possibly due to high prevalence of β-thalassemia (blood condition linked to abnormalities in the β-chains of Hb) in this geographical loci (130,131).

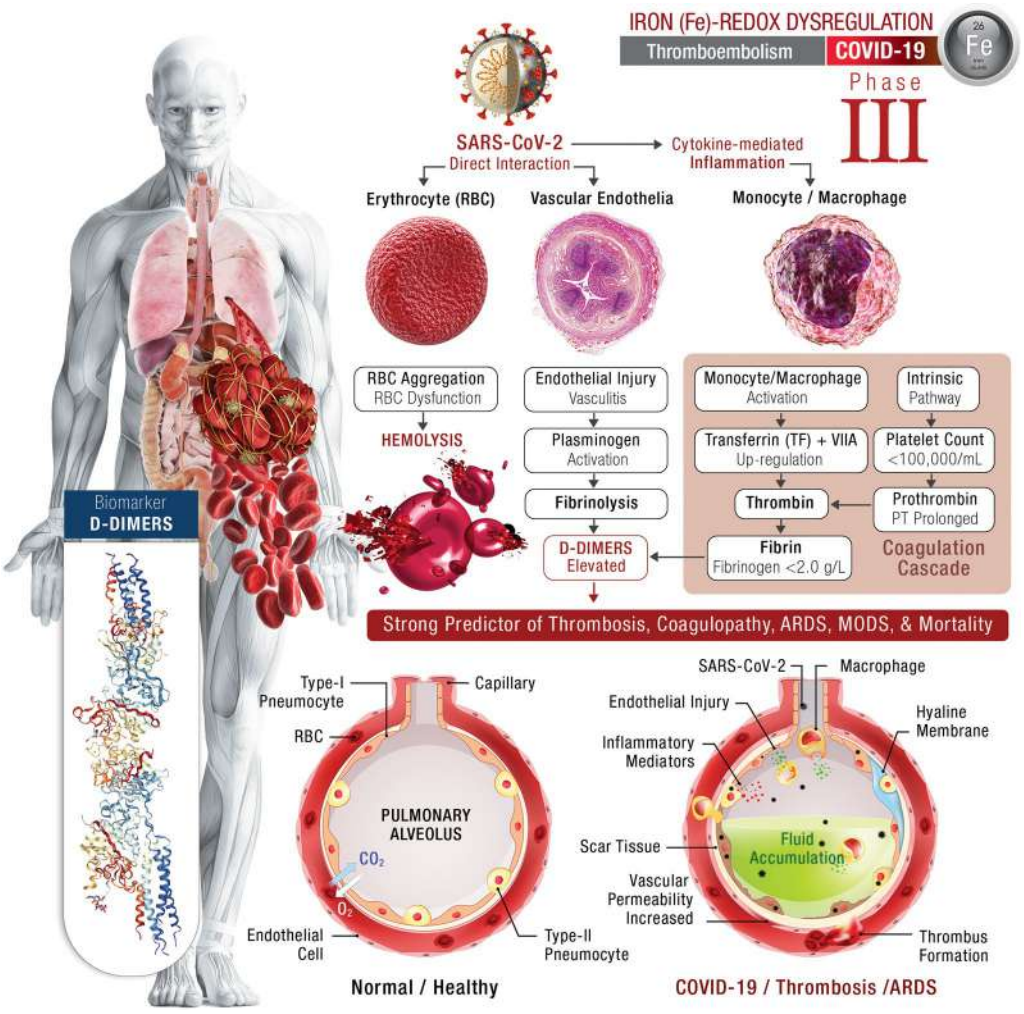

Figure 4. COVID-19/Phase-III: Thromboembolism. The hallmark of iron toxicity and oxidized iron is to modulate several pathways of coagulation cascade leading to thromboembolism. SARS-CoV-2 could invade blood vessels, induce vascular damage, and activate systemic thrombotic events with severe to fatal coagulopathies in COVID-19 patients. Such coagulopathies are characterized by elevated procoagulant factors such as fibrinogen, along with high levels of D-dimers linked to increased CFR. Hematological parameters such as AI, reduced numbers of peripheral blood lymphocytes and eosinophils with increased polymorphonuclear-to-lymphocyte ratios are recognized as major risk factors. This clinical state along with hypoxia, could show the signs of hemolysis with release of heme proteins and accumulation of free heme. The hemolysis-derived heme could initiate oxidative and inflammatory stress that may cause microvascular thrombosis, organ ischemia and MODS in severe COVID-19 cases. Phase-III Biomarker: D-Dimer (PDB 2Z4E) consists of two small D fragments of the fibrin protein joined by a cross-link, after a blood clot is degraded by fibrinolysis. Coagulopathies are characterized by elevated procoagulant factors such as fibrinogen, along with high levels of D-dimers. The D-dimer dynamics reflect disease severity, and its level >1000 ng/mL is considered an independent risk factor for mortality in hospitalized COVID-19 patients.

In silico studies revealed that the protein sequences of SARS-CoV-2 form a complex with porphyrin, affect the heme on the 1-β chain of Hb, and release free iron (132). SARS-CoV-2 interacts with Hb molecule, *via* ACE2, CD147, CD26 and other receptors located on RBC and/or blood cell precursors (8). Also, the SARS-CoV-2 envelope (E) protein directly binds to heme (from Hb) released from damaged RBC and lysed phagocytes (133). The viral genomic ORF8 protein could interact with the 1β-chain of Hb, captures the porphyrin and inhibits the human heme metabolism (135). SARS-CoV-2 could invade host cells *via* CD147 (known as *basigin*), an RBC receptor (134). Another receptor, the DPP4 (CD26), has a functional role in hematopoiesis and interacts with the spike (S)-protein of SARS-CoV-2 (135). Such an array of interactions of this CoV pathogen with Hb could induce hemolysis and/or form complexes with released heme, generate a dysfunctional Hb ('hemoglobinopathy') with reduced ability to transport O_2/CO_2 and lead to O_2 deprived multi-faceted syndromes, including coagulation disorders (8, 115). In severe stages of COVID-19, other Hb-associated markers, such as bilirubin and ferritin, progressively increase and worsen the clinical outcomes (82).

COVID-19 and neutrophil extracellular traps (NETs)

Incidence of microthrombi formation (blood clots) in veins or arteries is a striking feature in severe COVID-19 (136). Direct interaction of activated neutrophils with platelets, together with plasma coagulation factors during immune response, may develop immuno-thrombotic events during phase-III of COVID-19 (137). Acute thrombosis with coagulopathies also appears due to dysregulated *neutrophil extracellular trap* (NET) formation in COVID-19 (138,139). NETs are extracellular traps of DNA, histones, microbicidal proteins, and oxidative enzymes released by neutrophils to contain infections; however, when not properly regulated, NETs have the potential to initiate and propagate inflammation and thrombosis – including ARDS in the lungs of COVID-19 patients (140,141).

Neutrophils produce NETs *via* a regulated cell death (apoptosis) process termed as NETosis (142). Viruses could evade the host immune response through induction of classical ROS-dependent NETosis (143). Virus-induced NETosis could cause severe systemic response with the production of immune complexes, cytokines, and chemokines that trigger hyper-inflammation (144). Dysregulated NETosis may also cause vascular tissue damage with microthrombi leading to ARDS and MODS associated with high morbidity and mortality in COVID-19 patients (139, 145).

SARS-CoV-2-induced NETosis acts as a double-edged sword; on one side, works as a mechanical entrapment for the virus and on the other hand, the inflammatory and immunological reaction(s) triggered by the NETosis could compromise the host defense. SARS-CoV-2 could activate NETosis in human neutrophils and increase the intracellular levels of ROS/RNS (146). Clinical severity of COVID-19 correlates with coagulation dysfunction markers, mainly D-dimers, platelet reduction, increase in prothrombin time and fibrin degradation products (147). The D-dimers (indicator of hyperactive coagulation) has emerged as a reliable marker for severe COVID-19 (82). Excess NETosis also contributes to severe outcomes of COVID-19 by causing CRS and thrombosis (138). *Thromboembolism* with severe coagulopathies such as *deep vein thrombosis* (DVT), and *pulmonary embolism* (PE) are common, particularly among COVID-19 patients. Intra-vascular NETosis initiates thrombotic events in arteries, veins; and

COVID-19 in particular, the microvasculature, where thrombosis could trigger MODS in respiratory, cardiovascular, and urinary (kidneys) and other systems (148). The W.H.O. has recently taken into consideration the possible role of hematological changes in the pathobiological spectrum of COVID19 (8, 149).

Covid-19 interventions: physiological restoration of Fe-R-H balance

Dysregulation of Fe-R-H is highly prevalent among hospitalized COVID-19 patients. Serum levels of iron and hepcidin are low in COVID-19 patients, whereas the EPO and haptoglobin levels significantly drop in critical and deceased patients (150). Other biomarkers of iron metabolism (i.e. ferritin, TF, LF, etc.) and Hb could provide risk stratification strategies for COVID-19 management, as initial anemia is strongly linked to increased CFR. Altered Fe-R-H with elevated ferritin/TF ratio predicts subsequent insufficient pulmonary oxygenation with the need for ICU admission and mechanical ventilation (79). Serum TF levels decrease within the 1st week of hospitalization in many COVID-19 patients; however, a continuous decline is prominent among subjects with fatal outcomes (151). Therefore, therapeutic, and nutritional interventions to combat Fe-R-H dysregulation such as, AI, hyperferritinemia, ferroptosis and hemodynamics are critical for an effective clinical treatment of COVID-19 patients and post-recovery management of 'long COVID-19′ survivors (17, 152). Following sections elucidate the ongoing laboratory and clinical investigations that are aimed at maintaining optimum iron levels in cellular and circulatory pools with Fe-R-H regulators, as well as approved interventions to directly remove iron using Fe-chelators and anticoagulants (i.e. heparin) to lower the risks of thromboembolic events in severe cases of COVID-19.

Fe-R-H regulators for COVID-19 intervention

Innate Fe-R-H regulators, such as *lactoferrin* (LF), *erythropoietin* (EPO), *heme oxygenase-1* (HO-1) and *hepcidin* modulators could act as first barriers against CoV infection (Figure 5). Accordingly, LF has been suggested as a potential prophylactic and/or adjunct therapeutic in the clinical management of COVID-19 (153–155). LF could reversibly chelate two Fe^{3+} ions with high-affinity and remain stable at pH 3.0 (22). Through iron sequestration and restoration of Fe-R-H, LF could reduce oxidative stress and inflammation, particularly during the 'cytokine storm' in COVID-19 (6). In COVID-19 recovered patients, the Hb, ferritin, and TF levels gradually return to normal with resolution of dysregulated Fe-R-H, around a median of 122 days after discharge from the hospital (151).

SARS-CoV-2 mediated lung injury induces the death of inflammatory cells with sloughing of alveolar epithelia and damage to pulmonary vasculature with hemolytic consequences (156). Free heme released during hemolysis could induce pro-inflammatory, pro-oxidative, and pro-thrombotic effects. Heme could alter proteins, DNA, lipids (157) and affect the signaling of *damage-associated molecular pattern* (DAMP) and TLR-4, which play a critical role in the innate immunity (158). Normally, the free heme is

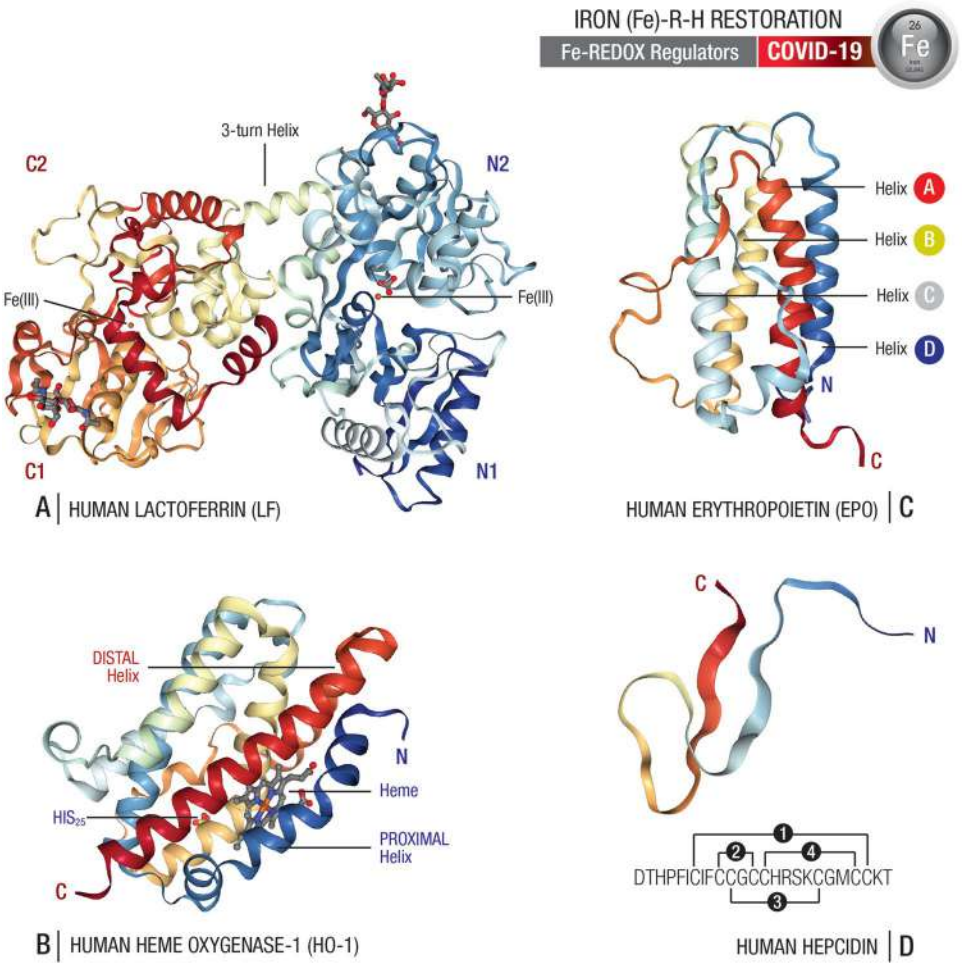

Figure 5. Fe-R-H regulators for COVID-19 intervention. Fe-R-H modulators are body's own bio-replenishment molecules with specific role to chelate/transport iron, neutralize iron-mediated free radicals, and modulate antioxidant responses to provide cytoprotection. Through iron sequestration and optimization, Fe-R-H, modulators could reduce oxidative stress and inflammation, particularly during the 'cytokine storm' in COVID-19 pathobiology. A) Human LF (PDB 1SQY) is an iron-binding transport protein secreted by exocrine glands and neutrophils. As a key component of innate host defense, LF could scavenge iron-catalyzed free radicals and establish physiological Fe-R-H. B) Human HO-1 (PDB 1N45), also known as the 'heat shock protein-32' (hsp32), is transcriptionally upregulated during acute lung injury (ALI). HO-1 mediates catalytic breakdown of heme to ferrous (Fe^{2+}) iron. As a Fe-R-H modulator, HO-1 could provide cytoprotective function and sustain body's antioxidant response against oxidative stress. C) Human EPO (PDB 1BUY) is a hypoxia-inducible growth factor synthesized *via* redox-sensitive signaling pathways and modulated by the plasma thiol-disulfide redox state. Activated EPO depletes serum iron levels and, limits systemic availability of Fe^{3+} ions for Fenton-type oxidative catalysis. D) Hepcidin (PDB 2KEF), a 25-amino acid peptide hormone secreted by the liver, is the master regulator of iron intake and systemic Fe-R-H. Hepcidin regulates iron levels by binding to FPN, and the FPN/hepcidin regulatory axis allows precise control of iron at both the systemic as well as the cellular level. Hepcidin is a clinical marker to assess the recovery of SARS-CoV-2 infection and an indicator to measure the efficacy of an anti-COVID intervention.

scavenged by *hemoxygenase-1* (HO-1) and *hemopexin* to counteract any detrimental effects (159). Alternative protective mechanisms against free heme are required for cellular survival and to prevent viral progression (157). HO-1 could effectively neutralize the free heme and lower the risk of SARS-CoV-2 infection (116). Administration of hemin and metalloporphyrin could upregulate HO-1 gene expression, decrease neutrophil infiltration, and inhibit viral replication (160,161).

Lactoferrin (LF)

Human lactoferrin (hLF), an iron-binding glycoprotein secreted by exocrine glands and neutrophils, is a key component of innate host defense. The LF structure consists of two homologous globular lobes (N-lobe and C-lobe), which are further arranged into two domains (N1 and N2) and (C1 and C2) (Figure 5A). Each lobe has an iron-binding sites located in the interdomain cleft that facilitates high-affinity binding to two ferric (Fe^{3+}) ions (22). Due to iron-chelation and iron-transport properties, LF is considered an innate Fe-redox regulator with a multifunctional role in scavenging iron-catalyzed free radicals (i.e. ROS, RNS) and establish physiological iron homeostasis (6). The positively charged (cationic) LF protein binds to large molecules with negative (anionic) charge, such as *glycosaminoglycans* (GAGs), which is one of the key mechanisms underlying its antiviral activity against SARS-CoV-2 (162). The ability of LF to sequester iron, to interact with anionic compounds, to translocate into the nucleus, to modulate immune/inflammatory responses and to regulate Fe-R-H, could provide a multifunctional spectrum of benefits as a prophylactic and therapeutic intervention against COVID-19.

LF and Fe-R-H regulation

In human body, the total iron content is ~3 g for women and ~4 g for men, distributed in two main forms as heme-iron, mostly found in the Hb, myoglobin, and cytochromes (2–2.7 g); and as non-heme-iron, a cofactor for several enzymes (163). Free iron levels in the human body fluids are regulated $<10^{-18}$ M to avert microbial infections as well as to prevent precipitation of insoluble ferric hydroxides and formation of free radicals *via* the Fenton reaction. LF sequesters Fe^{3+} to ensure that free available iron does not reach toxic levels (164). Accelerating the auto-oxidation of Fe^{3+} by apo-LF or apo-TF at acid pH is indicated by the disappearance of Fe^{3+}, the uptake of O_2, and the binding of iron to LF or TF. Apo-LF or apo-TF and Fe^{3+} could generate OH• *via* an H_2O_2 intermediate and such a mechanism may contribute to the microbicidal activity of phagocytes (164). In the body, superoxide ($O_2^{\cdot-}$) anions are scavenged by redox enzymes such as *superoxide dismutase* (SOD) and catalases, whereas peroxides by GSH- and Trx-dependent peroxidases, and *peroxiredoxins* (Prdx) (165). Any decline in redox enzymes may increase free radical generation with subsequent induction of lipid peroxidation, protein oxidation, and DNA/RNA oxidative damage. While moderate oxidation triggers apoptosis, severe oxidative stress could lead to tissue necrosis or even cellular death (15, 166).

LF binding to Fe^{3+} ions block iron-mediated catalysis and oxidative disturbances in the cell membranes. LF has stronger binding affinity to Fe^{3+} than Hb, myoglobin or

TF. The ability of LF to chelate Fe^{3+} could effectively terminate the cycle of ROS production by heme iron. Oral supplementation of LF could prevent oxidative damage by heme iron and reverse the ferritin-bound iron overload that accompanies chronic inflammation and aging (167). This antioxidant (free radical scavenging) mechanism of LF involves stimulated glycolysis, increased ATP generation and sustain ion gradient with membrane potential and morphology of the cell (168). LF may prevent iron-mediated tissue damage by reducing 'free' synovial iron when inflammatory stimuli dysregulated the IRP-mediated iron homeostasis (169). Endogenous LF could prevent lipid, protein and nucleic acid oxidation through iron-binding and metal-sequestration (170). Notably, both oxidative stress and related metabolic syndromes are considered as potential risk factors in COVID-19 pathology (94). As an innate regulator of Fe-R-H, LF could combat oxidative stress at cellular level, modulate inflammatory responses at tissue level (171) and play a therapeutic role in clinical management of COVID-19.

LF and antiviral activity

Several studies have elucidated a broad-spectrum antiviral activity for LF against SARS-CoV-2 (6, 154, 172–174). Breast milk from several positive COVID-19 mothers were found negative for SARS-CoV-2 pathogen (177, 175). *In vitro* studies demonstrated that milk LF could inhibit early phase of viral infection of SARS-CoV as well as SARS-CoV-2 (173, 176). The antiviral spectrum of milk LF include: i) direct interaction with the viral protein target(s) and blockade of viral attachment to host target cells (177); ii) binding to heparan sulfate proteoglycans (HSPGs) on the host cell surface with subsequent inhibition of viral attachment and cell entry (176); and iii) interference with intracellular trafficking of the virus (178).

The SARS-CoV-2 has acquired a unique polybasic cleavage site (*R-R-A-R*) at the junction of the spike (S) protein's S1 and S2 domains, which facilitates an effective cleavage by furin and other proteases (179). This novel virulence trait is linked to the enhanced infectivity, host tropism, and pathobiological spectrum of COVID-19 (94, 180). Competitive blocking of SARS-CoV-2 polybasic cleavage site with highly basic innate host proteins or peptides with a stretch of 'arginine (R)' residues may serve as a potential viral intervention strategy. LF is considered the most polybasic protein in host defense against tissue injuries and infections. The best characterized LF targets are anionic molecules, which include proinflammatory microbial factors (i.e. lipopolysaccharide), as well as host cellular components such as DNA, GAG chains of proteoglycans, and cell surface receptors (CSRs) (6, 155, 181,182). These LF-CSR interactions could influence signaling pathways that modulate complex immune machinery and regulate cytokine release (183). A peptide derived from the N-terminus region of *human* $LF^{(1\text{-}11)}$ *(GRRRRSVQWCA)* avidly binds and activates monocyte function. The stretch of 'arginine (R)' residues from position 2 to five and the cysteine residue at position 10 are pivotal in the immunomodulatory properties of LF (184). Interestingly, LF also demonstrates serine protease activity and cleaves arginine-rich sequences in a variety of microbial virulence proteins, contributing to its long-recognized antimicrobial effects (185). These cationic structure-function characteristics of LF could play a pivotal role in the development of anti-COVID interventions.

LF and anti-inflammatory activity

LF regulates both pro-inflammatory and anti-inflammatory responses (171); thereby could prevent viral insult-induced 'cytokine storm' (186). The anti-inflammatory activity of LF is associated with its ability to enter host cell nucleus and inhibit the synthesis of proinflammatory cytokine genes. Both IL-6 and IL-1β levels are elevated during inflammation due to up-regulation of cytosolic ferritin, down-regulation of FPN, membrane-bound *ceruloplasmin*, and TfR1 (172). This inflammatory response results in intracellular iron overload that may increase host susceptibility to infections and manifest as blood iron deficiency (i.e. anemia). Establishing the Fe-R-H by rebalancing iron levels between tissues/secretions and blood anemia could be critical during inflammation. Iron-binding proteins such as LF, TF, and ferritin play a pivotal role in human ferrokinetics (187). LF is an effective down-regulator of both IL-6 and IL-1β, as well as in preventing the activation of FPN, membrane-bound ceruloplasmin, cytosolic ferritin, and TfR1 in macrophages (52, 188). LF also activates plasminogen that regulates coagulation cascade and antithrombotic activity, a common clinical condition observed in SARS-CoV-2 infection (189,190).

LF and immune modulation

Both immunomodulatory as well as anti-inflammatory effects of LF could positively influence host responses to COVID-19 infections (6, 155). LF down-regulates pro-inflammatory cytokines and potentiates adaptive immune response (191). LF also modulates antigen-specific adaptive immune responses (i.e. APC activation, maturation, migration, and antigen presentation) and bridges the functions of both T- and B-cells (183). Structural changes in the N-terminal 'basic' domain of LF facilitates its molecular interactions with B lymphocytes (192).

LF for clinical management of COVID-19

Ferroportin (FPN), the only known mammalian iron exporter from cells to blood, is negatively regulated by *hepcidin*, a hormone peptide that binds and degrades FPN. LF is a potent anti-inflammatory agent that modulates hepcidin and FPN synthesis through down-regulation of IL-6 (193,194); thereby inhibits intracellular iron overload (163). Oral administration of 20-30% iron-saturated milk LF (corresponding to 70-84 μg of elemental iron) twice a day could down-regulate IL-6 and restore FPN-mediated iron export from cells to blood in both hepcidin-dependent or independent pathways (194).

The iron-binding synthetic chelator *desferoxamine* (DFO), is a pharmacological mimetic of hypoxia. Like the DFO, apo-LF is a normoxic mimetic of hypoxia, and effectively stabilizes the redox-sensitive multifunctional transcription factors HIF-1α and HIF-2α (195). LF also activates the HIF-1α gene expression, thereby upregulates EPO and induce the nuclear translocation of Nrf2. During hypoxia these transcription factors exert synergistic protection through activation of the Keap1/Nrf2 signaling pathway (196). Also, LF could block HIF-1α activity and may provide therapeutic benefits to retinal neuronal cells (6, 197).

An LF-derived peptide (LRPVAA) is shown to block the ACE receptor activity *in vitro* (198). Furthermore, a LF hydrolysate and its derived peptides could block binding to ACE receptors and thus inhibit angiotensin (ANG) II-induced vasoconstriction (199). The nuclear localization of LF in different human epithelia, allows this iron-binding protein to inhibit intracellular replication of viruses through induction of antiviral cytokines such as IFN-α/β. LF administration also enhances natural killer (NK) cell activity and T_H1 cytokine response, imparting protection against viral infections (200,201). Taken together, milk LF could reverse iron overload and dysregulation of Fe-R-H, both considered as critical factors in the pathogenesis of SARS-CoV-2 infection; accordingly, LF could serve as a promising all-natural intervention in the clinical management of COVID-19.

Heme oxygenase-1 (HO-1)

Heme oxygenase-1 (HO-1) also known as the '*heat shock protein-32*' (hsp32), is an inducible intracellular enzyme encoded by the HMOX gene, which is transcriptionally upregulated up to 100-fold during infections, radiation, toxins, and clinical conditions such as sepsis, renal ischemia-reperfusion injury and acute lung injury (Figure 5B) (202). HO-1 is present throughout the body with highest concentration in the spleen, liver, and kidneys. At cellular level, HO-1 is primarily located in the endoplasmic reticulum, mitochondria, nucleus, and plasma membrane (206). HO-1 catabolizes heme to ferrous (Fe^{2+}) iron, *carbon monoxide* (CO), and *biliverdin* (BV) (that converts to *bilirubin* (BR) by the BV-reductase). This endoergic process makes BR a highly electrophilic molecule with increased affinity to *Keap1-Nrf2* and facilitates antioxidant gene induction (203). HO-1 may also serve as a chaperone protein that engages in protein-protein interactions and participates in several cellular functions beyond its catalytic activity (204). The end-products, CO and BV/BR are commonly known for antioxidant, anti-inflammatory, and anti-apoptotic effects (205).

HO-1 and Fe-R-H regulation

HO-1 mediates catalytic breakdown of heme, a potent pro-oxidant and pro-inflammatory molecule (206). Heme is an iron chelate with an essential role in O_2 transport/detoxification, cellular respiration, and signal transduction. Due to its potential toxicity, heme is formed and degraded within an individual nucleated cell (207) and the HO enzymes serve this function for cellular defense (208). The redox-active iron released from HO-1 activity stimulates ferritin synthesis for ultimate iron detoxification and cytoprotection with its ferroxidase activity (209). Elevated ferritin levels provide an adaptive response to maintain a low redox-active iron pool; thereby reduce Fenton chemistry and oxidative stress (214). The HO-1-regulated Fe-R-H provides cytoprotective function *via* endogenous mechanisms involving genes like TIGAR ('TP53-induced glycolysis and apoptosis regulator') to sustain body's antioxidant response against oxidative stress (210). The role of HO-1 to protect against SARS-CoV-2 is probably an emergency inducible defense mechanism to ameliorate oxidative stress from heme-released oxidants.

HO-1 and anti-inflammatory effects

The term 'cytokine storm syndrome' or *cytokine release syndrome* (CRS) is perhaps one of the critical hallmarks of COVID-19 disease severity, characterized by an overwhelming host inflammatory response (211). The redox-sensitive transcription factor Nrf2 serves as a 'master regulator' of antioxidant defense enzymes to counteract oxidative stress and modulate redox signaling pathways during host inflammatory responses (212). The Nrf2 also regulates the HO-1 axis, in particular, the CO generated from HO-1 activity could modulate the release of proinflammatory or anti-inflammatory cytokines and mediators. HO-1 and CO also demonstrate immunomodulatory effects and regulate the functions of antigen-presenting cells (APC), dendritic cells (DC), and regulatory T cells (Tregs) (202). Human HO-1 binds to the SARS-CoV-2 *open reading frame (ORF)-3a* protein (213), this HO-1 interaction could inhibit viral-induced inflammation and tissue damage *via* the NLRP3 pathway (214). Therefore, the cytoprotective HO-1 pathway is an attractive therapeutic target to control SARS-CoV-2 infection and alleviate COVID-19-induced CRS and subsequent ARDS (215,216).

HO-1 and anti-thrombotic effects

The cytokine storm, thromboembolism and pulmonary tropism are responsible for ARDS and respiratory failure leading to MODS with high CFR in COVID-19 patients. The thromboembolic events include elevated D-dimers (a biomarker reflecting activation of hemostasis and fibrinolysis), and low platelet count (thrombocytopenia) (217). HO-1-induced anti-thrombotic activity prevents endothelial injury, expression of adhesion molecules, inflammatory responses and down-regulates the pro-coagulant factors. Since inflammation induced-coagulopathy is associated with high fatality in COVID-19 patients; its attenuation by HO-1 induction may be a promising strategy (218). In earlier studies, stimulation of HO-1 synthesis could inhibit platelet-dependent thrombus formation. Such enhanced HO-1 expression due to oxidative stress may represent an adaptive response to down-regulate platelet activation under prothrombotic conditions (219). Systemic induction of HO-1 and BR delays microvascular thrombus formation *via* reduction of *endothelial P-selectin* (220). In response to inflammation and oxidative stress, the stimulated HO-1 regulates Fe-R-H and prevents vascular damage from thrombosis and ROS (221). Therefore, induction/upregulation of HO-1 may prove beneficial in preventing thrombotic events associated with vascular inflammation and reduce severity of COVID-19.

HO-1 as an adjuvant therapy for COVID-19

Natural compounds that could modulate HO-1 pathway could prove as potential therapeutics or prophylactics for COVID-19 management. *Nimbolide*, a limonoid tetranortriterpenoid with an α, β-unsaturated ketone system and a δ-lactone ring isolated from neem plant (*Azadirachta indica*) could upregulate the HO-1 enzyme and mRNA expression (222). Phytochemicals such as, the *Resveratrol* (3,4′,5-trihydroxy stilbene) and the *Curcuminoids* (with *α*, *β*-unsaturated carbonyl groups) are potential inducers

of HO-1 expression through Nrf2/antioxidant-responsive element (ARE) pathway (223,224). *Quercetin*, a polyphenolic flavonoid found in a variety of fruits and vegetables could induce *in vitro* HO-1 expression *via mitogen-activated protein kinase* (MAPK)/Nrf2 pathway (225). Also, *hyperbaric oxygen therapy* (HBOT) could improve clinical outcomes of COVID-19 cases, when administered at early stages as soon as a reduction in arterial O_2 level is detected (226). HBOT is known to activate Nrf-2-mediated oxidative stress response that releases HO-1 for cytoprotection (227). Taken together, the inducible HO-1 cytoprotective pathway could be a promising target to control SARS-CoV-2 infection and relieve COVID-19-induced CRS and subsequent ARDS.

Erythropoietin (EPO)

Erythropoietin (EPO) is a hypoxia-inducible growth factor expressed in various organs and tissues of the body (Figure 5C) (228). Physiological regulation of the RBC formation depends on enhanced transcription of the EPO-gene in response to hypoxia (229). EPO synthesis involves redox-sensitive signaling pathways triggered by the ROS and modulated by thiol compounds (i.e. *N-acetylcysteine*) or changes in the plasma thiol-disulfide redox state (230). Critical and deceased patients demonstrate significantly lower serum levels of EPO, haptoglobin, and hepcidin compared to survivors or mild cases of COVID-19 (150).

EPO and Fe-R-H regulation

The RBC production (erythropoiesis) is the single largest consumer of iron in the body. Iron is essential for Hb synthesis during terminal erythropoiesis. Crosstalk between erythropoietic demand and Fe-redox state of the milieu regulates the transport of iron and O_2 to cells. Therefore, EPO treatment after SARS-CoV-2 infection may help restore Hb levels, increase RBC count, and improve O_2 delivery to the tissues (231). Activated EPO depletes serum iron levels, limits the systemic availability of Fe^{3+} ions for Fenton-type oxidative catalysis (232); thereby, protect COVID-19 patients against free radical-induced vascular damage.

EPO and anti-inflammatory effects

The severity of COVID-19 with ARDS is linked to the overexpression of proinflammatory cytokines induced by the host immune response. An excessive inflammatory response results in the progression of ARDS, with the NLRP3 inflammasome as key player. The ensuing CRS leads to the development of *acute lung injury* (ALI)/ARDS. Proinflammatory cytokines mediate *nitric oxide* (NO•) release that inhibit EPO synthesis and trigger anemia of inflammation (AI) (233). Accordingly, fatal cases of COVID-19 demonstrate 2.5 times lower serum EPO (2.8 vs. 7.1 mU/mL), and 1.24 times lower Hb levels (14.0 vs 17.4 g/dL) compared to survivors (234). Thus, EPO may be considered as a Fe-redox bio-replenishment for COVID-19 treatment if administered at an early stage of SARS-CoV-2 infection (235,236).

EPO suppresses proinflammatory cytokines, protects cells from apoptosis and promotes wound healing. Specific EPO receptors expressed on different immune cell cascades directly modulate host immune response (237,238). EPO promotes production of endothelial progenitor cells and reduce inflammatory responses by inhibition of NF-κB and JAK-STAT3 signaling pathways (239). Furthermore, EPO effectively attenuates lung injury through suppression of NLRP3 inflammasome and inhibition of NF-kB pathway (240). Also, EPO could stimulate NO• production in the hypoxic lung and support ventilation by interacting with respiratory centers of the brainstem (234). A combination of EPO as anti-inflammatory/immunomodulatory agent with antiviral drugs may prove even more effective.

COVID-19 patients show ground-glass opacities localized to alveoli indicating the presence of ALI (241,242). EPO could protect pulmonary vascular beds and counteract hypoxic pulmonary vasoconstriction (243). In a clinical study, recombinant human (rh)-EPO showed effective attenuation of ARDS symptoms and facilitated recovery from COVID-19 *via* multiple mechanisms including cytokine modulation, anti-apoptotic effects and leukocyte release from the bone marrow (231).

EPO as an adjuvant therapy for COVID-19

Neurological manifestations of COVID-19 patients are increasingly reported (6, 244). EPO could potentially improve COVID-19 patients with acute and chronic-progressive downstream sequelae of the central and peripheral nervous system. Growing evidence suggests that SARS-CoV-2 infection may also predispose patients to thrombosis (13). Co-treatment of EPO with anti-coagulants or anti-thrombotic agents, such as heparin could circumvent complications in hospitalized COVID-19 patients (243). Therapeutic benefits of EPO on COVID-19 patients may include: i) respiratory improvement at several levels including lung, brainstem, spinal cord, and respiratory muscles (245); ii) counteract hyperinflammation caused by cytokine storm/inflammasome (238, 240); iii) neuroprotection and neuro-regeneration in brain and peripheral nervous system (235).

Hepcidin modulators

Hepcidin, a peptide hormone secreted by the liver, is the master regulator of iron intake and systemic Fe-R-H (Figure 5D) (246). Hepcidin regulates iron levels by binding to FPN, and the FPN/hepcidin regulatory axis that allows precise control of iron at both systemic as well as cellular levels (247). Hepcidin synthesis in the liver is controlled by four pathways: i) iron store-related regulation, ii) erythropoietic activity-driven regulation, iii) inflammation-related regulation, and iv) mandatory signaling pathway. These regulatory pathways interact with hepatocytes to initiate or inhibit the production of sufficient hepcidin to regulate Fe-R-H (248).

Hepcidin expression calibrates to alterations in iron levels, inflammatory cues, and iron requirements for erythropoiesis. Circulating factors (LF, TF, cytokines, erythroid regulators) might variably contribute to hepcidin modulation in different pathological conditions (194, 249). Bone morphogenetic proteins (BMPs) are members of the *transforming growth factor-β* (TGF-β) superfamily of signaling molecules. Specifically, BMP6 could activate hepato-cellular expression of hepcidin, the iron-regulatory hormone.

This activation occurs *via* cellular SMAD-signaling and is strongly modulated by the BMP co-receptor *hemojuvelin* (HJV) (250). A complex regulatory network involving TGF-β1 and BMP6 may control the sensing of systemic and/or hepatic iron levels (251).

Hepcidin as a drug target

Hepcidin is a promising drug target for COVID-19 patients with iron overload syndromes. (252,253). Several compounds are under development as hepcidin agonists to prevent iron overload resulting from hepcidin deficiency (254). *Homocysteine* up-regulates hepcidin expression through the BMP6/SMAD pathway, suggesting a novel approach to rebalance iron homeostasis (255). *Calcitonin* is a potent inducer of hepcidin expression and provides an interventional strategy for treating perturbed Fe-R-H balance (256). *Auranofin*, the anti-rheumatoid arthritis drug is shown to upregulate hepcidin expression and ferroptosis *via* distinct mechanisms, seems to be a promising therapeutic against hepcidin-deficiency related disorders (257). Also, the drug *oncostatin M* could strongly induce hepcidin expression and significantly decrease systemic iron overload (258).

Genistein, a member of the isoflavone-related estrogen could induce hepcidin transcription. This modulation is mediated by both BMP and *signal transducer and activator of transcription* 3 (STAT3) signaling but does not require estrogen receptor signaling (259). Several dietary phytoestrogens could up-regulate hepcidin expression, control systemic iron levels, prevent iron-induced toxicity and provide protection against several oxidative stress-induced pathological disorders (260). *Quercetin* and related polyphenols such as *epigallocatechin-3-gallate* (EGCG), the most abundant catechin in tea, may reduce iron toxicity by chelation or blocking the iron release/efflux from cells (261,262). Quercetin elicits a strong post-prandial hepcidin induction (with serum iron and TF saturation) to reduce iron overload (263). As potential inducers of hepcidin expression, phytoestrogens are promising adjunctive supplements to reduce iron overload and prevent any sequelae of iron-induced toxicities such as hyperferritinemia, coagulopathies and/or thromboembolism, the prominent clinical manifestations among COVID-19 patients (17, 42, 264,265).

Ferroptosis inhibitors for COVID-19 intervention

Ferroptosis is an iron-catalyzed, non-apoptotic form of regulated necrosis that causes oxidative lipid damage in cell membranes and leads to mitochondrial dysfunction (266). Ferroptosis with characteristic accumulation of oxidized phospholipids (or their breakdown products) in myocardial and renal tissue is responsible for ischemia-reperfusion injury, could be a detrimental factor for cardiac damage and MODS in COVID-19 patients (104). Ferroptosis is more immunogenic than apoptosis and plays an detrimental role in hyper-inflammation such as the CRS (267). Accordingly, ferroptosis might serve as a potential treatment target for COVID-19 management (105).

A hallmark of ferroptosis is iron-dependent lipid peroxidation, which could be inhibited by the key ferroptosis regulator *glutathione peroxidase 4* (Gpx4), free radical trapping antioxidants and ferroptosis-specific inhibitors that include: *ferrostatin-1 (Fer-1)*

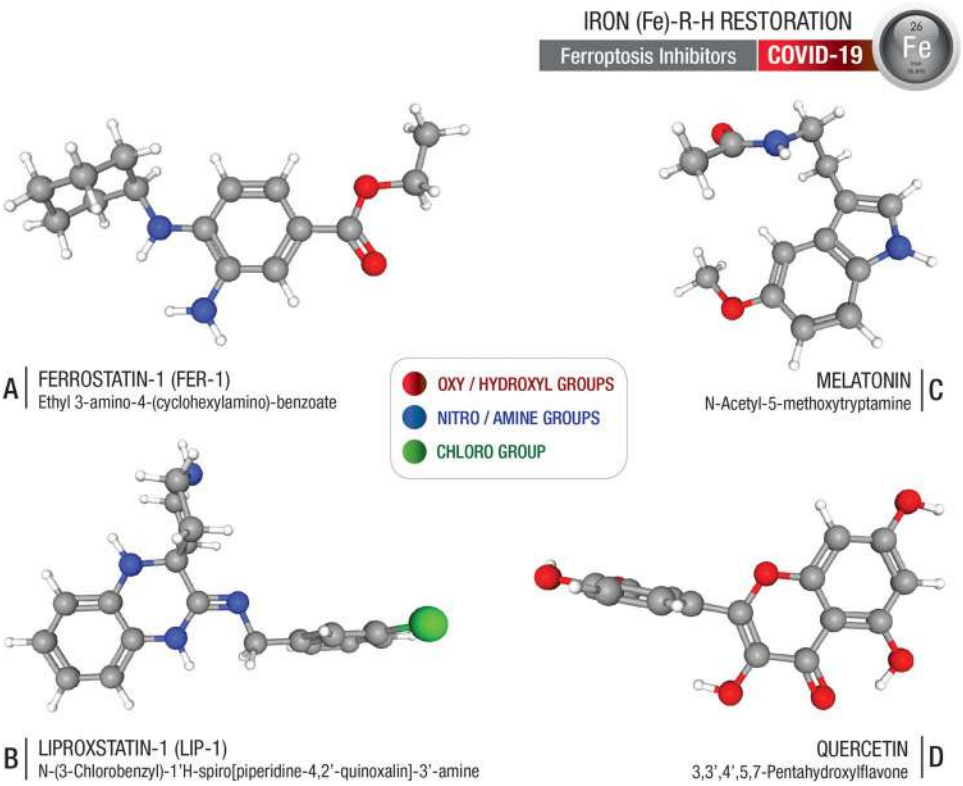

Figure 6. Ferroptosis inhibitors for COVID-19 intervention. Ferroptosis is an iron-catalyzed, non-apoptotic form of regulated necrosis that results in oxidative lipid damage in cell membranes and mitochondrial dysfunction. Ferroptosis plays an important role in hyper-inflammation such as the 'cytokine storm'; therefore, a potential intervention target for COVID-19. A) Ferrostatin-1 (Fer-1) is a potent lipophilic free radical scavenger that reduces cellular accumulation of lipid peroxides. The anti-ferroptic activity of Fer-1 depends on the electron transfer of aromatic N-atoms into a redox recycle. B) Liproxstatin-1 (Lip-1) prevents mitochondrial lipid peroxidation, restores GSH, and FSP1 synthesis, preserves Gpx4, and down-regulates acyl-CoA synthetase and COX2. C) Melatonin could inhibit ferroptosis through activation of Nrf2 and HO-1 signaling pathways. D) Quercetin could up-regulate the GSH levels and inhibit ferroptosis by reducing MDA and lipid ROS.

and *liproxstatin-1 (Lip-1)*, as well as iron chelator *deferoxamine* (DFO) (268). *Nuclear factor (erythroid-derived 2)-like 2* (Nrf2) could suppress ferroptosis and maintain cellular Fe-R-H balance (269). *Ferroptosis suppressor protein 1* (FSP1), a key component of a non-mitochondrial CoQ antioxidant system could act in parallel with the Gpx4 pathway and inhibit ferroptosis (270). The Gpx4 inhibition could also induce ferroptosis in oligodendrocytes (271). *Both Fer-1* and *Lip-1* are potent inhibitors of ferroptosis, an activity attributed to their ability to reduce the accumulation of lipid hydroperoxides. These two inhibitors subvert ferroptosis by preventing lipid peroxidation as free radical-trapping antioxidants (272) (Figure 6).

Ferrostatin-1 (FER-1, *Ethyl 3-amino-4-cyclohexylamino-benzoate)* is a potent lipophilic free radical scavenger that reduces cellular accumulation of lipid peroxides and chain-carrying peroxyl radicals (Figure 6A) (273). The anti-ferroptotic activity of *Fer-1*

is associated with it ability to scavenge alkoxyl radicals and remain unconsumed while inhibiting the iron-dependent lipid peroxidation (274). Though a potent inhibitor of oxidative lipid peroxidation, the presence of ester moiety in its structure could render a rapid hydrolysis of *Fer-1* into an inactive carboxylic acid form *in vivo* (275). Synthesis of novel ferroptosis inhibitors with steric modifications to amide and sulfonamide moieties could significantly improve molecular stability and ADME profile of this ROS-trapping antioxidant. The anti-ferroptic activity of *Fer-1* depends on the electron transfer of aromatic N-atoms into a redox recycle. Interestingly, dietary phytophenols such as *piceatannol* and *astringin* strongly inhibit ferroptosis *via* preferential transfer of hydrogen atoms at the 4′-OH position as conventional antioxidants. (106, 276). Therefore, dietary phytophenols could be considered as safer ferroptosis inhibitors for cellular rebalance than synthetic *Fer-1* derivatives.

Liproxstatin-1 (LIP-1, *N-1'H-spirol-3′-amine*) is a potent inhibitor of ferroptosis that could prevent mitochondrial lipid peroxidation and restore the expression of GSH, and FSP1 (Figure 6B) (271). The anti-ferroptic activity of *Lip-1* is associated with its ability to preserve *Gpx4*, down-regulate *acyl-CoA synthetase* and *COX2*. In addition, *Lip-1* down-regulates microglial activation as well as the release of IL-6, IL-1β, and TNF-α (277).

Hemin, a predominant degradation product during coagulopathies, is associated with SARS-CoV-2 infection. Hemin could induce ferroptosis in platelets *via* ROS-driven proteasome activity and inflammasome activation (8). *Melatonin (N-acetyl -5-methoxytryptamine)*, the chronobiotic hormone that controls circadian rhythms, is an endogenous antioxidant with strong free radical quenching capacity (Figure 6C). *Melatonin* could effectively reduce the level of ferroptosis through activation of Nrf2 and HO-1 signaling pathways (278). Its strong ability to inhibit ferroptosis and platelet activation, makes *melatonin* a potential intervention to treat hemolytic, thrombotic, and thrombocytopenic conditions (279), which are widespread among COVID-19 patients. Pretreatment with *N-acetyl cysteine (NAC)* and *Fer-1* could reverse the effect of IL-6 on lipid peroxidation and ferroptosis (280). IL-6 is known to promote ferroptosis in bronchial epithelia by inducing ROS-dependent lipid peroxidation and disrupt Fe-R-H in COVID-19 (281). *Frataxin* is an effective ferroptosis modulator that regulates Fe-R-H and mitochondrial function. Suppression of *frataxin* expression could destroy mitochondrial morphology, impede Fe-S cluster assembly, and activate iron starvation stress (282).

Phytonutrients as ferroptosis inhibitors

Several phytonutrients have been identified as potent inhibitors of ferroptosis. *Quercetin (Pentahydroxy flavone)*, a natural flavonoid, could up-regulate the GSH levels and inhibit ferroptosis by reducing *malondialdehyde* (MDA) and lipid ROS levels in the renal proximal tubular epithelia (Figure 6D) (277). Two tannin hydrolysates, *chebulagic acid* and *chebulinic acid*, have been reported as natural ferroptosis inhibitors (283). Their ferroptosis inhibition is mediated by regular antioxidant pathways (ROS scavenging and iron chelation), rather than the redox-based catalytic recycling pathway exhibited by *Fer-1*. *Curcumin* could inhibit *myoglobin* (Mb)-induced ferroptosis in renal tubular cells. *Curcumin* could reduce Mb-mediated inflammation and oxidative stress

by inhibiting the TLR4/NF-κB axis and activating the cytoprotective enzyme HO-1 (284). *Glycyrrhizin*, the main extract from licorice (*Glycyrrhiza glabra*), is a natural antioxidant, anti-inflammatory, antifibrotic and antiviral agent widely used in the treatment of chronic hepatitis (285). *Glycyrrhizin* shows significant reduction in the degree of ferroptosis and inhibits oxidative stress. *Glycyrrhizin* treatment could provide anti-ferroptotic liver protection through up-regulation of Nrf2, HO-1 and Gpx4; and down-regulation of *lactate dehydrogenase* (LDH), Fe^{2+}, MDA, and ROS (286).

Anticoagulants for COVID-19 intervention

Since the beginning of COVID-19 pandemic, disease severity and respiratory failure were attributed to markers of coagulopathy such as *prothrombin time* (PT) prolongation, elevated fibrin degradation products, reduced platelet count, and highly elevated D-dimers (52, 82, 287,288). Therefore, anticoagulant therapy is widely practiced as a COVID-19 clinical management protocol is several hospitals worldwide.

Heparin

Heparin, a member of the heparan sulfate family of glycosaminoglycans (GAGs), is a linear polysaccharide with alternate disaccharide sequences of sulfated uronic acid and amino sugars (289). Sulfated moieties confer heparin with the highest negative charge density of any known biological molecule. These anionic glycans are vital for several cellular functions such as cell growth, adhesion, angiogenesis, and blood coagulation (112). The anionic property endows specific high-affinity interaction of heparin with an array of proteins, most classic being the *serine protease inhibitor antithrombin-III* (AT3), which results in anticoagulant activity (290, 296). Heparin is a globally used anticoagulant and antithrombotic agent with well-characterized bioavailability, safety, stability, and pharmacokinetic profiles (297; 291).

Heparin and anti-inflammatory effects

Heparin elicits anti-inflammatory effects on the vasculature as well as in the respiratory airways to alleviate cytokine response in COVID-19/ARDS (292). The anti-inflammatory spectrum of heparin and its constituent heparan sulfate GAG fragments fall into two mechanisms: i) down-regulate inflammation *via* interactions with proinflammatory cytokines, and ii) prevent adhesion and influx of inflammatory cells into the diseased area (290). Accordingly, heparin regulates several inflammatory mediators including IL-6, IL-8, *platelet growth factor 4* (PGF4), *stromal-derived factor 1a*, *neutrophil elastase*, *P-* and *L-selectin*, CD11b/CD18, *major basic protein* (MBP), and *eosinophil cationic protein* (ECP) (293,294). Heparin also down-regulates NF-κB signaling in human endothelial cells and monocytes (295). Anti-inflammatory therapies that alleviate the cytokine responses, especially IL-6, may alleviate severe symptoms and decrease the CFR in COVID-19 patients. Heparin binding to integrin adhesion molecules inhibits activation and adhesion of leukocytes to the endothelium. Such heparin-mediated low recruitment of immune cells could suppress the subsequent immune activation and

cytokine release (296,297). In a retrospective clinical study, treatment of COVID −19 patients with *low molecular weight heparin* (LMWH) significantly lowered plasma levels of IL −6, a key mediator of CRS (296). Heparin therapy could also relieve hypoxia-mediated clinical manifestations in COVID-19 patients (298).

Anti-coagulant and anti-thrombotic effects of heparin

Among the coagulation parameters related to COVID-19, the most characteristic feature is the acute rise in *D-dimers* (up to 45% of patients) and such elevated levels correlate with the disease severity (82, 299). A dramatic increase of *fibrin(ogen) degradation product* (FDP) that follows the coagulation activation indicates a secondary hyper-fibrinolysis (300). Thrombocytopenia is also observed in COVID-19 patients with low platelet counts associated with elevated risk of disease severity and mortality (301). As coagulopathy plays a critical role in the progress and prognosis of SARS-CoV-2 infections, an effective clinical management of hyper-thrombotic conditions in COVID-19 patients is highly desirable. Heparin is a promising prophylactic also against *venous thromboembolism* (VTE) in COVID-19 patients (59).

Heparin and anticoagulant therapy for COVID-19

Heparin, as an anticoagulant therapy for COVID-19 was first reported in a retrospective study ($n = 449$ patients) from Wuhan, China, where such prophylactic treatment is relatively uncommon due to low incidence of VTE (302). Heparin therapy, particularly in COVID-19 patients with significantly elevated D dimers and in those with severe *sepsis induced coagulopathy* (SIC) score, improved prognosis, and decreased CFR (120, 299). The multifunctional benefits of anticoagulant therapy of COVID-19 patients with heparin include: (i) inhibition of heparinase activity, responsible for endothelial leakage; (ii) neutralization of chemokines, and cytokines; (iii) interference with leukocyte trafficking; (iv) blocking of viral cellular entry, and (v) neutralization of extracellular cytotoxic histones (303). Taken together, anticoagulant therapy with heparin and heparin-derivatives seem to reduce mortality of severe COVID-19 patients (120, 304).

The clinical features of COVID-19/ARDS include diffused alveolar damage with extensive pulmonary coagulation activation, fibrin deposition in the microvasculature and formation of hyaline membranes in the air sacs. ARDS is extremely life-threatening for COVID-19 patients with a high mortality rate of 40% to 50% (299). The anti-coagulant and mucolytic actions of nebulized unfractionated heparin could be effective in ameliorating respiratory symptoms, lowering pulmonary dead space and reducing ventilatory support in COVID-19 patients (305).

Contra-indications

Heparin as a therapeutic anticoagulant is linked to a 10 – 15% risk of significant bleeding (306). Factors that may increase bleeding risk include old age, recent trauma or surgery, cardiopulmonary resuscitation, longer hospital stay, and decreased white blood cell/platelet counts (307). These risk factors are common among patients with COVID-19. *Heparin-induced thrombocytopenia* (HIT), a rare complication of heparin

therapy, is estimated to occur in 0.2–3% of patients (308). The adverse HIT reaction results from the development of antibodies against *platelet factor 4*, which triggers thrombocytopenia. Repurposing of heparin and its derivatives as first-line therapeutics against SARS-CoV-2 is promising; however, this clinical approach needs an in-depth evaluation (309).

Iron (Fe)-chelators for COVID-19 intervention

Dysregulated Fe-R-H is one of the potential causes of diffuse endothelial inflammation with systemic involvement (8). Elevated iron levels could trigger oxidative and nitrosative stress that subsequently activate NF-κB and upregulate proinflammatory mediators such as IL-1β, IL-6 and TNF-α that promote the course of viral infection (38). Such clinical state could also contribute to an array of respiratory diseases, including ARDS and pulmonary fibrosis (310,311). Endothelial inflammation is considered as the main pathobiological mechanism involved in MODS during SARS-CoV-2 infection. Therefore, iron chelators might prove useful to ameliorate any such systemic manifestations of COVID-19 (312). Iron chelators could control ARDS and attenuate SARS-CoV-2 infection through multiple mechanisms including: i) inhibition of viral replication, ii) decrease of iron availability, ii) upregulate B cells, iv) improve neutralizing anti-viral antibody titer, v) inhibit endothelial inflammation, and vi) prevent pulmonary fibrosis and lung decline by reducing pulmonary iron accumulation (313) (Figure 7).

Desferoximine (DFOA)

Deferoxamine B (DFOA) is a natural siderophore, a hydroxamic acid metabolite of the soil bacterium *Streptomyces pilosus*. The exquisite affinity of DFOA for Fe^{3+} identified its potential to remove excess iron from patients with transfusion dependent Hb disorders (314). DFOA binds to Fe^{3+} in the vascular space at 1:1 ratio and forms a water-soluble *ferrioxamine* (FOA) complex (315). In the hepatocytes, the FOA complex is excreted through bile and in plasma or tissue milieu, the FOA is filtered out by the kidneys. DFOA can remove Fe^{3+} only from storage proteins (*ferritin* and *hemosiderin*) and not from Hb, cytochromes, LF, and TF (23, 315). This selective iron-binding activity makes DFOA a physiologically relevant drug chelate for iron detoxification in many diseases and organ dysfunctions.

Iron-chelation, free radical scavenging, and antioxidant effects of DFOA

The DFOA structure consists of three bidentate hydroxamic functional groups that wrap around the Fe^{3+} ion to form a neutral and highly stable octahedral complex (Figure 7A). Although the most important property of DFOA is iron sequestration, this chelator is a powerful free radical scavenger (316). Free iron overload in biological systems triggers Fenton-type redox reactions to generate toxic free radicals (ROS/RNS), highly reactive hydroxyl radical (OH•) and membrane damaging lipid radicals. Moreover, free Fe^{3+} ions could target highly vascular tissues (i.e. hepatic,

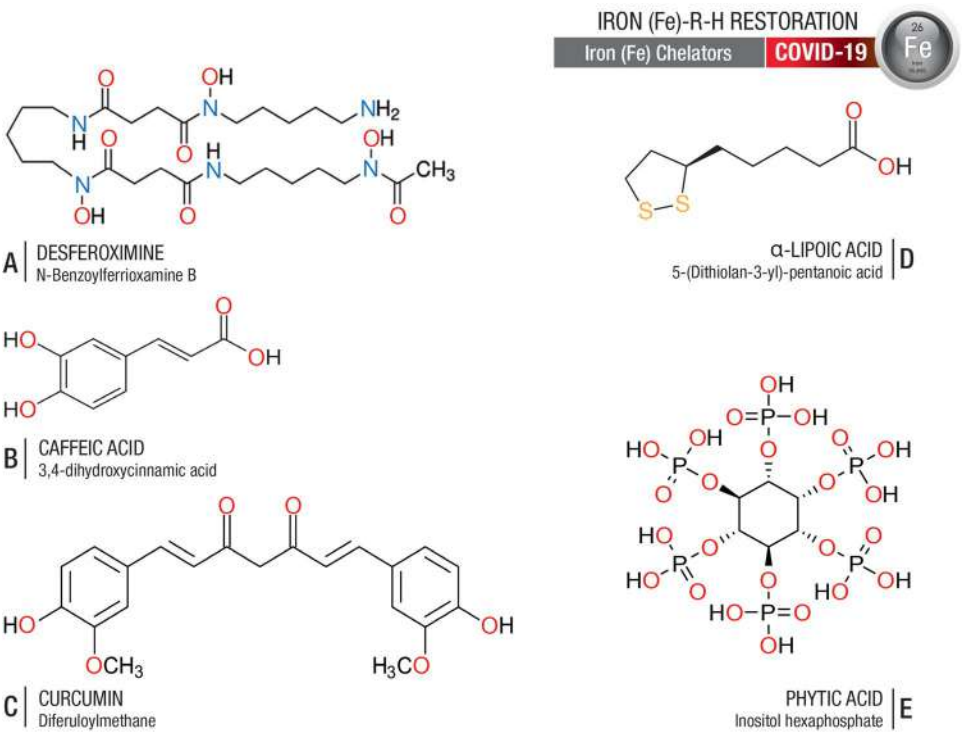

Figure 7. Iron chelators for COVID-19 intervention. Dysregulated Fe-R-H is one of the potential causes of diffused endothelial inflammation with systemic involvement which may trigger an array of pathobiological events involved in MODS during SARS-CoV-2 infection. Therefore, iron chelators could play a potential role to ameliorate the systemic manifestations of COVID-19. A) Deferoxamine B (DFOA) is a natural siderophore that binds to Fe^{3+} in the vascular space and forms a water-soluble ferrioxamine (FOA) complex. DFOA removes Fe^{3+} selectively from storage proteins (ferritin and hemosiderin) and not from Hb, cytochromes, LF, and TF, which makes it a physiologically relevant drug chelate for iron detoxification. B) Caffeic acid acts as both metal-chelator and hydrogen (H^+) donor to prevent harmful effects of lipid-derived peroxyl and alkoxyl radicals (lipid peroxidation) on biological membranes. C) Curcumin (CUR) could protect hematopoiesis from immune and iron overload-induced apoptosis, and its iron-chelation effect is more effective than DFOA. D) α-lipoic acid (ALA) upregulates intracellular GSH levels and prevents activation of Nrf2 pathway. This activity could significantly reduce HO-1, mtSOD, and FPN1 expression during iron overload and restore mitochondrial membrane integrity, redox potential, and function. E) Phytic acid inhibits Fe^{2+}-catalyzed hydroxyl (OH•) radical formation and blocks linoleic acid autoxidation and Fe^{2+}/ascorbate-induced peroxidation of erythrocytes.

cardiac and endocrine cells), and significantly damage the corresponding organ function (317). Oxidative stress, ROS/RNS induced tissue damage, thrombosis, and RBC dysfunction, are major risk factors in COVID-19 disease severity (318). The potent antioxidant and free radical scavenging activities of DFOA could be beneficial for highly vulnerable COVID-19 patients. DFOA also exhibits antiviral, antioxidant and immunomodulatory effects *in vitro* and *in vivo*, particularly against RNA viruses (37, 319).

DFOA and iron-chelation therapy for COVID-19

Iron toxicity triggers ROS/RNS generation and elevate serum ferritin levels that cause oxidative COVID-19 patients (320,321). The cellular Fe-R-H imbalance due to Fe^{3+} overload could elicit endothelial inflammation, pulmonary fibrosis and ARDS, all prominent clinical features of severe COVID-19 (117, 310, 322). The hyper-inflammatory response could evoke 'cytokine storm', promote hepcidin synthesis and enhance iron sequestration by macrophages (17), a cellular target for SARS-CoV-2 (323). Excess iron is known to facilitate viral replication and exacerbate severity of the infection (36). Iron-chelation therapy with DFOA could effectively diminish such accrued pulmonary Fe^{3+} levels, prevent airway fibrosis and restore lung function (324,325). Pulmonary fibrosis is associated with an increase in 'iron-sequestering $TfR1^{+}$ macrophage population. The DFOA treatment could reduce such inflammatory cells and provide potential anti-SARS-CoV-2 protection (310, 313). Furthermore, DFOA could lower the IL-6 levels and reduce endothelial inflammation *in vitro* (325), which is a major risk factor for MODS in COVID-19 patients. DFOA also has an immunomodulatory effect and improves the immune response against enteroviral infection through up-regulation of B cells and elevation of neutralizing antibodies (326). Therefore, DFOA could possibly ameliorate clinical manifestations of COVID-19 from viral-induced lymphopenia (324).

The mesylate salt of DFOA, known as Desferal®, is considered an 'Essential Medicine' by the W.H.O. (37), a potential chelator drug for treating iron overload (i.e. serum ferritin levels >800-3000 ng/mL) (327). It is relatively safe and well-tolerated by patients and regular DFOA therapy should not exceed 200 mg/day. Other iron chelators approved by the U.S. Food and Drug Administration (FDA) for clinical use include *Deferiprone* (DFP, Ferriprox®), and *Deferasirox* (DFX, Exjade®) (40, 328).

Contra-indications of DFOA

Data on combination therapy are limited; however, this could be equally safe compared to DFOA monotherapy (329). Interestingly, vitamin C could potentiate the therapeutic effects of DFOA by mobilizing the iron reserves and increasing the 'chelatable' free iron levels. However, the elevated free iron could potentiate iron toxicity and impair cardiac function (330). Therefore, the FDA warns that vitamin C supplementation should be avoided in cardiac patients. Acute side effects such as GI complications, skin discoloration, skin irritation, and anaphylaxis also have been reported in DFOA-sensitive patients (23).

Caffeic acid

Caffeic acid is a plant-based iron-chelator, redox modulator, and a powerful natural antioxidant (331). Caffeic acid acts as both metal-chelator and hydrogen (H) donor to prevent harmful effects of lipid-derived peroxyl and alkoxyl radicals (lipid peroxidation) on biological membranes (Figure 7B) (332). Caffeic acid inhibits several viral pathogens such as the herpes simplex (HSV), influenza and immunodeficiency viruses (HIV) and its antiviral activity is potentiated >100-fold in the presence of iron. Caffeic chelates seem to target and interfere with viral attachment to *heparan sulfate*

proteoglycans (HSPG) on cell surface (333). Caffeic acid effectively inhibits the replication of human coronavirus NL63 in a cell-type independent manner (IC_{50}=3.54 μM), and specifically blocks the viral attachment (IC_{50}=8.1 μM) (334). A *phenethyl ester* (from propolis) of caffeic acid is shown to interact with the substrate-binding pocket of SARS-CoV-2 M^{pro} with affinity and binding energies (ΔG= −4.79 kcal/mole) comparable to N3 (ΔG= −5.68 kcal/mole), the reference viral protease inhibitor (335). Several caffeic acid-derivatives (*Khainaoside C, 6-O-Caffeoylarbutin, Khainaoside B, Khainaoside C* and *Vitexfolin A*) demonstrate higher binding energies (ΔG) than the antiviral drug nelfinavir against COVID-19 M^{pro}, Nsp15, SARS-CoV-2 spike S2 subunit, spike open state and closed state structures. Caffeic acid forms H-bonds with Asn_{142} and Glu_{166} residues of SARS-CoV-2 M^{pro} enzyme (336).

Curcumin

Curcumin (CUR, *diferuloylmethane*) from the Indian herb turmeric (*Curcuma longa*) is an iron-chelator that modulates proteins of iron metabolism in cells and in tissues (Figure 7C) (337). CUR inhibits iron-catalyzed pathways of oxidative stress and protects cellular DNA, lipids, and protein from free radical damage (338). CUR also affects hematological parameters of iron homeostasis including of Hb, hematocrit, serum iron, and TF saturation. CUR activates *iron regulatory proteins* (IRPs) during iron-deficiency and cause translational ferritin repression. Conversely, during iron overload, CUR inactivates IRPs and increases the translation of ferritin mRNA (339). CUR protects hematopoiesis from immune and iron overload-induced apoptosis, and its iron-chelation effect is more effective than DFOA (340). CUR regulates expression of both pro- and anti-inflammatory factors such as IL-6, IL-8, IL-10, and COX-2, promotes apoptosis of neutrophils, and scavenges ROS. Accordingly, CUR is considered as an effective intervention against pneumonia and ALI/ARDS resulting from CoV infections (341). CUR also exerts direct antiviral activity by allosteric inhibition of viral proteases (342,343). Several molecular docking studies have demonstrated a potent inhibitory effect of CUR on SARS-CoV $3CL^{pro}$, the *main protease* (M^{pro}) enzyme critical for viral replication (344–346). The cyclo-CUR from turmeric showed significantly more anti-M^{pro} activity than antiviral drug *remdesivir* (347). CUR showed high-affinity interaction (ΔG= −8.1 kcal/mol) with active site of the SARS-CoV-2 M^{pro} and exhibited an optimal structure rotational capacity to bind the viral receptor pocket (312).

α-Lipoic acid

α-lipoic acid (ALA, *5-dithiolan-3-yl-pentanoic acid*) protects cellular systems from oxidative and nitrosative stress by chelating iron and regenerating endogenous antioxidants such as vitamin E, vitamin C and GSH (Figure 7D) (348). ALA could increase intracellular levels of GSH and prevent the activation of Nrf2 pathway. This ALA activity could significantly reduce HO-1, mtSOD, and FPN1 expression in the presence of an iron overload and restore mitochondrial membrane integrity, redox potential, and function (349,350). Also, ALA demonstrates high-affinity binding (ΔG= −8.0 kcal/mol) to SARS-CoV-2 M^{pro} enzyme, critical for viral replication (312).

Phytic acid

Phytic acid (*myo-inositol hexaphosphate*, IP6) is abundant in edible legumes, cereals, and seeds. As an iron chelator, phytic acid is a potent antioxidant that inhibits iron-catalyzed hydroxyl (OH•) radical formation (Figure 7E) (351). This phytochemical also blocks linoleic acid autoxidation and iron/ascorbate-induced peroxidation of erythrocytes (352). Phytic acid could ameliorate lung inflammation and limit lymphocyte functions that may cause pulmonary fibrosis (353). The antiviral activity of IP6 relates to the inhibition of HIV-1 replication in T cells and peripheral blood mononuclear cells (354). Phytic acid could form H-bonds with a single amino acid residue (Glu_{3429}) as well as with other external sites (His_{3435}, Tyr_{3398}, Asp_{3460}, Ser_{3402}) on SARS-CoV-2 M^{pro}; however, these interactions seem to be unstable with low docking score (ΔG= −1.5 kcal/mol), due to interference with surrounding water molecules in its structure (312).

Conclusions

Viruses, including the CoV pathogens, rely on host cellular metabolic machinery to acquire specific substrates for their multiplication and propagation. During the infection process, SARS-CoV-2 reprograms and activates several complex host-viral interactions, induces host-dependent Fe-R-H dysregulation, alters mitochondrial function and decreases the levels of TCA cycle metabolites to synthesize amino acids, lipids, and nucleotides required for viral replication (355–357). Such Fe-R-H dysregulation in an infected host could also affect immune responses, and trigger an array of COVID-19 outcomes, ranging from asymptomatic infections to severe manifestations such as ARDS, vascular dysfunction, MODS, and death. Comprehensive analysis of host Fe-R-H restoration to re-wire host metabolism (HMR) could provide strategies to develop novel clinical biomarkers and identify potential targets for therapeutic intervention of COVID-19. Innate Fe-R-H regulators, such as *LF, EPO, HO-1,* and *hepcidin* modulators are vital bioactive molecules in host iron metabolism, in scavenging the iron-mediated free radicals, in modulating the antioxidant responses and act as the first barriers against CoV infection. These Fe-R-H regulators, *via* iron sequestration and optimization, could reduce oxidative stress and inflammation, particularly during the 'cytokine storm' in COVID-19 pathobiology. Notably, the multifunctional antiviral spectrum of *milk LF*, with its ability to sequester/transport iron, interact with anionic compounds (HSPG, ACE2 etc.), translocate into the nucleus, modulate immune as well as inflammatory responses, and regulate the Fe-R-H, could provide benefits in both prophylactic and therapeutic interventions against COVID-19. Currently, several LF-based intervention technologies are undergoing extensive clinical trials for management of COVID-19 infections worldwide.

Abnormal ferroptosis could disrupt systemic Fe-R-H, which may lead to erythropoiesis suppression and anemia, the prominent clinical features in COVID-19 pathobiology. Therefore, treatments that target ferroptosis could alleviate thromboembolism and improve prognosis in COVID-19 patients. Both *ferrostatin-1* (Fer-1) and *liproxstatin-1* (Lip-1) are potent lipophilic free-radical trapping antioxidants that could prevent lipid peroxidation and subvert ferroptosis. *Melatonin*, the chronobiotic hormone, could

inhibit ferroptosis through activation of Nrf2 and HO-1 signaling pathways. *Quercetin*, a natural flavonoid could up-regulate the GSH levels and inhibit ferroptosis by reducing MDA and lipid-generated ROS.

Since the beginning of COVID-19 pandemic, disease severity and respiratory failure are attributed as clinical indicators of coagulopathy (i.e. highly elevated D-dimers). Therefore, anticoagulant therapy with heparin has emerged as a prominent COVID-19 clinical management protocol in several hospitals worldwide. *Heparin* is a promising prophylactic also against VTE in COVID-19 patients. The anti-coagulant and mucolytic actions of nebulized unfractionated heparin could be effective in ameliorating respiratory symptoms, lowering pulmonary dead space, and reducing ventilatory support in COVID-19 patients. Heparin-induced thrombocytopenia (HIT), a rare complication of heparin therapy, is estimated to occur in few patients. Repurposing of heparin and its derivatives as first-line therapeutics against SARS-CoV-2 is promising; however, this clinical approach needs further evaluation.

Dysregulated Fe-R-H is a major cause of diffused endothelial inflammation with systemic involvement that could trigger an array of pathobiological during SARS-CoV-2 infection. Therefore, iron chelators could play a potential role to ameliorate the systemic manifestations of COVID-19. *DFOA* is a natural siderophore that selectively removes iron from ferritin and hemosiderin to reduce the iron overload. Natural phytochemicals such as *caffeic acid*, *curcumin, α-lipoic acid* (ALA), and *phytic acid* could protect cells from iron overload and restore mitochondrial membrane integrity, redox potential, and function.

Several patients recovered from COVID-19 may sustain a post-infection sequela known as 'long COVID' or 'COVID long-haulers' (152). The 'post-acute sequelae of SARS-CoV-2 infection (PASC)' is a multi-organ disorder ranging from mild symptoms to an incapacitating state and reduced quality of life that could last for weeks or longer following recovery from COVID-19 (358,359). The pathobiology of PASC may include, but not limited to, direct or indirect invasion of the virus into the brain, immune dysregulation, hormonal disturbances, elevated cytokine levels due to hyper-inflammatory response, direct tissue damage to other organs, and persistent low-grade infection (358). The five most common symptoms include fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%), and generally have an impact on everyday functioning. (360). Symptoms might be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. In addition, COVID-19 survivors had higher risk of developing heart failure, arrythmias and myocardial infarction associated with persistent/de novo cardiac injury (361).

These long-term health consequences in COVID-19 survivors seem to be an extended Fe-R-H dysregulation. Accordingly, the clinical phases of mitochondrial dysfunction, HMR and altered host biomarker patterns persist for >3 months despite a negative RT-PCR for SARS-CoV-2 (362). Symptomatic biomarkers such as systolic blood pressure, erythrocyte sedimentation rate (ESR), CRP and D-dimer remain elevated in COVID-19 survivors. From host biomarker standpoint, specific enzymes i.e. *alanine aminotransferase* (ALT), *aspartate aminotransferase* (AST), *gamma-glutamyl transpeptidase* (GGT), and *alkaline phosphatase* (ALP) are elevated, while the serum albumin remains low in COVID-19 survivors. Also, the levels of serum lipase, amylase and albuminuria have been reported significantly high among COVID-19 survivors.

Taken together, Fe-R-H dysregulation with HMR and altered mitochondrial function is the decisive factor in the symptomatic onset and progressive clinical phases of COVID-19. The Fe-R-H dysregulation and its associated physiological disorders or disease states are sustained for extended periods (for weeks or even months) in COVID-19 patients discharged as RT-PCR (SARS-CoV-2) negative survivors. These observations strongly emphasize the therapeutic and prophylactic potential for Fe-R-H restorative nutritional/adjunctive interventions in the global management of COVID-19. Identifying the host metabolic perturbations in specific biochemical pathways associated with Fe-R-H dysregulation using biomarker analysis, especially metabolomic alterations in bioenergetic pathway intermediates, lipids, antioxidants, and amines reflect the molecular phenotype of subjects infected by SARS-CoV-2; which may open new perspectives on targeted therapeutic/prophylactic interventions for both COVID-19 as well as 'long'-COVID management.

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About the authors

Dr. Sreus A.G. Naidu has earned Doctorate in Pharmacy and MS in Regulatory Science from the University of Southern California. Sreus has over 15 years of experience working at N-terminus Research Laboratory based in California, which specializes in the isolation, purification, and activation of bioactive molecules. He is co-inventor on multiple patents with applications in human nutrition and animal healthcare.

Professor Roger A. Clemens is Associate Director of the Regulatory Science program and Adjunct Professor of Pharmacology and Pharmaceutical Sciences within the USC School of Pharmacy. Dr. Clemens was the Director of Analytical Research at USC for 5 years, and the Scientific Advisor for Nestlé USA for more than 21 years. He has published more than 50 original manuscripts in nutrition and food science, participated in more than 200 invited domestic and international lectures, and served as an expert panel member for the food industry, scientific organizations, trade associations and regulatory agencies in the United States and Canada.

Professor A Satyanarayan Naidu is the Director of N-terminus Research Laboratory in California, USA. After receiving PhD in Medical Microbiology (1985) from the Osmania University in India, Dr. Naidu served the Directorate of Public Health Services (DPHS), the Government of A.P., India and the World Health Organization (WHO) Surveillance program. He performed post-doctoral research at the Medical University of Pécs, Hungary and the Biomedical Center-Uppsala, Sweden. Dr. Naidu joined the faculty at the Lund University; Sweden (1988-1992), the University of North Carolina at Chapel Hill, USA (1993-1997). He was appointed as the Director at the Center for Antimicrobial Research, California State University-Pomona, USA (1998-2000). Dr. Naidu's discoveries on Staphylococcal toxic shock syndrome (TSS) and *E. coli* hemolytic uremic syndrome (HUS) have garnered international recognition. He was principal investigator for several NIH grants, published more than 100 peer-reviewed research

publications, written over 30 book chapters, and authored 4 reference volumes in the field of medical sciences. He holds 24 core patents, and his technology transfers in biomedical technology reach worldwide. Dr. Naidu is an elected fellow of the Royal Society for Medicine, the Linnean Society of London, the American College of Nutrition, and the International Society for the Study of Vulvovaginal Disease.

ORCID

Sreus A.G. Naidu http://orcid.org/0000-0003-3517-8135
Roger A. Clemens http://orcid.org/0000-0002-5898-9793
A. Satyanarayan Naidu http://orcid.org/0000-0002-6008-0482

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