Heme/Hemoxygenase-1 System Is a Potential Therapeutic Intervention for COVID-19 Patients with Severe Complications

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Cite This: *ACS Pharmacol. Transl. Sci.* 2020, 3, 1032–1034

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ABSTRACT: Acute respiratory distress syndrome (ARDS) is one of the critical stages of COVID-19, leading to lung injury and hemolysis. Dysfunctional hemoglobin (Hb) suffers low-level oxygenation, overloaded iron, and down-regulation of hemoxygenase-1 (HO-1), representing potential therapeutic interventions. This Viewpoint outlines the Hb–HO-1 system as a host-cell target, and proposes possible therapies, including iron chelation and CO therapies, against COVID-19 with ARDS.

KEYWORDS: COVID-19, Hb–HO-1 system, iron homeostasis, iron chelation therapy, CO therapy

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggers many biological events in its host, resulting in a viral infectious disease, coronavirus disease-19 (COVID-19), that severely affects mainly the respiratory system.¹ Respiratory-related diseases, such as acute respiratory distress syndrome (ARDS), is one of the hallmarks of a serious stage in patients with COVID-19, which is caused by low oxygenation levels in the blood.¹ Obviously, hemoglobin (Hb) is a biochemical indicator of oxygenation levels in blood. Clinical manifestation of COVID-19 shows that generally men are more vulnerable than women due to their higher levels of Hb in blood. COVID-19 also has negative clinical outcomes in diabetic patients due to their high level of glycated-hemoglobin complex.¹ Therefore, the virus markedly impacts the host due to its toxic effect in blood.

In its initial stage, SARS-CoV-2 invades the host cell by binding with human angiotensin-converting enzyme 2 (hACE2), which is thought to be the main (but not exclusive) entry door into a cell for the virus.² The virus has another recognition site, porphyrin in hemoglobin, with a binding affinity higher than that to hACE2, resulting in oxygen deprivation.³ Recently, based on computational and sequence studies, Li and Liu have reported that the function of hemoglobin is altered by the interaction between porphyrin and nonstructural proteins, specifically, ORF3a of SARS-CoV-2.³ The Arg134 residue in ORF3a may interact with the iron in heme and then kick off the iron from the heme through a redox reaction, generating dysfunctional hemoglobin (Figure 1). In this regard, Ehsani has noticed a remarkable distant sequence similarity between the cysteine-rich cytoplasmic tail of SARS-CoV-2 spike glycoprotein and hepcidin protein.⁴ Hepcidin is a key iron regulator in humans, interacting with ferroportin to facilitate iron entry into a cell.⁴ With a similar sequence, SARS-CoV-2 seems to show hepcidin-like activity, leading to impaired iron metabolism.

The dysfunction of hemoglobin leads to an altered cascade of several biochemical events, which includes low-level oxygenation, elevated free iron level, and down-regulation of heme

Figure 1. Graphic showing the dysfunction of hemoglobin (Hb) and hemoxygenase-1 (HO-1) in host cell by SARS-CoV-2. Heme, FeN₄; BD, biliverdine; BR, biliverbin; ROS, reactive oxygen species; ORF, nonstructural protein in SARS-CoV-2.

oxygenase-1 (HO-1) (Figure 1).^{5,6} Therefore, Hb, HO-1, and overloaded iron are possible targets for treatment of COVID-19. This Viewpoint sheds light on the Hb–HO-1 system as a potential therapeutic intervention against COVID-19 patients with severe complications and also outlines the probable therapies.

Generally, free iron generates reactive oxygen species (ROS) that trigger oxidative stress. Experimental and clinical data suggest that excessive oxidative stress may lead to the

Received: September 16, 2020

Published: September 28, 2020

development of ARDS.⁶ Moreover, iron is also vitally important for replication of viruses including CoVs in the host cells.⁶ Therefore, an unhealthy competition occurs between the host and virus for iron. Several clinical reports indicate that an overload of iron is observed in infected patients. For instance, the mortality rate of human immunodeficiency virus (HIV)-infected patients is increased upon intake of iron supplement.⁷

Thus, impairment of iron homeostasis with elevated iron levels may boost viral infections associated with various respiratory diseases, including ARDS.⁶ Currently, no suitable drugs/therapies are available in the market. Ongoing clinical therapies mostly rely on standard respiratory and ventilator treatment of COVID-19 patients with ARDS. Therefore, it is essential to consider alternative drugs/therapies to treat this pandemic.

As discussed above, the dysfunction of hemoglobin caused by the virus and the iron dependence of viral replication mark the significance of cellular iron homeostasis in the viral life cycle, including that of CoVs.^{6,8} Therefore, depletion of cellular iron would be a promising strategy for the treatment of viral infection. Iron chelators⁸ significantly reduce the formation of HO* as well as the availability of iron in the cell via formation of a stable Fe–chelator complex and thereby reduce cell injury as well as viral replication. FDA-approved iron chelators, such as deferoxamine, deferiprone, deferasirox, and particularly, deferoxamine (DFO), have been used clinically for the treatment of an overload of iron in various pathogens in vitro and in vivo.⁸ DFO, a nontoxic, clinically approved iron chelator drug, is useful for iron chelation therapy in beta-thalassemia and other diseases associated with elevated iron. DFO forms a stable complex with iron and thereby arrests the iron-mediated hydroxyl radical formation. For instance, DFO treatment of Enterovirus 71 (EV71)-infected mice shows a decrease in mortality by reducing the iron level.⁸ Due to its antiviral effects, DFO may be beneficial for antiviral actions against SARS-CoV-2.⁸ More importantly, an iron chelator may reduce the availability of cellular iron that plays a key role in viral replication in RNA viruses including West Nile virus, HIV, and hepatitis C virus (HCV).^{7,8} Therefore, iron chelator treatment may reduce the overload of cellular iron and thereby retard the replication of SARS-CoV-2.

Dysfunction of Hb caused by the virus leads to decreased expression of HO-1 in human cells, representing a potential therapeutic intervention.⁵ The primary role of HO-1 is to degrade heme to free iron (increasing ferritin synthesis), bilirubin (antioxidant), and CO (anti-apoptotic), which are involved in cellular defense and a variety of crucial physiological functions (Figure 1).^{5,6} Iron derived from HO-1 is stored in an intracellular iron storage protein, ferritin, that prevents iron-mediated cell toxicity.⁶ A remarkable observation states that genetic deficiency of HO-1 in humans and a mice model is linked with an overload of cellular iron in the liver and kidney.⁵ Emerging literature data have suggested that overexpression of HO-1 plays a role in antiviral activity against a variety of viruses including HIV, dengue virus (DENV), and hepatitis B virus (HBV).^{5,6} Moreover, overexpression HO-1 can reduce viral replication, as in the case of HCV.^{5,6} Therefore, this activity of HO-1 can be employed on CoV-2.

CO is an important metabolite of HO-1 and acts in an anti-inflammatory and anti-apoptotic manner, although it is generally considered a toxic gas. Therefore, CO can be considered a promising therapeutic molecule under physiological/pathological conditions. CO derived from HO-1 can restrict the growth of several pathogens including HIV and HCV.^{6,7,9} For instance,

CO suppresses ROS generation in EV71-infected cells, thus retarding viral replication.⁹ Another study states that heme catabolite CO also suppresses the NF- κ B signaling pathway and thereby impedes replication of porcine reproductive and respiratory syndrome virus (PRRSV).¹⁰ Therefore, CO would be a promising therapy for the treatment of SARS-CoV-2 infection. Recent reports highlight that endogenous HO-1 and CO levels correlate with complications of COVID-19 illness.¹¹ Most studies state that endogenous CO has a positive correlation with ARDS as protective molecule. On the basis of this result, inhaled CO therapy has been recommended for treating ARDS.¹¹ Abnormally high levels of endogenous CO may contribute to complications of COVID-19. A recent report highlights that exogenous CO also causes the same symptoms and complications of COVID-19 as a high level of endogenous CO.¹¹ In lungs, CO may protect from infection at a low concentration, while a higher concentration of CO may strongly bind deoxygenated Hb and thereby reduce survival. Therefore, direct inhalation is not a good choice because it raises the COHb level (>10%) and has a lack of tissue selectivity. To overcome this problem, we can propose metal–carbonyl complexes as model of HO-1 that are able to release CO in a controlled manner in vivo and do not effect the oxygen transport of hemoglobin.¹² For instance, CO-releasing molecule II (CORM-2) significantly reduces viral replication in an RNA virus, such as PRRSV.¹⁰ This result encourages use of CORM treatment for SARS-CoV-2.

Overall, no therapies/drugs are available in the market to treat COVID-19 illness via dysfunction of the Hb–HO-1 system. Therefore, the Hb–HO-1 system represents a potential therapeutic intervention for SARS-CoV-2 infection. The usage of iron chelation and CO therapies would be a promising step for the management of severe complications in COVID-19 patients.

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Notes

The author declares no competing financial interest.

ACKNOWLEDGMENTS

The author thanks the National Institute of Technology Sikkim, India.

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