



Perspective

Iron: Innocent bystander or vicious culprit in COVID-19 pathogenesis?

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ARTICLE INFO

Article history:

Received 5 May 2020

Received in revised form 26 May 2020

Accepted 27 May 2020

Keywords:

Hyper-ferritinemia

Hypercoagulability

Iron homeostasis

Ferroptosis

Oxidative stress

Mitochondria

ABSTRACT

The coronavirus 2 (SARS-CoV-2) pandemic is viciously spreading through the continents with rapidly increasing mortality rates. Current management of COVID-19 is based on the premise that respiratory failure is the leading cause of mortality. However, mounting evidence links accelerated pathogenesis in gravely ill COVID-19 patients to a hyper-inflammatory state involving a cytokine storm. Several components of the heightened inflammatory state were addressed as therapeutic targets. Another key component of the heightened inflammatory state is hyper-ferritinemia which reportedly identifies patients with increased mortality risk. In spite of its strong association with mortality, it is not yet clear if hyper-ferritinemia in COVID-19 patients is merely a systemic marker of disease progression, or a key modulator in disease pathogenesis. Here we address implications of a possible role for hyper-ferritinemia, and altered iron homeostasis in COVID-19 pathogenesis, and potential therapeutic targets in this regard.

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Introduction

The coronavirus 2019 (COVID-19) pandemic has taken the world by surprise as it viciously spread through the continents with rapidly increasing mortality rates. Current management of COVID-19 is based on the premise that respiratory failure is the leading cause of fatalities (Zhou et al., 2020). Nevertheless, mounting evidence points to drastic systemic events taking place that contribute to accelerated COVID-19 pathogenesis. The “cytokine storm” is a notion that is reportedly hailed as the hallmark of the COVID-19 hyper-inflammatory state (Mehta et al., 2020). Consecutive studies linked COVID-19 related hyper-inflammation to systemic events including hypercoagulability, oxidative stress and altered iron metabolism (Mehta et al., 2020; Phua et al., 2020). These events were linked to accelerated pathogenesis in gravely ill COVID-19 patients as highlighted in a recent perspective (Moore and June, 2020). Several components of the heightened inflammatory state have been proposed as

therapeutic targets, particularly IL-6 blockers as drugs of more relevance in COVID-19 management than steroids, however concerns of prolonging viral clearance were stated (Moore and June, 2020).

Hyper-ferritinemia has been described as a cardinal feature that predicted with high significance the increased mortality risk (Mehta et al., 2020; Phua et al., 2020). These studies demonstrated serum ferritin levels in COVID-19 non-survivors that exceeded the levels in the survivors by two-fold. In spite of the strong association with mortality, it is not yet clear if hyper-ferritinemia in COVID-19 patients is merely a systemic marker of disease progression, or a key modulator in disease pathogenesis.

Recently we showed that hepcidin, the key iron regulatory molecule, plays a major role during inflammatory processes (Bessman et al., 2020). However, the role and management of a dysregulated iron state in COVID-19 pathogenesis has not yet been addressed.

Is iron a key strategic player in COVID-19 pathogenesis?

Increasing evidence shows that inflammation, oxidative stress and altered iron homeostasis are inevitably linked at a systemic level (Kernan and Carcillo, 2017). This perspective elaborates on the potential aspect of altered iron homeostasis, marked by hyper-

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ferritinemia, and its potential role in COVID-19 pathogenesis and management strategies.

Iron is an essential trace element that plays a role in systemic oxygen transfer, and acts as an electron donor or acceptor in many biological functions. Ferritin is the primary site of iron storage in the cell mainly in its ferric state (Fe³⁺). Ferritin can carry up to 4500 iron molecules in its core (Kell and Pretorius, 2014). Generally, systemic inflammations are associated with increased serum ferritin levels. During a heightened inflammatory state, cytokines, particularly IL-6, stimulate ferritin and hepcidin synthesis (McDermid et al., 2013; Daher et al., 2017).

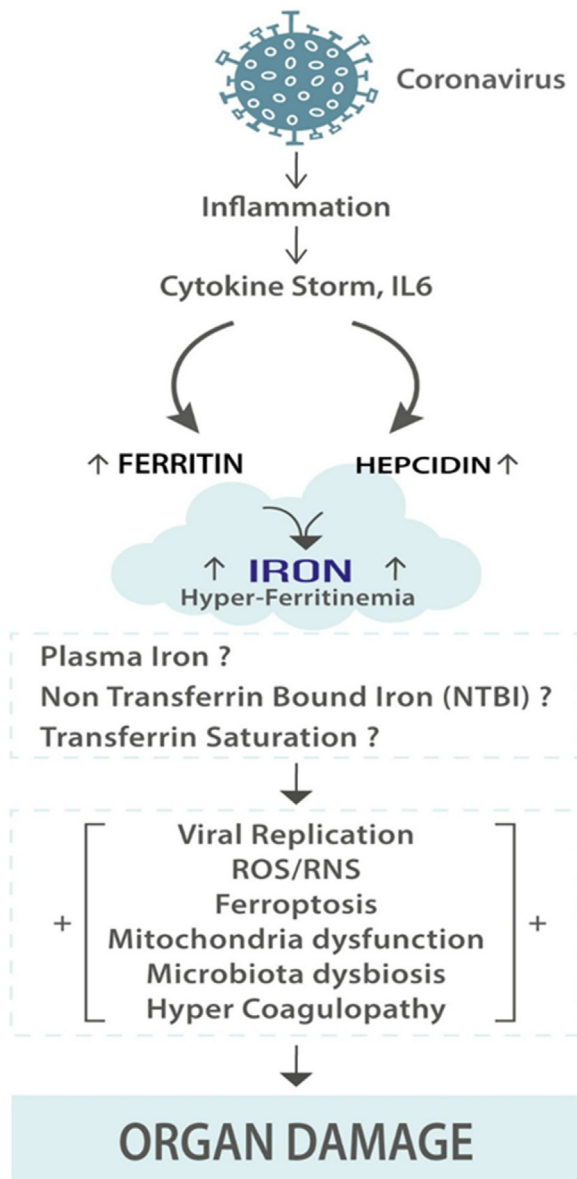


Figure 1. COVID-19 infection and Iron dysregulation.

COVID-19 infection results in an inflammatory state involving a cytokine storm in COVID-19 patients. IL-6 stimulates ferritin and the synthesis of hepcidin. Hepcidin sequesters iron in the enterocytes and macrophages, leading to increased intracellular ferritin, and preventing iron efflux from enterocytes and macrophages. Excess intracellular iron interacts with molecular oxygen, generating reactive oxygen species (ROS) through Haber-Weiss and Fenton reactions and reactive nitrogen species (RNS) and reactive sulfur species (RSS). The intracellular iron excess leads to ferroptosis, a process of programmed cell death. Iron overload may also affect extra and intracellular mitochondria function and microbiota diversity (lungs and gut) and blood coagulation.

Hepcidin, the key iron regulatory hormone, sequesters iron in the enterocytes and macrophages, leading to increased intracellular ferritin, and preventing iron efflux from enterocytes and macrophages (Daher et al., 2017) (Figure 1). Thereby, we speculate that increased serum ferritin levels as a result of COVID-19 related hyper-inflammation signify a vicious cycle of events where increased ferritin levels may lead to further tissue damage (Kell and Pretorius, 2014).

Excess intracellular iron interacts with molecular oxygen, generating reactive oxygen species (ROS) (Kell and Pretorius, 2014). This may largely contribute to oxidative damage of cellular components of different organs (lungs, liver, kidney, heart). Mounting evidence links increased ferritin levels to various inflammatory pathologies including cardiovascular events (Knoevich et al., 2009). Moreover, the complex interplay between iron metabolism and reactive nitrogen species (RNS) and reactive sulfur species (RSS) in addition to ROS suggests a clear interaction between iron metabolism and the newly defined reactive species interactome (Cortese-Krott et al., 2017) (Figure 1).

Interestingly, recent studies implicated that ferroptosis, which is the process of programmed cell death mediated by iron-dependent peroxidation mechanisms (Ursini and Maiorino, 2020) in inflammatory pathologies, involves multiple organs including liver, kidney, heart and lung (Sun et al., 2020). Ferroptosis was found to be linked to neurological disturbances including cognitive impairment (Sun et al., 2020), ageusia and anosmia (taste and smell loss) (Osaki et al., 1996; Dinc et al., 2016) that are regular manifestations of COVID-19 disease (Vaira et al., 2020). Iron chelators and ferroptosis inhibitors had protective effects by inhibiting intracellular iron induced lipid peroxidation (Kernan and Carcillo, 2017). The impact of iron overload on extra and intracellular mitochondria dysfunction (Rouault, 2016), on microbiota dysbiosis (lungs and gut) (Yilmaz and Li, 2018) and on other pathogens may be strongly implicated as shown in Figure 1.

Furthermore, serum coagulability is a major concern in COVID-19 pathogenesis, and rapidly recognized as a key risk factor in susceptible patients (Giannis et al., 2020; Lodigiani et al., 2020; Oxley et al., 2020; Zhang et al., 2020). In the context of the cellular iron overload, it has long been documented that coagulopathy is a hallmark of iron toxicity. Oxidized iron accelerates serum coagulation by interacting with proteins of coagulation cascade (Jankun et al., 2014).

Coagulation and cardiac biomarkers have been described to be elevated in COVID-19 patients, reflecting an inflammatory status characterized by coagulation activation and vascular endothelial dysfunction, found to be predictors of mortality (Giannis et al., 2020; Lodigiani et al., 2020). A recent report demonstrated acute formation of large vessel strokes in young adults infected with COVID-19 (Oxley et al., 2020). The inflammation in the blood vessel walls and platelets mitochondria alteration may be driving thrombosis formation (Giannis et al., 2020; Lodigiani et al., 2020; Oxley et al., 2020; Zhang et al., 2020).

Conclusion

Hyper-ferritinemia observed in COVID-19 patients may be induced in response to inflammation. However, its role in COVID-19 disease progression has not been fully established. It has been reported that hyper-inflammation in association with altered iron homeostasis may play a key role in pathogenesis of disease including viral infections (Drakesmith and Prentice, 2008; Schmidt, 2020) (Figure 1). It may be postulated that hyper-ferritinemia is associated with a state of iron toxicity which may result from increased ferritin leakage from damaged tissue releasing free iron in the process. There is no established consensus to exclude this possibility. Therefore, it is crucial to investigate coexisting iron parameters in COVID-19

patients including transferrin saturation, plasma iron levels, non-transferrin bound iron (NTBI) as well as hepcidin. The association of hyper-ferritinemia with increased transferrin saturation may reflect a state of iron overload. In this case, we suggest that targeting the intracellular iron overload may be a strategy of vital importance needed to be taken into consideration in future controlled clinical trials.

We suggest, in addition to treatment of the inflammatory state (Moore and June, 2020), to envisage the application of approved iron chelators, ferroptosis inhibitors, hepcidin modulators and erythropoietin (Monti et al., 2002; Pinto et al., 2008; Eshagh Hossaini and Haeri, 2019; Bessman et al., 2020; Hadadi et al., 2020). This promising therapeutic approach can be associated with drugs that specifically target extra and intracellular mitochondria dysfunction or even the reactive species interactome production and ferroptosis (Cortese-Krott et al., 2017; Kernan and Carcillo, 2017) (Figure 1).

Funding source

None.

Ethical approval

Approval was not required.

Conflict of interest

No conflict of interest to declare.

Acknowledgements

We thank Dr. Laurent Chatre, ISTCT-CNRS, Université de Caen-Normandie, CEA, for his valuable discussions.

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