Mitochondria and Microbiota dysfunction in COVID-19 pathogenesis

Running Title: Targeting intra and extracellular mitochondria in Covid-19 pathogenesis

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Abstract

The COVID-19 pandemic caused by the coronavirus (SARS-CoV-2) has taken the world by surprise into a major crisis of overwhelming morbidity and mortality. This highly infectious disease is associated with respiratory failure unusual in other coronavirus infections. Mounting evidence link the accelerated progression of the disease in COVID-19 patients to the hyper-inflammatory state termed as the "cytokine storm" involving major systemic perturbations. These include iron dysregulation manifested as hyperferritinemia associated with disease severity. Iron dysregulation induces reactive oxygen species (ROS) production and promotes oxidative stress. The mitochondria are the hub of cellular oxidative homeostasis. In addition, the mitochondria may circulate "cell-free" in non-nucleated platelets, in extracellular vesicles and mitochondrial DNA is found in the extracellular space. The heightened inflammatory/oxidative state may lead to mitochondrial dysfunction leading to platelet damage and apoptosis. The interaction of dysfunctional platelets with coagulation cascades aggravates clotting events and thrombus formation. Furthermore, mitochondrial oxidative stress may

contribute to microbiota dysbiosis, altering coagulation pathways and fueling the inflammatory/oxidative response leading to the vicious cycle of events.

Here, we discuss various cellular and systemic incidents caused by SARS-CoV-2 that may critically impact intra and extracellular mitochondrial function, and contribute to the progression and severity of the disease. It is crucial to understand how these key modulators impact COVID-19 pathogenesis in the quest to identify novel therapeutic targets that may reduce fatal outcomes of the disease.

Key words: Hyper-inflammation; Hypercoagulability; Iron; Oxidative Stress; Extracellular Mitochondria; Platelet Mitochondria; Microbiota.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA betacoronavirus that emerged in December 2019 in Wuhan, China causing coronavirus disease 2019 (COVID-19). The COVID-19 pandemic is spreading rapidly and to date has led to more than 430,000 deaths worldwide. Unfortunately, there are no effective antivirals and vaccines to treat or prevent COVID-19 pandemic. Clinical trials have been launched worldwide including the European study DISCOVERY which shows that the tested antiviral drugs (remdesivir, lopinavir and ritonavir in combination, the latter being administered with or without interferon beta and hydroxychloroquine) are unable to efficiently fight COVID-19 progression (Cao *et al*, 2020)(Mahevas *et al*, 2020).

Mainly COVID-19 patients develop a respiratory tract infection; unfortunately, a significant number of patients develop severe fatal consequences attributed to a surge of inflammatory events described as the "cytokine storm". This heightened inflammatory state is reportedly associated with deleterious systemic events including oxidative stress, dysregulation of iron homeostasis, hypercoagulability and thrombus formation (Zhou *et al*, 2020)(Phua *et al*, 2020)(Moore & June, 2020)(Kernan & Carcillo, 2017).

Several biomarkers of inflammation and thrombosis are indicated as mortality predictors among critically ill COVID-19 patients. Lymphopenia was reported as a key feature, and was suggested as a potential prognostic marker. In addition, increased D-dimer and Interleukin-6 (IL-6) increased with worsening of the disease (Terpos *et al*, 2020), and correlated with increased mortality (Tang *et al*, 2020).

The largest prospective cohort published in the United States, which focused on patients who required intensive care, reported that 10% increased mortality risk occurred for every 10% increase of IL-6 or D-dimer concentration providing further insight into COVID-19 pathogenesis regarding activation of systemic inflammation and endothelial-vascular damage (Cummings *et al*, 2020).

Hyperferritenimia is also highlighted as a predictor of increased mortality of the disease (Mehta *et al*, 2020). Also oxidative stress was indicated as a major player in COVID-19 pathogenesis and severity (Delgado-Roche & Mesta, 2020). Several lines of evidence have established a link between inflammation and oxidative stress (Khomich *et al*, 2018)(Brand *et al*, 2014). In this context, we have shown that hepcidin, the key iron regulatory molecule, plays a major role during inflammatory processes (Bessman et al, 2020). We also addressed the role and management of a dysregulated iron state in COVID-19 pathogenesis (Edeas et al, 2020).

Despite its central role in maintaining oxidative homeostasis, and ROS generation, the mitochondrion has received limited attention regarding its role in COVID-19 pathogenesis and management (Edeas *et al*, 2020)(Keshav et al. 2020). Many questions remain unanswered about the role of the mitochondria during the inflammatory "cytokine storm" in COVID-19 patients. Here we propose a hypothetical scheme, based on existing evidence, describing the potential role of the inflammatory signals in perpetuating a cycle of events that aggravate mitochondrial oxidative damage and contribute to major systemic alterations including coagulopathy, ferreptosis and microbial dysbiosis. We propose that not only the intracellular mitochondria dysfunction is a consequence of COVID-19 infection, but the less explored extracellular mitochondria (specifically platelets mitochondria) may affect blood coagulation, clot and thrombosis formation (Lodigiani *et al*, 2020)(Giannis *et al*, 2020)(Zhang *et al*, 2020b)(Oxley *et al*, 2020). These extracellular mitochondria may represent critical mediators and may serve as strategic therapeutic targets in COVID-19 pathogenesis.

Interplay between mitochondria, oxidative stress and inflammation

Normally, body tissues and organs require a large number of functional mitochondria to provide energy and regulate cellular functions according to body needs. Increased demand is met by mitochondrial biogenesis while removal of excess mitochondria occurs through mitophagy. Mitochondrial defects have been implicated in numerous pathologies including diabetes, cardiovascular diseases, gastrointestinal

disorders, cancer and aging. Mitochondria, is the major source of reactive oxygen species (ROS) that contributes to normal cell function, but also linked to increased intracellular oxidative stress (Anatoly A Starkov, 2008)(Herst *et al*, 2017).

Inflammatory cytokines such as TNF-α induces calcium-dependent increase in mitochondrial ROS. Furthermore, interferon-γ was shown to upregulate genes inducing mitochodrial ROS generation. IL-6 and IL-10 were found to modulate mitochondrial ROS generation through mechanisms, independent of its nuclear factor activity, by directly modulating the activity of the electron transport chain. Mitochondrial ROS was found to directly stimulate the production of proinflammatory cytokines as well (Li *et al*, 2013). Shao et. al. reported the upregulation of mitochondrial genes and genes responding to oxidative stress in peripheral blood mononuclear cells (Shao *et al*, 2006) further supporting the interplay between inflammation and oxidative stress.

Recent studies identified a role for the mitochondria in regulating innate immunity and inflammatory responses. It has been implicated that antiviral immunity *may arise against* viral DNA which could act as danger associated molecular pattern (DAMP), and modulate inflammatory responses *via* its capacity to generate ROS (Mohanty *et al*, 2019). The impact of mitochondrial dysfunction on inflammation happens in both directions. Inflammatory mediators and immune sentinels trigger intracellular cascades that alter mitochondrial metabolism. Cytokines such as TNF-alpha and IL-6, that are found in COVID-19 serum, impede mitochondrial oxidative phosphorylation and associated ATP production and initiate mitochondrial ROS production in the cell (Jo *et al*, 2016)(Naik & Dixit, 2011). This may cause mitochondrial membrane permeabilization, altered mitochondrial dynamics, and might ultimately result in cell death (apoptosis).

On the other hand, when severely damaged, the mitochondria contents (spinoffs such as mtDNA) are released into the cytosol and extracellular environment (Twig & Shirihai, 2011)(Mittal *et al*, 2014). ROS production is accompanied by upregulation of Ca^{2+} levels and release of mitochondrial DNA into the cytosol (Kozlov *et al*, 2017)(West *et al*, 2015). This response drives pro-inflammatory cytokines

production such as IL-1β by activating NLRP3 inflammasomes and induces IL-6 production through inflammasome-independent transcriptional regulation (Jo *et al*, 2016)(West *et al*, 2015)(Naik & Dixit, 2011)(Nakahira *et al*, 2011). These cytokines are hallmarks of COVID-19 disease severity.

Several studies have shown the impact of dysfunctional mitochondria on the immune response. For example, a recent study revealed that human alveolar epithelial cells with dysfunctional mitochondria displayed increased production of pro-inflammatory cytokines (CXCL-8, IL-6, CCL20, CCL3, CCL4 and IL-12) all of which were found to be increased in COVID-19 (Zhang *et al*, 2020a)(Zhou *et al*, 2020). Moreover, these cells presented impaired repair responses and reduced responsiveness to corticosteroids. These findings highlight a potential impact of dysfunctional mitochondria on modulating immune responses by favoring positive feedback loop that cause alveolar tissue damage that is the case in COVID-19 severe form (Hoffmann *et al*, 2013)(Hoffmann *et al*, 2019)(Zhang *et al*, 2020a). For instance, upregulation of chemoattractants such as CXCL-8 promotes neutrophil infiltration into the lung, contributing to ROS generation and protease activation that further contribute to the damage of the mitochondria (Hoffmann *et al*, 2013)(Hoffmann *et al*, 2019). Noteworthy, the mitochondrial transfer from bone marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury (Islam *et al*, 2013).

Overall, a vicious inflammatory/oxidation cycle, involving further mitochondrial injury, leads to lung damage. The immune response to COVID-19 is dominated by increased levels of cytokines and chemokines including IL-6 and CXCL-8. The same exacerbated immune response was detected in the Broncho Alveolar Lavage (BAL) with an upregulation of several markers such as CD163, CD226, CCR5, CCR6, CXCR1, CXCR2, CXCR7, etc. (Zhang *et al*, 2020a)(Wang *et al*, 2020).

Together, the proinflammatory cytokines affect diverse physiological processes by driving cellular oxidative stress ROS generation. In turn, increased ROS production stimulates proinflammatory mediator release that contributes to mitochondrial dysfunction (Figure 1).

The role of Iron in mitochondria dysfunction

The extensive studies of COVID-19 biomarkers have confirmed with no doubt the association of systemic hyperferritinemia with increased illness severity and adverse outcomes (Huang *et al*, 2020). Besides being a marker of inflammation, ferritin is also released by exhausted dying cells.

One of the targets of iron-mediated oxidative stress is the mitochondrion. Appropriate mitochondrial functioning relies on iron uptake that is primarily utilized for three essential activities: heme synthesis, iron-sulfur cluster biogenesis, and storage in mitochondrial ferritin. Briefly, heme and iron-sulfur clusters play an essential role in maintaining a variety of cellular and systemic processes by facilitating oxidation-reduction reactions (Rouault, 2016). Hence, disruption of cellular iron levels or mitochondrial iron metabolism can result in cellular stress or death (Jouihan *et al*, 2008)(Aguirre & Culotta, 2012).

In line with the importance of these factors, the complication observed in COVID-19 patients may be attributed to high levels of ferritin which in turn, may cause elevated oxidative and cellular stress translated by massive release of inflammatory mediators, free radicals and ROS (Lyngsie *et al*, 2018) (Edeas *et al*, 2020). This systemic iron overload phenomenon is also observed in several diseases such as hereditary hemochromatosis (HH) (Jouihan *et al*, 2008). It has been described to impair mitochondrial functions by reducing mitochondrial oxygen consumption leading to enhanced oxidative damage, lipid peroxidation and disturbed glucose tolerance (Kim *et al*, 2013)(Aguirre & Culotta, 2012)(Lyngsie *et al*, 2018). Moreover, reduced mitochondrial respiration causes abnormal metal distribution including manganese, copper and zinc (Kim *et al*, 2013)(Jouihan *et al*, 2008)(Skalny *et al*, 2020). Subsequently, reduced mitochondrial manganese may result in mitochondrial dysfunctions, likely due to decreased activity of mitochondrial manganese-dependent superoxide dismutase, an enzyme that protects mitochondria from respiration-generated free radicals (Kim *et al*, 2013)(Jouihan *et al*,

2008)(Manes & Cota-Gomez, 2016). Unquestionably, hyperferritinemia disrupting mitochondrial homeostasis drives mitochondrial respiration from an aerobic into an anaerobic state. Interestingly, anaerobic respiration favors pyruvate reduction into lactate that is ensured by lactate dehydrogenase (LDH), which is highly upregulated marker in COVID-19 illness (Yetkin-Arik *et al*, 2019)(Young *et al*, 2020)(Huang *et al*, 2020)(Skalny *et al*, 2020).

In addition, the iron overload may be another major concern due to the susceptibility of loosely bound iron to catalyze production of ROS (Torti & Torti, 2013). ROS accumulation can damage cellular components including lipids, which interferes with cellular integrity, membrane fluidity, and permeability (Dix & Aikenst, 1993)(Pietrangelo, 1998)(Niemelä *et al*, 1999). ROS radicles are known to damage the mitochondria as well (Pietrangelo, 1998)(Niemelä *et al*, 1999)(Gao *et al*, 2009). Consequently, injured mitochondria can result in diminished cellular respiratory function as was shown in cardiac myocytes with excess iron loading (Gao *et al*, 2009). This result gives solid ground to consider the role of mitochondria in COVID-19 illness, which leads to respiratory failure. These ROS induced mitochondrial impairments could have serious consequences including iron-dependent ferroptosis, leading to tissue damage and eventually organ failure (Dixon *et al*, 2012)(Dixon & Stockwell, 2014) (Edeas *et al*, 2020).

The role of Ferroptosis

Ferroptosis is a newly identified type of programmed cell death that depends on iron accumulation. Peculiarly, ferroptosis causes irreversible alteration of mitochondrial morphology (Twig & Shirihai, 2011). Furthermore, substantial evidence revealed that ferroptosis is involved in bacterial infection induced cell death and tissue damage (Zhu *et al*, 2019). For instance, *Pseudomonas aeruginosa* was shown to trigger ferroptosis in host bronchial epithelium through generating lipoxygenase, that is involved in the initiation of lipid peroxidation, by oxidizing host arachidonic acid–phosphatidylethanolamines (Dar *et al*, 2018). Moreover, recently Amaral and colleagues demonstrated the capacity of *Mycobateruim tuberculosis* to trigger ferroptosis of infected macrophages that correlated with iron overload, reduced glutathione and mitochondrial superoxide (Amaral *et al*, 2019). These observations raise an important

question about the ability of the SARS-CoV-2 to trigger ferroptosis of bronchial epithelium and macrophages *via* hyperferritinemia.

Altogether, a dysfunctional mitochondrion would result in iron accumulation due to its incapacity to metabolize iron. This might cause deficient iron sequestration leading to ROS production through Fenton and Haber-Weiss-type reactions (Lane *et al*, 2015). These reflections are highlighted in figure 1.

Thrombocytopenia and Hypercoagulability in COVID-19

Increasing concerns point out coagulation abnormalities that are associated with COVID-19 substantial mortality rate (Giannis *et al*, 2020)(Tang *et al*, 2020). The comparison of coagulation parameters between survivors and non-survivors highlighted an increase of D-dimers, fibrin degradation product (FDP) levels, longer prothrombin time and activated partial thromboplastin time (Giannis *et al*, 2020)(Tang *et al*, 2020)(Levi *et al*, 2020). Unexpectedly, platelet count was relatively decreased in association with increased mortality (Tang *et al*, 2020)(Huang *et al*, 2020)(Giannis *et al*, 2020)(Levi *et al*, 2020). Growing evidence points towards stroke incidents in COVID-19 patients, including younger adults (Oxley *et al*, 2020). The inflammation in the blood vessel walls may be driving thrombosis formation (Lodigiani *et al*, 2020)(Zhang *et al*, 2020c) (Oxley *et al*, 2020).

Thrombocytopenia is the clinical condition describing abnormally low platelet count (van der Meijden & Heemskerk, 2019). In a critical review by Terpos et al., thrombocytopenia was reported to be more prominent in severe *versus* non severe cases (Terpos *et al*, 2020). A recent meta-analysis of nine heterogeneous studies suggested that thrombocytopenia is significantly associated with COVID-19 severity mostly in non-survivors, and was suggested among the factors that determined prognosis and identified patients at risk, particularly in association with disseminated intravascular coagulation (DIC) (Lippi *et al*, 2020). These findings underlined that platelet function should be seriously addressed in

association with hypercoagubilty in COVID-19 patients, which may contribute to developing novel therapeutic targets in limiting COVID-19 related mortality.

Extracellular Mitochondria: An intriguing localisation and role

Extracellular mitochondria can be found free, enclosed by a membrane as inside platelets or vesicles. Mitochondria outside cell can induce paracrine or endocrine responses in an organism. Extracellular mitochondria regulate cell-to-cell communication, regeneration, danger sensing and provoke an immune response (Wang *et al*, 2017)(Miliotis *et al*, 2019).In addition to extracellular mitochondria, release of mtDNA outside of the cell during apoptosis has been described (McArthur *et al.* 2018).

Recently, Dache et al. reported that blood contains intact cell-free full-length mitochondrial DNA in dense and biologically stable structures over 0.22 μm in diameter and that these structures have specific mitochondrial proteins, double membranes and a morphology resembling that of mitochondria (Al Amir Dache *et al*, 2020). The potential role for circulating free mitochondria or its spinoffs in blood of COVID-19 patients remain to be elucidated.

Platelet Mitochondria and Coagulopathy

The platelet is an anucleated cell with the primary pathophysiological function of hemostasis and wound healing (Holinstat, 2017). In the absence of nuclear control, platelet health is largely determined by the health of their mitochondria. Other critical roles of platelets include thrombosis, injury response, and immunoregulation. In the absence of genomic DNA, platelets preserve organells including mitochondria from megakaryocytes to maintain its structure and function. The, platelet' s lifespan is (7–10 days), is determined by the mitochondria (Melchinger *et al*, 2019). The packaging of 5–8 mitochondria is critical for vital platelet functions including aerobic respiration and metabolism. The role played by mitochondria in platelet function and survival is essential. Mitochondrial dysfunction in disease may also

affect platelet survival and apoptosis, and potentially increase the risk for thrombus formation. (Hayashi *et al*, 2011). Importantly, it has been recently shown that apoptotic platelets may induce clotting ≥ 50-fold faster than normal platelets (Melchinger *et al*, 2019). In addition, platelets have recently gained attention as important mediators of the of the immune system (van der Meijden & Heemskerk, 2019). Mitochondria act as the main energy suppliers in platelets during thrombus formation, a process that was shown to be reversed by inhibiting mitochondrial respiration using pharmacological antagonists to the electron transport chain such as nitric oxide and cyanide (Wang *et al*, 2017).

Further actions for platelet mitochondria include; platelet activation of permeability transition, ROS generation, reduction of mitochondrial membrane potential and platelet apoptosis. It is noteworthy that an increase in mitochondrial ROS production in platelets leads to severe oxidative stress that alters ATP production and mitochondrial membrane potential leading to further platelet activation (Ran *et al*, 2009)(Tang *et al*, 2011)(Wang *et al*, 2017)(Melchinger *et al*, 2019). Moreover, the upregulation of ROS drives thrombosis through cytochrome-C release by mitochondria triggers the apoptotic caspase cascade driven by BAX and BAD resulting in mitochondrial damage and apoptosis (Wang *et al*, 2017)(Melchinger *et al*, 2019). This may explain the reduced number of platelet in COVID-19 sickness despite of thrombosis occurrence. Moreover, COVID-19 patients probably suffer from mitophagy impairment because of environmental stress caused by hyperinflammation. In healthy context, mitophagy protects platelets from oxidative stress and mitochondrial destruction by removing damaged mitochondria to prevent platelet apoptosis (Lee *et al*, 2016). When platelet mitophagy is impaired, which is implicated in COVID-19 pathogenesis, increased platelet apoptosis occurs contributing in enhanced thrombosis (Lee *et al*, 2016)(Wang *et al*, 2017)(Melchinger *et al*, 2019). Therfore, preserving platelet mitochondrial function may be an additional means of decreasing the risk of potentially fatal thrombotic events in COVID-19 pathogenesis.

On the other hand, increasing evidence suggests that the iron overload is a causative agent of platelet dysfunction. Iron excess alters mitochondrial function and favors oxidative stress. We believe that there

is a certain association between iron overloads and high levels of ROS, where ROS represent an important parameter involved in platelet receptor activation that can result in thrombosis (García-Yébenes *et al*, 2018). Further investigations are needed to define the implication of iron in coagulopathy events.

Furthermore, activated platelets may release microvesicle–associated mitochondria to the extracellular medium upon exposure to oxidative stress. Subsequently, secreted phospholipase A2 could hydrolyse the platelet- released mitochondria generating inflammatory mediators such as lysophospholipids, fatty acids, and mitochondrial DNA, and cardiolipin which then promote endothelial inflammation (Coly & Boulanger, 2019).

Thus, extracellular mitochondria and its "spinoffs" may represent critical mediators in progression of the inflammatory setting leading to coagulopathy associated with inflammatory signalling pathways.

Mitochondria and mitochondria embedded in microvesicles constitute a major subset of extracellular vesicles released by activated monocytes, and their proinflammatory activity on endothelial cells is determined by the activation status of their parental cells. Thus, mitochondria may represent critical intercellular mediators in cardiovascular disease and other inflammatory settings associated with type I IFN and TNF signalling (Puhm *et al*, 2019)(Coly & Boulanger, 2019).

Role of Mitochondrial Cardiolipin in COVID-19 infection

Cardiolipin is a mitochondrial phospholipid which participates in the maintenance of the structural integrity of the mitochondrial membrane. The highest concentration of cardiolipin is concentrated in the monolayer of the inner mitochondrial membrane. Interestingly, serological findings of critically ill COVID-19 patients with coagulopathy and thrombocytopenia, showed the presence of anticardiolipin IgA antibodies in serum. Cardiolipin maintains the stability of cytochrome-c of the electron transport chain, however, it is also oxidation sensitive. The presence of anticardiolipin IgA antibodies may signify

oxidative mitochondrial impairments associated with COVID-19 pathogenesis. However, not excluding the possibility that this could result from other thrombotic events in the patients (Zhang *et al*, 2020b).

COVID19 microbiota dysbiosis disturbs mitochondrial homeostasis *via* metabolites production

It is of great importance to consider mitochondria-microbiota crosstalk in COVID-19 for several reasons. First, some patients had concurrent gastrointestinal symptoms, including diarrhea. Then, SARS-CoV-2 nucleic acid was detected in the stool of patients with COVID-19 pneumonia (Wong *et al*, 2020). These observations indicate the ability of SARS-CoV-2 to colonize the gastrointestinal tract, which would disturb gut microbiota. Interestingly, fecal metabolomic analysis suggested potential amino acid-related pathways linking gut microbiota to inflammation explaining the predisposition of certain individuals to develop severe COVID-19 (Gou *et al*, 2020). Addressing the impact of COVID-19 microbiota on mitochondrial function would give new avenues for therapeutic strategies.

The interaction between microbiota and mitochondria appears to occur primarily through signaling from the gut microbiota to mitochondria and from mitochondria to the gut microbiota by means of endocrine, immune, and humoral links (Mottawea *et al*, 2016)(Saint-Georges-Chaumet *et al,* 2016)(Paule *et al*, 2018)(Durand *et al.* 2018). Understandings from studies on mitochondrial functions during bacterial infection provide direct evidence on the connection between microbiota and mitochondria. These studies shed the light on the different strategies developed by bacterial pathogens to subvert functions related to calcium homeostasis, maintenance of redox status and mitochondrial morphology (Saint-Georges-Chaumet *et al*, 2016)(Lobet *et al*, 2015). Pathobionts such as *Fusobacterium, Veillonella*, and *Atopobium parvulum* are another microorganisms who were shown to control mitochondrial activity in favor of infection and inflammation *via* the production of hydrogen sulfide (H_2S) and nitrogen oxide (NO) (Mottawea *et al*, 2016). These gases are toxic and induce mitochondrial dysfunction.

H_2S toxicity is attributed to the inhibition of mitochondrial complex IV of the respiratory chain, which results in shutdown of mitochondrial electron transport and cellular ATP generation (Searcy, 2003)(Catharina Duvigneau & Kozlov, 2017)(Saint-Georges-Chaumet et al, 2016). NO displays a high affinity to iron in metalloproteins, especially in hemoproteins that requires O_2 for their enzymatic activities (Radi, 1996)(Henry & Guissani, 1999)(Erusalimsky & Moncada, 2007).

NO can compete with O_2 binding to hemoproteins leading to its inhibition. Hence, NO mediated hematoproteins inhibition plays an important role for the modulation of mitochondrial function and may lead to enhanced generation of ROS and mitochondrial dysfunction (Henry & Guissani, 1999)(Erusalimsky & Moncada, 2007). In addition, NO have a significant role in inflammation *via* its interaction with O_2 and superoxide anion to produce reactive nitrogen species (RNS) that cause cellular stress and promote pro-inflammatory destructive response (Korhonen *et al*, 2005)(Erusalimsky & Moncada, 2007).

Moreover, commensal gut microbiota influence mitochondrial functions related to energy production, mitochondrial biogenesis, redox balance and inflammatory cascades, making it a potential therapeutic target for endurance through metabolites production including the beneficial short chain fatty acids (SCFA) and secondary bile acids (Circus & Aw, 2012)(Bär *et al*, 2013)(Den Besten *et al*, 2013)(Mottawea *et al*, 2016) (Durand *et al.* 2018). Interestingly, SCFA such as N-butyrate by gut commensal microbiota reduce oxidative stress and subsequent ROS production (Mottawea *et al*, 2016)(Saint-Georges-Chaumet et al, 2016). On the contrary, mitochondrial functions could alter gut microbiota composition and activity. Indeed, as described above, under stressful conditions such as bacterial or viral infection conditions, mitochondria can modulate immune responses leading to heightened inflammation (Green *et al*, 2011). This unbalanced immune response can result in microbiota dysbiosis. Moreover, mitochondria was shown to alter microbial community by affecting the activities of intestinal functional effector cells, such as immune cells, epithelial cells and enterochromaffin cells (Cunningham *et al*, 2016).

Conclusion

COVID-19 disease management is still an ongoing challenge in the absence of available efficient treatments. Strategies to predict, protect and treat billions of people are urgently required. Therefore, it is essential to understand and analyse the complex mechanism of Covid-19 pathogenesis.

Among the fatal events that clinicians try to avoid when treating COVID-19 patients are blood coagulation, clot formation, stroke and thrombus formation (Lodigiani *et al*, 2020; Giannis *et al*; Zhang *et al*, 2020c; Oxley *et al*, 2020). In this context, we highlight two mechanisms; First, the vicious circle where inflammation cytokine storm, oxidative stress, microbiota dysregulation, iron overload and ROS accumulation indefinitely cause intra and extra mitochondrial dysfunction. Second, dysfunctions that affect the platelet mitochondria and its "spinoffs" which represent critical mediators in progression of the inflammatory setting leading to coagulopathy associated with inflammatory signalling pathways (Figure 1). In addition to treatment of the inflammatory state (Mehta *et al*, 2020), we envisage the application of approved iron chelators, ferroptosis inhibitors, hepcidin modulators and erythropoietin in management of CODID-19 (Eshagh Hossaini & Haeri, 2019)(Monti *et al*, 2002). Iron chelators would be a more adapted option with minimal side effects (Edeas *et al*, 2020). This strategy consists of selectively binding excess of iron and increases its excretion by urinary and fecal routes (Wongjaikam *et al*, 2015). Different chelating substances are available for this clinical purpose such as deferoxamine, deferiprone and deferasirox (Taher *et al*, 2016)(Botzenhardt *et al*, 2017). These inhibitors can also inhibit ferroptosis by decreasing intracellular iron levels (Dixon *et al*, 2012)(Dixon & Stockwell, 2014).

The characterization of COVID-19 microbiota may also be considered to develop strategies to manage COVID-19 pathogenesis. This will encourage doctors to introduce probiotics or prebiotics to reestablish gut homeostasis, which would limit inflammation and the exacerbated immune response as well as preventing mitochondrial stress.

Targeting the mitochondrial metabolic pathways and redox balance may provide useful therapeutic strategies that specifically target extra and intracellular mitochondria dysfunction or even the reactive species interactome production (Cortese-Krott *et al*, 2017; Kernan & Carcillo, 2017).

The pathophysiological role played by platelets and their mitochondria in COVID-19 pathogenesis has not been established. It remains unclear whether these organelles provide energy as healing or pro-inflammatory factors. The complex interplay between platelet mitochondrial dysfunction, oxidative stress and mitophagy requires further investigation regarding their role in COVID-19 pathogenesis. Overall this may also provide promising therapeutic targets for halting the fatal progression of the disease.

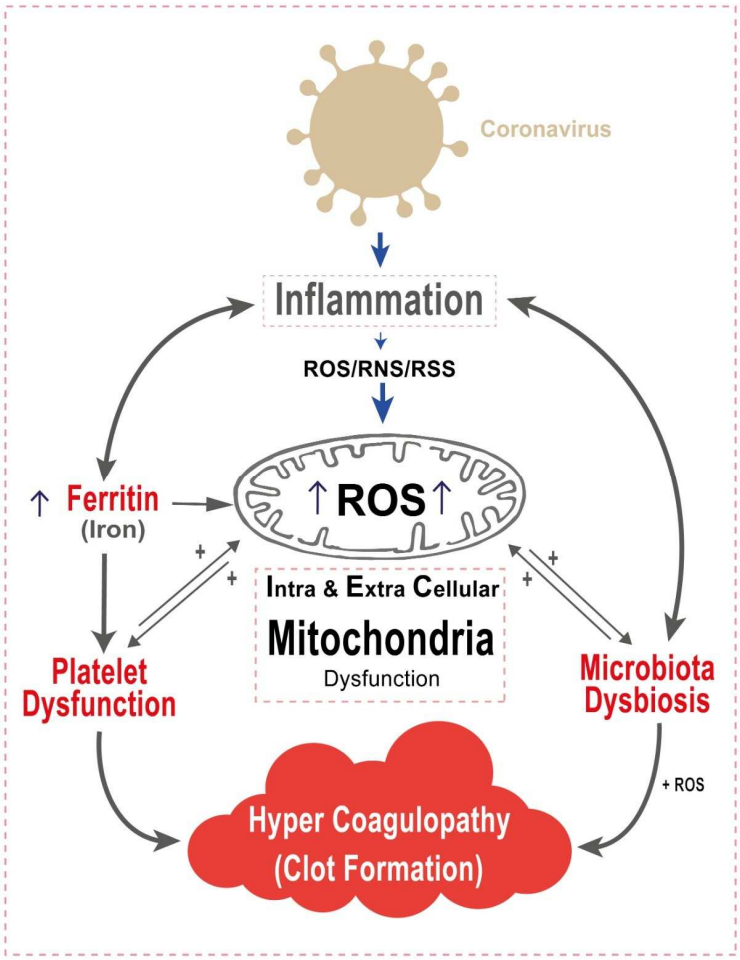
Interestingly, blood mitochondria provides a new avenue with promising potential as a biomarker, target for therapies, and a therapeutic agent (Al Amir Dache *et al*, 2020).

In spite of potential therapeutic and management strategies described in this perspective, several aspects remain to be elucidated mainly; the role of blood and platelet mitochondria, its quality and functionality on the severity of COVID-19 pathogenesis, mortality risk and its clinical applications.

Another point of concern would be convalescent blood and plasma from COVID-19 survivors that may contain extracellular blood mitochondria or its products from platelets or activated monocytes that could raise concerns regarding blood transfusions. In light of this exceptional pandemic, and major systemic disturbances induced by the COVID-19 virus, novel aspects of the disease should be carefully considered for debate and discussion.

Figure 1. Mitochondria dysfunction in pathogenesis of COVID-19

A hypothetical scheme describing events initiated by the COVID-19 pro-inflammatory surge of cytokines and ferritin levels leading to oxidative stress and cellular damage. 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 mitochondria is the central organelle of ROS generation. Increased ROS generation leads to intra and extra mitochondrial damage which in turn leads to **1)** Microbiota dysbiosis and **2)** Platelet dysfunction which plays a major role in blood clotting and coagulopathy events. Mitochondrial damage cause the release of contents including proteins, lipids and DNA "spinoffs" that further aggravate the inflammatory response in a vicious cycle of events contributing to COVID-19 disease progression.



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Ethical approval

Approval was not required.

Conflict of interest

No conflict of interest to declare.

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