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Roles of host mitochondria in the development of COVID-19 pathology

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Abstract

The recent emergence of Severe Acute Respiratory Syndrome-Corona Virus 2 (SARS-CoV-2) in late 2019 and its spread worldwide caused an acute pandemic of Coronavirus disease 19 (COVID-19). COVID-19 pathologies are currently under intense scrutiny as its outbreak led to immense and urgent changes worldwide. Although many theories have been introduced on how SARS-CoV-2 enters the host, the ACE-2 receptor is shown to be the primary mechanism of SARS-CoV-2 entry. However, the mechanism behind the establishment and pathology of infection is poorly understood. As recent studies show that host mitochondria play an essential role in virus-mediated innate immune response, in this review, we will discuss, in detail, the entry and progression of SARS-CoV-2 and how mitochondria play a role in the establishment of viral infection and the development of an immune response, whether it is beneficial or not. We will also review the possible treatments that could be used to prevent the surgency of COVID-19 infection with respect to the role of mitochondria. Understanding the mitochondria-mediated SARS-CoV-2 establishment may provide a unique mechanism and conceptual advancement in finding a novel treatment for COVID-19.

Roles of host mitochondria in the development of COVID-19 pathology

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ABSTRACT

The recent emergence of Severe Acute Respiratory Syndrome-Corona Virus 2 (SARS-CoV-2) in late 2019 and its spread worldwide caused an acute pandemic of Coronavirus disease 19 (COVID-19). COVID-19 pathologies are currently under intense scrutiny as its outbreak led to immense and urgent changes worldwide. Although many theories have been introduced on how SARS-CoV-2 enters the host, the ACE-2 receptor is shown to be the primary mechanism of SARS-CoV-2 entry. However, the mechanism behind the establishment and pathology of infection is poorly understood. As recent studies show that host mitochondria play an essential role in virus-mediated innate immune response, in this review, we will discuss, in detail, the entry and progression of SARS-CoV-2 and how mitochondria play a role in the establishment of viral infection and the development of an immune response, whether it is beneficial or not. We will also review the

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possible treatments that could be used to prevent the surgency of COVID-19 infection with respect to the role of mitochondria. Understanding the mitochondria-mediated SARS-CoV-2 establishment may provide a unique mechanism and conceptual advancement in finding a novel treatment for COVID-19.

KEYWORDS

COVID-19, SARS-CoV-2, Mitochondria, ORFs, ACE-2 receptor, Cytokine storm, inflammation

INTRODUCTION

COVID-19 is caused by a new coronavirus identified as a severe acute respiratory syndrome- coronavirus 2 (SARS-CoV-2), which has been stirring the globe since the start of its outbreak in late 2019. At the time of this draft submission, around ˜90.7 million people have been infected with SARS-CoV-2, and more than 1.9 million died with a 2% death rate across the globe (https://www.worldometers.info/coronavirus/). The only possible prevention method so far is a combination of social distancing and improved personal hygiene in addition to the current vaccine programs on the roll. As cases continue to rise, there is an emergent need for research concerning disease pathology as it is crucial to discovering effective prevention and treatment of the disease. Like most notable human disease-causing viruses, SARS-CoV-2 also contains positive single-stranded RNA and belongs to a subgroup of the coronavirus family known as beta-coronavirus. The other notable RNA viruses are those that cause the common cold, dengue, Ebola, hepatitis C, hepatitis E, influenza, measles, MERS, polio, rabies, SARS, and West Nile fever. Among these, SARS-CoV-2 is more contagious than its counterparts because this virus originated in animals and then transferred to humans at an exceptionally high infection rate as our immune systems were never exposed to this specific strain before. The infection is particularly lethal in patients with compromised immunity and preexisting conditions. Beta coronaviruses known to cause mild upper respiratory tract infections include strains such as HCoV 229E, HKU1, NL63, and OC43 (Liu, Liang & Fung, 2020). In contrast, the three strains that cause severe life-threatening diseases are SARS-CoV, MERS-CoV, and the recently identified SARS-CoV-2 (Memish, Zumla, Al-Hakeem, Al-Rabeeah & Stephens, 2013; Tiwari, Upadhyay, Nazam Ansari & Joshi, 2020; Zhu et al., 2020b).

Angiotensin-converting enzyme-2 (ACE-2) receptor-mediated entry of the virus is considered the primary mechanism of infection; however, the consequence of the entry and mechanisms of pathologies leading to mortality, such as cytokine storm and inflammation, is unclear. Many newfound studies suggest the potential involvement of host mitochondria in COVID-19 infection, which is believed to be the key mechanism for COVID-19 pathology (Edeas, Saleh & Peyssonnaux, 2020; Guzzi, Mercatelli, Ceraolo & Giorgi, 2020; Kloc, Ghobrial & Kubiak, 2020; Singh, Chaubey, Chen & Suravajhala, 2020). Therefore, in this review, we seek more clarity surrounding mitochondria and their role in the establishment of COVID-19 infection. We also discuss possible strategies involving the use of mitochondria as potential therapeutic targets for COVID-19.

SARS -CoV-2 structure and virulence

The SARS-CoV-2 genome structure is about 29.9 kb in length and encodes four major structural proteins as well as several non-structural accessory proteins (**Figure 1**). The major proteins encoded are surface spike glycoprotein (S), the envelope glycoprotein protein (E), membrane glycoprotein (M), and nucleocapsid protein (N) (**Figure 1**) (Chan et al., 2020; Huang, Yang, Xu, Xu & Liu, 2020). Similar to SARS-CoV, the recent CoV-2 virus also enters the host cell by using the 150 kDa 'S' spike protein. One of the major mechanisms of virus entry known to date is that the virus uses the 'S' protein and the ACE-2 host receptor to facilitate its access into the host cell, where S is primed by the host cell serine protease, TMPRSS2 (Hoffmann et al., 2020; Walls, Park, Tortorici, Wall, McGuire & Veesler, 2020). Although ACE-2 is widely expressed in many organs and tissues, the respiratory tract remains the major port of entry. ACE-2 expression is known to be less in children in comparison to adults, and expression increases with smoking and chronic obstructive pulmonary disease (COPD) (Saheb Sharif-Askari et al., 2020; Sungnak, Huang, Becavin, Berg & Network, 2020). Infection is also reported in other tissues, including heart, liver, skin, kidney, intestinal tract, and adipose tissue (Al-Benna, 2020; Edler et al., 2020).

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On the other hand, the heavily phosphorylated SARS-CoV-2 'N' glycoprotein is associated with the viral genome and localizes to the ER-Golgi region, where it regulates viral replication (Fehr & Perlman, 2015). At the same time, other post-translational modifications are also identified (Fung & Liu, 2018). While the coronavirus 'M' protein is involved in determining the structure and shape of the virus, including stabilizing the N protein-RNA complex (Escors, Ortego, Laude & Enjuanes, 2001), the E structural protein helps in the production and maturation of the virus (Schoeman & Fielding, 2019). Their individual roles are reviewed in more detail elsewhere (Fung & Liu, 2018). Although these viruses also cause respiratory symptoms, the severity and the region of their manifestations are different. For example, MERS-CoV presents more gastrointestinal manifestation and kidney failure while SARS-CoV mainly manifests in the lower respiratory tract (LRT), possibly due to the difference in the host surface receptor affinity and distribution (Paules, Marston & Fauci, 2020). SARS-CoV entry is through the ACE-2 receptor, which is predominantly found in cells of the lower respiratory tract. On the other hand, MERS-CoV facilitates access through surface enzyme dipeptidyl peptidase 4 (DPP4), also known as CD26, which is widely expressed in the LRT, kidney, and gastrointestinal tract (GIT) (Park et al., 2019; Song, Gui, Wang & Xiang, 2018; Wan, Shang, Graham, Baric & Li, 2020). In comparison to these two viruses, the recent SARS-CoV-2 is highly infectious and aggressive, as evident from its exponential spread. SARS-CoV-2 is shown to have a higher affinity for the ACE-2 receptor than SARS-CoV (Song, Gui, Wang & Xiang, 2018). A wide distribution of this receptor across species depicts its transmission from animals to humans (Li, Qiao & Zhang, 2020).

ACE-2 mediated SARS-CoV-2 entry and comorbidities

Based on recent data, COVID-19 causes mild disease in most infected people. Still, it can progress to a more severe version of respiratory disease accompanied by hyper inflammation, multi-organ failure, and death in patients with immunocompromising and preexisting conditions. This can include conditions such as diabetes, cardiovascular disease, renal, digestive, cancer, COPD and immunodeficiency (Sanyaolu et al., 2020). SARS-CoV-2 is capable of entering human cells by binding to the ACE2 receptor, a carboxypeptidase that usually functions as a counterbalance to the angiotensin-converting enzyme (ACE) of the renin-angiotensin-aldosterone system (RAAS) by converting angiotensin II to angiotensin (1-7) (**Figure 2**). As a result, cells expressing ACE-2 are at a higher risk of establishing infection. SARS-CoV-2 has Open Reading Frames (ORFs) that are responsible for various steps of its disease progression. ORF1ab is responsible for most enzymatic proteins, including S, E, M, and N (Khailany, Safdar & Ozaslan, 2020). The ACE-2 receptor is commonly expressed in the lungs, intestine, kidneys, and heart (Crackower et al., 2002; Donoghue et al., 2000; Hamming, Timens, Bulthuis, Lely, Navis & van Goor, 2004; Tikellis et al., 2003). Recent studies have raised the concern that RAAS blockers such as ACE inhibitors and angiotensin receptor blockers (ARBs) may increase the expression of the ACE-2 receptor, which could potentially increase the susceptibility to SARS-CoV-2 infection in patients taking these medications. Therefore, raising questions about using these vascular medications in COVID-19 patients is crucial, although firm evidence is lacking (Sommerstein, Kochen, Messerli & Grani, 2020; Vaduganathan, Vardeny, Michel, McMurray, Pfeffer & Solomon, 2020). A study also revealed an association between heart disease and COVID-19 in which congestive heart failure was the second most common comorbidity with a 42.9% rate in patients diagnosed with COVID-19, which itself can cause heart injury (Arentz et al., 2020; Lippi et al., 2020). One possibility is that the increased expression of ACE-2 in the heart of COVID-19 patients may aggravate cardiovascular disease compared to healthy people; however, large sample sized studies are warranted to confirm these findings (Paramasivam, Priyadharsini, Raghunandhakumar & Elumalai, 2020). Besides, preexisting conditions in other organs such as the gastrointestinal tract (GIT), kidney, and lungs may influence comorbidities. On the other hand, metabolic dysfunctions in states such as obesity and diabetes are also found to be significant players in comorbidities in COVID-19 (Costa, Rosario, Ribeiro Farias, de Souza, Duarte Gondim & Barroso, 2020; Pugliese, Vitale, Resi & Orsi, 2020; Ritter, Kreis, Louwen & Yuan, 2020).

SARS-CoV-2 and mitochondrial alteration

Since ACE-2 has a clear association with mitochondrial function (Cao et al., 2019; Shi et al., 2018), SARS-CoV-2 may have an effect on mitochondrial function as well. ACE-2 knockout mice exhibit impaired mi-

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tochondrial respiration and ATP production, which are compensated by overexpressing ACE-2 (Shi et al., 2018). Also, genetic variations in ACE-2 may influence the susceptibility of SARS-CoV-2 and affect mitochondrial function, as substantial variation in ACE-2 has been reported around the world (Cao et al., 2020b). Therefore, it is possible that any specific variation of ACE-2 can modulate mitochondrial function and make the host especially vulnerable to SARS-CoV-2 infection. As TMPRSS2 is also responsible for SARS-CoV-2 invasion, the infection may also alter mitochondrial function through TMPRSS2, which via ERRa (estrogen-related receptor alpha), may regulate mitochondrial function (Xu et al., 2018). ERRα is a ligand-independent nuclear receptor that, together with its coactivator PGC-1α, transcriptionally regulates mitochondrial (ROS) production, energy homeostasis and mitochondrial biogenesis (Giguere, 2008; Sonoda et al., 2007). Detailed studies are warranted to know whether manipulation of mitochondrial function by SARS-CoV-2 through these receptors influences pathogenesis. There is recent evidence for this hypothesis that ORF-9b of SARS-CoV-2 is capable of manipulating mitochondrial function through ACE-2 regulation and the release of mitochondrial DNA (mtDNA) to suppress host immunity (Shi et al., 2014). ORF-9b accomplishes this by localizing the viral RNA genome in the host mitochondria (Shi et al., 2014). The same study showed that ORF-9b facilitates the degradation of Dynamin-1-like protein (DNML1), also referred to as dynamin-related protein 1 (Drp1), through ubiquitination. DNML1 is required for mitochondrial elongation and fission (Shi et al., 2014), which is an essential process by which dysfunctional mitochondria are eliminated through mitophagy that requires for preventing the accumulation of dysfunctional mitochondria, otherwise may lead to accumulation of dysfunctional mitochondria that may lead to cell death (Ikeda, Shirakabe, Brady, Zablocki, Ohishi & Sadoshima, 2015; Lin et al., 2020; Rana et al., 2017; Shirakabe et al., 2016; Vantaggiato et al., 2019). In addition, ORF-9b also manipulates the mitochondrial antiviral signaling (MAVS) protein through modulation of poly (C)-binding protein 2 (PCBP2) and a E3 Ubiquitin Protein Ligase, AIP4 in a way that degrades MAVS and TNF Receptor Associated Factor (TRAF) 3 and 6 as well. This may lead to the decreased IFN mediated antiviral response, allowing the virus to evade the host's innate immunity (Shi et al., 2014).

Alongside, SARS-CoV-2's ORFs7a and 8a may also aid with localization of the viral genome to the mitochondria, or interact directly or indirectly with them, and support disease progression (Schaecher, Touchette, Schriewer, Buller & Pekosz, 2007; Singh, Chaubey, Chen & Suravajhala, 2020; Tan et al., 2007). On the other hand, ORF3a may target mitochondrial ubiquitin specific peptidase 30 (USP30), a mitochondrial deubiquitinase involved in mitochondrial homeostasis and mitophagy control (Freundt, Yu, Park, Lenardo & Xu, 2009). SARS-CoV-2 can control mitochondrial function through the above mechanisms to help with host immunosuppression. Similar to other viruses, SARS-CoV-2 can also induce the Neutrophil extracellular trap (NET)osis mechanism, which is an inflammatory response that involves mitochondrial biogenesis, mitochondrial fusion, fission, and mtDNA release to the outside of the cell (Schonrich & Raftery, 2016; Singh, Chaubey, Chen & Suravajhala, 2020). The release of mtDNA into the cytoplasm triggers the innate immune response and inflammation, a well-known phenomenon that has been recently demonstrated (Rongvaux et al., 2014; West et al., 2015; White et al., 2014). As mtDNA levels increase, the damage and severity of the illness can progress to multi-organ failure (Aswani et al., 2018). Other SARS-CoV-2 viral proteins such as ORF9c and Nsp7 were also predicted to interact with mitochondrial proteins NDUFAF1 and 2, respectively (Singh, Chaubey, Chen & Suravajhala, 2020). As it is well known that NDUFAF1 and 2 are critical players involved in the assembly of Complex I, such interaction may augment Complex-I function. This is crucial for the initiation of electron flow and ROS production, which is required for proper cellular signaling and immune response (Jin, Wei, Yang, Du & Wan, 2014; West et al., 2011). The SARS-CoV-2 protein interacts with mitochondrial proteins that play crucial parts in the mitochondrial metabolic pathways (Gordon et al., 2020). Other viral interactions of significance may also include Tom 70, a mitochondrial importer that plays a critical role in transporting proteins into the mitochondria and, more importantly, in modulating antiviral cellular defense pathways (Gordon et al., 2020; Liu, Wei, Shi, Shan & Wang, 2010). Such interactions provide a means of viral manipulation of the host mitochondria that suppresses immunity and promotes disease progression (**Figure 3**). However, a detailed and comprehensive study may require identifying the crucial mitochondrial proteins targeted by SARS-CoV-2. Preventing such interactions between SARS-CoV-2 and mitochondrial proteins during virus establishment is a potential area of research in identifying potential

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targets and treatments.

SARS-CoV-2 and mitochondrial dysfunction

Although there is a high possibility that SARS-CoV-2 might hijack host mitochondria, it is not clear whether it suppresses its function to escape from mitochondria-mediated immune response or whether it uses mitochondria to establish its infection. But a possible hypothesis proposed is SARS-CoV-2 benefits from causing mitochondrial dysfunction for survival. Thus, it is suspected that the hijacking of host mitochondria by SARS-CoV-2 suppresses immunity and aids in the manipulation of mitochondrial function, including the immune pathways involving the MAVS protein. Recent studies have shown that MAVS is activated by the retinoic acid-inducible gene I (RIG-1), which can sense the presence of viral RNA (Furr, Moerdyk-Schauwecker, Grdzelishvili & Marriott, 2010; Kowalinski et al., 2011). By interacting with viperin, an antiviral protein, MAVS is also capable of affecting interferon levels, thereby acting as a means of antiviral defense (Hee & Cresswell, 2017).

An understanding of mitochondrial hijacking by SARS-CoV-2 is imperative as mitochondria are known to have various ties to the host's immune system. They are capable of altering signaling and metabolic pathways and the transcription of genes within immune cells. For example, by changing the type of respiration, the mitochondria can switch the phenotype between pro and anti-inflammatory (Mills et al., 2016; Mills & O'Neill, 2016). Furthermore, the virus relies on the mitochondria's production of energy for sustenance, which leads to the theory that modulation of mitochondrial metabolism may prove to be an effective method against the virus. It is also known that replication of this virus relies on the production of double-membrane vesicles (DMVs) from the endoplasmic reticulum (Cortese et al., 2017; Knoops et al., 2008; Maier et al., 2013; Ulasli, Verheije, de Haan & Reggiori, 2010). The virus replicates on the location of these DMVs and uses them to escape the host cell's immune defenses. It has also been theorized that SARS-CoV-2 manipulates mitochondria through the formation of double-membrane mitochondrial-derived vesicles (MDVs) (Singh, Chaubey, Chen & Suravajhala, 2020; Wu, Fazal, Parker, Zou & Chang, 2020). However, there is still no clear evidence proving MDVs promote viral replication. Therefore, it is essential to focus on such areas to reveal the importance of mitochondrial dysfunction and SARS-CoV-2 establishment in the COVID-19 pathogenesis. If these hypotheses are true, improving mitochondrial function in SARS-CoV-2 host cells could prevent or decrease the infection or pathogenesis.

Mitochondria and cytokine storm in COVID-19

As mitochondria are shown to be one of the critical components in eliciting the innate immune response, specifically in response to viruses, the SARS-CoV-2 mediated immune response could involve mitochondria. In support of this hypothesis, a master regulator analysis of combined SARS-CoV-2 specific interactome with MERS and SARS- CoV transcriptome using the human lung RNA-sequence data set validates the interaction with ACE-2 and TMPRSS, in addition to certain mitochondrial proteins (Guzzi, Mercatelli, Ceraolo & Giorgi, 2020). These mitochondrial proteins are MCL-1, a regulator of apoptosis, as well as the Complex I subunit NDUFA10 network, which is downregulated (Guzzi, Mercatelli, Ceraolo & Giorgi, 2020). However, the proposed mechanism is that the virus strategizes to down-regulate mitochondrial function and uses host cells for replication. This is not executed by mitochondrial-dependent elimination, controlling host cell metabolism and apoptosis. At normal physiological conditions, the MAV protein present on the mitochondrion's outer membrane interacts with mitofusin-2 (Mfn2), which is essential for mitochondrial fusion. During viral entry, mitochondrial associated membranes at the ER tether mitochondria using Mfn2 and RIG-1. Using other protein recruits, the virus binds to MAVS, which then induces phosphorylation and nuclear translocation of IRF3, resulting in the production of cytokines and interferon I/III through activation of NFKba and IRFs (3/7), respectively (Lin, Heylbroeck, Pitha & Hiscott, 1998). As in vitro data showed that MAVS is required for the induction of IFN production by activating NFKb and IRF3, recent evidence also shows that mice lacking MAVS failed to induce IFN production in response to viral infection. This suggests the involvement of mitochondria in the viral-mediated immune response (Sun et al., 2006) (**Figure 3)** .

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A clue from a previous study carried out in peripheral blood mononuclear cells (PBMCs) infected with SARS-CoV (Li et al., 2003; Li et al., 2004) showed that upregulation of genes encoding mtDNA, as well as genes involved in oxidative stress, heat shock, and transcription, coincides with cytokine elevation, compared to PBMCs from control samples (Shao et al., 2006). The mtDNA genes included 16S rRNA (a ribosomal subunit), NADH dehydrogenase subunit 1 (ND1), and cytochrome c oxidase subunit I (COX1), whereas the genes involved in oxidative stress are peroxiredoxin 1 (PRDX1) and ferritin heavy polypeptide 1 (FTH1), heat shock response are DnaJ (Hsp40), homolog subfamily B member 1 (DNAJB1), and cytokine IL-1B as well (Shao et al., 2006). These SARS-CoV-infected patients are also shown to have a significantly increased number of mitochondria in their PBMCs compared to PBMCs from control subjects. This may be one of the reasons why more mtDNA gene expression is observed. Interestingly, the electron microscopic structure of PBMCs from SARS-CoV infected patients showed increased lysosome-like granules, which was not seen in the control. This could possibly be the activation of mitochondria in PBMCs, causing an increased immune response and cytokine storm. We hypothesize that this could be more cell-specific as it depends on whether the cell is more immunogenic or not. Likewise, a recent study has shown a similar observation of SARS-CoV-2 infection in PBMCs and lymphoma along with the cytokine storm, but the involvement of mitochondria, which is likely, was not investigated in this study (Liu et al., 2020). This study further showed that cytokines IL-6, IL-10, IL-2 and IFN-γ are significantly increased in severe COVID-19 cases than mild cases, displaying that these levels are associated with the disease severity. Therefore, a possible cytokine storm induced by mitochondria in COVID-19 could be heterogeneous among the infected population. It could also be influenced by preexisting metabolic dysfunction, which further determines the intensity of the cytokine storm and whether it eliminates the virus or causes multi-organ failure.

Mitochondria and inflammatory response in COVID-19

Identifying the critical players of sepsis and inflammatory response resulting from SARS-CoV-2 infection is essential to developing better diagnostic and therapeutic strategies as well. It is known that during sepsis, the infected bacteria release their DNA, which, along with the other proteins, are recognized as pathogen-associated molecular patterns (PAMPs), which stimulate the inflammatory response in the host cells. In this process, released DNA binds to the toll-like receptor 9 (TLR) and the formyl peptides bind to the formyl peptide receptor-1 (FPR1) on the surface of host cells. This further releases cytokines through activation of p38 MAP kinase (MAPK) and attracts neutrophils while establishing immune response activation (Dorward, Lucas, Chapman, Haslett, Dhaliwal & Rossi, 2015). On the other hand, a similar pattern is also observed with no infection, but any trauma or damage to the system by external stimuli could result in the release of molecules called damage-associated molecular patterns (DAMPs), which could initiate an inflammatory response similar to PAMPs. A breakthrough study by Zhang group found that mitochondria are evolutionarily conserved bacteria, sharing a similar structural motif with prokaryotes. They could release their DNA (mtDNA) and peptides (formyl peptides), which are recognized as DAMPS similar to PAMPs, suggesting that bacteria and mitochondria use a similar tactic while eliciting an immune response. Some of the DAMPs released by the mitochondria are mtDNA, TFAM, formyl peptides and ROS (Goulopoulou, Matsumoto, Bomfim & Webb, 2012; Wenceslau, McCarthy, Goulopoulou, Szasz, NeSmith & Webb, 2013; Wenceslau, McCarthy, Szasz, Goulopoulou & Webb, 2015; Zhang et al., 2010). Specifically, formyl peptides are present only in bacteria and mitochondria in nature, suggesting that the injury response caused by DAMPs is analogous to sepsis caused by bacterial infection. Furthermore, these groups showed that intravenous injection of mitochondrial DAMPs caused severe systemic inflammation, including severe lung injury (Zhang et al., 2010), which is most commonly observed in COVID-19 (Chen et al., 2020; Li, Huang, Wang, Ingbar & Wang, 2020; Zhang, Wang, Huang & Wang, 2020). Also, the ATP required for immune cells comes from mitochondria, whereas calcium buffering and ROS are critical components regulated by mitochondria for antigen-presenting, processing and activation of signaling pathways containing inflammatory proteins (Carr et al., 2010; Le et al., 2012). Specifically, in T cells, the deficiency of mitochondrial transcription factor TFAM causes energy deficiency, resulting in T cell metabolic failure. This induces the circulation of cytokines, thereby establishing chronic inflammation and senescence phenotype (Desdin-Mico et al., 2020). Additionally, autophagy, which is a mechanism in which viruses and their proteins are elimi-

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nated by being presented to lysosomes is impaired during mitochondrial dysfunction in SARS-CoV/CoV-2, resulting in decreased autophagy in T cells, thereby establishing the infection (Baixauli et al., 2015). This is in agreement with the observation of life-threatening casualties in COVID-19 subjects with metabolic compromised preexisting conditions such as cancer (Liang et al., 2020; Robilotti et al., 2020), heart diseases (Bohm, Frey, Giannitsis, Sliwa & Zeiher, 2020; Guo et al., 2020; Montone, Iannaccone, Meucci, Gurgoglione & Niccoli, 2020), diabetes (Zhu et al., 2020a), aging (Palaiodimos et al., 2020), obesity (Anderson et al., 2020; Klang, Kassim, Soffer, Freeman, Levin & Reich, 2020; Lighter et al., 2020; Palaiodimos et al., 2020) and COPD (Lippi & Henry, 2020), all which are reported in the SARS-CoV-2 infection.

Mitochondria and iron dysregulation in COVID-19

Mitochondria are the hub for iron metabolism, and since iron is associated with various physiological and pathological roles, it is not surprising that iron dysregulation is observed in patients with SARS-CoV-2 infection (Huang et al., 2020; Mehta et al., 2020; Phua et al., 2020). As iron is an essential element in cells, its role in oxygen transfer, electron transfer or accepting, and signaling are necessary for normal physiological functions. Most iron is normally stored in the form of ferritin in the Ferric state (Fe3+). Iron is required for optimal mitochondrial function, which primarily utilizes the iron stored in ferritin and involved in Fe-S cluster biosynthesis for heme synthesis (Levi & Rovida, 2009). Many of the mitochondrial enzymes involved in metabolism and oxidative phosphorylation contain an Fe-S cluster, which helps in facilitating oxidation-reduction reactions (Levi & Rovida, 2009; Rouault, 2016).

Hyperferritinimea is a condition reported in COVID-19 patients where there is an excess presence of iron beyond the average level in the blood (Huang et al., 2020; Mehta et al., 2020; Phua et al., 2020). A large number of studies conducted during the early stages of the COVID-19 pandemic clearly show the association between blood ferritin levels and the severity of the disease pathology. Patients who tested positive for SARS-CoV-2 had higher levels of ferritin compared to those who had tested negative. Specifically, severe cases of COVID-19 had 1.5 to 5.3 times mores ferritin in the blood compared to mild cases (Gomez-Pastora et al., 2020). On the other hand, it's been reported that COVID-19 non-survivors showed 3-4 times more serum ferritin levels compared to survivors (Gomez-Pastora et al., 2020). Interestingly, there was a strong correlation between ferritin and cytokine levels (ex., IL-6) with disease severity (Gomez-Pastora et al., 2020; Zhou et al., 2020). Such correlation explains a possible feedback mechanism where inflammation-induced cytokines increase the secretion of ferritin, majorly through iron overloaded cells (ex., macrophages)(Ganz, 2012). But the functional consequences of elevated ferritin are not clear. As expected, ferritin levels went down in patients who recovered from COVID-19, showing that ferritin could be a potential biomarker in tracing the severity of the inflammatory reaction, including in COVID-19 patients. Hyperferritinimea is also reported in other viral diseases such as Dengue (van de Weg et al., 2014). It is not clear whether the high ferritin is a defense mechanism or if it is destructive. However, it is wise to speculate that it could be defensive at acute or low levels of elevation but become dangerous when it is secreted in excess. Although the consequences of increased ferritin in serum on mitochondrial function are unclear, the overall iron dysregulation increased serum levels is expected to reduce mitochondrial Fe levels. This could reduce mitochondrial respiration overall and upregulate anaerobic respiration, resulting in glycolysis mediated lactic acid accumulation, which is consistent with the upregulation of Lactate dehydrogenase in COVID-19 cases (Henry et al., 2020). Therefore, iron-dependent dysregulation of mitochondria could have serious consequences that may potentiate COVID-19 pathologies if left untreated.

COVID-19 and demographic factors

Mitochondrial quality is relevant to COVID-19 pathology, which could also be influenced by age and gender. Aging is proven to lead to poor mitochondrial function, which may contribute to the suppression of immunity and altered inflammation (Miller & Allman, 2003; Miller & Allman, 2005; Min, Montecino-Rodriguez & Dorshkind, 2004). Mitochondrial dysfunction induces senescence, which accumulates during aging and contributes to inflammation that also impairs macrophages (Franceschi et al., 2000; Wiley et al., 2016). This could contribute to susceptibility to COVID-19 in older patients. Another relevant principle is that mitochondrial inheritance is maternal. The mitochondria in the egg's cytoplasm may contain mutations

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harmful for females, which could be eliminated by quality control mechanisms [114] but may not be eliminated for males. This phenomenon may also impact mitochondrial function and contribute to additional factors where more severe infections could affect males. Additionally, it is claimed that the secondary sex characteristics that men develop come at the cost of immunity, as androgens are anti-inflammatory (Newsome, Flores, Ayala, Gregory & Reichner, 2011; Rettew, Huet-Hudson & Marriott, 2008). Also, in females, the X chromosome mosaicism where X chromosomes are randomly inactivated can also influence the gender difference in viral progression. The ACE-2 receptor encoded by the ACE-2 gene from the X chromosome is responsible for the entry of the SARS-CoV-2 virus. Since the gene is on the X chromosome, it may have a random distribution in cells leading to a heterogeneous expression in females. However, males are capable of expressing only one ACE-2 allele as every cell has the same X chromosome. This may limit infectibility and give females a relative resistance to the infection in comparison to males (Kloc, Ghobrial & Kubiak, 2020). The ties between gender and immune defenses to the mitochondria reveal a potential area of research that could lead to the identification of effective treatment options.

Potential treatment and prophylactics in COVID-19

Despite recent advancements in technology, the prevention/treatment for COVID-19 is still unpredictable, where many factors are involved in finding prophylaxis or treatment. Whether mitochondria could be a potential target in treating the COVID-19 disease is still a very premature question. However, based on existing literature, strong evidence, and manipulation of mitochondrial function by SARS-CoV-2, it is apparent that mitochondria are a potential target in COVID-19 treatment. Hence, improving mitochondrial function could by any means be detrimental to virus establishment. Therefore, when concerning the mitochondria, treatment options can include compounds that modulate mitochondrial bioenergetic functions as the virus relies on energy from the mitochondria. On the other hand, virus-induced mitochondrial dysfunction could be alleviated by increasing mitochondrial function by employing mitochondrial modulators, thereby preventing mitochondrial hijacking by the virus. Although vaccines are the ultimate prophylactic option, the development of multiple vaccines for SARS-CoV-2 is actively underway at a rapid rate, with numerous potential candidates and involving various strategies (RNA, DNA, proteins and antibodies).

While most of the other proposed, practicing treatments vary between the demographics, no one possible strategy is favorable currently. It is unclear because it has not been studied whether these strategies involve direct or indirect mitochondrial manipulation. On the other hand, potential drugs are antiviral drugs previously developed for other coronaviruses. Some of them include Lopinavir and Ritonavir, which are HIV protease inhibitors that have proven to be effective against SARS-CoV in vitro and in studies involving non-human primates infected with the Middle East respiratory syndrome-CoV (MERS-CoV) (Chan et al., 2015; Chu et al., 2004). However, they did not show efficacy or a faster recovery time in patients with COVID-19 (Cao et al., 2020a; Yang, Tekwani & Martin, 2020). On the other hand, the FDA approved Remdesivir, a nucleoside analog, has shown to be effective against SARS-CoV and MERS-CoV in vitro (Agostini et al., 2018; Sheahan et al., 2020). However, there is insufficient strong clinical evidence proving its effectiveness against COVID-19. Nevertheless, this regimen is shown to decrease the hospitality rate and improve the discharge rate compared to the placebo, and it has also displayed a shortened recovery time in COVID-19 patients (Beigel et al., 2020; Paladugu & Donato, 2020). However, their role in influencing mitochondrial function is not known.

In addition, a class of anti-malarial drugs, chloroquine (CQ) and hydroxychloroquine (HCQ) have been shown to inhibit SARS-CoV and CoV-2 establishment in vitro (Vincent et al., 2005; Wang et al., 2020). Since then, multiple clinical trials have been initiated to study the effects of these anti-malarial drugs on COVID-19 disease and it is getting controversial as only one report showed a beneficial effect (Gao, Tian & Yang, 2020). There are many proposed theories that CQs inhibit cellular entry of the virus, including by inhibiting lysosomal uptake (Hashem et al., 2020; Mauthe et al., 2018). However, the effects of CQs on mitochondrial function are not so intensively investigated, but it has been shown that CQ inhibits mitochondrial respiration, ATP production and function (Deepalakshmi, Parasakthy, Shanthi & Devaraj, 1994; Redmann et al., 2017) and whether this influence the treatment is not clear. When ACE-2 was identified as the primary mediator

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for SARS-CoV and CoV-2 entry, small molecule and peptide inhibitors of ACE-2, recombinant proteins, and phytoconstituents were being actively investigated as a potential treatment for COVID-19. However, their outcomes are not clear as well (Guy, Jackson, Jensen, Hooper & Turner, 2005; Han, Penn-Nicholson & Cho, 2006; Monteil et al., 2020; Mores, Matziari, Beau, Cuniasse, Yiotakis & Dive, 2008; Pedersen, Sriramula, Chhabra, Xia & Lazartigues, 2011; Trask et al., 2010; Ye et al., 2012).

On the other hand, melatonin also emerges as one of the potential enhancers in COVID-19 treatment (Zhang et al., 2020). As evidence suggests that melatonin is synthesized in mitochondria, the protective effect of melatonin is also proposed and shown (Tan, Manchester, Qin & Reiter, 2016). Melatonin is shown to improve mitochondrial function by increasing oxidative phosphorylation and ATP production in addition to upregulating antioxidant enzymes, scavenging ROS, and RNS (Absi, Ayala, Machado & Parrado, 2000; Bromme, Morke, Peschke, Ebelt & Peschke, 2000; Ding et al., 2014; Jou et al., 2007; Kilanczyk & Bryszewska, 2003). Therefore, it is possible that melatonin treatment may potentiate and improve outcomes in COVID-19 treatment. But, whether all these regimens affect mitochondrial function in preventing SARS-CoV-2 infection needs to be explored.

Conclusion

The COVID-19 pandemic has prompted numerous research studies to investigate its pathology and the potential therapies that could be effective against this virus. The various studies discussed in this article present different theories concerning SARS-CoV-2 progression and some tie it to mitochondrial processes. Overall, these articles have demonstrated that the manipulation of host mitochondria by SARS-CoV-2 is an integral part of its success in replication and disease progression through modulating various functions **(Figure 4)** . Further research on how SARS-CoV-2 hijacks mitochondrial functions to replicate and suppress the immune system would provide insight into novel therapy and prevention. Specifically, research should be conducted on how the virus localizes RNA in the host mitochondria and why this localization aids with the progression of the infection. Moreover, mitochondrial ties to the ACE-2 receptor and whether this receptor is more harmful than beneficial for the host should be further researched as well due to a lack of clear clinical evidence. Investigating the interactions between mitochondrial and viral proteins and how they could be prohibited would provide insight into better treatment options as well. Furthermore, ties to aging and gender should be examined to produce therapies that are better catered for those demographics. Studying these topics would ultimately provide a better understanding of not only SARS-CoV-2 but of any similar future viruses, which can facilitate the breakthrough of more successful treatment and prevention approaches.

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Figure 1

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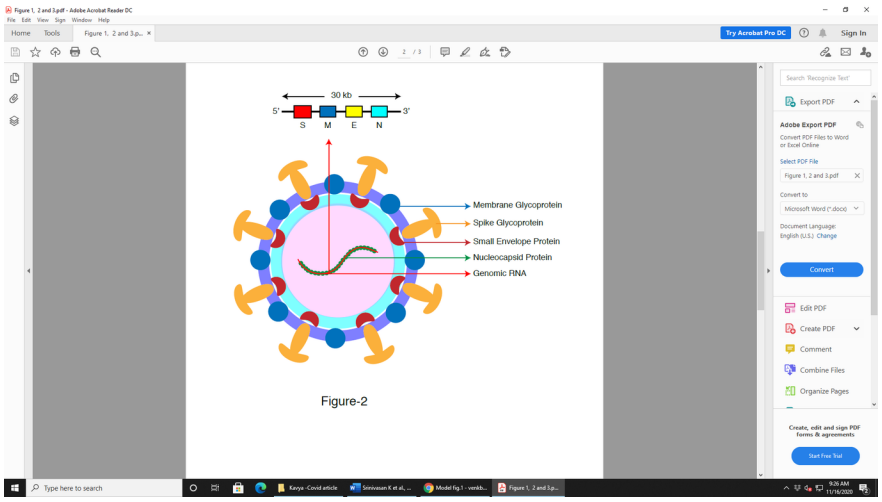

Figure 1. Schematic representation of the structure of SARS-CoV-2 virus. SARS-CoV-2 virus is made up of primarily spike (S), membrane (M), envelope (E), and nucleocapsid (N) structural proteins, embedded in the lipid bilayer of the viral envelope. In contrast, the N glycoprotein is associated with the genomics RNA, which is approximately 30 kb, of the virion.

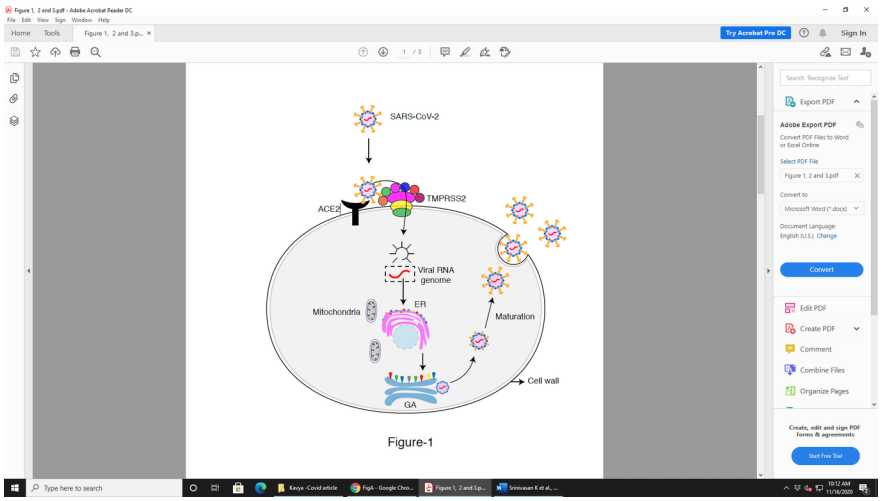

Figure 2

Figure 2. Schematic representation of SARS-CoV-2 entry and replication in host cells. SARS-CoV-2 enters host cells through its spike 'S' protein by interacting with host's ACE-2 receptor where S is primed by the host cell serine protease, TMPRSS2. Upon entry, release of viral genomic RNA subsequently leads to genomic replication by using host cell's translational and transcriptional machineries. Structural proteins are synthesized and assembled at Endoplasmic reticulum (ER) and Golgi apparatus (GA) respectively, followed by their maturation and release.

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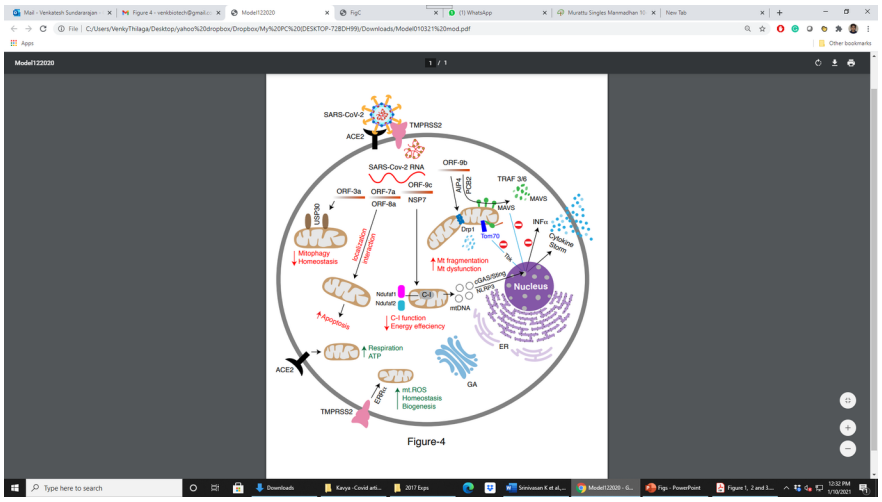

Figure 3

Figure 3. SARS-CoV-2 entry and its possible influence on mitochondrial function in establishing Covid-19 infection. Upon SARS-CoV-2 entry, RNA genome is released and interact with various parts of mitochondria. ORF-9b localize the viral RNA genome in the host mitochondria as ORF-9b could facilitate the degradation of Dynamin related protein (Drp1) through ubiquitination. ORF-9b also manipulates the mitochondrial antiviral signaling (MAVS) protein through modulation of poly (C)-binding protein 2 (PCBP2) and a E3 Ubiquitin Protein Ligase, AIP4 to degrade MAVS and TNF Receptor Associated Factor (TRAF) 3 and 6, thereby limits INF production and host immunity. On the otherhand, ORFs7a and 8a may localize RNA genome to mitochondria, ORF3a may target mitochondrial ubiquitin specific peptidase 30 (USP30) and decrease mitophagy. Also, ORF9c and Nsp7 were predicted to interact with mitochondrial proteins NDUFAF1 and 2, respectively which may reduce complex I function, required for ROS and ATP production in immune signaling. Mitochondrial Tom 70 also shown to interact with SARS-CoV2- genome, in modulating antiviral cellular defense pathways. MtDNA released during these process may activate cytokine storm through cGAS/STING and NLRP3 pathways.

Figure 4

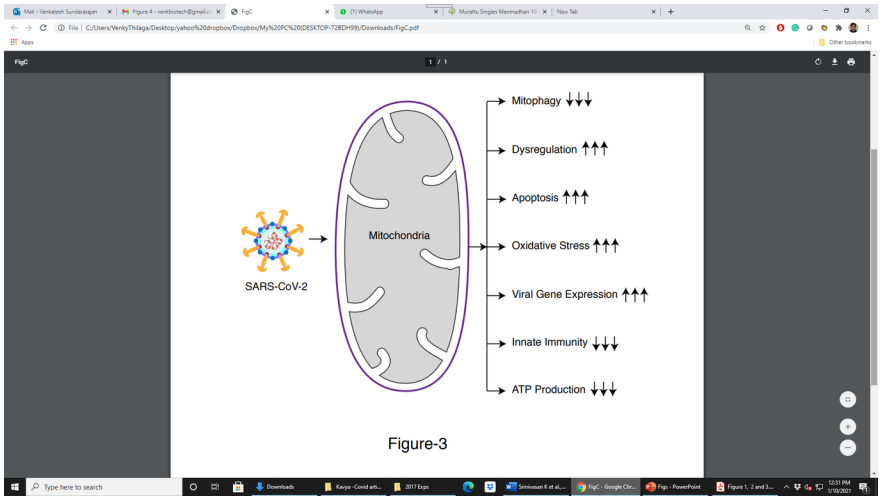

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Figure 4. SARS-CoV-2 and it's effect on mitochondrial function in establishing infection. SARS-CoV-2 interacts with mitochondria in multiple ways through its genetic material and proteins resulting in impaired various mitochondrial function require to defend the virus establishment and promote cellular dysfunction as shown.

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