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LONG-COVID: AN OUTCOME OF MITOCHONDRIAL DYSFUNCTION (A BRIEF NARRATIVE REVIEW)

Virology

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ABSTRACT

A significant proportion of patients who recovered from SARCoV-2 infection develop chronic symptoms lasting weeks or months, referred as Long COVID. Though the exact etiology of Long COVID is unknown; however, one of major symptom experienced by these patients is chronic fatigue syndrome which is associated with several mitochondrial disorders or viral diseases. In this review, a systematic approach has been performed to explain Long COVID as possible outcome of mitochondrial dysfunction. The review highlights what is known in literature about the dysfunctional pathways which can develop in mitochondria and their relationship to viruses and associated mitochondrial disorders. It also identifies potential areas which require urgent, further research in order to help clinical management and interventional studies for better long-term outcomes.

KEYWORDS

Long COVID; mitochondrial dysfunction; SARCoV-2

Overview Of Long Covid

Uncertainty, still prevails around the origin of *Severe Acute Respiratory Syndrome Coronavirus 2 (SAR-CoV-2)* which has led to fifth documented pandemic disease in humans, since the 1918 flu pandemic. The disease was officially named by World Health Organization (WHO) as COVID-19 on 12 February 2020 (**Cucinotta and Vanelli, 2020**). Based on the phylogenic analysis, the disease was first symptomatically reported in Wuhan, Hubei Province, China, in 1 December 2019 (**Cucinotta and Vanelli, 2020**). COVID-19 patients present clinically diverse manifestations ranging from asymptomatic patients to critically ill patients with severe pneumonia, respiratory failure, acute respiratory distress syndrome or multiple organ failure **(Tsai et al., 2021)**. Till date, the spread of COVID-19 signified a big threat to public health, social life and the economy; and no particular drug therapy or effective vaccines are yet accessible for prevention and treatment of this unforeseen and lethal illness.

Of concern, many patients who recovered from SARCoV-2 infection experience persistent post-acute sequelae of COVID-19 (PASC) with range of symptoms clinically manifested as headache, breathlessness, chest pain, abdominal symptoms, fatigue, myalgia, cognitive difficulties, as well as depression and anxiety **(Chippa et al., 2022)**. While as of yet there is no consensus upon the clinical definition of these set of symptoms; however, for the sake of convenience, the WHO coined these range of clinical symptoms collectively as **Long COVID** *(the terminology first used by Perego in social media)*. Based upon the studies which included cross-sectional or cohort observational studies with large cohorts, the National Institute for Health and Care Excellence (NICE) has categorized **Long COVID** into two general phases – *post acute COVID* where symptoms extend beyond 3 weeks, but less than 12 weeks, and *chronic COVID* where symptoms extend beyond 12 weeks **(Venkatesan, 2021)**. Notably, most of the patients experiencing Long COVID are PCR negative and show modest biochemical and radiological recovery.

The exact cause, long term effects and diagnosis of **Long COVID** has remained a major challenge due to disparities in reported incidences and mortality rates between countries owing to many reasons including population assessed, symptoms examined, the length of follow-up period, accuracy of self-reporting, lack of inclusion of controls, invalidated measurement instruments, COVID-19-related stigma etc. Despite these discrepancies and conflicting data, **Long COVID** has gained widespread attention as it provides early evidence to aid in the identification of people who are at high risk. As per the available data, the predominant pathological factors that may contribute these long-term sequelae of COVID-19 include the following: dysregulation and hyper-stimulation of inflammatory mediators; endothelial damage and microvascular injury; hypercoagulability with resultant in situ thrombosis and macro-thrombosis; and maladaptation of the angiotensin-converting enzyme 2 (ACE2) pathway (**Gustine and Jones, 2021; Canale et al., 2022; Mondal et al., 2020 & Gheblawi et al., 2020)**. Such complex clinical picture indicates that there exists a dysregulated host response post SARCoV2 infection and thus understanding the pathophysiology will be key to implement optimum management strategies and improve outcomes for patients.

Ongoing studies indicate chronic fatigue syndrome (CFS) as the most common clinical long term symptom among patients who have recovered from COVID-19 **(Bansal et al., 2022)**. There is considerable evidence that mitochondrial dysfunction plays important role in CFS and importantly, it has been shown that mitochondrial dysfunction is associated with pathogenesis of several viral and age related diseases **(Myhill et al., 2009)**. Thus it will to interesting to understand the role of mitochondria in COVID-19 to provide answers to some of the key perplexing questions.

Overview Of Mitochondria

Mitochondria are double membrane intracellular organelles present in all mammalian cells (except red blood cells) which perform plethora of different functions, from energy production in the form of ATP (it is estimated around 95% of energy demands are met by this organelle) to regulating key cellular biological processes such as apoptosis, calcium signaling, ROS generation, cell cycle and cell growth, by the combined actions of glycolysis and mitochondrial oxidative phosphorylation (**Friedman & Nunnari, 2014**).

Once believed to be a solitary and rigid, mitochondria are now regarded as important organelle that play vital role in bio-energetic and biosynthetic pathways of the cell. Alterations of mitochondrial function, dynamics, and biogenesis can have many pathophysiological consequences **(Suarez-Rivero et al., 2017)**. They have a quality control system (QCS) which serves as a compensatory mechanism to respond to energy demands that can affect the mitochondrial homeostasis. The QCS includes cycles of fission / fusion, biogenesis and mitophagy. Increased demand is met by mitochondrial biogenesis and fusion of individual mitochondria into dynamic networks, whereas a decrease in demand results in the removal of superfluous mitochondria though fission and mitophagy. The fission and fusion processes are coordinated by dynamin-related proteins (DRPs), of which, Mitofusins (Mfn1 and Mfn2) and optic atrophy 1 protein (OPA1) regulate the fusion pathways while as dynamin-related protein 1 (Drp1) alongwith the accessory proteins Mid49, Mid51, and mitochondrial fission factor (Mff) commands the fission pathway. In case, the stress induces irreversible damage to mitochondria, they are completely eliminated by mitophagy (a kind of autophagy) in Parkin-dependent, and Parkin independent mechanisms. Parkin dependent mitophagy involves display of serine/threonine kinase, PTEN-induced putative kinase 1 (PINK1) on damaged mitochondria followed by Parkin recruitment which ubiquitinates and mediates degradation of DRPs such as Mfn1, Mfn2 and TOM complex essential for

proteosomal degradation. On the other hand, Parkin independent mitophagy does not involve Parkin as supported by various studies.

Given the central role of mitochondria in regulating a range of cellular activities, the mitochondria are very susceptible to metabolic or environmental stresses which can lead to a situation referred as *mitochondrial fatigue*. Clinically, fatigue is often manifested as lack of energy, diminished endurance, mental or physical tiredness and the need for prolonged recovery from physical activity. A consequence of the mitochondrial fatigue is the generation of reactive oxygen species (ROS) and abnormal generation of reactive nitrogen species like nitric oxide (NO) that affect mitochondrial function by different ways which can be summarized as – damage to macromolecules like proteins, lipids & DNA; inactivation of the iron-sulfur (Fe-S) centers of electron-transport chain complexes I, II, and III, and tricarboxylic acid cycle aconitase; change in mitochondrial potential due to perturbed mitochondrial Ca^{2+} homeostasis etc (**Inoue et al., 2003**). Such events in turn result in non-availability of necessary substrates or loss of efficiency in electron transport or ATP-synthesis machinery which can lead to mitochondrial dysfunction.

Mitochondria can also sense innate immune response through activation of the NLRP3 and NLRP6 inflammasomes; activation of pattern recognition receptors (PRR); release of alarmins like pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) during cellular stress and loss of homeostasis **(Chen et al., 2018)**. Impaired mitochondrial function has been widely implicated in spectrum of diseases such as neurodegenerative diseases, neurobehavioral and psychiatric diseases, cardiovascular diseases, diabetes, autoimmune diseases, musculoskeletal diseases, fatiguing illnesses, cancer, chronic infections and viral diseases (**Gorman et al., 2016**).

Alteration In Mitochondrial Homeostasis Upon Viral Infection

That viral infection can alter mitochondrial function, was first discovered in patients infected with Hepatitis C virus (HCV), a positive-strand RNA virus. The HCV induced mitochondrial dysfunction occurs by two main pathways: indirectly through membrane depolarization, caused by excess intake of calcium released from ER-stress pathway and directly by association of HCV proteins with mitochondrial and localization to OMM & MAM like perturbation of complex 1 activity and promotion of mitochondrial permeability transition by HCV core and NS5a proteins; localization of HCV NS3/4a protease to MAM to cleave MAM-associated MAVS to protect to overcome innate immune response; inhibition of mitochondrial electron transport, and an increase in the production of reactive oxygen species (ROS) by direct recruitment of HCV Core, E1, and NS3 proteins on OMM and promoting mitochondrial fission and mitophagy through phosphorylation of Drp1 (Ser616) and expression of Parkin and PINK1 (**Brault et al., 2013; Wang & Weinman, 2013**). Likewise, HBV a partially double stranded virus encodes a regulatory protein, termed HBx that alters mitochondrial membrane potential through its association with voltage-dependent anion channel (VDAC), ultimately causing elevated levels of calcium and ROS **(Rahmani et al., 2000)**. Besides, in a study it was showed that HBx is sufficient to promote mitochondrial damage and alter mitochondrial dynamics by regulating PINK1 or DRP1 expression **(Kim et al., 2013)**. Few other notable examples include Epstein–Barr virus (EBV), influenza virus, Human cytomegalovirus (HCMV), Pseudorabies virus (alpha-herpesvirus), Measles virus and Newcastle disease virus (NDV) and Severe acute respiratory syndrome-coronavirus. The viral proteins responsible for altering mitochondrial dynamics can be summarized as the viral latent membrane protein 2A (LMP2A) of EBV that induces Drp1 expression through Notch pathway leading to enhanced mitochondrial fission in gastric and breast cancer cells; a viral mitochondrion localized inhibitor of apoptosis (vMIA) of HCMV that generates punctate and dispersed mitochondria in fibroblasts; fusion events mediated by glycoprotein B (gB) that leads to intracellular Ca2+ increase and altered mitochondrial transport; binding of influenza A viral protein PB1-F2 to MAVS manifested as altered IFN synthesis mitochondrial fragmentation, reduction of mitochondrial membrane potential and NLRP3 inflammasome activation; dampening of innate immune response mediated by RIG-I/MAVS signaling and activation of p62-mediated mitophagy in cells infected with the Edmonston strain of Measles virus (MV-Edm) and the NDV (**Elesela & Lukacs, 2021; Khan et al., 2015**).

Altered Mitochondrial Metabolism Upon Viral Infection

Mitochondrial represent a highly active organelle within cell that are required to maintaining the balance of cellular energy metabolism through coordinated action of various processes which include TCA, FAO, oxidative phosphorylation (OXPHOS), calcium buffering, and heme biosynthesis. Being obligate parasites, the viruses often reprogram the metabolic processes of host cell for their survival and proliferation as indicated by various studies for example, HCV / DENV infection can enhance the mitochondrial fatty acid oxidation, carbohydrate flux during glycolysis and limit the activities of oxidative phosphorylation and the citric acid cycle by modulating expression of critical components of the mitochondrial respiratory chain complex; HIV infection leads to metabolic reprogramming from oxidative phosphorylation to aerobic glycolysis in $CD4^+$ T cells etc **(Thaker et al., 2019)**.

Mitochondrial, Viral Infection And Innate Immunity

Over the recent years, various studies have highlighted that viruses can influence mitochondrial function by a mechanism known as mitochondrial antiviral signaling (MAVS) **(Refolo et al., 2020).** MAVS sense RNA viruses in the cytosol through a prototypical pattern recognition receptors (PRRs) such as Retinoic acid-Inducible Gene-I (RIG-I), Melanoma Differentiation-Associated gene5 (MDA5) and once activated triggers a signaling platform and recruits TNF receptor-associated factor (TRAF) 3 and TRAF6, inducing type I IFN and inflammatory responses, respectively. The expression and function of MAVS are regulated at various levels such as transcriptional, posttranscriptional, and posttranslational levels. There are variety of mechanisms by which regulators specifically modulate MAVS expression and/or signaling, with a focus on those that regulate by (1) protein–protein interactions, (2) alterations in mitochondrial dynamics, and/or (3) post-translational modifications MAVS can modulate mitochondrial dynamics.

Classical examples which highlight modulation of MAVS by viruses include cleavage of the N-terminal fragment of MAVS by NS3/4A of HCV which prevents the production of IFN **(Li et al., 2005)**; cleavage of MAVS at Glu^{463}/Gly^{464} by Bat Hepatovirus 3ABC protease to inhibit the activation of IRF3 and NF-κB, observed as inhibition of type I interferon **(Feng et al., 2019)**; cleavage of the MAVS by Seneca Valley virus 3C protease which prevents the production of IFN **(Liu et al., 2022)**; degradation of MAVS through the proteasome pathway by HBV HBx protein, NDV V protein & Rotavirus VP3 protein which leads to low production of IFN **(Kong et al., 2019); Li et al., 2021)**. There are other ways also by which viruses can inhibit the RLR signaling pathway like blocking binding of RIG-1 or MDA5 to MAVS by Zika virus NS3 and DENV NS4A **(Riedl et al., 2019**); and induction of microRNAs (miR-576-3p by Stomatitis Virus (VSV) and miR-3570 by Rhabdovirus) that modulate MAVS expression to reduce type I expression interferon (**Yarbrough et al., 2014**).

Similarities Between Biomarkers Of Long Covid And Other Mitochondrial Disorders

Mitochondrial disorders refer to a heterogeneous group of disorders manifested as defective production of adenosine-triphosphate (ATP) due to abnormal oxidative phosphorylation (oxphos) (**Gorman et al., 2020)**. There are two types of mitochondrial disorders namely primary mitochondrial disease (PMD) and secondary mitochondrial dysfunction (SMD). The former occurs as a result of germline mutations in mitochondrial DNA (mtDNA) and/or nuclear DNA (nDNA) genes encoding ETC proteins while as latter involves inherited diseases with germline mutations in non-oxphos genes and adverse environmental effects which can cause oxidative stress (**Niyazov et al., 2016**).

According to a multilevel study a number of dry and wet biomarkers have been proposed for diagnosing mitochondrial disorders (**Finsterer & Zarrouk-Mahjoub, 2018**). Of these, dry markers included the history and clinical neurological exam and structural and functional imaging studies of the brain, muscle, or myocardium by ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), MR-spectroscopy (MRS), positron emission tomography (PET), or functional MRI and the organs most frequently affected were the muscle (97%), the central nervous system (CNS) (72%), endocrine glands (69%), the heart (58%), intestines (55%), and the peripheral nerves (50%), together referred as mitochondrial multiorgan disorder syndrome. On the other hand, a significant change in wet markers like lactate, creatine-kinase, pyruvate, organic acids, amino acids, carnitines, oxidative stress markers, retinol-binding protein (RBP),

albumin and circulating cytokines (FGF-21 and GDF-15) allowed the delineation of patients with specific or non-specific mitochondrial disorders from healthy controls. In addition, this study also highlighted the aerobic capacity of mitochondria during exercise tests and showed that oxygen consumption ($peakVO_2$) is decreased, that peak power (Wmax) is decreased, peak arterio-venous oxygen difference is decreased and lactate increases significantly during exercise in mitochondrial disorders.

Interestingly, the people with LONG COVID manifest one or more symptoms that overlaps with symptoms associated with mitochondrial disorders. A report got published in American Journal of Respiratory Critical Care Medicine wherein **Dr. Petrache (2022)** and his team investigated 50 patients with Long COVID and reported low fatty acid oxidation and higher blood levels of lactate in these subjects. Similarly, a study published in Chest reported defect in oxygen exchange in the muscles of patients with Long COVID **(Singh et al., 2022)**. Both of these preliminarily findings indicate defect in mitochondria. Profound chronic fatigue has also been found to a be a common symptom in almost 50% of people who recovered from SARCoV2 infection **(Raveendran et al., 2021)**. Such fatigues are commonly observed in other viral diseases where the condition is usually called post-viral fatigue syndrome and studies have shown that the disruption of the mitochondria metabolic pathway as one of the possible causes of the syndrome (**Behan & Behan, 1988**). Interestingly, a study showed that SARCoV2 infection can lead to decrease in the expression of nuclear-encoded genes related to the mitochondrial Complex I **(Miller et al., 2021)**, which further reinforces the fact that mitochondria dysfunction may be involved in people with LONG COVID.

Likewise, altered lactate levels have also been noticed in COVID patients which clearly indicates involvement of mitochondrial dysfunction in these patients **(Boer et al., 2022)**. A systemic literature review by **Giovanni Carpene et al. (2021)** showed that overall COVID-19 patients tend to display substantially elevated lactate values and worst outcome. **Esther et al. (2022)** reported significant impairment in fat β-oxidation and increased blood lactate accumulation during exercise in patients with LONG COVID. Similarly, previous studies such as prospective international observation study published in Annals of intensive care found that lactate and its kinetics are valuable tools for outcome prediction in critically ill old patients with COVID-19 **(Bruno et al., 2021)**. In a paper published in American Journal of Emergency Medicine, **Brandon et al. (2020)** showed that elevated LDH levels were associated with a ~6-fold increase in odds of developing severe disease and a ~16-fold increase in odds of mortality in patients with COVID-19.

A large body of evidence supports the importance of creatine kinase (CK) in mitochondrial disorders with large and fluctuating energy demands and protection of mitochondria form the so-called permeability transition leading to apoptosis or necrosis (**Stadhouders et al., 1994; Okamoto et al., 2011)**. Mammalian cells express two types of CK isoenzymes, a cytosolic and a mostly Mitochondrial CK which together maintain the cellular energetics. In situations, like mitochondrial dysfunction and over-production of reactive oxygen and nitrogen species, these CK isoenzymes are extremely affected by inactivation or may overexpress to compensate for a low energy state. Of note, a number of studies have shown that patients who deceased from COVID-19 revealed that hyperCKemia (increased levels of creatine kinase, CK) was more frequently found as one of the biochemical parameter associated with increased mortality, worst prognosis and severity in patients with COVID-19 **(Orsucci, 2021; Rosa et al., 2021; Soto-Fajardo et al., 2022; Akbar et al., 2021)**. A recent study also showed that Long COVID-19 patients displayed marked increase in creatine kinase (CK), lactate dehydrogenase (LDH), cholesterol C.reactive protein (CRP), cortisol and ferritin, which alter ATP production and cause increased muscle fatigue and low endurance (**Proal & VanElzakker, 2021)**. Moreover, multiple factors like gender and diabetes mellitus has been found to contribute towards poor prognosis of COVID-19 patients as reported in a study which showed that serum creatine kinase was significantly elevated in male's patients with diabetes mellitus **(Hussain et al., 2020)**.

Pyruvate, an end product of glycolysis in the cytoplasm under normal physiological circumstances is located at a metabolic branch point between glycolysis and mitochondrial oxidation (**McCommis & Finck, 2015)**. Pyruvate maintains cellular energy needs by two ways: metabolism of pyruvate to lactate to produce ATP in the cytoplasm and incorporation into TCA cycle in the mitochondria to yield ATP. The lactate-to-pyruvate ratio often reflects the redox state of the cell and many studies show that this ratio can indicate mitochondrial dysfunction in wide spectrum of diseases. Given that mitochondrial myopathies are generally manifested as increases in the plasma lactate and in the lactate-to-pyruvate ratio, there is likelihood that it might have some role in progression or last longing effects in COVID-19 also **(Niyazov et al., 2016)**. Though the reports of pyruvate in context to COVID-19 are scanty; however, the available data suggests that it does play some role in predicting the outcome of COVID-19 patients. A pilot study published recently in Journal of personalized medicine showed that majority of COVID-19 patients (82.5%) admitted in ICU had normal lactate levels and a normal LP ratio while as a small, yet significant, percentage of critically ill COVID-19 patients had elevated lactate levels or high LP ratios with poor outcome (**Vassiliou et al., 2022)**. **Shuba Krishnan et al. (2021)** in its paper published in Molecular and cellular proteomics observed the effect of SARS-CoV-2 infection on metabolic dysregulation in COVID-19 patients and reported significant increase in metabolites, such as pyruvate, lactate, and α-ketoglutarate (more pronounced in mild patients) in COVID-19 patients.

Alteration in several amino acids (alanine, proline, citrulline, glycine and thronine and organic acids (malate and fumarate) in body fluids are often observed in patients with possible mitochondrial disorders **(Clarke et al., 2013)**. Serum metabolomic profiling of COVID-19 patients with severe illness by **Laura Ansone et al. (2021)** highlighted several functional metabolic markers such as tryptophan, arginine, phenylalanine and tyrosine in shaping disease progression and severe clinical outcome. Similarly, a study published in Amino Acids demonstrated that 20 amino acids showed significant differences in patients with asymptomatic, mild, moderate, and severe/critical SARS-CoV-2 infection. In yet another study, metabolomics analysis revealed dysregulation of pathways linked to energy production (Krebs cycle, Warburg effect) and amino acid catabolism [BCAA (branched chain amino acids)], threonine, glutamine and glutamate) in COVID-19 patients with altered oxygen levels (**Paez-Franco et al., 2021)**. **Chris et al. (2021)** reported low arginine-to-ornithine ratio in patients with COVID-19 or multisystem inflammatory syndrome in children (MIS-C). **Michele and Vassilios (2021)** reported consistent decrease of aspartate and perturbations in the alanine-aspartate-glutamate pathway in COVID-19 patients under hypoxic conditions. In a murine model of SARS-CoV-2–induced systemic toxicity **Shen Li et al. (2021)** observed that the TCA cycle metabolites citrate, fumarate, malate, and aconitate were significantly lower in the hACE2/SARS-CoV-2 group compared with the control group. **Li Bo-Wen et al. (2021)** uncovered over 100 metabolites on an LC-MS platform that were associated with COVID-19. Among them included enzymes in TCA cycle like ACO2, IDH, OGDH, DLD, SDH, and MDH which were significantly downregulated and associated with disease outcome. Besides these there are several other findings which further support the link between SARCoV2 infection and changes in mitochondrial metabolomics. However, such broad study is beyond the scope of our current review.

Dysregulated fatty acid oxidation (FAO) is yet another feature well documented in various mitochondrial disorders **(Jang et al., 2020)**. The gold standard for diagnosing this defect is done by measuring characteristic fatty acids, as well as their carnitine and glycine derivatives. In metabolic handbook for the COVID-19 pandemic written by **Ayres (2020)**, it has been clearly highlighted that long-chain fatty acids β-oxidation is impaired in mitochondria upon SARCoV-2 infection as evidenced by accumulation of long-chain acylcarnitines. Furthermore, proteomic analysis of autopsy samples from COVID-19 patients revealed activation of FAO in most organs, implying reprogramming to a more efficient energy production mode **(Nie et al., 2021)**. **Tiffany Thomas et al. (2020)** demonstrated increased circulating levels of glucose and free fatty acids as correlates of COVID-19.

Mitochondrial Oxidative Stress In Mitochondrial Disorders And Covid

Oxidative stress refers to a condition marked by increase in reactive oxygen species (ROS) and decrease in antioxidant defense system which includes superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase together with a number of low molecular weight antioxidants such as α-tocopherol and ubiquinol **(Pizzino et al.,**

2017). In healthy cells, there exists a delicate balance between generation of free radicals and chelation by antioxidant defense system. Under normal physiological conditions, most of cellular ROS is generated by mitochondria through a mechanism known as oxidative phosphorylation **(Zorov et al., 2014)**. In instances, where generation of free radicals exceeds the body's antioxidant capacity, the persistent oxidative stress can damage mitochondria and disrupt its function by mechanism such as causing mutations in the mitochondrial genome which can result in decreased expression of critical proteins important for electron transport, promoting mitochondrial permeability transition, disturbed Ca^{2+} homeostasis etc **(Guo et al., 2013)**. This impaired function of mitochondria can predispose an individual to wide range of pathological conditions as demonstrated by various studies in mitochondrial disorders.

Parallel changes in mitochondrial biogenesis / dynamics are the two vital processes that maintain the physiological balance essential for cell growth and cell death. Excess ROS accumulation within cells can alter these processes as evidenced by some studies which include mito-fission promoted in presence of hydrogen peroxide, hypoxia and prolonged exposure to saturated free fatty acids; opposite effect on mito-fusion leading to fragmented mitochondrial morphology; activation of mitophagy to remove defective mitochondria; induction of mitochondrial hyper-fusion by GSSG in an Mfn1- and Mfn2-dependent manner; promoting biogenesis mainly by upregulating PGC-1α activity and post-translational modification of Drp1, OPA1 and Mfns to promote mitochondrial fragmentation (**Scott &Youle, 2010; Jezek et al., 2018; Meyer et al., 2017**).

An exacerbated inflammatory response as demonstrated by abnormal levels of the pro-inflammatory cytokines and chemokines namely IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, M-CSF, G-CSF, GM-CSF, IP-10, IFN-γ, MCP-1, MIP 1-α, hepatocyte growth factor (HGF), TNF-α, and vascular endothelial growth factor (VEGF) have been implicated to be a major pathological event in COVID-19 patients with poor disease outcome (**Afroja & Sacchetti, 2021**). Interestingly, these cytokines have been recognized to modulate mitochondrial activity in diverse mitochondrial disorders ranging from diabetes, to immune-mediated disorders, infection, cardiovascular pathology, neurodegeneration, metabolic syndrome, and cancer, to aging (**Missiroli et al., 2020; Marchi et al., 2022**). Increasing evidence supports the notion that aberrant generation and accumulation of ROS may form a positive feedback loop which eventually exacerbates production of inflammatory markers in COVID-19 patients **(Ye et al., 2020)**. In this context, a study was published by **Silvia et al. (2021)** in Frontiers of Immunology in which they demonstrated persistence of altered inflammasome and stress responses in patient recovery from COVID-19 and suggested oxidative stress/NLRP3 signaling pathway as a potential therapeutic target for to mitigate early COVID-19 hyper-inflammation and also its long-term outcomes. A strong relationship between oxidative stress and COVID is also quite evident from other studies which showed perpetuation of the cytokine storm, cellular hypoxia, coagulopathy, red blood cell dysfunction and the secretion of inflammatory cytokines in COVID-19 patients **(Bhaskar et al., 2020; Darif et al., 2021)**.

Respiratory viral diseases are often accompanied with overproduction of ROS and disturbance of antioxidant defences **(Khomich et al., 2018)**. This is further supported by the experimental and clinical findings that demonstrate protective effects of antioxidants such as vitamin E, vitamin C, and *N*-acetyl-cysteine (NAC) towards respiratory viral diseases **(Peterhans, 1997)**. The fact that SARCoV2 infected patients share lot of clinical symptoms to those of Respiratory viral diseases suggests that altered antioxidant defence system might be one of the mechanism that might predispose COVID-19 patients to Long COVID. Indeed, enough evidence suggest that overproduction of ROS and a deprivation of antioxidant system play a significant role in the SARS-CoV-2 infections in humans as well as in the progression and severity of the related diseases **(Flora et al., 2021; Wu, 2020; Colunga et al., 2020; Loffredo & Violi, 2020**). Furthermore, various antioxidants have also been proposed as anti-SARS-CoV-2 agents and one of the most promising drugs is NAC which is under clinical trials **(Flora et al., 2021)**.

Ace-2 Receptor In Connection To Mitochondria

Today it is well established that SARCoV-2 enters the host cell through ACE2 receptor, 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) **(Shang et al., 2020)**. The plausible association of ACE-2 with mitochondrial function was shown in a study wherein ACE-2 knockout mice exhibited impaired mitochondrial respiration and ATP production, which are compensated by overexpressing ACE-2 **(Ting-Ting et al., 2018)**. Moreover, **Behnaz Bakhshandeh et al. (2021)** showed that genetic variations in ACE2 receptor can alter mitochondrial function and make the host especially susceptible to SARS-CoV-2 infection. Another possibility of ACE-2 association with mitochondria is evident from the study wherein TMPRSS2 has been found to be responsible for SARCoV2 invasion **(Hoffmann et al., 2020)**. TMPRSS2 via ERRα together with its coactivator PGC-1α, transcriptionally regulates mitochondrial (ROS) production, energy homeostasis and mitochondrial biogenesis. A study was published in Redox Biology in which authors discovered that ACE2 concentration was much higher in brain mitochondrial and that the MrgE receptor is a major target for the ACE2-related peptides Ang1-7 and alamandine, which induce mitochondrial NO production, suggesting important role of this enzyme in mitochondrial dysfunction (**Valenzuela et al., 2021**). It is important to highlight that about 36 % of COVID-19 patients show neurological abnormalities and a lesion of the brainstem neurons has been proposed to be a major cause in the respiratory failure of this COVID-19 patients **(Tan et al., 2021)**. Similarly, co-expression and protein interaction network analysis of angiotensin converting enzyme (ACE2), TMPRSS2, and host susceptibility genes implicated in COVID-19 was performed by **Jian Yuan et al. (2020)** which revealed that genes within the ACE2 cluster were mainly related to mitochondrion functions, such as the mitochondrial inner membrane and mitochondrial electron transport, further suggesting association between mitochondria and COVID-19 susceptibility.

Paradoxically, ACE-2 is protective in nature as evidenced in studies related to cardiovascular system; however, its expression can have profound effect on mitochondrial stability **(Patel et al., 2016)**. A study published in Nature Medicine showed that SARS-CoV-1 S protein decreased the level of ACE2 in the infected lungs and its direct impact on mitochondrial function was endorsed by a study which showed that compared to wild type receptor overexpression of mutant ACE-2 receptor enhanced mitochondrial fragmentation, had reduced basal mitochondrial respiration, ATP production, indicating altered mitochondrial dynamic **(Kuba et al., 2005)**. In addition there are other emerging studies which indicate association of ACE-2 receptor and alteration in mitochondrial dynamics **(Yuan et al., 2020; Patel et al., 2016; Escobales et al., 2019)**.

Interaction Of Sarcov2 Proteins With Host Mitochondria

A genomic structural insight into novel SARS-CoV-2 reveals that it resembles very close to SARS-CoV (~80% sequence identity with that of SARS-CoV) which was responsible for the 2003 outbreak in China **(Abdelrahman et al., 2020)**. Interestingly, one of the hallmark of pathogenesis of diseases caused by SARCoV is mitochondrial dysfunction e.g., in SARS-CoV, it has been found that ORF-9b induces the degradation of MAVS and some of its downstream effectors (TRAF-3 and -6) **(Shi et al., 2014)**, while ORF 3b inhibits the expression of type 1 IFNs (**Choi & Shin, 2021**). Interestingly, many newfound studies also suggest the potential role of SARCoV2 proteins in modulation mitochondrial function through various mechanisms. Among these, ORF-9b of SARS-CoV-2 promotes the degradation of Dynamin-1-like protein (DNML1) essential for removal dysfunctional mitochondria and degradation of MAVS and TNF Receptor Associated Factor (TRAF) 3 and 6 for evading host's innate immunity; ORF9c & Nsp7 may interact with mitochondrial Complex I assembly proteins i.e., NDUFAF1 & 2, suggesting a possible link to OXPHOS; SARS-CoV-2's ORFs7a and 8a may promote localization of the viral genome to the mitochondria directly or indirectly with them; ORF3a may affect mitochondrial homeostasis and mitophagy by targetting a mitochondrial deubiquitinase i.e., mitochondrial ubiquitin specific peptidase 30 (USP30); Nsp8 has been reported to interact with components of mitochondrial ribosomes and so on **(Suryawanshi et al., 2021; Leemput & Han, 2021)**.

CONCLUSION

Overall, this review demonstrates a plausible explanation that the hijack / manipulation of host mitochondria by SARS-CoV-2 may be an important event that can answer the long term COVID sequelea. Henceforth, it is imperative to investigate the areas which reveal interactions between host mitochondrial and SARS-CoV-2 proteins that 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. Importantly, such studies will not only aid to get better insight of long term COVID sequelea but also facilitate the more successful treatment of any similar future viruses.

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