Molecular and Cellular Biochemistry (2023) 478:1325–1343
https://doi.org/10.1007/s11010-022-04593-z

Pathophysiological involvement of host mitochondria in SARS-CoV-2 infection that causes COVID-19: a comprehensive evidential insight

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Received: 18 April 2022 / Accepted: 13 October 2022 / Published online: 29 October 2022

Abstract

SARS-CoV-2 is a positive-strand RNA virus that infects humans through the nasopharyngeal and oral route causing COVID-19. Scientists left no stone unturned to explore a targetable key player in COVID-19 pathogenesis against which therapeutic interventions can be initiated. This article has attempted to review, coordinate and accumulate the most recent observations in support of the hypothesis predicting the altered state of mitochondria concerning mitochondrial redox homeostasis, inflammatory regulations, morphology, bioenergetics and antiviral signalling in SARS-CoV-2 infection. Mitochondria is extremely susceptible to physiological as well as pathological stimuli, including viral infections. Recent studies suggest that SARS-CoV-2 pathogeneses alter mitochondrial integrity, in turn mitochondria modulate cellular response against the infection. SARS-CoV-2 M protein inhibited mitochondrial antiviral signalling (MAVS) protein aggregation in turn hinders innate antiviral response. Viral open reading frames (ORFs) also play an instrumental role in altering mitochondrial regulation of immune response. Notably, ORF-9b and ORF-6 impair MAVS activation. In aged persons, the NLRP3 inflammasome is over-activated due to impaired mitochondrial function, increased mitochondrial reactive oxygen species (mtROS), and/or circulating free mitochondrial DNA, resulting in a hyper-response of classically activated macrophages. This article also tries to understand how mitochondrial fission–fusion dynamics is affected by the virus. This review comprehends the overall mitochondrial attribute in pathogenesis as well as prognosis in patients infected with COVID-19 taking into account pertinent in vitro, pre-clinical and clinical data encompassing subjects with a broad range of severity and morbidity. This endeavour may help in exploring novel non-canonical therapeutic strategies to COVID-19 disease and associated complications.

Keywords COVID-19 · SARS-CoV-2 · Mitochondria · Oxidative stress · Bioenergetics · Inflammatory response · Antiviral signalling

Introduction

While few of COVID-19-affected individuals displayed mild or no clinical symptoms, the majority of infected exhibited upper respiratory tract disease or even fatal pneumonic complications. Acute respiratory distress syndrome, pulmonary oedema, severe septic shock and sometimes multi-organ failure are linked with the maximum rates of mortality [1]. Host–pathogen interactions in this regard has been intricately studied for therapeutic opportunities [2]; however, in COVID-19 pathogenesis, comprehensive compilation of the vital roles of relevant intracellular signalling in an organelle-specific manner is still missing.

Mitochondria have generally been considered to be one of the most important organelles of the cell owing to its ability to produce ATP through oxidative phosphorylation, housing fatty acid oxidation; Ca2 + storage and playing important role in innate immunity, production of lipids, amino acids and carbohydrates, stress management, autophagy, apoptosis, necrosis and so on [3]. Apart from that, it also participates in the biosynthesis and development of several cofactors including heme, biotin and iron–sulphur (Fe/S) clusters [4]. However, with time,

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mitochondria have been shown to play other important roles such as induction of apoptosis upon loss of its membrane potential or inhibition of electron transport chain [5–7]. It is known to play a major role in reactive oxygen species (ROS) generation [8] which are capable of inducing plethora of downstream signalling [9], instrumental in cellular function and autophagy in the state of cellular stress [10] and many other functions [11].

The crosstalk between mitochondria and severe acute respiratory syndrome coronavirus infection has hypothesised and observed before [12]. In this scenario, with the recent rise of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and given the importance of mitochondria in cellular housekeeping and stress functions, it was not long before a connection between mitochondria and SARS infection was drawn [13]. Early SARS-CoV-2 connection with mitochondria was drawn using information from SARS-CoV-1 outbreak in 2003 which shared significant sequence similarities with SARS-CoV-2 while simultaneously maintaining uniqueness in its manner of cellular infection. Both viruses belong to the beta coronavirus genera of the Coronaviridae family and both have a 30 kb long positive-sense RNA genome. Their spike (S) protein was found to have 76.2% identity and 87.2% similarity and also showed antigenic similarity to some degree. It was observed that the SARS-CoV-1 open reading frame 9b (ORF-9b) targeted the mitochondria to suppress the host innate immune system [14] and displayed the ability to cause cellular apoptosis through the mitochondrial pathway [12]. Other accessory proteins of SARS-CoV-1 such as ORF-3a and ORF-8a were found to induce apoptosis via the mitochondrial pathway, while ORF-7a, associated with the viral replication, was discovered to be localised in the mitochondria [15]. These studies were used as clues for where to look for information on the impact of SARS-CoV-2 on mitochondrial cellular machinery. SARS-CoV-2 has the ability to modulate mitochondrial function and integrity as well as evident from the localisation of viral proteins and RNA in mitochondria to reside in host cell mitochondria which is recently termed as viral hijacking of mitochondria [16–18]. Not only in the primary infected organs like lungs or immune cells, spike protein or SARS-CoV-2 induces significant mitochondrial pathology systemically as evident from reduction in mtDNA content in infected microglia cells [19]. This study tried to comprehend the virus-mitochondrial nexus in COVID-19 disease based on experimental evidences and tried to exclude hypotheses and speculations based on the data related to previous renowned coronaviruses, namely SARS-CoV and MERS-CoV. This review summarises, in a comprehensive approach, how SARS-CoV-2 infection affects host cell mitochondria in the process of pathogenesis.

Inflammatory response and mitochondrial redox status in SARS-CoV-2 infection

Cells need to maintain precise levels of ROS and reactive nitrogen species (RNS) as per requirement as they are used for signalling, while out of control levels may create trouble for the cells in multiple ways [20–22]. One of the ways mitochondrial ROS (mtROS) impacts the cell is through heightened inflammatory response (Fig. 1). Among the mitochondria-associated inflammatory cascade, NLRP-3 signalling [23] plays a pertinent role in COVID-19 which is responsible for generating pro-inflammatory signals by activating cytokines [24, 25].

Mitochondria induces NLRP-3 -based inflammatory response

Mitochondria generates significant amount of superoxide ions as a side product of the functioning of electron transport chain (ETC) [26], and it plays roles in various functions such as apoptosis [27] in stress and viral infections [28]. Previous studies [29] found that bone marrow macrophages (BMM) stimulated with coronavirus 3a protein were found to induce IL-1Beta-mediated inflammatory response and owing to the K^+ ion channel activity of the ORF-3a, they fulfilled the requirement of ion channels in the activation of Nod-like receptor family pyrin domain containing 3 (NLRP-3) [25]. This pathologies were rescued by use of Mito-TEMPO [29], a renowned scavenger of mitochondrial ROS [30]. Recent studies suggest that this cascade of events is occurring in SARS-CoV-2 infection as well [31, 32]. How mitochondrial ROS generation may aid in the closely related SARS-CoV-2 infection using NLRP-3 signalling is depicted in Fig. 1. It is known that with increasing age, NLRP-3-based inflammasome increases [33], which may explain the exacerbation of infection by the virus in aged patients [34]. Indeed, transcriptomic and proteomic study of SARS-CoV-2-infected Vero-E6 cells by Appelberg et al. [35], found up-regulation of NLR proteins. A study [36] of cell samples from SARS-CoV-2-infected patients found low calcium levels and altered calcium homeostasis in mitochondria and endoplasmic reticulum (ER). It is possible that this might be associated with activation of NLRP-3 as ER Ca^{2+} channel activation is required for NLRP-3 activation [25] and that the closely related coronavirus protein E has been shown to work as a Ca^{2+} ion channel and activate the NLRP-3 inflammasome [37].

Mitochondrial ROS induces extended oxidative stress aggravating pro-inflammatory response

The study by Singh et al. [38] compared gene expression differences between healthy and SARS-CoV-2-infected

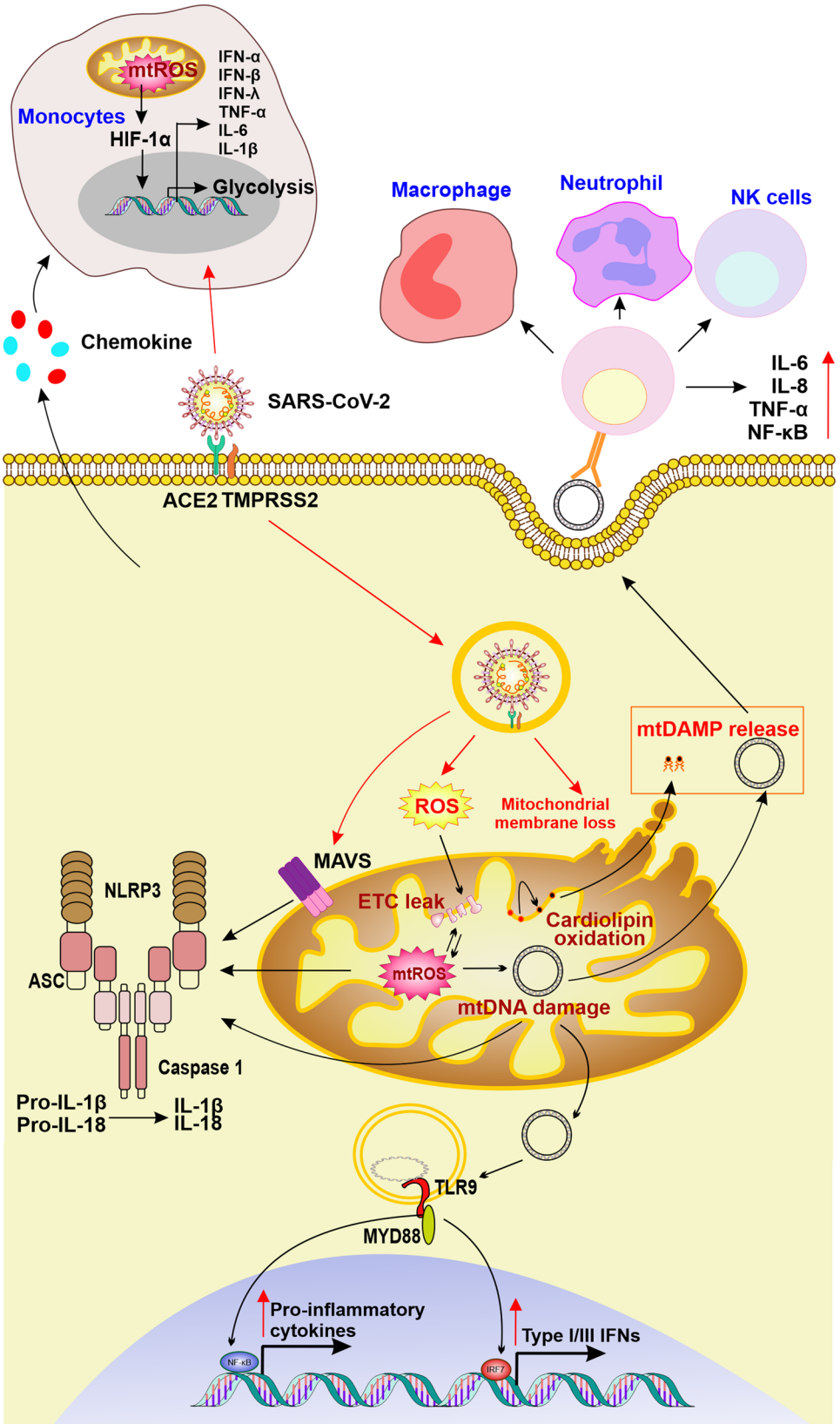

Fig. 1 SARS-CoV-2-induced mitochondrial redox imbalance fuels hyper-inflammation in Covid-19 infection. SARS-CoV-2 invasion in cells expressing ACE2 and TMPRSS2 proteins initiates the following series of downstream events that trigger NLRP-3-mediated inflammatory signalling,- (i) heightened ROS generation triggering ETC leak leading to increased mtROS formation; (ii) mitochondrial DNA (mtDNA) damage; and (iii) stimulation of mitochondrial antiviral signalling (MAVS). Moreover, mitochondria are taken over by SARS-CoV-2 to form double-membrane vesicles that destabilise mitochondrial membrane integrity. Release of mtDNA and mitochondrial cardiolipin into the cytosol through disrupted mitochondrial membrane acts as damage-associated molecular patterns (DAMPs) and in circulation they activate the deregulated hyperinflammatory state. Increased mtROS is noted in infected as well as chemokine-activated monocytes with up-regulation of pro-inflammatory genes such as TNF-α, IL-6 and IFN-Alpha, beta and gamma as well as shift towards glycolytic metabolism with compromised mitochondria generating mtROS and Hypoxia inducible factor-1alpha. In SARS-CoV-2-infected cells mtROS-associated mitochondrial dysfunction and mtDNA leak leads to activation of TLR9 and NF-kB, and release of inflammatory cytokines

lung cells and found down-regulation of genes related to oxygen sensing. As Castro et al. [36], showed disrupted membrane and ETC complexes, it hints towards greater ROS production as loss of membrane potential leads to ROS generation [39]. This was backed by Wang et al. [40], who showed higher mitochondrial ROS in SARS-CoV-2-infected human pulmonary alveolar epithelial cells (HPAEpiC) cells compared to mock-infected cells of the same kind. However, extracellular increase of ROS was very mild compared to mitochondrial ROS increase. Further proteomics analysis showed that IL1-α was up-regulated in these cells which was annotated as a response to ROS. Further study by Codo et al. [41] found enrichment of oxidative stress-associated genes in bronchoalveolar lavage (BAL) in severely infected patients and showed increased mtROS generation in SARS-CoV-2-infected monocytes from patients using MitoSOX study. This prompted them to administer antioxidants such as mitoquinol (MitoQ) or the reductant N-acetyl cysteine (NAC) to the cells which were able to inhibit viral replication and prevent up-regulation of pro-inflammatory genes such as TNF-α, IL-6 and IFN-Alpha, beta and gamma. Studies suggest that SARS-CoV-2 could infiltrate peripheral monocytes straightaway or can activate them by circulating chemokines. These, in turn, becomes one of the primal sources of pro-inflammatory cytokines and chemokines accompanying poor prognosis [42] (Fig. 1).

Studies reported that mitochondrial DNA (mtDNA), if released into cytosol, acted as damage-associated molecular patterns (DAMPs) leading to the "cytokine storm" and deregulated hyperinflammatory responses and is an early biomarker of severe illness and mortality from COVID-19 [43]. Higher production of anti-cardiolipin antibodies in COVID-19 patients [44] also pointed towards similar DAMP activity of mitochondrial membrane cardiolipin. SARS-CoV-2-infected human endothelial cell, HUVECs, expressing angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) proteins, have been shown to increase mtROS-associated mitochondrial dysfunction and mtDNA leak, leading to activation of Toll-like receptor 9 (TLR9) and NF-κB, and release of inflammatory cytokines. These events lead to endothelial cell dysfunction, possibly aggravating severity of COVID-19 [45]. Moreover, recent findings indicate that mitochondria are taken over by SARS-CoV-2 to form double-membrane vesicles. These mitochondrion-hijacking vesicles destabilise mitochondrial membrane integrity. This leads to release of mtDNA into circulation that activates immune response, which may culminate into a severe pro-inflammatory state [46] (Fig. 1).

Mitochondrial morphology and structural alteration in SARS-CoV-2 infection

Mitochondria are dynamic in nature and show the ability to divide and fuse as per the requirements of the cell. They have been shown to undertake fission at around 1.26 ± 1.01 fission events per mm mitochondrion/minute [47]. Studies presented the importance of mitochondrial fission–fusion dynamics by discussing how mitochondrial fission is required to supply newly dividing cells with mitochondria while on the other hand, knockout of fusion promoting genes; Mfn1 and Mfn2 lead to embryo death in mice [48]. Mitochondrial morphological alteration and/or destabilisation of normal physiological fission–fusion dynamics of the organelle is instrumental in many pathological states as well [49].

Alteration of mitochondrial dynamics in SARS-CoV-2 infection

Once SARS-CoV-2 infects the cell, it starts interfering with a multitude of signalling pathways which leads to modifications in levels of protein expression both in cytosol and mitochondria which causes changes in usual mitochondrial morphology (Fig. 2). The effect of SARS-CoV-2 invasion is somewhat ambiguous and includes both fusogenic and fissogenic responses. Early experiments running WGCNA (Weighted gene co-expression network analysis) and GeneMANIA analysis of SARS-CoV-2-infected ACE2 expressing A549 cell lines revealed down-regulation of genes related to mitochondrial ribosome synthesis, mitochondrial complex I synthesis, translocases and mitochondrial fission-promoting proteins MTFP1 and SOCS6 [38]. Outside mitochondria, mTORC1 complex expression was also observed to be down-regulated which was seen as the primary cause behind reduced expression of mitochondrial fission process 1 (MTFP1) and Complex I since it acts as their inducer [50, 51]. It was found that reduced MTFP1 and suppressor of cytokine signalling 6 (SOCS6) expression may lead to hyper-fused mitochondria. Coronavirus ORF-9b was found to be localised in mitochondria of artificially infected A549 cells and exhibited elongated mitochondria compared to control [52]. However, this phenomenon was observed due to ORF-9b-mediated proteasomal degradation of DRP1 the principal protein responsible for executing mitochondrial fission, by up to 70%. They also observed that lowered DRP1 levels lead to somewhat impaired MAVS-induced IFN-β response and suggested that ORF-9b ubiquitinated DRP1 to reduce the protein. This, however, goes against the general trend that mitochondrial fusion enhances MAVS-mediated signalling

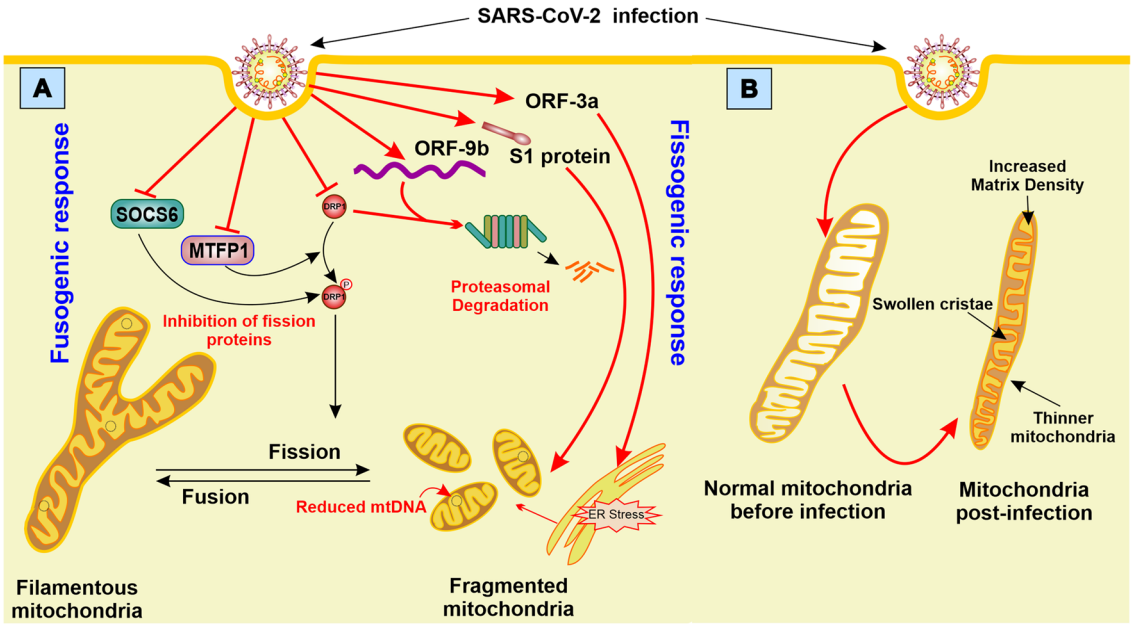

Fig. 2 Modification of mitochondrial structure and dynamics in SARS-CoV-2 infection. **A** SARS-CoV-2-infected cells revealed down-regulation of mitochondrial fission-promoting proteins MTFP1 and SOCS6 [38] leading to hyper-fused mitochondria. ORF-9b mediates proteasomal degradation of important fission protein DRP1. mtDNA copy number decreases with increasing severity in patients that in turn triggers mitochondrial fusion. In some cases in contrast, mitochondrial fragmentation is evident in HULEC-5a cells and in pulmonary arterial endothelial cells (PAEC) upon treatment with S1 protein. Based on the duration of stress mitochondria stays is in a fused or fragmented state. Fissogenic response along with ER stress initially causes mitochondrial fragmentation, followed by fusion and then fragmentation again if the stress persists for longer periods. **B** Mitochondria of the infected cells are found to be significantly thinner with swollen cristae and condensed matrix

and subsequent IFN activation [52]. It has also been shown that hyper-fusion up-regulates NF-κB activation [53]. Recent study by Krishnan et al. [54] observed gradually decreasing mtDNA copy numbers with increasing severity in patients which hinted towards mitochondrial fusion as a compensatory response. This was backed by a dry laboratory study [55] that checked for mitochondrial transcriptomic response to the infection, found that mtDNA gene expression levels to be mostly constant or somewhat down-regulated. Nuclear-encoded mitochondrial genes such as mitochondrial ribosomal and ETC-related genes also appeared to be down-regulated. However, contrarian evidence was provided by Wang et al. [44], who observed mitochondrial fragmentation using transmission electron microscopy in SARS-CoV-2-infected HPAEpiC and HULEC-5a cells. Similarly, confocal imagery by Lei et al. [56] yielded images of fragmented mitochondria in pulmonary arterial endothelial cells (PAEC) upon treatment with S1 protein. The viral-load and active multiplication creates a stressful environment interfering with a plethora of signalling, functions and metabolism of the cell. It was observed that SARS-CoV-2 ORF3a overrides autophagy impairing ER homeostasis to induce ER stress [57]. It could be relevant to note that the duration of stress in cell plays a role in whether the mitochondria is in a fused or fragmented as Lebeau et al. [58] found that ER stress initially caused mitochondrial fragmentation, followed by fusion and then fragmentation again after the stress persisted for 24 h (Fig. 2A).

Alteration of mitochondrial membrane in SARS-CoV-2 infection

The mitochondrial membrane integrity post SARS-CoV-2 infection was found to be hampered. Serological study in SARS-CoV-2 patients with cardiomyopathy and thrombocytopenia found anti-cardiolipin IgA antibodies, suggesting mitochondrial impairment post SARS-CoV-2 infection [36]. It is known that cardiolipin helps attach ETC proteins to the mitochondrial membrane [59]. Not surprisingly, the study by Soria-Castro et al. [36] also found ETC Complex II and IV in the cytosol and outside mitochondrial outer matrix, thus hinting at lack of mitochondrial structural integrity and ETC disruption. Ehrlich et al. [60] also showed loss of mitochondrial membrane potential in their primary lung cells expressing individual viral proteins with ORF-3a causing a 45% decrease in the organelle's membrane potential. A study [61] aimed at understanding impact of SARS-CoV-2 on pregnant women, found differential expression of genes related to mitochondrial membrane permeability and ETC

in ACE-2 (+) and TMPRSS-2 (+) syncytiotrophoblasts compared to its ACE-2 (−), TMPRSS (-) counterparts. It is important to remember that ACE-2 (+) and TMPRSS (+) cells are more susceptible to SARS-CoV-2 infection and thus warrants further study of the interplay of the mitochondrial membrane regulating genes pre and post infection.

Alteration of mitochondrial intra-structure in SARS-CoV-2 infection

Study by Cortese et al. [62] found greater intracristal space and matrix density in infected Calu-3 cells observed under FIB scanning electron microscope compared to control. They also found the mitochondria of the infected cells to be significantly thinner (Fig. 2B). Their study revealed that the mitochondria were displaced from their usual locations and were found to be accumulated in the surrounding of viral dsRNA containing double-membrane vesicles (DMV) which are formed in infected cells. This was supported by Nardacci et al. [63] conducting study on status of lipids, who found that under electron microscope, SARS-CoV-2-infected Vero cells showed mitochondria with swollen cristae and unusual morphology. They also found the mitochondria to be in close contact with lipid droplets which were formed after the cells were infected with the virus. Such contact sites were also seen in electron microscopic analysis of lung tissue cells of the virus-infected patients. It is relevant to note that such DMV regions are also known as viral replication organelles as they are used for + ssRNA viral replication in host cells [64]. Soria-Castro et al. [36] too observed loss of mitochondrial matrix and disruption of outer mitochondrial membrane in cardinal cell samples from infected patients. In their unpublished work under review, RNA-seq analysis of infected human bronchial cells by Ehrlich et al. [60] showed enrichment of lipid metabolism genes. It is, thus, possible that such contact sites may have been created to fuel the energy requirements of the cell under stress as lipid droplets have been known to interact with mitochondria during cell starvation for oxidation of lipids with greater efficiency [65].

Alteration of mitochondrial Ca^{2+} signalling and intra-organellar crosstalk in SARS-CoV-2 infection

An interaction study [66] found that there were 18 interactions between SARS-CoV-2's ORF3a, M protein and mitochondria-associated membrane (MAM), the region of ER responsible for vesicle transportation to mitochondria. The MAM acts as a connective tissue between the ER and mitochondria and plays an important role Ca^{2+} cycling between the two organelles [67]. The study by Lee et al. [66], via Contact-ID, a technique used to detect changes in organelles by checking for biotinylation, found that ORF3a expressing HEK293 cells displayed more biotinylated proteins compared to control leading to the conclusion that ORF3a induced significant changes in MAM's proteome. They also showed increased MAM formation after expression of ORF3 and hypothesised that the increased MAM allows for transport of the cytosolic calcium to mitochondria released from the ER as ORF3a has been shown to be a calcium ion transporter [68]. Using Gene Ontology (GO) and western blotting, Davis et al. [69] found non-structural proteins nsp2 and nsp4 to be enriched in MAMs. They observed interactions of nsp2 and nsp4 with ERLIN1/2 complex and prohibitions which are functional in regulating Ca^{2+} signalling from ER to mitochondria. This allowed them to hypothesise that the non-structural proteins manipulate proteins in the MAM to increase Ca^{2+} uptake by mitochondria as ERLIN1/2 is known to degrade ER Ca^{2+} receptors used in MAM formation [70]. Furthermore, it was observed that nsp2 interacted with STOML2 which is associated with increasing ATP synthesis [71], while nsp4 interacted with LONP1 which is known for conducting mitochondrial protein chaperone activities [72]. It is relevant to note that the Hepatitis C virus, also a positive-strand RNA virus, has demonstrated the ability to cause leakage of Ca^{2+} due to ER stress which is then taken up by surrounding mitochondria [73]. The same Hepatitis C virus study discovered that when Hepatitis C ORFs expressing UHCVcon-57.3 cells were treated with a mitochondria-specific Ca^{2+} uniporter inhibitor, ruthenium red, many of the pathologic alterations in the mitochondria such as inhibition of ETC complex I, loss of mitochondrial membrane potential, ROS homeostasis loss, conditions also observed in mitochondria during SARS-CoV-2 infection, were brought back to normal.

Mitochondrial energetics, metabolism and SARS-CoV-2 infection

Mitochondria, aptly called "the powerhouse of the cell", are the location which deals with energy requirements of the cells. While glycolysis itself occurs in the cytosol, its end products heading for the TCA cycle move to the mitochondria wherein the NADH produced are utilised by ETC to create ATP. Lipid oxidation occurs in mitochondria as well.

Down-regulation of mitochondrial function and associated genes

Early studies [74], in May 2020 using hierarchical clustering of proteome analysis of infected cells over time also found a cluster of genes associated with carbon metabolism were differentially expressed. RNA-Seq-mediated differential gene expression analysis revealed that, in SARS-CoV-2-infected nasopharyngeal cells, mitochondria-related genes were

predominantly down-regulated in infected cells [38]. Recent studies have confirmed that SARS-CoV-2 can take over host mitochondria to manipulate metabolic pathways in their favour [17, 75–77]. In one of such investigations, metabolic shift to glycolysis and high levels of mitokines, e.g. FGF-21 in peripheral blood mononuclear cells (PBMCs) owing to mitochondrial dysfunction and subsequent energy deficit in COVID-19 patients was noted [78] (Fig. 3). Owing to greater morbidity associated with diabetes in SARS-CoV-2-infected patients [79], the patients studied by Castro et al. [36] to

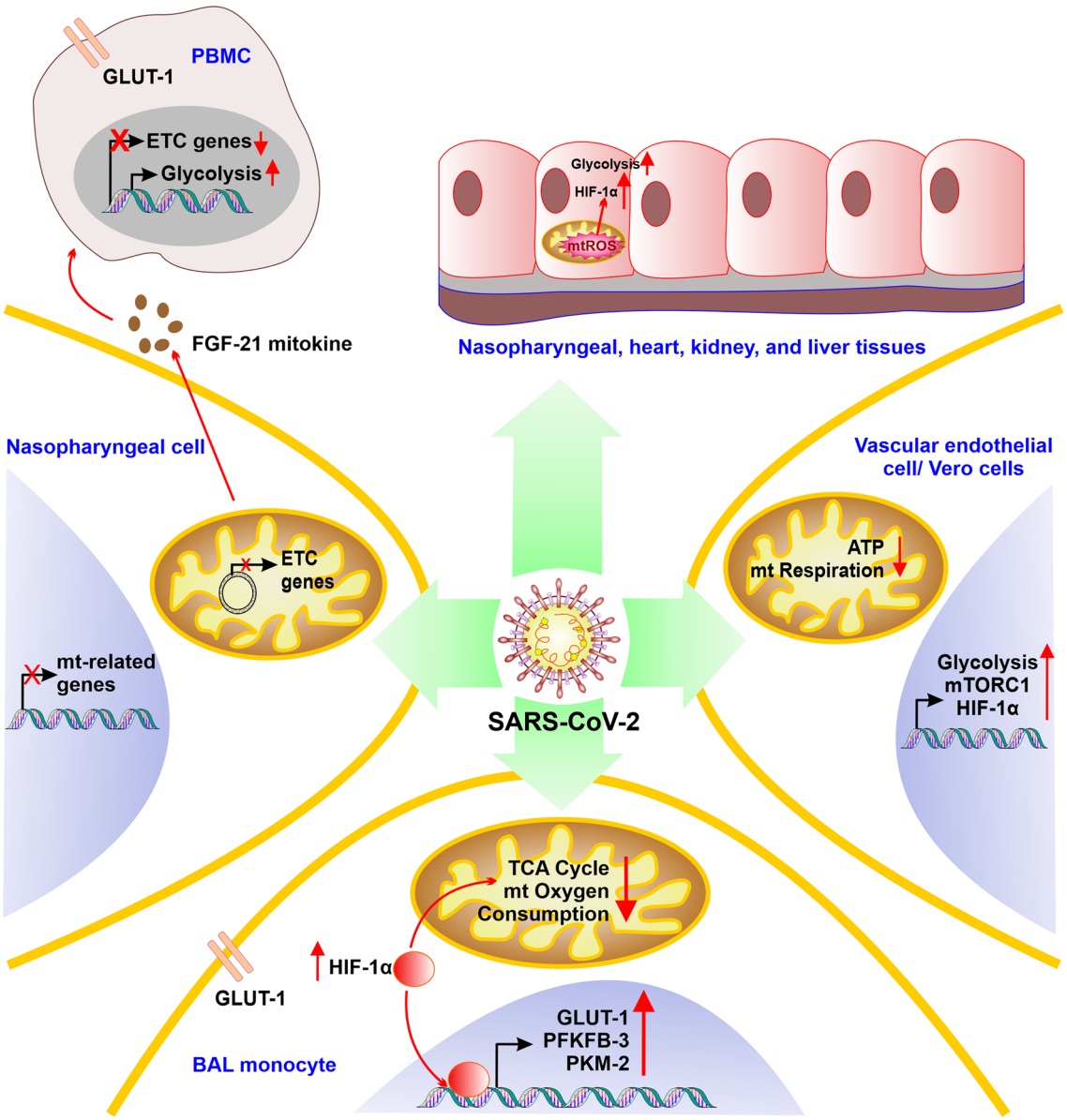

Fig. 3 Representative events suggestive of impairment of mitochondrial function and metabolism in SARS-CoV-2 infection. RNA-Sequencing analysis of SARS-CoV-2-infected nasopharyngeal cells shows that expression of mitochondria-related gene were largely down-regulated in infected cells. Metabolic alteration to glycolysis and high levels of mitokine generation, e.g. FGF-21 in PBMCs induce mitochondrial dysfunction leading to ETC suppression and higher glucose transporter GLUT-1 expression suggestive of higher glucose catabolism in COVID-19 patients. RNA-seq data also found enrichment of glucose metabolism genes. Intracellular flux analysis showed spike proteins caused reduction basal mitochondrial respiration, ATP production along with increased glycolytic capacity in vascular endothelial cells. Targeted transcriptomics data showed impairment of mitochondrial OXPHOS and antioxidant gene expression due to heightened mtROS which alleviates HIF-1α, known to induce glycolysis, in tissue samples of nasopharyngeal, heart, kidney and liver. Bronchoalveolar lavage (BAL) monocytes from infected patients had higher HIF-1alpha target genes such as GLUT-1, phosphokinase/fructose bisphosphatase (PFKFB-3) and pyruvate kinase (PKM-2) and showed greater HIF-1alpha expression, which is known to induce and repress mitochondrial oxygen consumption and probable down-regulated TCA cycle genes

understand carbon metabolism in SARS-CoV-2-infected patients showed higher lactate and plasma glucose levels which was hypothesised to have occurred due to low aerobic respiration in mitochondria on account of disrupted ETC and loss of membrane potential which is also known to cause ROS generation [39]. The study by Ehrlich et al. [60] using RNA-seq data also found enrichment of glucose metabolism genes. Using seahorse flux analysis, Lei et al. [56] showed spike proteins in vascular endothelial cells lowered basal mitochondrial respiration, ATP production, increased glucose induced glycolysis and maximised glycolytic capacity (Fig. 3). This was backed by Krishnan et al. [54] who also found up-regulated levels of glucose and lactate in mild patients along with alterations of a series of metabolites in COVID-19 patients compared to healthy cases suggestive of higher glycolysis/gluconeogenesis metabolism as well as toxic metabolic deregulation in SARS-CoV-2 infection in Calu-3 cells (Table 1). However, this change was seen only in Calu-3 cells, which are lung epithelial cells but not seen in Caco-2 and Huh-7 cells, indicating that different cell types may show different alterations in carbon metabolism upon the viral infection. Most recent targeted transcriptome analysis revealed impairment of mitochondrial OXPHOS and antioxidant gene expression in clinical samples of nasopharyngeal, heart, kidney and liver tissues, which was correlated with enhanced mtROS which stabilises HIF-1α [80], which is known to induce glycolysis [81] and repress mitochondrial oxygen consumption [82] as well. The study also confirms with the help of clinical autopsy samples that, with reducing viral load, mitochondrial integrity is rescued that repairs tissue damage. However, this rescue mechanism fails in case of overwhelming damage to mitochondria in multiple organs like heart, kidney, and liver ultimately leading to death. Table 1 summarises the series of alteration in the mitochondria-associated metabolic profile of host in SARS-CoV-2 infections.

Up-regulation of glycolysis is coupled with suppression of mitochondrial OXPHOS

To understand the effects of glycolysis on the viral replication rate, Bojkova et al. [74] infected Caco-2 cells with the virus and then treated them with 2-deoxy-D-Glucose, an inhibitor of hexokinase and found that nontoxic concentrations of 2-DG prevented SARS-CoV-2 replication in the cells. Similar studies also reported a 50-fold decrease in infectivity of the virus in Calu-3 cells when treated with 2-DG [54]. The role of glycolysis and HIF-1alpha allowed Icard et al. [86] to hypothesise that the Warburg effect might play a positive role in enhancing SARS-CoV-2 replication in infected cells by promoting PI3/ALT/mTOR pathway. Early studies by Gassen et al. [89] found down-regulated AMPK in SARS-infected VeroFM cells and indicated high levels of mTORC1 by checking levels of mTORC1 dependent phosphorylation of ULK1 in infected VeroFM cells. Transcriptomic and proteomic data obtained by Appelberg et al. [35] showed up-regulated PI3K-AKT, HIF1 and mTOR signalling pathways in virus-infected Vero-E6 cells (Fig. 3). However, they also raised concerns regarding its validity in airway cells which might be of importance as it has been observed [38] that SARS-CoV-2-infected ACE-2 expressing A549 cells, which are adenocarcinomic human alveolar basal epithelial cells, show down-regulated mTORC1 expression and hence unenhanced aerobic glycolysis. This was further backed by Miller et al. [55], who found different levels of expression of genes related to oxidation–reduction across different cell lines and concluded that the virus' impact may affect metabolism differently in different cell types. It is relevant to note that mTORC1 has been found to have an antagonistic relationship with AMPK, increase GLUT1 and GLUT4 glucose transporters along with positive regulation of glycolysis and inhibition

Table 1 Change in levels of metabolically important molecules in SARS-CoV-2-infected cells

Molecules	Alteration in levels	Probable mechanism for alteration	References
Lactate	⇧	Increased carbon metabolism	[54]
Glucose	⇧	Increased expression of glucose transporter, GLUT1	[54]
Pyruvate	⇧	Increased glucose intake and glycolysis	[54]
α-ketoglutarate	⇧	Increased glutaminolysis for SARS-CoV-2-induced anaplerotic replenishment of TCA substrate	[54]
Oxaloacetate	⇧	Increased pyruvate carboxylase (PC)	[83, 84]
ATP	⬇	Down-regulation of TCA cycle	[56]
Citrate	⬇	Incomplete TCA, shunted for FAO, Up-regulation of ATP citrate lyase (ACLY)	[83][85, 86]
Aconitate	⬇	Depression in TCA cycle, Low aconitase	[85]
Serum and mitochondrial calcium	⬇	High intracellular calcium intake by virus-induced expression of permeable calcium channel	[36, 87, 88]

of glycogenesis [90], thus hinting at it potential role in promoting anaerobic respiration during infection.

Alteration in glycolysis-OXPHOS equilibrium by key mediators in immune cells

Proteomic analysis by Codo et al. [91] also found down-regulation of proteins associated with TCA cycle. Naturally, reduced spare respiratory capacity was also seen in the virus-infected monocytes. This was further backed up by their data which showed that BAL monocytes from patients had higher HIF-1alpha-target genes such as GLUT-1, phosphokinase/fructose bisphosphatase (PFKFB-3) and pyruvate kinase (PKM-2) and showed greater HIF-1alpha expression (Fig. 3), Ehrlich et al. [60] proposed probable down-regulated TCA cycle genes from their RNA-seq data while observing an up-regulation of ATP citrate lyase (ACLY) which converts citrate to acetyl CoA indicating lipid biogenesis and adds more context to close interaction between lipid droplets and mitochondria as described earlier. Krishnan et al. [54] also found similar metabolic state of mitochondria as they found higher surface GLUT-1 expression in $CD8^+$ T-cells and monocytes of severe SARS-CoV-2-infected patients. They too found lower expression levels of TCA cycle, oxidative phosphorylation-associated protein levels in patients. However, the study by Appelberg et al. [35] saw reduced HIF-1alpha expression post infection.

The study conducted by Codo et al. [91] detected high levels of monocytes in fluid extracted from SARS-CoV-2-infected patients through bronchoalveolar lavage (BAL) and used this information to study metabolic changes in monocytes by infecting test human monocytes with the virus and blocking certain pathways. When pyruvate carrier to mitochondria was inhibited using UK-5099, viral replication was unaffected in monocytes while blocking lactate fermentation with oxamate severely affected it thus suggesting that both SARS-CoV-2 replication and anti-SARS-CoV-2 monocyte response are energetically fed by anaerobic glycolysis and not mitochondrial ATP synthesis. Further proteomic analysis of monocytes by Codo et al. [91] showed down-regulation of NDUFV (Complex 1), SDHA (Complex 2), COR1 (cytochrome c reductase), UQCRC2 (Complex 3) and ARP5PF, ATP5F1A, ATP5PD, F-type ATPase A and PPA2 (ATP Synthase). Cortese et al. [62] found decrease in ATP synthase subunit 5B (ATPB5B) using FIB scanning electron microscopy on infected Calu-3 cells. This was backed by Miller et al. [55], which showed down-regulation of Complex I genes (NDUFB11, NDUFB2, etc.) after infection across all primary cell cultures.

Mitochondrial antiviral signalling in SARS-CoV-2

MAVS or mitochondrial antiviral signalling pathway is responsible for eliciting innate immune response through mitochondria upon viral infection. The mitochondrial membrane-anchored mitochondrial antiviral signalling protein MAVS is a critical factor in cellular antiviral defence system.

MAVS and associated key proteins in eliciting inflammatory response in case of viral infection

MAVS is composed of three functional domains, a caspase activation and recruitment domain (CARD) at the N-terminus, a proline-rich domain (PRR) and a C-terminal transmembrane (TM) domain [92]. It executes its function by the help of retinoic acid inducible gene (RIG-1), Melanoma differentiation associated gene 5 (MDA-5) and Laboratory of genetics and physiology 2 (LGP2) receptors (RIG-I-like receptor or RLRs) which are able to detect viral pathogen-associated molecular patterns (PAMPs) entering the host cell. More specifically, RIG-I detects 5'-di/ tri-phosphorylated RNA sequences rich in poly-U whereas MDA-5 binds to high molecular weight viral RNA. This causes RIG-1 and MDA-5 present on the outer mitochondrial membrane to undergo conformational changes and interact with MAVS present on the mitochondria using its CARD domain. Upon receiving such activation signal, MAVS proteins oligomerise and forms "MAVS signalosome" complex. Formation of MAVS complex is mediated by interaction with translocase of the outer mitochondrial membrane proteins (TOMs) leading to activation of TANK-binding kinase (TBK1) and phosphorylation as well as activation of IRFs. IRF-3 then associates with cytosolic chaperone heat shock protein 90 (HSP90) to robustly trigger a series of downstream effectors. Triggered by MAVS complex, E3 ligases tumour necrosis factor receptor-associated factors 3 and 6 (TRAF3 and TRAF6) offer protection against virus by activating nuclear factor kappa light chain enhancer of activated B cell (NF-κB) and interferon regulatory factors (IRFs). Upon translocation to nucleus, NF-κB initiates pro-inflammatory cytokine gene expression and IRFs increase production of interferons [93] (Fig. 4). A succinct review by Koshiba [94] describes how MAVS form homo-dimers which interact with multiple molecules belonging to TRAF family, TRAF-associated NF-κB activator, receptor interacting protein 1 and so on which lead to downstream signals to the mitochondria to finally activate the NF-κB which goes on to activate Type I interferons and other pro-inflammatory signals.

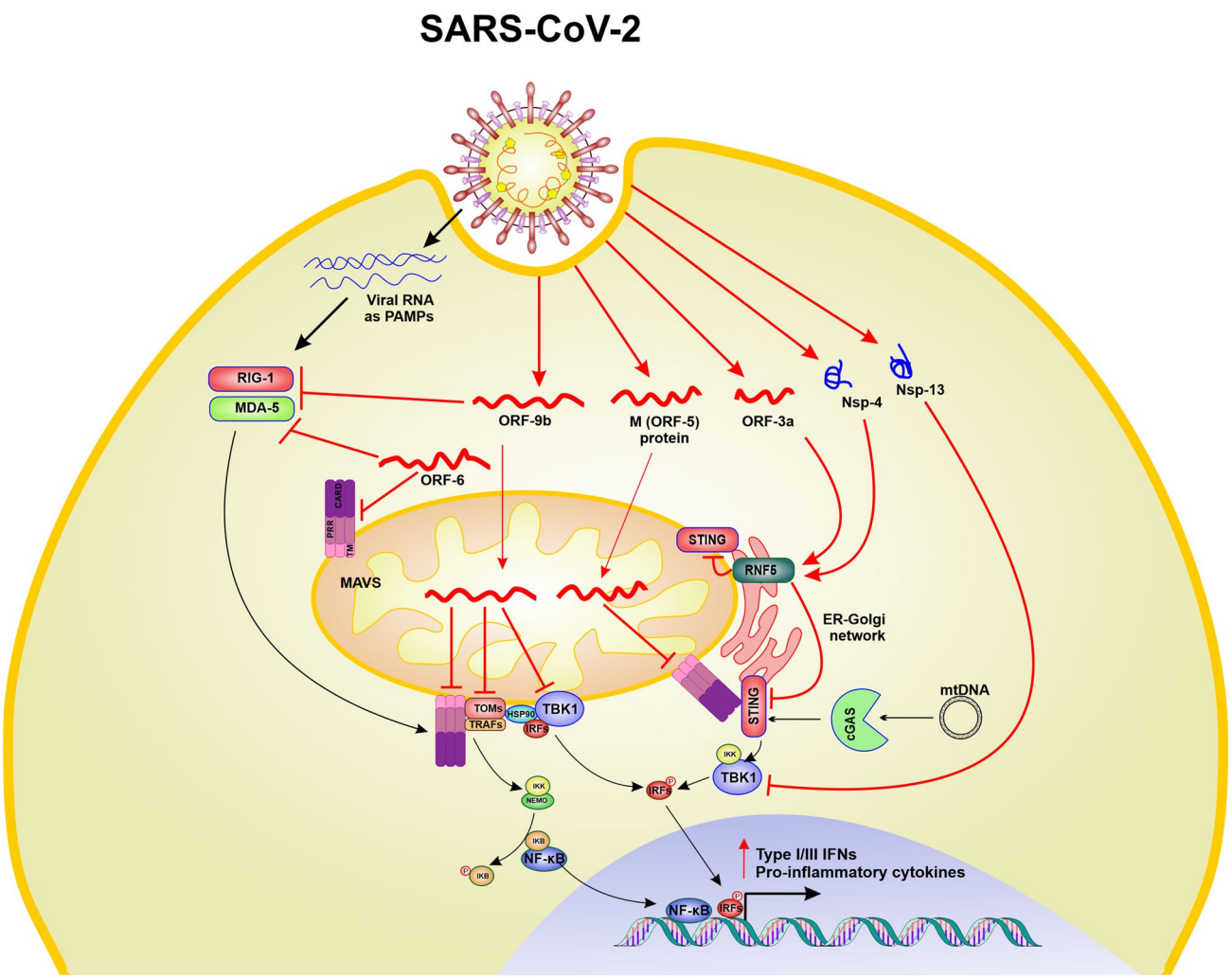

Fig. 4 Alteration of Mitochondrial Antiviral signalling in SARS-CoV-2. MAVS offer antiviral defence system with assistance of RIG-1, MDA-5 and LGP2 receptors which are able to detect PAMPs, as for example viral genome (DNA/RNA), entering the host cell. This causes RIG-1 and MDA-5 present on the outer mitochondrial membrane to undergo conformational changes and interact with MAVS present on the mitochondria using its CARD domain. This is followed by MAVS proteins oligomerisation to forms MAVS signalosome which is mediated by interaction with mitochondrial TOMs leading to activation of TANK-binding kinase (TBK1) and activation of IRFs. IRF-3 then interacts with cytosolic HSP90 to activate downstream signalling. Triggered by MAVS complex, TRAF3 and TRAF6 offer antiviral protection by activating NF-κB and IRFs. Nuclear translocation of NF-κB initiates pro-inflammatory cytokine gene expression and that of IRFs increase production of interferons. SARS-CoV-2 ORF-9b is shown to inhibit RIG-1, MDA-5, MAVS, TOM70 and TBK1 inhibiting downstream IRFs signalling eventually blocking IFN activation. M protein (ORF-5) of SARS-CoV-2 down-regulates MAVS related pathway as well restricting recruitment of TRAF3, TBK1 and IRF3 to the MAVS complex. ORF-6 of SARS-CoV-2 was able to prevent interferon induction by MDA-5, MAVS and TBK1. A non-structural protein 13 (nsp13) interact with only TBK1 impairing the downstream MAVS signal resulting in lower IFN-β levels. STING (MITA) helps activate IRF3 in MAVS upon "sensing" DAMPS like mitochondrial dsDNA in cytosol with help of cGAS. One of the sources of cytosolic mtDNA in SARS-CoV-2 infection are dysfunctional mitochondria. Cellular RNF5 protein interacts with viral ORF-3a and nsp4, to down-regulate MAVS signalling by ubiquitinating STING

SARS-CoV-2 ORF-9b acts as a key molecular stimulus in alteration of MAVS signalling to impair inflammatory response

Research conducted by Yin et al. [95] indicated that MDA-5 and MAVS knockout lung epithelial cells showed greater viral infection and lower IFN response as opposed to RIG-1 knockout cells, essentially highlighting the importance of MDA-5 over RIG-1 in triggering the MAVS pathway upon detection of viral PAMPs. Coronavirus ORF-9b was shown to localise in host mitochondria and trigger degradation of MAVS and its signalling leading to hindered type 1 IFN response from the host. It also exhibited the ability to alter mitophagy rates by reducing DRP1 levels [14]. Using previously available

information from studies with coronaviruses, Wu et al. [96] found increased IFN-β production in wild type HEK293T cells when compared to RIG-1, MDA-5 and MAVS deficient mutant cells where IFN induction was absent. By measuring IFN-β1 mRNA levels and ORF-9b protein levels in Caco-2 and HPAEpiC cells, they found barely increased IFN-β1 levels. Furthermore, they found that in the absence of ORF-9b, SARS-Cov-2 RNA induced IFN-β1 expression in HPAEpiC cells. They also reported that IFN-β expression induction by vesicular stomatitis virus (VSV) was inhibited by ORF-9b in BEAS-2B, Calu-3 and HEK293T cell lines. Their study also discovered that ORF-9b inhibited RIG-1 and MAVS expression but not IRF3. Similarly, study by Han et al. [97] found SARS-CoV-2 to hinder Type 1 and Type 3 Interferon by interfering with the MAVS pathway. They found that SARS-CoV-2 ORF-9b expressing HEK293T cells showed weaker IFN-β and IFN-L1 induction compared to control. Using luciferase reporter assay, ORF-9b was shown to inhibit RIG-1 N, MDA-5, MAVS and TBK1 luciferase reporters but not that of IRF3-5D suggesting that ORF-9b interacts with proteins upstream at IRF3 and inhibits them from doing their regular signalling duties (Fig. 4). This was further backed by confocal microscopy data and co-IP which showed ORF-9b co-localisation and immunoprecipitation with RIG-1, MDA-5, TBK1, TRIF and STING [98]. They found that ORF9b was able to impair TBK1 phosphorylation, an effector molecule whose activation is necessary for movement of the signalling cascade from mitochondria to cytosol and then to nucleus for eventual IFN activation.

Study by Jiang et al. [99] found that the ORF-9b interacted and bound strongly with TOM70. It was shown that, by binding to TOM70, it was able to reduce IFN responses. This was backed by Gao et al. [100] who found strong interactions between TOM70 and ORF-9b using X-ray crystallography and using the data, concluded that ORF-9b seemed to keep TOM70 in a rigid state (Fig. 4). It should come as no surprise that TOM70 has been shown to play an important role in activating IFN responses by interacting with TBK1 through HSP90 for taking the signal outside mitochondria [101]. It could be relevant that a study of mutant TOM70 showed lower steady state levels of Complex I, IV and V in mitochondria as it is involved in transport of ETC complex assembly-associated proteins [102]. It could be speculated that ORF-9b's interaction with TOM70 alters ETC functioning in mitochondria by not allowing it to function normally as it will be shown later how SARS-CoV-2 infection affects the ETC in mitochondria.

Other ORFs behind modulation of MAVS signalling restricting proper inflammatory response

Interestingly, it has been shown that the M (ORF-5) protein of SARS-CoV-2 participates in a similar, albeit more focused function when compared to ORF9b where it seemed to lower IFN activation by down-regulating MAVS-related pathway [97, 103]. By using luciferase assay, Fu et al. [103] showed that the M protein interacted with RIG-1-CARD, MDA-5 and MAVS, co-IP studies showed only MAVS interacted with M protein in over-expressed mammalian cell systems. Further co-IP studies showed M protein inhibited recruitment of TRAF3, TBK1 and IRF3 to the MAVS complex but did not hinder interaction of RIG-1 and MDA-5 with MAVS thus hinting its activity further downstream of the MAVS signalling pathway (Fig. 4). Yet another ORF, ORF-6 of SARS-CoV-2 was able to prevent interferon induction by MDA-5, MAVS and TBK1 as per luciferase assays conducted by Yuen et al. [104].

Lee et al. hypothesised that RNF5 interacts with ORF-3a [66], although the consequence of such interaction has not been elucidated yet. It is, however, worth noting that RNF5 is known to regulate MAVS signalling by ubiquitinating MITA, a protein that helps activate IRF3 in MAVS [105]. STING (MITA) is a transmembrane protein residing at the ER, mitochondria, and mitochondrial-associated membrane that helps activate IRF3 in MAVS upon "sensing" cytosolic dsDNA with the help of cyclic-GMP-AMP (cGAMP) synthase (cGAS) [106] (Fig. 4). Interaction between RNF5 and nsp4 has also been observed [69] (Fig. 4). It is, however, relevant to note that in ORF-3a of previously known coronaviruses have been shown to down-regulate IFN-1 activity by inducing ubiquitination of Interferon-Alpha Receptor Subunit 1 (IFNAR1) [107], as IFNAR 1 is the cognate receptor through which IFN-1 is activated [108].

SARS-CoV-2 non-structural proteins behind modulation of MAVS signalling

Another interesting interaction that has been observed by Guo et al. [109] is that of non-structural protein 13 (nsp13). It has been found to interact with only TBK1 on its scaffold binding domain (SBD) which is required for interacting with TRAFs thus inhibiting it from doing so and abruptly ending the downstream MAVS signal (Fig. 4). Naturally, over-expression of nsp13 in HEK293T cells was followed by lower IFN-β levels. Predicting hijacking of host de-ubiquitination by the virus, Guo et al. checked for interactions between host de-ubiquitinase and nsp13 and found USP13 to interact with it and observed that loss of USP13 led to greater ubiquitinated nsp13. Addition of Spautin-1, an USP13 inhibitor, to host cells was seen to lead to reduction in nsp13 levels. A study by Xia et al. [110] also observed that nsp6 and nsp13 inhibited luciferase activity in luciferase assay when IFN-β promoter was activated by MAVS and TBK1 adding another set of viral proteins that interact with and affect MAVS. They also found that nsp13 inhibited

TBK1 phosphorylation which confirmed its role blocking downstream of the MAVS pathway.

Comorbidities involving mitochondrial aetiology in COVID-19 pathogenesis

Since outbreak, previous medical histories and existing health conditions have been associated with higher complexities and increased risk of serious disease outcomes and mortality in SARS-CoV-2 infection [111]. SARS-CoV-2 infection has been shown to have adverse effects in pregnancy. A placental role in protecting the foetus from SARS-CoV-2 infection has been documented. In placentas of COVID-19 positive mothers, mtDNA, antioxidant (e.g. CAT, GSS) and mitochondrial respiratory chain protein (NDUFA9, SDHA, COX4I1) expression were decreased [112].

Recent reports suggest that severity of the respiratory syndrome is exacerbated by pre-existing conditions such as diabetes, and renal disease, cardiovascular disorders, gut problems, cancer and pulmonary disorders, along with immunodeficiency or hyper-inflammation [113]. Since outbreak, SARS-CoV-2 infection age, in this regard, has been proved to be one of the most imperative prognostic factors culminating into lethality in contrast to younger individual having healthy mitochondria that enforces a defensive attribute against COVID-19 [114]. Mitochondrial damage is associated with multifaceted age-related disorders including malfunctioning immune response which can be accountable to many of the poor prognosis and comorbidities and in COVID-19 [115]. Not only that, studies reported many environmental chemicals (ECs), malnutrition and enhanced socioeconomic stress can induce mitochondrial damage negatively affecting prognosis in COVID-19 [116]. Studies reported mtROS-associated abrupt activation of NLRP3-inflammosome, caspase-1 activity and interleukin have been observed in aged lung that lead to critical hyper-inflammatory cascade [117].

Metabolic disorders such as diabetes and obesity have always been correlated with alteration in mitochondrial integrity, which recently were also proved to be inducing susceptibility and poor outcome in SARS-CoV-2 infection [79, 118–120]. Renowned metabolic disorders in association with lifestyle diseases like cardiovascular and liver diseases, which is already known to have mitochondrial aetiology aggravate mortality significantly in COVID-19 [121, 122].

Therapeutic strategies against COVID-19 involving mitochondria

Recent studies suggest that much of the alteration in the mitochondria can be decreased by a combined therapeutic strategy. The first phase of this strategy would be to lower the viral load that is the source and origin of the chronic inflammatory condition leading to severe sepsis, multiple organ failure and mitochondrial damage. The second phase should be aimed to decrease alterations in the mitochondria which may be lowered by the use of antioxidants such as melatonin and N-acetyl-cysteine that have the capacity of restoring and protecting the mitochondrial function [123]. In addition, the use of direct-acting antivirals, in particular, the nucleoside/nucleotide analogues such as the remdesivir, can efficiently inhibit viral replication by inhibiting the viral polymerase activity. However, these drugs may exert off-target effects by inhibition of mitochondrial DNA polymerase, resulting in a reduction of mtDNA copy number [124]. Given the scope of our paper, we found multiple researchers treating cells with molecules which seemed to ease the stress on mitochondria of the infected cells and showed direct results such as reduction of viral load and suppression of a strong IFN response. Table 2 summarises the most recent mitochondria-associated therapeutic strategies against COVID-19 that shows significant potential for future clinical studies.

Table 2 Mitochondria-associated therapeutic strategies against COVID-19

Potential molecules	Mode of action	References
Melatonin	Address mitochondrial redox imbalance	[123]
Mitoquinol	Antioxidants managing mtROS	[91]
Mito-TEMPO	Scavenge mitochondrial superoxide and reduce mtROS	[29, 91, 130, 131]
Mito-MES	mitochondrial antioxidant	[130]
N-acetyl cysteine	Antioxidants used in restoration of mitochondrial function	[91]
2-DG	Glycolysis inhibition	[74, 126]
Limonoids, triterpenoids	Block nsp 13	[127]
Spautin 1	Inhibit USP 13 to deubiquitinate nsp 13	[109]
Ruthenium red	Mitochondrial calcium uniporter inhibitor to fix calcium imbalance	[129]

As previously mentioned, SARS-CoV-2-infected cells thrive predominantly on glycolysis for bioenergetic demand because of mitochondrial respiratory dysfunction. 2-DG was tested and shown to restrict viral proliferation, by inhibition of glycolysis in infected Caco-2 cells [74]. The therapeutic potential of 2-DG as an antiviral in viruses like influenza and herpes is not new and has shown beneficial effects on patients and animals suffering from respiratory syncytial virus as appropriately reviewed [125] by Kang et al.. Given its role as a hexokinase inhibitor, proven safety of usage in other diseases, and the prognostic improvement in SARS-CoV-2-infected cells in in vitro studies [126], 2-DG deserves further rigorous trials as a potential treatment for SARS-CoV-2-infected patients.

Recent studies explored the therapeutic potential of limonoids and triterpenoids in inhibiting nsp-13 [127], a viral protein playing a role in suppressing MAVS of the host. Spautin-1 was shown to inhibit USP-13, a de-ubiquitinase of the host cell hijacked by the SARS-CoV-2 which led to successful ubiquitination of nsp-13 [109]. It is a relatively new therapeutic agent first brought to notice by Liu et al. [128] for its ability to inhibit USP-13. Lack of any further studies necessitates understanding its possible effect on viral replication in cells by allowing nsp13 ubiquitination.

The possibility of mitochondrial calcium homeostasis had been previously discussed while also observing how mitochondrial calcium uniporter (MCU) inhibitor ruthenium red had successfully restored mitochondrial morphology and function back to normal in HIV C-infected cells [73]. Woods et al. [129] identified Ruthenium265, mitoxantrone and the antibiotic doxycycline among many other MCU inhibitors. Of them, Ruthenium265 is known to offer the advantage of not harming energetic activities and membrane potential of the mitochondria. However, there is serious concern regarding its toxicity in animals and therefore requires preliminary study on SARS-CoV-2-infected cell lines for greater information. A combinatorial dose of 2-DG and MCU inhibitor together could provide much needed respite for the otherwise stressed mitochondria and would allow it to move back to creating ATP through TCA cycle and ETC rather than the virus-preferred anaerobic glycolytic respiration.

Both mitochondrial antioxidants Mito-TEMPO and mitoquinol have been previously used in studies to reduce mitochondrial oxidative stress [30], but only few studies [29, 91] have been conducted to test their effect on the Coronavirus family. Given the findings that mtROS is significantly increased compared to extracellular ROS [44], a targeted approach to bringing ROS levels back to normal would be beneficial and hence further studies with mitochondrial antioxidants on infected cells are required. Recent studies exploited other mitochondrially targeted antioxidants like mitoquinone/mitoquinol mesylate (Mito-MES), which showed significant antiviral activity against SARS-CoV-2 and lower viral titre by nearly 4 log units which led to reduced hyper-inflammation in the host as well [130]. Not only might these antioxidants show positive signs as therapeutics, they might also provide greater insight into the role mtROS plays in assisting SARS-CoV-2 infection of host cells.

Conclusion and future perspective

SARS-CoV-2 was found to affect a plethora of structures and functions of mitochondria which further highlighted the need to study the virus' impact on the organelle in greater detail. Upon infection, the organelle seemed to show signs of morphological alterations in its shape, structure, its inner cristae-matrix arrangement and hampered membrane potential. The MAVS, triggered from the mitochondria was concluded to have interacted with a lot of SARS-CoV-2 proteins such as the ORF-9b, ORF-3a, nsp4 and nsp13 which mounted a multipronged attack on the MAVS and strongly suppressed and cut off its activity. The virus also managed to cause a sudden increase in mtROS generation in the organelle as a by-product of its disruption of the electron transport chain which seemed to be manageable by mitochondrial antioxidants. It severely interfered and unsettled oxidative phosphorylation and ETC to ensure shut down of aerobic respiration and promotion of glycolysis and associated anaerobic respiration. Such disruption was discovered to be part of a larger scheme of the virus to hijack the intracellular machinery to make the cell more conducive to the virus. With a suppressed MAVS and aerobic glycolysis, SARS-CoV-2 would then go on to successfully replicate and spread further in the host body and elsewhere. These findings unboxed novel non-canonical paths for therapeutic interventions which has become absolute necessity recently worldwide to combat the deadly COVID-19 disease as well as to manage the comorbidities associated with it in acute phase as well as in long-term perspectives.

Acknowledgements The authors thank Dr. Swatilekha Ghosh for reviewing the language and grammar of the manuscript.

Author contribution CB and RD conceptualized the idea; CB, SG and RD conducted literature survey and formal analysis; CB and RD wrote original draft; SG and RD prepared illustrative image; DG performed critical scrutiny for logical, grammatical, and formatting errors; RD acquired funding; RD supervised project administration.

Funding This work was supported by the Start-Up Research Grant provided by the Science & Engineering Research Board (SERB) Under Department of Science and Technology, Government of India (File No. SRG/2020/001621).

Data availability As this is a review article, relevant information collected and presented from the public domain is available to the scientific community.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval As this is a review article, therefore, no IRB, consent, or animal protocol approval was required.

Consent to participate All the authors give their consent for participation.

Consent for publication All the authors give their consent for publication.

Informed consent All authors agreed to publish.

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