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

Chandan Bhowal1 · Sayak Ghosh1 · Debapriya Ghatak2 · Rudranil De1

Received: 18 April 2022 / Accepted: 13 October 2022 / Published online: 29 October 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 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 pneumonia 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,
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 Ca²⁺ channel activation is required for NLRP-3 activation [25] and that the closely related coronavirus protein E has been shown to work as a Ca²⁺ 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-κB, and release of inflammatory cytokines.
lungs 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, become 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 fissionogenic 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 MTPF1 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 (MTPF1) and Complex I since it acts as their inducer [50, 51]. It was found that reduced MTPF1 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.
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 if the stress persisted for longer periods. B Mitochondria of the infected cells are found to be significantly thinner with swollen cristae and condensed matrix

**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 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

**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 Ca²⁺ 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 Ca²⁺ 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 Ca²⁺ signalling from ER to mitochondria. This allowed them to hypothesise that the non-structural proteins manipulate proteins in the MAM to increase Ca²⁺ uptake by mitochondria as ERLIN1/2 is known to degrade ER Ca²⁺ 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 Ca²⁺ 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 Ca²⁺ unipporter 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
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.

### 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]|
| Aconitase                  | ↓                    | 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]|

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.
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), UQCRCC2 (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 (ATP5B) 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 (NDUBF11, 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 trans-membrane (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-1 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.
SARS-CoV-2 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

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
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.

References

1. Zaim S, Chong JH, Sankaranarayanan V, Harky A (2020) COVID-19 and multiorgan response. Curr Probi Cardiol 45:100618. https://doi.org/10.1016/j.cpcardiol.2020.100618

2. Varghese PM, Tsolaki AG, Yasmin H, Shastri A, Ferluga J, Vatish M, Madan T, Kishore U (2020) Host-pathogen interaction in COVID-19: pathogenesis, potential therapeutics and vaccination strategies. Immunobiology 225:152008. https://doi.org/10.1016/j.imbio.2020.152008

3. Koch RE, Josefson CC, Hill GE (2017) Mitochondrial function, ornamentation, and Rnucincompetence. Bio Rev Camb Philos Soc 92:1419–1474. https://doi.org/10.1111/brc.12291

4. Lill R (2009) Function and biogenesis of iron-sulphur proteins. Nature 460:831–838. https://doi.org/10.1038/nature08301

5. Marchetti P, Castedo M, Susin SA, Zamzami N, Hirsch T, Macho A, Haefliger A, Hirsch F, Geuskens M, Kroemer G (1996) Mitochondrion permeability transition is a central coordinating event of apoptosis. J Exp Med 184:1155–1160. https://doi.org/10.1084/jem.184.3.1155

6. Tada-Oikawa S, Hiraku Y, Kawanishi M, Kawanishi S (2003) Mechanism for generation of hydrogen peroxide and change of mitochondrial membrane potential during rotenone-induced apoptosis. Life Sci 73:3277–3288. https://doi.org/10.1016/j.lfs.2003.06.013

7. Li N, Ragheb K, Lawler G, Sturgis J, Rajwa B, Melendez JA, Robinson JP (2003) Mitochondrial complex I inhibitor rotenone induces apoptosis through enhancing mitochondrial reactive oxygen species production. J Biol Chem 278:8516–8525. https://doi.org/10.1074/jbc.M210432200

8. Murphy MP (2009) How mitochondria produce reactive oxygen species. Biochem J 417:1–13. https://doi.org/10.1042/BJ20081386

9. Hanamana RB, Chandel NS (2010) Mitochondrial reactive oxygen species regulate cellular signaling and dictate biological outcomes. Trends Biochem Sci 35:505–513. https://doi.org/10.1016/j.tibs.2010.04.002

10. Li L, Chen Y, Gibson SB (2013) Starvation-induced autophagy is regulated by mitochondrial reactive oxygen species leading to AMPK activation. Cell Signal 25:50–65. https://doi.org/10.1016/j.cellsig.2012.09.020

11. Zorov DB, Krasnikov BF, Kuzminova AE, Vysokikh M, Zorova LD (1997) Mitochondria revisited. Altern Funct Mitochondria Biosci Rep 17:507–520. https://doi.org/10.1023/a:1027304122259

12. Zhang L, Wei L, Jiang D, Wang J, Cong X, Fei R (2007) SARS-CoV nucleocapsid protein induced apoptosis of COS-1 mediated by the mitochondrial pathway. Artif Cells Blood Substit Immobil Biotechnol 35:237–253. https://doi.org/10.1080/1073190601188422

13. Wu KE, Fazal FM, Parker KR, Zou J, Chang HY (2020) RNA-GPS predicts SARS-CoV-2 RNA residency to host mitochondria and nucleolus. Cell Syst 11(102–108):e3. https://doi.org/10.1016/j.cels.2020.06.008

14. Kumar S, Mauya VK, Prasad AK, Bhatt MLB, Saxena SK (2020) Structural, glycosylation and antigenic variation between 2019 novel coronavirus (2019-nCoV) and SARS coronavirus (SARS-CoV). Virusdisease 31:13–21. https://doi.org/10.1007/s13337-020-00571-5

15. McBride R, Fielding BC (2012) The role of severe acute respiratory syndrome (SARS)-coronavirus accessory proteins in virus pathogenesis. Viruses 4:2902–2923. https://doi.org/10.3390/v4112902

16. Gatti P, Ilamathi HS, Todkar K, Germain M (2020) Mitochondria targeted viral replication and survival strategies-prospective on SARS-CoV-2. Front Immunol 11:578599. https://doi.org/10.3389/fimmu.2020.578599

17. Shang C, Liu Z, Zhu Y, Lu J, Ge C, Zhang C, Li N, Jin N, Li Y, Tian M, Li X (2021) SARS-CoV-2 causes mitochondrial dysfunction and mitochondrial impairment. Front Microbiol 12:780768. https://doi.org/10.3389/fmicb.2021.780768

18. Valdes-Aguayo JJ, Garza-Veloz I, Vargas-Rodriguez JR, Martinez-Vazquez MC, Avila-Carrasco L, Bernal-Silva S, Gonzalez-Fuentes C, Comas-Garcia A, Alvarado-Hernandez DE, Centeno-Ramirez ASH, Rodriguez-Sanchez JP, Delgado-Enciso I, Martinez-Fierro ML (2021) Peripheral blood mitochondrial dna levels were modulated by SARS-CoV-2 infection severity and its lessening was associated with mortality among hospitalized patients With COVID-19. Front Cell Infect Microbiol 11:754708. https://doi.org/10.3389/fcimb.2021.754708

19. Pliss A, Kuzmin AN, Prasad PN, Mahajan SD (2022) Mitochondrial dysfunction: a prelude to neuropathogenesis of SARS-CoV-2. ACS Chem Neurosci 13:308–312. https://doi.org/10.1021/acschemneuro.1c00675

20. Cheriyath V, Kaur A, Davenport A, Khalel A, Chowdhury N, Gaddipati L (2018) GI P3 (IF I6), a mitochondrial localised antiapoptotic protein, promotes metastatic potential of breast cancer cells through miROS. Br J Cancer 119:52–64. https://doi.org/10.1038/s41416-018-0137-3

21. Shida M, Kitajima Y, Nakamura J, Yanagihara K, Baba K, Wakiyama K, Noshiro H (2016) Impaired mitophagy activates mtROS/HIF-lalpha interplay and increases cancer aggressiveness in gastric cancer cells under hypoxia. Int J Oncol 48:1379–1390. https://doi.org/10.3892/ijo.2016.3359

22. Song JQ, Jiang LY, Fu CP, Wu X, Liu ZL, Xie L, Wu XD, Hao SY, Li SQ (2020) Heterozygous SOD2 deletion deteriorated chronic intermittent hypoxia-induced lung inflammation and vascular remodeling through mitROS-NLRP3 signaling pathway. Acta Pharmacol Sin 41:1197–1207. https://doi.org/10.1038/s41401-019-0349-y

23. Zhou R, Yazdi AS, Men P, Tschopp J (2011) A role for mitochondria in NLRP3 inflammasome activation. Nature 469:221–225. https://doi.org/10.1038/nature09663

24. Burtscher J, Cappellano G, Omori A, Koshiba T, Millet GP (2020) Mitochondria: In the Cross Fire of SARS-CoV-2 and Immunity. iScience 23:101631. https://doi.org/10.1016/j.isci.2020.101631

25. He Y, Hara H, Nunez G (2016) Mechanism and regulation of nlrp3 inflammasome activation. Trends Biochem Sci 41:1012–1017. https://doi.org/10.1016/j.tibs.2016.09.002

26. Boveris A (1977) Mitochondrial production of superoxide radical and hydrogen peroxide. Adv Exp Med Biol 78:67–82. https://doi.org/10.1007/978-1-4615-9035-4_5
27. Cai J, Jones DP (1999) Mitochondrial redox signaling during apoptosis. J Bioenerg Biomembr 31:327–334. https://doi.org/10.1023/a:1004523818200

28. Khomich OA, Kochetkov SN, Bartosch B, Ivanov AV (2018) Redox biology of respiratory viral infections. Viruses. https://doi.org/10.3390/v100800392

29. Chen YI, Moriyama M, Chang MF, Ichinohe T (2019) Severe acute respiratory syndrome coronavirus S protein promotes NLRP3 inflammasome activation and hyper-fission along with aberrant mitophagy in the gut mucosa in rodent model of stress-related mucosal disease. Free Radic Biol Med 113:424–438. https://doi.org/10.1016/j.freeradbiomed.2017.10.009

30. Pan P, Shen M, Yu Z, Ge W, Chen K, Tian M, Xiao F, Wang Z, Wang J, Jia Y, Wang W, Pan P, Zhang J, Chen W, Lei Z, Chen X, Luo Z, Zhang Q, Xu M, Li G, Li Y, Wu J (2021) SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation. Nat Commun 12:4664. https://doi.org/10.1038/s41467-021-25105-6

31. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodriguez L (2020) SARS-CoV-2 infection: the role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev 54:62–75. https://doi.org/10.1016/j.cytogfr.2020.06.001

32. Volt H, Garcia JA, Doerrer C, Diaz-Casado ME, Guerrero-Librero A, Lopez LC, Escames G, Tresguerres IA, Acuna-Castroviejo D (2016) Same molecule but different expression: aging and sepsis trigger NLRP3 inflammasome activation, a target of melatonin. J Pineal Res 60:193–205. https://doi.org/10.1111/jpi.12303

33. Zhou Z, Zhang M, Wang Y, Zheng F, Huang Y, Huang K, Yu Q, Cai C, Chen D, Tian Y, Lei J, Xiao X, Clercq E, Li G, Xie Y, Gong G (2020) Clinical characteristics of older and younger patients infected with SARS-CoV-2. Aging 12:11296–11305. https://doi.org/10.18632/ageing.103535

34. Appelberg S, Gupta S, Svensson Akusjarvi S, Ambikan AT, Mikaeloff F, Saboon E, Vegvari A, Benfeitas R, Sperk M, Stahl-Paz S, Miramontes E, Neogi U (2020) Dysregulation in Akt/mTOR/HIF-1 signaling identified with the SARS-CoV-2 infection. Histol Histopathol 36:947–965. https://doi.org/10.1080/22221751.2020.1799723

35. Soria-Castro E, Soto ME, Guarner-Lans V, Rojas G, Perezpenci-Diazconti M, Criales-Vera SA, Manzano Pech L, Perez-Torres J (2021) The kidnapping of mitochondrial function associated with the SARS-CoV-2 infection. Histol Histopathol 36:947–965. https://doi.org/10.14670/HH-18-354

36. Nieto-Torres JL, Verdía-Bagueua C, Jimenez-Guardeno JM, Regla-Nava JA, Castano-Rodriguez C, Fernandez-Delgado R, Torres J, Aguilera VM, Enjuanes L (2015) Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. Virology 485:330–339. https://doi.org/10.1016/j.virol.2015.08.010

37. Singh K, Chen YC, Hassanzadeh S, Han K, Judy JT, Seifuddin F, Tunc I, Sack MN, Pirozimia M (2021) Network analysis and transcription profile identify autophagic and mitochondrial dysfunctions in SARS-CoV-2 infection. Front Genet 12:59261. https://doi.org/10.3389/fgene.2021.59261

38. Starkov AA, Fiskum G (2003) Regulation of brain mitochondrial H2O2 production by membrane potential and NAD(P)H redox state. J Neurochem 86:1101–1107. https://doi.org/10.1046/j.1471-4159.2003.01908.x

39. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Qin X, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y, Zhang S (2020) Coagulopathy and antiphospholipid antibodies in patients with COVID-19. N Engl J Med 382:e38. https://doi.org/10.1056/NEJMc2007575

40. Codo AC, D’Avanzo GB, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV, Prodonoff JS, Carregari VC, de Biagi Junior CAO, Crucini F, Jimenez Restrepo JL, Vendramini PH, Reis-de-Oliveira G, Bispo Dos Santos K, Toledo-Teixeira DA, Parise PL, Martini MC, Marques RE, Carmo HR, Borin A, Coimbra LD, Boldrini VO, Brunetti NS, Vieira AS, Mansour E, Ulaf RG, Bernardes AF, Nunes TA, Ribeiro LC, Palma AC, Agrella MV, Moretti ML, Sposito AC, Pereira FB, Velloso LA, Vinola MAR, Damasio A, Pioenca-Modena JL, Carvalho RF, Mori MA, Martins-de-Souza D, Nakaya HI, Farias AS, Moraes-Vieira PM (2020) Elevated glucose levels favor sars-cov-2 infection and monocyte response through a HIF-1alpha/glycolysis-dependent axis. Cell Metab 32:498–499. https://doi.org/10.1016/j.cmet.2020.07.015

41. Zhang D, Guo R, Lei L, Liu H, Wang Y, Wang Y, Qian H, Dai T, Zhang T, Lai Y, Wang J, Liu Z, Chen T, He A, O’Dwyer M, Hu J (2021) Frontline Science: COVID-19 infection induces readily detectable morphologic and inflammation-related phenotypic changes in peripheral blood monocytes. J Leukoc Biol 109:13–22. https://doi.org/10.1002/JLB.HB.5720-470R

42. Scozzi D, Cano M, Ma L, Zhou D, Zhu JH, O’Halloran JA, Goss C, Rauos AM, Liu Z, Sahuk SK, Peritore V, Rocco M, Ricci A, Amodeo R, Aimati L, Ibrahim M, Hachem R, Kreisel D, Mudd PA, Kulkarni HS, Gelman AE (2021) Circulating mitochondrial DNA is an early indicator of severe illness and mortality from COVID-19. JCI Insight. https://doi.org/10.1172/jci.insight.143299

43. Wang P, Luo R, Zhang M, Wang Y, Song T, Tao T, Li Z, Jin L, Zheng H, Chen W, Zhao M, Zheng Y, Qin J (2020) A cross-talk between epithelium and endothelium mediates human alveolar-capillary injury during SARS-CoV-2 infection. Cell Death Dis 11:1042. https://doi.org/10.1038/s41419-020-03252-9

44. Costa TJ, Potje SR, Fragia-Silva TC, da Silva-Neto JA, Barros PR, Rodrigues D, Machado MR, Martins RB, Santos-Eichler RA, Benatti MN, de Sa KG, Almado CEL, Castro IA, Pontelli MC, Serra L, Carneiro FS, Becarri C, Louzada-Junior P, Oliveira RDR, Zamboni DS, Arruda E, Auxiliadora-Martins M, Giachini FRC, Bonato VLD, Zachara NE, Bomfim GF, Tostes BC (2022) Mitochondrial DNA and TLR9 activation contribute to SARS-CoV-2-induced endothelial cell damage. Vascul Pharmacol 142:106946. https://doi.org/10.1016/j.vph.2021.106946

45. Valdes-Aguayo JJ, Garza-Veloz I, Badillo-Almaraz JJ, Bernal-Silva M, Martinez-Vazquez MC, Juarez-Alcala V, Vargas-Rodriguez JR, Gaeta-Velasco ML, Gonzalez-Fuentes C, Avila-Carrasco L, Martinez-Fierro ML (2021) Mitochondria and mitochondrial dna: key elements in the pathogenesis and exacerbation of the inflammatory state caused by COVID-19. Medicina. https://doi.org/10.3390/medicina57090928

46. Ji WK, Hatch AL, Merrill RA, Strack S, Higgs SN (2015) Actin filaments target the oligomeric maturation of the dynamin GTPase Drp1 to mitochondrial fission sites. Elife 4:e11553. https://doi.org/10.7554/elife.11553

47. Youle RJ, van der Bliek AM (2012) Mitochondrial fission, fusion, and stress. Science 337:1062–1065. https://doi.org/10.1126/science.1219855

48. De R, Sarkar S, Mazumder S, Debsharma S, Siddiqui AA, Saha SJ, Banerjee C, Nag S, Saha D, Pramanik S, Bandyopadhyay U (2018) Macrophage migration inhibitory factor regulates mitochondrial dynamics and cell growth of human cancer cell lines
through CD74-NF-kappaB signaling. J Biol Chem 293:19740–19760. https://doi.org/10.1074/jbc.201803935
50. Morita M, Prudent J, Basu K, Goyon V, Katsumura S, Hulea L, Pearl D, Siddiqui N, Strack S, McGuiurk S, St-Pierre J, Larsson O, Topisirovic I, Vali H, McBride HM, Bergeron JJ, Sonenberg N (2017) mTOR Controls mitochondrial dynamics and cell survival via MTPP1. Mol Cell 67(922–935):e5. https://doi.org/10.1016/j.molec.2017.08.013
51. Morita M, Gravel SP, Hulea L, Pollak M, St-Pierre J, Topisirovic I (2015) mTOR coordinates protein synthesis, mitochondrial activity and proliferation. Cell Cycle 14:473–480. https://doi.org/10.4161/15384101.2014.991572
52. Shi CS, Qi HY, Boularan C, Huang NN, Abu-Asab M, Shelhammer JH, Kehrl JH (2014) SARS-coronavirus open reading frame-9b suppresses innate immunity by targeting mitochondria and the MAVS/TRAFF3/TRAFl6 signalling. J Immunol 193:3080–3089. https://doi.org/10.4049/jimmunol.1303196
53. Zemirli N, Porciet M, Ambroise G, Hatchi E, Vazquez A, Krishnan S, Nordqvist H, Ambikan AT, Gupta S, Sperk M, Svenne H (2014) Mitochondrial hyperfusion promotes coronavirus nonstructural protein 2 binding cardiolipin and regulates mitochondrial biogenesis and function. Mol Cell Biol 31:3845–3856. https://doi.org/10.1128/MCB.05393-11
54. Ehrlich A, Uhl S, Ioanidis K, Hofree M, tenOever BR, Nahmias Y (2020) The SARS-CoV-2 ORF3a ORF3a induces RETREG1/FAM13B1-dependent reticulophagy and triggers sequential ER stress and inflammatory responses during SARS-CoV-2 infection. Autophagy. https://doi.org/10.1080/15548627.2022.2039992
55. Paradies G, Paradies V, De Benedictis V, Ruggiero FM, Petrosillo G (2014) Functional role of cardiolipin in mitochondrial bioenergetics. Biochim Biophys Acta 1837:408–417. https://doi.org/10.1016/j.bbabio.2013.10.006
56. Ehrlich A, Uhl S, Ioanidis K, Hofree M, tenOever BR, Nahmias Y (2020) The SARS-CoV-2 transcriptional metabolic signature in lung epithelium. SSRN Electron J. https://doi.org/10.2139/ssrn.3605499
57. Ashary N, Bhide A, Chakraborty P, Colaco S, Mishra A, Chhabria K, Jolly MK, Modi D (2020) Single-Cell RNA-seq identifies cell subsets in human placenta that highly express factors driving pathogenesis of SARS-CoV-2. Front Cell Dev Biol 8:783. https://doi.org/10.3389/fcell.2020.00783
58. Cortese M, Lee JY, Cerikan B, Neufeldt CJ, Oorschot VMJ, Kohrer S, Hennesy J, Schieber NL, Ronchi P, Mizzon G, Romero-Brey I, Santarella-Mellwig R, Schorb M, Boerme M, Mocaer K, Beckwith MS, Templin R, Gross V, Pape C, Tischer C, Frankish J, Horvat NK, Laketa V, Stanifer M, Boulant S, Ruggeri A, Chatel-Chaux L, Schwab Y, Bartenschlager R (2020) Integrative imaging reveals sars-cov-2-induced reshaping of subcellular morphologies. Cell Host Microbe 28(853–866):e5. https://doi.org/10.1016/j.chom.2020.11.003
59. Nardacci R, Colavita F, Castilletti C, Lapa D, Matusali G, Meschi S, Del Nonno F, Colombo D, Capobianchi MR, Zumla A, Ippolito G, Piacentini M, Falasca L (2021) Evidences for lipid involvement in SARS-CoV-2 cytopathogenesis. Cell Death Dis 12:263. https://doi.org/10.1038/s41419-021-03527-9
60. Wolff G, Melia CE, Snijder EJ, Barcena M (2020) Double-membrane vesicles as platforms for viral replication. Trends Microbiol 28:1022–1033. https://doi.org/10.1016/j.tim.2020.05.009
61. Thiam AR, Dugail I (2019) Lipid droplet-membrane contact sites—from protein binding to function. J Cell Sci. https://doi.org/10.1242/jcs.230169
62. Leaf Y-B, Jung M, Kim J, Kang M-G, Kwak C, Mun J-Y, Kim J-S, Rhee H-W (2020) Endomembrane systems are reorganized by ORF3a and membrane (M) of SARS-CoV-2. SSRN Electron J. https://doi.org/10.2139/ssrn.3742314
63. Shi CS, Qi HY, Boularan C, Huang NN, Abu-Asab M, Shelhammer JH, Kehrl JH (2014) SARS-coronavirus open reading frame-9b suppresses innate immunity by targeting mitochondria and the MAVS/TRAFF3/TRAFl6 signalling. J Immunol 193:3080–3089. https://doi.org/10.4049/jimmunol.1303196
64. Davies JP, Almasy KM, McDonald EF, Plate L (2020) Comparative multiplexed interactomics of SARS-CoV-2 and homologous coronavirus nonstructural proteins identifies unique and shared host-cell dependencies. ACS Infect Dis 6:3174–3189. https://doi.org/10.1021/acsinfecdis.0c00500
65. Lu JP, Wang Y, Sliter DA, Pearce MM, Wojcikiewicz RJ (2011) RNF170 protein, an endoplasmic reticulum membrane ubiquitin ligase, mediates inositol 1,4,5-trisphosphate receptor ubiquitination and degradation. J Biol Chem 286:24426–24433. https://doi.org/10.1074/jbc.M111.251983
66. Christie DA, Lemke CD, Elias IM, Chau LA, Kirchhof MG, Li B, Ball EH, Dunn SD, Hatch GM, Madalens J (2020) Stomatolin-like protein 2 binds cardiolipin and regulates mitochondrial biogenesis and function. Mol Cell Biol 31:3845–3856. https://doi.org/10.1128/MCB.05393-11
67. Shin CS, Meng S, Garbis SD, Moradian A, Taylor RW, Swere- doski MJ, Lomenick B, Chan DC (2021) LONP1 and mtHSP70 cooperate to promote mitochondrial protein folding. Nat Struct Mol Biol 28:573–582. https://doi.org/10.1038/ s41594-021-00619-0
68. Cinatl J, Munch C (2020) Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. Nat Commun 12:265. https://doi.org/10.1038/s41467-020-20597-z
69. Piccoli C, Scrima R, Quartaro G, D’Aprile A, Ripoli M, Lecce L, Boffoli D, Moradpour D, Capitanio N (2007) Hepatitis C virus protein expression causes calcium-mediated mitochondrial bioenergetic dysfunction and nitro-oxidative stress. Hepatology 46:58–65. https://doi.org/10.1002/hep.21679
70. Bojkova D, Klann K, Koch B, Widera M, Schorb M, Boermel M, Romero-Brey I, Santarella-Mellwig R, Schorb M, Moradian A, Taylor RW, Swere- doski MJ, Lomenick B, Chan DC (2021) LONP1 and mtHSP70 cooperate to promote mitochondrial protein folding. Nat Commun 12:265. https://doi.org/10.1038/s41467-020-20597-z
pathogenesis. Am J Physiol Cell Physiol 319:C258–C267. https://doi.org/10.1152/ajpcell.00224.2020

77. Moolamalla STR, Balasubramanian R, Chauhan R, Priyakumar UD, Vinod PK (2021) Host metabolic reprogramming in response to SARS-CoV-2 infection: a systems biology approach. Microb Pathog 158:105114. https://doi.org/10.1016/j.micpath.2021.105114

78. Ajaz S, McPhail MJ, Singh KK, Mujib S, Trovato FM, Napoli S, Agarwal K (2021) Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19. Am J Physiol Cell Physiol 320:C57–C65. https://doi.org/10.1152/ajpcell.00426.2020

79. Zhu L, She ZG, Cheng X, Qin J, Zhang XJ, Cai J, Lei F, Wang H, Xie J, Wang W, Li H, Zhang P, Song X, Chen X, Xiang M, Zhang C, Bai L, Xiang D, Chen MM, Liu Y, Yan Y, Liu M, Mao W, Zou J, Liu L, Chen G, Luo P, Xiao B, Zhang C, Zhang Z, Lu Z, Wang J, Lu H, Xia X, Wang D, Liao X, Peng G, Ye P, Yang J, Yuan Y, Huang X, Guo J, Zhang BH, Li H (2020) Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 31(1068–1077):e3. https://doi.org/10.1016/j.cmet.2020.04.021

80. Guarnieri JW, Dybas JM, Fazelinia H, Kim MS, Frere J, Zhang Y, Albrecht YS, Murdoch DG, Angelin A, Singh LN, Weiss SL, Best SM, Lott MT, Cope H, Zakas V, Saravia-Butler A, Meydan C, Fox J, Mozes MK, Kidane YH, Priebre H, Emmett MR, Melner R, Singh U, Bram Y, tenOever BR, Heise MT, Moorman NY, Madden EA, Taft-Benz SA, Anderson EJ, Sanders WA, Dickmanner RJ, Baxter VK, Baylin SB, Wurtele ES, Moraes-Vieira PM, Taylor D, Mason CE, Schisler JC, Schwartz RE, Behebshti A, Wallace DC (2022) Targeted down regulation of core mitochondrial genes during SARS-CoV-2 infection. bioRxiv. https://doi.org/10.1101/2022.02.19.481089

81. Semenza GL, Roth PH, Fang HM, Wang GL (1994) Transcriptional regulation of genes encoding glycolytic enzymes by hypoxia-inducible factor I. J Biol Chem 269:23757–23763

82. Papandreou I, Cairns RA, Fontana L, Lim AL, Denko NC (2006) HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption. Cell Metab 3:187–197. https://doi.org/10.1016/j.cmet.2006.01.012

83. Mullen PJ, Garcia Jr, Purkayastha A, Matulonis N, Schmid EW, Momcilovic M, Sen C, Langerman J, Ramaiah A, Shackelford DB, Damoiseaux R, French WW, Plath K, Gomperts BN, Arumugaswami V, Christofk HR (2021) SARS-CoV-2 infection rewires host cell metabolism and is potentially susceptible to mTORC1 inhibition. Nat Commun 12:1876. https://doi.org/10.1038/s41467-021-22166-4

84. Cash A, Kaufman DL (2022) Oxaloacetate treatment for mental and physical fatigue in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long-COVID fatigue patients: a non-randomized controlled clinical trial. J Transl Med 20:295. https://doi.org/10.1186/s12967-022-04388-3

85. Li S, Ma F, Yokota T, Garcia G Jr, Palermo A, Wang Y, Farrell C, Wang YC, Wu R, Zhou Z, Pan C, Morselli M, Teitteli MA, Ryazantsev S, Fishbein GA, Hooe JT, Arboleda VA, Bloom J, Dillon B, Pellegrini M, Lusis AJ, Graeber TG, Arumugaswami V, Deb A (2021) Metabolic reprogramming and epigenetic changes of vital organs in SARS-CoV-2-induced systemic toxicity. JCI Insight. https://doi.org/10.1172/jci.insight.145027

86. Icard P, Lincet H, Wu Z, Coquerel A, Forget P, Alifano M, Fournel L (2021) The key role of Warburg effect in SARS-CoV-2 replication and associated inflammatory response. Biochimie 180:169–177. https://doi.org/10.1016/j.biochi.2020.11.010

87. Alemzadeh E, Alemzadeh E, Ziaee M, Abedi A, Salehiniya H (2021) The effect of low serum calcium level on the severity and mortality of Covid patients: a systematic review and meta-analysis. Immuno Inflamm Dis 9:1219–1228. https://doi.org/10.1007/s10837-021-00358-2

88. Zhou X, Chen D, Wang L, Zhao Y, Wei L, Chen Z, Yang B (2020) Low serum calcium: a new, important indicator of COVID-19 patients from mild/moderate to severe/critical. Biosci Rep. https://doi.org/10.1042/BSR20202690

89. Gassen NC, Pajies J, Bajaj I, Emanucl J, Dethloff F, Chua RL, Trimpert J, Heinemann N, Niemeyer C, Weege F, Honzke K, Aschman T, Heinz DE, Weckmann K, Ebert T, Zellner A, Lenmarz N, Wyler E, Schroeder S, Richter A, Niemeyer D, Hoffmann K, Meyer TF, Heppner FL, Corman VM, Landthaler M, Hocke AC, Morkel M, Osterrieder N, Conrad C, Eils R, Radbruch H, Giivaliscio P, Drostenc C, Muller MA (2021) SARS-CoV-2-mediated dysregulation of metabolism and autophagy uncovers host-targeting antivirals. Nat Commun 12:3818. https://doi.org/10.1038/s41467-021-24007-w

90. Tamargo-Gomez I, Marino G (2018) AMPK: regulation of metabolic dynamics in the context of autophagy. Int J Mol Sci. https://doi.org/10.3390/ijms19123812

91. Codo AC, Davanzo GG, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV, Prodonoof JS, Carregari VC, de Biagi Junior CAO, Crucifulli F, Jimenez Restrepo JL, Vendramini PH, Reis-de-Oliveira G, Bispo Dos Santos K, Toledo-Teixeira DA, Parise PL, Martini MC, Marques RE, Carmo HR, Borin A, Coimbra LD, Boldrini VO, Brunetti NS, Vieira AS, Mansour E, Ulaf RG, Bernardes AF, Nunes TA, Ribeiro LC, Palma AC, Agrela MV, Moretti ML, Sposito AC, Pereira PB, Velloso LA, Vinolo MAR, Damasio A, Prenocia-Modena JL, Carvalho RF, Mori MA, Martins-de-Souza D, Nakaya HI, Farias AS, Moraes-Vieira PM (2020) Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1alpha/glycogenolysis-dependent axis. Cell Metab 32(437–446):e5. https://doi.org/10.1016/j.cmet.2020.07.007

92. Refolo G, Vescovo T, Piacentini M, Fimia GM, Ciccosanti F (2020) Mitochondrial interactome: a focus on autoviral signaling pathways. Front Cell Dev Biol 8:8. https://doi.org/10.3389/fcell.2020.00008

93. Elesela S, Lukacs NW (2021) Role of mitochondria in viral infections. Life. https://doi.org/10.3390/life11030232

94. Koshiba T (2013) Mitochondrial-mediated antiviral immunity. Biochim Biophys Acta 1833:225–232. https://doi.org/10.1016/j.bbamcr.2012.03.005

95. Yin X, Riva L, Yu Y, Martin-Sancho L, Kamamune J, Yamamoto Y, Sakai K, Gotob S, Miorin L, De Jesus PD, Yang CC, Herbert KM, Yoh S, Hulquist JF, Garcia-Sastre A, Chanda SK (2021) MD5 Gatters the innate immune response to SARS-CoV-2 in lung epithelial cells. Cell Rep 34:108628. https://doi.org/10.1016/j.celrep.2021.108628

96. Wu J, Shi Y, Pan X, Wu S, Hou R, Zhang Y, Zhong T, Tang H, Du W, Wang L, Wo J, Mu J, Qiu Y, Yang K, Zhang LK, Ye BC, Qi N (2021) SARS-CoV-2 ORF9b inhibits RIG-I-MAVS antiviral signaling by interrupting K63-linked ubiquitination of NEMO. Cell Rep 34:108761. https://doi.org/10.1016/j.celrep.2021.108761

97. Zheng Y, Zhuang MW, Han L, Zhang J, Nan ML, Zhan P, Kang D, Liu X, Gao C, Wang PH (2020) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) membrane (M) protein inhibits type I and III interferon production by targeting RIG-I/MDA-5 signaling. Signal Transduct Target Ther 5:299. https://doi.org/10.1038/s41392-2020-00438-7

98. Han L, Zhuang MW, Deng J, Zheng Y, Zhang J, Nan ML, Zhang XJ, Gao C, Wang PH (2021) SARS-CoV-2 ORF9b antagonizes type I and III interferons by targeting multiple components of the RIG-I/MDA-5-MAVS, TLR3-TRIF, and cGAS-STING signaling pathways. J Med Virol 93:5376–5389. https://doi.org/10.1002/jmv.27050
99. Jiang HW, Zhang HN, Meng QF, Xie J, Li Y, Chen H, Zheng YX, Wang XN, Qi H, Zhang J, Wang PH, Han ZG, Tao SC (2020) SARS-CoV-2 Orf9b suppresses type I interferon responses by targeting TOM70. Cell Mol Immunol 17:998–1000. https://doi.org/10.1038/s41423-020-0514-8

100. Gao X, Zhu K, Qin B, Olieric V, Wang M, Cui S (2021) Crystal structure of SARS-CoV-2 Orf9b in complex with human TOM70 suggests unusual virus-host interactions. Nat Commun 12:2843. https://doi.org/10.1038/s41467-021-23118-8

101. Liu XY, Wei B, ShiHX, Shan YF, Wang C (2010) Tom70 mediates activation of interferon regulatory factor 3 on mitochondria. Cell Res 20:994–1011. https://doi.org/10.1038/cr.2010.103

102. Wei X, Du M, Xie J, Luo T, Zhou Y, Zhang K, Li J, Chen D, Xu P, Jia M, Zhou H, Fang H, Lyu J, Yang Y (2020) Mutations in TOM70 lead to multi-OXPHOS deficiencies and cause severe anemia, lactic acidosis, and developmental delay. J Hum Genet 65:231–240. https://doi.org/10.1038/s10038-019-0714-1

103. Fu YZ, Wang SY, Zhang QZ, Yi H, Li WW, Xu ZS, Wang YY (2021) SARS-CoV-2 membrane glycoprotein M antagonizes the MAVS-mediated innate antiviral response. Cell Mol Immunol 18:613–620. https://doi.org/10.1038/s41423-020-00571-x

104. Yuen CK, Lam JY, Wong WM, Mak LF, Wang M, Cai SM, Smith JA (2020) STING, the endoplasmic reticulum, and mitochondrial stress and immune cells abrogate melanoma progression. iScience 24:102653. https://doi.org/10.1016/j.isci.2021.102653

105. Palaidimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene K, Arora S, Southern WN, Mantzoros CS (2020) Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx. New York Metabolism 108:154262. https://doi.org/10.1016/j.metabol.2020.154262

106. Holder K, Reddy PH (2021) The COVID-19 effect on the immune system and mitochondrial dynamics in diabetes, obesity, and dementia. Neuroscientist 27:331–339. https://doi.org/10.1177/1073858420960443

107. Mavrogianaki AN, Migdalis IN (2013) Nonalcoholic fatty liver disease, diabetes mellitus and cardiovascular disease: newer data. Pan J Endocrinol 2013:450639. https://doi.org/10.1155/2013/450639

108. Costa FF, Rosario WR, Ribeiro Farias AC, de Souza RG, Duarte Gondim RS, Barroso WA (2020) Metabolic syndrome and COVID-19: an update on the associated comorbidities and proposed therapies. Diabetes Metab Syndr 14:809–814. https://doi.org/10.1016/j.dsx.2020.06.016

109. Soto ME, Guarnier-Lans V, Soria-Castro E, Manzano Pech L, Perez-Torres I (2020) Is antioxidant therapy a useful complementary measure for COVID-19 treatment? An Algorithm Appl Medicine. https://doi.org/10.3390/medicine58080386

110. Cu Q, Zhang S, Li Y, Wang Y, Peppelenbosch MP, Pan Q (2019) Mitochondria in the biology, pathogenesis, and treatment of hepatitis virus infections. Rev Med Virol 29:e2075. https://doi.org/10.1002/rmv.2075

111. Kang HT, Hwang ES (2006) 2-Deoxyglucose: an anticancer and antiviral therapeutic, but not any more a low glucose mimetic. Life Sci 762. https://doi.org/10.1016/j.lfs.2022.120411

112. Wang XN, Qi H, Zhang J, Wang PH, Han ZG, Tao SC (2020) SARS-CoV-2 Orf9b suppresses type I interferon responses by targeting TOM70. Cell Mol Immunol 17:998–1000. https://doi.org/10.1038/s41423-020-0514-8

113. Yang Y, Kuang L, Li L, Wu Y, Zong B, Huang X (2021) Distinct mitochondria-mediated T-cell apoptosis responses in children and adults with coronavirus disease 2019. J Infect Dis 224:1333–1344. https://doi.org/10.1093/infdis/jiab400

114. Moreno Fernandez-Ayala DJ, Navas P, Lopez-Lluch G (2020) Age-related mitochondrial dysfunction as a key factor in COVID-19 disease. Exp Gerontol 142:111147. https://doi.org/10.1016/j.exger.2020.111147

115. Yao Y, Lawrence DA (2021) Susceptibility to COVID-19 in populations with health disparities: Posited involvement of mitochondrial disorder, socioeconomic stress, and pollutants. J Biochem Mol Toxicol 35:e22626. https://doi.org/10.1002/jbt.22626

116. Palaidimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene K, Arora S, Southern WN, Mantzoros CS (2020) Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx. New York Metabolism 108:154262. https://doi.org/10.1016/j.metabol.2020.154262

117. Mavrogiannaki AN, Migdalis IN (2013) Nonalcoholic fatty liver disease, diabetes mellitus and cardiovascular disease: newer data. Pan J Endocrinol 2013:450639. https://doi.org/10.1155/2013/450639

118. Costa FF, Rosario WR, Ribeiro Farias AC, de Souza RG, Duarte Gondim RS, Barroso WA (2020) Metabolic syndrome and COVID-19: an update on the associated comorbidities and proposed therapies. Diabetes Metab Syndr 14:809–814. https://doi.org/10.1016/j.dsx.2020.06.016

119. Soto ME, Guarnier-Lans V, Soria-Castro E, Manzano Pech L, Perez-Torres I (2020) Is antioxidant therapy a useful complementary measure for COVID-19 treatment? An Algorithm Appl Medicine. https://doi.org/10.3390/medicine58080386

120. Cu Q, Zhang S, Li Y, Wang Y, Peppelenbosch MP, Pan Q (2019) Mitochondria in the biology, pathogenesis, and treatment of hepatitis virus infections. Rev Med Virol 29:e2075. https://doi.org/10.1002/rmv.2075

121. Kang HT, Hwang ES (2006) 2-Deoxyglucose: an anticancer and antiviral therapeutic, but not any more a low glucose mimetic. Life Sci 762. https://doi.org/10.1016/j.lfs.2022.120411

122. Bhatt AN, Kumar A, Rai Y, Kumari N, Vedagiri D, Harshan KH, Agote A, Moya-Rull D, Vilas-Zornoza A, Tarantino C, Romero JP, Jonsson G, Oria R, Leopoldi A, Hagelkruys A, Gallo M, Gonzalez F, Domingo-Pedrol P, Avelar CA, Del Pozo CH, Hasen Ali O, Ventura-Aguia P, Campistol JM, Prosper F, Mirzamini A, Boulant S, Penninger JM, Montserrat N (2022) A diabetic milieu increases ACE2 expression and cellular susceptibility to SARS-CoV-2 infections in human kidney organoids and patient cells. Cell Metab 34(857–873):e9. https://doi.org/10.1016/j.cmet.2022.04.009

123. Soto ME, Guarnier-Lans V, Soria-Castro E, Manzano Pech L, Perez-Torres I (2020) Is antioxidant therapy a useful complementary measure for covid-19 treatment? An Algorithm Appl Medicine. https://doi.org/10.3390/medicine58080386

124. Qu C, Zhang S, Ly Y, Wang Y, Peppelenbosch MP, Pan Q (2019) Mitochondria in the biology, pathogenesis, and treatment of hepatitis virus infections. Rev Med Virol 29:e2075. https://doi.org/10.1002/rmv.2075

125. Kang HT, Hwang ES (2006) 2-Deoxyglucose: an anticancer and antiviral therapeutic, but not any more a low glucose mimetic. Life Sci 762. https://doi.org/10.1016/j.lfs.2022.120411

126. Bhatt AN, Kumar A, Rai Y, Kumari N, Vedagiri D, Harshan KH, Agote A, Moya-Rull D, Vilas-Zornoza A, Tarantino C, Romero JP, Jonsson G, Oria R, Leopoldi A, Hagelkruys A, Gallo M, Gonzalez F, Domingo-Pedrol P, Avelar CA, Del Pozo CH, Hasen Ali O, Ventura-Aguia P, Campistol JM, Prosper F, Mirzamini A, Boulant S, Penninger JM, Montserrat N (2022) A diabetic milieu increases ACE2 expression and cellular susceptibility to SARS-CoV-2 infections in human kidney organoids and patient cells. Cell Metab 34(857–873):e9. https://doi.org/10.1016/j.cmet.2022.04.009
127. Vardhan S, Sahoo SK (2022) Exploring the therapeutic nature of limonoids and triterpenoids against SARS-CoV-2 by targeting nsp13, nsp14, and nsp15 through molecular docking and dynamics simulations. J Tradit Compl Med 12:44–54. https://doi.org/10.1016/j.jtcme.2021.12.002

128. Liu J, Xia H, Kim M, Xu L, Li Y, Zhang L, Cai Y, Norberg HV, Zhang T, Furuya T, Jin M, Zhu Z, Wang H, Yu J, Li Y, Hao Y, Choi A, Ke H, Ma D, Yuan J (2011) Beclin1 controls the levels of p53 by regulating the deubiquitination activity of USP10 and USP13. Cell 147:223–234. https://doi.org/10.1016/j.cell.2011.08.037

129. Woods JJ, Wilson JJ (2020) Inhibitors of the mitochondrial calcium uniporter for the treatment of disease. Curr Opin Chem Biol 55:9–18. https://doi.org/10.1016/j.cbpa.2019.11.006

130. Petcherski A, Sharma M, Daskou M, Satta S, Vasilopoulos H, Hugo C, Ritou E, Dillon BJ, Fung E, Garcia G, Scafoglio C, Purkayastha A, Gomperts BN, Fishbein GA, Arumugaswami V, Liesa M, Shirihai OS, Kelesidis T (2022) Mitoquinone mesylate targets SARS-CoV-2 and associated lung inflammation through host pathways. bioRxiv. https://doi.org/10.1101/2022.02.22.481100

131. Tangos M, Budde H, Kolijn D, Sieme M, Zhazykbayeva S, Lodi M, Herwig M, Gomori K, Hassoun R, Robinson EL, Meister TL, Jaquet K, Kovacs A, Mustroh J, Evert K, Babel N, Fagyas M, Lindner D, Puschel K, Westermann D, Mannherz HG, Paneni F, Pfaender S, Toth A, Mugge A, Sossalla S, Hamdani N (2022) SARS-CoV-2 infects human cardiomyocytes promoted by inflammation and oxidative stress. Int J Cardiol 362:196–205. https://doi.org/10.1016/j.ijcard.2022.05.055

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.