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Review

Severe acute respiratory syndrome coronaviruses contributing to mitochondrial dysfunction: Implications for post-COVID complications

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ABSTRACT

Mitochondria play a central role in oxidative phosphorylation (OXPHOS), bioenergetics linked with ATP production, fatty acids biosynthesis, calcium signaling, cell cycle regulation, apoptosis, and innate immune response. Severe acute respiratory syndrome-associated coronavirus (SARS-CoV) infection manipulates the host cellular machinery for its survival and replication in the host cell. The infectiaon causes perturbed the cellular metabolism that favours viral replication leading to mitochondrial dysfunction and chronic inflammation. By localizing to the mitochondria, SARS CoV proteins increase reactive oxygen species (ROS) levels, perturbation of Ca^{2+} signaling, changes in mtDNA copy number, mitochondrial membrane potential (MMP), mitochondrial mass, and induction of mitophagy. These proteins also influence the fusion and fission kinetics, size, structure, and distribution of mitochondria in the infected host cells. This results in compromised bioenergetics, altered metabolism, and innate immune signaling, and hence can be a key player in determining the outcome of SARS-CoV infection. SARS-CoV infection contributes to stress and activates apoptotic pathways. This review summarizes how mitochondrial function and dynamics are affected by SARS-CoV and how the mitochondria-SARS-CoV interaction benefits viral survival and growth by evading innate host immunity. We also highlight how the SARS-CoV-mediated mitochondrial dysfunction contributes to post-COVID complications. Besides, a discussion on targeting virus-mitochondria interactions as a therapeutic strategy is presented.

1. Introduction

Mitochondria are versatile cellular organelles that play a central role in many biochemical pathways linked with ATP production, biosynthesis of fatty acids, calcium signaling, cell cycle regulation, apoptosis, and innate immune response (Friedman and Nunnari, 2014). Human mitochondrial DNA (mtDNA) is 16569 bp in size, encodes for 13 polypeptides, two ribosomal RNA, and 22 transfer RNA genes (Young and Copeland, 2016). The 13 polypeptides are essential for oxidative phosphorylation pathway function, and the nuclear genome encodes all the remaining proteins required for the structure and function of the mitochondria (Young and Copeland, 2016). Mitochondria are highly dynamic organelles that undergo a coordinated cycle of fusion and fission. These transient morphological adaptations of mitochondria are essential for several molecular processes such as control of cell cycle, immune function, mitochondrial quality, and apoptosis (Tilokani et al., 2018).

The mitochondria are highly vulnerable to both physiological and environmental stress including bacterial, fungal, and viral infections (Khan et al., 2015). Viral infections have been shown to adversely affect mitochondrial structure and functions, and impact the metabolism and immune signalling (Khan et al., 2015). Recent scientific investigations have suggested the critical role of mitochondria in eliciting parts of innate and adaptive immune responses as several immune signaling pathways converge inside the mitochondria (Banoth and Cassel, 2018). Mitochondria-mediated immune signalling has been associated with activation, transcription, differentiation as well as the survival of

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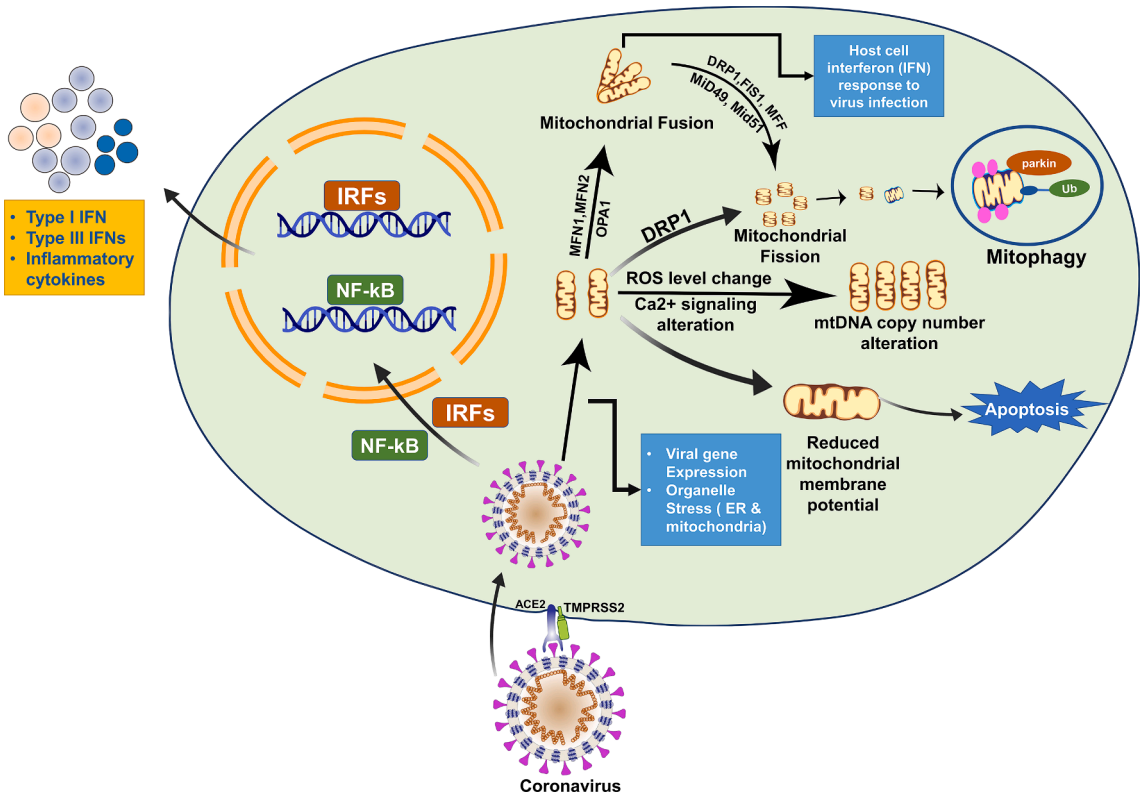

Fig. 1. Illustration demonstrating the effect of SARS-CoV infection on mitochondrial structure and function. Host cell interferon (IFN) response to virus infection: ORF-9b degrades DRP1 leading to mitochondrial fusion and host cell interferon (IFN) response to virus infection. Changes in mtDNA copy number: SARS-CoV proteins can influence ROS level, perturbation of Ca2 + signaling, changes in mtDNA copy number. Apoptosis: ORF9b degrades MAVS, TRAF3 and TRAF6 induce structural and functional change resulting in apoptosis.

various types of immune cells (Angajala et al., 2018). It is now clear that viruses use various mechanisms to target host cell mitochondria for their growth and survival, further weakening the host cellular immune response and enhancing cell killing (Ganji and Reddy, 2020). Linking mitochondrial functions as a mechanism of the viral hijacking of host immune response is an emerging and promising field that can be exploited for clinical management of viral infection and its control.

RNA viruses are the virus-containing single-stranded or double-stranded RNA as genetic material protected by a capsid covered by glycoproteins (Carrasco-Hernandez et al., 2017). RNA viruses cause several human diseases including Severe Acute Respiratory Syndrome (SARS), polio, influenza, hepatitis, among others (Carrasco-Hernandez et al., 2017). Mitochondrial changes documented in response to RNA virus infection include mitochondrial depolarization, oxidative stress, changes to mitochondrial fusion and fission kinetics, and mitophagy (Elesela and Lukacs, 2021). Targeting mitochondrial dynamics by proteins encoded by RNA virus including SARS-CoV appears to be one of the mechanisms by which viruses escape from the anti-viral innate immune response (Burtscher et al., 2020; Ganji and Reddy, 2020; Nunn et al., 2020). For instance, Open reading frame-9b (orf9b) protein encoded by Severe acute respiratory syndrome coronavirus 1 (SARS-CoV1) degrades dynamin-related protein 1 (DRP1) leading to fusion of mitochondrial and host cell interferon (IFN) response to virus infection (Shi et al., 2014b). Orf9b severely affects the host cell interferon response by degrading MAVS, TRAF3, and TRAF6 (Shi et al., 2014b). A study by Jiang and the group showed the high-affinity interaction of orf9b and TOM70 in inhibiting type I interferon response (Jiang et al., 2020b). Additionally, the *orf9b* expression leads to the induction of autophagy in the host cell. RNA viruses are known regulators of mitochondrial-mediated apoptosis, which is an essential mechanism for the survival, propagation, and dissemination of virus inside the host cell. For example, PB1-F2 protein encoded by Influenza A virus localizes to mitochondria and disrupts the organization of mitochondria induction of cell death. HIV viral protein R targets Mfn2 disrupts MMP and induces cell death (Chanturiya et al., 2004).

2. SARS family of coronaviruses and mitochondria:

Coronaviruses are a class of positive-sense single-stranded RNA viruses belonging to the Coronavirinae subfamily with a genome size ranging from 26 to 32 kb consisting of at least six open reading frames (ORFs) and four structural proteins (Yang et al., 2020). The structural proteins include spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. The major difference between the SARS-CoV and SARS-CoV-2 are in orf3b, spike S1, orf8 (Chan et al., 2020). SARS coronavirus, commonly known as SARS-CoV causes severe acute respiratory syndrome (SARS) in humans. The common human coronaviruses included alpha coronavirus (229E, NL63), and beta coronavirus (OC43, HKU1). MERS-CoV, SARS-CoV, and SARS-CoV-2 are other human coronaviruses discovered recently causing respiratory syndromes in humans.

Mitochondria acts as a master regulator of apoptosis. SARS genome encoded proteins may target and modulate anterograde and retrograde signaling to control the mitochondrial function (Burtscher et al., 2020; Singh et al., 2020). Besides, SARS also modulates the function of mitochondria as a mechanism to escape from the host immune system (Burtscher et al., 2020). For instance, a study by Ying-Xim and co-workers showed that protein 7A encoded by SARS-CoV-1 targets *Bcl-Xl,* a pro-survival gene, to induce apoptosis (Tan et al., 2007). SARS-CoV-1 7a induces apoptosis in a variety of cell types such as the lung, kidney, and liver by activation of caspases (McBride and Fielding, 2012a). Also, protein 7a is found in the Golgi body (GB), endoplasmic reticulum (ER), and partially localized within the mitochondria (McBride and Fielding, 2012a). The 7a protein-mediated apoptosis is a

Table 1
Viral and host function of coronavirus genes.

Gene	Start	Stop	Size	Protein	Protein Similarity	Viral Function	Host Factor	References
S (SARS-CoV-1)	21,492	25,259	3768	Spike Protein	75.96%	Facilitates viral entry and replication	Induces apoptosis	Chow et al., 2005; Jin and Zheng, 2009
S (SARS-CoV-2)	21,563	25,384	3821					
SARS3a (SARS-CoV-1)	25,268	26,092	825	Hypothetical protein sars3a	72.36%	Antiviral interferon (IFN) response	Induces Necrosis and apoptosis	Kopecky-Bromberg et al., 2007; Law et al., 2005
ORF3a (SARS-CoV-2)	25,393	26,220	827					
SARS3b (SARS-CoV-1)	25,689	26,153	465	Hypothetical protein sars3b	–	Antiviral interferon (IFN) response	Induces both necrosis and apoptosis	Kopecky-Bromberg et al., 2007
E (SARS-CoV-1)	26,117	26,347	231	Envelope protein	94.74%	Controls viral replication, inhibition of anti-apoptotic protein	Stress response and apoptosis pathways	DeDiego et al., 2011; Yang et al., 2005
E (SARS-CoV-2)	26,245	26,472	227					
M (SARS-CoV-1)	26,398	27,063	666	Matrix protein	90.54%	Defines the shape of the viral envelope, Allow the budding of virions	Pro-apoptotic functions in host cells	Neuman et al., 2011; Tsoi et al., 2014
M (SARS-CoV-2)	26,523	27,191	668					
SARS6 (SARS-CoV-1)	26,913	27,265	353	Hypothetical protein sars6	68.85%	Reduces production of INF	Induces host cell apoptosis	Neuman et al., 2011; Ye et al., 2008
ORF6 (SARS-CoV-2)	27,202	27,387	185					
SARS7a (SARS-CoV-1)	27,273	27,641	369	Hypothetical protein sars7a	85.25%	Activates antiviral signaling	Caspase-dependent apoptosis	Tan et al., 2007
ORF7a (SARS-CoV-2)	27,394	27,759	365					
SARS7b (SARS-CoV-1)	27,638	27,772	135	Hypothetical protein sars7b	85.37%	Pathogenesis of SARS-CoV infection	Induces apoptosis	Schaecher et al., 2007a
ORF7b (SARS-CoV-2)	27,756	27,887	131					
SARS8a (SARS-CoV-1)	27,779	27,898	120	Hypothetical protein sars8a	–	Viral replication	Induces apoptosis	Chen et al., 2007; Shi et al., 2019a
ORF8 (SARS-CoV-2)	27,894	28,259	365	ORF8 protein	–			
SARS8b (SARS-CoV-1)	27,864	28,118	255	Hypothetical protein sars8b	–	Viral replication	Activation of autophagy	Chen et al., 2007; Shi et al., 2019a
N (SARS-CoV-1)	28,120	29,388	1269	Nucleocapsid protein	90.52%	Actin reorganization	Antagonist of IFN signaling	Kopecky-Bromberg et al., 2007; Surjit et al., 2004
N (SARS-CoV-2)	28,274	29,533	1259					
SARS9b (SARS-CoV-1)	28,130	28,426	297	Hypothetical protein sars9b	–	Suppress the innate immunity	Induces apoptosis	Shi et al., 2014b
ORF10 (SARS-CoV-2)	29,558	29,674	116	ORF10 protein	–	–	–	–

p38-MAPK dependent process and has been reported to inhibit protein synthesis (Kopecky-Bromberg et al., 2006). The 7a protein of SARs-CoV-1 show 85.37% similarity with its counterpart of SARS-CoV-2 and hence may impart a similar effect on mitochondria. SARS-infected patients show CD4+, CD8+, and lymphocytes depletion (Diao et al., 2020). Thus, detection of the viruses in these types of cells and their depletion suggests that SARS might induce apoptosis in them. Based on these observations, it is proposed that induction of apoptosis might be an important mechanism to escape from the host immune system. This review summarizes the current knowledge on the effect of SARS-CoV on mitochondrial structure and function and associated signaling pathways as an escape mechanism from the host immune system. Besides, the review article also discusses the potential of targeting the virus-mitochondria network via mitochondrial pharmacological approach. The effect of SARS-CoV infection on mitochondrial structure and function is demonstrated (Fig. 1). Table 1 lists proteins of SARS-CoV which show deleterious effects on host cells in association with mitochondria. The preceding section describes the role of SARS-CoV proteins and their interaction with mitochondria.

2.1. Non-structural proteins (NSP)

SARS-CoV genome encodes 16 non-structural proteins designated as nsp1-nsp16 (Malone et al., 2022). Nsps plays a vital role in suppressing the host immune pathway. Various nsp proteins have been reported to target host cellular proteins that are required for maintaining the mitochondrial structure and function. For instance, it is reported that nsp2, by targeting mitochondrial biogenesis genes, affect the

Table 2
Function of non-structural peptides.

Mature Peptide	Nucleotide Start	Nucleotide End	#Base	aa-size	Protein Product	MPP Cleavage site		Function	References
						Position	Probability		
nsp1	266	805	540	180	Leader protein	30G	0.044	Antagonism against IFN signaling	Kamitani et al., 2009
nsp2	806	2719	1914	638	Counterpart of MHV p65	47G	0.014	Aid in growth and proliferation of the viruses	Cornillez-Ty et al., 2009
nsp3	2720	8554	5834	1944	Nsp3-pp1a/pp1ab	31I	0.000	SG-mRNA synthesis	LaStarza et al., 1994
nsp4	8555	10,054	1500	500	Nsp4-pp1a/pp1ab	56D	0.041	Causes disrupted mitochondrial morphology	Freundt et al., 2009
nsp5	10,055	10,972	918	306	3C-like proteinase	41H	0.003	Proteolytic processing of the replicase polyproteins	Stobart et al., 2013
nsp6	10,973	11,842	870	290	Nsp6-pp1a/pp1ab (TM3)	6 T	0.019	Initiate cellular autophagy and a general ER stress response	Fung et al., 2016; Prentice et al., 2004
nsp7	11,843	12,091	249	83	Nsp7-pp1a/pp1ab	22 V	0.000	Viral replication	Subissi et al., 2014
nsp8	12,092	12,685	594	198	Nsp8-pp1a/pp1ab	58 K	0.000	Viral RNA synthesis	Subissi et al., 2014
nsp9	12,686	13,024	339	113	Nsp9-pp1a/pp1ab	11Q	0.065	Involved in the replicative cycle	Slanina et al., 2021; Sutton et al., 2004
nsp10	13,025	13,441	417	139	Formerly known as growth-factor-like protein (GFL)	79C	0.000	Regulates replication	Bouvet et al., 2014
nsp11	13,442	13,480	39	13	Nsp11-pp1a short peptide	7F	0.005	Viral replication	Deming et al., 2007
nsp12	13,442	16,236	2769	923	RNA-dependent RNA polymerase	34A	0.035	Viral replication	Subissi et al., 2014
nsp13	16,237	18,039	1803	601	Nsp13-pp1ab (ZD, NTPase/HEL; RNA 5′-triphosphatase)	23P	0.037	Viral replication	Jang et al., 2020
nsp14	18,040	19,620	1581	527	3′-to-5′ exonuclease	54L	0.035	Proofreading exoribonuclease	Ma et al., 2015
nsp15	19,621	20,658	1038	346	EndoRNAse	62 N	0.000	Limits apoptosis in macrophages	Deng et al., 2017
Nsp16	20,659	21,552	893	297	2′-O-ribose methyltransferase	20 M	0.037	Viral RNA synthesis and viral replication	Wu et al., 2020

intracellular signaling pathways linked to apoptosis and anti-viral defense (Cornillez-Ty et al., 2009). Nsp2 interacts with prohibitin 1 (PHB1) and prohibitin 2 (PHB2). The PHB1 and PHB2 are coupled with cell cycle, migration, differentiation, and mitochondrial biogenesis (Cornillez-Ty et al.). Thus, the interaction between nsp2 with PHB1 and PHB2 suggests its effect on mitochondrial biogenesis, and host cell proliferation and differentiation, which might facilitate the growth and proliferation of the viruses as well as escape from the host defense (Cornillez-Ty et al., 2009). To the best of our knowledge, nsp3 does not directly target mitochondria. However, the murine cells infected with coronavirus (Alb ts6 icv) shows partial localization of nsp3 and nsp4 to mitochondria (Clementz et al., 2008). Besides, the infected cells show larger mitochondria with vacuoles. Bioinformatic analysis of SARS-CoV-2 interactome identified nsp4, nsp8, Orf9c to interact with the mitochondria. Lai et al. (2007) demonstrated that in HL-CZ cells, 36% of genes upregulated in response to SARS-CoV 3CLpro overexpression were linked with mitochondrial function and pro-apoptotic genes such as *apoptosis-inducing factor (AIF), ATP synthase beta chain (Atp2), and cytochrome c oxidase* (Lai et al., 2007). This suggested that CoV 3CLpro might play a key role in mitochondria-mediated apoptosis. SARS-CoV nsp6 protein is associated with autophagosomes formation from ER (Cottam et al., 2011). Further, studies have reported the lipids for membranes of autophagosomes can also come from mitochondria. In this connection, more detailed studies are required to understand the contribution of mitochondria in the formation of autophagosomes and its relation with mitophagy and host cell apoptosis. The computational analysis identified nsp8 of SARS-CoV-2 to interact with the proteins associated with mitochondrial function (Gordon et al., 2020b). Nsp10 is another non-structural protein encoded by SARS-CoV. A study by Li and co-workers showed that nsp10 interacts with both host genes (*BTF3* and *ATF5*) and mitochondrial genes (*NADH 4L subunit and cytochrome oxidase II*) (Li et al., 2005). Nsp10 alters the NADH-cytochrome activity in lung fibroblast cells (Li et al., 2005). Besides, nsp10 also depolarizes the inner mitochondrial membrane to induce severe damage to the cells (Li et al., 2005). Nsp15 encoded from SARS–CoV by inhibiting mitochondrial anti-viral signaling adaptor protein induces apoptosis. By regulating pRB, nsp15 controls the cell cycle and is proposed to impact metabolic status and immune response (Bhardwaj et al., 2012). Those nsps which does not target mitochondria are reported to target other cell organelles (ER and GB) important for an anti-viral response. Thus, SARS-CoV uses multiple nsp to induce organelle stress, activate stress-responsive cell death pathways to induce a cytotoxic effect. Analysis to identify mitochondrial localization was performed on nsp using MitoFates tool (Fukasawa et al., 2015), potential MMP cleavage sites and the probability score along with the function of each nsp is shown in Table 2.

2.2. *Orf3a protein of SARS-CoV*

It is the first accessory protein encoded by the SARS-CoV genome. Initial studies have indicated Orf3a protein is localized to the ER, plasma membrane (PM), and GB. In SARS infected lung section, ORF3a is predominantly found in the cytoplasm of pneumocytes (McBride and Fielding, 2012b). The Orf3a mediated pro-apoptotic function involves both caspase 8 and caspase 9, suggesting the involvement of both extrinsic and intrinsic pathways of apoptosis (Ren et al., 2020). Besides, Orf3a also targets Bax, p53, and p38MAPK for the induction of host cell death (Hemmat et al., 2021). More specifically, Orf3a induces apoptosis by activation of p38MAPK and subsequent leakage of cytochrome *C* (Hemmat et al., 2021). These data suggest that Orf3a can directly affect the mitochondrial function to induce apoptosis.

2.3. Structural protein

The four structural proteins encoded by the SARS-CoV genome are spike, envelope, nucleocapsid, and membrane (Hemmat et al., 2021). Herein, we discuss the role of various structural proteins and their role in altering mitochondrial function. The spike protein (S protein) is a highly glycosylated type I transmembrane protein that assembles as trimers on the surface of the virions to give the crown-like appearance. The interaction between the Spike proteins and the Angiotensin-converting enzyme 2 (ACE2) receptor facilitates the entry of the virus into the host cell. McBride and co-workers have demonstrated that spike protein contains an ER retrieval signal sequence for interaction with the membranes (McBride and Fielding, 2012a). In addition to facilitating the entry of the virus inside the cells, spike protein also induces apoptosis in Vero E6 cells (Wu et al., 2004). A recent study by Kalashnyk et al. (2021), demonstrated that the SARS-Cov-2 spike protein α7 nAChR-binding portion prevents mitochondrial-driven apoptosis (Kalashnyk et al., 2021). This study shows that when the virus is inside the cell and when uncoated, will facilitate the viral replication cycle and make the host cell vulnerable. Detailed studies are required to understand the precise interaction between mitochondria and spike proteins.

The envelope (E) protein is another protein encoded by SARS-CoV required to complete the viral life cycle. The envelope protein of SARS-CoV is demonstrated to participate in stress response and apoptosis pathways. The E protein downregulates the inositol-requiring eanzyme 1 (IRE-1) of the unfolded protein response to reduce the apoptosis rate (DeDiego et al., 2011). This suggests that SARS-CoV controls the apoptosis of the host cell as per the requirement of the stages of viral life cycle. *In vitro* transfection experiments indicated that the E protein alone managed to reduce the mitochondrial stress by inhibiting the expression of hsp10 E1 (DeDiego et al., 2011). Yang et al. (2005) reported the role of E protein in SARS-CoV-induced lymphopenia. Transfection of *E* gene of SARS-CoV in Jurkat T-cells showed induction apoptosis by inhibition of anti-apoptotic protein *Bcl-Xl(*Yang et al., 2005*)*. Although E protein does not localize to the mitochondria, it effectively regulates nuclear-encoded genes associated with mitochondrial functions to regulate stress response and apoptosis. This may be important for controlling viral replication.

The nucleocapsid (N) is another structural protein of SARS-CoV. In COS-1 cells, N protein-induced mitochondria-mediated apoptosis pathway (Zhang et al., 2007). Besides, the induction of apoptosis by N protein also involves actin reorganization. The membrane Glycoprotein M protein induces apoptosis in HEK293T cells via altering the expression of PDK-1 and Akt kinase and the release of cytochrome *c* (Chan et al., 2007). Another study by Tsoi and co-workers demonstrated that M−protein induces apoptosis by targeting PDK1-PKB/Akt signaling and induction of caspases 8 and 9 (Tsoi et al., 2014). Thus, approaches targeting the interaction between M−protein and PDK1 may be useful for treating SARS-CoV.

2.4. Accessory proteins

The accessory proteins are a group of proteins encoded by SARS-CoV that are not required for replication of the coronavirus. However, accessory proteins are very important to counteract the host immune system. The SARS coronavirus encodes eight accessory proteins designated as orf3a, orf3b, orf6, *orf7a*, *orf7b*, *orf8a*, *orf8b*, and *orf9b* (Astuti and Ysrafil, 2020a). Many of the accessory proteins target mitochondria and are described below.

2.5. Orf3b

The localization of orf3b inside mitochondria is controversial. A study showed that SARS-CoV orf3b localizes to mitochondria in infected Vero E6 cells (Chan et al., 2005). Further, the study also demonstrated that the amino acids from 80 to 138 were critical for orf3b mitochondrial translocation. Iitially, Orf3b accumulates within the nucleolus, then translocates to the OMM and take part in G0/G1 arrest as well as induction of apoptosis. Activation of type-I interferon (IFN-β) is required for activation of mitochondria-mediated anti-viral response. orf3b downregulates IFN-β, thereby inhibiting mitochondrial-mediated anti-viral response (Burtscher et al., 2020). Orf3b interacts with RUNX1b, activates AP-1 via JNK/ERK signaling, and induces both necrosis and apoptosis (Varshney and Lal, 2011). The upregulation of cytokines and chemokines has also been reported to interfere with both the structure and function of the mitochondria and the induction of apoptosis and necrosis.

2.6. Orf6

The orf6 of SARS-CoV 2 is approximately 61 amino acid protein in size (Dehipawala et al., 2021). The orf6 is found in the ER and GB of the infected cells and is likely to impact the viral replication and pathogenesis by antagonizing the function of STAT1. Orf6 along with orf3b and N proteins are reported as antagonists of IFN signalling (Lei et al., 2020). Further, orf6 is predominantly localized in ER and GB (Lee et al., 2021). Inhibition of interferon production by orf6 is coupled with induction of caspase 3 with concomitant ER stress and JNK dependent apoptosis. Mitochondria play a decisive role in caspases activation and caspase-mediated apoptosis. Although there is no report of orf6 localization inside the mitochondria, activation of caspase 3 suggests the involvement of mitochondria in SARS-CoV induced host cell apoptosis (Ye et al., 2008). By localizing to the membranes of ER and GB of the host cells, orf6 interferes with karyopherin alpha 2 and karyopherin beta 1 mediated nuclear import complex formation leading to loss of Signal Transducer and Activator of Transcription 1 (STAT1) nuclear transport (Frieman et al., 2007). STAT1 nuclear transport is linked with antiviral signaling. By preventing the nuclear translocation of the STAT1, orf3b down modulates the host antiviral defense system. Zhongde and co-workers showed that orf6 induces apoptosis in infected host cells by caspase-3- ER-stress-JNK axis (Ye et al., 2008). These data suggested that orf6 targets nuclear transport machinery to antagonize the host interferon production.

2.7. Orf7

The *orf7* codes for two accessory proteins, namely *orf7a* and *orf7b*. *Orf7a* is associated with caspase-dependent apoptosis (Schaecher et al., 2007b). *Orf7a* interacts with Bcl-xL protein for induction of apoptosis in the infected host cell (Tan et al., 2007). Additionally, *orf7a* inhibits protein synthesis in the infected cell *via* activation of NF-kB and p38MAPK and inhibition of the cell cycle progression (Schaecher et al., 2007b). Additionally, *orf7* protein interacts with transcription factor SGT and anti-apoptotic protein *Bcl-Xl.* Bone marrow stromal antigen 2 (*BST2*) acts as antiviral genes and target diverse viral families by tethering budding virions and restricting their release. Upon viral infection, *BST2* activates LILRA4/ILT7 antiviral signaling in plasmacytoid dendritic cells. Through physical interaction, *orf7a* inhibits the glycosylation of *BST2* (Taylor et al., 2015). Orf7a is found to be localized in GB, ER, ER-GB intermediate compartment, mitochondria, and cytoplasm of the infected cells. In contrast to this, *ORF7b* is predominantly localized to GB and is alone capable of inducing apoptosis. Cao and co-workers showed that SARS-CoV-2 manipulates the host ubiquitin system to enhance the ability of orf7a to antagonize the INF-I response (Cao et al., 2021).

2.8. Orf8

The *orf8* encodes for two proteins, namely *orf8a* and *orf8b*. *Orf8a* is important for SARS-CoV replication. *Orf8a* induced apoptosis involves mitochondria-mediated caspase-3 activation (Fang et al., 2021). Besides, overexpression studies demonstrated that *orf8a* is localized inside

Table 3
Coronavirus genes and mitochondrial targeting.

Gene	Mitochondrial Function	References
ORF1ab	Cause disruption of mitochondrial morphology	Freundt et al., 2009
S	Prevents mitochondria-driven apoptosis when the virus is uncoated inside the cell	Kalashnyk et al., 2021
ORF3a	Affect mitochondrial function to induce apoptosis. ORF3a induces mitochondrial damage leading to activation of NLRP3 inflammasome	Law et al., 2005, Shi et al., 2014
ORF3b	Activation of mitochondria-mediated anti-viral response. ORF3b at first accumulates within the nucleolus and then gets translocated to the OMM and demonstrated to take part in G0/G1 arrest and induction of apoptosis	McBride and Fielding, 2012a
E	Reduce mitochondrial stress. Regulates nuclear-encoded genes associated with mitochondrial functions to regulate stress response and apoptosis	DeDiego et al., 2011
M	Induce mitochondria-mediated apoptosis, also induces apoptosis via altering the expression of PDK-1 and Akt kinase and the release of cytochrome *c*	Surjit et al., 2004, Tsoi et al., 2014
ORF6	Activation of the mitochondrial signaling pathway. Involves in activation of caspase 3 with involvement of mitochondria to induce host cell apoptosis	Sawicki et al., 2005
ORF7a	Involved in Caspase-dependent mitochondria-mediated apoptosis	Tan et al., 2007
ORF7b	Involved in Caspase-dependent mitochondria-mediated apoptosis	Tan et al., 2007
ORF8a	ORF8a is localized inside the mitochondria and induced MMP and rROS production. Involved in Caspase-3 dependent mitochondria-mediated apoptosis	Chen et al., 2007
ORF8b	Involve in mitochondrial dysfunction, damage to the lysosome, and activation of autophagy	Shi et al., 2019b
N	Reduces mitochondrial membrane potential, increased ROS production, and apoptosis induction by cytochrome release into the cytoplasm	Zhang et al., 2007
ORF9b	Induces both structural and functional changes to the mitochondria also induces apoptosis	Shi et al., 2014

the mitochondria and induced MMP, and ROS production. Recently, *orf8b* involvement in the activation of NLR family pyrin domain containing 3 (NLRP3) inflammasomes and stress pathways is reported (Shi et al., 2019b). Further, *orf8b* aggregates in the cytoplasm cause ER stress, mitochondrial dysfunction, damage to the lysosome, and activation of autophagy. In epithelial cells and macrophages, *orf8b* causes cell death and inflammasomes, respectively.

2.9. Orf9b

SARS-CoV uses *orf9b* to suppress innate immunity by targeting mitochondria and the MAVS/TRAF3/TRAF6 signalosome (Shi et al., 2014b). By localizing to the OMM, *orf9b* induces mitochondrial elongation by inhibiting the expression of DRP1 (Shi et al., 2014b). Another study by Gordon et al. revealed that orf9b forms a complex with mitochondrial import receptor TOM70 in SARS-CoV and SARS-CoV2 (Gordon et al., 2020a; Gordon et al., 2020b). Besides, *orf9b* limits the interferon response of the host cell by degrading MAVS, TRAF3, and TRAF6 (Jiang et al., 2020a; Shi et al., 2014a; Shi et al., 2014b). Thus, *orf9b* induces both structural and functional changes to the mitochondria to escape from host defense and immune evasion.

3. SARS-CoV regulation of mitochondrial dynamics

SARS-CoV-mitochondrial interaction is one of the mechanisms by which the virus escapes from mitochondria mediates immunity. SARS-CoV infection leads to changes in the morphology of the infected cells and alters the expression of nuclear-encoded genes associated with mitochondrial functions. Therefore, SARS-CoV may have the ability to affect and compromise mitochondrial function. SARS-CoV can affect bioenergetics, innate immunity, apoptosis, and mitophagy by affecting retrograde and anterograde signaling. Herein, we discussed the role of SARS-CoV and its effect on mitochondrial structure and function (Table 3).

Table 4
Coronavirus protein impact on mitochondrial structure and functions.

Mitochondrial Impact	Coronavirus Protein	Virus Type	Targeting gene, enzyme, and pathway	Reference
Mitochondrial Dynamics	ORF9b	SARS-CoV	*DRP1*, IFN-g, *PCBP2*, *AIP4*, MAVS signalling, *TRAF3*, and *TRAF6*	Gordon et al., 2020a
mtDNA Copy Number	–	SARS-CoV-2	ROS, Ca^{2+} signaling	Valdes-Aguayo et al., 2021; Wiedmer et al., 2008
Mitochondrial Membrane Potential	ORF8a, nsp10	SARS-CoV	ROS, caspase-3 activation,	Keng et al., 2006
Mitochondrial Structure, Size	ORF9b, *ORF7a, ORF7b,* ORF3b, *ORF1ab*	SARS-CoV	*DRP1*, MAVS, *TRAF3 & TRAF6*	Freundt et al., 2009; Shi et al., 2014b
Oxidative Stress	*ORF7a,* nsp5 (3C-like protease), Nucleocapsid, ORF3a	SARS-CoV-2 SARS-CoV	Ap4A-hydrolase, ROS, NF-kB signalling, *IL*-1β	Chernyak et al., 2020; Lin et al., 2006; Zhang et al., 2007
Mitophagy	ORF9b, ORF10	SARS-CoV-2	*DRP1, NIX*	Li et al., 2022; Zhu et al., 2016
Antiviral Immunity	ORF9a	SARS-COV	MAVS, *NLRP3* inflammasome pathway, IL-1β and IL-18	Zhou et al., 2012
Mitochondrial Fusion	ORF9b	SARS-CoV-2 SARS-CoV	*DRP1*, *MFN1*, *MFN2*, *OPA1*	Alavi and Fuhrmann, 2013; Astuti and Ysrafil, 2020b; Shi et al., 2014b
Mitochondrial Fission	ORF9b	SARS-CoV-2 SARS-CoV	*DRP1*, *FIS1*, *MFF*, *MiD49*, *Mid51*	Astuti and Ysrafil, 2020b; Shi et al., 2014b

Transfection studies in HEK293 showed that orf9b is localized inside the mitochondria and induces the proteasomal degradation of Drp1 and affects mitochondrial fusion (Shi et al., 2014b). Further, reduced Drp1 levels also affect MAVS signaling. By promoting degradation of MAVS, TRAF3, and TRAF6, orf9b disrupts MAVS signaling and production of IFN-γ (Jiang et al., 2020a; Jiang et al., 2020b). Targeting of poly (rC) binding protein 2 (PCBP2) and the HECT domain E3 ligase (AIP4) by *orf9b* results in repression of the MAVS signaling pathway (Shi et al., 2014b). The localization of *orf9b* inside the mitochondria facilitates the interaction between *PCBP2* and *AIP4* (Shi et al., 2014b). The impact of coronavirus proteins on mitochondrial structure and functions is depicted in Table 4. Analysis of mitochondrial DNA mutation in whole transcriptome data sets from control and SARS-CoV-2 infected patients lung tissue, blood, and infected cell line model showed increased mtDNA variation in SARS-CoV-2 infected lung tissue (Table 5-6). Interestingly, we observed variation in nuclear mitochondrial genes which are associated with mitochondrial DNA replication (*POLG, POLG2, PRIMPOL, TOP1MT, TOP3A*), and repair (*APEX1, DDX5, UNG*) (Table 7). Gene expression of nuclear-encoded mitochondrial genes involved in mtDNA maintenance was downregulated in SARS-CoV-2 infected lung tissue

Table 5
Mitochondrial DNA variants identified in whole transcriptome data of control and SARS-CoV-2 infected patients' tissue, blood, and infected cell line model.

Subjects	SARS-CoV-2 status	Subject ID	Tissue type	No. of variants	Reference
Autopsy samples from patients deceased due to SARS-Cov2 infection	Positive	SRR12340086	Lung-RLL	79	Desai et al., 2020
		SRR12340087	Lung-RML	68	
		SRR12340088	Lung-RUL	73	
		SRR12340089	Lung-LUL	77	
Transcriptional profile of leukocytes in PCR negative COVID-19 controls	Negative	SRR12313439_control	leukocyte	32	Gill et al., 2020
		SRR12313441_control		12	
		SRR12313442_control		17	
		SRR12313444_control		11	
		SRR12313446_control		47	
		SRR12313449_control		8	
		SRR12313450_control		16	
Transcriptional profile of leukocytes in PCR positive COVID-19 patients	Positive	SRR12313440_covid	leukocyte	10	
		SRR12313443_covid		14	
		SRR12313445_covid		29	
		SRR12313447_covid		28	
		SRR12313448_covid		22	
		SRR12313451_covid		23	
		SRR12313452_covid		25	
Primary human lung epithelium (NHBE) were mock-treated	Negative	NHBE_1	Primary human lung epithelium (NHBE)	15	Blanco-Melo et al., 2020
		NHBE_2		15	
		NHBE_3		15	
Primary human lung epithelium (NHBE) were infected with SARS-CoV-2.	Positive	NHBE_4	Primary human lung epithelium (NHBE)	15	
		NHBE_5		15	
		NHBE_6		16	
Uninfected human lung biopsies	Negative	Healthy_1	Lung tissue	22	
		Healthy_2		35	
lung samples derived from COVID-19 deceased patient	Positive	Covid_1	Lung tissue	50	
		Covid_2		55	

Lung-RLL, right lower lobe, Lung-RML, right middle lobe, Lung-RUL, right upper lobe,

(Table 8).

4. SARS-CoV alter mtDNA copy number

Alteration in mtDNA copy number is known to affect both the structure and function of the mitochondria. Infection with viruses such as Herpes simplex virus 1 and Epstein Barr virus is known to alter the mtDNA content. For example, the UL12.5 protein of HSV1 induces mtDNA depletion during productive infection of mammalian cells (Saffran et al., 2007). Another study reported that the Zta protein of EBV depleted mtDNA in the host cells (Wiedmer et al., 2008). By interacting with mitochondrial single-stranded DNA binding protein, the Zta protein of EBV reduces mtDNA replication. HCV *via* induction of ROS and NO-mediated pathways induces mtDNA damage. Further, mtDNA depletion is also reported in HIV-HCV confected humans. A study by Collins et al. (2004) reported the inflammatory nature of the mtDNA (Collins et al., 2004). SARS-CoV impact on mtDNA copy number requires detailed investigation.

5. SARS-CoV alters the mitochondrial membrane potential (MMP)

The infection with SARS-CoV causes an extensive cytopathic effect. MMP plays an important role in the segregation and sorting of the defective mitochondria for subsequent repair or elimination process in which inner and outer mitochondria membrane proteins play a crucial role. The SARS-CoV nucleocapsid protein reduced the MMP while inducing apoptosis in COS-1 cells (Zhang et al., 2007). Overexpression of orf3b did not significantly alter the MMP of the host cell (Kopecky-Bromberg et al., 2007). The perturbation of MMP by *orf8a* of SARS-CoV is also reported. Nsp10 interacts with the cellular oxidoreductase system and causes the cytopathic effect. Transfection of nsp10 gene to KMB-17 cells showed a decrease in MMP at 24hrs followed by a recovery at 48 hrs post-transfection (Li et al., 2005). Also, pull down and Western blot analysis showed that nsp10 interacts with cytochrome oxidase complex, thus affecting the mitochondrial oxidoreductase system. A study by Schneider et al. reported the loss of MMP in mitochondria upon viral infection (Schneider et al., 2019).

6. SARS-CoV and mitochondrial mass

Several studies have reported that viral infection alters mitochondrial mass. Viral genome encoded proteins induce mitophagy to reduce the mitochondrial mass (Gou et al., 2017). Total mitochondrial mass is an essential factor contributing to MMP. Transmissible gastroenteritis virus (TGEV) infected IPEC-J2 showed a reduced mitochondrial mass (Zhu et al., 2016). The reduction of mitochondrial mass could be due to the degradation of mitochondria by activation of mitochondrial degradation machinery.

7. SARS-CoV proteins influences size, structure, and distribution of mitochondria

SARS-CoV infection exerts its effect *via* targeting the structure, distribution, and function of mitochondria. The orf9b of SARS-CoV localizes inside the mitochondria and causes elongation of mitochondria in HEK293 cells (Barbier et al., 2017). Besides, orf9b activates ubiquitination and proteasomal degradation of DRP1, thereby inhibiting mitochondria fission. Besides, the elongated mitochondria also showed interaction with autophagosomes. The interaction between autophagosome and mitochondria may induce mitophagy. Thus, alteration in the mitochondrial structure may contribute to compromised antiviral response and signaling. Not all the SARS-CoV encoded proteins are translocated to mitochondria. For example, a study by Schaecher and colleagues (2007) showed in Vero cells that, SARS-CoV *orf7a* and *orf7b* are localized to GB but not to mitochondria. Orf4b is another protein that is not reported inside mitochondria (Schaecher et al., 2007b). A study by Matthews et al.(2014) showed that Middle East respiratory

Table 6
Number of mitochondrial DNA variants in mitochondrial protein-coding genes identified in whole transcriptome data of control and SARS-CoV-2 infected patients tissue specimens.

	Desai et al., (2020)				Blanco-Melo et al., (2020)								
Gene	SRR12340086	SRR12340087	SRR12340088	SRR12340089	COVID-1	COVID-2	Healthy-1	Healthy-2	NHBE-1	NHBE-2	NHBE-3	NHBE-4	NHBE-5	NHBE-6
ND1	4	4	4	4	3	5	1							
ND2	4	2	2	4	3	2	1	2	1	1	1	1	1	1
COX1	7	7	5	5	4	5	1	2						
COX2	1	1	1	1	4	2								
ATP8	2	2	3	1										
ATP6	3	3	4	5	2	2	2	2	1	1	1	1	1	1
COX3	4	3	3	3		2		1						
ND3	3	2	2	2	1	2		1						
ND4L	2	2	2	2	1									
ND4	3	3	2	3	4	4		3						
ND5	13	12	11	12	11	6	1	2						
ND6	2	2	2	2		1		1						
CYTB	4	3	4	4	9	6	2	5	2	2	2	2	2	2
	52	46	45	48	42	37	8	19	4	4	4	4	4	4

syndrome coronavirus (MERS-CoV) encoded orf4b localizes to the nucleus and not to mitochondria (Matthews et al., 2014). Another study by Freundt et al. (2009) showed that, inside the host cells, the protein encoded by the SARS-CoV are distributed between the mitochondria and nucleus (Freundt et al., 2009). Live imaging and confocal microscopy studies showed that orf3b is localized in both nucleus and mitochondria in Vero cells. Very interestingly, orf3b is also reported to affect the spatiotemporal distribution within the infected cells. For instance, orf3b was initially detected in the nucleus and gets translocated to the mitochondria over time with the help of a mitochondrial translocation signal (Freundt et al., 2009). Besides, orf3b has a nuclear export sequence rich in leucine to be transported from the nucleus. The interaction between leucine-rich nuclear export and CRM1 facilitates the nuclear transport of orf3b. Murine coronavirus replication protein nsp4 is partially localized to mitochondria and causes disrupted mitochondrial morphology (Freundt et al.). Also, the cells infected with Alb ts6 icv showed larger and extensively vacuolated mitochondria (Clementz et al., 2008). Changes in the mitochondrial structure are also linked with host cell response against viruses. For instance, *orf9b* by inducing degradation of DRP1 to elongate mitochondria, which is linked with host cell interferon response against SARS-CoV. SARS-CoV also targets the respiratory chain complex I proteins. A study by Pfefferle and co-workers have shown that the respiratory chain complex I proteins is one of the key targets of SARS-CoV (Pfefferle et al., 2011).

8. SARS-CoV induction of oxidative stress

It is now well established that viruses induce oxidative stress in the host cell for their survival. Studies on SARS-CoV also suggest a similar mechanism. A study by Lin and colleagues (2006) has demonstrated that SARS-CoV induces oxidative stress in the host cells. An increase in ROS and defective ROS scavenging/anti-oxidant systems contributes to oxidative stress, inflammation, and activation of immune responses. SARS-CoV 3CLpro significantly increases the ROS levels and activation of the NF-kB pathway in HL-CZ cells (Lin et al., 2006). Besides, the increase in ROS was linked with the induction of apoptosis in HL-CZ cells. While 3CLpro induced nuclear factor-kappa B pathway, it significantly inhibited AP1-dependent transcription. Oxidative stress-induced transcription of NF-kB signaling is reported as an inducer of apoptosis in several types of cells. Another study by Zhang et al. (2007) demonstrated that the apoptosis induction by the SARS-CoV nucleocapsid protein is a mitochondrial-dependent pathway. Transfection of nucleocapsid gene into COS-1 cells reduced MMP, increased ROS production, and apoptosis induction by cytochrome release into the cytoplasm, caspase-3 activation, and PARP cleavage (Zhang et al., 2007). Very interestingly, the SARS-CoV membrane gene (M) and spike gene (S) were incapable of inducing apoptosis in COS-1 cells.

Acute lung injury upon infection with SARS-CoV is one of the causes of respiratory failure and a high mortality rate. Activation of oxidative stress pathway together with pro-inflammatory host response is proposed to contribute to the onset of lung injury. Oxidative stress is reported to induce the expression of pro-inflammatory cytokine genes (Mirowsky et al., 2016). SARS-CoV infected aged macaques showed a stronger pro-inflammatory response as opposed to young macaques (Smits et al., 2010). *Orf7a* encoded by SARS-CoV is reported in various pathological condition, including inappropriate induction of apoptosis and inhibition of protein synthesis inside the host cell. Screening by yeast two-hybrid approach and co-immunoprecipitation analysis identified orf7a to interact with Ap4A-hydrolase. Further, the Ap4A-hydrolase level gets elevated upon oxidative stress.

SARS-CoV orf3a protein stimulates the secretion of IL-1β via efflux of K^+ and ROS production. By disrupting intracellular ionic concentration, orf3a induces mitochondrial damage leading to activation of NLRP3 inflammasome. SARS-CoV papain-like protease (PLpro) upregulates the pro-fibrotic responses in lung cells. PLpro triggered TGF-β1 activation in an Egr-1 dependent manner by ROS/p38 MAPK/STAT3 pathway. By

Table 7
Deleterious protein-coding variants in nuclear mitochondrial genes identified in whole transcriptome data of SARS-CoV-2 infected patients lung tissue specimens.

Gene symbol	Function	Mutation identified	Mutation type	SIFT	PolyPhen	Subject ID	Sample type	Reference
APEX1	mtDNA repair	p.Pro311Ser	missense_variant	Deleterious	probably_damaging	SRR12340086	Lung	Desai et al., 2020
APEX1	DEAD-box RNA helicase	p.Pro311Leu	missense_variant	Deleterious	probably_damaging		tissue	
DDX5		p.Ala441Val	missense_variant	Deleterious	probably_damaging			
UNG	mtDNA repair	p.Val272Ala	missense_variant	Deleterious	probably_damaging	SRR12340087	Lung	
POLG	mtDNA replication	p.Pro412Leu	missense_variant	Deleterious	probably_damaging		tissue	
TOP3A	mtDNA decatenation and	p.Ile70Asn	missense_variant	Deleterious	probably_damaging	SRR12340088	Lung	
POLG2	segregation	p.Trp295Arg	missense_variant	Deleterious	probably_damaging		tissue	
	mtDNA replication							
PRIMPOL	mtDNA replication	p.Tyr402Cys	missense_variant	Deleterious	probably_damaging	SRR12340089	Lung	
TOP1MT		p.Leu552Arg	missense_variant	Deleterious	probably_damaging		tissue	
POLG		p.Thr599Ile	missense_variant	Deleterious	probably_damaging			
TOP3A		p.Asp484Tyr	missense_variant	Deleterious	probably_damaging			
POLG2		p.Val441Phe	missense_variant	Deleterious	probably_damaging			

localizing inside the mitochondria and targeting the MAVS/TRAF3/TRAF6 axis *orf9b* suppresses innate immunity and targets the MAVS/TRAF3/TRAF6 axis to suppress innate immunity (Shi et al., 2014a). Further, another SARS-CoV protein, *orf8a* is reported within mitochondria. *Orf8a* protein plays a critical role in increasing MMP and ROS production, cellular oxygen consumption rate, inducing apoptosis by caspase-3 activation in Vero, HEK293, and Huh7 cells (Keng et al., 2006).

9. SARS-CoV proteins induce mitophagy

Virus-induced mitophagy is implicated in viral propagation. Studies have documented the induction of mitophagy upon infection by SARS-CoV. Zhu et al. (2016) showed the induction of mitophagy upon TGEV infection. Virus infection induces mitophagy to escape from host immunity and completion of the viral life cycle. Orf9b counteracts the stress, which fragments and aggregates mitochondria to promote host cell survival during viral replication (Zhu et al., 2016).

10. Molecular determinants of mitochondrial localization of SARS-CoV

SARS-CoV encoded proteins have been shown to affect both structure and function of mitochondria. The mitochondrial dysfunction could be due to the localization of SARS-CoV proteins into mitochondria. Interestingly, both proteins and RNA of SARS-CoV possess a distinct mitochondrial translocation signal (Singh et al., 2020). The accessory protein orf3b encoded by the SARS-CoV2 genome is localized in the outer membranes of mitochondria. Besides mitochondria, orf3b is also localized to the nucleus. Orf3b possesses a nuclear export sequence-dependent on CRM1 and is predicted to process an amphipathic α-helix sequence containing two lysine residues, which may bind to the outer membranes of the mitochondria (Freundt et al., 2009). Another study reported the presence of mitochondrial translocation signals in the 5′- and 3′-untranslated regions of SARS-CoV2 (Singh et al., 2020; Wu et al., 2020). Further, we have predicted the mitochondrial signal peptides, signal peptide cleavage site, and mitochondrial processing peptidase cleavage site in SARS-CoV2 encoded proteins using SignalP v5.0 tool, MitoFates, and TargetP tools (Almagro Armenteros et al., 2019; Emanuelsson et al., 2000; Fukasawa et al., 2015). Our bioinformatic analysis of the SARS-CoV-2 genome identified Spike protein, orf7a, and orf8 to possess a mitochondrial signal peptide cleavage site (Fig. 2). However, these findings need to be experimentally confirmed. Experiments are ongoing in our laboratories to identify the function of these proteins in manipulating host mitochondria by SARS-CoV-2.

11. SARS-CoV target mitochondria for anti-viral immunity

Mitochondria play a critical role in generating anti-viral immunity to protect the host cell. Mitochondria, through MAVS, plays a vital role in the production of IFN. Orf9a physically binds and promotes K48 mediated ubiquitination-dependent proteasomal degradation of MAVS to disrupt the production of IFN. Mechanistic studies have reported that both ROS or mtDNA from damaged mitochondria are reported to activate the NLRP3 inflammasome pathway. By associating with mitochondrial antiviral signaling (MAVS) or mitofusin 2, activated NLRP3 is translocated to the outer mitochondrial membrane leading to caspase-1 activation. Active caspase-1 triggers IL-1β and IL-18 secretion. Another study showed the upregulation of genes encoded by the mtDNA in the peripheral blood mononuclear cell (PBMC) of convalescent SARS patients (Zhou et al., 2012). Besides, gene-related to oxidative stress, heat shock proteins, and cytokines were also significantly elevated. The co-upregulation of mitochondrial genes and cytokines connects the possible cross-talk between mitochondria and antiviral immunity. However, comprehensive studies are required to investigate the molecular mechanism behind the role of compromised mitochondrial function with antiviral immunity.

12. Prospects of targeting the virus-mitochondria interactions

The proteins of SARS-CoV2 have been shown to trigger apoptosis and cytokine storm in the host cell. Patients with severe and acute respiratory syndrome show significantly higher levels of pro-inflammatory cytokines in their peripheral blood (Costela-Ruiz et al., 2020). The uncontrolled increase in pro-inflammatory cytokines or cytokine storm has been shown to manifest severe distress leading to organ dysfunction (Ye et al., 2020). Mitochondrial dysfunction is a key source of ROS and has been speculated to trigger inflammatory response and induction of cytokine storm. Both mitochondrial dysfunctions leading to increased ROS and inflammation have been linked with innate immune system activation and induction of NLRP3 inflammasome, and induction of cytokine storms (Kaivola et al., 2021). For instance, CoV Envelope protein, ORF3a, and ORF8b have been shown to activate the inflammasome. The CoV envelope protein-induced calcium influx stimulates mitochondria to generate ROS (Kaivola et al., 2021). ORF3a induced K + efflux have been shown to participate and promote the assembly of inflammasomes via the promotion of TRAF3-ORF3a interaction resulting in NF- κβ activation and transcription of pro-inflammatory cytokines notably pro–IL-1β and IL-18 (Siu et al., 2019; Yap et al., 2020). ORF8b has been shown to directly interact and stimulate NLRP3. Activation of NLRP3 has been shown to induce pores in mitochondria and plasma membranes and may stimulate the IL-1β/IL-18 secretion and induction of a series of cascades leading to cytosolic secretion of cytochrome-C and apoptosis (Shah, 2020). These data collectively suggest that the SARS-COV2 encoded proteins induced structural and functional alteration in mitochondria can induce mitophagy. Thus, SARS-CoV2 infection can initiate signaling events leading to apoptosis activation via mitochondrial damage, induction of ROS and inflammasome, and cytokine storm.

Table 8
Downregulation of mitochondrial DNA maintenance genes identified in whole transcriptome data of SARS-CoV-2 infected patients lung tissue (from: Blanco-Melo et al., 2020).

Gene symbol	logFC	Gene description	Function
RECQL4	3.301125548	RecQ like helicase 4	mtDNA maintenance
METTL4	0.960866022	methyltransferase like 4	mtDNA maintenance
POLB	0.775953276	DNA polymerase beta	mtDNA maintenance
APEX1	0.184002807	apurinic/apyrimidinic endodeoxyribonuclease 1	mtDNA maintenance
PIF1	0.064341063	PIF1 5′-to-3′ DNA helicase	mtDNA maintenance
SSBP1	−0.095574337	single stranded DNA binding protein 1	mtDNA maintenance
POLDIP2	−0.215238656	DNA polymerase delta interacting protein 2	mtDNA maintenance
PPA2	−0.222606157	inorganic pyrophosphatase 2	mtDNA maintenance
DNA2	−0.290150169	DNA replication helicase/ nuclease 2	mtDNA maintenance
EXOG	−0.314869688	exo/endonuclease G	mtDNA maintenance
MTERF1	−0.323074621	mitochondrial transcription termination factor 1	mtDNA maintenance
LIG3	−0.363345113	DNA ligase 3	mtDNA maintenance
POLG2	−0.423754726	DNA polymerase gamma 2, accessory subunit	mtDNA maintenance
UNG	−0.431007241	uracil DNA glycosylase	mtDNA maintenance
MGME1	−0.936039411	mitochondrial genome maintenance exonuclease 1	mtDNA maintenance
OGG1	−1.067414664	8-oxoguanine DNA glycosylase	mtDNA maintenance
MTERF2	−1.133486683	mitochondrial transcription termination factor 2	mtDNA maintenance
POLRMT	−1.320205504	RNA polymerase mitochondrial	mtDNA maintenance
TFAM	−1.324537142	transcription factor A, mitochondrial	mtDNA maintenance
MUTYH	−1.34437367	mutY DNA glycosylase	mtDNA maintenance
POLG	−1.536793488	DNA polymerase gamma, catalytic subunit	mtDNA maintenance
ENDOG	−1.94800646	endonuclease G	mtDNA maintenance
PRIMPOL	−2.032059322	primase and DNA directed polymerase	mtDNA maintenance
TOP1MT	−1.906133073	DNA topoisomerase I mitochondrial	mtDNA maintenance
TFB2M	−2.002097354	transcription factor B2, mitochondrial	mtDNA maintenance
RNASEH1	−2.236099433	ribonuclease H1	mtDNA maintenance
TOP3A	−3.016484079	DNA topoisomerase III alpha	mtDNA maintenance
ATAD3A	−3.560998784	ATPase family AAA domain containing 3A	mtDNA maintenance
TWNK	−3.597778413	twinkle mtDNA helicase	mtDNA maintenance
ATAD3B	−4.024036831	ATPase family AAA domain containing 3B	mtDNA maintenance

Given the important role of mitochondrial role in inflammation and cytokine storm during SARS-COV2 pathogenesis, protecting the mitochondria from inflammation-induced damage might be very attractive. In recent times, several molecules that can protect mitochondria have been developed. Since, mitochondrial damage appears to be an upstream event in the induction of inflammation and inflammasome assembly, targeting this crosstalk could be a promising approach for improved management of COVID-19 patients. We thus, propose that targeting the virus and mitochondria nexus may boost the host immune pathways and promote cell survival and prevent premature apoptosis of the cell. Towards this, mitochondrial pharmacology may be attempted to target the virus-mitochondria interaction. Besides, mitochondria-mediated ROS is one of the drivers of inflammation. The use of antioxidant agents may be an attractive and safe approach to inhibit ROS and inflammation. OXPHOS modulators, mitochondrial pyruvate carrier, pharmacological induction of mitochondrial biogenesis, mitochondrial redox state, mitochondrial dynamic needs detailed investigation as pharmacological targets for the management of COVID-19 patients. Moreover, blocking the interaction between SARS-CoV protein with mitochondria and induction of inflammasome by RNAi approach may represent a viable strategy to prevent the anti-immune signaling for SARS-CoV2 and prevent the upstream events amplifying the effects of ROS, inflammasome, and cytokine storm.

13. Altered mitochondrial function in individuals with post-COVID complications

The COVID-19 pandemic has ravaged most of the world, with Asian countries, including India, being most affected. Earlier studies have shown that viral infections are linked with impaired mitochondrial function causing long-term cognitive and metabolic perturbation in patients (Katz et al., 2010; Sweetman et al., 2020). Studies have shown that individuals with primary mitochondrial disorders are at high risk of developing severe complications post-SARS-CoV-2 exposure (Pizzamiglio et al., 2022; Singh et al., 2020). The mechanism of altered metabolic adaptation is due to the SARs virus regulating the host metabolism machinery and redirecting them to viral replication (Elesela and Lukacs, 2021). Research studies have also indicated that patients with post-COVID complications, including long COVID, have been associated with chronic fatigue, and neuropsychiatric and neurometabolic disorders (Kedor et al., 2022). These studies indicated that there is a possibility that post-SARS-CoV-2 infection, patients with long COVID symptoms involving CNS symptoms, myalgic encephalomyelitis, and cognitive dysfunction due to perturbed mitochondrial metabolic pathway (Booth et al., 2012; Paul et al., 2021). Post-COVID complications may arise from perpetual metabolic imbalance contributed by mitochondrial dysfunction and chronic inflammation leading to long COVID symptoms (de Boer et al., 2022; Nunn et al., 2022). An earlier study has shown that SARS-CoV-2 can regulate mitochondrial oxidative phosphorylation (OXPHOS), apoptosis, and ATP levels in the airway epithelial cells in the host, contributing to hypoxemia in patients (Archer et al., 2022). Yet another study has shown that patients with long COVID may have limited capacity to return to normal exercise routine due to impaired oxygenation in muscle tissue (Singh et al., 2022). Mitochondrial therapy, including antioxidant CoQ10, glycolysis inhibitors, Vitamin E, and minerals, along with regular exercise, may help patients with long COVID symptoms for faster recovery (Wood et al., 2021).

14. Conclusion

Despite significant progress, the role of mitochondria in the pathophysiology of COVID-19 remains poorly understood. Experimental evidence suggests the potential role of mitochondria in controlling immunity against SARS-CoV-2. Research has shown that coronavirus infection leads to alteration in both structure and function of the mitochondria. These mitochondrial alterations are likely to alter cross-talk between mitochondria and the nucleus during SARS-CoV infection. The relevance of these interactions during SARS pathogenesis requires detailed investigation. Mechanistic studies about mitochondrial dynamics may open new avenues to design and target novel therapeutic strategies against SARS-CoV. Since many SARS-CoV proteins localize to mitochondria, inhibiting their translocation can be useful as a treatment strategy against SARS infection. In conclusion, studies focusing on SARS-CoV-2 manipulation of key mitochondrial functions such as energetics, anterograde and retrograde signaling, anti-viral signaling, crosstalk

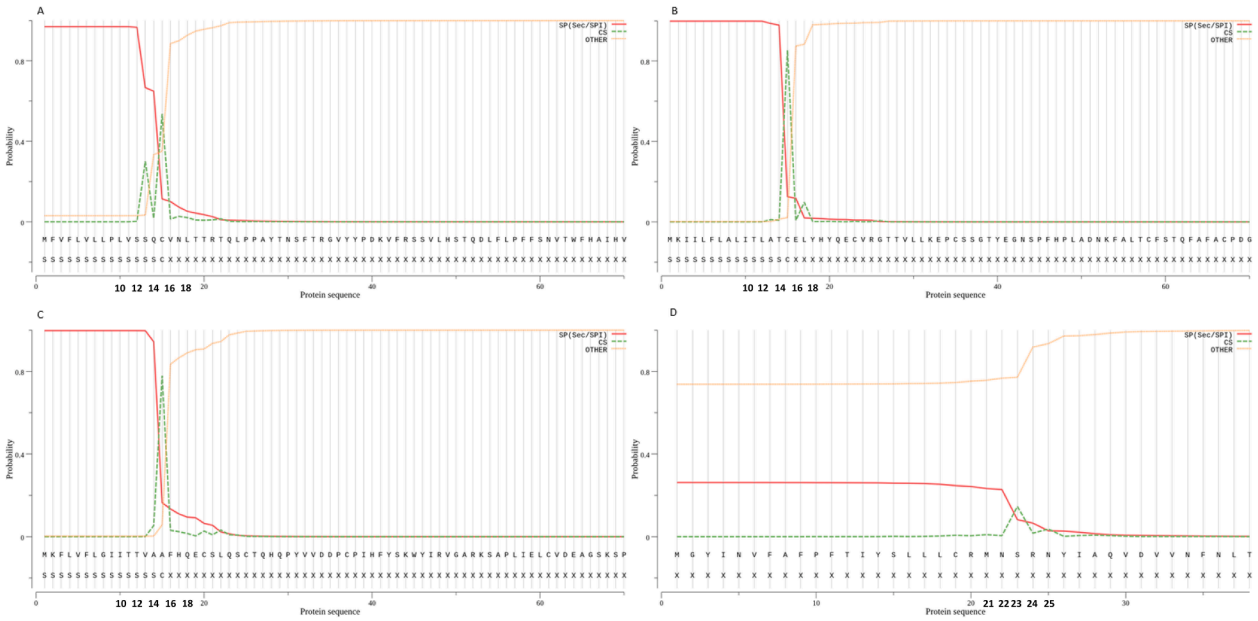

Fig. 2. Signal peptide cleavage sites in SARS-CoV2 peptides. A) spike protein with a probability score of 0.968. B) ORF7a protein with a probability score of 0.998. C) ORF8 protein with a probability score of 0.997. D) ORF10 protein with a probability score of 0.262.

between mitochondria, and crosstalk between mitochondria and other organellar should fill the existing gap to advance prevention or treatment of COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The raw data is available from public database Gene Expression Omnibus with GEO IDs: GSE150316, GSE147507 and GSE154998. The analyzed result are provided in the respective table in the manuscript.

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Author contributions

S.P. Kabekkodu , S. Chakrabarty and K. Satyamoorthy designed study, P. Jayaram and S. Mallya analyzed data, SP. Kabekkodu, S. Chakrabarty and K. Satyamoorthy wrote the paper, K. Thangaraj, K.K. Singh and K. Satyamoorthy revised and updated the manuscript.

Reference

Alavi, M.V., Fuhrmann, N., 2013. Dominant optic atrophy, OPA1, and mitochondrial quality control: Understanding mitochondrial network dynamics. BioMed Central.

Almagro Armenteros, J.J., Tsirigos, K.D., Sønderby, C.K., Petersen, T.N., Winther, O., Brunak, S., von Heijne, G., Nielsen, H., 2019. SignalP 5.0 improves signal peptide predictions using deep neural networks. Nat. Biotechnol. 37, 420–423.

Angajala, A., Lim, S., Phillips, J.B., Kim, J.H., Yates, C., You, Z., Tan, M., 2018. Diverse roles of mitochondria in immune responses: novel insights into immuno-metabolism. Front. Immunol. 9, 1605.

Archer, S.L., Dasgupta, A., Chen, K.H., Wu, D., Baid, K., Mamatis, J.E., Gonzalez, V., Read, A., Bentley, R.E., Martin, A.Y., Mewburn, J.D., Dunham-Snary, K.J., Evans, G. A., Levy, G., Jones, O., Al-Qazazi, R., Ring, B., Alizadeh, E., Hindmarch, C.C., Rossi, J., Lima, P.D., Falzarano, D., Banerjee, A., Colpitts, C.C., 2022. SARS-CoV-2 mitochondriopathy in COVID-19 pneumonia exacerbates hypoxemia. Redox Biol. 58, 102508.

Astuti, I., Ysrafil, 2020a. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes Metab Syndr 14, 407-412.

Banoth, B., Cassel, S.L., 2018. Mitochondria in innate immune signaling. Transl. Res. 202, 52–68.

Barbier, V., Lang, D., Valois, S., Rothman, A.L., Medin, C.L., 2017. Dengue virus induces mitochondrial elongation through impairment of Drp1-triggered mitochondrial fission. Virology 500, 149–160.

Bhardwaj, K., Liu, P., Leibowitz, J.L., Kao, C.C., 2012. The coronavirus endoribonuclease Nsp15 interacts with retinoblastoma tumor suppressor protein. J. Virol. 86, 4294–4304.

Blanco-Melo, D., Nilsson-Payant, B.E., Liu, W.-C., Uhl, S., Hoagland, D., Møller, R., Jordan, T.X., Oishi, K., Panis, M., Sachs, D., Wang, T.T., Schwartz, R.E., Lim, J.K., Albrecht, R.A., TenOever, B.R., 2020. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. Cell 181, 1036-1045.e1039.

Booth, N.E., Myhill, S., McLaren-Howard, J., 2012. Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Int. J. Clin. Exp. Med. 5, 208–220.

Bouvet, M., Lugari, A., Posthuma, C.C., Zevenhoven, J.C., Bernard, S., Betzi, S., Imbert, I., Canard, B., Guillemot, J.C., Lécine, P., Pfefferle, S., Drosten, C., Snijder, E.J., Decroly, E., Morelli, X., 2014. Coronavirus Nsp10, a critical co-factor for activation of multiple replicative enzymes. J. Biol. Chem. 289, 25783–25796.

Burtscher, J., Cappellano, G., Omori, A., Koshiba, T., Millet, G.P., 2020. Mitochondria: In the Cross Fire of SARS-CoV-2 and Immunity. iScience 23, 101631.

Cao, Z., Xia, H., Rajsbaum, R., Xia, X., Wang, H., Shi, P.-Y., 2021. Ubiquitination of SARS-CoV-2 ORF7a promotes antagonism of interferon response. Cell. Mol. Immunol. 18, 746–748.

Carrasco-Hernandez, R., Jacome, R., Lopez Vidal, Y., Ponce de Leon, S., 2017. Are RNA viruses candidate agents for the next global pandemic? A review. ILAR J. 58, 343–358.

Chan, C.M., Ma, C.W., Chan, W.Y., Chan, H.Y., 2007. The SARS-Coronavirus Membrane protein induces apoptosis through modulating the Akt survival pathway. Arch. Biochem. Biophys. 459, 197–207.

Chan, J.F., Kok, K.H., Zhu, Z., Chu, H., To, K.K., Yuan, S., Yuen, K.Y., 2020. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect 9, 221–236.

Chan, W.S., Wu, C., Chow, S.C., Cheung, T., To, K.F., Leung, W.K., Chan, P.K., Lee, K.C., Ng, H.K., Au, D.M., Lo, A.W., 2005. Coronaviral hypothetical and structural proteins

were found in the intestinal surface enterocytes and pneumocytes of severe acute respiratory syndrome (SARS). Mod. Pathol. 18, 1432–1439.
Chanturiya, A.N., Basanez, G., Schubert, U., Henklein, P., Yewdell, J.W., Zimmerberg, J., 2004. PB1-F2, an influenza A virus-encoded proapoptotic mitochondrial protein, creates variably sized pores in planar lipid membranes. J. Virol. 78, 6304–6312.
Chen, C.-Y.C.Y., Ping, Y.-H.Y.H., Lee, H.-C.H.C., Chen, K.H.K.-H., Lee, Y.-M.Y.M., Chan, Y.J.Y.-J., Lien, T.-C.T.C., Jap, T.-S.T.S., Lin, C.-H.C.H., Kao, L.-S.L.S., Chen, Y.-M.A.Y. Ming A., 2007. Open Reading Frame 8a of the Human Severe Acute Respiratory Syndrome Coronavirus Not Only Promotes Viral Replication but Also Induces Apoptosis. The Journal of Infectious Diseases 196, 405-415.
Chernyak, B.V., Popova, E.N., Prikhodko, A.S., Grebenchikov, O.A., Zinovkina, L.A., Zinovkin, R.A., 2020. COVID-19 and Oxidative Stress. Biochemistry (Mosc.) 85, 1543–1553.
Chow, K.Y.C., Yeung, Y.S., Hon, C.C., Zeng, F., Law, K.M., Leung, F.C.C., 2005. Adenovirus-mediated expression of the C-terminal domain of SARS-CoV spike protein is sufficient to induce apoptosis in Vero E6 cells. FEBS Lett. 579, 6699–6704.
Clementz, M.A., Kanjanahaluethai, A., O'Brien, T.E., Baker, S.C., 2008. Mutation in murine coronavirus replication protein nsp4 alters assembly of double membrane vesicles. Virology 375, 118–129.
Collins, L.V., Hajizadeh, S., Holme, E., Jonsson, I.-M., Tarkowski, A., 2004. Endogenously oxidized mitochondrial DNA induces in vivo and in vitro inflammatory responses. J. Leukoc. Biol. 75, 995–1000.
Cornillez-Ty, C.T., Liao, L., Yates, J.R., Kuhn, P., Buchmeier, M.J., 2009. Severe Acute Respiratory Syndrome Coronavirus Nonstructural Protein 2 Interacts with a Host Protein Complex Involved in Mitochondrial Biogenesis and Intracellular Signaling. J. Virol. 83, 10314–10318.
Costela-Ruiz, V.J., Illescas-Montes, R., Puerta-Puerta, J.M., Ruiz, C., Melguizo-Rodriguez, L., 2020. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. Cytokine Growth F R 54, 62–75.
Cottam, E.M., Maier, H.J., Manifava, M., Vaux, L.C., Chandra-Schoenfelder, P., Gerner, W., Britton, P., Ktistakis, N.T., Wileman, T., 2011. Coronavirus nsp6 proteins generate autophagosomes from the endoplasmic reticulum via an omegasome intermediate. Autophagy 7, 1335–1347.
de Boer, E., Petrache, I., Goldstein, N.M., Olin, J.T., Keith, R.C., Modena, B., Mohning, M. P., Yunt, Z.X., San-Millan, I., Swigris, J.J., 2022. Decreased Fatty Acid Oxidation and Altered Lactate Production during Exercise in Patients with Post-acute COVID-19 Syndrome. Am. J. Respir. Crit. Care Med. 205, 126–129.
DeDiego, M.L., Nieto-Torres, J.L., Jiménez-Guardeño, J.M., Regla-Nava, J.A., Álvarez, E., Oliveros, J.C., Zhao, J., Fett, C., Perlman, S., Enjuanes, L., 2011. Severe acute respiratory syndrome coronavirus envelope protein regulates cell stress response and apoptosis. PLoS Pathog. 7, e1002315–e.
Dehipawala, S., Cheung, E., Tremberger, G., Cheung, T., 2021. Entropy and Fractal Dimension Study of the TDP-43 Protein Low Complexity Domain Sequence in ALS Disease Severity and SARS-CoV-2 Gene Sequences in Virulence Variability. Entropy (Basel) 23.
Deming, D.J., Graham, R.L., Denison, M.R., Baric, R.S., 2007. Processing of open reading frame 1a replicase proteins nsp7 to nsp10 in murine hepatitis virus strain A59 replication. J. Virol. 81, 10280–10291.
Deng, X., Hackbart, M., Mettelman, R.C., O'Brien, A., Mielech, A.M., Yi, G., Kao, C.C., Baker, S.C., 2017. Coronavirus nonstructural protein 15 mediates evasion of dsRNA sensors and limits apoptosis in macrophages. P Natl Acad Sci USA 114, E4251-E4260.
Desai, N., Neyaz, A., Szabolcs, A., Shih, A.R., Chen, J.H., Thapar, V., Nieman, L.T., Solovyov, A., Mehta, A., Lieb, D.J., Kulkarni, A.S., Jaicks, C., Xu, K.H., Raabe, M.J., Pinto, C.J., Juric, D., Chebib, I., Colvin, R.B., Kim, A.Y., Monroe, R., Warren, S.E., Danaher, P., Reeves, J.W., Gong, J., Rueckert, E.H., Greenbaum, B.D., Hacohen, N., Lagana, S.M., Rivera, M.N., Sholl, L.M., Stone, J.R., Ting, D.T., Deshpande, V., 2020. Temporal and spatial heterogeneity of host response to SARS-CoV-2 pulmonary infection. Nat. Commun. 11.
Diao, B., Wang, C., Tan, Y., Chen, X., Liu, Y., Ning, L., Chen, L., Li, M., Liu, Y., Wang, G., Yuan, Z., Feng, Z., Zhang, Y., Wu, Y., Chen, Y., 2020. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). Front. Immunol. 11, 827.
Elesela, S., Lukacs, N.W., 2021. Role of Mitochondria in Viral Infections. Life (Basel) 11.
Emanuelsson, O., Nielsen, H., Brunak, S., Von Heijne, G., 2000. Predicting subcellular localization of proteins based on their N-terminal amino acid sequence. J. Mol. Biol. 300, 1005–1016.
Fang, P., Fang, L., Zhang, H., Xia, S., Xiao, S., 2021. Functions of coronavirus accessory proteins: overview of the state of the art. Viruses 13.
Freundt, E.C., Yu, L., Park, E., Lenardo, M.J., Xu, X.-N., 2009. Molecular determinants for subcellular localization of the severe acute respiratory syndrome coronavirus open reading frame 3b protein. J. Virol. 83, 6631–6640.
Friedman, J.R., Nunnari, J., 2014. Mitochondrial form and function. Nature 505, 335–343.
Frieman, M., Yount, B., Heise, M., Kopecky-Bromberg, S.A., Palese, P., Baric, R.S., 2007. Severe acute respiratory syndrome coronavirus ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum/Golgi membrane. J. Virol. 81, 9812–9824.
Fukasawa, Y., Tsuji, J., Fu, S.C., Tomii, K., Horton, P., Imai, K., 2015. MitoFates: Improved prediction of mitochondrial targeting sequences and their cleavage sites. Mol. Cell. Proteomics 14, 1113–1126.
Fung, T.S., Liao, Y., Liu, D.X., 2016. Regulation of stress responses and translational control by coronavirus. MDPI AG.
Ganji, R., Reddy, P.H., 2020. Impact of COVID-19 on Mitochondrial-Based Immunity in Aging and Age-Related Diseases. Front. Aging Neurosci. 12, 614650.
Gill, S.E., dos Santos, C.C., O'Gorman, D.B., Carter, D.E., Patterson, E.K., Slessarev, M., Martin, C., Daley, M., Miller, M.R., Cepinskas, G., Fraser, D.D., 2020. Transcriptional profiling of leukocytes in critically ill COVID19 patients: implications for interferon response and coagulation. Intensive Care Med. Exp. 8.
Gordon, D.E., Jang, G.M., Bouhaddou, M., Xu, J., Obernier, K., Meara, M.J., Guo, J.Z., Swaney, D.L., Tummino, T.A., Huttenhain, R., Kaake, R.M., Richards, A.L., Tutuncuoglu, B., Foussard, H., Batra, J., Haas, K., Modak, M., Kim, M., Haas, P., Polacco, B.J., Braberg, H., Fabius, J.M., Eckhardt, M., Soucheray, M., Bennett, M.J., Cakir, M., McGregor, M.J., Li, Q., Naing, Z.Z.C., Zhou, Y., Peng, S., Kirby, I.T., Melnyk, J.E., Chorba, J.S., Lou, K., Dai, S.A., Shen, W., Shi, Y., Zhang, Z., Barrio-Hernandez, I., Memon, D., Hernandez-Armenta, C., Mathy, C.J.P., Perica, T., Pilla, K. B., Ganesan, S.J., Saltzberg, D.J., Ramachandran, R., Liu, X., Rosenthal, S.B., Calviello, L., Venkataramanan, S., Liboy-Lugo, J., Lin, Y., Wankowicz, S.A., Bohn, M., Sharp, P.P., Trenker, R., Young, J.M., Cavero, D.A., Hiatt, J., Roth, T., Rathore, U., Subramanian, A., Noack, J., Hubert, M., Roesch, F., Vallet, T., Meyer, B., White, K.M., Miorin, L., Rosenberg, O.S., Verba, K.A., Agard, D., Ott, M., Emerman, M., Ruggero, D., Garc, amp, amp, iacute-Sastre, A., Jura, N., von Zastrow, M., Taunton, J., Ashworth, A., Schwartz, O., Vignuzzi, M., Enfert, C., Mukherjee, S., Jacobson, M., Malik, H.S., Fujimori, D.G., Ideker, T., Craik, C.S., Floor, S., Fraser, J.S., Gross, J., Sali, A., Kortemme, T., Beltrao, P., Shokat, K., Shoichet, B.K., Krogan, N.J., 2020a. A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing. bioRxiv, 2020.2003.2022.002386-002020.002303.002322.002386.
Gordon, D.E., Jang, G.M., Bouhaddou, M., Xu, J., Obernier, K., White, K.M., O'Meara, M. J., Rezelj, V.V., Guo, J.Z., Swaney, D.L., Tummino, T.A., Huttenhain, R., Kaake, R. M., Richards, A.L., Tutuncuoglu, B., Foussard, H., Batra, J., Haas, K., Modak, M., Kim, M., Haas, P., Polacco, B.J., Braberg, H., Fabius, J.M., Eckhardt, M., Soucheray, M., Bennett, M.J., Cakir, M., McGregor, M.J., Li, Q., Meyer, B., Roesch, F., Vallet, T., Mac Kain, A., Miorin, L., Moreno, E., Naing, Z.Z.C., Zhou, Y., Peng, S., Shi, Y., Zhang, Z., Shen, W., Kirby, I.T., Melnyk, J.E., Chorba, J.S., Lou, K., Dai, S.A., Barrio-Hernandez, I., Memon, D., Hernandez-Armenta, C., Lyu, J., Mathy, C.J.P., Perica, T., Pilla, K.B., Ganesan, S.J., Saltzberg, D.J., Rakesh, R., Liu, X., Rosenthal, S.B., Calviello, L., Venkataramanan, S., Liboy-Lugo, J., Lin, Y., Huang, X.P., Liu, Y., Wankowicz, S.A., Bohn, M., Safari, M., Ugur, F.S., Koh, C., Savar, N.S., Tran, Q.D., Shengjuler, D., Fletcher, S.J., O'Neal, M.C., Cai, Y., Chang, J. C.J., Broadhurst, D.J., Klippsten, S., Sharp, P.P., Wenzell, N.A., Kuzuoglu-Ozturk, D., Wang, H.Y., Trenker, R., Young, J.M., Cavero, D.A., Hiatt, J., Roth, T.L., Rathore, U., Subramanian, A., Noack, J., Hubert, M., Stroud, R.M., Frankel, A.D., Rosenberg, O. S., Verba, K.A., Agard, D.A., Ott, M., Emerman, M., Jura, N., von Zastrow, M., Verdin, E., Ashworth, A., Schwartz, O., d'Enfert, C., Mukherjee, S., Jacobson, M., Malik, H.S., Fujimori, D.G., Ideker, T., Craik, C.S., Floor, S.N., Fraser, J.S., Gross, J. D., Sali, A., Roth, B.L., Ruggero, D., Taunton, J., Kortemme, T., Beltrao, P., Vignuzzi, M., Garcia-Sastre, A., Shokat, K.M., Shoichet, B.K., Krogan, N.J., 2020b. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 583, 459–468.
Gou, H., Zhao, M., Xu, H., Yuan, J., He, W., Zhu, M., Ding, H., Yi, L., Chen, J., 2017. CSFV induced mitochondrial fission and mitophagy to inhibit apoptosis. Oncotarget 8, 39382–39400.
Hemmat, N., Asadzadeh, Z., Ahangar, N.K., Alemohammad, H., Najafzadeh, B., Derakhshani, A., Baghbanzadeh, A., Baghi, H.B., Javadrashid, D., Najafi, S., Ar Gouilh, M., Baradaran, B., 2021. The roles of signaling pathways in SARS-CoV-2 infection; lessons learned from SARS-CoV and MERS-CoV. Arch. Virol 166, 675–696.
Jang, K.J., Jeong, S., Kang, D.Y., Sp, N., Yang, Y.M., Kim, D.E., 2020. A high ATP concentration enhances the cooperative translocation of the SARS coronavirus helicase nsP13 in the unwinding of duplex RNA. Sci. Rep. 10, 1–13.
Jiang, H.-W., Zhang, H.-N., Meng, Q.-F., Xie, J., Li, Y., Chen, H., Zheng, Y.-X., Wang, X.-N., Qi, H., Zhang, J., Wang, P.-H., Han, Z.-G., Tao, S.-C., 2020. SARS-CoV-2 Orf9b suppresses type I interferon responses by targeting TOM70. Cell. Mol. Immunol. 17, 998–1000.
Jin, D.Y., Zheng, B.J., 2009. Roles of spike protein in the pathogenesis of SARS coronavirus. Hong Kong Med. J. 15, 37–40.
Kaivola, J., Nyman, T.A., Matikainen, S., 2021. Inflammasomes and SARS-CoV-2 Infection. Viruses-Basel 13.
Kalashnyk, O., Lykhmus, O., Izmailov, M., Koval, L., Komisarenko, S., Skok, M., 2021. SARS-Cov-2 spike protein fragment 674–685 protects mitochondria from releasing cytochrome c in response to apoptogenic influence. Biochem. Biophys. Res. Commun. 561, 14–18.
Kamitani, W., Huang, C., Narayanan, K., Lokugamage, K.G., Makino, S., 2009. A two-pronged strategy to suppress host protein synthesis by SARS coronavirus Nsp1 protein. Nat. Struct. Mol. Biol. 16, 1134–1140.
Katz, B.Z., Boas, S., Shiraishi, Y., Mears, C.J., Taylor, R., 2010. Exercise tolerance testing in a prospective cohort of adolescents with chronic fatigue syndrome and recovered controls following infectious mononucleosis. J Pediatr 157, 468-472, 472 e461.
Kedor, C., Freitag, H., Meyer-Arndt, L., Wittke, K., Hanitsch, L.G., Zoller, T., Steinbeis, F., Haffke, M., Rudolf, G., Heidecker, B., Bobbert, T., Spranger, J., Volk, H.D., Skurk, C., Konietschke, F., Paul, F., Behrends, U., Bellmann-Strobl, J., Scheibenbogen, C., 2022. A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. Nat. Commun. 13, 5104.
Keng, C.T., Choi, Y.W., Welkers, M.R.A., Chan, D.Z.L., Shen, S., Gee Lim, S., Hong, W., Tan, Y.J., 2006. The human severe acute respiratory syndrome coronavirus (SARS-CoV) 8b protein is distinct from its counterpart in animal SARS-CoV and down-regulates the expression of the envelope protein in infected cells. Virology 354, 132–142.
Khan, M., Syed, G.H., Kim, S.J., Siddiqui, A., 2015. Mitochondrial dynamics and viral infections: A close nexus. BBA 1853, 2822–2833.

Kopecky-Bromberg, S.A., Martínez-Sobrido, L., Frieman, M., Baric, R.A., Palese, P., 2007. Severe Acute Respiratory Syndrome Coronavirus Open Reading Frame (ORF) 3b, ORF 6, and Nucleocapsid Proteins Function as Interferon Antagonists. J. Virol. 81, 548–557.
Kopecky-Bromberg, S.A., Martinez-Sobrido, L., Palese, P., 2006. 7a protein of severe acute respiratory syndrome coronavirus inhibits cellular protein synthesis and activates p38 mitogen-activated protein kinase. J. Virol. 80, 785–793.
Lai, C.C., Jou, M.J., Huang, S.Y., Li, S.W., Wan, L., Tsai, F.J., Lin, C.W., 2007. Proteomic analysis of up-regulated proteins in human promonocyte cells expressing severe acute respiratory syndrome coronavirus 3C-like protease. Proteomics 7, 1446–1460.
LaStarza, M.W., Lemm, J.A., Rice, C.M., 1994. Genetic analysis of the nsP3 region of Sindbis virus: evidence for roles in minus-strand and subgenomic RNA synthesis. J. Virol. 68, 5781–5791.
Law, P.T.W., Wong, C.H., Au, T.C.C., Chuck, C.P., Kong, S.K., Chan, P.K.S., To, K.F., Lo, A.W.I., Chan, J.Y.W., Suen, Y.K., Chan, E., Fung, K.P., Waye, M.M.Y., Sung, J.J. Y., Lo, Y.M.D., Tsui, S.K.W., 2005. The 3a protein of severe acute respiratory syndrome-associated coronavirus induces apoptosis in Vero E6 cells. J. Gen. Virol. 86, 1921–1930.
Lee, J.-G., Huang, W., Lee, H., van de Leemput, J., Kane, M.A., Han, Z., 2021. Characterization of SARS-CoV-2 proteins reveals Orf6 pathogenicity, subcellular localization, host interactions and attenuation by Selinexor. Cell & Bioscience 2021 11:1 11, 1-12.
Lei, X., Dong, X., Ma, R., Wang, W., Xiao, X., Tian, Z., Wang, C., Wang, Y., Li, L., Ren, L., Guo, F., Zhao, Z., Zhou, Z., Xiang, Z., Wang, J., 2020. Activation and evasion of type I interferon responses by SARS-CoV-2. Nat. Commun. 11, 3810.
Li, Q., Wang, L., Dong, C., Che, Y., Jiang, L., Liu, L., Zhao, H., Liao, Y., Sheng, Y., Dong, S., Ma, S., 2005. The interaction of the SARS coronavirus non-structural protein 10 with the cellular oxido-reductase system causes an extensive cytopathic effect. J. Clin. Virol. 34, 133–139.
Li, X., Hou, P., Ma, W., Wang, X., Wang, H., Yu, Z., Chang, H., Wang, T., Jin, S., Wang, X., Wang, W., Zhao, Y., Zhao, Y., Xu, C., Ma, X., Gao, Y., He, H., 2022. SARS-CoV-2 ORF10 suppresses the antiviral innate immune response by degrading MAVS through mitophagy. Cell. Mol. Immunol. 19, 67–78.
Lin, C.W., Lin, K.H., Hsieh, T.H., Shiu, S.Y., Li, J.Y., 2006. Severe acute respiratory syndrome coronavirus 3C-like protease-induced apoptosis. FEMS Immunol. Med. Microbiol. 46, 375–380.
Ma, Y., Wu, L., Shaw, N., Gao, Y., Wang, J., Sun, Y., Lou, Z., Yan, L., Zhang, R., Rao, Z., 2015. Structural basis and functional analysis of the SARS coronavirus nsp14-nsp10 complex. P Natl Acad Sci USA 112, 9436–9441.
Malone, B., Urakova, N., Snijder, E.J., Campbell, E.A., 2022. Structures and functions of coronavirus replication-transcription complexes and their relevance for SARS-CoV-2 drug design. Nat. Rev. Mol. Cell Biol. 23, 21–39.
Matthews, K.L., Coleman, C.M., van der Meer, Y., Snijder, E.J., Frieman, M.B., 2014. The ORF4b-encoded accessory proteins of Middle East respiratory syndrome coronavirus and two related bat coronaviruses localize to the nucleus and inhibit innate immune signalling. J. Gen. Virol. 95, 874–882.
McBride, R., Fielding, B.C., 2012a. The role of severe acute respiratory syndrome (SARS)-coronavirus accessory proteins in virus pathogenesis. Multidisciplinary Digital Publishing Institute (MDPI) 2902–2923.
McBride, R., Fielding, B.C., 2012b. The role of severe acute respiratory syndrome (SARS)-coronavirus accessory proteins in virus pathogenesis. Viruses 4, 2902–2923.
Mirowsky, J.E., Dailey, L.A., Devlin, R.B., 2016. Differential expression of pro-inflammatory and oxidative stress mediators induced by nitrogen dioxide and ozone in primary human bronchial epithelial cells. Inhal. Toxicol. 28, 374–382.
Neuman, B.W., Kiss, G., Kunding, A.H., Bhella, D., Baksh, M.F., Connelly, S., Droese, B., Klaus, J.P., Makino, S., Sawicki, S.G., Siddell, S.G., Stamou, D.G., Wilson, I.A., Kuhn, P., Buchmeier, M.J., 2011. A structural analysis of M protein in coronavirus assembly and morphology. J. Struct. Biol. 174, 11–22.
Nunn, A.V.W., Guy, G.W., Brysch, W., Bell, J.D., 2022. Understanding Long COVID; Mitochondrial Health and Adaptation-Old Pathways, New Problems. Biomedicines 10.
Nunn, A.V.W., Guy, G.W., Brysch, W., Botchway, S.W., Frasch, W., Calabrese, E.J., Bell, J.D., 2020. SARS-CoV-2 and mitochondrial health: implications of lifestyle and ageing. Immun. Ageing 17, 33.
Paul, B.D., Lemle, M.D., Komaroff, A.L., Snyder, S.H., 2021. Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome. PNAS 118.
Pfefferle, S., Schöpf, J., Kögl, M., Friedel, C.C., Müller, M.A., Carbajo-Lozoya, J., Stellberger, T., von Dall'Armi, E., Herzog, P., Kallies, S., Niemeyer, D., Ditt, V., Kuri, T., Züst, R., Pumpor, K., Hilgenfeld, R., Schwarz, F., Zimmer, R., Steffen, I., Weber, F., Thiel, V., Herrler, G., Thiel, H.-J., Schwegmann-Weßels, C., Pöhlmann, S., Haas, J., Drosten, C., von Brunn, A., 2011. The SARS-Coronavirus-Host Interactome: Identification of Cyclophilins as Target for Pan-Coronavirus Inhibitors. PLoS Pathogens 7, e1002331-e1002331.
Pizzamiglio, C., Machado, P.M., Thomas, R.H., Gorman, G.S., McFarland, R., Hanna, M. G., Pitceathly, R.D.S., Mito, C.-S.-G., 2022. COVID-19-related outcomes in primary mitochondrial diseases: an international study. Neurology 98, 576–582.
Prentice, E., Jerome, W.G., Yoshimori, T., Mizushima, N., Denison, M.R., 2004. Coronavirus replication complex formation utilizes components of cellular autophagy. J. Biol. Chem. 279, 10136–10141.
Ren, Y., Shu, T., Wu, D., Mu, J., Wang, C., Huang, M., Han, Y., Zhang, X.Y., Zhou, W., Qiu, Y., Zhou, X., 2020. The ORF3a protein of SARS-CoV-2 induces apoptosis in cells. Cell. Mol. Immunol. 17, 881–883.
Saffran, H.A., Pare, J.M., Corcoran, J.A., Weller, S.K., Smiley, J.R., 2007. Herpes simplex virus eliminates host mitochondrial DNA. EMBO Rep. 8, 188–193.
Sawicki, S.G., Sawicki, D.L., Younker, D., Meyer, Y., Thiel, V., Stokes, H., Siddell, S.G., 2005. Functional and genetic analysis of coronavirus replicase-transcriptase proteins. PLoS Pathog. 1, e39–e.
Schaecher, S.R., Mackenzie, J.M., Pekosz, A., 2007a. The ORF7b protein of severe acute respiratory syndrome coronavirus (SARS-CoV) is expressed in virus-infected cells and incorporated into SARS-CoV particles. J. Virol. 81, 718–731.
Schaecher, S.R., Touchette, E., Schriewer, J., Buller, R.M., Pekosz, A., 2007b. Severe acute respiratory syndrome coronavirus gene 7 products contribute to virus-induced apoptosis. J. Virol. 81, 11054–11068.
Schneider, A., Kurz, S., Manske, K., Janas, M., Heikenwälder, M., Misgeld, T., Aichler, M., Weissmann, S.F., Zischka, H., Knolle, P., Wohlleber, D., 2019. Single organelle analysis to characterize mitochondrial function and crosstalk during viral infection. Sci. Rep. 9, 1–11.
Shah, A., 2020. Novel coronavirus-induced NLRP3 inflammasome activation: a potential drug target in the treatment of COVID-19. Front. Immunol. 11, 1021.
Shi, C.-S., Qi, H.-Y., Boularan, C., Huang, N.-N., Abu-Asab, M., Shelhamer, J.H., Kehrl, J. H., 2014. SARS-coronavirus open reading frame-9b suppresses innate immunity by targeting mitochondria and the MAVS/TRAF3/TRAF6 signalosome. J. Immunol. 193, 3080–3089.
Shi, C.S., Nabar, N.R., Huang, N.N., Kehrl, J.H., 2019a. SARS-coronavirus open reading frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell Death Discovery 5.
Shi, C.S., Nabar, N.R., Huang, N.N., Kehrl, J.H., 2019b. SARS-coronavirus open reading frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell Death Discov 5, 101.
Singh, I., Joseph, P., Heerdt, P.M., Cullinan, M., Lutchmansingh, D.D., Gulati, M., Possick, J.D., Systrom, D.M., Waxman, A.B., 2022. Persistent exertional intolerance after COVID-19: insights from invasive cardiopulmonary exercise testing. Chest 161, 54–63.
Singh, K.K., Chaubey, G., Chen, J.Y., Suravajhala, P., 2020. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. American Journal of Physiology-Cell Physiology 319, C258-C267.
Siu, K.L., Yuen, K.S., Castano-Rodriguez, C., Ye, Z.W., Yeung, M.L., Fung, S.Y., Yuan, S., Chan, C.P., Yuen, K.Y., Enjuanes, L., Jin, D.Y., 2019. Severe acute respiratory syndrome coronavirus ORF3a protein activates the NLRP3 inflammasome by promoting TRAF3-dependent ubiquitination of ASC. FASEB J. 33, 8865–8877.
Slanina, H., Madhugiri, R., Bylapudi, G., Schultheiß, K., Karl, N., Gulyaeva, A., Gorbalenya, A.E., Linne, U., Ziebuhr, J., 2021. Coronavirus replication–transcription complex: Vital and selective NMPylation of a conserved site in nsp9 by the NiRAN-RdRp subunit. Proceedings of the National Academy of Sciences 118.
Smits, S.L., De Lang, A., Van Den Brand, J.M.A., Leijten, L.M., Van Ijcken, W.F., Eijkemans, M.J.C., Van Amerongen, G., Kuiken, T., Andeweg, A.C., Osterhaus, A.D. M.E., Haagmans, B.L., 2010. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathogens 6.
Stobart, C.C., Sexton, N.R., Munjal, H., Lu, X., Molland, K.L., Tomar, S., Mesecar, A.D., Denison, M.R., 2013. Chimeric exchange of coronavirus nsp5 proteases (3CLpro) identifies common and divergent regulatory determinants of protease activity. J. Virol. 87, 12611–12618.
Subissi, L., Posthuma, C.C., Collet, A., Zevenhoven-Dobbe, J.C., Gorbalenya, A.E., Decroly, E., Snijder, E.J., Canard, B., Imbert, I., 2014. One severe acute respiratory syndrome coronavirus protein complex integrates processive RNA polymerase and exonuclease activities. P Natl Acad Sci USA 111, E3900-E3909.
Surjit, M., Liu, B., Jameel, S., Chow, V.T.K., Lal, S.K., 2004. The SARS coronavirus nucleocapsid protein induces actin reorganization and apoptosis in COS-1 cells in the absence of growth factors. Biochem. J 383, 13–18.
Sutton, G., Fry, E., Carter, L., Sainsbury, S., Walter, T., Nettleship, J., Berrow, N., Owens, R., Gilbert, R., Davidson, A., Siddell, S., Poon, L.L.M., Diprose, J., Alderton, D., Walsh, M., Grimes, J.M., Stuart, D.I., 2004. The nsp9 Replicase Protein of SARS-Coronavirus, Structure and Functional Insights. Structure 12, 341–353.
Sweetman, E., Kleffmann, T., Edgar, C., de Lange, M., Vallings, R., Tate, W., 2020. A SWATH-MS analysis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome peripheral blood mononuclear cell proteomes reveals mitochondrial dysfunction. J. Transl. Med. 18, 365.
Tan, Y.-J.-Y.-X., Tan, T.H.P., Lee, M.J.R., Tham, P.-Y., Gunalan, V., Druce, J., Birch, C., Catton, M., Fu, N.Y., Yu, V.C., Tan, Y.-J.-Y.-X., 2007. Induction of Apoptosis by the Severe Acute Respiratory Syndrome Coronavirus 7a Protein Is Dependent on Its Interaction with the Bcl-XL Protein. J. Virol. 81, 6346–6355.
Taylor, J.K., Coleman, C.M., Postel, S., Sisk, J.M., Bernbaum, J.G., Venkataraman, T., Sundberg, E.J., Frieman, M.B., 2015. Severe acute respiratory syndrome coronavirus ORF7a inhibits bone marrow stromal antigen 2 virion tethering through a novel mechanism of glycosylation interference. J. Virol. 89, 11820–11833.
Tilokani, L., Nagashima, S., Paupe, V., Prudent, J., 2018. Mitochondrial dynamics: overview of molecular mechanisms. Essays Biochem. 62, 341–360.
Tsoi, H., Li, L., Chen, Z.S., Lau, K.F., Tsui, S.K.W., Chan, H.Y.E., 2014. The SARS-coronavirus membrane protein induces apoptosis via interfering with PDK1PKB/Akt signalling. Biochem. J 464, 439–447.
Valdes-Aguayo, J.J., Garza-Veloz, I., Badillo-Almaraz, J.I., Bernal-Silva, S., Martinez-Vazquez, M.C., Juarez-Alcala, V., Vargas-Rodriguez, J.R., Gaeta-Velasco, M.L., Gonzalez-Fuentes, C., Avila-Carrasco, L., Martinez-Fierro, M.L., 2021. Mitochondria and Mitochondrial DNA: Key Elements in the Pathogenesis and Exacerbation of the Inflammatory State Caused by COVID-19. Medicina (Kaunas) 57.
Varshney, B., Lal, S.K., 2011. SARS-CoV accessory protein 3b induces AP-1 transcriptional activity through activation of JNK and ERK pathways. Biochemistry 50, 5419–5425.
Wiedmer, A., Wang, P., Zhou, J., Rennekamp, A.J., Tiranti, V., Zeviani, M., Lieberman, P. M., 2008. Epstein-barr virus immediate-early protein Zta co-opts mitochondrial

single-stranded DNA binding protein to promote viral and inhibit mitochondrial DNA replication. J. Virol. 82, 4647–4655.
Wood, E., Hall, K.H., Tate, W., 2021. Role of mitochondria, oxidative stress and the response to antioxidants in myalgic encephalomyelitis/chronic fatigue syndrome: a possible approach to SARS-CoV-2 'long-haulers'? Chronic Dis Transl Med 7, 14–26.
Wu, K.E., Fazal, F.M., Parker, K.R., Zou, J., Chang, H.Y., 2020. RNA-GPS predicts SARS-CoV-2 RNA residency to host mitochondria and nucleolus. Cell Syst. 11, 102–108. e103.
Wu, X.D., Shang, B., Yang, R.F., Yu, H., Ma, Z.H., Shen, X., Ji, Y.Y., Lin, Y., Wu, Y.D., Lin, G.M., Tian, L., Gan, X.Q., Yang, S., Jiang, W.H., Dai, E.H., Wang, X.Y., Jiang, H. L., Xie, Y.H., Zhu, X.L., Pei, G., Li, L., Wu, J.R., Sun, B., 2004. The spike protein of severe acute respiratory syndrome (SARS) is cleaved in virus infected Vero-E6 cells. Cell Res. 14, 400–406.
Yang, Y., Xiao, Z., Ye, K., He, X., Sun, B., Qin, Z., Yu, J., Yao, J., Wu, Q., Bao, Z., Zhao, W., 2020. SARS-CoV-2: characteristics and current advances in research. Virol. J. 17, 117.
Yang, Y., Xiong, Z., Zhang, S., Yan, Y., Nguyen, J., Ng, B., Lu, H., Brendese, J., Yang, F., Wang, H., Yang, X.F., 2005. Bcl-xL inhibits T-cell apoptosis induced by expression of SARS coronavirus E protein in the absence of growth factors. Biochem. J 392, 135–143.
Yap, J.K.Y., Moriyama, M., Iwasaki, A., 2020. Inflammasomes and Pyroptosis as Therapeutic Targets for COVID-19. J. Immunol. 205, 307–312.
Ye, Q., Wang, B.L., Mao, J.H., 2020. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infection 80, 607–613.
Ye, Z., Wong, C.K., Li, P., Xie, Y., 2008. A SARS-CoV protein, ORF-6, induces caspase-3 mediated, ER stress and JNK-dependent apoptosis. Biochim. Biophys. Acta Gen. Subj. 1780, 1383–1387.
Young, M.J., Copeland, W.C., 2016. Human mitochondrial DNA replication machinery and disease. Curr. Opin. Genet. Dev. 38, 52–62.
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. Artificial Cells, Blood Substitutes, and Biotechnology 35, 237–253.
Zhou, P., Li, H., Wang, H., Wang, L.F., Shi, Z., 2012. Bat severe acute respiratory syndrome-like coronavirus ORF3b homologues display different interferon antagonist activities. J. Gen. Virol. 93, 275–281.
Zhu, L., Mou, C., Yang, X., Lin, J., Yang, Q., 2016. Mitophagy in TGEV infection counteracts oxidative stress and apoptosis. Oncotarget 7, 27122–27141.