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MITOCHONDRIAL STRESS IN CORONAVIRUS INFECTIONS

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Abstract

Cellular injury induced by coronaviruses use mitochondria as central targets and regulators. SARS-CoV-2 and related betacoronaviruses disrupt mitochondrial homeostasis through multiple mechanisms, including direct localization of viral proteins to mitochondria, inhibition of oxidative phosphorylation (OXPHOS), excessive reactive oxygen species (ROS) production, altered mitochondrial dynamics, and the release of mitochondrial DNA (mtDNA). These modifications have as a result the reprogram of cellular metabolism, lead to innate antiviral signaling, and activate various programmed cell death pathways, exacerbating inflammatory responses and contributing to disease severity. Mitochondrial dysfunction is considered a critical factor in coronavirus pathogenesis. Elucidating the interplay between coronaviruses and mitochondria is essential for understanding coronaviruses pathogenesis and developing new ways for prevention and therapy.

Key words: coronavirus, mitochondria, cellular stress

Introduction

Mitochondria are dynamic, double-membrane-bound organelles that are essential to energy production via oxidative phosphorylation and act as regulators of innate immunity, calcium signaling, and programmed cell death (Xu et al., 2022; de las Heras et al., 2020). When a cell is infected by a virus, the mitochondria have a double role: they control antiviral defenses through mitochondrial antiviral signaling protein (MAVS)–mediated interferon pathways while simultaneously acting as sites that viruses use for their replication and to evade immune surveillance.

The studies upon SARS-CoV-2 infection have showed the involvement of mitochondria in the pathology of coronavirus disease. The virus induces widespread mitochondrial dysfunction characterized by impaired respiratory activity, elevated oxidative stress, altered mitochondrial fusion and fission dynamics, and the release of mitochondrial damage-associated molecular patterns (Mozzi et al., 2023).

Metabolic Reprogramming and Inhibition of Oxidative Phosphorylation

SARS-CoV-2 reprograms host cell metabolism by suppressing mitochondrial oxidative phosphorylation (OXPHOS) and redirecting metabolism toward glycolysis and the pentose phosphate pathway (PPP). This Warburg-like effect supports viral replication while reducing mitochondrial ATP production. Viral proteins such as ORF8 and ORF10 transcriptionally repress nuclear and mitochondrial genes encoding electron transport chain components, thereby restricting OXPHOS capacity (Guarnieri et al., 2023).

It was observed that in the infected cells, the mitochondrial proteome was altered, having a reduced number of ATP synthase subunits and ADP/ATP translocases (SLC25A4), which has negative effects on the respiratory efficiency. Elevated mitochondrial reactive oxygen species (mROS) stabilizes HIF-1α, which upregulates glycolytic enzymes and supports this metabolic reprogramming (Li et al., 2019).

In vivo studies using SARS-CoV-2-infected hamsters reveal decreased oxygen consumption rates alongside increased lactate levels in affected tissues, linking these metabolic alterations to heightened inflammation (de Oliveira et al., 2022).

Direct Viral Protein Interactions with Mitochondria

SARS-CoV-2 encodes numerous proteins that localize to mitochondria or modulate their function. These viral proteins disrupt mitochondrial integrity through diverse mechanisms. The envelope (E) protein promotes VDAC1 oligomerization, facilitating mtDNA release into the cytosol and activation of cGAS-

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STING and inflammasome pathways (Shteinfer-Kuzmine et al., 2024). In cardiomyocytes, the S1 subunit of the spike protein induces mitochondrial damage, contributing to the cardiac complications observed in COVID-19 (Šerý O, Dziedzinska R, 2024). Meanwhile, proteins M, ORF9b, and ORF6 antagonize MAVS-mediated antiviral signaling, helping in immune evasion (Hu MM and Shu HB, 2023).

Oxidative Stress and Reactive Oxygen Species Production

Coronaviruses infection elevates mitochondrial reactive oxygen species (mROS) production, which drives tissue damage in COVID-19 through mechanisms that involve electron transport chain (ETC) disruption causing electron leakage, mitochondrial calcium overload, and diminished cellular antioxidant capacity (Cevallos et al., 2025). Consequences of heightened mROS include NLRP3 inflammasome activation with increased inflammatory cytokine release, oxidative injury to mtDNA leading to its cytosolic extrusion, and facilitation of viral replication, as mROS scavenging impairs SARS-CoV-2 propagation (Pan et al. 2021).

Mitochondrial Dysfunction

Infection by coronaviruses disturbs the balance between mitochondrial fusion, fission, and mitophagy. Marked fission is observable through spike S1-induced mitochondrial fragmentation and membrane depolarization (Šerý O, Dziedzinska R., 2024). Concurrently, mitophagy is notably compromised, as ORF3c disrupts autophagic flux, allowing for the accumulation of dysfunctional mitochondria (Mozzi et al., 2024). Complementarily, the processes of mitochondrial fusion are also affected. Cells sampled from individuals that were recovering from severe COVID-19 presented modifications in the expression patterns of the regulator factors involved in fusion.

Mitochondrial dysfunction activates a multitude of regulated cell death pathways during coronavirus infections. Apoptosis begins as E protein-driven VDAC1 oligomerization aids in the liberation of cytochrome c, triggering caspases, causing the failure of lymphocytes and leading to tissue disorders (Shteinfer-Kuzmine et al., 2025). Ferroptosis in hepatocytes is initiated concurrently through lipid peroxidation linked to mitochondrial ROS; the application of ferrostatin-1 can lessens this pathway, identifying ferroptosis as a path for possible therapeutic strategies (Cevallos et al, 2025). Furthermore, pyroptosis worsens with the discharge of mtDNA and heightened ROS levels, triggering inflammasome pathways that lead to the breakdown of inflammatory cells (Pan et al., 2021). Necroptosis may also play a role in tissue damage during severe infections, although its exact action mechanism remains to be further studied and elucidated (Rurek M, 2024).

Clinical Implications

Clinical observations indicate that mitochondrial dysfunction is strongly associated with the severity of COVID-19 and its long-term health consequences (Delpino MV and Quarleri J., 2025; Gonzalez-Garcia et al., 2023; Ramakrishnan et al., 2021). Growing quantities of circulating mitochondrial DNA (mtDNA), signifying a failure in the mitochondrial membrane, are connected to harmful health consequences and amplified systemic inflammation (Gómez-Delgado et al., 2025; Hu MM and Shu HB, 2023-). In addition, metabolic changes favoring glycolysis are seen in clinical practice as elevated levels of blood lactate, which are indicators of oxidative stress—like lipid peroxidation by-products and reduced antioxidant effectiveness—show a connection with unfavorable clinical consequences (de Las Heras et al., 2020). These mitochondrial anomalies contribute to organ-specific pathologies. Within the heart, spikes that harm mitochondria could lead to myocarditis, irregular heart rhythms, and compromised contractile strength (Chang et al., 2023; Šerý O, Dziedzinska R., 2024; Xu et al., 2022). In the central nervous system, the disruption of mitochondrial homeostasis in neurons and glial cells may determine cognitive deficits and other neurological manifestations (Chandra A and Johri A, 2022; de Oliveira et al., 2022). In the liver, elevated levels of mitochondrial ROS and lipid peroxidation facilitate ferroptotic cell death, thus producing liver injuries (Cevallos et al., 2021). The studies upon post COVID-19 patients showed that troubles linked to mitochondrial processes regularly undergo beyond the acute stage of infection. Those who are healing from severe COVID-19 typically demonstrate compromised mitochondrial respiration, irregular fusion and fission processes, heightened ROS concentration, and lowered metabolic adaptability (Ramakrishnan et al., 2021; Chen et al., 2025; Guarnieri et al., 2023; Molnar et al., 2024).

Therapeutic Strategies that Target Mitochondrial Dysfunction

Several therapeutic strategies are currently under investigation to improve the mitochondrial dysfunction induced by coronaviruses. Using

antioxidants specifically for mitochondria—like MitoTEMPO, N-acetylcysteine (NAC), and vitamin D—could be effective in lowering mitochondrial reactive oxygen species and improving cellular processes (de Las Heras et al., 2020; Li et al., 2019). Also, ferroptosis inhibitors, such as ferrostatin-1, could provide protection to tissues from lipid peroxidation produced by viral activity and the resulting organ impairment (Cevallos et al., 2025). The restoration of mitophagy appears to be another promising research strategy; augmentation of PINK1/Parkin-mediated mitochondrial quality control could facilitate the elimination of compromised mitochondria and limit inflammatory signaling pathways (Zhou et al., 2024). Furthermore, metabolic agents including metformin, NAD^+ precursors, and dichloroacetate (DCA) might contribute to the restoration of mitochondrial homeostasis, support oxidative phosphorylation, and ease inflammation (Voltan et al., 2016). In addition to these methodologies, various innovative strategies—including mitochondrial transplantation, interventions targeting cytosolic mitochondrial DNA signaling, and inhibitors that interfere with viral protein interactions with mitochondrial constituents—are currently being studied and may present new therapeutic pathways for addressing both acute and chronic mitochondrial pathologies associated with coronavirus infections (Mahmoodpoor et al., 2022).

CONCLUSIONS

Mitochondrial dysfunction represents an important feature of coronavirus infection, associated with metabolic reprogramming, innate immune dysregulation, and multi-organ pathology. The coronavirus proteins disturb the mitochondrial metabolism, thus leading to a modified cellular environment that favors viral replication and disadvantages the host cell. The studies regarding the relationships between virus-mitochondria interactions will enhance the understanding of how mitochondrial injury influences disease severity and progression. The identification of mitochondrial markers is important for diagnostic and to detect the therapeutic responses The evolution of therapeutics that specifically aim mitochondria—comprising antioxidant strategies, metabolic regulators, mitophagy facilitators, and inhibitors of ferroptosis—constitutes a potentially worthwhile path for treatment of coronavirus infections.

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