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HYPOTHESIS

Is mitochondrial bioenergetics and coenzyme Q_{10} the target of a virus causing COVID-19?

Gvozdjakova A[1], Klauco F[2], Kucharska J[1], Sumbalova Z[1]

Comenius University in Bratislava, Faculty of Medicine, Pharmacobiochemical Laboratory of 3rd Department of Internal Medicine, Bratislava, Slovakia. **anna.gvozdjakova@fmed.uniba.sk**

ABSTRACT
COVID-19 – a coronavirus disease, affected almost all countries in the world. It is a new virus disease, nobody has prior immunity to it, human population is prone to infections. In March 11 2020, WHO declared the pandemic status. The main symptoms include: fever, dry cough and fatigue. Virus proteins need mitochondrial energy for their own survival and replication. Upon viral infections, mitochondrial dynamics and metabolism can be modulated, which can influence the energy production in the host cells. Coenzyme Q_{10} is an integral component of mitochondrial respiratory chain and the key component of mitochondrial ATP production. The exact pathobiochemical mechanism of the disease is unknown. Modulated mitochondrial dynamics and metabolism with lower CoQ_{10} levels in viral infections leads us to the hypothesis that one of the main pathobiochemical effects of SARS-Cov-2 virus could be mitochondrial bioenergetics dysfunction with CoQ_{10} deficit leading to the reduction of its endogenous biosynthesis. The mechanism might be virus induced oxidative stress causing a mutation of one or more of the nine COQ genes, resulting in primary CoQ_{10} deficiency. New perspective for patients with COVID-19 may be supportive targeting therapy with coenzyme Q_{10} to increase the energy production, immunity and decrease oxidative stress *(Fig. 1, Ref. 51)*.
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KEY WORDS**:** COVID-19, virus, mitochondrial bioenergetics, coenzyme $Q_{10,}$ oxidative stress.

Introduction

COVID-19 – a coronavirus disease affected almost all countries in the world. In March 11 2020, WHO declared pandemic status. COVID-19 is the third new corona virus infection in the last years, which caused problems globally in the world. In 2003, a new coronavirus originated from southeast China, was named SARS (Severe Acute Respiratory Syndrome) coronavirus. In 2012, novel coronavirus originated from Middle East, was named MERS (Middle East Respiratory Syndrome) coronavirus (1). At the end of 2019, a novel virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) caused a series of pneumonia in Wuhan (Hubei, China) (2, 3). WHO named the diseases caused by SARS-CoV-2 as „COVID-19" (COrona VIrus Disease 2019) (4).

Coronaviruses (CoVs) belong to the family of *Coronaviridie,* which include four subfamilies: α-coronavirus, β-coronavirus, γ-coronavirus and δ-coronavirus. Coronaviruses primarily cause zoonotic infections in birds and mammals and they are capable to infect humans (5). Genome structure of SARS-CoV-2, SARS and MERS belong to the β-coronavirus subfamily (6, 7, 8).

SARS-CoV-2 virus causing COVID-19 is an enveloped positive strand RNA virus with the genome 30-32 kb, the largest known RNA virus. This virus mutates at a high rate and can survive up to 3 hours in droplets. COVID-19 affects mainly seniors with comorbidity, with non-communicable diseases, such as: cardiovascular diseases, diabetes, obesity, chronic lung disease and cancer (9). The structure of SARS-CoV-2 virus contains shaped surface proteins (Fig. 1). SARS-CoV-2 infection is triggered by binding of the spike protein of the virus to Angiotensin-converting enzyme 2 (ACE2), which has been identified as a functional receptor for coronaviruses (10). SARS-CoV-2 virus might pass through the nasal and larynx mucous, then enters the lung through respiratory tract. Virus SARS-CoV-2 primarily infects the lower respiratory tract (11, 12, 13). The main clinical symptoms of COVID-19 infections include fever, dry cough, dyspnoea and fatigue. Myalgia or fatigue was in 44–60 % of Asian cases (11, 14). The pathophysiology of COVID-19 includes an induced overproduction of early response proinflammatory cytokines (tumour necrosis factor (TNF), IL-6 and IL-1β) in the host, what was described as „cytokine storm", leading to increased vascular hyperpermeability and multiorgan failure such as: heart, renal system and gastrointestinal tract (11, 15, 16).

[1]Comenius University in Bratislava, Faculty of Medicine, Pharmacobiochemical Laboratory of 3rd Department of Internal Medicine, Bratislava, Slovakia, and [2]Comenius University in Bratislava, Faculty of Medicine, Slovakia, student Faculty of Medicine, Bratislava, Slovakia

Address for correspondence: A. Gvozdjakova, Comenius University in Bratislava, Faculty of Medicine, Pharmacobiochemical Laboratory of 3rd Department of Internal Medicine, Sasinkova 4, SK-811 08 Bratislava, Slovakia.
Phone: +421 90119 873

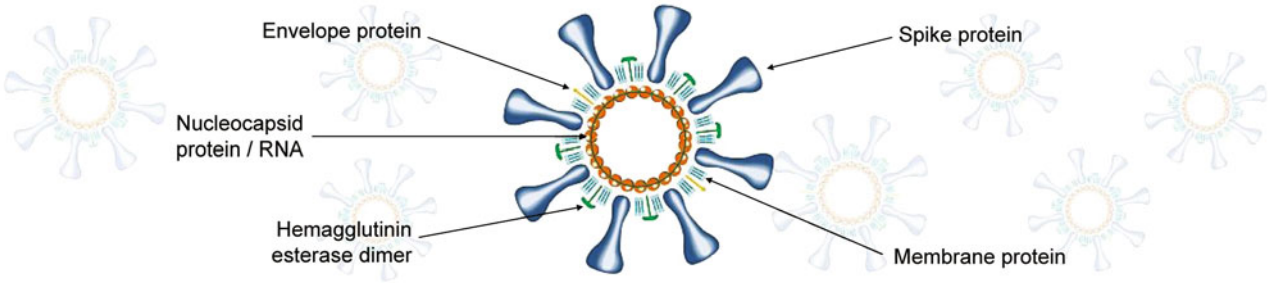

Fig. 1. Structure of SARS-CoV-2 virus (internet).

Viruses effect on mitochondrial function in organism

Mitochondria, the main source of cells energy production, are found in the cytoplasm of almost all eukaryotic cells. They are important for regulation of the metabolism of carbohydrates, amino acids and fatty acids. Under physiological conditions, mitochondrial oxidative phosphorylation generates a sufficient amount of ATP for cells (17). However, rapidly dividing cells, as activated immune cells or cancer cells, which have the highest request for energy production, receive ATP also by upregulated alternative way, aerobic glycolysis (18, 19). Mitochondria are dynamic structures. The dynamics of mitochondria is controlled by the processes that regulate the morphology of mitochondria. Mitochondrial fission is important process for removing old or damaged mitochondria implicated in stress response and apoptosis. Damaged mitochondria are removed by mitophagy. A small number of large and prolonged mitochondria are formed by fusion. The loss of mitochondrial fusion protein leads to mitochondrial fragmentation (20). Under mitochondrial fragmentation dynamin related protein 1 (DRP-1) is transported from cytosol to the outer mitochondrial membrane and released cytochrome c from mitochondria into the cytoplasm leads to apoptosis (21).

Mitochondria have been implicated in many metabolic functions, in many diseases, in antiviral responses. Virus proteins need mitochondria for their own survival and replication. Mitochondrial antiviral signalling protein (MAVS), associated with the outer mitochondrial membrane, mediates the activation of NF_K-B and the induction of interferons in response to viral infection (22, 23). Many viruses target mitochondrial dynamics and metabolism, modulate mitochondrial bioenergetics, mitochondrial membrane potential, mitochondrial ion permeability, induce reactive oxygen species production, alter the Ca^{2+} regulatory activity and cause oxidative stress in host cells. Viruses can modulate apoptosis and mitochondrial antiviral immunity, alter intracellular distribution of mitochondria, cause host mitochondrial DNA depletion for their survival in the cell (24, 25, 26, 27).

Viral infections activate immune cells for energy production by aerobic glycolysis. Different effect of virus infection on mitochondrial respiratory chain and ATP production was found in the beginning and the progress of the infections. At the beginning of the viral infections, mitochondrial respiration was enhanced related to complex I of the electron transport chain and after the progress of the infection, complex I and complex II of mitochondrial respiratory chain and ATP content decreased (28). Viruses can modulate the host mitochondrial metabolism by different ways. Herpes virus human cytomegalovirus (HCMV) enhances glycolytic flux, directly elevates mitochondrial biogenesis and increases mitochondrial respiration. Herpes simplex virus type-1 (HSV-1) induces Krebs cycle. Hepatitis C virus (HCV) infection enhances mitochondrial fatty acid oxidation (29). Sindbis virus infection causes mitochondrial bioenergetics alterations, which participate in the molecular mechanism of encephalitis (21, 26). Influenza A viral protein targets mitochondria, leads to mitochondrial fragmentation and loss of mitochondrial membrane potential (30). Dengue virus inhibits DRP 1 protein and induces mitochondrial fusion and elongation. Mitochondria play the central role in the primary host defence mechanisms against viral infections and in these processes a number of novel viral and mitochondrial proteins are involved.

SARS-CoV is a large single-positive-strand RNA virus. The virus genome encodes accessory eight open reading frame proteins (ORF). ORF-3a and ORG-8a trigger cellular apoptosis; ORF-7a activates NF-kB; ORF-3b upregulates the expression of several cytokines and chemokines; ORF-6 reduces IFN production; ORF-8b induces cellular DNA synthesis (31). Protein ORF-9b localizes to the outer mitochondrial membrane, alters host cell mitochondria morphology, elongates mitochondria and disrupts mitochondrial antiviral signalling. SARS-CoV ORF-9b manipulates host cell mitochondria and mitochondrial functions (32).

Viral infections induce production of reactive oxygen species (ROS) that control replication, as different viruses are able to modulate antioxidative enzymes. Increased ROS production might contribute to the alterations in mitochondrial bioenergetics (21, 32). Exact pathobiochemical mechanisms of SARS-CoV-2 virus effect on mitochondrial bioenergetics is not known. We assume that SARS-CoV-2 virus might manipulate mitochondrial dynamics and metabolism like the SARS-CoV.

Is coenzyme Q_{10} the target of SARS-CoV-2 virus causing COVID-19?

Coenzyme Q_{10} (CoQ_{10}) was discovered by Frederick Loring Crane in the year 1957. CoQ_{10}, located within the inner mitochondrial membrane, is an integral component of the mitochondrial respiratory chain that transports electrons from complex I and

complex II to complex III. CoQ_{10} is the key component of ATP production in mitochondria. FL Crane showed its effect between a plasma membrane and autism (33, 34, 35, 36).

Primarily, CoQ_{10} is endogenously synthetized in the endoplasmic reticulum from tyrosine by mevalonate pathway, including vitamins C, B_2, B_6 B_9, B_{12} and transported in the plasma by low-density lipoproteins. Currently, nine genes are known to be involved in endogenous CoQ_{10} biosynthesis, which are called "COQ genes": COQ2 (coenzyme Q2 - polyprenyltransferase), COQ4 (coenzyme Q4), COQ6 (coenzyme Q6 - monooxygenase), COQ7 (coenzyme Q7 - hydroxylase), COQ8A (coenzyme Q8A), COQ8B (coenzyme Q8B), COQ9 (coenzyme Q9), PDSS1 (prenyl diphosphate synthase, subunit 1), PDSS2 (prenyl diphosphate synthase, subunit 2). CoQ_{10} biosynthesis involves a number of metabolic reactions such as: methylation, decarboxylation and hydroxylation (37). Low levels of CoQ_{10} may be caused by a damage to endogenous CoQ_{10} synthesis, or by mutation of one or more of the COQ genes, or by its increased utilization. Significantly lower serum level of CoQ_{10} were found in patients with an acute influenza infection (15), in patients with chronic kidney disease (38, 39), in endomyocardial biopsies of patients after heart transplantation (40) in patients with cardiomyopathy (41), in infertile men (42, 43). CoQ_{10} has shown the potential to decrease pain and fatigue in patients with fibromyalgia (44). In patients with septic shock, a significant association between CoQ_{10} and IL-2 and TNF-alpha was found (45). Statins therapy may also decrease the levels of CoQ_{10}, induce mitochondrial dysfunction, fatigue, myopathy and myalgia (46, 47). New roles of CoQ_{10} in cardiovascular disease discovered by a single group were summarized (35, 48). Targeted therapy of mitochondrial disturbances with CoQ_{10} was documented (49). A beneficial role of CoQ_{10} is related to its antioxidant activity, and its effect on cytokine production by human peripheral blood mononuclear cells (PMBC) may modulate human immune function. Authors incubated PMBC with varying doses of CoQ_{10} for 24 hours and reported a decreased TNF-alpha and IL-2 secretion in PMBC (50). Coenzyme Q_{10} decreases inflammatory biomarkers and cytokines (51).

Conclusion

Modulated mitochondrial dynamics and metabolism with lower CoQ_{10} levels in viral infections leads us to the hypothesis that one of the main pathobiochemical effects of SARS-Cov-2 virus could be mitochondrial bioenergetics dysfunction with CoQ_{10} deficit leading to its reduced endogenous biosynthesis. The mechanism may be virus induced oxidative stress causing a mutation of one or more of nine COQ genes, resulting into primary CoQ_{10} deficiency. New perspective for patients with COVID-19 may be supportive targeted therapy with coenzyme Q_{10} to increase energy production, immunity and decrease oxidative stress.

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