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$_{10}$ deficiency 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).

KEY WORDS: COVID-19, virus, mitochondrial bioenergetics, coenzyme Q$_{10}$, oxidative stress.
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-κB 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 Ca²⁺ 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 ORF-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 Q₁₀ the target of SARS-CoV-2 virus causing COVID-19?

Coenzyme Q₁₀ (CoQ₁₀) was discovered by Frederick Loring Crane in the year 1957. CoQ₁₀, 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 synthesized in the endoplasmic reticulum from tyrosine by mevalonate pathway, including vitamins C, B$_2$, B$_6$, B$_9$, 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 - polypropenyltransferase), COQ4 (coenzyme Q4), COQ6 (coenzyme Q6 - monoxygenase), 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 document (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-alfa 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 lead us to the hypothesis that one of the main pathobiocchemical 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.

References

1. Hilgfeld R, Peiris M. From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. Antiviral Res 2013; 100: 286–295.

2. World Health Organization. WHO Director-General’s opening remarks at the media briefing on COVID-19 – 11 March 2020.

3. Lu H, Stratton CW, Tang YY. Outbreak of pneumonia of unknown etiology in Wuhan, China. The mystery and the miracle. J Med Virol 2020; 92: 401–402.

4. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. J Chin Med Assoc 2020; 83: 217–220.

5. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J 2019; 16: 19. https://doi.org/10.1186/s12985-019-1045-4.

6. Cohen J, Normolle D. New SARS-like virus in China triggers alarm. Science 2020; 367: 234–235. https://doi.org/10.1126/science.367.6475.234.

7. Zhu N, Zhang D, Wang L, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao G, Tan W. A novel coronavirus from patients with pneumonia in China. 2019. N Engl J Med 2020; 382 (8): 727–733. https://doi.org/10.1056/NEJMoa2001017.

8. Chen Y, Liu Q, Guo D. Coranaviruses, genome structure, replication and pathogenesis. J Med Virol 2020; 92 (4): 418–423. https://doi.org/10.1002/jmv.25681.

9. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol 2020; 92: 479–490.

10. Shi T, Yang FY, Liu C, Cao X, Lu J, Zhang XL, Yuan MX, Chen C, Yang JK. Angiotensin-converting enzyme 2 regulates mitochondrial function in pancreatic beta-cells. Biochem Biophys Res Commun 2018; 495 (1): 860–866.

11. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M*, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506. Published online 2020/01/24 DOI: 10.1016/S0140-6736(20)30183-5.

12. Li JY, You Z, Wang Q, Zhou ZJ, Qin Y, Luo R, Ge XY. The epidemic of 2019-novel-coronavirus (2019-nCoV) pneumonia and insight for emerging infectious diseases in the future. Microbes and Infection 2020; 22: 80–85.

13. Luptia T, Scabini S, Pinna SM, De Perri G, De Rosa FG, Corcione S. 2019 novel coronavirus (2019-nCoV) outbreak: A new challenge. J Global Antimicrobial Resistance 2020; 21: 22–27.

14. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, Yong-Zhong J, Yan X, Yong-Jun L, Xing-Wang L, Hui L, Gou-Hui F, Xiao-Ying G, Yan X, Hong G, Jiu-Yang X, Fan Y, Xin-Ming W, Chai-Fou W, Lan C, Yi-Wei L, Bo L, Jian Y, Xiao-Rui W, Jie D, Li L, Chao-Lin H, Jian-Ping Z, Yi H, Zhen-Shun C, Lin-Lin L, Zhao-Hui Q, Chuan Q, Qi J, Bia C, Jian-Wei W. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chinese Medical Journal 2020; 133 (9): 1015–1024. 10.1097/CMA.000000000000722.

15. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci 2004; 25: 291–294.

16. Chase M, Cocchi MN, Liu X, Andersen LW, Holmberg MJ, Donnell LW, Ren L, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, Yong-Zhong J, Yan X, Yong-Jun L, Xing-Wang L, Hui L, Gou-Hui F, Xiao-Ying G, Yan X, Hong G, Jiu-Yang X, Fan Y, Xin-Ming W, Chai-Fou W, Lan C, Yi-Wei L, Bo L, Jian Y, Xiao-Rui W, Jie D, Li L, Chao-Lin H, Jian-Ping Z, Yi H, Zhen-Shun C, Lin-Lin L, Zhao-Hui Q, Chuan Q, Qi J, Bia C, Jian-Wei W. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chinese Medical Journal 2020; 133 (9): 1015–1024. 10.1097/CMA.000000000000722.

17. Gvozdjakova A, Cornelissen G, Singh RB (Eds). Recent advances in mitochondrial medicine and coenzyme Q$_{10}$ NOVA Science, NY, USA, 2018, pp.418.

18. Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol, 1927; 8/6: 519–530.

19. Zhao H, Raines LN, Ching-Cheng Huang S. Carbohydrate and amino acid metabolism as hallmarks for innate immune cell activation and function. Cells 2020; 9: 562. DOI: 10.3390/cells9030562
20. Longo DL, Archer SJ. Mitochondrial dynamics – mitochondrial fission and fusion in human diseases. N Engl J Med 2013; 369: 2236–2251.

21. Tiku V, Tan MW, Dikie I. Mitochondrial functions in infection and immunity. Trends Cell Biol 2020; 30 (4): 263–275.

22. Seth RB, Sun L, Ea CK, Chen ZJ. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-κB and IRF3. Cell 2005; 122 (5): 669–682.

23. Sun Q, Sun L, Liu HH, Chen X, Seth RB, Forman J, Chen ZJ. The specific and essential role of MAVS in antiviral innate immune responses. Immunity 2006; 24: 633–642. DOI: 10.1016/j.immuni.2006.04.004.

24. Anand SK, Tikoo SK. Viruses as modulators of mitochondrial functions. Hindawi, Advances in Virology, Volume 2013; Article ID 738794, 17 pages; http://dx.doi.org/10.1155/2013/738794.

25. Ohta A, Nishiyama Y. Mitochondria and viruses. Mitochondrion 2011; 11 (1): 1–12.

26. Ripoli M, D’Aprile A, Quarto G, Sarasin-Filipowicz M, Gouttenoire J, Scrima R, Cella O, Bozzoli D, Heim MH, Moradpour D, Capitanio N, Piccoli C. Hepatitis C virus linked mitochondrial dysfunction promotes hypoxia-inducible factor 1alpha-mediated glycolytic adaptation. J Virology 2010; 84 (1): 647–660.

27. Di Gennaro F, Pizzol D, Marotta C, Antunes M, Racalbuto V, Veronese N, Smith L. Coronavirus diseases (COVID-19) current status and future perspectives: A narrative review. Int J Environ Res Public Health 2020; 17, 2690. DOI: 10.3390/ijerph17082690.

28. Kaarbo M, Ager-Wick E, Osenbroch PO, Kilander A, Skinnes R, Carlsson A, Crane FL, O_AHB, Ládal D, Crane FL. Ubiquinol improves symptoms in children with autism. Biologics 2014; 8: 199–205.

29. Vastag L, Koyuncu E, Grady SL, Shenk TE, Rabinowitz JD. Innate immunity by targeting mitochondria and the MAVS/TRAF3/TRAF6 signalosome. J Immunol 2014; 193: 3080–3087.

30. Di Guardo G, Alleva E, OĎA, Zinsmeister AR, Pirrotta V. SARS-Coronavirus open reading frame-9b suppresses inflammatory cascade in septic shock. Crit Care 2011; 15 (4): R189. http://ccforum.com/content/15/4/R189.

31. McBride R, Fielding BC. The role of severe acute respiratory syndrome (SARS)-coronavirus accessory proteins in virus pathogenesis. Viruses 2012; 4: 2902–2923.

32. Shi CH, Qi HY, Boulanar C, Huang NN, Abu-Asab M, Shelhamer JH, Kehri JH. SARS-Coronavirus open reading frame-9b suppresses innate immunity by targeting mitochondria and the MAVS/TRAF3/TRAF6 signaling. J Immunol 2014; 193: 3080–3089.

33. Crane FL, Löw H, Sun I, Navas P, Gvozdjaková A. Plasma membrane coenzyme Q: evidence for a role in autism. Biologies 2014; 8: 99–205.

34. Gvozdjaková A, Kucharská J, Ostatniková D, Babinská K, Nakládal D, Crane FL. Ubiquinol improves symptoms in children with autism. HINDAWI, Oxidative Medicine and Cellular Longevity, 2014; Article ID 798 957, 6 pages; http://dx.doi.org/10.1155/2014/798957.

35. Gvozdjaková A, Takahashi T, Singh RB, De Meester F, Wilson DG, Crane FL. New roles of coenzyme Q$_{10}$ in cardiovascular diseases discovered by a single group. World Heart J 2013, 5 (3): 159–171.

36. Teske BE, Sun IL, Gvozdjaková A, Low H, Crane FL. Plasma membrane CoQ, Porin, and Redox Control of Autism. In: Quinones, eds: ER Price and SC Johnson, 2013; 157–172, Nova Science Publishers, Inc. ISBN: 978-1-62618-323-0.

37. Laredj LN, Licitra F, Puccio HM. The molecular genetics of coenzyme Q biosynthesis in health and disease. Biochimie 2014; 100: 76–87.

38. Gvozdjaková A, Sumbalová Z, Kucharská J, Komlósi M, Raušová Z, Vančová O, Számošová M, Mojto V. Platelet mitochondrial respiration, endogenous coenzyme Q$_{10}$ and oxidative stress in patients with chronic kidney disease. Diagnostics 2020, 10, 176. DOI: 10.3390/diagnostics10030176.

39. Gvozdjaková A, Sumbalová Z, Kucharská J, Chládeková A, Raušová Z, Vančová O, Komlósi M, Uličná O, Mojto V. Platelet mitochondrial bioenergetics analysis in patients with nephropathies and non-communicable diseases: a new method. Bratisl Med J 2019; 120 (9): 630–635.

40. Gvozdjaková A, Kucharská J. Implication of coenzyme Q depletion in heart transplantation. In: Coenzyme Q: Molecular Mechanisms in Health and Disease, eds. Kagan VE, Quinn PJ, CRC Press, Boca Raton, London, New York, Washington, D.C. 2001: 293–304.

41. Gvozdjaková A, Kucharská J, Dhallá NS, Šimko F. Mitochondrial cardiology. Gvozdjaková A, Cornélissen G, Singh RB (eds). Recent Advances in Mitochondrial Medicine and Coenzyme Q$_{10}$, NOVA Science, USA, 2018; 131–144.

42. Gvozdjaková A, Kucharská J, Dúbřavický J, Mojto V, Singh RB. Coenzyme Q$_{10}$ α-tocopherol, and oxidative stress could be important metabolic biomarkers of male infertility. Disease Markers, Volume 2015, Article ID 827941.

43. Gvozdjaková A, Dúbřavický J, Singh RB. Mitochondrial reproductory medicine. Gvozdjaková A, Cornélissen G, Singh RB (Eds). Recent Advances in Mitochondrial Medicine and Coenzyme Q$_{10}$, NOVA Science, USA, 2018; 229–240.

44. Cordero MD, Altecor-Gómez E, de Miguel M, Culic O, Carrión AM, Alvarez-Suarez JM, Bullón P, Battino M, Fernández-Redriguez A, Sánchez-Alcazar JA. Can coenzyme Q$_{10}$ improve clinical and molecular parameters in fibromyalgia? Antioxidants Redox Signaling, 2013; 19 (12): 1356–1361. DOI: 10.1089/ars.2013.5260 PMID: 23458405.

45. Donnino MW, Cocchi MN, Salciccioli JD, Kim D, Naini A, Buettner C, Akuthota P. Coenzyme Q$_{10}$ levels are low and may be associated with the inflammatory cascade in septic shock. Crit Care 2011; 15 (4): R189. http://ccforum.com/content/15/4/R189.

46. Gvozdjaková A, Kucharská J, Singh RB, Vančová O, Uličná O, Mojto V, Fedočko J, Pella D, Verma NS, Cornélissen G, Stadín. Mitochondrial dysfunction and targeting coenzyme Q$_{10}$ therapy. World Heart J 2016; 8 (2): 171–181.

47. Littarru GP, Tiano L. Clinical aspects of coenzyme Q$_{10}$. An update. Nutrition 2010; 26: 250–254.

48. Gvozdjaková A, Mikulecký M, Crane FL, Kucharská J, Cornélissen G, Kumar A, Pałecka P, Singh RB. Mitochondrial cardiomyopathy and coenzyme Q$_{10}$. World Heart J 2014; 6 (1): 29–46.

49. Gvozdjaková A, Kucharská J, de Cabo R, Tiano L, Navas P. Coenzyme Q$_{10}$ targeting therapy of mitochondrial disturbances. Gvozdjaková A, Cornélissen G, Singh RB (eds): Recent Advances in Mitochondrial Medicine and Coenzyme Q$_{10}$, NOVA Science, USA, 2018; 269–292.

50. Bessler H, Bergman M, Blumberger N, Djaldetti M, Salama H. Coenzyme Q$_{10}$ supplementation on inflammatory biomarkers. A systematic meta-analysis of randomized controlled trials. Pharmacol Res 2017; 119: 128–136.

Received June 1, 2020. Accepted August 18, 2020.