VOLUME - 12, ISSUE - 09, SEPTEMBER - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper | Medical Science

SECRECY OF SARS-COV-2 AND MITOCHONDRIAL DYSFUNCTION

Dr. Raghavendra Rao M.V*	Scientist Emeritus, Director of Research Laboratory, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India, *Corresponding Author
Dr. G. Pavani	Professor and Infection Control Officer, Department of Clinical Microbiology, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. Srinivasa Kumar	Professor General Medicine, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr Panigrahi Aswani Kumar	Associate professor,General Medicine, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. S. Krishna Reddy	Associate Professor,Orthopedics, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. P. Somasekhara Reddy	Professor Orthopedics, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. V. Shalini Reddy	Professor,Radiology, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. R. Satyaprasad	Associate Professor,Radiology, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. G. Ram Gopal	Professor, Radiology, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. M. Rajabhushanam	Professr, Anaesthesia, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. J. Seetha NandaGopal	Professor,Anaesthesia, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. P. Sanath Reddy	Professor,Anaesthesia, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. S. Avanthi	Associate Professor,Anaesthesia, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. D. V. S. L. N. Sarma	General surgery, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. Ramesh Vasudevan	Professor General Surgery, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. Soma Madan Reddy	Associate Professor, General Surgery, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. Sanjeev Kumar Khulbay	Associate Professor,General Surgery, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India,
Dr. M. V. Nagabhushanam	Principal, Hindu college of Pharmacy, Guntur, AP,India,
Dr. RajKumar. Kudari	Professor, Department of pharmaceutical analysis, Hindu college of Pharmacy, Guntur, AP,India
Dr. Chennamchetty Vijay Kumar	Associate Professor, Department of Pulmonary Medicine, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India

VOLUME - 12, ISSUE - 09, SEPTEMBER - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

ABSTRACT

Mitochondria are known as power houses and energy suppliers for our cells, but they also contribute to safeguard against pathogens. They can take action in immune responses. Viable mitochondria are critical for cellular function and homeostasis.Functional mitochondria are a key to normal physiological processes. Conversely, dysfunctional and defective mitochondria are linked to various human diseases including viral infections, cancer, and metabolic disorders. Mitochondrial dysfunction in the respiratory muscle in the lung may have relevance that may explain the respiratory failure in COVID-19 patients as an outcome and may serve as indirect evidence of mitochondrial dysfunction and COVID-19 outcome. The SARS-CoV-2 membrane protein can directly cause mitochondrial apoptosis, which may lead to enhanced lung injury.Viruses affect mitochondrial functions and impact mitochondrial metabolism and innate immune signaling. Mitochondria are closely involved in SARS-CoV-2 replication. Mitochondrial dysfunction and associated oxidative stress drive the production of pro inflammatory cytokines that, in turn, play an important role in the immune response. FGF-21 was proposed as a biomarker of mitochondrial dysfunction, and many diseases are characterized by alterations of myokine secretion

KEYWORDS :

INTRODUCTION

Disruption of normal mitochondrial function is detrimental to cell viability. Neurons are particularly dependent on mitochondria for calcium buffering and ATP production and, therefore, are highly susceptible to mitochondrial defects.(1)

Human mitochondria encodes for 13 polypeptides, two ribosomal RNA, and 22 e transfer RNA genes (2)

Mitochondria are essential for control of the cell cycle, immune function, mitochondrial quality, and apoptosis (3)

The critical role of mitochondria in eliciting innate and adaptive immune responses immune signaling pathways (4)

Mitochondria-mediated immune signaling, activation, transcription, differentiation as well as the survival of various types of immune cells (5)

Viruses use various mechanisms to target host cell mitochondria for their growth, survival, weakening the host cellular immune response and cell killing (6)

Several clinical studies have suggested that COVID-19 is led by a novel coronavirus that shares structural features with the virus that causes severe acute respiratory syndrome (SARS) (7,8)

Viral infections adversely affect mitochondrial structure and functions, and impact the metabolism and immune signalling(9)

Recent scientific investigations have suggested the critical role of mitochondria in eliciting parts of innate and adaptive immune responses (10)

Mitochondria controls various cellular processes including metabolic and death processes (11,12)

Mitochondria-mediated the survival of various types of immune cells (13)

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 (14)

Importantly, the secondary mitochondrial disorders such as lung COPD, idiopathic pulmonary fibrosis (IPF), cancer, or acute respiratory distress syndrome (ARDS) in relation to old age and COVID-19 (15,16)

Cytokine storm, one of the hallmarks of COVID-19, is known for creating heightened inflammation in COVID-19 patients, specifically higher implications in the old age population (17,18)

Fibroblast growth factor 21 (FGF-21), also known as myokine, regulates many important metabolic pathways (19).

SARS genome encoded proteins may target and modulate anterograde and retrograde signaling to control the mitochondrial function (20)

Structure of SARS-Co2

Coronaviruses are large, violently globular molecules with peculiar surface protrusions. Their size to a great extent fluctuates with 80 to 120 nm. They are surrounded by a number of protein molecules. The envelope is made up of a dual lipid layer, the membrane (M), envelope (E) and spike (S) structural proteins . The E and M protein are the structural proteins and justify its size The M protein provides the overall shape.It consists of 218 to 263 amino acids.It has three domains, a short N-terminal ectodomain, a triple-spanning transmembrane domain,and a C-terminal endodomain.The C-terminal domain forms a matrix-like lattice.Different species can have either N- or O-linked glycans .The M protein is crucial during budding,and envelope formation.The E proteins are minor structural proteins They are responsible for virion assembly, and morphogenesis.The spikes are the most distinguishing feature of coronaviruses.

Each spike is about 20 nm long.The S protein has S1 and S2 subunits.S protein is a fusion protein that interferes with the binding and membrane fusion of the virus and host cell.The S1 subunit forms the head of the spike The S2 subunit forms the stem of the spike. The virus binds and fuses with the host cell with cathepsin and transmembrane protease serine 2 (TMPRSS2) of the host cell

How corona infects cells

The Coronavirus enters through the nose or mouth,and reaches the airways.The coronavirus outer spike hooks onto specific receptors on the surface of the cell's of the respiratory tract. COVID-19,hooks on to the ACE2 receptor. Coronaviruses first bind to a cell surface receptor for viral attachment, subsequently enter endosomes, and eventually fuse viral and lysosomal membranes.Then the virus fuses into human cells, and allowing the virus to release the genetic material into the cell.The genetic blueprint of the virus is RNA,acts as a message, and translate it into proteins that make up new virus particles.It has been shown that TMPRSS2 and lysosomal proteases are both important for SARS-CoV-2 entry.The virus hijacks the host cell's functions to produce the components needed for it to create copies of itself. Those components self-assemble into new viruses, which eventually burst from the host cell and go on to infect other cells, either in the original host or in a new host.The protein spikes covering the virus's envelope allow it to bind to receptors on the host cell's lipid membrane, leading to infection and sometimes illness.

Clinical manifestations of COVID-19.

!. Heart---Hypotension,Arrhythmias,Ischaemia,Cardiogenic shock
2. Lungs---Pneumonitis,Pulmonary oedema,ARDS

3. Vascular--Cytop[enia,Coagulopathy,Endothelial damage
4. GIT-Nausea,Vomiting,Anorexia,Diarrhea,Vomiting
5. Liver--Hepatomegaly,Increased ALT,LDH
6. General--Fever,Headache,Fatigue
7. Renal--Acute kidney injury,Proteinuria,Renal failure
8. Nervous System--Confusion,Delirium, Encephalopathy, Stroke

Immunopathology

SARS-CoV-2 has an involuntary orientation by an organism for ACE2-expressing epithelial cells of the respiratory tract with people with severe COVID 19 have symptoms. Clinical laboratory findings of elevated IL 2, IL 7, IL 6,GM CSF, interferon gamma, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 alpha(MIP 1 alpha), and (TNF α) are elevated

The cytotoxic T cells kill the virus cells and the antibody-producing B cells. SARS-CoV-2, controls the MHC class I and II molecules, which inhibits the T-cell mediated immune responses. COVID-19,patients have lower total lymphocyte counts and higher plasma concentrations of a number of inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF). CD4+ helper T cells, CD8+ cytotoxic T cells, and natural killer cells are all significantly reduced in patients with severe COVID 19 infections. The pro-inflammatory T cell subsets and cytotoxic T cells are elevated.

The Glycolytic Pathway

SARS-CoV-2 membrane protein can directly cause mitochondrial apoptosis, which may lead to enhanced lung injury . In SARS-CoV-2 have been found to modulate mitochondria.The glycolytic pathway is a metabolic pathway of foremost importance in supporting life in almost all organisms (aerobic or anaerobic). It occurs in the cytosol and, under aerobic conditions, aims to convert the active form of glucose (glucose-6-phosphate) (C6H11O9P) into pyruvate (C3H4O3) (21)

In this pathway, pyruvate and NADH (C21H29N7O14P2), as shown in the following equation "C6H12O6 + 2ADP + 2Pi+ 2NAD + → 2C3H4O3 + 2ATP + 2NADH + 2H+"(22)

These intermediates are subsequently used in the mitochondria, in the tricarboxylic acid (TCA) cycle for the cell respiration process and oxidative phosphorylation (OXPHOS), which in turn produces other intermediates that are used in the electron transport chain for production of large amounts of adenosine triphosphate (ATP) (C10H16N5O13P3), which is the most important form of chemical energy for the cell (23)

At the end of the glycolytic pathway, only two molecules of ATP are produced per glucose molecule, whereas through OXPHOS the yield rises to 32 molecules of ATP per glucose molecule Under aerobic conditions, the pyruvate produced in the glycolytic pathway is transported into the mitochondria and by the action of the pyruvate dehydrogenase enzyme complex, it is converted into acetyl CoA (C23H38N7O17P3S), which is used in oxidative phosphorylation to produce important intermediates for the electron transport chain Oxygen is used as the final electron acceptor at the end of the electron transport chain, and part of this oxygen is transformed into reactive oxygen species (ROS) by mitochondria, which are the main generators of ROS, even in a physiological context (24)

The cells modulating SARS-CoV-2 mitochondrial function

COVID-19 patients do have populations of T-cells displaying mitochondrial dysfunction, as well as altered mitochondrial markers in monocytes .

Severe acute respiratory syndrome coronaviruses contributing to mitochondrial dysfunction

Severe acute respiratory syndrome-associated coronavirus (SARS-CoV) infection manipulates the host cellular machinery for its survival and replication in the host cell. The infection perturbed the cellular metabolism that favors viral replication leading to mitochondrial dysfunction and chronic inflammation.(25)

SARS-CoV-2 inhibits P62 and LC3 binding which plays a critical role in selective envelopment of mitochondria into autophagosomes.(26)

High-resolution of mitochondrial complex I—Insights into the proton pumping mechanism

These complexes are known as NADH: ubiquinone oxidoreductase (complex I), succinate dehydrogenase (complex II), ubiquinol–cytochrome c oxidoreductase (complex III, or cytochrome bc1 complex), cytochrome c oxidase (complex IV), and ATP synthase (complex V). Complex I is the first enzyme of the respiratory chain.Mitochondrial complex I (NADH:ubiquinone oxidoreductase) is a crucial enzyme in cellular metabolism, central to NAD+ homeostasis, respiration, and oxidative phosphorylation, and a key contributor to the production of cellular reactive oxygen species (ROS) (27)

Impact of COVID 19 on Mitochondria

At the cellular level, mitochondria, essential organelles that regulate energy homeostasis and cell death, may be critically impacted by COVID-19, contributing to disease progression and severity (28)

Since mitochondria are the chief cellular regulators of oxidative homeostasis, increased inflammation may lead to platelet damage and apoptosis as a result of mitochondrial dysfunction(29)

In healthy subjects, mitochondrial turnover through mitophagy, an auto-phagocytic process, is critical for maintaining proper cellular functions (30)

Mitochondria are constantly undergoing fusion and fission in a process of dynamic equilibrium, facilitated by movement of mitochondria within the cell (31)

In COVID-19 patients, mitochondrial fission is inhibited while fusion is promoted, causing mitochondrial elongation and providing a receptive intracellular environment for viral replication (32)

SARS-CoV-2 and Mitochondria

The SARS-CoV-2 uses its spike glycoprotein on the angiotensin-converting enzyme-2 (ACE-2) host receptor to enter human host cells (33,34)

The virus particle enters the cell via endocytosis, and it has been proposed that the spike protein needs to be cleaved by host enzymes for viral entry to take place (35)

ACE-2 influences mitochondrial functions and a lack of ACE-2 correlates with decreased ATP production and altered activation of NADPH oxidase 4 in the mitochondria, which is normally used for ROS production that can both protect the cell by destroying pathogens or trigger the infected cell to go into apoptosis.(36)

With the SARS-CoV-2 virus using ACE-2 receptors for its entry, the availability of ACE-2 for its usual functions may be impaired and contribute to symptom development (37)

Researchers Identify Mitochondrial Dysfunction in Heart and Organs

A recent study published in the journal Science Translational Medicine showed a link between the coronavirus and mitochondrial genes, which are crucial in generating energy within human cells. The study highlighted that the coronavirus can adversely affect these genes, leading to dysfunction in various organs beyond just the lungs.

They also observed that the period of highest viral load in the lungs also did not coincide with the presence of the virus in the brain. However, even in the cerebellum, a part of the brain, the expression of mitochondrial genes appeared to be suppressed. Dr. Douglas C. Wallace, Ph.D., co-senior author of the study, emphasized the significance of these findings, suggesting a paradigm shift in the understanding of COVID-19 .(38)

How do Covid-19 damage lungs and mitochondria?

Because viruses can't reproduce without a host, they've been attacking bacteria for millions of years. Some of those bacteria eventually became mitochondria, synergistically adapting to life within eukaryotic cells.

Interferon signaling

Besides their main metabolic roles, mitochondria are well recognized as pivotal organelles in controlling signaling pathways essential to restrain viral infections. In particular, a major role in antiviral defense is played by mitochondrial antiviral signaling (MAVS) protein, an adaptor protein that coordinates the activation of IFN inducing pathways and autophagy at the mitochondrial level.

Innate Immunity and Mitochondria

The innate immune response is the first line of defense against invading pathogens that is activated following the recognition of specific entities, called pathogen-associated molecular patterns (PAMPs), through a series of receptors, termed pattern recognition receptors (PRRs). Upon detection of PAMPs, the transcription of a myriad of antiviral genes is activated, establishing a cellular antiviral state that helps cells to restrict and/or clear infection (39)

Based on their structures, locations, and functional specificities, PRRs are separated into discrete families, which include the membrane bound Toll-like receptors (TLRs), the cytosolic nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), cyclic GMP-AMP (cGAMP) synthase (cGAS), and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs). The activity of these PRRs has been described to be influenced at various levels by mitochondria.(40)

The TLRs are a family of transmembrane PRRs that are activated by the binding of ligands to their C-terminal leucine-rich repeats. (41)

Inflammatory response and mitochondrial redox in SARS-CoV-2 infection

Cells need to maintain precise levels of ROS and reactive nitrogen species (RNS) as per requirement as they are used for signalling, while out of control levels may create trouble for the cells in multiple ways (42,43)

One of the ways mitochondrial ROS (mtROS) impacts the cell is through heightened inflammatory response Among the mitochondria-associated inflammatory cascade, NLRP-3 signalling (44)

plays a pertinent role in COVID-19 which is responsible for generating pro-inflammatory signals by activating cytokines (45,46)

SARS-CoV-2 manipulation of mitochondrial machinery and emergence of cytokine storm

Mitochondria are capable of altering signaling and metabolic pathways and the transcription of genes within immune cells. For example, mitochondria can switch the phenotype between pro and anti-inflammatory in immune cells (47,48)

Furthermore, the virus relies on the mitochondria's energy production for sustenance, which leads to the theory that modulation of mitochondrial metabolism may be effective against the virus. It is also known that replication of this virus relies on the production of double-membrane vesicles (DMVs) from the endoplasmic reticulum.(49)

Mitochondrial Fission and Fusion

Mitochondrial fusion allows the transfer of gene products between mitochondria for optimal functioning, especially under metabolic and environmental stress. On the other hand, fission is crucial for mitochondrial division and quality control.Mitochondria are highly dynamic organelles that maintain their morphology via continuous fission and fusion, also known as mitochondrial dynamics.

Mitochondrial dysfunction and human diseases

Dysfunctional and defective mitochondria are linked to various human diseases including viral infections, cancer, and metabolic disorders

Primary mitochondrial disorders (PMDs) are considered as inherited and genetic defects due to germline mutations in mitochondrial DNA (mtDNA) and/or nuclear DNA (nDNA) genes that encode proteins involved in oxidative phosphorylation (50)

In the context of PMDs, notable ones are mitochondrial myopathy, Leber's hereditary optic neuropathy (LHON), Leigh syndrome, and MERRF syndrome and other disorders. Among many PMDs, mitochondrial myopathies affect the debilitation of skeletal muscle and also respiratory muscle of lung airway and quadriceps. (51)

Secondary mitochondrial dysfunction in human diseases are known to refer to a number of different genetic disorders that includes Friedreich ataxia, Wilson disease, aging, cancer, and lung fibrosis (52)

Mitochondrial disorders could be developed as acquired or induced by drugs and other stress factors. (53)

CONCLUSION

Mitochondria are capable of altering signaling and metabolic pathways and the transcription of genes within immune cells. Thousands of people infected with the SARS-CoV-2 suffer long-term symptoms, such as "brain fog", fatigue, clotting problems, immune imbalance, incomplete viral clearance and potentially, mitochondrial dysfunction. To determine the impact of the SARS-CoV-2 virus on mitochondria, scientists analyzed tissues of different organs collected from individuals affected by the virus. The scientists observed that while mitochondrial gene expression recovered in the lungs, its functionality in other vital organs, such as the heart, kidneys, and liver, was compromised.

REFERENCES

1. Liu, F., Lu, J., Manaenko, A., Tang, J. & Hu, Q. Mitochondria in ischemic stroke: new insight and implications. Aging Dis. 9, 924–937 (2018).
2. M.J. Young, W.C. Copeland, Human mitochondrial DNA replication machinery and disease.Curr. Opin. Genet. Dev., 38 (2016), pp. 52-62
3. L. Tilokani, S. Nagashima, V. Paupe, J. Prudent Mitochondrial dynamics: an overview of molecular mechanisms.Essays Biochem., 62 (2018), pp. 341-360
4. B. Banoth, S.L. Cassel, Mitochondria in innate immune signaling.Transl. Res.,

202 (2018), pp. 52-68
5. Angajala, S. Lim, J.B. Phillips, J.H. Kim, C. Yates, Z. You, M. Tan.Diverse roles of mitochondria in immune responses: novel insights into immuno-metabolism.Front. Immunol., 9 (2018), p. 1605
6. R. Ganji, PH. Reddy, Impact of COVID-19 on Mitochondrial-Based Immunity in Aging and Age-Related Diseases Front. Aging Neurosci., 12 (2020), Article 614650
7. Arvin AM, Fink K, Schmid MA, et al. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. Nature. 2020;584(7821):353–363.
8. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020;323(20):2052–2059.
9. M. Khan, G.H. Syed, S.J. Kim, A. Siddiqui,Mitochondrial dynamics and viral infections: A close nexus BBA, 1853 (2015), pp. 2822-2833
10. B. Banoth, S.L. Cassel,Mitochondria in innate immune signaling,Transl. Res., 202 (2018), pp. 52-
11. Costa R, Peruzzo R, Bachmann M, et al. Impaired mitochondrial ATP production downregulates wnt signaling via ER stress induction. Cell Rep. 2019;28(8):1949–1960.
12. Picard M, Sandi C. The social nature of mitochondria: implications for human health. Neurosci Biobehav Rev. 2021;120:595–610
13. A. Angajala, S. Lim, J.B. Phillips, J.H. Kim, C. Yates, Z. You, M. Tan Diverse roles of mitochondria in immune responses: novel insights into immuno-metabolism
14. R. Ganji, PH. Reddy,Impact of COVID-19 on Mitochondrial-Based Immunity in Aging and Age-Related Diseases
15. K, Barnes PJ. COPD as a disease of accelerated lung aging. Chest. 2009;135(1):173–180.
16. Raghu G, Weycker D, Edelsberg J, et al. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174 (7): 810–816.
17. Matheson NJ, Lehner PJ. How does SARS-CoV-2 cause COVID-19? Science. 2020;369(6503):510–511.
18. Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci U S A. 2020;117(21):11727–11734
19. Tezze C, Romanello V, Sandri M. FGF21 as a modulator of metabolism in health and disease. Front Physiol 10: 419, 2019. doi:10.3389/fphys.2019.00419.
20. Burtscher, J., Cappellano, G., Omori, A., Koshiba, T., Millet, G.P., 2020. Mitochondria: In the Cross Fire of SARS-CoV-2 and Immunity. eScience 23, 101631.
21. Li, Y., Lu, B., Sheng, L., Zhu, Z., Sun, H., Zhou, Y., et al. (2018). Hexokinase 2-Dependent Hyperglycolysis Driving Microglial Activation Contributes to Ischemic Brain Injury. J. Neurochem. 144 (2), 186–200
22. Dunn, J.-O., Mythen, M., and Grocott, M. (2016). Physiology of Oxygen Transport. BJA Edu. 16 (10), 341–348.
23. Ostroukhova, M., Goplen, N., Karim, M. Z., Michalec, L., Guo, L., Liang, Q., et al. (2012). The Role of low-level lactate production in airway inflammation in asthma. Am. J. Physiol. Lung Cel Mol Physiol 302 (3), L300–L307. doi:10.1152/ajplung.00221.2011Ostroukhova
24. Chen, W., Gong, P., Guo, J., Li, H., Li, R., Xing, W., et al. (2018). Glycolysis Regulates Pollen Tube Polarity via Rho GTPase Signaling. Plos Genet. 14 (4), e1007373.
25. Shama Prasada Kabekkodu a 1, Sanjiban Chakrabarty a 1, Pradyumna Jayaram a 1, Sandeep Mallya b, Kumarasamy Thangaraj c d, Keshav K Singh e, Kapaettu Satyamoorthy ,Severe acute respiratory syndrome coronaviruses contributing to mitochondrial dysfunction.MitochondrionVolume 69, March 2023, Pages 43-56
26. Chao Shang1† Zirui Liu2†,Yilong Zhu3 ,Jing Lu4, Chenchen Ge4 ,Cuiling Zhang1 ,Nan Li1 ,Ningyi Jin1,3,5 ,Yiquan Li3* ,Mingyao Tian1,5* ,Xiao Li, SARS-CoV-2 Causes Mitochondrial Dysfunction and Mitophagy Impairment, Front. Microbial., 06 January 2022.
27. KRISTIAN PAREY HTTPS://ORCID.ORG/0000-0002-4842-6479, JONATHAN LASHAM HTTPS://ORCID.ORG/0000-0001-6393-9654, DERYCK J. MILLS HTTPS://ORCID.ORG/0000-0003-0904-1119, AMINA DJURABEKOVA, OUTI HAAPANEN HTTPS://ORCID.ORG/0000-0002-1958-8997, ETIENNE GALEMOU YOGA, HAO XIE HTTPS://ORCID.ORG/0000-0002-2422-2527, WERNER KÜHLBRANDT HTTPS://ORCID.ORG/0000-0002-2013-4810, VIVEK SHARMA HTTPS://ORCID.ORG/0000-0002-8838-3151 , [...], AND VOLKER ZICKERMANN HTTPS:,High-resolution structure and dynamics of mitochondrial complex I—Insights into the proton pumping mechanismSCIENCE ADVANCES,12 Nov 2021 Vol 7, Issue 46
28. Singh KK, Chaubey G, Chen JY, Suravajhala P. 2020. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. Am J Physiol Cell Physiol 319(2):C258–67.
29. Saleh J, Peyssonnaux C, Singh KK, Edeas M. 2020. Mitochondria and microbiota dysfunction in COVID-19 pathogenesis. Mitochondrion 54:1–7.
30. Reddy PH, Oliver DM. 2019. Amyloid beta and phosphorylated tau-induced defective autophagy and mitophagy in Alzheimer's disease. Cells 8(5):488
31. Meyer JN, Leuthner TC, Luz AL. 2017. Mitochondrial fusion, fission, and mitochondrial toxicity. Toxicology 391:42–53.
32. Shi CS, Qi HY, Boularan C, Huang NN, Abu-Asab M, Shelhamer JH, and others. 2014. SARS-coronavirus open reading frame-9b suppresses innate immunity by targeting mitochondria and the MAVS/TRAF3/TRAF6 signalosome. J Immunol 193(6):3080–9.
33. Cao, Y., Li, L., Feng, Z., Wan, S., Huang, P., Sun, X., et al. (2020). Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov. 6:11. doi: 10.1038/s41421-020-0147-1
34. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., et al. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181, 271.e8–280.e8. doi: 10.1016/j.cell.2020.02.052
35. Ou, X., Liu, Y., Lei, X., Li, P., Mi, D., Ren, L., et al. (2020). Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat. Commun. 11:1620. doi: 10.1038/s41467-020-15562-9
36. Singh, K. K., Chaubey, G., Chen, J. Y., and Suravajhala, P. (2020). Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. Am. J. Physiol. Cell Physiol. 319, C258–C267. doi: 10.1152/ajpcell.00224.2020
37. Xu, Z., Wang, Y., Xiao, Z. G., Zou, C., Zhang, X., Wang, Z., et al. (2018). Nuclear receptor ERR and transcription factor ERG form a reciprocal loop in the regulation of TMPRSS2:ERG fusion gene in prostate cancer. Oncogene 37, 6259–6274. doi: 10.1038/s41388-018-0409-7
38. Source:https://www.daijiworld.com/news/newsDisplay?newsID=1108590
39. Brubaker, S. W., Bonham, K. S., Zanoni, I., and Kagan, J. C. (2015). Innate immune pattern recognition: a cell biological perspective. Annu. Rev. Immunol. 33, 257–290. doi: 10.1146/annurev-immunol-032414-112240
40. Streicher, F., and Jouvenet, N. (2019). Stimulation of innate immunity by host and viral RNAs. Trends Immunol. 40, 1134–1148. doi: 10.1016/j.it.2019.10.009
41. Kawai, T., and Akira, S. (2011). Toll-like Receptors and Their Crosstalk with Other Innate Receptors in Infection and Immunity. Immunity 34, 637–650. doi: 10.1016/j.immuni.2011.05.006
42. Shida M, Kitajima Y, Nakamura J, Yanagihara K, Baba K, Wakiyama K, Noshiro H (2016) Impaired mitophagy activates mtROS/HIF-1alpha interplay and increases cancer aggressiveness in gastric cancer cells under hypoxia. Int J Oncol 48:1379–1390.
43. Song JQ, Jiang LY, Fu CP, Wu X, Liu ZL, Xie L, Wu XD, Hao SY, Li SQ (2020) Heterozygous SOD2 deletion deteriorated chronic intermittent hypoxia-induced lung inflammation and vascular remodeling through mtROS-NLRP3 signaling pathway. Acta Pharmacol Sin 41:1197–1207.
44. Zhou R, Yazdi AS, Menu P, Tschopp J (2011) A role for mitochondria in NLRP3 inflammasome activation. Nature 469:221–225.
45. Burtscher J, Cappellano G, Omori A, Koshiba T, Millet GP (2020) Mitochondria: In the Cross Fire of SARS-CoV-2 and Immunity. iScience 23:101631.
46. He Y, Hara H, Nunez G (2016) Mechanism and regulation of nlrp3 inflammasome activation. Trends Biochem Sci 41:1012–1021.
47. Mills EL, Kelly B, Logan A, Costa ASH, Varma M, Bryant CE, et al. Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. Cell. 2016;167(2):457–470 e413.
48. Mills EL, O'Neill LA. Reprogramming mitochondrial metabolism in macrophages as an anti-inflammatory signal. Eur J Immunol. 2016;46(1):13–21.
49. Cortese M, Goellner S, Acosta EG, Neufeldt CJ, Oleksiuk O, Lampe M, et al. Ultrastructural characterization of zika virus replication factories. Cell Rep. 2017;18(9):2113–23
50. Picard M.Sandi C. The social nature of mitochondria: implications for human health. Neurosci Biobehav Rev. 2021;120:595–610.
51. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020;323(20):2052–2059.
52. Barnes PJ. COPD as a disease of accelerated lung aging. Chest. 2009;135(1):173–180.
53. Kang JS. Theoretical model and characteristics of mitochondrial thermogenesis. Biophys Rep. 2018;4(2):63–67.