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ANTIVIRAL SIGNALING IN MITOCHONDRIA: A POSSIBLE TARGET TO ATTENUATE CORONA VIRUS INFESTATION

Deepali Jat

Zoology Department, Doctor Hari Singh Gour Vishwavidyalaya, Sagar, M.P.-470003
Email: deepalipunia@gmail.com

ABSTRACT

Mitochondria antiviral signaling form the basis of new technological innovations in the emergence of therapeutic concerns in virus pathogenesis. In this perspective mitochondria antiviral signaling may provide the main stream of evolution of host-virus protein interaction, anti-apoptotic and pro-apoptotic signaling and resolving the medical interventions by assessing the role of mitochondrial bioenergetics in virus invading mechanisms. The coronaviruses belong to the family mimiviridae in its unique feature of producing the VMC-I (Viral Mitochondrial Carrier Protein-I) that mimic the mitochondrial protein. VMC-I inhibit the mitochondrial protein to invade the infected cell hence lead to ATP insufficiency. Depleted ATP transmigrate the cell to death progression. Also, viral invasion triggers the pro-apoptotic signaling in the cell via caspase activated pathway on the contrary anti-apoptotic signaling of Bcl-2 and Bcl-xL genes provide the regulation of mitochondria mediated rescue for host cell.

Key words: Coronaviruses, mimiviridae, viral mitochondrial carrier protein-I, pro-apoptotic signaling

INTRODUCTION

Emergence of coronaviruses and its evolved mutants caused a new pathogenetic programming by the molecular signaling in the eukaryotic mammalian cell. Mitochondria persisted throughout the course of evolution, however, after the phylogenetic divergence of eukaryotes into animals, fungi and plants, differences in evolution of the mt DNA occurs due to different adaptations to cope up with mutation within these clades. This will have an evolutionary effect on the mitochondrial genome and have a profound effect on human adaptations, fertility, reproduction mt DNA disease (Otten et al. 2015). Mitochondria act as a ROS (Reactive Oxygen Species) generating site trigger by viral pathogenicity. The oxidative stress generated by ROS will lead to disrupted oxidative phosphorylation and decrease the functioning of immune system.

Mitochondrial protein kinases have been found to phosphorylate a number of mitochondrial proteins (Sardanelli et al. 1995; Papa et al. 1996), which might have a role in the control of mitochondrial functions and/or biogenesis. The inhibition of mitochondrial function via viral signaling may lead to pathophysiological response to the cell and cell become more viable for virus pathogenesis. The mitochondrial enzymes show a definite compart-mentalization. The outer membrane contains NADH-cytochrome-c-reductase, which consists of a flavoprotein and cytochrome b5. Monoamine oxidase is a specific enzyme marker of this membrane. The outer compartment contains adenylate kinase and other soluble enzymes.

The inner membrane carries all the components of the respiratory chain and of oxidative phosphorylation. Taken together, these components represent 35% of the protein of the membrane. In addition to other bound enzymes the inner membrane contains several specific carriers or translocation proteins involved in the permeation of metabolites. The mitochondrial matrix contains soluble enzymes of the kreb's cycle, DNA, RNA and other components of the machinery for protein synthesis of the mitochondrion.

The pro-apoptotic signaling of viral infection can cause the dysfunction of cytochrome c and ATP synthase enzyme complex hence interference in the mitochondrial bioenergetics inhibiting oxidative phosphorylation. Thus, the evolved mechanisms of viruses to control over and mimic the mitochondrial proteins may resolve the host-virus pathogenesis interaction and therapeutic blueprint for virus mediated pro-apoptotic signaling.

MITOCHONDRIAL DYNAMICS FOR CORONA VIRUS INFESTATION

Mitochondria an energy liberating organelle of cell possess its unique feature of having its own DNA and electron transport chain. Apart from strengthening the cell's survival capability it releases oxygen free radical if the organelle encounters with the viral infestation that can initiate the intermediate reaction of pro-apoptotic signaling that have the physiological significance in cell death progression. Steady process of generating ATP molecules makes the organelle one of the important entities of cell instead pro-apoptotic viral signaling make it more vulnerable to the pathogenesis that causes the dependent or independent caspase activation.

Although repair processes efficiently preserve mitochondrial structure and function, this line of defense is evaded by ROS attack occurring under conditions of severe or prolonged damage of mitochondrial components becomes detectable. The mitochondrial genome is a 16.6 kb double helical, closed-circular molecule. It encodes two rRNAs, 22tRNAs and 13 polypeptides (Each of these polypeptides is a highly hydrophobic subunit of one of four respiratory enzyme complexes that are located in mitochondrial membrane (Helen et al. 2010). Mitochondrial genes show maternal inheritance; this is possibly because the number of mitochondrial DNA copies in the egg is 103 fold greater than that in sperm.

This review is therefore formulated to aim at assessing the mitochondrial functions via the modulation of coronaviruses and to resolve the mechanisms of viral pro-apoptotic signaling and mitochondrial anti-apoptotic signaling through mitochondria DNA. Antiviral therapeutically administered effectively for several viral infections in human however still not very effective and subjected to the specific responsiveness. There are little therapeutics available that specifically target human coronaviruses and treatment strategy are only supportive. Anti-apoptotic signaling via mitochondrial proteins, Bcl-2 and Bcl-xL and immunological interventions to develop interferons (IFNs) with specific antibody responsiveness could help preventing the transmission of viral infections.

REDOX SIGNALING DUE TO VIRUS MEDIATED ROS

Virus triggered reactive oxygen intermediates may act secondary messengers of redox signalling. This can cause the disruption in normal cellular signalling pathways. The overburden of oxidative burst is the cause of diminishing cell's capability of surviving and to meet the challenges of change in the environment with respect to time. Accumulation of reactive oxygen species causes loss of cell's integrity in terms of deleterious changes that lead to oxidative damage. Oxygen molecules have been intensely studied acceptable intermediate that initiate the physiological changes in cell. It's pathogenicity and collection of damage bring about the innumerable loss of cell's survival capability. Distinguishing offerings of oxygen free

radicals in the form of protein, lipid adducts lead to mistakenly transformations of these molecules in the cell.

Oxidative damage refers to the distorted balance between transformation of the reactive oxygen species from one form to other indulging beneficial components of cell or biomolecules. Perturbed reduction state of cell produces lipid peroxides, protein carbonyls further these adducts in cell deposits in clumps to inactivate the normal cell functioning. This may lead DNA damage, strand breaks etc.

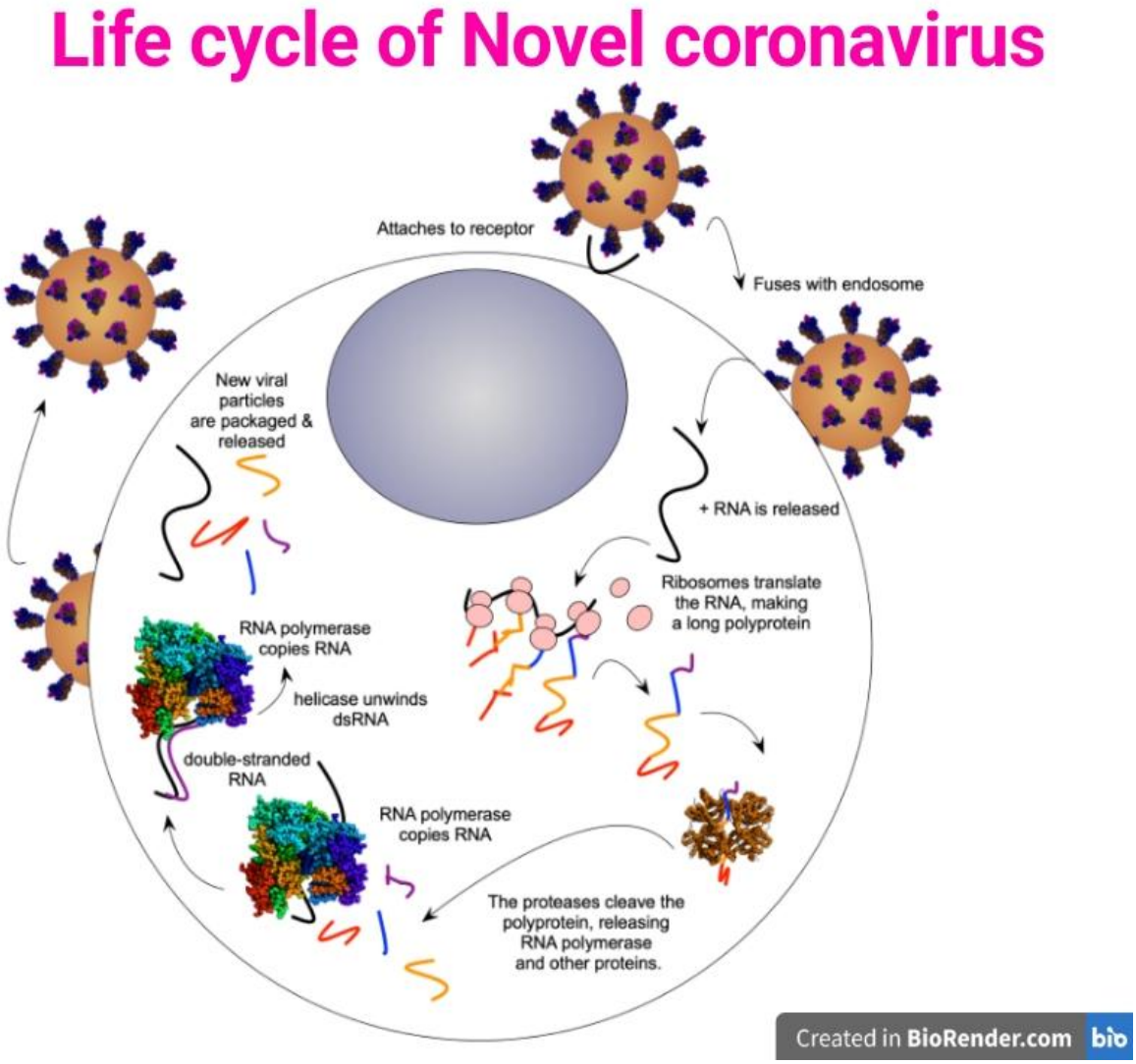
The reactive oxygen species generated through the process of oxidative stress are superoxide radical, hydroxyl radical and hydrogen peroxide. The observed ROS associated decline of glutathione redox state in mitochondria reflect a widening of the imbalance between antioxidants and pro-oxidants during the virus invasion process. Such a decline most likely entails a relatively more rapid rate of augmentation of oxidatively modified macromolecules as a cell encounters the infection. One major implication of the virus mediated increase in the level of oxidative stress/ damage may be that if such stress were indeed a causal factor in the pathogenic response, then the rate of severity of infection could also be speculated to increase exponentially.

EMERGENCE OF MICRO RNA PROCESSING

Evidences indicate that viral pathogenesis plays an important role in mitochondrial bioenergetics. Coronaviruses induce pro-apoptotic signaling is accompanied by a progressive oxidation of glutathione and other thiolic compounds in eukaryotic cell. This results in changes of the redox (GSSG/GSH) ratio that are much more striking in the mitochondria than in the extramitochondrial compartment and lead to oxidative damage of the mt DNA. Despite of upcoming scientific advancement in molecular biology research and medical sciences for the treatment of various diseases the prevention and control of viral pathogenesis remained challenged.

Therefore, an understanding of host- viral protein interaction, pro-apoptotic and anti-apoptotic signaling and using RNA interference (micro RNA processing and SiRNA) is essential in developing antiviral therapy and vaccines. The miRNA is conserved throughout the evolution and once the novel miRNA emerges in a metazoan lineage, they very rarely lost. Thus, miRNAs are thought to represent strong phylogenetic marker, and through their ability to fine-tune gene expression, appear to be major drives of biological complexity.

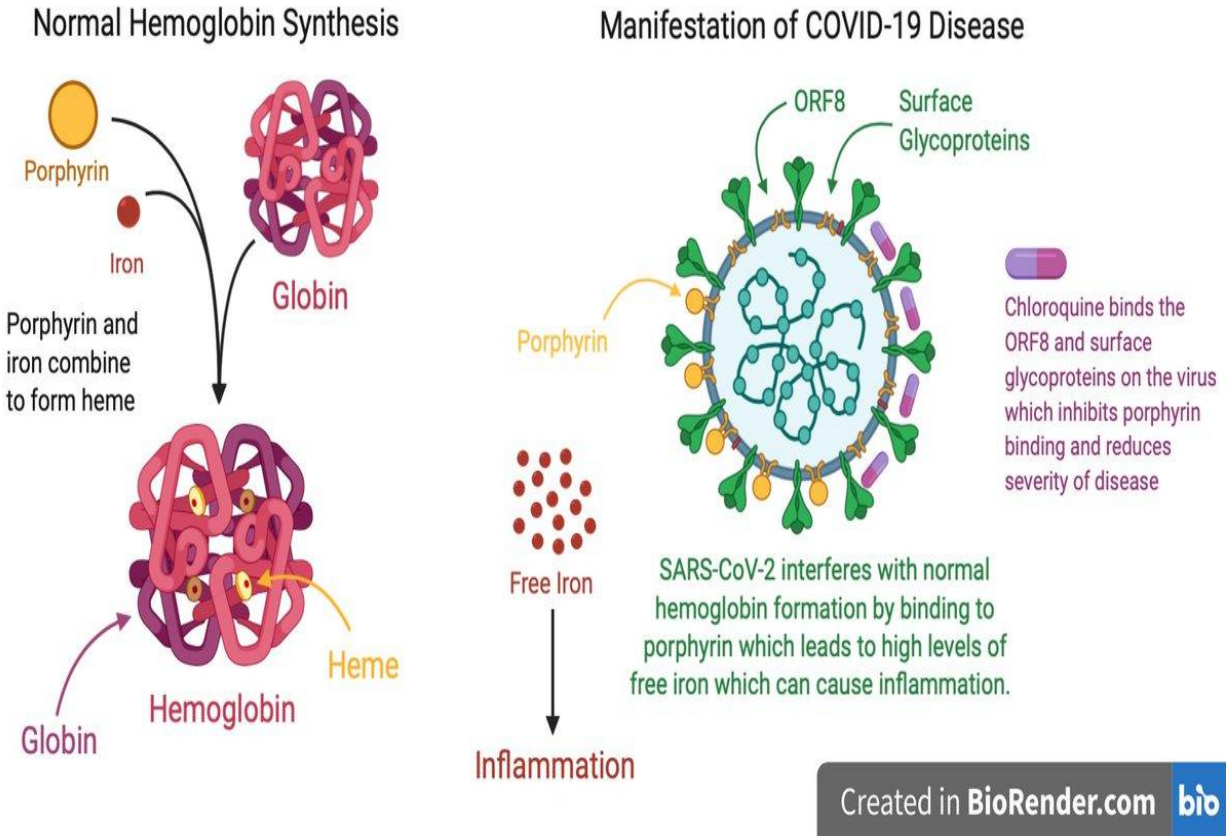
Figure 1 : Emergence of copies of RNA



DISCUSSION

In nationwide perspectives various scientists in India are working with viral pathogenesis since long. Some leading institutions in India like ICMR and many other continually trying and succeeded to make preventive strategies against the vulnerability of the re-emerging family of respiratory viruses. The therapeutic strategies using peptide dendrimer uncovers the viral molecular interactions to control emerging and re-emerging viruses (V.G. Joshi et al., 2013). Despite many formulations and successful prevention some curative measures are still under consideration. Variety of emerging viruses and their strains need to cover the therapeutic interventions at this age. Scientists working with peptides, diagnostics and anti-viral vaccines in the nation is noted during the discussion (Seth RB et al., 2005).

Figure 3: Figure describes the molecular structure of coronaviruses, normal hemoglobin synthesis and inflammatory action of the corona virus particle



To study mitochondrial dynamics with viral infections various scientists are trying to uncover the complex molecular mechanisms of host-virus protein interaction worldwide (M Khan, 2015). Virus mediated mitochondrial pro-apoptotic signaling, mitochondrial caspase activation, anti-apoptotic responsiveness is the main concerns among scientists globally. Evidences form various pioneer approaches manifested the viral mediated compromise in mitochondrial dynamics and progression in cell death that can be controlled by unleashing the puzzle of micro RNA processing, pro-apoptotic and anti-apoptotic signaling and interferon based combinational drugs (Latif R, et al. 2018). Scientific evidences from various study group suggest that genome of mimiviridae family of viruses encodes mitochondrial carrier that transport dATP and dTTP (M Monn'e Robinson AJ, Boes C, Harbour ME, Fearnley IM, 2007) that will help in understanding the role of mitochondrial bioenergetics to uncover the complex virus pathophysiological response in the cell.

CONCLUSION

The present review enlightens role of the host-virus protein interaction, viral mitochondrial carrier protein-I inhibitory mechanisms, anti-apoptotic signaling via mitochondrial membrane transporters and caspase deactivation and Bcl-2 and Bcl-xL anti-apoptotic signaling in viral pathogenesis. We expect the approach of mitochondrial viral signaling will prove to be an essential framework to resolve the complex mechanism of viral pathogenesis, its mitochondrial modulatory mechanism, anti-apoptotic signaling via mitochondrial proteins and miRNA processing in therapeutic convergence of molecular tools to control virus mediated pathophysiological changes. In spite of successful therapeutic interventions to target viral pathogenesis (e.g. HIV, Hepatitis B and respiratory viruses) antiviral drug development

continues to difficult in achieving due to their re-emergence and obligatory parasitic nature. Micro RNA processing techniques, DNA inhibition, host-parasitic immune response, via interferon therapy and utilization of combination therapy is instead a revolving strategy to which the nation is working with.

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