Covid-19 Induced Oxidative Damage Leading to Mitochondrial Dysfunction and Aging

1. Abu Bakar Siddique
2. Usman Ashraf
3. Sumaira Zulfiqar
4. Muhammad Adeel
5. Saqib Shehzad
6. Shoaib Akhtar
7. Muqaddas Shaheen
8. Muhammad Usman Majeed

Abstract: Covid-19 is a viral disease with surging respiratory diseases and rising mortality rates. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with several clinical symptoms and taken the world into severe crises. Viruses target specific cell organelles like mitochondria, nucleus, peroxisomes, endoplasmic reticulum and take a way to survive and proliferate in them. Mitochondria is a key organelle which impart a vital role in host defense and immunity. COVID-19 causes several mitochondrial dysfunctions including ROS production leading to impaired functions and aging. ROS production favors the environment for increased viral infections as well as for oxidative damage. The exacerbated ROS production is one of the main causes of morbidity and mortality by this respiratory syndrome in patients susceptible to this viral infection. Here we discuss how mitochondria combat viral infection to maintain cellular homeostasis. We also enlist different steps to explain how the balance between ROS and antioxidants could be maintained to overcome severe oxidative effects of coronavirus. Finally, we discuss various steps and precautions can be taken out to improve immunity and patient’s physiological responses after being affected by coronavirus.

Key words: Covid-19, mitochondria, mitochondrial dysfunction, aging, ROS, oxidative stress, antioxidants.
COVID-19 worldwide impacts

COVID-19 (Coronavirus Disease 2019) is a viral disease caused by SARS-CoV-2 (severe acute respiratory syndrome-Coronavirus 2), a new strain of coronavirus which causes a complex respiratory and thrombogenic disease (Chen et al., 2020) and is belonged to family (coronaviridae) and order (Nidovirales) (Vallamkondu et al., 2020). Genetically, it is a RNA virus belongs to β sub group of coronaviruses with the diameter of about 120-160 nm (Zhou et al., 2020). Spike protein (S protein), a petal shaped projection, is also a part of its structure with two vital functions during infection like virus binding and membrane fusion (King et al., 2012). COVID-19 was at first identified in December 2019 in Wuhan, China. To date it has affected the human population worldwide and still leaving health threats by different variants. As of June 2022, the confirmed cases have been approximately 551,231,344 and death cases around 6,354,593 (WHO, 2022).

In humans, three types of coronaviruses MERS-CoV, SARS-CoV and SARS-CoV-2 cause severe respiratory infections and even deaths (Paules et al., 2020). Among these three types, the SARS-CoV-2 become the cause of viral disease COVID-19. It can transmit from person to person either by contact with contaminated surfaces or by respiratory secretions (Hung, 2003). Symptoms manifested by the spread of COVID-19 may vary from asymptomatic to minor intensity in children and in young ages to even death rates.

Symptoms like cough, muscle pain, sore throat, shortness of breath, difficulty breathing, chills, loss of smell or taste, fever and headache are the severe respiratory symptoms, depending upon patient medical physiology and demographic makeup, resultantly appeared by COVID-19 attack (Li et al., 2020; Huang et al., 2020). The chances of mortality manifest around 20% in old age people (Chen et al., 2020) due to weak immune system and physiological responses.

Epithelial layers of alveolar sacs are the main targets of coronavirus. We know that viruses target specific cell organelles (mitochondria, nucleus, peroxisomes, endoplasmic reticulum and lipid droplets) and take a way to survive and proliferate in the target cells. These effected organelles impart a key role in host defense and immunity (Kagan, 2012).

Role of mitochondria to combat viral infections

Besides being a power houses of the cell, mitochondria play a vital role in maintaining cellular homeostasis. They are generally involved in most vital cellular functions such as innate immunity, energy metabolism, calcium homeostasis, apoptosis, aging and many other signaling pathways (Glingston et al., 2019). So, mitochondria contribute to host immunity in response to an infection by apoptosis, a programmed cell death induced through engaging interferon system and altering their structure (Ohta and Nishiyama, 2011).

Mitochondria, in order to maintain the quality of their vital cellular functions, try to remain more dynamic rather than static. Due to this dynamic property mitochondria can easily adapt against several metabolic environmental changes and decide about cell death or survival. The properties that make mitochondria dynamic includes fission, fusion, biogenesis as well as mitophagy processes (Lahtera et al., 2017).

In order to escape from the mitochondrial viral responses, to promote efficient replication, and to maintain cellular homeostasis, viruses interfere with most of the metabolic pathways of mitochondria (Claus and Liebert, 2014). Moreover, viruses need lipids, fatty acids and nucleotides for efficient replication and in order to maintain the availability of these biomolecules, viruses use glucose as an energy source by promoting aerobic glycolysis (Munger et al., 2008; Munger et al., 2006)

When viruses cause infection through binding themselves to certain receptors on cellular membranes (intracellularly or extracellularly), their molecular patterns (like DNA/RNA and protein sequences) are
recognized by innate immune system. Upon recognition, signaling pathway is activated, leading to inflammatory response. In cellular membranes, various types of protein receptors are found to which viral components attach, including retinoic acid-inducible gene-I-like receptors and toll-like receptors (Takeuchi and Akira, 2009). The cytosolic receptor Retinoic acid-inducible gene-I-like receptors (RLRs), in nonimmune cells, are responsible for the production of type-I interferon, an inflammatory cytokine (Takeuchi and Akira, 2009) and also associated with mitochondria (Tal and Iwasaki, 2009). Rather, toll-like receptors are responsible for the activation of type-I interferon and for the production of chemokine. These are located on endosome, cell surface and ER membranes (Takeuchi and Akira, 2009).

Programmed cell death or apoptosis, on the other hand, is among the important functions triggered by mitochondria. Two pathways are responsible for apoptosis, one of them is intrinsic which is controlled by mitochondria itself and, other is extrinsic which is controlled by ligands bonding to death receptors (Brenner and Mak, 2009). The mechanism of intrinsic pathway depends upon the disrupted mitochondrial membrane potential (MMP) due to their increased permeability and hence the proteins present in intermembrane spaces enter into cytoplasm (Shawgo et al., 2008). Among the intermembrane space proteins, some important are caspase-9 (Du et al., 2000), cytochrome c (Liu et al., 1996) and apoptosis protease activating factor 1. These proteins work together to stimulate final caspases by forming an apoptosome to carry out apoptosis (Cain et al., 2002).

**Covid 19 induced impacts on mitochondria**

Mitochondrial dysfunction is a key factor to induce aging and age-related disorders (Lopez-Lluch et al., 2015). Obesity and aging are two among the many factors associated with mitochondrial dysfunction (Lopez-Lluch, 2017b). Immune system is also affected by deteriorated functions of mitochondria and consequently causes increased viral susceptibility, inflammaging and impaired T lymphocytes immunity in aged people (McGuire, 2019). T-cell activity, on the other hand, activates cytokine storm in many other tissues (Desdin-Mico et al., 2020).

Coronavirus may also impart some indirect effects to patients with impaired mitochondrial functions by increasing alcoholic consumption or by losing multisystem checks or even by the number of cigarettes smoked during recent pandemic lockdowns (Zaslavsky and Margolin, 2021). Impaired mitochondria accumulate by malfunctioning and disruption of various nutrient sensor mechanisms in cells and consequently induce oxidative damage leading to aging, obesity and other metabolic disorders (Lopez-Lluch et al., 2018). Coronavirus show high level mortality and severity above the age of 50 years when the relationship between inflammation and mitochondrial dysfunction increases (McGuire, 2019).

Several disorders associated with aging including type 2 diabetes (T2D), metabolic syndrome (MS), obesity, cardiovascular diseases (CVD) and hypertension can exacerbate COVID-19 severity (Zheng et al., 2020c; Pirola and Sookoian, 2020). In aged individuals, the COVID-19 severity may also associate with impaired immune system and aged immunity (Akbar and Gilroy, 2020). Aging, by natural age progression, results in gradual deterioration of immune system (Pangrazzi and Weinberger, 2020; De Martinis et al., 2007) and such impaired immune system is called immunosenescence (Currie, 1992).

Consequently, several mitochondrial dysfunction responses like endothelial inflammatory reactions, vascular thrombosis and cytokine storm (uncontrolled and imbalanced cytokine response) are triggered by severe coronavirus infections leading to ARDS (acute respiratory distress syndrome), a major cause of mortality in infected aged patients (Varga et al., 2020; Wu et al., 2020).

Many clinical studies revealed that mitochondrial health is severely affected by ROS production. While the truth that can never be denied lies in the positive effects of ROS in the cells as the
Antioxidant functions have been stimulated and redox reactions have been balanced by them to keep the cell healthy (Yang and Hekimi, 2010; Schulz et al., 2007).

**Covid 19 triggers ROS damage:**

Oxidative stress by many infectious viruses may triggered by different mechanisms as earlier was elaborated for Sendai virus in 1979 (Peterhans, 1979). Later, several pathological studies including respiratory diseases, confirm the induction of oxidative stress by different infectious viruses (Khmich et al., 2018). Elevated level of ROS has also been observed during influenza infection (Buffinton et al., 1992), alveolar endothelium (Hendricks et al., 2016) and alveolar epithelium (Amatore et al., 2015).

Oxidative stress is always the result of different respiratory viral infections including rhinoviruses (Biagioli et al., 1999), syncytial virus (Martinez et al., 2016), and several other viruses. Studies also show that high level oxidation of different biomolecules, including proteins, lipids and DNA, is the consequence of influenza virus (Ng et al., 2014; Lim et al., 2014). Generally, chronic oxidative stress is the result of every kind of viral infection (Reshi et al., 2014).

Increased and uncontrolled ROS production upon COVID-19 infection is the major cause of mortality and morbidity in affected patients. So, to rid of excessive oxidative damage it is hereby necessary to find out the organelles and substances which are responsible for the oxidative stress (Ntyonga-Pono, 2020; Delgado-Roche and Mesta, 2020).

Mitochondrial reactive oxygen species (mtROS), produced as a result of impaired mitochondrial functions, trigger oxidative damage during metabolic diseases and aging (Lopez-Lluch et al., 2018). Reactive oxygen species (ROS), in mitochondria, are generated as a result of viral infection and affect the production of antioxidants and oxidizing agents. In ROS rich environment, the growth and replication of many pathogens is increased to higher levels. The first evidence published by Peterhans (Peterhans, 1979) indicates that by inducing ROS production, a virus can trigger oxidative stress. According to recent studies, many others RNA, DNA and retroviruses are responsible for the cell death by triggering the production of ROS (Reshi et al., 2014; Muller, 1992). Balance between reactive oxygen species production and antioxidant enzymes to scavenge them is mandatory for optimal cellular functions (Dan Dunn et al., 2015).

**Oxidative effects leading to ageing process:**

In fact, age is the major factor in inducing severe viral infection, as in the case of coronavirus. Hence, people above the age of 65 show high susceptibility to influenza (Etard et al., 2020, McGuire, 2019). Upon viral infections, the aged patient become more susceptible to hyperinflammation, the phenomenon which is called as Inflammaging (Soysal et al., 2016; Hager et al., 1994). The cause of inflammaging is the permeability of mitochondrial membranes and therefore infected mitochondria release their proteins and DNA (mtDNA) into the cytosol and trigger hyperinflammation by activating toll-like receptor-9. These receptors trigger cytokine production by monocytes and neutrophil recruitment (Jang et al., 2018).

After five decades of age, levels of circulating mitochondrial DNA gradually increase (Pinti et al., 2014). Mitochondrial DNA (mtDNA) is more susceptible to mutational changes as compared to nuclear DNA. Oxidative stress and age related mutated mtDNA are closely connected with each other (Oliver D. M. A. and Reddy, 2019; Kuka et al., 2013; Reddy, 2006; Reddy and Beal, 2005; Kang et al., 2016). The reason for this close connectivity is that the mtDNA are located close to respiratory chains generating ROS (Chistiakov et al., 2014). Consequently, mutated mtDNA can trigger more production of ROS and dysfunction of mitochondria (Wallace, 2010).

Another factor which leaves detrimental effects on mitochondrial health is the opening of mitochondrial permeability transition pores (mPTP). These mPTP sits on internal mitochondrial
membrane (IMM) and open up in response to high calcium level (Panel et al., 2018), and the cell under high oxidative stress increases the sensitivity of mPTP to calcium (Halestrap and Richardson, 2015). As the age increases, pores of mPTPs open in the presence of excessive calcium levels in mitochondria (Panel et al., 2018).

Studies reveal that calcium plays a communication role between mitochondria and sarcoplasmic reticulum, so the disturbed level has severe effect on cardiac muscle. Increase in ROS production, low energy yield, disturbed calcium levels and unregulated calcium transfer into cytosol without the control of mPTP in older patients may altogether lead to heart failure (Fernandez-Sanz et al., 2014; Kohlhaas and Maack, 2013; Szalai et al., 2000). These may also lead to Alzheimer’s disease, a neurological disease which induce detrimental effects on health like elevated ROS levels leading to oxidative stress, impaired ATP synthesis and malfunctioning of mitochondria (Reddy and Beal, 2005, 2008; Beal, 2005). In skeletal muscles, despite malfunctioning of mitochondria, the number of mitochondria also decreases with age (Crane et al., 2010) and decreased biogenesis with the age is the key factor for this decrease in number (Chistiakov et al., 2014).

The dysfunction of nutrient sensor mechanisms and increased number of damaged mitochondria with impaired functions is a hallmark obesity, aging and other metabolic syndrome (Lopez-Lluch et al., 2018). Disrupted mitochondrial dynamics, increased damaged mitochondria, auto/mitophagy and biogenesis altogether lead to age related mitochondrial dysfunctions (Lopez-Lluch et al., 2015; Lopez-Lluch, 2017a, 2017b).

There are some other factors which link oxidative stress to coronavirus infections, severity and mortality such as low socioeconomic status, older age, being male, Black and South Asian ethnicity, obesity and hyperglycemia (Williamson et al., 2020). Oxidative stress is induced by all these factors (King and Loeken, 2004; Skulachev et al., 2009).

**How to manage a balance between ROS and antioxidants**

Viruses, after getting entry to cells may attack to inhibit the expression of enzymatic antioxidants like glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT). Inhibition of non-enzymatic antioxidants such as carotenoids, vitamin c, cofactors and minerals take place as the cellular homeostasis disturbed by viral regulatory proteins (Camini et al., 2017; Broz and Monack, 2011; Reshi et al., 2014). Free radicals scavenged by these antioxidants such as vitamin D and E both have high scavenging powers, but the former has comparatively higher activity (Sardar et al., 1996).

It is expected that use of antioxidants seems to be more affective during the infection when virus try to induce cytokine storm. Use of antioxidants may fight against oxidative stress and cytokine storm induced tissue damage (Poe and Corn, 2020; Assimakopoulos and Marangos, 2020). Moreover, antioxidants work to decrease viral load by minimizing oxidative stress. During coronavirus infection thrombogenesis is a dangerous outcome, and antioxidants may compete against its mechanisms. In endothelial cells, ROS dependent apoptosis is the consequence of cytokine storm (Winn and Harlan, 2005). Induction of endogenous antioxidant systems is another important approach to combat oxidative damage during coronavirus infection (Wang et al., 2018). Moreover, some agents have been proposed with antioxidant properties to lower the risk of viral infections or to use as treatment to get rid of severe coronavirus variants (Soto et al., 2020).

**Steps to keep body healthy after covid infection:**

Several drugs, some of which are used upon other viral infections, have been approved for use during coronavirus infection such as ribavirin, darunavir, hydroxychloroquine, favipiravir, remdesivir, lopinavir-ritonavir, arbidol, and cobicistat along with several other therapies (Kandimalla et al., 2020; Bhatti et al., 2020). Vaccines, targeting spike proteins, have also been inoculated against SARS-CoV-2.
(Kandimalla et al., 2020)). But for the old patients, these are not so much affective because of impaired immunity at this stage of life.

Exercise is necessary to fight against mitochondrial dysfunction and aging (Garatachea et al., 2015; Fiuza-Luces et al., 2013). Strong muscle mass and vasculature is necessary to keep your body healthy and alive.

Long term exercise with consistency for several years encourages the body to become stress resistant, homeostatic and protected against chronic disorders ((Nilsson et al., 2019)). Moreover, taking food with antioxidant properties like matcha, kale, raw cacao, beets, berries, artichokes, spinach, and pecans makes an individual able to get rid of oxidative stress. Anti-inflammatory foods like nuts, fish, fruits, garlic, healthy oils, chocolate and herbs can also be used against viral infections.