Opinion

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Is Long COVID a Syndrome from Mitochondrial Dysfunction?

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Long COVID, a condition characterized by persistent symptoms following acute COVID-19 infection, has emerged as a significant health concern affecting a growing number of individuals worldwide. As researchers delve deeper into the complexities of long COVID, a potential link between mitochondrial dysfunction and the prolonged symptoms experienced by patients is being explored. Mitochondria, known as the powerhouse of the cell, play a crucial role in energy production and cellular function. Understanding the interplay between long COVID and mitochondrial dysfunction could provide valuable insights into the underlying mechanisms of this condition and find the way for novel therapeutic approaches.

Keywords: Long COVID; Mitochondrial Dysfunction; Energy Imbalance; Therapeutic Implications; Outcomes

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INDIVIDUALS who have recovered from the acute phase of COVID-19 are said to have Long COVID, which is characterized by persistent symptoms (Toepfner et al., 2024). Some researchers have proposed that mitochondrial dysfunction, a condition in which the energy-producing organelles in cells fail to function effectively, may be associated with long COVID (Al-Aly & Topol, 2024; Cezar et al., 2024).

In nearly every cell of the body, mitochondria are indispensable organelles that generate energy in the form of adenosine triphosphate (ATP). Cells are unable to generate sufficient energy when mitochondria are malfunctioning, resulting in a variety of symptoms such as cognitive impairment, muscle lethargy, and fatigue (Tripathi & Ben-Shachar, 2024). Some researchers have suggested that mitochondrial dysfunction may be a potential underlying mechanism for the condition, as these symptoms are also frequently reported by individuals who have a long COVID (Chen et al., 2023; Dirajlal-Fargo et al., 2024).

The link between mitochondrial dysfunction and long COVID has been supported by numerous studies. In comparison to healthy controls, individuals who had a prolonged COVID-19 infection exhibited diminished mitochondrial function (Noonong et al., 2023; Nunn et al., 2022; Tripathi & Ben-Shachar, 2024). Additionally, individuals with long COVID have been discovered to have elevated levels of markers of oxidative stress and inflammation, both of which are linked to mitochondrial dysfunction (Chang & Wei, 2024).

Although the precise mechanisms that underlie the correlation between long COVID and mitochondrial dysfunction are

still being investigated, it is hypothesized that the immune response to the SARS-CoV-2 virus may be involved. Additionally, the virus has the potential to induce oxidative stress and inflammation in the body, which can result in mitochondrial injury and disruption of their functionality (Zhang et al., 2024). Furthermore, the long-term consequences of the virus on the immune system and the body's overall health may contribute to mitochondrial dysfunction in individuals with long COVID.

Developing effective treatments for individuals who are experiencing persistent symptoms necessitates an understanding of the potential connection between long COVID and mitochondrial dysfunction (Chen et al., 2023; Guntur et al., 2022; Noonong et al., 2023; Nunn et al., 2022). Through interventions such as mitochondrial enhancers, antioxidants, and lifestyle modifications, the quality of life of individuals with long COVID may be enhanced. To develop targeted therapies for this emerging syndrome and to completely understand the mechanisms that underlie this connection, additional research is required.

Therefore, the hypothesis that mitochondrial dysfunction may contribute to the development and persistence of symptoms in individuals with long COVID is increasingly supported by the growing body of evidence while the relationship between long COVID and mitochondrial dysfunction is still being investigated.

Link between Long COVID and Mitochondrial Dysfunction

The fact that COVID-19 is known to induce inflammation and oxidative stress in the body is one connection between long COVID and mitochondrial dysfunction (Pozzi, 2022). One or both of these factors can have a detrimental effect on mitochondrial function, resulting in a reduction in energy production and an increase in cellular injury. This can lead to a variety of symptoms that are frequently encountered by individuals with long COVID, including cognitive impairment, muscle weakness, and fatigue.

COVID-19 has been demonstrated to directly impact mitochondrial function by disrupting the electron transport chain (Tandon et al., 2024), which is responsible for the production of ATP, the cell's energy currency. Research has demonstrated that SARS-CoV-2 has the ability to enter mitochondria and disrupt their typical operation, resulting in a decrease in ATP production and an increase in reactive oxygen species (ROS) production (Ashok et al., 2024; Dirajlal-Fargo et al., 2024). This can exacerbate mitochondrial dysfunction and contribute to the development of long COVID symptoms.

Individuals who have preexisting conditions that impact mitochondrial function, such as metabolic disorders or mitochondrial diseases, may be at an increased risk of developing long COVID (Böhmwald et al., 2024; Saito et al., 2024). This is due to the fact that their mitochondria are already compromised, rendering them more susceptible to the effects of SARS-CoV-2 infection on mitochondrial function. In these individuals, the virus may further disrupt mitochondrial function, resulting in more severe and prolonged long COVID symptoms.

Long COVID may induce a dysregulated immune response, referred to as a cytokine storm, which may exacerbate mitochondrial dysfunction. Cytokines are signaling molecules that regulate the immune response; however, an excessive production of cytokines can result in tissue injury and excessive inflammation (Huang et al., 2024; Kang et al., 2024; Kumar, 2021). This inflammatory response can directly impact mitochondria, resulting in dysfunction and contributing to the persistent symptoms observed in long COVID.

The cardiovascular system, which is frequently affected in individuals with long COVID, can also be influenced by mitochondrial dysfunction. By modulating cellular function and producing energy for cardiac muscle contraction, mitochondria are essential for the maintenance of the health of the heart and blood vessels (Mostafa & Moustafa, 2024). Individuals with long COVID may experience symptoms such as chest pain, palpitations, and shortness of breath as a result of mitochondrial dysfunction, which can result in cardiac damage and impaired blood flow (Kusumawardhani et al., 2023; Mostafa & Moustafa, 2024; Sakellaropoulos et al., 2022).

Additionally, the respiratory system's functionality may be compromised by mitochondrial dysfunction, which can exacerbate respiratory symptoms in individuals with Long COVID (Ryback & Eirin, 2022). Mitochondria are essential for the production of energy and the sensing of oxygen in the lungs. Impaired lung function and diminished oxygen uptake can result from dysfunction in these organelles (Chen et al., 2023; Chen et al., 2024). This can lead to symptoms such as chest constriction, coughing, and shortness of breath in individuals with long COVID.

Additionally, neurological symptoms are frequently reported in individuals with long COVID due to mitochondrial dysfunction, which can impact the brain and nervous system. Cognitive impairment, brain fog, and migraines can result from mitochondrial dysfunction, which is crucial for the maintenance of neuronal function and energy production in the brain (Al-Aly & Topol, 2024; Ladds et al., 2024; Tripathi & Ben-Shachar, 2024). This may elucidate the reason why a significant number of individuals with long COVID experience cognitive difficulties and neurologic symptoms even after the initial infection has resolved.

Potential Therapeutic Targets of Mitochondria to Long COVID

The electron transport chain (ETC) is a potential therapeutic target for mitochondria in long COVID (Guo et al., 2022). The ETC is a sequence of protein complexes situated within the inner mitochondrial membrane that are responsible for the production of ATP, the central energy source of the cell. Researchers may be able to optimize energy production in cells affected by long COVID and potentially alleviate symptoms such as fatigue and muscle weakness by targeting the ETC (Arun et al., 2016).

Oxidative stress is an additional target. Mitochondria are a significant source of ROS, which can result in cell damage if not correctly managed. In the context of long COVID, symptoms such as cognitive impairment and brain confusion may be exacerbated by increased oxidative stress. Researchers may enhance cognitive function and reduce oxidative stress in individuals with long COVID by targeting mitochondrial ROS production

(Damiano et al., 2023; Mantle et al., 2024).

Another potential therapeutic target for long COVID is mitochondrial biogenesis, which is the process by which new mitochondria are formed (Cervia-Hasler et al., 2024; Pozzi, 2022). Energy production in cells affected by long COVID may be restored and overall cellular function may be enhanced by increasing mitochondrial biogenesis. Furthermore, the promotion of mitochondrial biogenesis may aid in the reduction of inflammation, which is another prevalent symptom of long COVID, as mitochondria are essential for the regulation of immune responses (Fernández-Ayala et al., 2020).

Another area of potential therapeutic intervention in long COVID is mitochondrial dynamics, which is the equilibrium between mitochondrial fusion and fission. Dysfunction and a variety of health issues can be the consequence of imbalances in mitochondrial dynamics (Xu et al., 2024). We can alleviate symptoms associated with long COVID by targeting mitochondrial dynamics and restoring normal mitochondrial function.

Mitophagy and the unfolded protein response, which are mitochondrial quality control mechanisms, are also potential therapeutic targets for long COVID (Appelman et al., 2024; Ruf, 2024). These mechanisms are instrumental in the removal of damaged mitochondria and the preservation of the overall health of the mitochondria. Researchers may enhance mitochondrial function and alleviate symptoms associated with long COVID by focusing on mitochondrial quality control.

The potential of targeting mitochondria as a therapeutic for long COVID is promising. It could be realized through enhancing energy production, reduce inflammation, and restore cellular function in individuals affected by long COVID by concentrating on critical components of mitochondrial function, including the electron transport chain, oxidative stress, biogenesis, dynamics, and quality control. Additional research is required to investigate the potential advantages of targeting mitochondria in long COVID and to develop effective therapeutic strategies to address this intricate and multifaceted condition.

In conclusion, mitochondria are essential cellular organelles that are responsible for energy production. When they are dysfunctional, they can result in a variety of health issues. Studies demonstrated that individuals with long COVID suffer from impaired mitochondrial function, which may account for the persistent fatigue and malaise that are frequently observed. In addition, mitochondrial dysfunction has been associated with other chronic conditions, including chronic fatigue syndrome and fibromyalgia, underscoring its potential influence on long COVID. Understanding the relationship between mitochondrial dysfunction and long COVID could facilitate the development of targeted treatments and interventions that can enhance patient outcomes via elucidating the underlying mechanisms of this condition.■

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