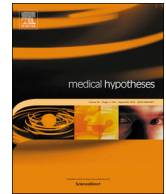




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Mitochondrial-targeted ubiquinone: A potential treatment for COVID-19

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ABSTRACT

Immune dysregulation characterized by T cell exhaustion and high level of inflammatory cytokines is associated with severe COVID-19. Figuring out the early event of immune dysregulation would provide a potential treatment for COVID-19. Recent evidence indicate that mitochondrial dysfunction participates in the development of COVID-19 and may be responsible for the dysregulated immune response. Mitochondrial-targeted ubiquinone (MitoQ), a mitochondrial-targeted antioxidant, shows beneficial effects on various diseases through improving mitochondrial dysfunction. We hypothesize that MitoQ could act as a potential treatment in COVID-19. MitoQ may alleviate cytokine storm and restore the function of exhausted T cells in COVID-19 patients through improving mitochondrial dysfunction. In this article, we provide evidence to support the use of MitoQ as a potential treatment or adjunct therapy in the context of COVID-19.

Background to hypothesis

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 in Wuhan, China [1]. The virus has spread rapidly to other countries and became pandemic. As of May 17, 2020, a total of 4,719,849 confirmed cases of COVID-19 and 313,228 deaths have been reported across the globe. The clinical manifestation of COVID-19 could vary from an asymptomatic course to severe pneumonia, multiple organ injury and mortality [2]. The morbidity and mortality of COVID-19 patients have been reported to be associated with elderly age, male and the comorbidities such as hypertension, diabetes, cardiovascular disease and chronic obstructive lung disease [3,4]. Although a lot of treatments such as chloroquine or hydroxychloroquine, antiviral drugs including remdesivir, interleukin-6 inhibitor and mesenchymal stem cell-based therapy are under investigation currently, unfortunately, none of them has been approved for treatment of COVID-19 [5,6].

Recent studies have indicated that lymphopenia, exhaustion of T cells (immunodeficiency) and cytokine storm (hyperinflammation) are hallmarks of severe COVID-19 patients, suggesting that the broken homeostasis of the immune response plays a critical role in the development of COVID-19 [7]. In severe COVID-19 patients, the lymphocyte counts are markedly decreased with elevated levels of exhaustion markers and reduced functional diversity [8]. The lymphocyte counts are inversely correlated with serum IL-6, IL-10 and TNF- α and with

high levels of exhaustion markers such as PD-1, Tim-3, TIGIT [8–10]. Figuring out the early events of the dysregulated immune function may provide a potential treatment for COVID-19 patients.

Mitochondria play pivotal roles in cell homeostasis. They are the powerhouse of cells as well as the main source of reactive oxygen species (ROS) within the cells. Furthermore, mitochondria regulate innate and adaptive immunity [11]. Mitochondrial dysfunction is typically characterized by a disturbance of the basic mitochondrial bioenergetic, antioxidant and regulatory function which results in a decrease in ATP synthesis, dysregulated cell death processes and increased ROS production [12]. Mitochondrial dysfunction is involved in the development of various diseases, e.g. diabetes, COPD, ischemia-reperfusion injury and respiratory virus infection [13]. A study by Zhang et al. showed that SARS-CoV-1 nucleocapsid protein induced apoptosis of COS-1 cells with mitochondrial dysfunction, which was demonstrated by increase of ROS and loss of mitochondrial potential [14]. Recent study using master regulator analysis demonstrated that a member of the mitochondrial complex I is downregulated by SARS-CoV-2-infection, suggesting the virus may use the strategy of attacking the host cells through disruption of mitochondria [15]. Another study of gene expression analysis by single cell RNA seq reported that lung cell line A549 infected with SARS-CoV-2 upregulated genes in the interferon, cytokines, nuclear factor kappaB (NF- κ B) and ROS processes, while downregulated the genes in the mitochondrial organization and respiration processes [16]. The above studies indicate that

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mitochondrial dysfunction plays a significant role in the development of COVID-19 and may be partly responsible for the dysregulated immune response of COVID-19.

Mitochondrial-targeted ubiquinone (MitoQ) is a mitochondrial-targeted antioxidant which consists of the antioxidant quinone moiety linked to a lipophilic triphenyl phosphonium (TPP) cation by a 10-carbon alkyl chain [17]. The lipophilic TPP moiety on MitoQ enables it targetedly accumulate within mitochondria driven by the membrane potential and sequester the ROS [17]. MitoQ exhibits stronger protective ability against oxidative stress by ROS compared with other untargeted antioxidants [18].

The hypothesis

We hypothesize that MitoQ could be a potential treatment agent in COVID-19 through improving mitochondrial dysfunction and restoring the dysregulated immune response. In this article, we provide evidence to support the use of MitoQ as a treatment or adjunct therapy for COVID-19.

Evaluation of the hypothesis

Association of aging and comorbidities of COVID-19 with mitochondrial dysfunction

Mitochondrial dysfunction is a hallmark of aging which is accompanied by increased ROS production [11]. The increased ROS activates several pathways including NF- κ B pathway and results in increased secretion of pro-inflammatory cytokines and a state called chronic low-grade inflammation [12]. Mitochondrial dysfunction and chronic low-grade inflammation are also prevalent in cardiovascular and metabolic disease including hypertension, obesity and type 2 diabetes [19]. It is plausible that elderly populations or people with comorbidities (diabetes and cardiovascular disease) in a state of mitochondrial dysfunction are susceptible to SARS-CoV-2 infection and progress to severe infection. The beneficial effects of MitoQ on aging and cardiovascular as well as metabolic disease through improving mitochondrial dysfunction and alleviating inflammation have been widely described [20–23]. For example, MitoQ treatment modulates oxidative stress and reduces the production of TNF- α in type 2 diabetes [21]. Therefore, we speculate MitoQ used in the early stage should be effective in halting or delaying the disease progression in elderly COVID-19 patients or those with comorbidities.

Association of cytokine storm with mitochondrial dysfunction

ROS are signaling molecules which are responsible for the production of cytokines and chemokines. However, ROS over-production, a characteristic of mitochondrial dysfunction, could mediate hyper-activation of the immune response termed cytokine storm [24]. ROS over-production results in activation of NLRP3 inflammasome and increase of IL-1 secretion [25]. Studies have demonstrated that MitoQ could ameliorate ROS over-production, suppress NLRP3 inflammasome activation and decrease the inflammatory cytokine (IL-1, IL-6 and TNF- α) in concanavalin A-induced hepatitis, diabetes, experimental mouse colitis and sepsis-induced acute lung injury [21,26–28]. In the context of respiratory syncytial virus (RSV) infection, MitoQ limited RSV infection through reducing mitochondrial ROS production [29]. It is plausible that MitoQ may alleviate cytokine storm in severe COVID-19 patients.

Association of T cell exhaustion with mitochondrial dysfunction

Mitochondrial dysfunction is regarded to be the early driver for the development of T cell exhaustion. In the mouse model of chronic LCMV infection, dysregulated mitochondrial energetics is one of the hallmarks

of exhausted T cells which depends at least in part on elevated PD-1 signaling [30]. In chronic HCV infection, exhausted HCV-specific CD8⁺ T cells display mitochondrial dysfunction characterized by depolarized mitochondria, increased ROS production and mass biogenesis, which rely on P53 upregulation [31,32]. Similar to T cells in patients of chronic viral infection, T cells in patients of COVID-19 also upregulate exhaustion markers such as PD-1, Tim-3, TIGIT. Transcriptomic analysis shows TP53 gene is upregulated in T cells of COVID-19 patients [33]. Whether mitochondrial dysfunction exists in T cells of COVID-19 needs to be validated. We speculate that elevated PD-1 expression and upregulated p53 may drive early mitochondrial dysfunction which further leads to T cell exhaustion in COVID-19 patients. Studies have reported that manipulation of dysfunctional mitochondria with mitochondrial-targeted antioxidants could rescue the function of exhausted T cells [34]. In chronic HBV infection, exhausted HBV-specific CD8⁺ T cells display defective mitochondrial function which can be reinvigorated by mitochondria-targeted antioxidants MitoQ [34]. It is possible that MitoQ may prevent T cell exhaustion or restore their antiviral function in COVID-19.

Clinical trials

There have been several clinical trials of MitoQ. In a double-blind, randomized phase II study of chronic HCV patients, oral administration of MitoQ showed liver protection effect without toxicity [35]. Another randomized study elucidated that chronic supplementation with MitoQ improved vascular function in healthy older adults [22]. The tolerance and safety of MitoQ have been approved when administered orally for three weeks without adverse effects and it is now available as a dietary supplement [12].

Consequences of the hypothesis

Mitochondrial dysfunction may be an early trigger for subsequent cytokine storm and T cell exhaustion in COVID-19 patients. It is reasonable that MitoQ may alleviate cytokine storm and restore the function of exhausted T cells in COVID-19 patients through improving mitochondrial dysfunction. To test the hypotheses further, we recommend both the in vitro and in vivo studies investigating the tolerance, safety and efficiency of MitoQ on COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110161>.

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