Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The powerful immune system against powerful COVID-19: A hypothesis

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ABSTRACT

On March 11, 2020, the World Health Organization declared the coronavirus outbreak a pandemic. Since December 2019, the world has experienced an outbreak of coronavirus disease 2019 (COVID-19). Epidemiology, risk factors, and clinical characteristics of patients with COVID-19 have been reported but the factors affecting the immune system against COVID-19 have not been well described. In this article, we provide a novel hypothesis to describe how an increase in cellular adenosine triphosphate (c-ATP) can potentially improve the efficiency of innate and adaptive immune systems to either prevent or fight off COVID-19.

Background

Today, the rapid outbreak of Corona Virus Disease 2019 (COVID-19 or SARS-CoV-2) is the leading health issue. There is a paucity of studies investigating the factors affecting immune response to COVID-19. In addition, there has been no detailed report for this immune response. Given the genomic similarity of 79% with Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), nearly the same reaction to the immune system is expected for COVID-19 [1]. In response to SARS-CoV, both innate and adaptive immune systems are involved. SARS-CoV applies several mechanisms to overcome the immune response. First, it inhibits the rapid expression of interferon type 1 (IFN-1) [2]. IFN-1 is known as the "initial alarm" upon encounter with the virus that modulates the immune cells to the so-called "antiviral state". Moreover, SARS-CoV interferes with IFN-1 signaling through inhibition of STAT-1 phosphorylation [3]. The third defensive mechanism of SARS-CoV is immune exhaustion through exaggerated and prolonged IFN-1 production by plasmacytoid dendritic cells (pDCs). This process leads to the influx of activated neutrophils and inflammatory monocytes/macrophages, that in turn, results in lung immunopathology (e.g. acute respiratory distress syndrome) [4]. Finally, the resulted so-called "cytokine storm" further weakens the immune system through IFN-1-mediated T cell apoptosis [5]. In this article, we aim to provide a new hypothesis to describe how the repletion of cellular adenosine triphosphate (c-ATP) can promote immunity against COVID-19. Thereafter, we justify the current knowledge regarding the characteristics of COVID-19 infection by our hypothesis and give several approaches to improve the c-ATP.

The hypothesis

Considering the pivotal role of ATP in cellular function, c-ATP depletion can lead to cellular dysfunction [6]. Immune cells are not an exception. In this article, c-ATP is the index of cellular energy.

Evaluation of the hypothesis

Here, we show how c-ATP repletion can counteract with defensive mechanisms of COVID-19 and promote the immune system to the enhancement pathway.

ATP facilitates IFN production

COVID-19 interferes with a rapid rise in IFN-1. Therefore, it deactivates the so-called "initial alarm" of the innate immune system, by unknown mechanisms. This facilitates its replication. Zhang et al. have demonstrated that enhancement in the c-ATP can reverse this process. This occurs by the facilitation of IFN secretion through P38/JNK/ATF-2 signaling pathway [7]. Therefore, ATP-depleted cells are more susceptible to this effect of COVID-19.

ATP facilitates IFN signaling

Following IFN-1 secretion, fundamental changes occur in the immune cells that transform them into the so-called "antiviral state". One of the signaling pathways that take part in this process is the JAK/STAT pathway. JAKs are ATP-dependent enzymes that are bound to the cytoplasmic regions of cytokine receptors. Following attachment of IFN-1

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to the cytokine receptor, JAK activates the STAT through trans-phosphorylation [8]. Obviously, c-ATP depletion interferes with this process and further impairs transformation to "antiviral state".

ATP prevents the cytokine storm

Following deactivation of "initial alarm", COVID-19 easily proliferates *in-situ.* Among the passive host-cells, there are exceptions that can react to the COVID-19, the pDCs. They detect the virus by toll-like receptor 7 (TLR-7). Upon attachment to viral nucleic acids, TLR7 induces profound IFN-1 expression. This response recruits other immune cells and causes massive local inflammation [9]. At first glance, this robust immune response is beneficial for the elimination of COVID-19. However, two factors prevent it. First, impairment of IFN-1 signaling results in impairment of immune cell transformation to the "antiviral state". Therefore, they are not so effective in eliminating existing viruses [8]. Second, persistence profound inflammatory responses may lead to immune exhaustion [4]. The depletion of c-ATP can potentially enhance these detrimental processes in the following ways. In 2016, Rebbapragada et al. demonstrated the effect of ATP in the function of TLR7 by controlling the endo-lysosomal PH. They showed that ATP-depletion can increase the endo-lysosomal PH and improve the efficacy of TLR7. Therefore, ATP-depletion can potentially enhance profound IFN-1 secretion in this phase. Secondly, ATP-depletion can potentially prone the recruited immune cells to earlier exhaustion against COVID-19. Therefore, one may conclude that ATP-repletion can prevent the so-called "cytokine storm" and improve the cellular energy to better counteract with COVID-19.

ATP prevents T-cell apoptosis

Channappanavar et al. demonstrated that COVID-19 can promote T-cells to IFN-induced apoptosis, resulting in reduced numbers of virus-specific CD8 and CD4 T-cells [5]. From the perspective of cellular energy, this process potentially occurs through IFN-mediated T-cell activation that results in c-ATP depletion. In line with this hypothesis, Perl et al. have shown that following IFN-γ stimulation, mitochondrial hyperpolarization and ATP depletion occurs in T-cells that results in apoptosis [10]. Therefore, ATP-repletion can potentially prevent T-cell apoptosis following "cytokine storm".

Empirical data

In the following section, we use our hypothesis to demonstrate why specific groups of people are more susceptible to be infected with COVID-19 and why they have a worse prognosis.

Elderly population

The case-fatality rate of COVID-19 is the highest (14.8%) in elderly-population. In contrast, children have the lowest risk for both infection and mortality rates [11]. This difference can be demonstrated from the cellular energy aspect. Aging may potentially attenuate the respiratory capacity of mitochondria. This condition may be either due to impairment of peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) or age-related accumulation of mitochondrial DNA mutations [12]. Moreover, aging can wane the ability of immune cells to secrete IFN following viral infection [13]. As noted earlier, this may be due to ATP-depletion. Therefore, one can conclude that a gradual decline in prognosis with age may rely on a gradual decrease in c-ATP.

Tobacco smokers

The risk of long-lasting and serious COVID-19 infection is more among tobacco smokers. Apart from a direct effect on lung parenchyma and a decrease in pulmonary capacity, tobacco smoke can potentially induce immune dysfunction through a decrease in the ATP content of immune cells. This can be due to nicotine-induced mitochondrial dysfunction [14]. The resultant ATP-depletion increases the risk of immune dysregulation by COVID-19 (refer to the aforementioned defensive mechanisms of COVID-19).

Male gender

While men and women have the same susceptibility to COVID-19, men are more prone to higher morbidity and mortality independent of age [15]. This difference can be justified by the cell energy hypothesis. Estrogens (as the main sex steroid of females) are potent stabilizers of ATP production during oxidative stress (e.g. during COVID-19-induced inflammation) [16]. Therefore, it seems that women are more capable to maintain the c-ATP of their immune cells during the immune response to COVID-19. With this notion in mind, men are more susceptible to immune dysregulation following COVID-19 infection.

Serious chronic medical conditions

Recent reports have highlighted some chronic illnesses that increase the mortality of COVID-19. They include underlying conditions such as hypertension, diabetes, coronary heart disease, chronic obstructive lung disease, cancer, and chronic kidney disease [17]. Apart from a decline in cardiovascular reserve, the effect of these chronic conditions on the prognosis of COVID-19 can be justified by our hypothesis. Human cells need nutrients (including glucose, free fatty acids, essential amino acids, and O_2) to maintain their c-ATP level. The aforementioned illnesses impede the regular distribution of the nutrients secondary to compromising the function and structure of small and large vessels. Therefore, the human cells (including in-situ immune cells) confront ATP-depletion and results in further immune dysregulation (as mentioned above).

Approaches to improvement in c-ATP

In light of these considerations, the c-ATP level can potentially be considered as a crucial component in the infectivity and prognosis of COVID-19. With enhancing the c-ATP, improvement in both innate and adaptive immune systems is expected. Moreover, an increase in c-ATP can potentially have either preventive or therapeutic effects. The preventive effect through activation of initial IFN-1 secretion and signaling, as "initial alarm" of the innate immune system. The therapeutic effect through the prevention of "cytokine storm" and T-cell apoptosis. There are several approaches to improve c-ATP. Most of them are easily available through a change in lifestyle. First, regular exercise improves mitochondrial respiratory capacity through an increase in PGC-1α [18]. Smoking cessation is the second approach to improve mitochondrial capacity and improvement in c-ATP (as mentioned above). Consuming foods with low specific dynamic action (SDA), as the energetic budget for consuming food, can potentially boost the immune system through improving the c-ATP. In 2016, Luoma et al. demonstrated the effect of low-SDA meals in the up-regulation of the innate immune system in corn snakes [19]. On the other hand, several studies have reported the positive effect of xanthine oxidoreductase inhibitors on c-ATP [6].

Consequences of the hypothesis

This hypothesis provides a new concept to improve the immune system against COVID-19. It demonstrates how an increase in c-ATP can decrease the effect of COVID-19 on immune dysregulation. Considering the strategies to enhance cellular ATP, improvement of the immune system against COVID-19 is possible. It is hoped that this hypothesis will serve as a stimulus for further investigation into this issue.

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.2020.109762https://doi.org/10.1016/j.mehy.2020.109762.

References

[1] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet 2020;395(10224):565–74.

[2] Kindler E, Thiel V. SARS-CoV and IFN: too little, too late. Cell Host Microbe 2016;19(2):139–41.

[3] de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016;14(8):523.

[4] Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol 2020.

[5] Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, et al. Dysregulated Type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe 2016;19(2):181–93.

[6] Johnson TA, Jinnah HA, Kamatani N. Shortage of cellular ATP as a cause of diseases and strategies to enhance ATP. Front Pharmacol 2019;10:98.

[7] Zhang C, He H, Wang L, Zhang N, Huang H, Xiong Q, et al. Virus-triggered ATP release limits viral replication through facilitating IFN-β production in a P2X7-dependent manner. J Immunol 2017;199(4):1372–81.

[8] Seif F, Khoshmirsafa M, Aazami H, Mohsenzadegan M, Sedighi G, Bahar M. The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. Cell Commun Signaling 2017;15(1):23.

[9] Cervantes-Barragan L, Züst R, Weber F, Spiegel M, Lang KS, Akira S, et al. Control of coronavirus infection through plasmacytoid dendritic-cell–derived type I interferon. Blood 2007;109(3):1131–7.

[10] Perl A, Gergely Jr P, Nagy G, Koncz A, Banki K. Mitochondrial hyperpolarization: a checkpoint of T-cell life, death and autoimmunity. Trends Immunol 2004;25(7):360–7.

[11] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. Jama. 2020.

[12] Desler C, Hansen TL, Frederiksen JB, Marcker ML, Singh KK, Juel Rasmussen L. Is there a link between mitochondrial reserve respiratory capacity and aging? J Aging Res 2012;2012.

[13] Qian F, Wang X, Zhang L, Lin A, Zhao H, Fikrig E, et al. Impaired interferon signaling in dendritic cells from older donors infected in vitro with West Nile virus. J Infect Dis 2011;203(10):1415–24.

[14] Malińska D, Więckowski MR, Michalska B, Drabik K, Prill M, Patalas-Krawczyk P, et al. Mitochondria as a possible target for nicotine action. J Bioenerg Biomembr 2019;51(4):259–76.

[15] Jin J-M, Bai P, He W, Wu F, Liu X-F, Han D-M, et al. Gender differences in patients with COVID-19: Focus on severity and mortality. medRxiv. 2020.

[16] Kassi E, Moutsatsou P. Estrogen receptor signaling and its relationship to cytokines in systemic lupus erythematosus. Biomed Res Int 2010;2010.

[17] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020.

[18] Burelle Y, Hochachka PW. Endurance training induces muscle-specific changes in mitochondrial function in skinned muscle fibers. J Appl Physiol 2002;92(6):2429–38.

[19] Luoma RL, Butler MW, Stahlschmidt ZR. Plasticity of immunity in response to eating. J Exp Biol 2016;219(13):1965–8.