

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 and fight off COVID-19.

Keywords: COVID-19; ATP; Immune dysfunction

1. 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.

2. 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. Here, we show how c-ATP repletion can counteract with defensive mechanisms of COVID-19 and promote the immune system to the enhancement pathway. In this article, c-ATP is the index of cellular energy.

2.1. 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.

2.2. 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 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”.

2.3. 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. 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.

2.4. 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”.

3. Clinical implications of hypothesis

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.

3.1. 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 concept. Aging may potentially attenuate the respiratory capacity of mitochondria. This condition may be either due to impairment of peroxisome proliferator-activated receptor-gamma coactivator-1 α (PGC-1 α) 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.

3.2. 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 ATP content of immune cells. This can be due to nicotine-induced mitochondrial dysfunction (14). The resultant ATP-depletion increase the risk of immune dysregulation by COVID-19 (refer to the aforementioned defensive mechanisms of COVID-19).

3.3. 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.

3.4. 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 O₂) 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).

4. 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 cytotoxic immune systems is expected. Moreover, an increase in c-ATP can potentially have either preventive and 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-1 α (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).

Conclusion

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.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

Not applicable.

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