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The Aging Immune System and COVID-19: How Does the Aging Immune System Exacerbate COVID-19 Cases?

Abstract

The COVID-19 pandemic has infected and killed thousands of people around the world. In the hospital, patients with COVID-19 present symptoms that are similar to the seasonal flu. However, severe cases may lead to detrimental symptoms such as acute respiratory syndrome, organ failure, and death (Wadman et al.). One demographic in particular at greater risk is the elderly. One study with 4,021 cases of COVID-19 has shown that the mortality rate of people over the age of 60 was 5.3 percent while the people with the age of less than 60 had a mortality rate of 1.4 percent (Liu et al.). This literature review aims to examine what immunosenescence is, and how it plays a role in the exacerbation of COVID-19 symptoms overall. Furthermore, it explores potential treatment options that may help slow down or even reverse the effects of immunosenescence based on the mechanisms discussed.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 is the virus that is responsible for the COVID-19 outbreak. Originating in China in late 2019, the spread of the virus does not seem to be slowing down. As of early August 2020, there have been 18,406,862 cases of COVID-19 and 695,937 deaths all over the world(“COVID-19

CORONAVIRUS PANDEMIC"). Of these cases, those over 65 represent 80 percent of hospitalizations (Mueller et al.). Examining this, it is evident that age plays a major role in the severity of the COVID-19 cases, and understanding why age is a big factor that is crucial to develop future treatments for the elderly.

The immune system is a complex system that helps with protecting the body from foreign microbes such as bacteria and viruses. The immune system is divided into two major subsystems, the innate immune system, and the adaptive immune system. The innate immune system can be described as the first line of defense for the body. This subsystem is described as nonspecific, meaning the way they fight off various kinds of foreign microbes is the same. There are numerous types of cells in the innate immune system, among them being basophils, eosinophils, neutrophils, natural killer cells, dendritic cells, macrophage, monocytes, and mast cells. Together these cells are responsible for performing various tasks such as apoptosis, phagocytosis, and presenting antigens to the adaptive immune system ("Overview of the Immune System").

The second subsystem of the immune system is the adaptive immune system, which takes weeks to fully be engaged in fighting foreign microbes due to it being necessary to be activated. However, an advantage of the adaptive immune system is that it retains immunologic memory. This means that the cells in the adaptive immune system will remember the foreign microbe and if they get attacked by the same microbe, later on, the body will be able to fight it much more efficiently. The adaptive immune system has two key types of cells, the B-cells and the T-cells. The two main functions of the B-cell is to present antigens to T-cells (just like dendritic cells) and to mass-produce

antibodies, which helps neutralize foreign microbes. One thing to note is that there are two types of antibodies. The first is the B-cell receptor (BCR) which are receptors that sit on the surface of the B-cell. The second is the soluble form of antibody that the B-cell secretes. Given that they are from the same B-Cell, or it's a clone, these two types of antibodies are the same. T-Cells are another essential type of cells in the adaptive immune system. They cover a wide variety of functions and are divided into two main subsets, CD8+ and CD4+. The CD8+ T-cells are responsible for identifying and removing infected cells and cancer cells through apoptosis. There are four types of CD4+ T-cells, TH1, TH2, TH17, and Treg. Together they are responsible for coordinating immune responses and these functions are highly affected during immunosenescence("Overview of the Immune System"). In all, the adaptive immune response is initiated when B and T-cells are activated when presented with the correct antigens. When these two types of cells are activated, the cells start to clone themselves. The B-Cells start producing antibodies while the T-Cells conduct the various operations listed above. When the antigens are successfully removed, the remaining T and B-cells are now what is considered memory T and B-cells.

This study aims to answer the question: How does the aging immune system exacerbate COVID-19 cases? Furthermore, this paper will also talk about potential long term solutions to the aging immune system and possible clinical interventions that could help patients with advanced cases of COVID-19.

Methodology

To gather information for this literature review, information was gathered from various sources. Initially, using Google Scholar, an initial list of sources was gathered. Through these sources, basic information was gathered to answer the question. For example, it quickly became clear that Immunosenescence had a big role in answering the question. Furthermore, using the initial list of sources I was able to come up with more key terms to gather more information. Using these terms, I gathered even more sources using databases such as PubMed, ScienceDirect, AAAS, and Wiley Online Library.

For this literature review, the key terms and phrases used to gather information were: *COVID 19 and elderly, Immunosenescence, COVID 19 effects on the body, immunosenescence, and COVID 19, Symptoms of COVID 19 in elderly*.

Sources were chosen through several criteria. First, the sources must be from a credible database. Second, the sources must have been peer-reviewed. Third, research articles that were similar to my research topic were focused and valued more in this literature review. Fourth, articles that were written recently were prioritized over older research because the COVID 19 crisis is an evolving situation with new information coming out every day.

For examining data in the articles, information about how and where the data was gathered was analyzed. For qualitative data, information was reviewed multiple times to be certain of what the author meant in the context of the study. Then, the

information was evaluated on whether it provided useful information to answer the research question.

Results

Dysfunctioning Immune System

The four main functions that the immune system needs to perform when the COVID-19 virus attacks the body are to recognize, alert, destroy, and clear. As a person grows older, the immune system undergoes changes that prevent it from performing these four tasks effectively (Mueller et al.). The two main changes that occur in the immune system are immunosenescence, which refers to the slow decline in immune functions, and increased inflammation, which is when the immune system hyper reacts in a way that hurts the body. Inflammaging and immunosenescence share a close relationship. Although contemporary beliefs held that inflammation was caused by immunosenescence, recent studies have shown that both phenomena can contribute to the cause of the other (Fulop et al.). The combination of these two phenomena greatly decreases the effectiveness of the immune response for a COVID-19 attack.

Aging Innate immune System

The innate immune system goes through various changes as aging occurs. One detrimental change in the innate immune system that can be attributed to exacerbating COVID-19 cases is the decline of phagocytosis of numerous immune cells. Cells such as dendritic cells and neutrophils do not seem to decrease with age, but studies have shown that there is a great decrease in the cells performing phagocytosis (Aiello et al.). This results in ineffective eradication of the COVID-19 virus. Another functional decline

that occurs in the innate immune system is the dysfunction of epithelial barriers such as the skin and lungs (Frasca and Blomberg). This decline in function may explain the fast development of COVID-19 symptoms in older people. The gradual decline in immune cells to convert between pro- and anti-inflammatory states is also a hallmark of the aging immune system. The difficulty in cells converting to a pro-inflammatory state is likely due to defects in Toll-Like Receptors (Frasca and Blomberg). In the case of COVID-19 patients, defective TLRs on Alveolar macrophages (AM) that patrol the lungs for foreign invaders make it harder to detect the COVID-19 virus, resulting in TLR-induced pro-inflammatory cytokine production to decrease. Furthermore, in later stages of the disease, the inability to switch between pro- and anti-inflammatory states causes AM cells to damage the lung by attracting too many innate immune cells (Mueller et al.). This overreaction of the innate immune system is known as a cytokine storm and can affect many organ systems. This may explain how the COVID-19 virus attacks so many different body systems at once. Starting in the lungs, cytokine storms can cause acute respiratory distress syndrome (ARDS). Due to the damage the lungs receive, the cardiovascular system may fail due to the lack of oxygen reaching the heart. Furthermore, blood clots may form in vital organs such as the kidneys and the brain which are both life-threatening (Wadman et al.).

Aging Adaptive Immune System

The functionality of the adaptive immune system is a crucial factor in whether a COVID-19 case will be severe or not. One of the indications of the aging adaptive immune system is the involution of the thymus. The thymus is a lymphoid organ that is

situated above the organ and plays a monumental role in immune cell upkeep (Nikolich-Zugich et al.;Kadambari et al.). When aging, the thymus starts to decrease in size. By the age of 65, the thymus decreases in volume by about 40% (Gruver et al.). Due to this decrease in size, there is a significant decrease in thymopoiesis which in turn results in low naive T-cell and B-cell numbers while increased memory T-cell and B-cells (Ponnappan and Ponnappan). Another dysfunction of the adaptive immune system as age sets in is the decreased functionality of T-Cells. Studies have shown that in older mice, T-cells had reduced activation and delayed responses to the influenza virus (Frasca and Blomberg). The B-Cells are also no exception to immunosenescence. With increased age, B-cells exhibited decreased levels of Class Switch Recombination. This resulted in less antibody production and decreased amounts of B-cells converting to memory B-cells. On top of the potential decreased immune response to the COVID-19 virus, the decreases in Class Switch Recombination may also result in decreased effectiveness of vaccines if they are produced later during the pandemic (Frasca and Blomberg).

Age-related comorbidities

Numerous statistical analyses have shown that age-related comorbidities that are associated with immunosenescence have been huge factors in the severity of the COVID-19 case. In one study with 21 elderly patients with severe COVID-19 symptoms showed that 86% had age-related comorbidities such as CKD at 48%, congestive heart failure at 43%, chronic obstructive pulmonary disease (COPD) at 33%, and diabetes at 33%. Another study suggested that COVID-19 doubles the risk of mortality from

age-related comorbidity. David Spiegelhalter, a statistician, states that “getting COVID-19 is like packing a year’s worth of risk into a week or two” (Shahid et al.).

Dietary Interventions

Looking at how much of an impact immunosenescence has on the severity of COVID-19 cases, it is natural to look for ways to suppress or even reverse the effects of immunosenescence. Through numerous studies, it is believed that there is a relationship between nutrition, immunosenescence, and chronic inflammation. As a consequence, one of the proposed strategies to stop or even reverse immunosenescence is through dietary strategies.

One particular diet is the Mediterranean Diet. The diet includes a lot of fruits, vegetables, whole grains, legumes, and olive oil while cutting down on red meat and cured meat. Studies have shown that this diet helped lower inflammatory mediators such as Il-6, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM-1). This decreases inflammation and ultimately slows down immunosenescence (Aiello et al.).

Another form of dietary intervention that seems promising is caloric restrictions. Although there has been little research done, studies have shown that caloric restrictions downregulate the expression of proinflammatory genes that in turn helps suppress inflammation. In one particular study, ten healthy participants fasted for 72 hours and their suppressor cell numbers increased while other immune system cell numbers stayed the same (Aiello et al.).

Although these kinds of treatment do not have immediate effects for patients who have advanced cases of COVID-19, the proposed dietary interventions can help older people have a better chance of surviving COVID-19 or other forms of diseases if infected in the future.

Clinical Interventions

Since the COVID-19 outbreak, there have been numerous clinical trials for treatments that could help older patients with advanced cases of COVID-19. One promising treatment is Rapamycin. Rapamycin is an antifungal antibiotic that suppresses yeast growth and aging. Approved for human use since 1999, Rapamycin has been used for various applications such as cancer treatment, organ transplant, and as an anti-aging drug in general. One effect rapamycin has proven to possess is its ability to suppress hyperfunction in the immune system (Blagosklonny). This allows for slower immune system aging and suppresses cytokine storms (the main cause of death in COVID-19 patients). Furthermore, rapamycin has also shown to increase CD8+ T-cell response and increase adaptive immunity. Due to its properties, rapamycin was one of the first proposed forms of treatment for COVID-19 patients (Blagosklonny). However, rapamycin is still being tested to be used for symptoms such as pneumonia and acute respiratory failure.

Another drug that is being explored to help with severe COVID-19 cases is chloroquine. Chloroquine is an FDA approved drug that has been used for malaria and autoimmune diseases. Experiments have shown that chloroquine was able to interfere in viruses entering host cells by increasing the endosomal PH required for virus-cell

fusion (Shahid et al.). One non-randomized study with 20 patients concluded that after daily doses of hydroxychloroquine, a less toxic variant of chloroquine, patients were virus free in 6 days (Shahid et al.). Despite their success in clinical trials so far, chloroquine and rapamycin still have a lot of testing left before it can be approved for public use.

Conclusion

With the ever-evolving COVID-19 pandemic, new information is being released every day. However, one fact that has not changed through the pandemic is that elderly populations are more at risk of developing severe cases of COVID-19 due to immunosenescence and inflammaging. These two phenomena have been attributed to developing other age-related comorbidities that contribute to COVID-19 severity and increased likelihood of severe symptoms such as ARDS and various organ failures due to hyper inflammation of the innate immune system and deteriorating function of the adaptive immune system. Although there have been numerous studies towards the mechanisms behind Immunosenescence and aging in general, much is still unknown. Knowing this, it is evident that more research needs to go into understanding aging and developing new treatments to explore other possible interventions that effectively suppress immunosenescence and inflammaging to better help older adults fight diseases such as COVID-19.

Work Cited

Aiello, Anna, Farzin Farzaneh, Giuseppina Candore, Calogero Caruso, Sergio Davinelli, Caterina Maria Gambino, Mattia Emanuela Ligotti, Nahid Zareian, and Giulia Accardi. “Immunosenescence and Its Hallmarks: How to Oppose Aging Strategically? A Review of Potential Options for Therapeutic Intervention.” *Frontiers in Immunology* 10 (September 25, 2019): 2247. https://doi.org/10.3389/fimmu.2019.02247.

Blagosklonny, Mikhail V. “From Causes of Aging to Death from COVID-19.” *Aging* 12, no. 11 (June 12, 2020): 10004–21. https://doi.org/10.18632/aging.103493.

Frasca, Daniela, and Bonnie B. Blomberg. “Inflammaging Decreases Adaptive and Innate Immune Responses in Mice and Humans.” *Biogerontology* 17, no. 1 (February 2016): 7–19. https://doi.org/10.1007/s10522-015-9578-8.

Fulop, Tamas, Anis Larbi, Gilles Dupuis, Aurélie Le Page, Eric H. Frost, Alan A. Cohen, Jacek M. Witkowski, and Claudio Franceschi. “Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes?” *Frontiers in Immunology* 8 (January 10, 2018): 1960. https://doi.org/10.3389/fimmu.2017.01960.

Gruver, Al, Ll Hudson, and Gd Sempowski. “Immunosenescence of Ageing.” *The Journal of Pathology* 211, no. 2 (January 2007): 144–56. https://doi.org/10.1002/path.2104.

Kadambari, Seilesh, Paul Klenerman, and Andrew J. Pollard. “Why the Elderly Appear to Be More Severely Affected by COVID ‐19: The Potential Role of Immunosenescence and CMV.” *Reviews in Medical Virology*, July 15, 2020. https://doi.org/10.1002/rmv.2144.

Liu, Kai, Ying Chen, Ruzheng Lin, and Kunyuan Han. “Clinical Features of COVID-19 in Elderly Patients: A Comparison with Young and Middle-Aged Patients.” *Journal of Infection* 80, no. 6 (June 2020): e14–18. https://doi.org/10.1016/j.jinf.2020.03.005.

Mueller, Amber L., Maeve S. McNamara, and David A. Sinclair. “Why Does COVID-19 Disproportionately Affect Older People?” *Aging*, May 29, 2020. https://doi.org/10.18632/aging.103344.

National Institute of Allergy and Infectious Diseases. “Overview of the Immune System,” December 30, 2013. https://www.niaid.nih.gov/research/immune-system-overview.

Nikolich-Zugich, Janko, Kenneth S. Knox, Carlos Tafich Rios, Bhupinder Natt, Deepta Bhattacharya, and Mindy J. Fain. “SARS-CoV-2 and COVID-19 in Older Adults: What We May Expect Regarding Pathogenesis, Immune Responses, and Outcomes.” *GeroScience* 42, no. 2 (April 2020): 505–14. https://doi.org/10.1007/s11357-020-00186-0.

Ponnappan, Subramaniam, and Usha Ponnappan. “Aging and Immune Function: Molecular Mechanisms to Interventions.” *Antioxidants & Redox Signaling* 14, no. 8 (April 15, 2011): 1551–85. https://doi.org/10.1089/ars.2010.3228.

Shahid, Zainab, Ricci Kalayanamitra, Brendan McClafferty, Douglas Kepko, Devyani Ramgobin, Ravi Patel, Chander Shekher Aggarwal, et al. “COVID -19 and Older Adults: What We Know.” *Journal of the American Geriatrics Society* 68, no. 5 (May 2020): 926–29. https://doi.org/10.1111/jgs.16472.

Wadman, Meredith, Jennifer Couzin-Frankel, Jocelyn Kaiser, and Catherine Matacic. “A Rampage Through the Body.” *AAAS* 368, no. 6489 (April 24, 2020): 356–60. https://doi.org/10.1126/science.368.6489.356.

Worldometer. “COVID-19 CORONAVIRUS PANDEMIC.” Accessed August 12, 2020. https://www.worldometers.info/coronavirus/.