Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 6 Issue 7 July 2022

Research Article

Immune System Response to COVID-19. An Endless Story

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DOI: 10.31080/ASPS.2022.06.0610

Received: April 20, 2022

Published: June 16, 2022

Abstract

Background: Nowadays COVID-19 is the most widely spread viral infections all over the world. The relation between immune system response, coordination, existing comorbid conditions, viral proofreading, and severity of corona virus infection and increased mortalities requires some attention to be investigated and correlated.

Aim: Reviewing the immune system, types of immunity and investigating the effect of comorbidity and poly pharmacy on patients' immunity system and response finally, the correlation between viral proofreading and severity of COVID-19 infection.

Discussion: Severity of COVID-19 infection can be attributed to immune dysregulation and loss of bridging between innate and adaptive immunity. Several factors and comorbid conditions contribute in such dysregulation, like age, obesity, pre-existing diseases, stress conditions. Besides, viral mutations that occurs as a result of proofreading mechanisms contributes in such diseases severity. Clinical pictures showed high white blood cell count, lower lymphocyte count, and high levels of reactive protein (CRP) in those patients died from COVID-19 compared to those recovered individuals. Several drug choices like hydroxychloroquine, Baricitinib, Beta-glucans proved to be effective in management and regulation of disrupted immune responses and improving clinical pictures.

Conclusion: Immune dysregulation and other factors supporting such dysregulation showed to be the main leading cause for exacerbation of COVID-19 symptoms and increased mortalities. Different therapeutic choices showed to be effective in restoring immune coordination, and improving clinical signs and symptoms.

Keywords: COVID-19; Innate Immunity; Proofreading; Adaptive Immunity; Cytokines, Thymus-Derived Immunity

Introduction

Immune system

Immunity means a groups of cells, chemical substances, and processes that is functioning to provide protection for the skin, respiratory tract, intestinal tract and other body areas from foreign invading pathogens such as microbes, viruses, cancer cells, and toxins. Immunity can be classified into two lines of defense, which are innate immunity and adaptive immunity [1,2].

Innate immune system is considered as the first-line of defense against invading pathogens. It is characterized by being an antigen-independent (nonspecific) defense mechanism which the host can use immediately or within hours of facing an antigen. Also, it has no immunologic memory and so, it can't recognize or memorize the same pathogen again when the body exposed to it another time [3].

Adaptive immune system is depending and specific to certain antigen and so, it involves a lag time between antigen exposure and maximal response. The key feature of adaptive immunity is its

memory capacity, which implies that when infection occurs again, the host can develop a quicker and efficient immune response [4].

Innate immunity

This type of immune response to pathogens is dependent on what is called "pattern recognition receptors" (PRRs). Innate immune response allows a limited number of immune cells to recognize and respond quickly to a large variety of pathogens with similar structures, which is called "pathogen associated molecular patterns" (PAMPs). Examples of PAMPs include lipopolysaccharides (LPS) of bacterial cell wall components, and RNA produced during viral infection [5,6].

Furthermore, innate immunity provides one of the important immunological roles, including the rapid recruitment of immune cells to infection sites and activation of inflammation via the production of cytokines and chemokines [7].

Cytokines can activate many defensive systems. They also stimulate local cellular responses to infection or damage. The key inflammatory cytokines generated during the initial response to an infection includes, tumor necrosis factor (TNF), interleukin 1 and 6 (IL-1 and IL-6). When inflammatory cytokine production is dysregulated, this will be often associated with inflammatory or autoimmune disease. For that reason, cytokines are considered an important therapeutic targets [7].

The biochemical sequence that is important in identifying and opsonizing bacteria and other pathogens is called "complement system". It makes pathogens susceptible to phagocytosis that encourage getting rid of dead cells or antibody complexes and removes foreign substances present in tissues, blood, lymph, and organs. Moreover, the complement system stimulates the adaptive immune response by mobilizing and activating antigen-presenting cells (APCs) [4].

Natural killer (NK) cells are principally involved in tumor rejection and cell destruction infected by viruses. Perforins and granzymes released by NK-cell granules stimulate the destruction of infected cells, which also trigger apoptosis [8].

Furthermore, NK cells are a major producer of another cytokine, IFN-γ, which aids in the mobilization of APCs and promotes the development of antiviral immunity. One of the cell that contribute in selective production of cytokines such as IL-4, IFN-γ, and IL-17 is called innate lymphoid cells (ILCs). Examples of those cells include ILC-1, ILC-2, ILC-3. Cytokines production help to direct the appropriate immune response to specific pathogens and contribute to immune regulation [7].

Adaptive immune response begins after Innate immunity. The two main divisions of adaptive immunity, are antibodies and T-cell-mediated, which are mainly directed at different targets. Antibodies bind to free viral particles that result in blocking of viral infection to the host cell. T-cells act by identifying and destroying infected cells. All viruses replicate within cells and spread directly between cells without re-entering the extracellular environment and so, resolution of infection is mainly relaying on T-cell function than on antibody [9].

Antibodies is important as an immune-protective barrier against reinfection. Antibodies are present at portals of entry, most often mucosal surfaces. Thereby, investigators are designing vaccines that optimally induce mucosal antibody. Innate mechanisms that stimulate antigen-presenting cells are required for the onset of adaptive immunity (APC) [10].

Chemokine and cytokine signals drive APC and lymphocytes into lymphoid tissues and keep them there for a few days to allow for successful interactions between these cells. Secondary lymphoid tissues, through a supporting stromal cell network and local chemokine gradients, aid in the coordinated interactions of adaptive immune system cells [11].

If the virus reaches the circulation, the induction events occur in the lymph nodes draining the infection site or in the spleen. Virus antigens are often transported to lymph nodes by Dendritic Cells (DCs). Some viruses are capable to compromise APC function, such as herpes simplex virus and measles virus, which can inhibit Dendritic cells maturation [9].

Discussion

Clinical picture of COVID-19 infected and recovered versus deteriorated patients

A research study that included patients infected with coronavirus from which 109 who died during hospitalization and 116 patients recovered reported that the median age of the death

subject group was older than the recovered ones (69 versus 40 years). The white blood cell (WBC) values in those patients who died was significantly higher on admission (7.23 [4.87, 11.17]. versus 4.52 [3.62, 5.88]. ×10/L). Patients in the death group exhibited significantly lower lymphocyte count (0.63 [0.40, 0.79]. versus 1.00 [0.72, 1.27]. ×10/L) and lymphocyte percentage (7.10 [4.45, 12.73]. % versus 23.50 [15.27, 31.25]. %) on admission, and it continued to decrease during hospitalization (7.10 [4.45, 12.73]. % versus 2.91 [1.79, 6.13]. %) [12].

C-reactive protein (CRP) levels were also remarkably higher in the death group on admission (109.25 versus 3.22 mg/L) and showed no remarkable improvement after treatment (109.25 versus 81.60 mg/L). The death group patients experienced more complications such as (59.6% vs. 0.9%) acute cardiac injury, (89.9% versus 8.6%) ARDS, (18.3% versus 0%) acute kidney injury, (11.9% versus 0%) shock, and (6.4% versus 0%) disseminated intravascular coagulation [12].

Severity of COVID-19 in adult versus children and loss of bridging between innate and adaptive immunity

COVID-19 infection showed to be less severe in children than in adults in terms of symptoms, lung consolidation, and laboratory abnormalities. The bases of such mechanism remains unknown. It is postulated that this may be due to a fully functional thymus in children, that plays a vital role in both lymphatic and endocrine function and serves as a setting where T-cells develop which is responsible for adaptive immunity. Thus we can postulate that increased morbidity in COVID-19 infected older adults is mainly due to compromisation of immune system secondary to dysregulated adaptive immunity [13].

SARS coronavirus (SARS-CoV) is known to decrease the induction of IFN-α, and IFN-β that represent the innate immune system. When innate immune system fails to eliminate invading pathogens, the specific adaptive immune response starts by the 4^{th} to 7^{th} day following the infection. This duration correlates with the average time at which the patient symptoms exacerbate in COVID-19 infection. Postulations explain why older adults are more affected by SARS CoV-2 compared to children. The thymus-derived immunity in children can bridge the gap between innate and adaptive immune response. Innate immune responses in elderly is delayed, that's why they are more susceptible to develop worsening symptoms, and vulnerable to COVID-19 complications. Also, the decrease in plasmacytoid dendritic cells in the elderly besides their comorbidities depletes the immune envelope [14].

Immune response dysregulation

Infection with SARS-CoV-2 showed to activates both innate and adaptive immune response, that makes the resolution of COVID-19 sustained. On the other hand, fast and highly coordinated immune response is considered the main defense mechanism against viral infection. Excessive inflammatory response and dysregulated adaptive immune defence may result in tissue damage at the site of viral entry as well as systemic damage. Furthermore, excessive pro-inflammatory response results in a fast course of acute lung injury (ALI) and ARDS [15-17].

The massive cytokine and chemokine release which is called "cytokine storm", reflects a state of uncontrolled dysregulated immune defense [18].

Studies showed relevant changes occurring to innate immunity and adaptive immunity in COVID-19 infected patients. In particular, lymphocytopenia and a modulation in total neutrophils are common characteristic clinical pictures that seems to be directly correlated with disease severity and death [17].

Investigations showed that, in patients suffering from severe COVID-19, a remarkable decrease in circulating CD4+ cells, CD8+ cells, B cells, NK cells, monocytes, eosinophils, and basophils levels has been reported. Moreover, most of patients showed a significant increase in serum levels of pro-inflammatory cytokines like IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GMCSF, IP-10, MCP-1, CCL3, and TNFα) that is a strong predictive for in-hospital mortality, organ injury, and severe pneumonia [19-21].

Elevated levels of serum cytokine and chemokine, besides high neutrophil-lymphocyte-ratio (NLR) in SARS-CoV-2 patients has been connected with their possibility in hyper-inflammatory responses induction in COVID-19 and disease severity and adverse outcomes. Moreover, a recent study showed that patients infected with coronavirus had higher Hs-CRP and procalcitonin serum levels, which are main inflammatory markers associated with high risks of mortality [18].

Different immune cells like macrophages, THP-1 cells, and others have been shown to be infected by MERS-CoV. Furthermore, SARS-CoV has been shown to directly infect T-cells, and macrophages, which results in delayed response but higher pro-inflammatory cytokines and chemokines levels [22,23].

Although ACE2 receptor is modestly expressed in the lung monocytes, macrophages, and T cells, the mechanism of immune cells infection by which SARS-CoV and SARS-CoV-2 is still unknown [24].

A study in Wuhan that included 452 COVID-19 infected patients showed that, patients infected with severe COVID-19 had a considerably decreased number of total T cells, helper and suppressor T cells. In particular, among helper T cells, a decrease in regulatory and memory T cells has been observed, on the other hand, naïve T cells percentage was found increased [25].

Naïve T cells provide defenses against new and previously unrecognized infection. This occurs by a coordinated cytokine release. On the other hand, antigen-specific immune response is mediated by memory T cells. The disruption of immunological balance favoring naive T cell activity over regulatory T cell activity may play a significant role in hyper-inflammatory responses. Besides, the reduction in memory T cells could be involved in COVID-19 relapse, that is why the number of recurrences has been reported in recovered cases of COVID-19 [26].

Proofreading mechanism of coronavirus

Typically, a high error rate may exist in RNA virus replication. This results in the existence of various groups of viral genome mutation known as "quasispecies". This low replicative viral fidelity permits for RNA viruses to accommodate with different environments. Besides, it is also associated with an increased chance of error catastrophe which may lead to viral vanishing, that is why a finely tuned balance between quasispecies diversity and replicative fitness for viral virulence and evolution is needed [27,28].

As a result, researchers have a significant problem in developing antivirals against CoVs and other RNA viruses, because RNA viruses can rapidly develop resistance to drugs while maintaining viral replicative fitness. The unique 3' to 5' exonuclease (ExoN) proofreading function considered as an additional barrier in the development of Nucleoside analogs as antivirals against CoVs [29].

Coronavirus genomes are among the biggest and most complex RNA virus genomes, and nsp14 is highly conserved within the Coronaviridae family. The nsp14 exonuclease proofreading function have been a main contributor in the expansion and maintenance of such large genomes to ensure replication competence [30].

Coronavirus in animals

Coronaviridae have a broad host range and cause a wide variety of gastrointestinal, respiratory and systemic diseases in animals, including infectious bronchitis in birds, a fatal disease with multi-organ involvement in felines, and enteritis in pigs, cows, turkeys and dogs. In humans, coronaviruses cause respiratory disease and, to a lesser extent, gastroenteritis. SARS-CoV, which causes a severe respiratory disease, seems to be an Enzootic Virus in Southeast Asia. Several species that might be infected, such as masked palm civets, are consumed as food in parts of China, and the 'wet markets', at which live animals are bought and sold, are likely venues for the initial crossover event to humans. The 2002–2003 outbreak of SARS in humans probably resulted from an interspecific transfer of the virus by aerosols from live, exotic animals that were infected with SARS-CoV to workers in these wet markets [31].

Serum from masked palm civets, raccoon dogs, and Chinese ferret-badgers were shown to contain neutralizing antibodies that were specific for SARS-CoV, and virus that was nearly identical to the strains that were isolated from infected humans was detected in masked palm civets [32].

Impact of pre-existing comorbidities

Evidence has demonstrated that individuals with pre-existing comorbidities are susceptible to high mortality rates from COVID-19.

Immune dysfunction

Immunity becomes activated during SARS-CoV-2 infection, which result in a local inflammation, recruitment of monocytes, dendritic cells (DCs), natural killer (NK) cells, T and B cells. The immune response may result in a mild to moderate disease with fever, cough, and tiredness, but this will be followed by resolution of the infection.

The occurrence of severe lymphopenia and the buildup of fatigued T and NK cells in severe COVID-19 patients resulted in a lack of an efficient immune response to clear SARS-CoV-2 [33].

Besides, high levels of interleukin 6 (IL-6) remains elevated over time, and associated with increased levels of IL-2, -7, -10, TNF-α, CXCL-10, MCP-1, and MIP-1α that result in cytokine storm. The resulting uncontrolled systemic hyper-inflammation can cause critical and potentially life-threatening complications such as severe pneumonia, ARDS, and multiple organ failure [34].

Investigations on immune profiles in mild, moderate and severe COVID-19 patients revealed that proportions of naïve CD4+ T cells, TGFβ+CD28- naïve CD4+ T cells, DCs, and macrophages are associated with mild cases. While in severe cases, it was observed that a sharp decline in the percentage of CD8+ T and NK cells occurred [35].

Moreover, results from investigations on hospitalized COVID-19 patients that had developed ARDS revealed a novel population of developing neutrophils, which appeared to be closely related to plasmablasts. However, investigation is required to determine whether this novel subset of neutrophils contributes in development of ARDS and other complications [36].

In COVID-19 patients who are severely infected, CD8**+** T cells and NK cells exhibited more signs of exhaustion than mild to moderate patients. For example, elevated levels of programmed cell death protein-1 (PD-1). Besides, increased cytotoxic T-lymphocyte-associated protein - 4 (CTLA-4), T cell Ig, and ITM domain (TIGIT) on CD8**+** T cells and increased NKG2A on NK cells [33].

Impact of age

Individuals over the age of 60 are more vulnerable to severe COVID-19 symptoms and have a higher death risk [37]. Geriatric patients have more noticeable immune compromisation compared to younger patients, as lymphocyte counts are lower and pro-inflammatory cytokine levels higher. As immune systems become aged, they become associated with immunosenescence and chronic low-grade inflammation, called (inflammaging) [38].

Much of the drop in protective viral immunity resulting from defective T cell immunity. The decline of naïve T cell output due to thymic involution and the accumulation of senescent T cells leads to reduced viral host immunity. In mice studies, CD4+ T cells were shown to be crucial against SARS due to their important role in SARS-CoV clearance. This protection was lost in aged mice as senescent CD4+ T cells responded poorly to antigen. Moreover, the accumulation of senescent CD8+ T cells and B cells in older individuals results in elevated baseline inflammation, further increasing susceptibility to hyper-inflammation and cytokine storm upon SARS-CoV-2 infection [39].

Diabetes and obesity

Diabetes mellitus Type 2 is a disease characterized by chronic inflammation, and impaired metabolism and has become an increasing risk to human health. Diabetic individuals have an increased susceptibility to COVID-19 infection. A study on COVID-19 revealed that diabetic patients showed more likelihood to develop pneumonia and were responsible for 11.7% of severe cases [40].

Chronic inflammation in diabetic patients increases their susceptibility to hyper-inflammation and the development of cytokine storm. This has been already reported in COVID-19 patients, as C-reactive protein (CRP) and IL-6 levels were found to be significantly higher in diabetic patients. Also, hyperglycaemia can impair the immune response, increase oxidative stress and is associated with the onset of premature senescence [39].

DPP4 inhibitors commonly used to treat diabetes have an anti-inflammatory effect, resulting in reduced macrophage infiltration, which could impair the innate immune response during COVID-19. Obesity has also been associated to a weakened immunological response, with indications of weakened antibody and T cell responses. Furthermore, ACE2 expression is increased in obese people's adipocytes and therefore may act as a potential target for SARS-CoV-2 [39].

Effect of stress and depression

Chronic stress works as a trigger for anxiety and depressive disorders, resulting in an increase in pro-inflammatory cytokines and glucocorticoids, which contribute to behavioral alterations. It was reported that interleukin-6 (IL6) which is a pro-inflammatory cytokine was elevated in the blood of individuals suffering from depressive disorders. As per recent studies in major depression, it was concluded that only the basal blood levels of IL-6 and TNF were remarkably elevated [41].

Depression lead to immune system alteration leading to increase in blood pro-inflammatory cytokine levels like interleukin-6 and TNF which in turns induce cytokine storm in case of acute respiratory distress syndrome causing failure in management of critical cases with higher mortality rates in COVID-19 patients [42].

Drugs that affect immunity used in COVID-19 protocols:

Investigations showed that that immune-suppressive agents like hydroxychloroquine, interleukin (IL)-6, and IL-1 antagonists, are commonly used in rheumatology, and are also considered as treatment in therapeutic protocols of COVID-19 especially in severe cases [43].

Studies showed that patients treated with baricitinib had significant low mortalities (5%) compared to those patients not treated with baricitinib (45%). Moreover, patients showed to restore normal lymphocyte counts, increases IgG levels specific for SARS-CoV-2 spike protein, and decreases pro-inflammatory cytokine (e.g. IL-6, IL-1 β and TNF-α) levels in the blood [44].

Beta-glucans are naturally occurring polysaccharides derived from a variety of sources, including barley, yeast, algae, oats, bacteria, and mushrooms. A specific beta glucan from black yeast called Aureobasidium pullulans AFO-202 strain reported to have a powerful immune stimulator action that can activate macrophages and have positive immune actions on B-lymphocytes, natural killer cells, and suppressor T cells [45]. AFO-202 beta glucan supplementation showed to have immune-enhancing activity via increasing IFN-γ capability, and decreasing IL-6 levels [46].

Furthermore, AFO-202 beta glucan stimulates neutrophil activation, migration, and chemotaxis in order to destroy virus-infected cells via IL8. Besides it causes a decrease of CCL2 (Monocyte chemotactic protein 1; MCP-1) and decrease of CXCL10 levels, that will lead to prevention of chemo-attraction for monocytes/macrophages, T-cells, NK cells, and dendritic cells and so, suppressing immune response. This will lead to immune regulation enhancement [47].

Conclusion

Immune dysregulation and other factors like immune dysfunction, old age, obesity and diabetes, stress and depression showed to be the main leading cause for exacerbation of COVID-19 symptoms and increased mortalities. Different therapeutic choices like hydroxychloroquine, anti-interleukin (IL)-6, baricitinib, and AFO-202 beta glucan showed to be effective in restoring immune normal function, and improving immune response co-ordination, besides they showed to improve clinical signs and symptoms and alleviating disease severity and decrease mortalities.

Acknowledgments

The author would like to thank Drug Research Center for its support in data collection and manuscript writing.

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