Quest Journals
Journal of Medical and Dental Science Research
Volume 10~ Issue 5 (2023) pp: 51-56
ISSN(Online) : 2394-076X ISSN (Print):2394-0751
www.questjournals.org

Research Paper

Immune Response and Cytokine Storm in Corona Virus: A Review Study

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ABSTRACT: *Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) infectious disease is a world-wide threat. Infection by SARS-CoV-2 in serious cases causes tissue damage and activates and stimulates the immune response. Protein RNA and SRAS-CoV-2 interact and overly activate receptors in the immune system. Including macrophages and granulocytes, producing pro-inflammatory cytokines and enabling CD4 + T cells and CD8 + T cells. However, an excess immune response will lead to tissue damage and inflammation, a cytokine storm. If pro-inflammatory cytokines continue to be produced, they will make the disease worse and cause death. This literature review aims to describe and deepen studies on the effect of physical exercise on blood sugar levels, insulin hormones, and cortisol hormones in type II diabetes mellitus patients. The methodology used in this study is to collect and analyze the literature from various reputable journals and articles about Cytokine Storms. The articles reviewed are sourced from the Google Scholar database, PubMed, and medical research. Keywords include Cytokine Storm, a proinflammatory cytokine, COVID-19, SARS- CoV- 2*
KEYWORDS: *Cytokine Storm, a proinflammatory cytokine, COVID-19, SARS- CoV- 2*

R*eceived 05 May, 2023;* ***R****evised 14May, 2023;* ***A****ccepted 16 May, 2023 © The author(s) 2023.*
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I. INTRODUCTION

The infectious disease Coronavirus 2 from severe acute respiratory syndrome (SARS-CoV-2) is a global threat, declared pandemic by the WHO. SARS-CoV-2 infection is a public health issue and a challenge in China and around the globe. Indonesia has an increasing number of cases, since December 2020 there have been 617,820 positive cases, 505,836 recovered, 18,819 deaths, 63,698 suspected [1]. Infected patients with mild symptoms will usually recover within two to three weeks. Meanwhile, those infected who develop a more severe Acute Respiratory Distress Syndrome (ARDS) cause rapid deterioration of 10-15% and die from organ failure. Acute respiratory distress syndrome (ARDS) is a severe breathing disorder caused by fluid accumulation in the pulmonary alveoli, the first symptom being severe shortness of breath. SARS CoV-2 is a β-like coronavirus that causes outbreaks of illness (COVID-19). The SARS-CoV-2 infection can stimulate an immune response in the host, leading to a decrease in lymphocytes and an excessive increase in cytokines in patients. SARS-CoV-2 RNA and the protein interact with a variety of receptors that activate the antiviral immune response and regulate viral replication and propagation in the host in vivo. However, a highly active and excessive immune response will cause immunity damage and subsequent tissue inflammation [2, 3].

The immune system continues to evolve to protect the host against evolving pathogenic microorganisms. The immune system helps the body eliminate toxins or allergens that enter the surface of the mucosa. The main function of the immune system is the body's defense response to invading pathogens, toxins, or allergens and its ability to differentiate from pathogens. The body has innate defense mechanisms (innate immunity) and adaptive defense mechanisms to detect and rule out microbial pathogens from microbial attacks and other exogenous threats. Furthermore, it also identifies the location of altered immune function that causes damage to organs and tissues [4, 5] (Cavaillon and Adib-Conquy, 2010; F. -P. Chang et al., 2020; Chaplin, 2010; García, 2020)

The function of the immune system is not only to eliminate pathological microbes and toxic or allergic proteins but must be able to avoid responses or threats that can cause excessive damage to tissues or eliminate

commensal microbes that are beneficial to the body. The environment may contain many pathogenic microbes and toxics that stimulate the immune system through complex pathogenic mechanisms and protective mechanisms to control and eliminate organisms. The general characteristic of the immune system is the mechanism of detecting the structural features of pathogens or toxins that are recognized and differ from host cells. Detection of the difference between the host pathogen is very important to eliminate the threat without harming the tissue itself [6, 7].

This literature review is presented in narrative form as a literature review from various reputable journals and articles, which aims to identify and understand how an overactive/excessive immune response will cause tissue damage and inflammation, known as a cytokine storm. This occurred during the SARS-CoV-2 pandemic, which is now worldwide and is a global problem. In addition, if pro-inflammatory cytokines continue to be produced, known as cytokine storms, they will aggravate disease progression, prognosis and death in infected patients SARS-CoV-2.

II. METHOD

The method used in this study is to collect and analyze the literature from various reputable journals and articles about Cytokine Storms. The articles reviewed are sourced from the Google Scholar database, PubMed, and medical research. Keywords include Cytokine Storm, a proinflammatory cytokine, COVID-19, SARS-CoV- 2.

III. DISCUSSION

The innate immune system includes all aspects of immune defense mechanisms, encoded in functional form by genes from the host germline. Includes a layer of epithelial cells that express connections between cells; a secreted layer of mucus that covers the epithelium in the respiratory, gastrointestinal, and genitourinary tract; and epithelial cilia that clean the mucus layer after contamination with inhaled or ingested particles. The innate response includes bioactive proteins and small molecules that are constitutively present in biological fluids (complement proteins, defensins, and ficolins) or released from cells when activated (cytokines that regulate other cell functions, chemokines that attract inflammatory leukocytes, inflammatory lipid mediators, species reactive free radicals, bioactive amines and enzymes that contribute to tissue inflammation). The innate immune system consists of membrane receptors and cytoplasmic binding molecular proteins expressed on microbial surfaces [8, 9].

The adaptive immune system has a specific response to its target antigen. The adaptive response is mainly based on specific antigenic receptors expressed on the T and B lymphocyte surface. Unlike the recognition encoded in the innate immune response, the antigen-specific receptors of the adaptive response are encoded by genes made by microbes to form T cell receptors (T Cell Receptors), and immunoglobulins (B cell antigen receptors; Ig). Assembling antigen receptors from a pool of multi-coded genetic elements enables the generation of millions of different antigen receptors, each with potentially unique specificities for different antigens [10](Soy et al., 2020).

Innate and adaptive immune systems are often described as having different reactions, but they are continually interconnected and work together to carry out their functions. The innate immune reaction is the first line of the body's defensive system. The adaptive immune response will occur several days later due to the clonal expansion of antigen-specific T cells and specific B cells. Components of the innate system help activate antigen-specific cells. Antigen-specific cells amplify the innate immune response through innate effectors that lead to complete control of the invading microbe. Innate and adaptive immune responses differ fundamentally with respect to their mechanisms of action. Nevertheless, harmony and synergy between the two are essential for an intact and efficient immune response [10].

The mechanism of the invasion of SARS-CoV-2 into cells

The SARS-CoV-2 virus is encapsulated, with a single strand of RNA, about 30 kb positive, and infects various host species. Divided into four genera; α, β, γ, and δ based on the structure of the genome, α and β coronaviruses only infect mammals with common cold symptoms and are included in the α coronavirus. On the other hand, SARS-CoV, MERS-CoV and SARS-CoV-2 are categorized as coronavirus β [11, 12]. The lifecycle of the virus with its host consists of 5 stages: attachment, penetration, biosynthesis, maturation and release. Once viruses bind to the host receptor (adhesion), they penetrate the host cells through endocytosis or membrane fusion (penetration). After releasing the viral content inside the host cell, the viral RNA enters the nucleus to replicate itself. Viral m-RNA is used to make viral proteins (biosynthesis). Then, new virus particles are created (maturation) and released. The coronavirus consists of four structural proteins; Spike (S), membrane (M), envelope (E), and nucleocapsid (N). The spike consists of a transmembrane trimetric glycoprotein that protrudes from the virus's surface, determining the coronavirus's diversity and the host's tropism [13, 14]

The angiotensin-2 converting enzyme (ACE2) was determined to be a functional SARS-CoV-2 receptor. The EC2 expression is elevated in the lungs, heart, ileum, kidneys and bladder. In the lung, ACE2 is expressed in the form of lung epithelial cells. Following binding of SARS-CoV-2 to the host protein, protein cleaves occur. Protein cleavage consists of two steps for activation of the SRAS-CoV-2 protein. The spike coronavirus differs between viruses because different proteases can cleave and activate it [15, 16]. Symptoms of patients infected with SARS-CoV-2 range from minimal symptoms to severe respiratory failure with multiple organ failure. Because ACE2 is expressed on the apical side of lung epithelial cells in the alveolar spaces, this virus may be able to enter and destroy them [17, 18].

Pathogenesis of SARS-CoV-2 infection

Fever, dry cough, shortness of breath, myalgia, fatigue, tendency to leukopopenia and radiological signs of progressive pneumonia can lead to ARDS. Clinical and laboratory findings with respect to SARS-CoV-2, SARS-CoV and MERS-CoV infections indicate that the pathogenesis of the three (3) infections is the same. Trends in monocytosis, instead of lymphocytosis, include a low number of natural killer (NK) and cytotoxic T cells and the occurrence of cytokine storms. Increasing a glycoprotein is the most immunogenic part of the coronavirus, which binds to the receptor (ACE-2) to get into the host cells. The distribution of intense ACE-2 receptor expression on the surface of alveolar type II epithelial cells, heart, kidney, intestinal and endothelial cells is consistent with the target organs involved and the clinical picture in SARS-CoV-2 infection [19, 20].

SARS-CoV-2 occurs primarily through direct contact with saliva droplets or respiratory tract secretions when an infected person coughs or sneezes. After binding to the cell surface receptor ACE-2 by glycoprotein, the virus enters the cell cytoplasm, then releases its RNA genome and replicates, forming new virus particles so that the cell disintegrates and the virus spreads to other cells. When the immune system recognises viral antigens, the cells presenting the antigens transform them into killer natural T lymphocytes and CD8+ cytotoxic T lymphocytes through the major histocompatibility complex (MHC). This presentation activates inborn and adaptive immunity, producing large quantities of pro-inflammatory cytokines and chemokines. In certain patients, this activation becomes so massive that a cytokine storm develops, resulting in thrombotic tendencies, multiorgan failure, and death [21, 22].

Cytokine storm immune response in SARS-CoV-2 infection

Macrophages and DCs (dendritic cells) play an important role in inborn and adaptive immune responses. These cells stimulate T and B lymphocytes and induce and represent an innate and adaptive immune system. Immature dendritic cells are highly migratory, and mature dendritic cells can directly trigger T cells in the central regulatory pathways and support immune responses. Dendritic precursor cells differ by inducing dendritic cells, such as granulocyte-macrophage factor, interleukin-4 (IL-4) and tumor-alpha necrosis factor (TNF-α). CD4+ T cells and CD8+ T cells are essential to adjust the immune response to viruses and the risk of autoimmunity and inflammation. CD4+ T cells increase the production of virus-specific antibodies by stimulating B-cell activation, and CD8+ T cells are cytotoxic and can kill virus-infected cells [23, 24]. DCs and macrophages can phagocytose apoptotic cells infected by viruses. For instance, apoptotic epithelial cells infected with the virus can be phagocytized by CDs and macrophages, leading to the presentation of antigen to T cells. CD4+ T cells activate B cells to enhance the production of virus-specific antibodies, while CD8+ T cells work to kill virus-infected cells [7, 25].

Effective antiviral response of innate and adaptive immunity, including producing various proinflammatory cytokines and activating T cells, CD4+, and CD8+ cells, are essential for controlling viral replication, limiting viral spread, inflammation, and clearance of T cells and infected cells. Tissue damage from viruses leads to excessive production of proinflammatory cytokines and recruitment of proinflammatory macrophages and granulocytes, resulting in cytokine storms. Cytokine storms are called macrophage activation syndrome (MAS) or secondary hemophagocytic lymph histiocytosis (sHLH) as a cause of larger tissue damage. Carry on. Data obtained from patients heavily infected with SARS-CoV-2 showed a cytokine storm that continued to develop into ARDS. Some of the characteristics of patients with SARS-CoV-2 infection are increased levels of cytokines, serological markers, and clinical symptoms, resembling that sHLH is most often triggered by a viral infection. Another essential piece of evidence is that disease severity is related to levels of proinflammatory cytokines and immune cell subsets [25-27].

Both innate and adaptive immune cells synergistically participate in the anti-viral response during infection. In patients with severe cases of SARS-CoV-2 infection, there was an increase in the number of neutrophils, leukocytes, and neutrophil-lymphocyte ratio (NLR). Prominent lymphopenia, indicating impaired immune system, neutrophils, and lymphocyte leukocytes. The level of lymphocytes and T cell subsets, which play an essential role in balancing the immune response, varies according to the type of virus they cause. According to the pathological mechanism of the virus, many studies show that the total number of lymphocytes and T cell subsets is reduced in patients with SARS-CoV-2 infection [28, 29].

In addition to T cells, there was a decrease in B cells and NK cells due to strong associations between inflammatory markers, including ESR, CRP, and IL-6, and lymphocyte subsets. Decreases in CD8+ T and B cells are considered poor predictors of post-treatment clinical assessment. SARS-CoV-2 is responsible for immune dysregulation by induction of aberrant cytokine and chemokine responses. Changes in lymphocyte subgroup levels can result in cytokine storms and further tissue damage. An exaggerated inflammatory response with features of a cytokine storm contributes to a severe course and worsens the prognosis in patients with SARS-CoV-2 infection [30, 31].

Innate immune status of patients infected with SARS-CoV-2. In one report where 99 cases in Wuhan were examined, increased total neutrophils (38%), reduced total lymphocytes (35%), increased serum IL-6 (52%), and increased c-reactive protein (84%) were detected. Increased neutrophils and decreased lymphocytes were also associated with disease severity and mortality in COVID-19 patients. In addition, patients admitted to the ICU have increased plasma levels of several innate cytokines IP-10, MCP-1, MIP-1A, and TNFα. These clinical characteristics suggest the involvement of a pro-inflammatory state in disease progression and severity. An increase in serum pro-inflammatory cytokines at the start of SARS-CoV and MERS-CoV infection indicates a cytokine storm-mediated disease severity similar to SARS-CoV-2. A robust innate immune response against viral infection depends on type I interferon (IFN) response and complement cascade in managing viral replication and initiating an effective adaptive immune response [20, 32].

SARS-CoV-2 virus infection started as a superficial viral infection, then got out of control after a while and progressed to death with a cytokine storm and severe organ damage. For example, Innate immunity is a well-maintained defense mechanism for pathogen recognition and control and adaptive immune response. Adequate triggering of innate immunity relies on the detection of pathogenic molecular patterns (PAMPs) via receptors (PRRs: Pattern recognition receptors), including toll-like receptors (TLRs), Rig-I-Like Receptors (RLRs), nod-like receptors (NLRs) [33].

The following activity through the PAMPs, PRRs adsorb proteins, which comprise a complex signaling pathway involving multiple kinase pathways. This signaling pathway produces essential transcription factors. Synergistically, these agents release secreted type I interferon and act on the Interferon receptor α/β. The antiviral effect of type I interferon causes interference by a different mechanism. Chemokines and cytokines stimulate inflammatory reactions causing extensive tissue damage, through which PAMPs, including lipids, lipoproteins, proteins, and nucleic acids from bacteria, viruses, parasites, and fungi, are detected by TLRs. Recognition of PAMPs via TLRs can occur in cell membranes, lysosomes, endosomes, and endocytolysosomes. Different TLRs can trigger different biological reactions by stimulating multiple adapter proteins [34, 35].

Furthermore, helper T cells produce proinflammatory cytokines through signaling pathways (NF-kB: nuclear factor-kappaB); NF-κB regulates the immune response to infection. The cytokine interleukin 17 (IL-17) stimulates monocytes and neutrophils in the infected area through inflammation. It stimulates a cascade of other downstream cytokines and chemokines, including Interleukin 1 (IL-1), Interleukin 6 (IL-6), Interleukin 8 (IL- 8), interleukin 21 (IL-21), TNF-beta, and monocyte chemoattractant protein-1 (MCP-1). The T cell response to the SARS-CoV-2 infection protein shows that the structure of the viral protein can stimulate the dominant, influential, and long-term memory response to the virus. Humoral immunity is needed to control the continuous phase of the coronavirus disease. The Th1 type response is vital for controlling SARS-CoV, and MERS-CoV is the same for SARS-CoV-2. Patients infected with SARS-CoV-2 show significant mitigation in the number of CD8+ and CD4+ T cells, which can result in impaired memory T cell production and persistence in patients with SARS-CoV-2 [36, 37].

The complement system has a critical function in the immune response to infection with SARS-Cov-2 infection because this system allows detection and response to viral particles. Given its potential to damage host tissues, the complement system is regulated via serum protein inhibitors. C3a and C5a show proinflammatory activity that can initiate the recruitment of inflammatory cells, such as the activation of neutrophil cells. Activation of the complement and contact systems, through the formation of bradykinin, may play a role in SARS-CoV-2-induced pulmonary edema. The occurrence of pulmonary edema due to the induction of bradykinin and ACE2 are co-receptors for SARS-CoV-2[7, 38].

IV. CONCLUSION

The Effective antiviral response of innate and adaptive immunity, including producing various proinflammatory cytokines, activating T cells, CD4+, and CD8+ cells, is essential for controlling viral replication, limiting viral spread, inflammation, and clearance of infected cells. The existence of tissue damage caused by viruses causes excessive proinflammatory cytokine production and recruitment of proinflammatory macrophages and granulocytes, resulting in a cytokine storm as a cause of further tissue damage. Patients highly infected with SARS-CoV-2 show a cytokine storm advancing towards ARDS. It is hoped that a literature study on the immune system and cytokine storms can become a reference and discourse, a basis for thinking for research on SARS-

Cov-2 infection. It can increase knowledge of the immune system and apply it while continuing to enhance the immune system to combat the SARS -Cov-2 virus.

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