Immune System: A Determining Factor in the Severity, Pathogenesis, and Treatment of the SARS-CoV-2 Infection

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ABSTRACT

SARS-CoV-2 is the enveloped virus with a positive sense, single-stranded RNA genome which causes a new outbreak of acute respiratory disease and deadly epidemics. Bat is the important reservoir host of SARS-CoV-2. The robust immune system of bats turns viral strains with mild pathogenesis into a highly pathogenic species for humans. The interaction between SARS-CoV-2 and the immune system of the hosts plays a great role in the fate of the SARS-CoV-2 infection. Immunopathology of the SARS-CoV-2 infection needs to be taken into consideration in the development of preventative and therapeutic methods. Based on the accumulated data and knowledge on the previous related articles, this review hopes to help understand the role of the immune response in virulence exacerbation, pathogenesis, and ultimately immunological treatment of the SARS-CoV-2 infection.

KEYWORDS: SARS-CoV-2; Immune response; Pathogenesis; Immunotherapy, Coronavirus

INTRODUCTION

Viral infections are particularly important because they spread rapidly among people and can cause large epidemics or even pandemics. In the past few years, viral respiratory diseases such as influenza virus infection, middle eastern respiratory syndrome (MERS-CoV), highly pathogenic avian influenza, and severe acute respiratory syndrome (SARS-CoV) coronaviruses threat human health globally [1]. A short time ago, in November 2019, a novel coronavirus (SARS-CoV-2) was detected in Wuhan City which caused the outbreak of respiratory disease and death [2]. SARS-CoV-2 virus, like other Coronaviruses (CoVs), is the enveloped virus with a positive sense, single-stranded RNA genome [3]. CoVs are potentially lethal pathogens, characterized by the presence of spike proteins on the viral surface. They could cause acute respiratory distress syndrome (ARDS) and are associated with high mortality rates [4]. The SARS-CoV-2 infection has a probable asymptomatic incubation period about two weeks during which the virus can be transmitted [5]. Based on recent reports, it’s clear that symptomatic SARS-CoV-2 infection mainly consists of three phases, including a starting phase, spanning the acquisition of the virus and subsequent viremia; and in many but not all patients an accelerating phase, when virus-induced secondary damages occur in the lungs, the heart, the gastrointestinal tract, and even an overall inflammatory storm. The third phase is the final recovery phase [6]. The general symptoms of the SARS-CoV-2 infection are fever, fatigue, and respiratory symptoms, including cough, sore throat, and shortness of breath [7,8]. SARS-CoV-2 has evolved specific mechanisms to escape the innate and adaptive immune responses such as reducing interferon subtypes expression and disrupting their signaling pathways which are the initial factors to coronavirus infection pathogenesis [9]. It seems the response of the immune system to the virus plays an important role in causing the disease as well as its severity. The innate immune response to tissue damage caused by the virus could lead to ARDS which is the leading cause of mortality [10]. Additionally, the levels of inflammatory cytokines especially IL-1, TNF are high which are strong inducers of HA-

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synthase-2 (HAS2) in EpCAM+ lung alveolar epithelial cells, CD31+ endothelium, and fibroblasts [11]. During the incubation period, an effective immune response plays a substantial role in the outcome of the disease. A specific adaptive immune response can eliminate the virus and preclude disease progression to severe stages. Therefore, strategies to boost immune responses (anti-sera or pegylated IFNs) at this stage are certainly important [12]. On the other hand, it is determined when the virus, once severe lung damage occurs, efforts should be made to suppress the immune system and to manage the inflammatory mediators in order to treat the infection. It seems that the SARS-CoV-2 infection presents a virological and immunological conundrum. A growing body of reports revealed that the host immune response rather than direct SARS-CoV-2 damage primarily accounts for the pathologic changes. Therefore, finding the host immune system-related factors as well as virus-dependent factors is very important because they regulate the severity of the virus-associated disease. In addition, understanding the induced immune responses in SARS-CoV-2 infection can lead to the development of novel preventive and therapeutic strategies. The present review article, therefore, provides a brief overview of the contribution of the immune system in virulence, pathogenesis, and treatment of SARS-CoV-2.

Bat Immune system and CoVs virulence

Bats are a large group of mammals that have the capability of flight and also have a wide geographical distribution [13]. Studies have shown that bats are important reservoir hosts of viruses that cause outbreaks and deadly epidemics in recent years [14]. Bats demonstrate no obvious disease symptoms upon infection with pathogens that are highly virulent in non-Volant mammals. The importance of bats as a source of emerging viruses has been proven from numerous studies in the last two decades [15]. Bats may have a robust and effective immune system that turns viral strains with mild pathogenesis into a highly pathogenic species for humans [16]. Little is known about the bat’s immune system, although various studies have shown that the bat’s immune system is similar to the evolved mammalian immune system. B- and T-lymphocyte-like cells and macrophages were identified in the bone marrow of bats, denoting that lymphoid development are generally similar in bats and other mammals [17,18].

Additionally, immunoglobulin G (IgG), IgA, and IgM have been purified from sera of some kinds of bats [19]. Serological assays that detect IgG antibodies to Hendra virus, severe acute respiratory syndrome coronavirus (SARS-CoV)-like viruses and Ebola viruses in bats indicate that some virus-specific adaptive T- and B-cell responses occur despite persistent virus infection [20-22]. One of the challenging scientific questions is why many of the bat-borne zoonotic viruses are so lethal when they spill over into human and/or livestock animal populations. With our current knowledge, it is difficult to answer this question due to the lack of research tools for immunology and pathogenesis studies in bats. Several recent studies, however, start to reveal that bats may have evolved a more balanced innate defense system.

On the other hand, bats have an elevated levels of certain defense genes such as type I interferon and related pathways in order [23] to apoptosis [24] the infected cells at the same time. Bats exhibit more immune tolerance in different pathways, from inflammation [25] NK cell activation [26]. Bats employ a set of species-specific mechanisms to control viruses, which include constitutive expression of the antiviral cytokine, IFN-α [23]. Unlike human antiviral cytokines, IFN-α, that are produced in the presence of viral RNA or DNA in the cytoplasm, bat antiviral cytokines are expressed constitutively [27] which could achieve more rapid within-host transmission rates without causing pathology to bat [16]. Viruses that are affected and adapted to the immune system of bats can generate extreme virulence upon spillover to other organisms such as humans that have different immune response mechanisms. Therefore, the immune system plays a critical role in increasing virulence of cross-species pathogens such as SARS, MERS, Ebola, and Most probably even, the SARS-CoV-2 virus.

Immunopathogenesis of the SARS-CoV-2 Virus Infection

Clinical symptoms in infected people with emerging coronavirus infection are very varied from person to person. The variability in the severity of the disease in different individuals appears to be due to differences in the immune response. On the other hand, it is assumed that pulmonary damage in the SARS-CoV-2 virus infection is caused by immune-pathological factors as well as direct viral effects. The innate immune system is the first line of the immune defense against infectious agents when they enter the body. The cells of innate immune such as NK cells, subsets of DCs, and innate-like B cells can react to various lung viral infections [28]. Identifying the invasion of the viruses is the initial and critical step of the immune response. It is known that pathogen-associated molecular patterns (PAMPs) including endosomal RNA receptors, TLR3 (double-stranded RNA) and TLR7 (single-stranded RNA) and the cytosolic RNA sensor, RIG-1 (single-stranded and short double-stranded RNA) and MDA5 (long double-stranded RNA) need to recognize the invasion of RNA viruses such as coronavirus. This recognition event leads to activation of the downstream signaling cascade in the nuclei of the cells expressing PAMPs. Eventually, the expression of type I IFN, IFN-α/β, and pro-inflammatory cytokines increases which can suppress viral replication, regulate the cell growth, and activate the immune system [29,30]. But type I IFN production in coronavirus infection is much lower and is delayed compared to other IFN-Inducing Viruses. In fact, the disruption of IFN production as well as IFN-related signaling pathways is the defense mechanism of the coronavirus to escape the immune response [9,31]. The common immune-clinical features of SARS-CoV-2 infected patients of ICU including lymphopenia, neutrophilia, cytokine storm (especially increased serum IL-6) and, increased C - reactive protein [32,33]. Production of high levels of pro-inflammatory cytokines including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα can initiate viral sepsis and inflammatory-induced lung injury which lead to pneumonia, acute respiratory distress syndrome. The clinical signs of the coronavirus-related diseases are the same, but the severity of SARS and MERS is greater than that of SARS-CoV-2 infection [7,8]. The clinical features of SARS-CoV-2 infection suggesting a potential cytokine storm-mediated coronavirus related disease severity [33,34]. It is speculated that the delayed production of type I IFN leads to disruption of virus control in the early stages of infection, but subsequent overproduction of type I IFN type I leads to excessive induction of inflammatory immune cells i.e., neutrophils. In fact, immunoinflammatory lung disorders such as ARDS caused by virus infection is caused by the hyper-production of neutrophil pro-inflammatory cytokines [35,36]. A similar scenario is predicted with varying degrees of immune dysregulation for the SARS-CoV-2 virus infection [5]. In general, it can be concluded that the lung damaged cells which produce in SARS-CoV-2 infection, initiate the severe inflammatory cascade that is mediated by pro-inflammatory cells such as macrophages and granulocytes [10].
Immune responses to the SARS-CoV-2 Virus Infection

Mucosal parts of the body, especially the respiratory tract mucosa, are constantly exposed to the external environment, making the lung a vulnerable organ to a range of illnesses, especially viral infectious diseases such as SARS-CoV-2 infection. Mucosal SARS-CoV-2 infection plays a critical role not only in virus pathogenesis but also in the virus transmission [37]. Mucosal exposure to SARS-CoV-2 can initiate local, and systemic, cellular/humoral immune responses at specific mucosa-associated lymphoid tissue (MALT) [38].

In humans, MALT is populated by dendritic cells (DCs), macrophages (MQ), T cells, and B cells. Antigen presented by DC at the infected mucosa can activate T and B cells in situ. Furthermore, DCs can also migrate and also induce systemic immunity [37]. In coronavirus related-infections including SARS-CoV-2 virus infection, like any other viral infection, a T-helper type 1 (Th1) pattern of CD4 T cells play an important controlling role. T-helper cells orchestrate the overall function of the immune system by producing various cytokines. In addition, cytotoxic T cells can kill the cell harboring viruses.

Although the cytotoxic T cells cannot prevent Infectious agents’ entry, they contribute to the pathogen clearance by identifying and killing infected cells [39]. Apart from the cell-mediated immune response, the humoral immune response is also induced after viral mucosal infection. Mucosal B cells secrete antigen-specific secretory IgA antibody (sIgA) that is important for effective mucosal immunity. In fact, sIgA effectively neutralize infectious agents and their toxic products on the mucosal surfaces [40]. Furthermore, humoral immune response plays a protective role, limiting infection, by the production of long-lasting specific IgG [41,42].

HLA AND SARS-COV-2

The human leukocyte antigen (HLA) system is a gene complex encoding the highly polymorphic cell-surface proteins, major histocompatibility complex (MHC) proteins. MHC molecules are key to the control of the specificity of antigen presentation to the human immune system. MHC class I (A, B, and C) present peptides from inside the cell. In contrast, MHC class II (DP, DM, DQ, DQ, and DR) usually present foreign antigens such as viruses to T-helper lymphocytes which then stimulate cellular and humoral immunity to eliminate the pathogen.

On the other hand, HLA is the important candidates for genetic susceptibility to infectious diseases [43]. In fact, for the development of the protective immune response, the host should have appropriate HLA that elicits an effective antiviral immune response. Genetic background variations are well-known to contribute to individual differences in the immune response to pathogens [44] because, antigen receptors, on T-lymphocytes, recognize the conformational structure of the specific HLA together with the associated foreign antigen peptides. Therefore, different HLA haplotypes in individuals may be associated with sensitivity or even resistance to an infectious agent [45]. The consensus among scientists is that the susceptibility to various infectious diseases such as influenza, HIV, hepatitis B, and tuberculosis is associated with specific HLA. Based on this evidence, it is hypothesized that the anti-SARS-CoV-2 immunity and even the variation in disease severity among individuals may be due to diversity in HLA loci [12,46].

AGE-DEPENDENT IMMUNE RESPONSE AND SARS-COV-2

There is a complicating data concerning SARS-CoV-2 infected persons which explaining why it happened is breathtaking. Severe and fatal SARS-CoV-2 infections are more common in the elderly and immunocompromised individuals, as well as in infants. In contrast, healthy children usually show no signs of infection and are actually carriers of the disease. At first glance, it is clear that the body’s immune system plays a key role in the severity of the symptoms of the SARS-CoV-2 infected people [47,48]. It is completely defined that the exaggerated inflammatory response is associated with progression to organ dysfunction and failure. It has been observed that some patients, especially the old, weren’t able to turn off their inflammatory response, leading immune cells and inflammation-inducing molecules known as cytokines to flood into the lungs which are known as cytokine storm [49]. Studies have shown that age-associated immune deficiency in mucosal and systemic immunity is not concurrent in the elderly. Mucosal immunity is down-regulated earlier in the elderly [50]. Thus, the elderly population has increased susceptibility to severe viral pulmonary disease and also in increased mortality [51]. It seems that innate immunity is the initial and pivotal controlling factor for coronavirus related-disease outcome, because a mild disease has been reported in young people with healthy immune systems who do not have an underlying disease such as hypertension, diabetes, and cardiovascular disease [8]. In very young children the story is different, the innate and acquired immune system of infants are weak, which may be due to various reasons, such as reduced immune responses which leads to ineffective adaptive immune responses, the lack of immune memory as a result of the lack of prior pathogens exposure, CD4 and CD8 lymphocytes dysfunction, the similarity of the immunological pattern of infants to the fetus, which is Th2 (a successful Pregnancy is associated with Th2 immunological pattern in the uterine environment) [52,53]. Additionally, Primary airway epithelial cells from infant animals demonstrated decreased secretion of IFN-α and increased viral replication [54]. Infants had a significantly high level of pro-inflammatory cytokines which are associated with immune-pathologic changes during viral infection. Very young children have an immunologic predisposition to enhanced inflammation which is responsible for the morbidity of the infant [55]. Furthermore, it has been documented that the production of IL-12 is limited in young children after PRR stimulation [56]. By the way, B-cell maturation and antibody production and even response to the vaccine are ineffective in the newborn infants [57]. It has been recently reported that maternal antibodies may interfere with the humoral immune responses of the infants [58]. As a result, the impaired humoral and cellular immune systems influence the immune responses which lead to reduced viral clearance. It makes infants vulnerable to infectious agents.

IMMUNOLOGICAL MECHANISMS FOR THE TREATMENT OF CORONAVIRUS

The mortality rate of SARS-CoV-2 infection is approximately 3-7% [59]. Therefore, there is an urgent need for a therapeutic strategy for saving lives in the world. Since the main cause of death in SARS-CoV-2 infected patients is immunoregulation and cytokine release syndrome, a therapeutic approach to immune system modulation can be helpful. Herein, we discuss the newly proposed methods for SARS-CoV-2 infection treatment. This section will be restricted to attempts to use immunological methods in the treatment of SARS-CoV-2 infection.
One of the main causes of the severe form of SARS-CoV-2 infection is the cytokine storm. It seems blocking the signaling pathways of the pro-inflammatory cytokines such as IL-6, IL-1, and TNF can modulate the severity of the SARS-CoV-2 infection [60]. Based on the released evidence, the mesenchymal stem cells transfection as a cell-based therapeutic strategy can improve the survival of SARS-CoV-2 infected people by modulating the immune system and repair of the damaged lung tissue [61,62]. A high-dose intravenous immunoglobulin (IVIg) administered, passive immunization, at the early stage of clinical deterioration could successfully improve the outcome of SARS-CoV-2 infection. The mechanism of action of the IVIg includes viremia suppression, acceleration of infected cell clearance, and enhancement of opsonization [6]. Another possibility includes Leronlimab, humanized anti-CCR5 monoclonal antibody which has shown Therapeutic effects in deadly SARS-CoV-2 infection. The manufacturer claims that CCR5 antagonists can restore the immune cell number/function and relieve the inflammation [63]. Recently, an epidemiological study has shown that the survival of SARS-CoV-2 infected patients in countries receiving the Bacillus Calmette-Guérin (BCG) vaccine is higher than in countries that do not receive the BCG vaccine [64]. Clinical studies have shown that people who were previously BCG-vaccinated may be resistant to viral infections. A clinical trial demonstrated BCG-vaccination, significantly reduces the risk of respiratory tract infection in elderly people by increasing the IFN-γ and IL-10 levels [65]. In general immunological mechanisms involved in the induction of non-specific resistance to viral infections by BCG-vaccination include enhancement of non-specific memory in innate immune cells, induction of non-specific Th1 and Th17 responses, activation of Treg, activation of non-targeted antigens specific CD4+ and CD8+ memory cells. The BCG-vaccine is currently being studied as a promising candidate for the prevention and treatment of SARS-CoV-2 infection [66-69].

CONCLUSION

There is a lot of ignorance about the origin and virulence factor of SARS-CoV-2. But according to the published articles and reports, it seems that the real problem with SARS-CoV-2 is the host immune system. In this way, the bat’s immune system increases the virulence of the virus, and in humans, the immune system’s response to SARS-CoV-2 increases the pathogenesis and disease severity. The pathogenesis of the virus is related to immunological factors such as the innate immune responses, the paradigm of cellular immune responses (Th1, Th2, and Th17), humoral immune responses (neutralizing antibody) as well as production of pro-inflammatory/anti-inflammatory cytokines. The speed and strength of the immune system responses in people cause different clinical symptoms. Some people are the only carriers of the SARS-CoV-2 without any clinical symptoms, while others die from the SARS-CoV-2 infection. Finally, it can be concluded that the use of new therapeutic methods, especially immune system-based therapies, to modulate immune responses can be the most effective strategy to the treatment of SARS-CoV-2 infection. The bottom line is that immunological panacea can heal immune-mediated diseases such as the SARS-CoV-2 infection.

REFERENCES


