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Review

The Complement System During SARS-CoV-2 Infection

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly pathogenic coronavirus that posing a threat to human health and public safety. SARS-CoV-2, which comes from the same family as SARS-CoV and the Middle East respiratory syndrome-related coronavirus (MERS-CoV), has similar characteristics with them, as well as a different protein structure than them, which explains that it causes a larger epidemic than the SARS and MERS virus. It is aimed to stop the epidemic by examining the activities performed by SARS-CoV-2 in the cell and after its entry into the cell. Angiotensin-converting enzyme 2 (ACE2), the input mechanism of SARS-CoV-2, is important in this regard. A defense mechanism against SARS-CoV-2 is developed when it is introduced into our bodies. Complement system constitutes responses for this infection. In this review, the relationship between the complement system and SARS-CoV-2 was discussed.

Keywords: Complement system, COVID-19, SARS-CoV-2

The new type of coronavirus has been named coronavirus disease 2019 (COVID-19) after its emergence in Wuhan. Its most recent name is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is the new member of the family of coronavirus. In the last 20 years, there have been three epidemics caused by coronaviruses. The severe acute respiratory syndrome (SARS) first appeared in China in 2002 and infected approximately 8,000 people worldwide and the calculated mortality rate is approximately 10%.[1,2] The Middle East respiratory syndrome-related coronavirus (MERS-CoV) which appeared in Saudi Arabia in 2012 is another type of coronavirus and it infected approximately 2,500 people the calculated mortality rate is approximately 30%.[1] The SARS-CoV-2 belongs to the same family of SARS and MERS. Globally, over 278 million cases and just under 5.4 million deaths had been reported as of December 26.[3]

During coronavirus infections, it creates a cytokine storm of our immune system and affects adaptive immune responses. Coronaviruses are viruses that can be recognized by intracellular recognition receptors, resulting in the activation of signal chains. This causes cytokines and chemokines to be released.[4] The immune system tries to destroy the pathogen by producing defenses against it in different ways.

Cytokine and chemokine responses in the SARS and MERS viruses, as in the SARS-CoV-2, are present during infection. Cytokine storm is one of the first warnings in taking preventions against pathogens and has a complex network. Transforming growth factor-beta (TGF-β) is one of the transformative growth factors and allows T-helper 17 (Th-17) cells to differentiate from pure CD4+ T cells. Th-17 cells are pro-inflammatory cells defined by the production of interleukin 17 (IL-17). Th-17 cells produce IL-17, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-21 (IL-21), and interleukin-22 (IL-22). IL-17 itself increases the production of large amounts of proinflammatory cytokines and chemokines.[5] In people infected with SARS-CoV-2, interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α) rise during the disease and decrease during recovery. Patients admitted to the intensive care unit due to acute respiratory syndrome have significantly higher IL-6, IL-10, and TNF-α levels and fewer CD4+ and CD8+ T cells.[6]

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The complement system which often responds to viral attacks is part of the immune system. The general mechanism of the complement system is to create C3 and C5 convertibles. The resulting convertibles combine with other complement system elements, the components (C1-C9), to form a membrane attack complex (MAC). The complement system also plays an important role in cytokine storms, and killing pathogens is its main task. C3, the central molecule of the complement system, is of great importance in this regard. Long-term blocking of the C3 and C3 convertase, to which all roads are connected jointly, prevents/delays the operation of the complete system. However, short-term cessation or inhibition of C3 convertase may have beneficial effects on some diseases.[7] Complement receptor 1 (CR1), which is one of the coding regions of the complement system, is the cofactor that inactivates C3b and C4b. Inhibits the activation of C3 along all active paths.[5] In addition, C5a, which is also a powerful component of the complement system, is a good target for reducing pro-inflammatory responses to SARS-CoV-2.

STRUCTURE AND CHARACTERISTICS OF CORONAVIRUS

So far, four coronavirus genus have been identified as α-, β-, γ-, δ-. Coronaviruses; single helix RNA viruses with positive polarity.[8-10] Viral surface proteins have an embedded, host cell lipid membrane and enveloped viruses.[2,10] The genome of the virus encodes four basic structural proteins; Membrane protein (M) is a spike (S) protein containing envelope protein (E), a linked nucleocapsid (N) protein, and surface proteins.[8,11] SARS-CoV-2 has a genome of approximately 29.8 kilobases.[12] The genome of SARS-CoV-2 is similar to the genome sequencing of the SARS virus.[13] This helps us to understand the proteins of SARS-CoV-2. The SARS-CoV-2 has six other auxiliary proteins-ORF3a, ORF6, ORF7a, ORF7b, ORF8a, and ORF8b-except ORF3b and ORF9b found in the SARS virus.[12,13] SARS-CoV-2; ORF1ab has a total of 11 genes with ORF2 (spike protein), ORF4 (envelope protein), ORF5 (membrane protein), ORF9 (nucleocapsid protein), and ORF10.[13]

The SARS-CoV-2 enters the cell thanks to the human angiotensin-converting enzyme 2 (ACE2) receptor, just like SARS.[2,8,14-16] This S protein, which is owned by coronaviruses, recognizes ACE2 found on the surface of the host cell. Contains a receptor-binding domain (RBD) that specifically recognizes the ACE2 receptor.[14,17] The RBD of SARS-CoV-2 is crystallized and horizontal.[14] Such differences indicate that the RBD of SARS-CoV-2 has more affinity to bind to ACE2 than the SARS virus.

The trimeric SARS-CoV-2 S1, the peptidase domain (PD) of the ACE2, and the division of the ACE2 C-terminal segment by transmembrane protease serine 2 (TMPRSS2) strengthen the viral input driven by the S-protein.[18] Among the protease activating input, the cell surface contributes to the cell input of SARS-CoV-2 in lysosomal protease as well as protease TMPRSS2.[14]

The ACE2 is usually found in alveolar epithelial type II cells. For this reason, SARS-CoV-2 causes acute respiratory distress syndrome (ARDS) just like SARS.[2,10,11,15,19] Symptoms of SARS-CoV-2 patients such as unproductive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts are similar to SARS-CoV and MERS-CoV.[9] Research shows that SARS-CoV-2 damages many organs and tissues such as the heart, brain, lung, liver, kidneys as well as respiratory organs. Although viruses renounce their infectious properties to prolong their lives in the evolutionary process, SARS-CoV-2 has not lost any of this feature in its evolution. It causes more infectious and longer-lasting diseases than SARS.[14] In addition, the fact that SARS-CoV-2 gives less neutralized antibodies than the SARS virus indicates that it escapes our immune system better than SARS.

Although SARS-CoV-2 is known to enter the cell thanks to the ACE2 receptor, research on this subject continues. It will become easier for us to understand this input mechanism day by day.

THE COMPLEMENT SYSTEM

In our immune system, the complement system plays a large role. The task of the complement system; is to directly damage and kill tissues identified as foreign with a specific antibody and substances such as bacteria and viruses entered from the outside.[20] If we need to reorganize our responsibilities, it can initiate and increase inflammation, increase phagocytosis with chemotaxis, clean immune complexes, and kill directly with lysis. The complement system is also linked to many of our defense mechanisms, such as increasing humoral immunity, modulating T cells, editing antibody effector mechanisms.[21,22] It has effector mechanisms mediated by several specific receptors and consists of more than 30 proteins dissolved in the blood or associated with the membrane.[20,22-24] Thus, many proteins will reduce the damage caused by irregularities in the complement system. The system consists of components from C1 to C9, and the main

molecule is C3. There are three different activations: the classic pathway, the lectin pathway, and the alternative pathway. These activations merge in C3 and subsequently result in the formation of C3a, C3b, C5a, and membrane attack complex (C5b-9).[24]

Classic pathway; It begins with the formation of an immune complex as a result of IgG and IgM binding to non-essential antigens or pathogens.[24] The complex C1, which contains C1q, C1s, and C1r serine protease, is then connected to the Fc part of the IgG or IgM immune complex.[22,24,25] C1q performs C1s and C1r activities with its connection to the FC section.[21,24] After this structural change, C1s; divides C4 into C4a and C4b, while C2 separates C2a and C2b. Thioester occurs, causing C4b to bind cod to the cell surface.[21,25] Parts form C3 convertase as C4bC2a.

Lectin pathway; Mannose-binding lectin (MBL) or ficolin is activated when it binds to carbohydrate parts on the surfaces of pathogens, including yeast, bacteria, parasites, and viruses. The serum has proteins associated with MBL and ficolin. Pattern recognition molecule (PRM) and serine protease (SP) are examples of these structures.[26] They are found in the blood and check for dangerous substances. PRMs bind to it when they find dangerous particles. Initiates the first step of activation by giving the necessary signal in PRM-associated SP. This process classically proceeds similarly. Serine protease associated with MBL plays a role in the path of lectin and consists of four varieties. Mannose-binding lectin (MBL)-associated SPs (MASP) 1,2,3 and MASP19. MASP 2 has a similar structure to C1s.[21,22] With the onset of activation, MASP2 divides C4 and MASP1 divides C2.[20,21,24,26] C4b, which is formed as a result of these divisions, has enzymatic activity together with C2a and as a result, C3 convertase occurs as in the classical pathway.

The classic path and the lectin pathway are similar for some structural reasons. C3 and C4 are closely related to proteins containing thioester, which are the basic structures that make up the convertase complexes. Their tasks are; is to completely connect to the convertase activation surface and capture the SP components of the enzyme complex. C2 is the SP component of the C3 converter of the classical pathway and lectin pathway.[26] The alternative way works differently than these two activations.

Alternative pathway; it is triggered by carbohydrates, lipids, and proteins found on foreign, non-core surfaces. It begins with spontaneous hydrolysis of C3 in the bloodstream (C3(H2O)).[21,22,25,26] C3a and C3b are formed by the C3 compartment of C4bC2a, the C3 converter in the classical pathway and lectin pathway, and they are widely found in plasma. C3b binds factor B, the serine protease of the alternative pathway. Factor D, another alternative path SP found in the blood, divides factor B.[21,25,26] With the division of factor B, Bb serine esterase occurs. C3b combines with BB to create the C3 convertase, and C3bBb occurs. C3 converter binds to the residues on the cell surfaces as condensate with the thioester bond and localizes it. Stabilizes the environment so that the C3 can connect comfortably.[24,26] In addition, the alternative pathway acts as an amplification cycle for C3 convertase.

The process continues in common with the paths forming C3 converters differently. C5 convertase is formed with substrate specificity of C3 convertase.[21] C5 converters divide C5 by C5a and C5b. The division of C5 is the last enzymatic reaction incompleteness. After this step, the first step of the MAC is taken by connecting the C5b with C6. The resulting C5bC6 forms C5b-7, which is attached to the phospholipid membrane double layer with C7 and creates unstable pores by inducing the membrane inlet of C8α and C8β. C9 binds to C8α. As a result of these operations, the complement system defends by creating MAC, i.e. C5b-9.[20-22,24-27]

COMPLEMENT ACTIVATION IN CORONAVIRUS DISEASE

Based on the situation arising as a result of research and observations, complement system activation plays an important role in SARS-CoV-2 and SARS-CoV pathogenesis.[28,29] It has been recorded that the relationship of C3 activation, the complementary component, with the SARS virus exacerbates ARDS disease. They then observed its effect with the C3 component in experiments on mice.[2] They observed that mice with C3 deficiency had less respiratory distress than other mice. Samples taken from mice infected with the SARS virus and deficient in C3 showed a decrease in the number of inflammatory neutrophils and monocytes, immune cells known to play a role in CoV pathogenesis.[2,8,11,28] In addition, lower cytokine and chemokine levels were measured.[2] This has shown that Without a complete system, CoV cannot have an inflammatory effect. The relationship of complement system activation with SARS-CoV may be developing the disease. There are findings in the research that the complete system for the SARS virus causes systemically strong inflammation as demonstrated by the accumulation of complementary proteins in the kidneys.[2,30]

Studies are being carried out to understand, solve and stop the SARS-CoV-2 by generating hypothetical data. Recent research has concluded that the S protein of SARS-CoV-2 is heavily glycosides with residues rich in L-fucose or D-mannose.[11,16] Hypothetically, the virus is found in CL-11 or FCN-1 (they are found in alveolar epithelium and circulation.) it is thought that the complement pathway can be activated by its interaction with lectin. Circulating viral particles come into contact with MBL as well as ficolins and CL-11.[11] For this reason, it is perfectly appropriate that the interaction of SARS-CoV-2 with lectin can trigger inflammatory and clotting steps in the lungs and circulation. Likewise, a hypercoagulation condition other than spread intravascular coagulation can be put on top of SARS-CoV-2 infection. In the study, it was concluded that the results of the SARS-CoV-2 patient cohort did not coincide with acute spread intravascular coagulation, but instead supported hypercoagulation with severe inflammatory status.[31]

In another study, they reported finding strong immunohistochemical dyeing for MBL, MASP-2, C4, C3, and C5b-9 in a lung autopsy of the SARS-CoV-2 patient with ARDS, and suggested that type I and type II alveolar epithelial cells were the main tissue targets for complement accumulation.[11,32] By advancing and expanding the research, they found that SARS-CoV-2 gave a quiet inflammatory response which includes type I, type III interferons, and a large number of chemokines and cytokines as a result of comparison with other respiratory viruses.[1,11,32]

It is already known that SARS-CoV-2 causes ARDS. Studies are also being carried out to prevent this and reduce its destruction. In studies, C5a rose in peripheral blood samples and was accepted as a marker of ARDS associated with severe sepsis, cytokine storm, and multi-organ failure. Polymorphic nuclear neutrophil (PMN) aggregation in the injured lung was found to create a tendency to the development of ARDS, which coincided with an increase in C5a levels. In addition, PMN exposed to activated C5a can adhere to and damage the vascular endothelial, which leads to increased vascular permeability and the formation of ARDS.[11,33] The complement system can strongly interact with lung macrophages, altering their responses to different pathogens. Macrophages can perform the functions of the complementary effector by expressing the receptor that detects complementary components such as CR1, CR3, CR4, C3aR and C5aR1.[11,34] Complement anaphylatoxins C3a and C5a are pro-inflammatory and can trigger monocyte and macrophage activation.[11] C5a receptor signaling on monocyte-derived macrophages through IL-6 and TNF-α production may increase cell sensitivity to infection caused by certain viruses.[35] The blockade of complement anaphylatoxin C5a in experimental sepsis almost prevents the appearance of multiple organ failure and improves the result.[11,36]

In conclusion, although SARS-CoV-2 is a current virus, we have a preview of its structure and genome thanks to viruses from the same family before. Likewise, thanks to these reviews, we can say that research started faster and accurate results were reached. However, it is important to remember that the virus we are facing, however familiar, is very different. The responses generated by the complement system can mislead us before they reach a certain level. The fact that there are multiple complement system responses and that SARS-CoV-2 activates many ways can help us solve it more quickly, as well as confuse reaching a solution. However, in the mouse model experiment that lacks C3, we have seen that the complement system can contribute to the pathogenesis of the disease, which we have not yet explained; The effect of blocking C5 following C3 is to control the inflammation reduced in the complement system. Although the complement system appears to be next to SARS-CoV-2 in this arrangement, assuming that the drug can penetrate enough tissue to the complement activation zone with treatment and activation methods with complement inhibitors against C3 or C5, the complement system appears to be on our side. However, it tends to switch sides with irregularities that may occur within the system. What needs to be done is to synthesize the complement system responses well and determine with forward-thinking where the end will go.

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