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Review

Coronavirus Infections and T Lymphocyte-Dependent Immune Responses

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ABSTRACT

According to the most recent data from the World Health Organization, the new generation coronavirus disease 2019 (COVID-19) pandemic, which appeared after the old coronavirus infections severe acute respiratory syndrome and Middle East respiratory syndrome with various variants, caused the deaths of 6.4 million people globally until September 7, 2022, as a result of severe acute respiratory failure. Vaccines have been developed for the treatment of the epidemic and to protect people from the pandemic. Due to environmental factors, human body characteristics, and virus genome characteristics, the virus has mutated and gained resistance. However, the immune system, a natural defense mechanism of the human body, can protect from viruses, bacteria, and many other pathogens. T lymphocytes play a significant defensive role, and they use memory cells to create both long-lasting and transient responses. In this review, their important role in protection from COVID-19 and other coronavirus infections and the responses of T lymphocytes were evaluated

Keywords: Coronavirus, COVID-19, immunotherapy, MERS-CoV, SARS-CoV, T lymphocytes

Coronaviruses, four members of the circulating coronaviruses in the coronaviridae family cause mild colds, flu, and colds in the human circulation (NL63, HKU1, 229E, OC43).[1] It has caused epidemics known as severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), or severe acute respiratory failure sickness, and Middle East respiratory syndrome coronavirus (MERS-CoV), or Middle East respiratory syndrome.[2]

Recently, COVID-19 was used to refer to the virus that first appeared in Wuhan in December 2019. COVID-19's molecular structure resembles SARS by 80%. SARS-CoV-2, which stands for severe acute respiratory failure syndrome 2, is another name for COVID-19 for this reason. Different respiratory tract infections brought on by SARS-CoV-2, as well as pneumonia brought on by lung tissue inflammation, can be fatal. At the same time, variations like "omicron," "alpha," "beta," "gamma," and "gamma" have appeared. Various powerful mutations have occurred due to the immune mechanism of the human body and the genome characteristics of the virus. A number of preventive and protective investigations on the present coronavirus disease 2019 (COVID-19) pandemic have been made possible by the use of older coronavirus types. It has made the human body's response to the virus predictable, yet the response induced by SARS-CoV-2 has caused significant damage.[3] Despite this, scientists continue to produce protective vaccinations as a consequence of diverse investigations, thanks to their understanding. The natural defensive mechanism is crucial in vaccine development. It has been discovered that certain people have a strong tolerance to the virus. Individuals with a robust immune system, even if infected with the virus, have entered a simple and moderate sickness phase. Following several observations and tests, various diets and activities have been suggested in order to strengthen people's immune systems, and it has been emphasized in publications that virus prevention is also very important. This review focused on how the immune system's crucial T lymphocyte responded to COVID-19 in the context of earlier coronaviruses,

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including information on the reactions of innate immunity and adaptive immunity to coronavirus infections.

BIOLOGY OF CORONAVIRUSES

Some beta coronaviruses are capable of causing epidemics. Within the genus Betacoranavirus, these viruses created two subspecies, Sarbecovirus and Merbecovirus. [1]

Coronaviruses are single-stranded, enveloped ribonucleic acid (RNA) viruses. Since they have positive polarity, they lack RNA-dependent RNA polymerase but can encode it in their genome. On the surface sections, there are protrusions that resemble crowns. The term "coronavirus," which means "crowned virus," was established. The virus's genome is made up of four structural proteins: membrane (M), spike (S), nucleocapsid (N), envelope (E), 16 non-structural proteins (nsp1-16), and several auxiliary protein codes. The S antigen is the most important protective antigen, as it promotes the formation of powerful neutralizing antibodies (NAbs).[3] Furthermore, coronaviruses are engaged in the development of protective antibodies, as well as producing genetic code alterations and evading the immune system. Coronaviruses have the largest unsegmented genome size of any RNA virus, at 30 kb. Increased genomic flexibility, i.e., evolution, will allow for alterations and mutations via the recombination network as genome size increases. This makes the transfer between species easier.[4]

Bat-borne virus genomes are 75-95% identical to the SARS-CoV, SARS-CoV-2, and MERS-CoV viral genomes. Differences in non-structural helper protein composition, together with comparable structural genomes, can result in some recombination of similar virus strains.[1]

The common feature of SARS, MERS, and COVID-19 patients is a severe acute respiratory syndrome. According to the statistics, despite the fact that COVID-19 has a higher risk of transmission and mortality, it has evolved into a pandemic epidemic that has persisted despite the actions taken since December 2019.[5]

T LYMPHOCYTES

T cells, a subset of lymphocytes, play a crucial role in the immune system.[6,7] T cells acquire their name from the thymus organ, which is where these cells mature to their full potential. They develop from stem cells in the bone marrow, travel via the bloodstream to the thymus cortex, and grow quickly there. T cell antigen receptors (TCR) and surface cluster of differentiation (CD) antigens are found in their membranes, and T cells that induce a specific immune response to develop as markers. Lymphocytes arriving in the medulla have various shapes; those with a $CD4^+,8^-$ structure are helper T cells, while those with a $CD4^+,8^+$ structure are cytotoxic T cells.[8,9]

Cytotoxic T cells ($CD8^+$) exist to eliminate infected cells that they perceive to be alien or tumor cells. It forms a porous structure in the cell membrane, such as perforations, containing granules that induce the cell to die by secreting granzyme and perforin and causing apoptosis. These are known as deadly or cytotoxic cells, and they detect and remove antigens as targets.[8-10] Helper T cells ($CD4^+$) are regarded as mediators since they multiply quickly and produce cytokines that control and aid the function and activities of effector lymphocytes when activated. It is the most numerous kind of T cell.[9,10] Regulatory T cells ($CD4^+$ $CD25^+$), another kind of T cell in the immune system, keep the immune system in balance. When the equilibrium is upset, autoimmune disorders develop. Another type of memory cell is T memory cells, which are found in the immune system. Memory cells are in charge of ensuring that people who have been infected once produce antibodies quickly when they are exposed to the same disease again. The body that confronts the pathogen with the same or comparable impact is able to pass the sickness even without symptoms and is protected from major harm.[9] However, antigens are responsible for the surface features of T cell subtypes.[10]

INFECTIONS WITH THE CORONAVIRUS AND T LYMPHOCYTE-DEPENDENT IMMUNOLOGICAL RESPONSES

According to World Health Organization data, SARS-CoV, which arose in Guangdong Province of China in November 2002, has a 10% fatality rate and an elevated risk in senior patients over 60 years of age, infecting a total of 8,098 people worldwide and caused 774 fatalities. It was kept under control and prevented from generating a significant pandemic as a consequence of intensive efforts implemented in the summer of 2003.[11]

It has been regarded as the 21st century's first deadly and readily transmitted disease, conveyed through the airway, salivary tract, flu, and colds. The incubation period is 2-7 days, but it has been

shown to last up to 10 days. The lower respiratory phase occurs after 3-7 days, with symptoms such as low blood oxygen levels (hypoxia), a dry cough, and shortness of breath. Mechanical ventilation and intubation were necessary in cases of severe illness. Chest radiographs were typically considered normal. White blood cells are frequently decreased in the early stages of the disease, and a low platelet count is noticed at the most severe stage of the disease. SARS-CoV was discovered in bats in China and spread to people via civet cats. According to studies, locals have already developed tolerance to this pathogen. It is a beta-coronavirus that spreads by the consumption of such creatures, and it is unusual pneumonia that has spread to several countries.[1,11-13]

However, certain tissues are selected by the unique characteristics on the virion surface and the peplomers generated by the S protein in order for coronaviruses to enter animal cells. A binding domain of 190 amino acids is situated in the N-terminus of the spike protein. The structure of this domain distinguishes SARS-CoV from other viruses, and it has a highly changeable domain feature. Although SARS-like viruses may connect to the receptor angiotensin-converting enzyme 2 (ACE-2), most bat viruses cannot.[1] SARS-CoV-2, which infects humans, enters the cell via ACE-2 and infects airway and alveolar epithelial cells. The disease progressed severely and even caused death in individuals with weak immune systems. After infection, the virus has been found in a variety of tissues, including the brain, blood, spleen, and other organs. Excessive inflammation has caused tissue damage in other areas. COVID-19 has also been shown to exhibit similar characteristics.[4,13]

Following infection, lung tissue destruction and pneumonia have been documented, leading to respiratory failure and death. It is believed that the immune system plays a major part in the condition, which is severe in those over 60 and moderate in children. Although human and animal models have been utilized to study the immune system's response to SARS-CoV, there is a dearth of evidence on the impacts and activities of T cells during acute coronavirus infections. Following that, trials were conducted with mice, who are smaller animals, yet it has been found that mice are vulnerable to SARS, with young mice showing no sickness and aged mice showing minor symptoms. Transgenic mice were employed as a result of expressing the human ACE-2 gene in mice. The findings revealed pulmonary ailments as well as deadly encephalitis, or brain inflammation. In general, immune system responses are associated with high levels of proinflammatory chemokines and cytokines (e.g., CCL2, CCL3, CCL5, and CXCL10), interleukin (IL)-6, tumor necrosis factor (TNF), and interleukin 8 (IL-8). It has been completed.[12] All of these were discovered to be more prevalent in people with more severe illnesses. Lymphopenia, or a lack of lymphocytes, is a typical characteristic seen during acute sickness and in SARS patients, and T cell activation was also shown to be reduced, particularly in individuals with severe disease.[14] Impaired migration of pulmonary dendritic cells (DCs) from the lungs to the lymph nodes has been linked to poor T cell responses.[12] Dendritic cells are antigen-presenting cells in the immune system, and inhibiting these cells demonstrated that macrophages were damaged, but only partially. In addition, Zhao et al.[12] stated in their research that aging also affects the responses of T cells. In his investigation, he used numerous strains, such as the MA15 strain, and eventually discovered protection against the virus. Immunization with vaccines expressing CD4 or CD8 T cell epitopes or DCs coated with these peptides prior to SARS-CoV infection gives considerable protection from SARS-CoV fatalities. Type II interferon (IFN) actions in the lungs have resulted in enhanced DC and CD8 T cell responses that are reliant on interferon gamma (IFN-γ). According to research, immunopathological and eosinophilic infiltrates have an influence on immunity in SARS-CoV-infected mice, and immune responses against the virus will be successful with various treatment strategies and products in the future.[15,16]

MERS-COV

It is the Middle East respiratory syndrome coronavirus, which arose in various Middle Eastern, African, and South Asian countries in 2012 and was transmitted to humans by infected dromedary camels. It is a zoonotic virus that spreads by touch. Approximately 35% of MERS-CoV patients died, and 858 deaths due to infection and accompanying sequelae have been recorded from 27 countries since 2012.[17]

MERS-CoV infections have resulted in mortality as a result of asymptomatic or severe acute respiratory disease with moderate respiratory symptoms. Fever, coughing, and shortness of breath are symptoms of the condition. Serious sickness typically affects the elderly, persons with compromised immune systems, those with renal disease, cancer, chronic lung disease, and chronic disorders. Multiple organ failures have also resulted in deaths. Its therapy is palliative, and

no vaccination is available. They advised staying away from camel products and avoiding interaction with animals at risk of illness.[17]

Although there is limited evidence on the immune system's response to MERS-CoV, studies have been conducted. Researchers in Asia evaluated the innate immune response of the severe MERS outbreak using data from the Arabian Peninsula and nations exposed to MERS-CoV. The findings revealed that proinflammatory cytokines, including IL-6 and IFN-γ-derived protein 10 (CXCL10), as well as IL-8, chemokine ligand 5 (CCL5), and interferon alpha (IFN-α), were present in high concentrations.[18-20] In peripheral blood mononuclear cell samples, these increased cytokines are linked with a large frequency of neutrophils, macrophages, and lymphopenia, suggesting that they contribute to immunopathology. MERS-CoV replicates in human monocyte-transferred macrophages and DCs, as opposed to SARS-CoV, which only abortively infects macrophages and DCs, causing no symptoms even when exposed to the virus through the prompt involvement of T cells. As compared to SARS-CoV, it induces a significant increase in the synthesis of these cytokines in cells.[18,20]

In a noteworthy advance, vaccination with an immune enhancer expressing the N protein, CD4 T cell epitope in a SARS-CoV generated a favorable response against MERS-CoV with some degree of cross-protection, leading to decreased viral load. These two and related bat coronaviruses have a highly conserved epitope, the region of the antigen that binds to antibodies and memory (B) cells.[21] In experiments, it was shown that animals inoculated with the MERS-CoV-specific epitope, which is the homologous epitope in a MERS-like bat coronavirus, exhibited some protection against SARS-CoV infection and mediated protection against a MERS-CoV challenge (HKU 4). The suppression of CD8 T cells in a non-lethal MERS-CoV mouse model has been reported to reduce lung pathology and clinical illness without impacting virus titers, but it has also played a role in immunopathogenesis, in spite of these protective benefits for T cells in MERS-CoV infection.[10,21]

SARS-COV-2

It is a new generation coronavirus that emerged in December 2019 in China. COVID-19 has a molecular structure that is 80% identical to SARS. COVID-19 is also known as SARS-CoV-2, which stands for severe acute respiratory failure syndrome-2. SARS-CoV-2 is the eighth zoonotic CoV virus capable of infecting humans, but it is also the first and only human coronavirus with pandemic potential.[22] It is known that the virus affects the human body as a consequence of consuming a bat sold as food in the market, and that it is quickly disseminated to other nations as a result of travel and sanitary neglect, beginning in the near vicinity. Fever, diarrhea, cough, muscular pains, shortness of breath, acute respiratory failure, and pneumonia can all lead to mortality. Patients with symptoms range in age from 25 to 60, with severity rising in those over 65. Quarantine periods for symptomatic patients were set at 14 days; however, due to adaptive immunity and vaccine-induced immunity, various types of immunity and vaccinations did not display symptoms, and quarantine durations were adjusted due to minor disease processes. Although the number of cases and fatalities in 2022 vary by nation, the illness is still active. As of September 7, 2022, there were 603,711,760 confirmed COVID-19 cases worldwide, with 6,484,136 fatalities reported to the World Health Organization.[23]

SARS-CoV-2, like SARS-CoV, must be identified and attach to the host cell's ACE-2 receptor in order to enter the host cell. The spike protein's strong affinity for the ACE-2 receptor allowed the virus to propagate quickly. Due to the SARS-CoV-2 receptor on this virus, human organs have been the focus of infection in lung alveolar epithelial cells and intestine surface absorbent cells (enterocytes), which have significant ACE-2 expression.[24,25]

In a study researchers tested seven different antiviral medications in their hunt for one that would effectively treat SARS-CoV-2 infections: ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, remdesivir (GS-5734), and favipiravir (T-750). As immunosuppressants, ribavirin and chloroquine were used to treat COVID-19. Chloroquine has previously been used to treat autoimmune disorders. It has extensive antiviral properties. Following antiviral medication studies, chloroquine and remdesivir demonstrated the most powerful antiviral responses with little cytotoxicity. The effective concentrations for chloroquine and remdesivir were reported to be 0.77 M for chloroquine and 1.13 M for remdesivir, respectively. Chloroquine inhibited SARS-CoV-2 infection in Vero E6 cells at both the viral entry and post-entry stages, whereas Remdesivir only inhibited the post-entry stage.[5]

Many techniques have been used while studying treatments and preventative measures. The creation and use of compounds that resemble the

virus-associated pyramids (VAPs) and bind to cellular receptors are a few of these. In order to prevent the virus from infecting the host at an early stage, VAP comprises anti-idiotypic antibodies, natural receptor ligands, and anti-receptor antibodies.[26]

Cellular immune responses of ancient coronaviruses were required and given special attention for the control and eradication of the SARS-CoV-2 infection. With high antibody levels in SARS-CoV infection, increased inflammation, and a diversity of clinical outcomes, it was indicated that T cells can be an essential mediator of disease management in the context of evidence from SARS-CoV and MERS.[27] Viral loads have been found to have a crucial influence in acquired immunity, genetic characteristics, and acute infection interferon responses. With early and prolonged inflammation, a sluggish reduction in viral load and high IFN-α, TNF, and IFN-γ21 levels were observed in the poor clinical data results.[28,29]

Although SARS-CoV-2 specific T cells have high IL-2 levels and $CD4^+$ cells are multifunctional, IFN-α production is lower than that of other respiratory viruses. Post-infection investigations demonstrate a fast rise in cytotoxic $CD8^+$ and $CD4^+$ T cell variants. Another feature that suggests long-term persistent immunity is that $CD4^+$ responses are somewhat greater than $CD8^+$ responses, a difference that may expand with time. However, it is also mentioned that there is antigen persistence, which means that the lifetime of the reactions may result in a milder course of reaction to the disease and its variants in the future, as well as the removal of the viral load over time. In conducted investigations, strong immunity was undoubtedly maintained after six months and beyond, but prospective studies revealed some degree of rethinking of T cell specificity with time. Virus-specific cells have been found to have a half-life of 200 days. Long-lived T cell responses have a $CD45RA^+$ effector-memory phenotype and a type-specific interferon transcriptome (a cluster of all RNA transcripts).[29]

Due to their interaction with epitopes, $CD4^+$ and $CD8^+$ memory T cell responses specific to SARS-CoV-2 exhibit diversity. It is generally accepted that humans have between 17 and 19 distinct epitope-specific responses. During an infection, this can prevent viruses from leaving or hiding from T cells. Furthermore, pre-COVID-19 coronavirus and human virus infections serve to lessen the severity of memory cell illness. It brings up the term "cross-recognition" because of the viruses in question (immunity). T cells detected SARS-CoV through other coronaviruses and conferred neutralizing immunity in tests. However, this scenario did not continue long, as it was shown that viral load was unaffected by cross-immunity in some populations due to environmental, geographical, and other comparable variables.[30]

IMMUNOTHERAPY IN THE TREATMENT OF COVID-19

While exploring for therapeutic instruments and approaches to combat the infection, researchers discovered a wide variety of alternatives. The connection between the "immune system" and the new generation of coronavirus deserves special notice among these. Although there is no specific information to explain, it is apparent that it has the ability to suppress severe and severe symptoms following infection.

Coronaviruses, as is well known, block the synthesis of interferon, which interacts against them with M proteins. As immunotherapeutic agents, interferons and standard plasma therapies have been employed. Interferons have the ability to prevent viral replication in infected cells. Interferons, commonly known as cytokines, can disrupt viral replication. Activating natural killer cells and macrophages also establishes a network of communication among the immune system's defense components. It promotes and controls the expression of major histocompatibility complex antigens in order to improve host cell defense. We know that symptoms like muscular pain, fever, and illness are caused by the release of interferon and other cytokines. Humans and animals have around twenty distinct IFN genes and proteins. Type I IFN is often classified into two classes: Type II IFN and Type III IFN. They are immune system defenders and regulators in the defense against viral infections, many of which have significant reactions.[26]

Conventional plasma therapy, which is also used for COVID-19 and has good outcomes, is another option. The immune system's memory cells take the lead; that is, a sick individual who has been exposed to a viral infection and recovered from the condition has gained humoral immunity. In order to get plasma from donors, the symptoms of COVID-19 must be totally gone 14 days before the donations, and the molecular test results isolated from the blood must be negative, as well as the microbiological and serological tests. Plasma therapies have been put into practice via testing methods. When these products are transferred to other patients, a passive immune system is created in the patients. The infection has

been neutralized and might be entirely eradicated from the body as a result of the approach. Violent damage was avoided by stopping the disease from spreading to other individuals.[31]

The procedure neutralizes the infection and allows it to be totally cleared from the body. Violent damage was prevented by preventing the disease from spreading to other individuals. The importance of the immune system is therefore well appreciated. Immunotherapy approaches are not only effective, but owing to a lack of research, they now manufacture monoclonal antibodies that attach to viral infections with their particular linkages and employ the immune system as a trigger. Some of the data we have gathered are the results of this procedure.[26-32]

In conclusion, the research for the new generation of coronavirus has been helped by the knowledge gathered from past corona infections, and the information gathered about the functioning mechanism and the defense against the virus has been offered by conducting research using today's most cutting-edge technology. Immunity was acquired and had similar effects as a result of memory cells. T cells will respond strongly not just to viruses but also to other diseases and cancers, owing to the power of the immune system and the immunological responses elicited by these viruses. It is not difficult to vaccinate T cells and develop various protective-therapeutic products with increased or expanded research.

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