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The Role of Cellular Immunity in the Protective Efficacy of the SARS-Cov-2 Vaccine

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1. Abstract

Several severe acute respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccines have been approved for clinical use. However, most studies use the SARS-CoV-2-neutralizing antibody titers induced after immunization as an evaluation indicator, and the role of cellular immune responses in the protective efficacy of vaccines is rarely mentioned. The synergistic effect of virus-specific humoral immunity and the cellular immune response helps the host fight against viral infection. A follow-up analysis of SARS-CoV-2-infected individuals indicated that the early appearance of specific T cell responses is strongly correlated with mild symptoms and that individuals with pre-existing SARS-CoV-2 nonstructural protein-specific T cells are more likely to be immune to infection. These findings suggest the important role of cellular immunity in the fight against SARS-CoV-2 infection. With the increasing number of new SARS-CoV-2 variants, which can escape from neutralizing antibodies and break through the immune barrier of recovered patients and vaccinated individuals, breakthrough infections are inevitable. As such, the goal of coronavirus disease 2019 (COVID-19) vaccines needs to be modified from the prevention of infection to the prevention of severe diseases caused by infection and possible sequelae caused by virus latency. The resistance of the immune system to the virus is also transferred from the extracellular space to virus-infected cells, i.e., there is a shift from a humoral immune response to a cellular immune response. Therefore, more attention to cellular immune responses may provide new ideas for designing effective vaccines. This paper summarizes the new ideas.

2. Research and Development Progress in COVID-19 Vaccines

In December 2019, a severe infectious pneumonia outbreak occurred in Wuhan, Hubei Province, China, and scientists ultimately determined that the infectious pneumonia was caused by SARS-CoV-2 [1]. On March 11, 2020, the World Health Organization (WHO) officially named the pneumonia caused by SARS-CoV-2 infection as COVID-19 and declared a global pandemic. According to WHO statistics, the number of confirmed COVID-19 infections worldwide has exceeded 300 million, and the number of deaths directly caused by SARS-CoV-2 has exceeded 5 million (https://covid19.who.int/). SARS-CoV-2 has caused immeasurable losses to the lives and economy of human society. A variety of therapeutic drugs, such as small molecule inhibitors and neutralizing antibodies, have been developed for COVID-19 [2, 3]. However, due to the high transmission efficiency of SARS-CoV-2 and the continuous emergence of drug-resistant variants, an effective vaccine is still needed to help humans establish an immune barrier to block the transmission of COVID-19.

SARS-CoV-2, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV), the three viruses that cause severe respiratory diseases in humans, all belong to the coronavirus family, so named because the Spike (S) proteins on the surface of the outer capsular membrane of the virus form a crown-like shape. A sense RNA genome and Nucleoprotein (N) and other nonstructural proteins of the virus are encapsulated within the envelope [4, 5]. SARS-CoV-2 is endocytosed into host cells mainly through the S protein binding to host cell surface Angiotensin-Converting Enzyme-2 (ACE2) [5, 6]. Therefore, the S protein is currently the main target for the design of therapeutic neutralizing antibodies and preventive vaccines, and the effectiveness of targeting the S protein has been confirmed by preclinical and clinical trials [4, 6-8].

According to official WHO statistics, as of November 2021, there

are 326 SARS-CoV-2 vaccines under development worldwide (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines). These SARS-CoV-2 vaccines are being developed based on both traditional vaccine platforms, for example, inactivated vaccines, and nontraditional vaccine platforms, for example, messenger RNA (mRNA) vaccines. Subunit vaccines, virus-like particles, and attenuated virus vaccines are considered traditional vaccine platforms, and vaccines prepared based on DNA and replicable and nonreplicable viral vectors are considered nontraditional vaccine platforms [9]. Although different vaccine platforms are used, most vaccines have achieved an effective rate of greater than 50% in clinical trials, a benchmark specified by the WHO [10]. Currently, vaccines approved for marketing are being administered around the world, but the effective rates of different vaccines are significantly different. Currently, the studies of approved vaccines mainly use the neutralizing antibody titers induced by vaccine immunization as an immune evaluation indicator. However, increasing data indicate that cellular immune responses play an important role in the clearance of SARS-CoV-2 and the alleviation of COVID-19 [11]. Next, the differences in the induced immune responses and the differences in protective efficacy are summarized for several vaccines with disclosed clinical trial results.

3. Humoral and Cellular Immune Responses Induced by SARS-Cov-2 Vaccines

China has developed three inactivated virus vaccines: BBIBP-CorV from Sinovac Biotech and WIV04 and HB02 from Sinopharm. Randomized phase III clinical data indicate that the protective efficiency of inactivated virus vaccines against disease symptoms after infection is between 51% and 79.4% [12-15]. The levels of neutralizing antibodies induced by inactivated vaccines after inoculation are similar to the levels of serum neutralizing antibodies in patients infected with SARS-CoV-2, and cellular immune responses targeting SARS-CoV-2 proteins, such as S and N, are induced [16]. Typical nucleic acid vaccines include mRNA-1273, developed by Moderna (USA), and BNT162b2, developed by Pfizer, with clinical inoculation doses of 100 μg and 25 μg, respectively. After inoculation with these mRNA vaccines, high levels of neutralizing antibodies are induced in vaccinated individuals, with titers that are approximately 2-4 times those in convalescent serum from SARS-CoV-2 patients. The mRNA vaccine also induce strong humoral immunity through type 1 T helper (Th1)-type Cluster of Differentiation 4 (CD4) T cell and CD8 Cytotoxic T Lymphocyte (CTL) immune responses [17-19]. In phase III clinical trials, the protection efficiency of both mRNA-1273 and BNT162b2 was greater than 90% [20]. Several recent comparative studies have reported that after immunization with mRNA-1273, BNT162b2, and Johnson & Johnson's Ad26.COV2.S adenoviral vector vaccine, the induced neutralizing antibody titers are sequentially decreased, and the induced CTL immune response is sequentially increased. The neutralizing antibody titers induced by the two mRNA vaccines decreases significantly after six months, while those of Ad26.COV2.S increase. For the three vaccines, unlike the antibody response that decreases as the time since vaccination increases, the cellular immune response does not decrease at 8 months after immunization [21]. A real-world effectiveness study found that compared with those after BNT162b2 vaccination, the infection rate, symptomatic patient rate, hospitalization rate, severe disease rate and mortality rate after mRNA-1273 vaccination were reduced by 1.23%, 0.44%, 0.55%, 0.10% and 0.02%, respectively [22]. A comparative study among the three vaccines based on hospitalization rate reported protective efficacies of mRNA-1273, BNT162b2, and Ad26.COV2.S of 93%, 88%, and 71%, respectively [23]. A comparative study of inactivated virus vaccines and BNT162b2 indicated that the level of neutralizing antibodies induced by inactivated vaccines was only one-tenth of that induced by the mRNA vaccine and that the cellular immune response induced by inactivated vaccines was about one-half of that induced by the mRNA vaccine; however, cellular immune responses target more SARS-CoV-2 proteins [16, 24]. The immune characteristics and protection efficiency of the above vaccines indicate that there are large differences in the induced humoral immunity and cellular immunity between vaccines created using different platforms. Compared with inactivated vaccines, nucleic acid vaccines can induce stronger humoral and cellular immune responses; among various nucleic acid vaccines, adenovirus-delivered DNA vaccines and electroporation-delivered plasmid DNA vaccines can induce strong cellular immune responses, while mRNA vaccines favor humoral immune responses. Recent studies have found that there is a correlation between a strong antibody immune response and the protection efficiency of the vaccine [25-27]; however, the correlation between the cellular immune response and the protection efficiency of a vaccine is still unclear. The needle-free intradermal injection of a plasmid DNA vaccine developed by India has achieved a protection efficiency of greater than 60% in India, where the Delta variant is the dominant strain; this protection efficiency is similar to that reported for mRNA-1273 and BNT162b2. Immune assessments indicate that the level of neutralizing antibodies induced by the DNA vaccine is slightly lower than that in the convalescent serum but that the cellular immune response is stronger, suggesting that the cellular immunity induced by DNA vaccines also plays a role in protecting the host against viral infections [28-30]. Next, the possible role of cellular immunity in host defense against SARS-CoV-2 infection is discussed.

4. The Role of Cellular Immunity in COVID-19

To understand the role of cellular immunity in the fight against SARS-CoV-2 infection and COVID-19, it is necessary to understand the cellular immune response of individuals after SARS-CoV-2 infection. First, SARS-CoV-2 infection is usually accompanied by a decline in absolute CD4 T and CD8 T cell counts.

A correlation analysis of disease severity and patient prognosis indicated that the smaller is the decrease in the CD8 T cell count, the milder are the symptoms and the better is the prognosis, suggesting that CD8 T cell count can be used as a marker of recovery for COVID-19 patients [31, 32]. Subsequent studies have found that multiple memory cell subsets targeting different SARS-CoV-2 proteins can be detected in the convalescent blood of COVID-19 patients and that the proportion of virus-specific CD8 T cells in patients with mild disease is high [33, 34]. Other studies have used single-cell sequencing technology to analyze the immune cell subtypes in the Bronchoalveolar Lavage (BAL) fluid of patients with different disease severities and found clonal CD8 T cell proliferation in the alveoli of patients with mild disease and a disruption in T cell subset distribution in critically ill patients, suggesting that after SARS-CoV-2 infection, the human body produces a memory cellular immune response against SARS-CoV-2 and a virus-specific CD8 T cell immune response alleviates symptoms rather than aggravates a patient's condition [35]. Increasing evidence indicates that the cellular immune response plays an important role in protecting the host and fighting against SARS-CoV-2 [36]. First, studies have found that cellular immune responses capable of recognizing the constituent proteins of SARS-CoV-2 exist in individuals who have never been exposed to SARS-CoV-2; however, the exact reason is unclear. Another study has shown that these individuals with pre-existing SARS-CoV-2 cellular immunity have a significantly reduced risk for SARS-CoV-2 infection [37, 38]. These data show to some extent that the cellular immune response can help individuals fight against SARS-CoV-2 infection, an observation that is consistent with the results of previous studies, i.e., vaccine-induced airway memory CD4 T cells can protect animals from coronavirus infection [39]. For patients infected with SARS-CoV-2, a correlation analysis of prognosis and T cell count and the S protein-specific T cell immune response indicated that after SARS-CoV-2 infection, a high average T cell count and the early appearance of S-specific T cells are positively correlated with a good prognosis and mild symptoms; there is no such correlation between the level of S-specific antibodies and patient symptoms. These results further indicate the role of cellular immunity in controlling the severity of symptoms in patients infected with SARS-CoV-2 [40, 41]. In summary, the cellular immune response may play an important role in the prevention of infection and the prevention of the severe illness after infection.

5. The Effect of the Cellular Immune Response on SARS-Cov-2 Variants

The SARS-CoV-2 genome is a single-stranded RNA that is prone to mutations during the replication process. With the prolonged COVID-19 pandemic, the SARS-CoV-2 genome has accumulated numerous mutations, and new variants have formed. These variants are classified into two types based on transmission ability, pathogenicity, and tolerance to vaccines and drugs, i.e., Variants of Interest (VOIs) and Variants of Concern (VOCs). The transmission ability and pathogenic ability of VOCs are enhanced, and VOCs have a certain tolerance to therapeutic drugs and vaccines. Currently, five VOCs, namely, Alpha, Beta, Gamma, Delta, and Omicron, have been recorded around the world. Among the mutations accumulated in SARS-CoV-2 VOCs, the primary concern is amino acid mutations in the S protein because the current vaccines and neutralizing antibodies mainly target the S protein. Mutations in the S protein are likely to reduce the protective efficacy of vaccines and the therapeutic effect of antibodies. The N501Y mutation in the Receptor-Binding Domain (RBD) of the S protein is present in four VOCs, i.e., Alpha, Beta, Gamma, and Omicron. Studies have shown that the N501Y mutation enhances the transmission ability of the virus by enhancing its affinity to the ACE2 receptor [42]. Moreover, the N501Y mutation also reduces the neutralizing antibody titers and neutralizing titers in the convalescent sera of COVID-19 patients [43, 44]. The N439K mutation in the RBD also enhances the affinity to ACE2 and the escape of SARS-CoV-2 from neutralizing antibodies [45]. Another mutation in the RBD, E484K, reduces the neutralizing titers of vaccine recipients and neutralizing titers in convalescent sera of COVID-19 patients by 2 and 4.5 times, respectively [46, 47]. The L452R and Y453F mutations enhance the fusion of the virus to promote virus reproduction and make the epitope insensitive to cellular immunity [48]. The current VOCs contain one or more of the above mutations. For example, the recently emerged Omicron variant contains many important mutations that promote immune escape, for example, N501Y, E484A, and L452R. The latest research indicates that the Omicron variant can escape or reduce the neutralization of almost all currently approved vaccinees and promising vaccinees under development, accompanied by increased morbidity and mortality; therefore, Omicron has attracted widespread attention [49].

In summary, the emerging SARS-CoV-2 variants mainly escape the humoral immune response, and some S protein mutations may also escape the cellular immune response. However, for humoral immunity, antibodies, as the main effector, can only recognize viral particles that are free in blood and tissue fluid by binding to viral surface proteins, such as S, and cannot recognize viral internal proteins and viral particles that enter cells. For current SARS-CoV-2 vaccines, the types and locations (sites) of targets are limited; therefore, S protein mutations on the surface of the virus reduce the protective efficacy of the current vaccines that mainly induce humoral immunity and neutralizing antibody titers. Different from humoral immunity, cellular immunity relies on T Cell Receptors (TCRs) on the surface of T cells to recognize the antigen sequences presented by Major Histocompatibility Complex (MHC) molecules on antigen-presenting cells; therefore, cellular immunity allows recognition of both the surface proteins and internal proteins of the virus and facilitates the lysis of cells invaded by the virus. Therefore, compared with humoral immunity,

cellular immunity can recognize a variety of antigens and can attack cells invaded by the virus. Currently, the possibility of escape from cellular immunity by the major S protein mutations is lower than that of escape from humoral immunity. Based on this, a recent clinical trial was conducted on a peptide vaccine prepared using epitopes of SARS-CoV-2 proteins recognized by cellular immunity to analyze the ability of the existing variants to escape from this vaccine; the results indicated that the vaccine can indeed induce strong cellular immunity and that the current major VOCs cannot escape the cellular immune response induced by the vaccine [50].

6. The Role of Cellular Immunity in the Prevention of Severe Illness Caused by SARS-Cov-2 Variants

The Delta and Omicron variants have higher transmission efficiencies than does the original SARS-CoV-2 strain. Many studies have shown that the neutralizing ability of convalescent sera in COVID-19 patients, sera in vaccinated individuals, and therapeutic monoclonal antibodies against Omicron is significantly reduced. Recently, in Israel and the United States, people who have been vaccinated with three doses and those who have recovered from COVID-19 are still becoming infected by Omicron, leading to a record number of new infections worldwide and further aggravating the prevention and control of the COVID-19 pandemic and social and economic pressures. Omicron has forced a reconsideration of the effectiveness of vaccines. However, vaccination, whether with an mRNA vaccine, DNA vaccine, adenovirus vaccine, or recombinant subunit vaccine, still provides protective effects against severe disease caused by the Delta and Omicron variants. The goal of SARS-CoV-2 vaccines has been modified from the prevention of infection to the prevention of severe disease caused by SARS-CoV-2 infection. During this process, we have found that the humoral immunity represented by serum neutralizing antibodies seems to lose efficacy, with further evidence stemming from the significantly reduced neutralization capacity of therapeutic monoclonal antibodies against Omicron. Therapeutic monoclonal antibodies can generally represent the effect of humoral immunity, and the ineffectiveness of therapeutic monoclonal antibodies against Omicron may partially indicate that humoral immunity has little effect on patients with severe cases. From this perspective, the preventive effect of vaccines against severe disease is mainly caused by cellular immune function.

In principle, the virus particles inside virus-invaded cells that are released after the cells are lysed by cellular immune responses still require antibodies for clearance. Therefore, the organic combination of humoral immunity and cellular immunity can maximize the immune protection. However, it is difficult for current vaccines to strongly induce both cellular immunity and humoral immunity. With the emergence of variants, boosters have been implemented in many countries and regions. Therefore, whether the booster should be the original vaccine or whether other vaccines with complementary immune responses would provide greater protection than a booster of the original vaccine have become issues that need to be explored. In summary, the SARS-CoV-2 pandemic provides a broad application scenario for vaccines from various platforms and provides a real-world test platform for many previously unevaluable immunization strategies. This unprecedented public health crisis requires bold attempts from humankind.

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