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Dendritic cell vaccines: A potentially effective strategy for the SARS-CoV-2 pandemic

Yichun Wang

Capital Normal University High School, Beijing, China

Yichunwang2401@163.com

Abstract. The evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains unpredictable, and there is an urgent need for new and effective vaccines to mitigate the pandemic at a time when traditional vaccines may not be sufficient to deal with SARS-CoV-2 variants everywhere. The dendritic cell (DC) vaccine, a novel cancer immunotherapy, has achieved good results in clinical trials alone or combination with other interventions. Due to its strong immune activation ability and the relevant targets found by existing studies, it is expected to become a new immunotherapy against SARS-CoV-2 infection. This article discusses the mechanism of dendritic cells in the immune system and its strategies in cancer treatment, as well as analyzes the role of dendritic cell vaccines in coping with SARS-CoV-2 infection, and compares the advantages and disadvantages of existing vaccine types, in order to explore the possibility of dendritic cell vaccines as an effective strategy against the SARS-CoV-2 pandemic.

Keywords: SARS-CoV-2, Dendritic Cell, Immunotherapy, Vaccine.

1. Introduction

Currently, the global pandemic caused by SARS-CoV-2 is continuing in stages. In order to combat SARS-CoV-2 and alleviate the pressure on global health and economic systems, several effective vaccines have been developed, produced, and applied. Although the vaccines currently approved for marketing have demonstrated above-expected returns in clinical trials [1]. However, with the continuous emergence of SARS-CoV-2 variants, the protection and safety of the original vaccines are gradually decreasing [2]. Therefore, there is a need to find new vaccine development techniques and response systems that can rapidly develop responses to specific viruses in the event of a potential future outbreak of infection, with the ability to both cure the infection and prevent future infections. One potential therapeutic approach is dendritic cell (DC) vaccines against SARS-CoV-2. DC vaccines are one of the approaches in the immunotherapeutic approach to cancer [3]. Compared to the traditional approach of directly dealing with cancer cells, cancer immunotherapy effectively utilizes the inherent ability of the patient's immune system to deal with cancer cells indirectly and gives the patient long-lasting immunity and the ability to adapt to tumor changes.

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2. Dendritic Cell Tumor Vaccine Strategies in Cancer Therapy

2.1. Dendritic cells and tumor immunity mechanisms

Dendritic cells are the bone marrow-derived cells of the hematopoietic system and are by far the most functional antigen-presenting cells (APC). Their functions are phagocytosis, processing, and presentation of antigens. Based on their different regions of origin, dendritic cells are classified into five subpopulations: plasmacytoid DCs (PDCs); classical or tissue-resident DCs (cDCs); Langerhans cells (LS); migratory DCs; monocyte-derived DCs (Mo-DCs). These DC subpopulations display different phenotypic and functional characteristics and have specific functions to direct the development of different immune responses [4]. As critical cells in activating the immune response, DCs are known for their efficient delivery of antigens to CD8+ and CD4+ T cells, respectively, and their expression of major histocompatibility complex molecule class II (MHC II). In addition, dendritic cells migrate between lymphoid and non-lymphoid tissues, directing effector T cells that receive antigens for lymphocyte homing and triggering inflammation by modulating cytokine and chemokine gradients. These effector T cells can destroy surface-display specific antigenic cells. With the proper cytokine stimulation (e.g., IL-7 and IL-15), some effector T cells can transform into memory T cells. These T cells can undergo rapid clonal expansion [5] upon re-encountering the antigen [6].

Recognition of tumor cells by the immune system is complex because tumor cells carry original antigenic markers to the extent that it is difficult for immune cells to distinguish them from normal cells, and immunosuppression in the tumor microenvironment helps tumor cells evade immunity [7]. In the triple anti-cancer mechanism of cancer immunoediting, the immune system acts as a suppressor and a stimulator of tumor cells. The tumor cells' immunogenicity will gradually weaken, leading to tumor immune tolerance and successful immune evasion. Therefore, in tumor treatment protocols, researchers have focused on how to induce immune cells to recognize tumor cells and enhance their immunogenicity accurately. Due to DC cells' role in initiating and regulating immune responses, it is being widely investigated for use in cancer immunotherapy [8].

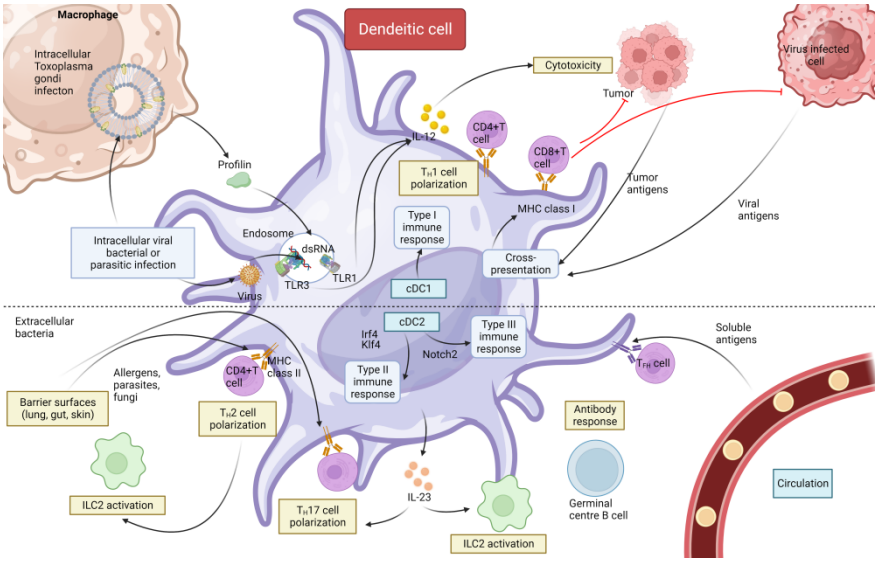

Figure 1. The mechanism of dendritic cells in the immune system of mouse.

2.2. Dendritic Cell Tumor Vaccine

Currently, there are three primary forms of DC vaccines: 1. in vivo DC induction; 2. in vivo induction with the addition of anti-DC antibodies; and 3. in vitro DC culture. Traditional vaccines mainly promote the maturation of immature DCs by adding antigens in the form of proteins or long peptides plus adjuvants that help DC maturation. However, the vaccines have had mediocre clinical results due to

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their lack of precise targeting. Currently, to improve the clinical efficacy of such vaccines, researchers are searching for vectors with high affinity for DCs. Compared with traditional vaccines, vaccines with increased anti-DC antibodies have more precise targeting of tumor cells and trigger a robust immune response. Therefore, this strategy is a promising one for the future. Finally, in vitro, DC culture involves extracting DCs from the host's blood or bone marrow, co-culturing them with IL-4 and Flt3 ligands as well as TNF- α in case of CD34+ cells and inducing DC differentiation, and finally injecting them into the host. In vitro cultured DC vaccines have shown remarkable results in in vitro experiments due to their highly high tumor cell targeting but still have limitations in clinical testing [8].

3. The role of dendritic cells in innate and adaptive immunity

The innate and adaptive immune response is the immune response that occurs in humans when defending themselves against an attack by a pathogen. When a pathogen enters the organism, monocytes-macrophages, neutrophils, and DCs capture and express its antigen. Subsequently, DCs migrate to the lymph nodes as primary antigen-presenting cells (APCs), directing T and B lymphocytes to develop a memory for that antigen. Adaptive immunity consists of both T-cell-mediated immunity and B-cell-mediated immunity. The critical role of the DC is to induce specific receptor expression on T and B lymphocytes and to present the corresponding antigen to them. DC has a higher efficiency in activating T cells than other APCs and is therefore considered one of the most essential APCs for bridging innate and adaptive immune responses [9].

4. Potential role of dendritic cells in SARS-CoV-2 infection

4.1. SARS-CoV-2

SARS-CoV-2 is an envelope-coated RNA virus belonging to the Coronaviridae family and the causative agent of COVID-19. There are three glycoproteins on the surface of the lipid membrane of this virus:

Spike protein (S) plays a role in receptor binding sites, cytolysis, and major antigenic sites; EnvelopeProtein (E), which binds to the cytosol membrane protein (M), is responsible for transmembrane transport of nutrients, release of nascent viral buds, and formation of the viral envelope and the outer viral envelope. There are also a few species of Haemaglutinin-esterase (HE). Among them, this virus mediates disease invasion mainly through spike protein (S) and determines the extent of infection of the host cell upon entry [10]. Therefore, this becomes one of the main targets of SARS-CoV-2 infection.

SARS-CoV-2 uses angiotensin-converting enzyme (ACE2) as a receptor, predominantly infecting ciliated bronchial epithelial cells and type II pneumocytes. Different SARS-CoV strains differ in their affinity for the human angiopoietin receptor protein (ACE2) and, therefore, in their infectivity and transmissibility. Some strains infect humans but cannot spread between humans, while others are highly infectious and can form cross-species transmission [11].

The transmembrane protease serine protease 2 (TMPRSS2) is one of the essential targets of SARS-CoV-2 infection. As a cell-surface protease, it significantly promotes viral binding to ACE2 receptors on the host cell surface, cutting and activating Spike(S) cuts. In addition, the expression level of TMPRSS2 is closely related to the replication ability of neocoronaviruses. Cells with high expression of TMPRSS2 were more susceptible to viral infection and had faster viral replication. Therefore, TMPRSS2 may regulate viral replication [12].

CD147 is likewise one of the primary targets of the SARS-CoV-2 vaccine.CD147 is a transmembrane protein found in various cell types, including immune cells, epithelial cells, and vascular endothelial cells. CD147 interacts with the C-terminal structural domain of Spike (S) and enhances the binding ability of the S protein to the ACE2 receptor. In addition to facilitating viral entry into cells, CD147 interacts with the nucleocapsid protein (N) and promotes nuclear nucleocapsid protein (N) localization. This may contribute to viral replication and transcription processes within the host cell. In addition, CD147 is involved in regulating fibrosis and angiogenesis processes, which are essential in severe cases of neo-coronavirus infection. It has been shown that interacting with matrix metalloproteinases (MMPs) may lead to the development of serious complications such as pulmonary fibrosis and acute respiratory distress syndrome (ARDS) [13].

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4.2. SARS-CoV-2 vaccine

SARS-CoV-2 vaccines are currently categorized as mRNA vaccines, adenovirus vector vaccines, inactivated vaccines, and protein subunit vaccines.

At the heart of an mRNA vaccine is an mRNA sequence that encodes a SARS-CoV-2 protein, such as the mRNA sequence of Spike(S). When injected into the body, it is transcribed into a protein. The newly synthesized viral proteins are captured by the intracellular antigen presentation mechanism and displayed on the cell surface. In this way, the immune system can recognize these proteins and generate an appropriate immune response. Major companies in the market developing mRNA vaccines include Pfizer-BioNTech's Comirnaty vaccine, Moderna's mRNA-1273 vaccine, and CureVac's CVnCoV vaccine. Comirnaty and mRNA-1273 use nucleotide modification and lipid nanoparticle technology to improve mRNA stability and cellular uptake efficiency, and both vaccines have demonstrated efficient protection in clinical trials. However, both vaccines are associated with some common side effects after vaccination, such as fatigue and headache.

Meanwhile, in the transportation conditions of the vaccines, both require extremely low temperatures to be transported. However, compared to Comirnaty, mRNA-1273 can be transported at slightly higher temperatures, but both increase the logistical costs and complexity. CVnCoV has shown a slightly lower protective effect than the previous two vaccines in clinical trials and lacks a significant high-technology breakthrough. However, less demanding conditions for vaccine transportation instead saved transportation costs.

Adenoviruses have a natural capacity for cellular invasion and enter cells by binding to the ACE2 receptor. An adenovirus vector vaccine is a vaccine that utilizes an adenovirus that has been modified to lose its ability to replicate as a vector and inserts key gene fragments of SARS-CoV-2 into the genome of the Adenovirus in order to deliver the genetic information of SARS-CoV-2, thereby triggering the human immune system to produce antibodies and immune response. In SARS-CoV-2, Adenovirus vectors commonly used are Adenovirus, such as Adenovirus type 5 (Ad5) or Adenovirus type 26 (Ad26). Johnson & Johnson's Janssen COVID-19 Vaccine and AstraZeneca AZD1222 vaccine from AstraZeneca are the primary adenovirus vaccines currently available. Clinical trials have shown that the AZD1222 vaccine is over 90% effective in preventing COVID-19 and has demonstrated better results in preventing severe illness and death. In addition, the vaccine does not require high transportation conditions and can be stored only at regular refrigerator temperatures. In comparison, the Janssen COVID-19 Vaccine offers mediocre protection but is more convenient because it is a single-dose vaccine.

Inactivated SARS-CoV-2 maintains the structural integrity of the virus but loses the ability to replicate it and is therefore classified as an inactivated vaccine. Compared to the other four vaccines, inactivated vaccines offer less protection; however, due to their long development and technical maturity, this class of vaccines has been developed quickly and safely. Among them, BBIBP-CorV from Sinopharm, CoronaVac from Sinovac Biotech, and Covovax from Novavax show similar results in all aspects without any significant difference in technical application.

The protein subunit vaccine packages only some of the proteins of SARS-CoV-2 and induces both humoral and cellular immunity. Humoral immunity mainly protects the body from infection by producing antibodies, while cellular immunity removes infected cells by activating T cells. There are currently fewer such vaccines on the market, including Novavax's NVX-CoV2373 vaccine, which has performed well in clinical trials but may face difficulties in distributing the vaccine globally due to production scale and supply chain constraints.

4.3. Dendritic cell-based SARS-CoV-2 vaccine

COVID-19 patients have abnormal IFN-19 responses and low IFN-1 and IFN-3 values. This finding may be related to pDC, which is the primary source of IFN-1 [14]. Therefore, it has been suggested that DC dysregulation plays a crucial role in SARS-CoV-2 immune escape, which makes DC a suitable target for vaccination. In addition, stimulation of DC generates a robust T cell response in which converted memory T cells respond to the virus for an extended period of time [15]. Thus,

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DC-based vaccines can acquire long-term immunity. Finally, DC-based vaccines can form B cells that recognize mutations, which may induce broader immunity in response to the rapid evolution of SARS-CoV-2. Thus, dendritic cell-based SARS-CoV-2 vaccines are a potentially effective strategy to combat the SARS-CoV-2 pandemic.

5. Conclusion

At present, although the global new crown pneumonia epidemic has improved, the intermittent recurrence of the new crown pneumonia epidemic still has serious harmful effects. People who are repeatedly infected with the virus will have progressively severe deterioration of health and weakened immunity, especially those with underlying medical conditions, which are more susceptible to this infection and its adverse effects. After discussing the mechanism of action of dendritic cells in the immune system, their application in the field of cancer, and the recently discovered potential relationship between DC dysregulation and SARS-CoV-2, we believe that dendritic cell-based SARS-CoV-2 vaccines have great potential.

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