Research Progress of Cancer Vaccine

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Abstract. Cancer has now become the major cause of pre-mature death around the world. In the past decades, research on tumor immunotherapy has advanced significantly, with numerous studies being evaluated in the clinical setting. The cancer vaccine is regarded as an advantageous approach in the immunotherapy of solid tumors. Preventive cancer vaccines can be injected in advance to reduce the risk of having cancer, while therapeutic vaccines can be used to trigger immunoresponse after having cancer. For example, recent studies have found that vaccination with one or more doses of the HPV vaccine produces more than 90 percent effective protection. In the meantime, the best and safest way to prevent hepatitis B is to get the hepatitis B vaccine. This paper introduces the mechanisms of both two types of cancer vaccines, and focuses on the explanation of the two cancer vaccine therapies. As a systematic review, it also highlights their current states and possible future improvements.

Keywords: Cancer; Preventive Vaccines; Cancer Treatment Vaccines; Cancer Immunotherapy.

1. Introduction

Malignant tumor, another name for cancer, is a term used to describe a condition that can occur in most of the body when aberrant cells lose control and cross their natural limits to infect surrounding tissues and other organs. According to statistics provided by World Health Organization (WHO), the number of those who die from cancer in 2020 is 9958133, to make it the major cause of pre-mature death [1]. The burden of cancer keeps increasing internationally, placing enormous physical and monetary strain on both human and healthcare systems. Many health systems in low - and middle-income countries do not have the capacity to address this contradiction, resulting in timely and effective treatment of patients, which is a factor in high mortality rates.

Researchers have worked hard to apply a similar approach to the prevention of cancer, creating a so-called "cancer vaccine," just as the invention of immunizations has opened up new paths [2]. A traditional vaccine is a man-made preparation for human immune system for certain kinds of diseases. One major component of which are attenuated or inactivated antigens, which can cause the formation of antibodies, matters in human body that can respond to immune infections. When these antibodies are formed, they can “memorize” the antigens and recognize them when similar viruses infect again. A vaccination for cancer, however, is one that either prevents or treats cancer. The preventive vaccines are like traditional vaccination, injecting the weakened viruses or bacteria into human body and “train” the immune system in advance. While the therapeutic vaccines, in contrast, are given to those who already have the disease and work to activate their immunoresponse to fight against a cancer.

Despite cancer vaccine, there are multiples of other immunotherapies regarding the treatment of cancer. So far, the top three most commonly used therapy for the treatment of cancers are surgery, chemotherapy, and radiotherapy. These therapies can successfully treat cancer in its initial stages, but they are typically useless when it comes to treating advanced or recurrent disease. When it comes to cancer vaccines, however, it is possible that this therapy can be helpful in treating the recurrent disease. CAR-T as an immunotherapy, also faces a hard nut to crack. It has strong toxicity, while both the inactivate vaccine therapy and personalized mRNA therapy do little harm to normal cells, or human body. Cancer vaccine is a milder way out. ICIs can activate the T cells leading to a wide range of irAEs. So, the injuries can happen in almost organ with varying frequency and severity, such as skin irAes, lower digestive irAEs, pulmonary irAES, hypothyroidism (hypophysitis), thyroid iRAEs, liver irAE, heart irAe, nerve irAEs, eye irAes, humidity irAES, kidney irAe, hematology irAE etc [3]. In

contrast, cancer vaccine works with little side effects. As a result, cancer vaccine is regarded as an ideal model for the treatment of cancer recently and many scientists are now digging into this field.

Through research, there is no work exist thoroughly talking about both vaccines. Because of that, students new to the field of cancer immunotherapy may not have a comprehensive view of this specific therapy of cancer vaccine. This paper introduces the research progress of both two cancer vaccines, and focuses on the explanation of two cancer vaccine therapies. As a systematic review, it also highlights their current research states and possible future improvements.

2. Vaccine for Prevention of Cancer

There are two main kinds of contributory components of preventive cancer vaccines: weakened viruses or weakened bacteria. Cancer vaccines that contain inactivated viruses are designed to treat those virus-caused malignant tumors, like certain kinds of cervical cancer. Approved in 2006, HPV (Human papillomavirus) vaccine is a great example as protecting woman against cervical cancer or other types of diseases caused by human papillomavirus. On the other hand, bacterial vaccines (vaccines containing parts of bacteria) can be used to treat those cancer caused by bacterial infections. For example, according to scientific study, Helicobacter pylori can cause stomach cancer so that this bacterial-caused cancer can be prevented through early injection of Helicobacter pylori vaccine [4].

2.1. Mechanism

A vaccine is a biological therapy whose efficacy and safety have been rigorously reviewed and validated. Vaccines are usually made from microbes, their toxins, or proteins on their surface, where a substance similar to the disease-causing bacteria is usually present. A pathogen is a bacterium or virus that can infect the human body and cause disease. The antigen part triggers the production of antibodies, which are an important part of the immune system. It helps our bodies defend themselves. Every antibody in the human body is used to recognize an antigen, and once the body is first exposed to an antigen, the immune system produces antibodies against that antigen [5]. Although patients are still susceptible to illness [5]. When antibodies that target antigens are created, they interact with the body's immune system as a whole to eliminate the pathogen and halt the sickness. As part of its initial defense against an antigen, the body can activate B cells, which can produce antibody; these cells keep working even after the pathogen has been destroyed [5]. The person's immune system will respond fastly in the future if they are exposed to the hazardous infection, preventing those illnesses from occurring [5]. The process of injecting weakened pathogens to create antigens without doing substantial harm in human body is called vaccination.

2.2. Types of preventive vaccines

An attenuated vaccine is a vaccine that is made "alive" or still alive by reducing its virulence. The infectious agent loses virulence through attenuation [6]. In fact, these vaccines are much like natural infections, producing an effective immune response. Only one or two doses of live vaccines can produce lifetime protection [7]. The antigenic components that make up inactivated vaccines are taken from pathogens like viruses or bacteria that have been rendered inactive, which means they make use of the killed version of the germ [7]. Inactivated vaccines induce a protective immunity to the pathogen when given to the patient [8]. Nowadays, this specific type of vaccine can be used to treat Hepatitis A, Flu, Polio, Rabies, and many other diseases [7]. Toxoid vaccines are primarily bacterial toxins that have been chemically reprocessed to become innocuous while retaining their immunogenic qualities, which means that rather than injecting the germ, they generate immunity to the germ components. By separating the bacterial exotoxin, toxins are turned into vaccines [9]. After being isolated, exotoxins' toxicity is subsequently reduced or rendered inactive—either by heat or by formaldehyde—to create toxoids [9]. Anti-toxoid antibodies are produced as a result of toxoid vaccination; these antibodies can attach to the toxin and counteract its harmful effects [9]. Toxoid vaccines provide protection against diphtheria and tetanus [7]. These vaccines use only part of the

bacteria's antigen to stimulate the body to produce enough antibodies or to activate an adaptive immune response [7]. Whooping cough, Pneumococcal disease, Meningococcal disease, Shingles, and Haemophilus influenzae type b disease are all preventable diseases with the use of these vaccines [7].

Viral vector vaccines have been extensively studied. One of the viral vectors, Adenovirus, is most used in vaccines, which were currently under clinical development [7]. To prevent COVID-19, vaccines targeting viral vectors are used [7]. Recent Ebola immunization uses viral vector technology [7]. Outer membrane vesicle, or OMV, is a naturally occurring pathogen that is secreted from Gram-negative bacteria [10]. Despite seeming like a pathogen on the surface, OMV cannot really cause disease because it is not a living organism. The main antigenic components needed to trigger a protective immune response are present in OMV since they are predominantly made up of bacterial outer membrane components [11]. Because of this, OMV were rapidly suggested as a platform for vaccines after their discovery [11]. Recently the three are extensive research on the topic of OMV vaccine. Certain malignancies brought on by viruses can be prevented in healthy individuals by vaccinations. These vaccines, like those used to defend against chicken pox or the flu, protect the body from these viruses. HPV and HBV vaccines are the only cancer-prevention vaccines recognized by the FDA.

2.3. Application

2.3.1. Human Papillomavirus Vaccine

HPV is the main risk factor for invasive cervical cancer. The majority of sexually transmitted infections, including HPV, have been connected to over 10 different malignant tumors, including oropharyngeal, vulvar, anal, and cervical cancers [12]. One of highest incidence malignancies among women, especially in low-resource nations, where the disease is most prevalent globally, is cervical cancer. Currently, administering HPV vaccinations together with regular cervical screening is the effective technique [13]. For the sake of public health, the HPV vaccine is essential. Bivalent, quadrivalent, and nonavalent HPV vaccinations are all readily available [13, 14], as shown in table 1.

Table 1. HPV Vaccines approved by FDA [14].

Human Papillomavirus Quadrivalent (Types 6,11,16,18) Vaccine, Recombinant	Gardasil
Human Papillomavirus 9-valent Vaccine, Recombinant	Gardasil 9
Human Papillomavirus Quadrivalent (Types 16,18) Vaccine, Recombinant	Cervarix

Individuals between the ages of 9 and 26, and those between the ages of 27 and 45, may have risk of HPV infection, and current HPV vaccine guidelines cover these individuals [12]. Vaccines against HPV are quite immunogenic. Young women who were HPV seronegative before immunization have extraordinarily high vaccine efficacy and efficiency rates [12]. Among adult women and women who had received vaccinations, vaccine effectiveness was reduced regardless of HPV DNA [12]. The decrease in the morbidity of HPV 6/11/16/18 in vaccinated women compared to the control group demonstrated the effectiveness of the vaccine [12]. In addition, HPV 6/11/16/18/31/33/45/52/58 reduce is the price of vaccination and bivalent and tetravalent vaccine cross protection a direct result of the [12]. In countries with high vaccination rates, the benefits of vaccinating women of childbearing age who are at high risk of HPV exposure have been clearly demonstrated. Vaccination with one or more doses of HPV vaccine can produce more than 90% effective protection [15].

2.3.2. Hepatitis B Vaccine

Hepatitis B is a liver condition brought on by the HBV. A lifelong infection, liver failure, liver cancer can be brought on by the hepatitis B virus (HBV) [16]. Currently, the best and safest way to prevent hepatitis B is by getting vaccination, according to CDC [16].

People who receive the hepatitis B vaccine, whether young or old, can prevent hepatitis B virus infection and have a good protective effect. All people under the age of 19, 19 and 59, and people 60 years of age and beyond who have risk factors for hepatitis B infection are encouraged to get it [16].

The HBV is also available to adults 60 years of age and older [16]. All individuals should undergo a hepatitis B test once in their lives, according to the CDC [16].

3. Vaccine for Treatment of Cancer

Therapeutic cancer vaccines are used by doctors to treat cancer once it has already developed rather than to prevent it. Therapeutic vaccinations function by teaching human body to defend itself against aberrant cells, including cancer cells that it produces on its own. Therapeutic cancer vaccines subject human immune system to distinctive markers that distinguish cancer cells from normal cells, known as antigens, linked to a particular cancer type. These vaccines stimulate antigen-presenting cells, which are subsequently activated by the immune system, providing the ability to recognize and eliminate cancer cells. Specific antigens are coupled with an adjuvant, a chemical that alerts the immune system that cancer is present, to create therapeutic cancer vaccines.

3.1. Mechanism

Tumor antigen vaccines teach the immune system to kill cells that carry the antigens utilized in the vaccine, in a manner similar to how viral immunizations function. While the antigens for viral vaccinations are generated from viruses or cells that have been exposed to the virus, the antigens for tumor antigen vaccines are acquired from cancer cells. Antigens known as tumor antigens are only found in cancer cells and not in healthy cells. Tumor antigen-containing vaccines should be created in a way that instructs the immune system to target cancer cells before healthy cells.

Examples of cancer-specific tumor antigens include protein-derived peptides which are generally absent in healthy cells but are activated in cancer cells, or peptides with cancer-specific mutations. APCs, Dendritic cells, engulf vaccine antigens, convert them into epitopes, and then transport these epitopes to T lymphocytes through Major Histocompatibility Complex proteins. The adaptive immune system is activated in cancer cells or peptides with cancer-specific mutations if T cells recognize the epitope as alien. When vaccine antigens are absorbed by APCs, such as dendritic cells, they become epitopes that the adaptive immune system recognizes as foreign targets, as shown in fig 1.

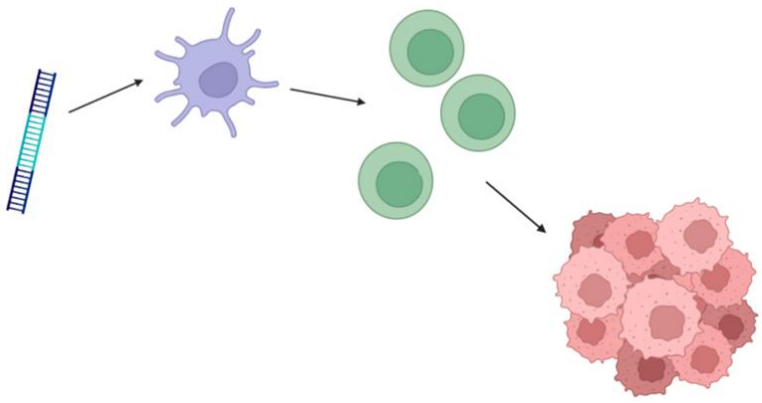


Fig 1. Mechanism of Cancer Treatment Vaccine [17].

3.2. Applications

Prostate cancer that has spread is currently approved for treatment with sipuleucel-T [18]. It is applied to men with hormone-resistant cancer who exhibit few or no symptoms [18]. Sepulture-T functions by mixing cells derived from a prostate cancer patient with a growth factor [19]. The patient receives the cells again, which may prompt T lymphocytes to attack prostate cancer cells [19]. The production of testosterone by the body is reduced by hormones such enzalutamide, apalutamide, or abiraterone combined with prednisone and LHRH analogs [19]. The proliferation of prostate cancer cells that depend on testosterone may be inhibited as a result [19]. Patients with metastatic castration-resistant prostate cancer who are using NHA and LHRH analogs may experience a greater reduction

in prostate cancer cell death while taking sipuleucel-T concurrently with new hormonal treatments [19].

The BCG vaccine, which is used to prevent tuberculosis infection, is also used to treat early bladder cancer [20]. The specific mechanism can be understood as when a vaccine made from inactivated TB bacteria is injected into the bladder in liquid form, it helps stimulate the activation of immune system cells that can kill tumor cells [20]. Nadofaragene firadonevec is approved for treatment of early-stage bladder cancers [20]. It consists of a weakened, engineered virus that activates an immune response [17]. It was delivered into the bladder through a catheter [20]. T-VEC is an oncolytic virus-based vaccine that is used to treat advanced melanoma that cannot be completely removed with surgery [20]. It is made of a virus that has been genetically modified to promote an anticancer immune response [20].

4. Limitations and Future Perspectives

4.1. High production cost

Since the therapeutic vaccine is personalized, it costs more than traditional means of treatment for the reason that the cancer-specific antigens are difficult to find.

In the future, scientists can work to reduce the cost through finding those DNA segments that are shared by tumor cells but not exist among normal cells. If the antigen exists on both normal and abnormal cells, the vaccine will attack the normal cells too. This causes unwanted side effects. As a result, finding more correct and accurate targets to reduce long-run cost is of great importance for the success of treatment.

4.2. Combination Method

Sometimes, immune-suppressive cells are present in large tumors, which can reduce the effectiveness of immune cells that are activated to combat them because larger or more advanced tumors are hard to get rid of using only one vaccine. As a result, vaccines can be used in conjunction with other therapies in order to trigger better immune response.

Combined strategies including immunotherapy, chemotherapy and radiotherapy were studied [21]. A potential combination method is to make use of the safety and long-term efficacy of cancer vaccines to support other kinds of therapy. It will then give a more cost-friendly and long-lasting effect.

5. Summary

Recently, cancer has become the second major cause of pre-mature death nowadays. There are two main sorts of cancer vaccines, one for prevention, and another for treatment. Cancer prevention vaccines focuses on giving the body a weakened immune “shot”. On the other hand, therapeutic vaccines work to help the immune system to recognize the tumor cells. After distinguishing, T-cells can kill the cancer cells and therefore cure the cancer. Through research, cancer vaccination is a good way to both prevent and treat cancer due to its great efficacy and low health risks. In addition, once injected, the patient is not likely to have the same tumor again. However, most of cancer vaccines are only in basic research or pre-clinical trials. Only a few types of cancer vaccines, such as HPV, HBV, BGC, and Stipuleucel-T, are approved by FDA. In the future, researchers have to reduce the cost of designing personalized cancer vaccines by looking for more targets that are commonly mutated. What’s more, combining tumor vaccine with other immunotherapies is conducive to a better therapeutic effect of larger tumors.

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