Virus vaccines in cancer immunotherapy: Principles, and Clinical manifestations

Yanning Li *

Dalhousie University, Halifax, Canada

* Corresponding Author Email: yn761201@dal.ca

Abstract. Immunotherapy has been of extraordinary significance in cancer treatment. There are many cancer vaccines, and viral vaccines are one type of cancer vaccine. Viral vaccines provide an encouraging solution for the treatment of solid tumors, which cannot be achieved by traditional therapies. Cancer therapy and prevention rely on the availability of virus vaccinations. Existing cancer vaccines have had remarkable success in treatment and prevention. This article summarizes several feasible cancer vaccines and their clinical applications, and analyzes the current limitations and future development of viral vaccines. This article's summary of virus vaccines can provide a helpful reference for future cancer vaccine research.

Keywords: Virus Vaccine, Cancer Therapy, Cancer Prevention

1. Introduction

Cancer is the leading cause of death around the globe. Every cell in the human body is susceptible to cancer, and the disease might begin in any one of them. When the body needs new cells, human cells divide and multiply to produce more of them. Cells die and are replaced as they get old or damaged [1]. Carcinoma is the most frequent kind of cancer.

Surgery, chemotherapy, and radiation therapy are the most common therapies for cancer (Figure 1). And targeted therapies, immunotherapy, et cetera. Although chemotherapy and radiation therapy are the most prevalent cancer treatments, their adverse effects are more severe. Chemotherapy kills or slows the growth of rapidly dividing healthy cells. Cancer cells are killed by radiation treatment using high doses of radiation. Radiation impacts neighboring healthy cells in addition to killing or slowing the formation of cancer cells. Inflicting damage on healthy cells might have harmful side effects [2].



Figure 1. Cancer Treatment Options [3]

Immunotherapy is an emerging technology for cancer treatment, of which viral vaccines are one of the more common. Scientists can alter viruses in the laboratory and use them as a vehicle to deliver cancer antigens into the body. They alter the viruses so that they do not cause severe disease. The altered viruses are called viral vectors. Some vaccines use viral vectors to deliver cancer antigens into the body, and the immune system responds to the viral vector [4]. Viral vaccines are currently divided

into two major categories: preventive and therapeutic. Hepatitis B (HBV) vaccinations protect against hepatitis B virus infection and help prevent HBV-associated liver cancer. Vaccinations against human papillomavirus (HPV) prevent certain HPV infections and the development of HPV-associated malignancies of the anus, cervix, head and neck, penis, etc. BCG is a vaccination that employs microorganisms that have been weakened to boost the immune system, and BCG bladder infusion treatment has been approved for individuals with early-stage bladder cancer. The treatment is known as Talimogene Laherparepvec (T-VEC), which is also known as IMLYGIC, performs a role that is analogous to that of a viral vaccine. It employs a modified herpes labialis virus (herpes simplex virus) by altering the genes that instruct the virus on how to act. It can now treat individuals with melanoma skin cancer who are unable to undergo surgical removal of their cancer.

2. BCG

The Mycobacterium Bovis in the BCG vaccine was first discovered in 1904, used in humans in 1921, and adopted by the League of Nations Health Committee (predecessor of the World Health Organization) in 1928. BCG has been a standard early bladder cancer treatment since 1977 [5].

There are approximately 382,660 new diagnoses of bladder cancer each year around the world, with 227,526 recent instances occurring annually in industrialized nations. Bladder cancer is the second most frequent tumor of the urinary tract. The age-standardized incidence of bladder cancer worldwide is 10.1/100,000 males and 2.5/100,000 women. The worldwide death rate for males is 4 per 100,000 and for women, it is 1.1 per 100,000 [6]. BCG therapy is intravesical immunotherapy. BCG therapy is usually performed after TURBT (transurethral resection of bladder tumors), a bladder procedure to remove any visible cancer [7]. It is exclusively used to treat early-stage bladder cancer, including carcinoma in situ (in its original place), bladder cancer, and bladder cancer that has not yet infiltrated the bladder wall muscles (NMIBC). Because BCG requires contact with cancer cells to be effective, it is unable to treat bladder cancer that has migrated to other bodily locations. When BCG comes into contact with cancer cells, it works. It is injected directly into the bladder with a catheter, reaching cancer cells and "activating" the immune system (Figure 2). It targeted the cancer cell by attracting immune system cells to the bladder [8].

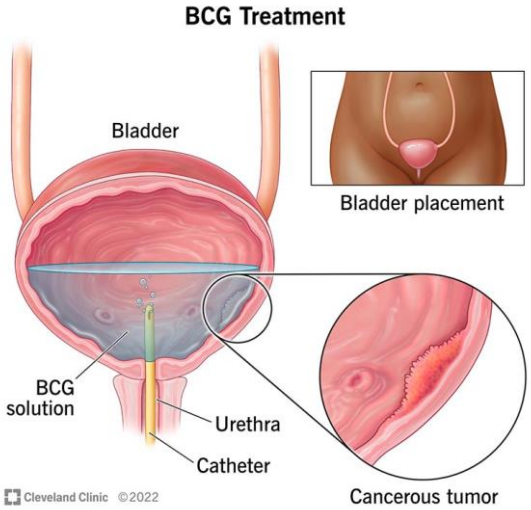


Figure 2. BCG Treatment [7]

BCG treatment is intended to activate the immune system to combat cancer. However, as with other cancers, there is still a 40% chance of recurrence after treatment of bladder cancer with BCG therapy [7]. About 35% of patients who fail the first BCG cycle find long-term success with a second BCG treatment. However, further BCG treatments had a lower chance of success (20%) and a higher possibility of tumor growth [9]. BCG therapy is also associated with many side effects. Common side effects include mild blood in the urine, low-grade fever, fatigue, frequent urination, muscle aches,

and a burning sensation in urination. There are also less common complications, such as high fever, loss of bladder control, urinary tract infections, and BCG sepsis [7]. Although these complications are unlikely to occur, they exist.

3. T-VEC

T-VEC, commonly known as IMLYGIC, is a topical local immunotherapy that eliminates skin and lymph node melanoma cells. The most lethal kind of skin cancer is melanomas. The relative 5-year survival rate from the time of diagnosis for localized, early melanoma is greater than 99 percent, 68 percent for regional spread, and 30 percent for distant spread [10]. Unresectable lesions of the skin, subcutaneous tissue, and lymph nodes can be treated locally with IMLYGIC, a genetically engineered lytic viral therapy. Oncolytic viruses are effective in cancer immunotherapy because they can promote the death of tumor cells and elicit a protective antitumor response from the host.

Oncolytic viruses are novel cancer treatments that use live viruses in their natural and changed forms. It can promote local and systemic anticancer immunity while preferentially replicating in tumor cells before lysing them. T-VEC is an oncolytic virus derived from a changed type 1 herpes simplex virus (HSV), which is used by IMLYGIC. It is meant to multiply specifically in tumor cells and then lyse them, while simultaneously increasing regional and systemic antitumor immunity. Although lysing viruses may infect both cancer and normal cells, only normal cells possess a method to eliminate the virus. As the virus replicates, it induces the rupture and death of cancer cells. After a three-week break from therapy, the patients received four milliliters of T-VEC injected at a concentration of 106 plaque-forming units (PFU) per milliliter. All successive injections were provided every two weeks with a maximum of 4 mL containing 108 PFU/mL. The injection of nodal or subcutaneous metastases was assisted by ultrasonography [11].

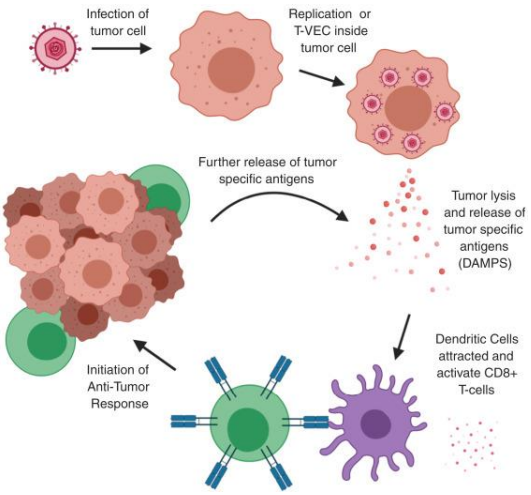


Figure 3. Mechanism of viral oncolysis and immunologic response [12]

According to the OPTiM trial, a randomized phase III research with 436 participants, the DRR was considerably greater with IMLYGIC than with GM-CSF (16.3% v 2.1%; P0.001). The IMLYGIC arm had a much higher overall response rate (26.4 percent v 5.7 percent; p0.001). It took an average of 23.3 months for patients treated with IMLYGIC to reach median OS, while it took an average of 18.9 months for patients treated with GM-CSF [13]. The vast majority of reported side effects were mild to moderate in intensity and vanished within 72 hours. Cellulitis was the most common grade 3 or higher adverse event. When IMLYGIC was administered to patients, malaise, chills, fever, and nausea were among the most common side effects (25 percent). No more than 2% of all adverse reactions reached grade 3, with chills, vomiting, and limb pain occurring in only 6%, 5%, and 4% of adverse reactions [13].

4. HPV

HPV stands for human papillomavirus. It is believed to be responsible for cervical intraepithelial neoplasia (CIN) and cervical cancer. It used to be the woman's most severe concern about cancer-related mortality, and men also can cause cancer by HPV. As of August 2020, the number of women diagnosed with cancer because of HPV is 21,100, and the number of men diagnosed with cancer is 14,800 per year in the U.S. In addition to cervical, vulvar, vaginal, etc., HPV can cause a wide range of cancers. Over 90 percent of malignancies caused by HPV and anal, vaginal, cervical, and precancerous lesions of the vulva (abnormal cells that might cause cancer) can be prevented by the HPV vaccine [14].

There are two types of human papillomaviruses: those that infect human epithelial cells and those that infect human cells (Figure4).

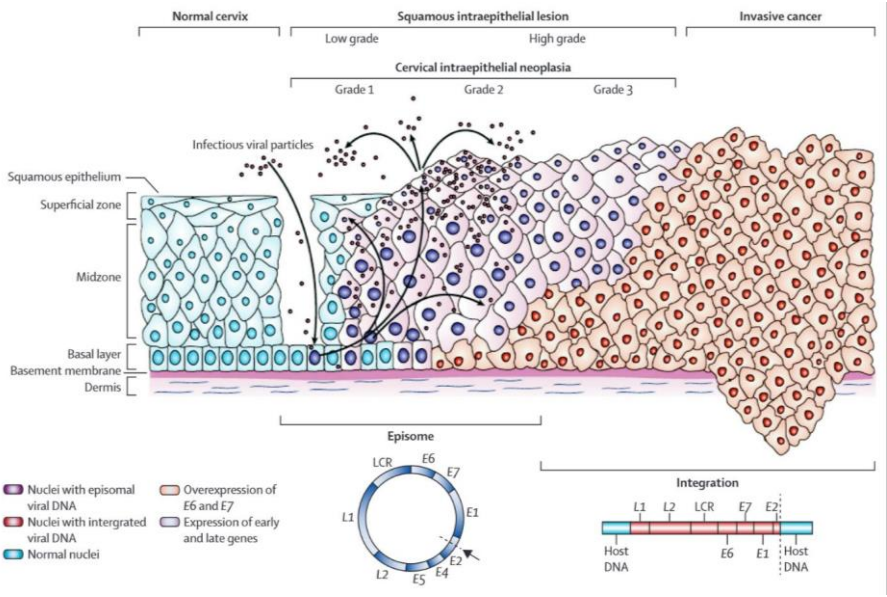


Figure 4. Human papillomavirus lifespan and genome organization [15]

HPV enters deep into the basal epithelial cells through microscopic pores on the surface [15]. After several hours of infectious internalization. Viral DNA is stripped and released to integrate into the host's genome or become extrachromosomal episomes. During the early stages of its life cycle, early genes of human papillomaviruses are expressed, of which E6 and E7 are the two most critical factors that help to overcome the host replication machinery. The natural replication mechanisms of differentiating basal epithelial cells are insufficient for virus survival. It is possible that E6 and E7 block inhibitors of cell cycle and apoptotic pathways (p53 and RB) in some high-risk papillomavirus infections, which might lead to genomic instability and ultimately lead to HPV-infected cells becoming malignant invasive carcinoma cells [16]. As it sheds the upper epithelium, basal epithelial cells, which previously carried the replicating viral genome, gradually replace the cells in the cells of the middle and superficial layer. It expressed late genes such as L1 and L2 to wrap the viral genome and form a native visual. After that, the shed virus can start a new infection [15].

The HPV vaccinations that are now available are all preventative. They are one of two forms of preventative cancer vaccines. They are bivalent (GSK Cervarix for type 16 and 18), quadrivalent (MSD Gardasil for type 16, 18, 6, and 11), and 9-valent (Gardasil, MSD, for type 6, 11, 16, 18, 31, 33, 45, 52, and 58). They are mixtures of HPV L1 self-assembling virus-like particles (VLP) [16]. Following immunization, antibodies may prevent HPV vision before it reaches the growing basal cell layer of the epithelium [17]. Ongoing research is evaluating the next generation L1 VLP vaccination, which includes additional carcinogenic HPV strains. Clinical trials are also underway for an anti-HPV minor capsid protein L2 vaccination. Despite the fact that several vaccines targeting HPV E6/E7, as well as other immunotherapies, are under rapid development, scientists still lack an effective therapeutic vaccine that can help our immune system destroy particular HPV or HPV-related tumors

without surgery. The capacity to evade the immune system may result in an off-target effect, the resemblance between the E6/E7i and homogenous cancer repressors may result in cytotoxicity, and the scarcity of a suitable way for the vaccine to gain access to the early-stage virus may also affect its efficacy.

5. HBV

HBV is the virus that causes hepatitis B, which may be prevented with a vaccination (HBV). Hepatitis B can be transmitted by blood, sperm, or other bodily fluids from an infected person to an uninfected person. Sex and drug injection equipment can be shared; delivery can also be a source of transmission. The presence of persistent HBV infection has been linked to the development of chronic hepatitis, cirrhosis, and hepatocellular cancer (HCC). The convent of HCC is a two-hit model. There are direct and indirect causes of HCC, the direct cause being the viral molecular mechanism contributing to this cancer and the indirect cause being the cellular response (immune response) to viral proteins in infected hepatocytes. With HBV infection, the indirect causes may play a significant role. The direct viral mechanism also creates a pro-tumorigenic environment [18].

The oncogenic role of HBV lies precisely in its life cycle. The latent phase of the HBV life cycle is thought to be central to developing chronic and persistent inflammation of HBV and other HCC conditions. Nonetheless, because HBV infection may persist for decades and the resulting immune-mediated damage can result in major alterations to the hepatic milieu, they are two of the most important risk factors for developing HCC. Unfortunately, doctors still do not have a curative solution for chronic HBV-induced human hepatocellular carcinoma. All people can do is prevent the development of HBV infection with three doses of vaccination. The absence of HBV viral therapies and the restricted therapeutic options for HDV necessitate further investigation. There have been three generations in the development history of currently available HBV vaccines. From the beginning, scientists have used inactivated HBV particles derived directly from the serum of infected individuals. This was the first generation of HBV vaccine as a natural human glycosylated one, comprising HBsAg, Pre-S1, and Pre-S2 antigens. However, this makes it the most controversial and difficult to cover more areas for safety and political reasons: this vaccine is intact HBV particles from recovered individuals, and it is too potent to establish an immune response. Because it is a plasma-derived vaccine, its safety in transmitting blood-borne pathogens such as HIV inevitably causes public anxiety, not to mention its high cost. As a result, second-generation vaccines were created and are now available on all continents. Using recombinant protein VLPs technology, companies can produce clean, safe, inexpensive, specific, and mass-produced HBsAg virus-like particles in yeast or mammalian CHO strains. The third generation HBV vaccine builds on the previous generation by producing recombinant HBV VLPs, including HBsAg, Pre-S1, and Pre-S2, in CHO cells. In addition, it has improved the envelope and antigen presentation systems to be more similar to the natural virus confirmation and have better immunogenicity. In clinical studies, the Sci-B-Vac vaccine is a third-generation vaccination (Figure 5).

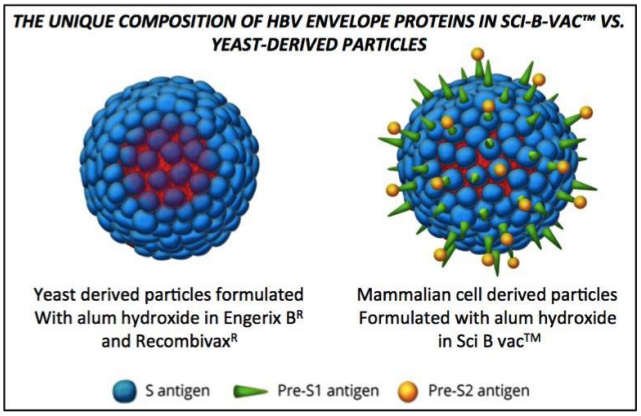


Figure 5. The third generation HBV vaccine [19]

6. Conclusions

Viruses can be immunogenic, stimulating an immune response, tumor-specific, and its ligand-receptor response principle allows scientists to design artificial scavengers for cancer cells. It can also be cell-accessible vectors, providing several practical approaches and platforms. It has many specific properties that scientists can exploit to treat cancer. As immunotherapies for cancer, viral vaccines offer quite an encouraging solution for dealing with solid tumors, which would be out of reach for immunotherapy as traditionally defined. It has proven true that T-VEC and BCG can treat cancer, and HPV and HBV vaccines can prevent cancer. Even more exciting is that this remains an area that has received relatively little attention. It certainly deserves more and more in-depth exploration and recognition. In the future, virus vaccines will gradually become a standard cancer therapy for people's continuous efforts. Also, more and more cancers will be treated and prevented by virus vaccines.

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