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Virus Particles and Virus-like Particles-based Vaccines for Cancer Treatment

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Abstract. Virus vaccines in cancer immunotherapy are a promising area in cancer treatments, utilizing viruses to augment the immune response against cancer cells and induce tumor cell death. Oncolytic virotherapy known as virus-based vaccine is an innovative cancer treatment leading by oncolytic virus (OVs) which has shown encouraging outcomes over the last twenty years. This therapy is able to effectively combine with other therapy, for instance radiotherapy and car-t cell therapy. Virus-like particles (VLPs) serve as an antigen presentation platform in cancer therapeutic and preventive applications. Compared with oncolytic virus vaccines, VPLs-based vaccines can directly uptake by immune cells without any infection. Initial virus-based and virus-like particle-based cancer treatments have shown little effectiveness, but progress in molecular engineering, genomics, and molecular analysis offer hope for improving and rejuvenating virus-vaccines in medical settings. However, there are still obstacles like OVs delivery and VLPs modifications in preclinical or clinical trials. It is crucial to figure out the research status and the difference of OVs-based and VLPs-based vaccines.

Keywords: Virus vaccines; cancer; oncolytic virus; virus-like particles.

1. Introduction

Cancer is caused by genetic mutations that result in transformation of cell structures, functions, and unrestricted cell proliferation. As neoplasm undergoes growth and development, distinct subsets of malignant cells may experience adaptations to tumor microenvironment (TME). In addition, some aggressive trails may form during this process. For instance, heightened metabolic activity, facilitation of angiogenesis, accelerated nutrition absorption, and metastasis. As a result, cancer cells inside a malignancy persistently undergo changes in response to specific stimuli such as fluctuations in blood circulation and the immune system of the host leading natural selection which causes the resistance of cnacer cells to medication and immunological responses [1].

Immunotherapy for cancer has shown significant success in recent studies. Cancer vaccines belong to a kind of immunotherapy. They may be categorized into two types: preventative vaccinations, such as human papillomavirus (HPV) vaccines, which aim to prevent cancer from occurring, and therapeutic vaccines, that are designed for patients who already have cancer. Oncolytic virus (OVs) was initially noted more than a century ago that individuals with certain viral infections saw a regression in their malignancy. According to Osaka University research, 37 out of 90 patients with terminal cancer who got therapy with non-attenuated mumps virus showed tumor regressions. Since then, oncolytic viral therapy for cancer has drawn more attention from researchers [2]. Recently, important tools to research the biology of viruses have been made available by revolutions in recombinant DNA technology, which has advanced biological treatments for cancer and produced a new generation of cancer therapies [3].

Vrius-like particles-based vaccines are preventive and therapeutic. It is commonly known that human oncoviruses, such as the hepatitis B virus (HBV), human papilloma virus (HPV), human T cell lymphotropic virus type I (HTLV-1), and others, are linked to and/or cause 15-20% of all human malignancies globally. Thus, prophylactic vaccinations capable of eliciting protective immune responses specific to the antigen and long-term immunological memory unique to the oncovirus have been developed. On the other hand, several therapeutic cancer vaccines based on VLPs have

undergone assessment in both preclinical and clinical studies for several cancer types, including colorectal, pancreatic, breast cancer, and melanoma. Moreover, the utilization of modern technology has facilitated the detection of neoantigens that are distinct to each patient. These neoantigens can then be utilized to modify the surface of VLPs in order to create customized anticancer vaccinations [4]. Hence virus vaccine has a positive influence for treatments of tumor with immunosuppressive and drug resistance properties. This paper is aimed to compare oncolytic virotherapy and virus-like particles for cancer treatments, and corresponding application and challenges in these areas.

2. Organization of the Text

OVs possess the capability to induce tumor cell lysis through multiplication within the cytoplasm, releasing offspring virions that then infect adjacent cells and lead to cascade of malignant cell death. Some researchers have shown that cancer cells possess multiple unique receptors that viruses can bind to and utilize in order to selectively invade the cells. For example, some cancer cells have a high susceptibility for virus infection because of an abundance of intercellular adhesion molecule-1 (ICAM-1) and decay-accelerating factor [5]. When tumor cells are lysed by a virus, tumor-associated antigens and neoantigens (TAAs and TANs) are released. Antigen-presenting cells, such as dendritic cells (DCs), have the ability to uptake and process these antigens upon infiltration of the tumor. Subsequently, TAAs are transferred onto the surface of these cells, where they interact with the major histocompatibility complex (MHC) class I and class II, ultimately establishing contact with T cell receptors. In turn, triggers T cell response specific to the tumor against a variety of the released antigens, result in secreting IL-2, IL-12, and interferon gamma (IFN-γ) with activating corresponding immune cells (CD4+, CD8+, and cytotoxic T lymphocytes) promotes various types of immunogenic cell death (ICD), such as necrosis, proptosis necroptosis and immunogenic apoptosis, which is followed by the release of danger-associated molecular patterns (DAMPs) and various pathogen-associated molecular patterns (PAMPs). They serve as "danger" and "eat me" signals when pattern recognition receptors on innate immune cells, such as dendritic cells (DCs) and natural killer (NK) cells, identify them. More DCs are drawn to the tumor microenvironment by this signaling, which in turn promotes the recruitment and maturation of T lymphocytes specific to tumors within the tumor microenvironment [6,7]. The DAMP most frequently linked to cancer is HMGB1. Tumor-derived HMGB1 suppresses CD8+ cytotoxic antitumor cells by increasing the production of IL-10 by regulatory T cells that function as important inhibitors of antitumor activity [8]. To enhance curative effect OV can be modified such as cytokine-expressing OVs armed with interleukin (IL) or uploading the granulocyte macrophage-colony stimulating factor (GM-CSF) gene, and some pathogenic genes are knocked down in order to reduce virus pathogenicity [9].

2.1. Herpes Simplex Virus

The Herpes simplex virus is classified as an alpha herpesvirus and possesses a double-stranded DNA genome of around 152kb. It also contains around 30kb of genetic material that encodes non-essential genes, which can be substituted with designed transgenes. HSV-1 replication occurs in the nucleus, although there is no occurrence of insertional mutagenesis. The FDA has approved Talimogene laherparepvec (T-VEC) as the initial oncolytic virus for cancer treatments. It is mostly applied for the melanoma treatment [5,10]. This kind of oncolytic virus was created by removing the ICP34.5 and ICP47 genes and replacing them with two copies of GM-CSF gene which express corresponding cytokines that activate T cells by DCs. Protein kinase R (PKR) activation in normal cells inhibits viral replication by phosphorylating eukaryotic initiation factor 2 (eIF2). The disturbed PKR-eIF2 pathway in melanoma cells leads to uncontrolled cell proliferation and increased susceptibility to viral replication. ICP34.5 induces dephosphorylation of eIF2 and inhibits PKR-triggered interference with protein synthesis. ICP34.5 deletion in T-VEC causes a non-productive infection in normal cells, allowing its replication to target cancer cells specifically. ICP47 reduces immune-mediated death of the host cell, therefore promoting the growth of HSV-1. Removing ICP47 enables the immune system

to target the virus in healthy cells, while also boosting the presence of MHC1 on melanoma cells and amplifying the display of tumor antigens by the infected cancer cells [3.10].

The T-VEC based mono-virotherapy has showed remarkable result in old patients. Because of low body function and underlaying diseases, it is unsuitable for old people to take chemotherapy, radiotherapy, and other traditional therapies for cancer treatments. Thus, a study was conducted to analysis T-VEC based vaccine for old patients. Outside of formal trials, twelve individuals received the T-VEC treatment with a median age of 83 years (75–89 years), and the efficient outcome had shown at the end of the research: A total of four patients (33%) experienced partial response (PR), three patients (25%) experienced progressive disease (PD), two patients (17%) had stable disease (SD), and two patients (17%) had attained complete remission (CR). It demonstrated high effectiveness in cancer treatments [11].

While T-VEC-based vaccine as a single treatment has previously demonstrated its effectiveness, evidence is mounting that T-VEC and immune checkpoint inhibitor (ICI) together may have further anti-tumor effects, because the T-VEC exhibit the ability to boost the immune system and transform cold tumor to the hot tumor which is more sensitive to immune response, hence enhancing the tumor's vulnerability to ICI therapy [12]. One study evaluated the effectiveness when ipilimumab (antiCTLA-4) combined with T-VEC therapy. All the tumors that were injected into mice models and around half of the tumors that occurs spontaneously within the organism (mice) were shown to be curable with ipilimumab monoclonal antibody and T-VEC therapy. After the injection, injected and non-injected tumors revealed a substantial rise in immune cells (CD3+ and CD8+ T cells), and ex vivo investigations demonstrated that these cytotoxic T-lymphocytes were specific to the tumors. Only the injected tumors showed increased levels of neutrophils, monocytes, and chemokines; in contrast, the experiment with anti-CD8 antibodies led to the depletion of CD8+ T cells, which eliminated all systemic efficacy and markedly reduced local efficacy. In a clinical trial, it was observed that patients with unresectable melanoma who were administered combination therapy exhibited a higher overall response rate and CR with 13% compared to those who got ICI solo therapy with CR 7% ($p = 0.033$) [10].

It is also possible for the resultful cancer treatments combining T-VEC with metabolism inhibitors. The effect of the treatment would improve when T-VEC combine with cancer cell metabolic inhibitors. The functional characteristics of local T cells and NK cells are significantly compromised by the buildup of tissue lactate and the absence of glycoses in the TME. Therefore, preventing the metabolism of cancer cells is essential for the therapy of cancer. Numerous pharmacological inhibitors that lower cancer cell metabolism have been found; these agents may work in tandem with virotherapy. Certain inhibitors may have little impact in this situation or may even promote OVs replication. One crucial step in the process of glycolysis is the overexpression and activation of hexokinase 2 (HK2), the first enzyme that limits the rate of glycolysis. Oncolytic alphavirus M1 replication was increased by lonidamine-induced HK2 inhibition. When combined with a glycolysis inhibitor, OVs based therapy can increase the demise of cancer cells. For instance, blocking HK using NDV and D-Mannoheptulose, a particular hexokinase inhibitor, reduced glycolysis and increased apoptotic cancer cell death [13].

2.2. Vaccinia Virus

Oncolytic vaccinia virus (VVs) is a new therapeutic approach being used in cancer therapy. VV is a certain type of double strains DNA virus which has genome roughly 200kb only replicating in the cytoplasm. With the aim of reducing virulence in the host cells, the thymidine kinase (TK), that is required for nucleic acid duplication, vaccinia growth factor and vaccinia type I IFN-binding protein were deleted. Additionally, enhanced cell lysis and specific replication in cancer cells was stimulated by VVs with an active EGFR-RAS pathway [5].

Numerous studies have shown that VVs-based treatments have proven to be advantageous in addressing various kinds of cancer. With the aim of improving the therapeutic efficacy of VVs-based

vaccine for preclinical and clinical trials, genetic engineering may be used to substitute the TK or VGF gene with specific therapeutic genes. Vaccinia virus of Guang9 strain expressing GM-CSF inserted with IL-24 gene (VG9-IL-24) into the TK locus has a positive anti-tumor effect for colorectal cancer and hepatocellular carcinoma. VG9-IL-24 suppressed the growth of colorectal cancer cells in the G2/M phase of the cell cycle and raised the number of apoptotic cells in vitro. Several apoptotic signaling pathways allowed VG9-IL-24 to trigger cancer cell apoptosis. After cell lysis, immune response is heightened [14]. Additionally, there was a notable enhancement of the antitumor effectiveness of the oncolytic VV in the A594 lung cell line, when the VVs equipped with T cell engagers composed of two single-chain variable segments targeting CD3 and the malignant cell surface antigen EphA2 [6].

However, monotherapy for VVs-based virotherapy is still inadequate in effectively controlling the growth of tumor. Although in some study using VV vectors alone as cancer vaccines have manifested generally unsatisfactory outcomes, there has been an improvement in clinical effectiveness when VVs vaccinations are used in conjunction with other therapy [15]. The integration of vaccinia virotherapy with chemotherapeutic medicines represents a highly promising approach for the cancer treatments. An instance of synergistic effect was observed when VVs was combined with paclitaxel, which was facilitated by the secretion of type I interferon shortly after infection and high-mobility group protein B1, that is released following cell death [16]. In an aggressive glioblastoma (GB) model, radiation with oncolytic ΔF4LΔJ2R vaccinia virus produces immunological protection and strong anticancer effectiveness. One essential component of first-line treatments for GB is radiotherapy which could significantly inhibit cancer cells growth. However, because the resistance of center group of GB cell to radiation and failure to detect invasive cancer cells, local recurrence frequently occurs. Thus, in this circumstance ΔF4LΔJ2R vaccinia virus is introduced to activate immune system and kill cancer cells with radiation resistance property. A mouse experiment demonstrated the combination ΔF4LΔJ2R VVs with radiotherapy remarkably increased the survival relative compared monotherapy and PBS controls. The PBS treatment had a median survival of 29 days, whereas radiation had a median survival of 39.5 days. The ΔF4LΔJ2R VACV treatment had a median survival of 41 days. The combination treatment had an unknown median survival, but it was more than 76 days ($p < 0.01$) [17]. For pancreatic cancer treatments, an effective systemically delivered therapy regimen is created by combining CAL-101, VVs armed with murine IL-21(VVL-21), and ICI of α-PD1. The administration of VVL-21 resulted in an increase in effector CD8+ T cells within the tumor, an increase in natural killer cells in circulation, and the ability to induce macrophages transform into an M1 phenotype both in vitro and in vivo. Consequently, the immune repressive TME is weakened. Utilizing a monoclonal antibody α-PD1 allowed for an increase in the regime's anticancer efficaciousness. To improve intravenous administration of VVL-21, CAL-101 was used to block macrophage absorption of the virus [18]. Clinical investigations have demonstrated significant efficacy in the combination of oncolytic VVs with adoptive cell transfer therapy (ACT). The efficacy of ACT in the management of hematological tumors has demonstrated encouraging outcomes. Nevertheless, the effectiveness of the CAR-T approach in treating solid tumors has been limited due to the inadequate recruitment of CAR T-cells to the tumor location and the immune suppressive TME. Thus, the combination strategy with VVs can solve this problem by altering immune inhibitory ability of TEM. The Tian Tan strain of vaccinia virus, which targets tumors and has a deleted TK gene (TTVTK), was strategically injected with IL-21 (rTTVTK-IL21) in conjunction with CAR-T cell in a mouse B16 melanoma model. The tumor volume of the combination therapy group decreased after 6 days of injection OVV, and 25 days later of the injection the tumor volume was about 100 mm3. By comparison the tumor volume of the signal treatment groups, and the control group grew to more than 500 mm3 ($p<0.05$). This combination demonstrated a strong anti-tumor effect compared to using a single therapy [9].

2.3. Adenovirus

Adenovirus (Adv) is a member of the Adenoviridae family. It is a nonenveloped virus that contains double-stranded DNA and has a genomic size of around 35 kb. Adenovirus-based the integration of

OV into the host genome is not observed, and thus presents a low risk of insertional mutagenesis. Due of its extensive genome, it possesses the capacity to accommodate manmade alterations [5]. Similar to other OVs, modified adenovirus has demonstrated efficacy in repressing tumor growth and facilitating tumor remission with the combination of traditional cancer therapy (chemotherapy and radiotherapy) and cancer immunotherapy. An engineered oncolytic Adv coding IL-2 (Ad5/3-E2F-d24-vIL2) combined with gemcitabine and nab-paclitaxel chemotherapy for the pancreatic ductal adenocarcinoma treatment. In vivo, a notable enhancement in survival rates was seen, with 80% of mice exhibiting long-term survival, in comparison to the use of chemotherapy alone and Adv-based mono-virotherapy [19]. The use of adenovirus with (tumor necrosis factor-α) TNFα and IL-2 enhances the ICI effectiveness of programmed cell death protein1 (PD-1) checkpoint in lung cancer. This combination therapy had an excellent outcome in a mouse tumor model of cell line LL/2. After 10 days treatment, the growth of the normalized tumor volume was minimum with approximately 500%, followed by the figure for PBS control group, virus only group and anti-PD-1 only group at roughly 1400%, 1550% and 1800% respectively ($p < 0.05$). Moreover, the combination group exhibited an increase in the proportion of cytotoxic NK cells that expressed granzyme B (GzmB) and IFNγ, as well as operational NK cells that expressed the transcription factor T-bet [20].

2.4. Challenge

OVs face the challenge of achieving optimal tumor regression by striking a balance between antiviral and anticancer immune responses. Cross-reactive antibodies may potentially be present and hinder the efficient reproduction of viruses when they have been previously exposed to viruses belonging to the same family known as preexisting immunity. In addition, it is worth noting that advanced-stage tumors may necessitate multiple OVs injections, perhaps leading to the development of neutralizing antibodies. Researchers are currently exploring methods that involve the use of protective coatings made of chemical polymers, liposomes, or cell-derived nanovesicles to physically shield OVs from immunological factors. Nevertheless, the storage of these OVs with protective coatings poses challenges and incurs elevated manufacturing expenses. Utilizing ex vivo OV-loaded cells is a method to restrict the early elimination of the virus. Tumor-infiltrating immune cells, including dendritic cells, mesenchymal stem cells, macrophages, and T cells, have the ability to invade tumor sites and serve as cellular carriers for OVs, but this may be limited by lack of experiments of certain cancer types and virus clearance in long term treatments [5, 21].

Additionally, some OVs are engineered with IFN with the aim of enhancing anti-tumor effect. However, the intrinsic antiviral characteristic of IFN has a detrimental effect on the suppression of oncolytic virus or the elimination of tumors. Hence, it is imperative to comprehend the mechanism underlying IFN modulation by oncolytic viruses. Defining this mechanism holds immense importance in enhancing the anticancer efficacy of oncolytic viruses [22].

The primary obstacle for OVs-based vaccines is the virus delivery. Intratumoral injections are the most effective and secure method for administering OVs in preclinical or clinical trials. While intratumoral injection does not induce the migration of OVs to metastatic tumors, it does stimulate the host's antitumor responses and leads to the control of metastatic tumors, a phenomenon known as the abscopal effect [5]. However, due to the limited efficacy of the abscopal effect in treating metastatic tumor, it can be replaced by intravenous injection which facilitates the extensive dissemination of OVs infection to all lesions, hence obviating the necessity for localization technicians, particularly in cases where tumors are not physically reachable. Whereas the clearance of viral particles by neutralizing antibodies may occur prematurely, so restricting the impact of treatments. Additionally, the ideal dosage remains uncertain due to the dilution of the virus in the peripheral circulation, resulting in unexpected bioavailable titers at the tumor site [21].

3. Virus-like Particles

Virus-like particles (VLPs) are nanoparticles composed of viral structural proteins that undergo spontaneous self-assembly. VLPs may serve as a platform for the surface presentation of several epitope classes in cancer therapeutic applications. They are categorized as enveloped or nonenveloped based on whether they have a lipid envelope which can be modified with particular ligands on their interior cavity or exterior surface to deliver peptides, genes, and medications to immune cells or specific tissues [4]. Virus-like particles (VLP) have the potential to be used as drug transportation carriers because of their biocompatibility, solubility, effective absorption, and small size. The VLP productivity, integrity, scalability, manufacturing expenses, and purity of the product, which are essential for vaccine stability, effectiveness, and safety, may be influenced by the choice of expression host and fermentation process. VLPs manufacturing may be accomplished using many methods. Chimeric VLPs can be created by genetic insertion. The coat protein undergoes genetic fusion with the foreign antigen, leading to the production of a chimeric VLPs inside a host system that is compatible. The formation of chimeric VLPs can also be achieved by the chemical bonding of exogenous peptides onto the surface of VLPs [23]. When compared to OVs, VLPs have the ability to transport a diverse range of medicinal payloads [24].

For the cancer immunotherapy, compared with OVs, VLPs can stimulate immune system in a direct manner. VLPs efficiently interact with DCs, which are the most potent cells responsible for presenting antigens. This interaction leads to the exhibition of viral antigens on MHC I and II molecules. DCs that have been activated go to lymph nodes to stimulate CD4+ T helper cells and CD8+ cytotoxic T cells that are specific to the antigen. Following by which, CD4+ T helper cells undergo differentiation into two primary subtypes, namely Th2 and Th1, which subsequently guide adaptive immunity by secreting proinflammatory cytokines towards either a humoral or a cellular immunological course, correspondingly [25]. Furthermore, B lymphocyte can also absorb VLPs. The VLPs-based vaccination has a well-structured and recurring surface geometry, which enhances its ability to be opsonized and phagocytosed by B cells through CD21 on cell surface. B cells engage in interactions with and get assistance from T helper (TH) cells following the uptake of VLPs through B cell receptors. The interaction between CD4+ T cells and B cells is of paramount importance in the efficient generation of passively transmitted antibodies that generate plasma cells, as well as in the maturation of memory B cells. Several VLPs contain RNA that is packaged during their formation, which activates TLR7/8 in B lymphocytes. This activation leads to a change in isotype towards protective TH1 IgG subclasses, ultimately resulting in the death of tumor cells [23, 25].

3.1. Preventive Vaccine

The virus types of human papillomavirus (HPV), hepatitis B (HBV) are widely recognized as prevalent causative agents of cancer. Immunizations targeting carcinogenic viruses are the sole effective treatment employed at the community level to prevent malignancies. At present, there exist three officially sanctioned preventive vaccinations that are produced from the viral capsid protein L1 (L1-VLPs). These vaccines are classified as bivalent, quadrivalent, and nonavalent. The global adoption of vaccinations has effectively prevented approximately 90% of HPV infections. HBV vaccines commonly have a small surface antigen called HBsAgS, along with an adjuvant consisting of aluminum hydroxide. Over the course of time, several versions of anti-HBV vaccinations have been created and have shown positive outcomes in both preclinical and clinical studies [4].

3.2. Therapeutic Vaccine

VLPs have attracted much interest as a promising vaccine platform because of their possession of a substantial concentration of repeating antigenic epitopes on their surface, which effectively induce both humoral and cellular immune responses. Therapeutic cancer vaccines have been created using VLPs that exhibit the B and T epitopes of ovalbumin, specifically the OVAB and OVAT peptide that are generated through somatic mutations within tumor cells. These peptides have the ability to activate the cytotoxic lymphocyte (CTL) response. OVAB-VLPs, in conjunction with the adjuvant

poly (I:C) and OVAT-VLPs can inhibit tumor growth by inducing a robust humoral immune response against the neoantigen.

The AX09 vaccination, which utilizes bacteriophage MS2 VLP, incorporates the human ECD3 peptide into VLP coat protein. ECD3 is one of the extracellular domains of the xCT protein which is overexpressed by breast cancer stem cells. This modification has been shown to significantly reduce the growth of breast tumors [26]. Cucumber mosaic VLPs that contained a tetanus toxin peptide decorated with microcrystalline tyrosine had greatly inhibitory effects on tumor development in a mouse model of B16F10 melanoma. 15 days after tumor transplant the tumor weight and volume were seen to be less than 500mg ($p<0.0001$) and 500mm3 [27]. A combination therapy of Anti-OX40 antibody and hepatitis B core VLPs has been observed to impede colon cancer in a mouse model. 20 days following tumor injection the tumor volume of combination therapy group was only about 400mm3 which was twice smaller compared with monotherapy group ($P < 0.05$) [28].

3.3. Challenge

By comparison with OVs, the synthesis of VLPs is a complex process that necessitates the expression and self-organization of viral proteins within host cells. This poses a problem as the viral constituents must possess noncytopathic properties and undergo appropriate folding and glycosylation processes in order to facilitate accurate self-assembly and genuine antigen presentation [24]. The aforementioned issues are expedited due to the inherent hydrophilicity of T cell epitopes, which renders them susceptible to aggregation. Furthermore, it is worth noting that the chosen linked, or fused epitopes may not elicit the most effective immune responses necessary for safeguarding against malignancies [25]. Additionally, there is exists a deficiency of studies in therapeutic vaccines, especially for combination therapy. Further investigation is warranted to explore the efficacy of combination therapy in various cancer models, with the aim of elucidating the antitumor effects under diverse conditions.

4. Conclusion

Virus particles-based vaccines (oncolytic virotherapy) and virus-like particles-based vaccines are new-type cancer immunotherapy which have been testified positive result in preclinical and clinical trials. Their emergence has provided new ideas for cancer treatments. When confronted with cancers that exhibit resistance to medicine and immune responses, or when patients are unable to undergo conventional therapy, this therapeutic modality may be considered optimal. However, the combination of traditional therapy (chemotherapy and radiotherapy) or other immunotherapy (ICI, ACT) and with virus particles-based vaccines has better results in anti-tumor effect than application of signal therapy. With the aim to improve therapeutic impact virus particles are usually engineered with gene expressing cytokines (IL, GM-CSF). It is remarkable that T-VEC is capable of combining with tumor metabolism inhibitors to change immunosuppressive TEM that holds potential for future treatment. VLPs-based vaccines are common vaccines to prevent cancer causing by virus infection, but as therapeutic vaccines, there is a lack of study particular for the combination therapy. Additionally, for both oncolytic virotherapy and therapeutic VLPs-based vaccines, there is scarcity data of application in patience, which means most of these therapies are still in preclinical trials or just in the early stage of clinical trials. Some obstacles are impeding the development. The most eager problem for oncolytic virotherapy is to locate an effective delivery method and regarding VLPs it is significant to optimize the assemble of viral component.

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