International Research Journal of Advanced Engineering and Science
ISSN (Online): 2455-9024

Viruses: A Novel Anticancer Weapons

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***Abstract*—** *The most crucial role in anticancer therapy using viruses is the oncolytic virus. The oncolytic virus is an anticancer therapy that reverses the characteristics of cancer cells that repeat infinite proliferation. When the oncolytic virus infects normal cells, the infected normal cells activate the apoptosis pathway and do not allow the virus to replicate inside cell. On the other hand, when the oncolytic virus infects cancer cells, the oncolytic virus is allowed to replicate due to the apoptosis resistance of the cancer cells, and the cancer cells are lysed. Furthermore, the oncolytic virus stimulates antigen-presenting cells around tumor tissue to induce the activity of immune cells to kill cancer cells.*

***Keywords*—** *Immunotherapy, Oncolytic Virus, HSV-1(Herpes Simplex Virus type-1), G47Δ, T-Vec, JX-594.*

I. INTRODUCTION

Immunotherapy is an innovative treatment approach that empowers the human immune system to overcome cancer. Immunotherapy is the most radical of several new approaches that recruit the immune system to attack cancers. Immunotherapy may help boost the body's immune response. New approach uses virus to trigger the immune system to react to the cancer cells. Immunology-based therapy is rapidly developing into an effective treatment option for a surprising range of cancers[1]. The powerful immune cells may be blocked by inhibitory regulatory pathways controlled by specific molecules often called immune checkpoints.[2,3] The development of a new therapeutic class of drugs that inhibit these inhibitory pathways has recently emerged as a potent strategy in oncology[2]. Three sets of agents have emerged in clinical trials exploiting this strategy[4]. These agents are antibody-based therapies targeting cytotoxic T-lymphocyte antigen 4 (CTLA4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1)[5]. These immune inhibitors have demonstrated extensive activity as single agents and in combinations[6]. Clinical responses have been seen in melanoma, renal cell carcinoma, small cell lung cancer, and several other tumor types[6]. The improvement of methods for efficient delivery and regulated expression of genetic material into mammalian cells has been a major objective of molecular and cellular biology, Viral oncolysis over the last 30 years and is still an area of intensive research[3,6]. Virus-derived vectors are one of the most promising transfer tool into tumor[7]. Herpes simplex virus type-1 (HSV-1) is one of the most promising viral platforms for oncolytic vectors that can target to tumor[8]. Enhanced efficacy and specificity of HSV-1-based vectors may be achieved by maintaining their activity during active viral replication in tumor[8].

II. ONCOLYTIC VIRUS

Oncolytic virus therapy has recently been recognized as a promising new therapeutic approach for cancer treatment[7,8,9]. An oncolytic virus is defined as a genetically engineered or naturally occurring virus that can selectively replicate in and kill cancer cells without harming the normal tissues(**Figure 1**)[9]. In contrast to gene therapy where a virus is used as a mere carrier for transgene delivery, oncolytic virus therapy uses the virus itself as an active drug reagent[8]. A study demonstrated that a genetically engineered herpes simplex virus type I (HSV-1) with a mutation in the thymidine kinase (TK) gene replicated selectively in cancer cells and was useful for treating experimental brain tumors[7]. Cellular TK is not expressed in quiescent, normal cells, but is expressed abundantly in rapidly dividing malignant cells[10]. Thymidine kinase (TK) is an enzyme that catalyzes the phosphorylation of deoxythymidine to deoxythymidine monophosphate[10]. Its activity is highest in G1-S translation checkpoint and then declines rapidly in the G2 phase of the cell cycle[11]. In cancer cells, the fetal isoform of TK is present in high levels in the cytoplasm and is cell-cycle regulated[12]. HSV-1 has a 158-kb genome with approximately 80 genes whose products are responsible for viral infectivity and replication, subversion of host antiviral mechanisms, and assembly of the structure of progeny virions.[13] The wild-type virus is naturally cytotoxic, destroying host cells by lysis in the course of its life cycle. HSV-1 can infect and replicate in a wide variety of cell types by interaction of its surface glycoproteins with cell surface receptors[8]. Most HSV-1 OVs are derived from laboratory virus strains and are engineered in various ways[7]. After the OV enters tumor cells, a coordinated viral transcriptional program leads to OV replication, cell death or lysis, and escape of progeny virions that can go on to infect other surrounding cells in subsequent waves (Figure 1**)**[9]. The HSV-1 viral genome consists of two unique sequences, unique long and unique short (denoted U_L and U_S, respectively), flanked by inverted repeat sequences, totaling approximately 152 kb[8]. Oncolytic herpes simplex virus (oHSV) is a promising agent for various types of cancers. It has been widely used in cancer research studies[7]. Furthermore, several oncolytic viruses have been tested in clinical trials, such as NV1020, G207, HF10, and T-VEC[7,8,9,18,20,21]. These viruses can safely and effectively target cancer cells[7,8].

Yun Ju Jung, "Viruses: A novel anticancer weapons," *International Research Journal of Advanced Engineering and Science*, Volume 3, Issue 2, pp. 282-286, 2018.

International Research Journal of Advanced Engineering and Science
ISSN (Online): 2455-9024

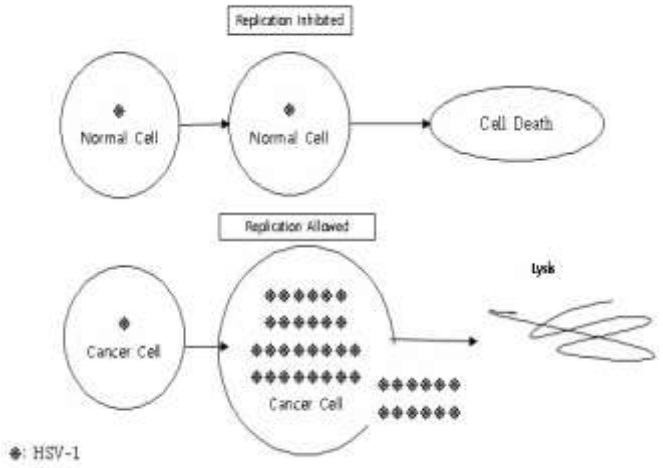

Fig. 1. HSV-1 Replication in tumor cells.

G47Δ: G47Δ is a third-generation oncolytic HSV vector. It is a multigene mutant of *HSV-1* that contains three main mutations (*γ34.5, ICP6*, and *α47*), which results in its selective cytotoxicity to tumor cells[14,16,17]. G207 is one of the world's fastest clinically applied growth-type recombinant viruses, the second generation genetically modified herpes simplex virus type 1. By genetic manipulation, two viral genes, γ 34.5 and ICP 6, are not working[9]. G47Δ is a third generation vector; it is generated from G207 by deleting the non-essential α-47 gene[15]. G207 contains deletions of both γ134.5 genes and has the ICP6 gene inactivated, which codes for RR(ribonucleotide reductase)[14]. The γ34.5 gene is a gene necessary for herpes simplex virus type 1 (herpes virus) to cause disease, and it will not cause disease without this gene. The γ34.5 gene also has the function of blocking the reaction that normally occurs when cells undergo viral infection, i.e., stopping the synthesis of proteins in the cell and causing *apoptosis[19]*. Therefore, without the γ34.5 gene, herpes virus can't proliferate because protein synthesis is impossible. However, cancer cells have *apoptosis resistance* in response to virus infection so that herpes virus can proliferate increase in cancer cells[22]. ICP4 is one of the indispensable gene products; at least one copy of the gene must be present for viral replication[23]. ICP4 blocks apoptosis and positively regulates many other genes in the HSV-1 genome[24].

The ICP6 gene encodes the large subunit of ribonucleotide reductase (RR) that is essential for viral DNA synthesis[25,26,27]. When ICP6 is inactivated, HSV-1 can replicate only in proliferating cells that express high enough levels of host RR to compensate for the deficient viral RR[28.29]. The ICP6 gene is a gene that makes RR (ribonucleotide reductase) necessary for DNA synthesis of herpes virus[30,31,32,33,34]. If the ICP6 gene does not work, herpes virus can't proliferate because it can't synthesize DNA even if infected cells. However, because cancer cells are rich in enzymes to replace the ICP6 gene, herpes virus can proliferate in cancer cells even if the ICP6 gene does not work[30]. The α47 gene acts to reduce the amount of MHC class 1 on the surface of cells infected with herpes virus[24]. MHC class 1 plays a role in presenting cancer antigens and viral proteins to immune cells. Therefore, in the absence of the α47 gene, the amount of MHC class 1 does not decrease, so cancer cells more strongly stimulate immune cells responsible for anticancer immunity. The *α47* gene product is responsible for inhibiting the transporter associated with antigen presentation (TAP), its absence led to increased *MHC class I* expression in infected cells[23].

Compared to G207, A previous study reported that G47Δ replicates and spreads better in infected cells[14]. Furthermore, G47Δ was found to be more efficient in inhibiting the growth of tumors[15]. G47Δ has also been employed in a phase I clinical trial of progressive glioblastoma[8]. To date, two genetically engineered oncolytic viruses have been approved for marketing as drugs. One is Oncorine was approved in China for head and neck cancer and esophagus cancer in 2005[9]. The use and clinical data of Oncorine is so far limited to China[9]. The use of oncolytic herpes simplex virus (oHSV) vectors has been shown to be a safe and effective therapeutic approach for different types of cancer. In particular, HSV can increase the efficiency of anticancer therapy by eliminating cancer cells with resistance to chemical drugs[16]. Paclitaxel in combination with an oHSV vector would present an enhanced killing effect when used against breast cancer cells[17]. The present study demonstrates that the combined use of the oHSV vector G47Δ and paclitaxel produced a synergistic effect against breast cancer cells both in vitro and in vivo[17].

T-Vec: T-Vec was approved for melanoma by the FDA in the USA in October 2015 and was subsequently approved in Europe in January 2016 and in Australia in May 2016[9]. T-Vec is an intra-lesional oncolytic virus therapy based on a modified herpes simplex virus type-1[35]. T-Vec selectively targets tumor cells, causing regression in injected lesions and inducing immunologic responses that mediate regression at distant sites[35]. T-Vec is attenuated by the deletion of the herpes neuro-virulence viral genes and enhanced for immunogenicity by the deletion of the viral ICP47 gene[36]. Immunotherapy is cancer treatment that directly kills cancer cells and stimulates the body's immune system to fight cancer, such as melanoma. T-Vec is a local immunotherapy treatment that kills melanoma cells in the skin and lymph nodes[9]. T-Vec is an oncolytic virus therapy, a treatment that uses a virus to infect and kill cancer cells while avoiding normal, healthy cells. T-Vec is made from a genetically modified herpes virus, commonly known as the cold sore virus[15]. The therapy is designed to replicate inside melanoma cells, it may also enhance the immune system's ability to fight cancer[15]. T-Vec was modified by disrupting the *γ*34.5 neuro-virulence gene to improve safety and also to allow for tumor-specific replication and the ICP47 gene that provides immuno-evasion functions[35]. Removing ICP47 thus would increase the immunogenicity of infected tumor cells[36]. T-Vec was further modified by the addition of a transgene coding for human GM-CSF, thus further increasing immune recognition.

JX-594: JX-594 is an oncolytic immunotherapy designed to selectively replicate in and destroy cancer cells with EGFR/Ras pathway activation which are abundant of *TK* (thymidine kinase), while simultaneously expressing GM-CSF, but do not replicate in normal cells, because of low cellular *TK[10]*. JX-594 can specifically target and destroy

Yun Ju Jung, "Viruses: A novel anticancer weapons," *International Research Journal of Advanced Engineering and Science*, Volume 3, Issue 2, pp. 282-286, 2018.

cancer cells in patients while leaving the surrounding healthy cells intact[11]. JX-594 was engineered to enhance this natural safety and cancer-selectivity by deleting its TK gene, thus making it dependent on the cellular TK expressed at persistently high levels in cancer cells[10]. To enhance product efficacy, JX-594 is also engineered to express the immunogenic GM-CSF protein. GM-CSF complements the cancer cell lysis of the product candidate, leading to a cascade of events resulting in tumor necrosis, tumor vasculature shutdown and sustained anti-tumoral immune attack[9]. TK is a very important enzyme in all of our dividing cells. Each time a cell divides, TK comes in to make sure that any errors in the DNA being copied are repaired[12]. This prevents the damage from being passed along to the new cell. Healthy cells have very few DNA errors to repair, so little TK is needed. Cancer cells, though, contain lots of DNA errors. Thus, they use lots of TK. Many studies are showing elevated levels of TK to be a very sensitive indicator of cancer cell division[11,12,13]. The more TK found in the blood, the more likely that cancer cell division is occurring. Most importantly, in patients previously treated for cancer and declared no evidence of disease, TK elevations correlate with a risk of recurrent cancer[13]. In conclusion, for patients with recurrent cancer, high tumor TK activity is a significant marker of poor clinical outcome on anticancer therapy[10].

TABLE I. Major oncolytic viruses[9,12,15,],

Recombinant Virus	Virus	Knockout Gene	Target Disease	Status
G47Δ	HSV-1	γ34.5. α47.ICP6	Glioblastoma	Phase 2
T-Vec	HSV-1	γ34.5.α47	Melanoma	2015 FDA USA
JX-594	Vaccinia Virus	Thymidine Kinase.	Hepatocellular carcinoma	Phase 3

III. VIRAL IMMUNOTHERAPY

Tumors promote immune tolerance through down-regulation of major histocompatibility complex (MHC) class I molecules and tumor-associated antigens (TAAs), thereby preventing recognition by T cells[37,38,39]. Immunology-based therapy is rapidly developing into an effective treatment option for a surprising range of cancers[36]. Powerful immune cells may be blocked by inhibitory regulatory pathways controlled by specific molecules often called immune checkpoints[3]. The development of a new therapeutic class of drugs that inhibit these inhibitory pathways has recently emerged as a potent strategy in oncology[4,5,6]. Three sets of agents have emerged in clinical trials exploiting this strategy[4]. These agents are antibody-based therapies targeting cytotoxic T-lymphocyte antigen 4 (CTLA4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1)[5.6]. These inhibitors of immune inhibition have demonstrated extensive activity as single agents and in combinations[4]. Clinical responses have been seen in melanoma, renal cell carcinoma, small cell lung cancer, and several other tumor types[5]. OVs(oncolytic viruses)are naturally occurring or engineered viruses that can exploit cancer-specific changes in cellular signaling to specifically target cancers and their microenvironment[9]. The indirect cytolytic effect of OVs on cancer cells is known to release antigens, which can begin a cascade of events that results in the induction of anti-cancer adaptive immunity[39]. Viral infection causes the release of viral pathogen-associated molecular patterns and cellular danger-associated molecular patterns, which activate the host innate immune system to secrete cytokines, such as TNF-α, TRAIL, IFNγ, IL-12, as well as dozens of other cytokines and chemokines[40,41]. Oncolytic viruses offer a novel treatment option, due to their eloquent multimodal mechanism of action. They are probably best known for their inherent ability to cause tumor debulking via direct tumor cell lysis; however, they additionally offer the potential to break immune tolerance and stimulate potent immune responses directed against uninfected tumor cells and distant metastases[42]. Combination of oncolytic virotherapy with immunomodulators is emerging as a promising therapeutic strategy for numerous tumor entities[41]. An oncolytic Maraba MG1 virus expressing IL-12 promotes the migration of activated natural killer (NK) cells to the peritoneal cavity in response to the secretion of IFNγ-induced protein-10 (IP-10) from dendritic cells[43]. The recruitment of cytotoxic, IFNγ-secreting NK cells was associated with reduced tumor burden and improved survival in a colon cancer model[43]. A viable approach to maximize the efficacy of OVs involves arming tumor with immune-enhancing cytokines that are capable of boosting the host's immune response to effectively attack tumor cells[44]. Interleukin-12 (IL-12) is a powerful cytokine with potent antitumor activities that activates both innate and adaptive anti-tumor responses. IL-12-expressing OVs improve the therapeutic index in pre-clinical tumor models by activating and recruiting dendritic cells (DCs), cytotoxic natural killer (NK) cells and cytotoxic T cells(CTLs), which subsequently improve tumor clearance[45]. A tumor-selective oncolytic vaccinia virus (vvDD) with the chemokine (CK) enhance its ability to attract antitumor CTLs and possibly NK cells to the tumor microenvironment (TME) and improve its therapeutic efficacy. vvDD attracted high numbers of tumor-specific T cells to the TME in a murine model[46]. Oncolytic viruses are known to stimulate the antitumor immune response by specifically replicating in tumor cells. It is an important aspect of the durable responses in immunotherapy. As a further means to engage the immune system, it is engineered a virus, vesicular stomatitis virus (VSV), to encode the proinflammatory cytokine interferon-σ[41]. The interferon-σ-encoding virus demonstrated greater activation of dendritic cells and drove a more profound secretion of proinflammatory cytokines compared to the parental virus[41]. From a therapeutic point of view, the interferon-σ virus slowed tumor growth, minimized lung tumors, and prolonged survival in several murine tumor models[41]. Vesicular stomatitis virus (VSV) represents a particularly attractive vector platform for viral-based Immunotherapies due to its inherent tumor specificity, its rapid replication and cell-killing kinetics, its natural ability to stimulate immune responses, NK cells require additional stimulatory signals, such as interferon (IFN) and interleukin[41,47,48]. Cytokine-bearing oncolytic adenoviruses improve and extend the usage of adoptive T cell therapy, a

Yun Ju Jung, "Viruses: A novel anticancer weapons," *International Research Journal of Advanced Engineering and Science*, Volume 3, Issue 2, pp. 282-286, 2018.

treatment known to benefit a portion of melanoma and leukemia patients[49]. The oncolytic adenoviruses induces immune responses against the tumor by revealing tumor antigens. Armed oncolytic viruses promote cytokines, interleukin (IL-2), a key role in recruiting and activating T cells, Further, it directly promotes tumor cell death by apoptosis and necrosis. Armed oncolytic viruses accomplish local, long-lasting, high-level cytokine expression Hamster pancreatic cancer model[47,48].

IV. Conclusion

Oncolytic virus is different from target chemotherapy which indirectly attacks cancer cells by blocking the growth pathway of cancer cells in that it directly attacks cancer cells. Anticancer drug therapy causes the resistance of cancer cells after a certain period of time. Cancer cells with drug resistance grow very quickly. Oncolytic viruses can effectively attack cancer cells with resistance. Oncolytic virus can be expected to produce synergy in conjunction with anticancer drug therapy. The ability of oncolytic virus to stimulate the antigen presenting cells is another advantage.

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