ISSN (Print) 1225-9918
ISSN (Online) 2287-3406
Journal of Life Science 2019 Vol. 29. No. 7. 824~835 DOI : https://doi.org/10.5352/JLS.2019.29.7.824

- Review -

Oncolytic Viruses - A New Era for Cancer Therapy

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Received July 23, 2019 / Revised July 26, 2019 / Accepted July 26, 2019

In recent decades, oncolytic viruses (OVs) have extensively been investigated as a potential cancer drug. Oncolytic viruses have primarily the unique advantage in the fact that they can only infect and destroy cancer cells. Secondary, oncolytic viruses induce the activation of specific adaptive immunity which targets tumor-associated antigens that were hidden during the initial cancer progression. In 2015, one genetically modified oncolytic virus, talimogene laherparepvec (T-VEC), was approved by the American Food and Drug Administration (FDA) for the treatment of melanoma. Currently, various oncolytic viruses are being investigated in clinical trials as monotherapy or in combination with preexistent cancer therapies like immunotherapy, radiotherapy or chemotherapy. The efficacy of oncolytic virotherapy relies on the balance between the induced anti-tumor immunity and the anti-viral response. Despite the revolutionary outcome, the development of oncolytic viruses for the treatment of cancer faces a number of obstacles such as delivery method, neutralizing antibodies and induction of antiviral immunity due to the complexity, variability and reactivity of tumors. Intratumoral administration has been successful reducing considerably solid tumors with no notable side effects unfortunately some tumors are not accessible (brain) and require a systemic administration of the oncolytic viruses. In order to overcome these hurdles, various strategies to enhance the efficacy of oncolytic viruses have been developed which include the insertion of transgenes or combination with immune-modulatory substances.

Key words : Clinical trials, combination therapy, immunotherapy, oncolytic viruses, tumor microenvironment

Oncolytic viruses (OVs)

The hypothesis for the usage of OVs for the treatment of cancer started back in the 1900s from anecdotal reports of cases of patients that were assumingly presenting tumor regression signs after viral infections [45]. The majority of patients had blood-related malignancy such as leukemia but the remission was short-lived (approximately one or two months) [30, 87]. These observations led to the hypothesis that under controlled condition, OVs might be developed as cancer drugs [34]. The invention of the electron microscope and the progress in molecular biology (genetics) allowed a better understanding of the virus life cycle and the beginning of investigations in animal models.

OVs, like most viruses, are the smallest known infectious agents and are unable to survive on their own without infecting a living organism. Their major components are: a genetic material (DNA or RNA, double or single strands), and a capsid that envelops and protects the genetic material. In addition, some OVs possess an envelope that contains glycoproteins and present various shapes.

Malignant cells undergo multiple transformations such as overexpression of cell surface receptors (such as epidermal growth factor receptor; EGFR) and aberrant signaling pathways (such as Ras/mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), and vascular endothelial growth factor (VEGF) pathways), or repress tumor suppressor genes (such as p53 and Rb) to acquire the hallmarks of cancer and overcome normal cellular restraints. The disruption in these pathways inhibits interferon (IFN) signaling which is the overall immune response to viral infection [46]. The IFN pathway is induced after recognition of (a) viral elements by toll-like receptors (TLRs), (b) dsRNA from RNA viruses by retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), and (c) viral DNA by the DNA sensor protein cyclic GMP-AMP synthase

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(cGAS) which activates the stimulator of interferon genes (STING) protein. IFNs prevent the viruses from infecting additional cells, inhibit protein synthesis and activate immune response through inflammation [26, 53].

The aberrations mentioned above are exploited by OVs and allow them to specifically replicate and kill only cancer cells. These proprieties make OVs ideal candidates for the development of specific anticancer products [1, 21, 80].

Immune system and OVs

OVs have two major mechanisms of eliminating cancer cells that involve direct cell lysis and destruction of intratumoral blood vessels or the activation of adaptive immunity.

Once cancer cells are infected with OVs, they can initiate the immune response by IFN through the interaction between released antigens and TLRs. The viral proteins or tumor-associated antigens will interact with TLRs on the cell surface or will be detected by intracellular components of TLRs [84].

The TLR pathways initiate the host antiviral responses via downstream proteins like TNF-associated factor 3 (TRAF3), IFN-related factor 3 (IRF3), IRF7 and RIG-I.

After cell death, tumor lysed cells release tumor-associated antigens that can flow through blood circulation and be captured by antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages, and presented to lymphocytes. Additionally, viral pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) such as high mobility group box 1 (HMGB1) protein, ATP, calreticulin, heat shock proteins, and uric acid are also released [39].

Tumor-associated antigens together with cytokines and DAMPs molecules can initiate an innate immune response with myeloid cells and adaptive immune response by the presentation of antigens to lymphocytes. This particular property is beneficial in cancer treatment as cold tumors can be activated in hot tumors. The activation of both innate and adaptive immune response provides a specific answer to distant tumors or metastasis. PAMPs and DAMPs can directly activate natural killer (NK) cells that will then specifically target and kill tumor cells even with a low expression of major histocompatibility complex (MHC) class I molecules which is the case in most cancers. Tumor-specific CD8+ have demonstrated in preclinical studies the ability to mediate tumor rejection.

The stimulation of long-lasting antitumor immune response likely plays a pivotal role in the duration and extent of clinical responses. With this increased appreciation for the role of immune stimulation in OV efficacy, many oncolytic viruses are now being designed to express transgenes encoding immune stimulatory cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), to enhance OV immunogenicity [44].

Barriers to oncolytic virotherapy

Neutralizing antibodies and complement

For the viruses to initiate a potential antitumor response, they need to reach the tumor site. Blood is the efficient vehicle for OVs, therefore, intravenous therapy (IV) is the most

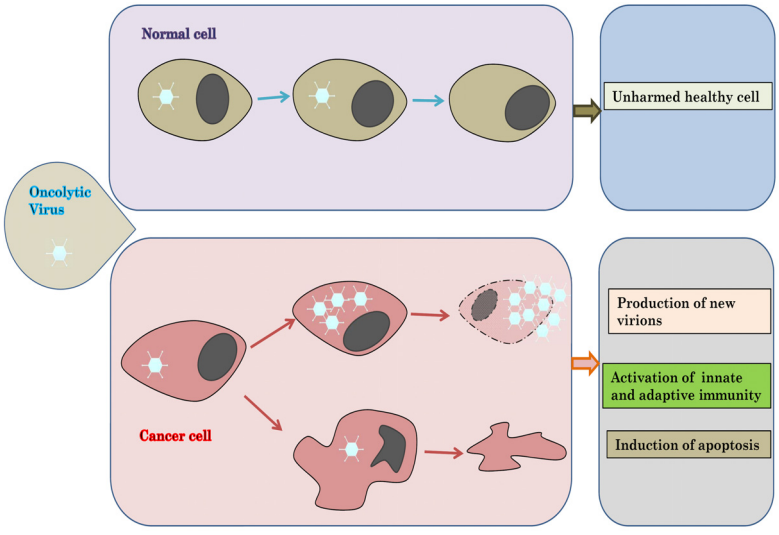

Fig. 1. Principle of oncolytic virotherapy. Oncolytic viruses are natural or programmed cancer-killing viruses. The infection of normal leads to the activation of antiviral pathway such as Type 1 interferons which will block the virus replication. In cancer cells, antiviral and cell proliferation pathways are altered and oncolytic viruses utilize these disruptions to specifically target and infect only cancer cells which lead to the lysis of infected cancer cells and the expansion of oncolytic viruses to other tumor cells.

privileged route for the administration of OVs and can reach the metastatic site. Unfortunately, the majority of patients, having been exposed to the viral family naturally or by vaccination, present preexistent neutralizing antibodies and the OVs are rapidly recognized and eliminated by the circulating antibody without or with help of complement molecules [22].

In absence of complement, recent studies have demonstrated that the neutralization of OVs was relatively weak almost absent but even in the absence of neutralizing antibodies, IV delivery of oncolytic viruses, such as herpes simplex virus (HSV) and vaccinia virus (VV), has been shown to be inhibited by antiviral activity present in serum as a result of the activation of the complement system. The complement system acts as the first line of innate immune defense, opsonizing and neutralizing foreign pathogens, targeting them for phagocytosis, and clearing them from the circulatory system. Antibody-mediated complement activation enhances the neutralizing capacity of antibodies, making complement of particular relevance for OVs in which preexisting immunity may be prevalent [89].

Tumor heterogeneity

The increasing resistance to cancer therapeutics, especially targeted therapy, is often attributed to the complexity within tumors and represents a major obstacle in the successful treatment of cancer.

The location of tumors in the brain limits the efficacy of brain tumors treatment due to the blood-brain barrier. One of the most investigated strategies is to develop oncolytic viruses with a natural tropism for the central nervous system (CNS) and some viruses such as poliovirus, parvovirus H1, and reovirus have shown the ability to reach glioblastoma multiforme (GBM) in clinical trials [20, 82].

Genetic alterations that occur in tumors present a problem for oncolytic virotherapy. The tumor microenvironment is a very complex structure in which stromal cells (endothelial cells, adipocytes, cancer associated fibroblasts; CAFs, and

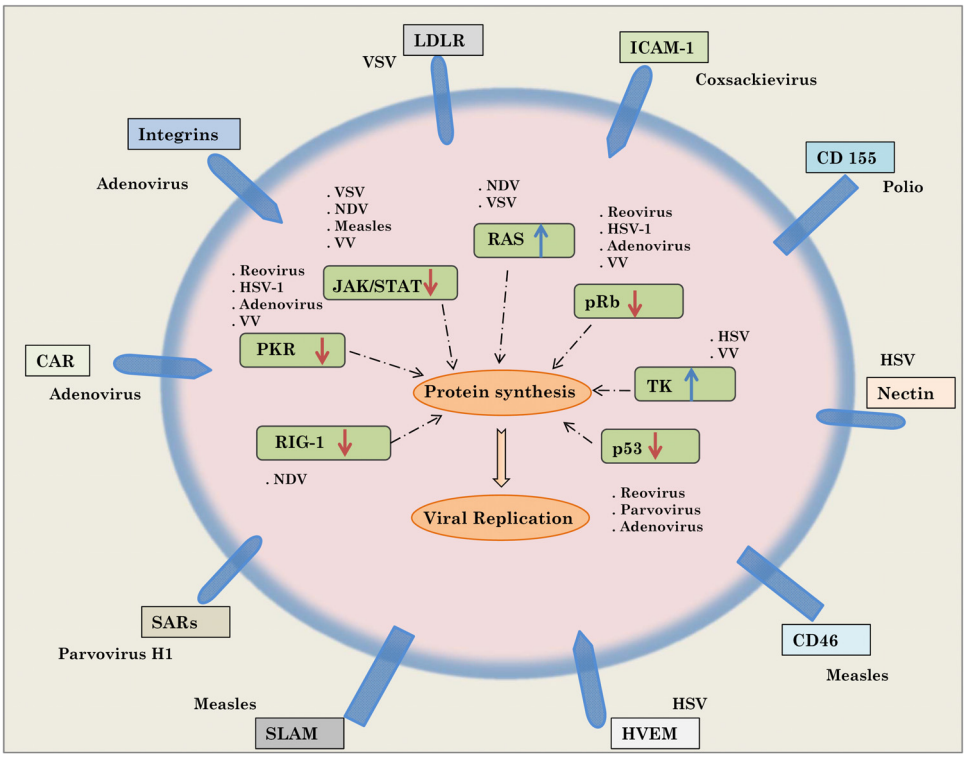

Fig. 2. Mechanisms of oncolytic viruses. Oncolytic viruses enter the cell through the interaction with cell receptors that are usually overexpressed in cancer. Some viruses utilize more than one specific receptor but different viruses can also share one receptor. Other viruses enter the cell via endocytosis through fusion of membranes. Once in the cell, viruses take advantage of aberrant pathways to replicate. CD, Cluster of differentiation; CAR, Coxsackievirus-adenovirus receptor; ICAM-1, Intracellular adhesion molecule 1; LDLR, Low density lipoprotein receptor; HSV, Herpes simplex virus; HVEM, Herpesvirus entry mediator; SARs, Sialic acid receptors; SLAM, Signaling lymphocyte activation molecule; JAK, Janus kinase; STAT, Signal transducer and activator of transcription; Rb, Retinoblastoma; PKR, Protein kinase R; RIG- I , Retinoic acid-inducible gene I ; TK, Thymidine kinase.

immune infiltrating cells) play an important role in the response to immunotherapy and oncolytic virotherapy. These cells are also responsible for creating physical barriers such as dense fibrotic capsules, necrosis, and acidosis, which can impede viral delivery into the tumor [60].

Strategies to enhance oncolytic virotherapy

Combination therapy

Conventional therapy such as chemotherapy and radiotherapy can be combined with oncolytic virotherapy. Cyclophosphamide, used both in chemotherapy and immunosuppression (B- and T-lymphocytes), is an alkylating agent regularly combined with OVs. Other immunosuppressants such as paclitaxel and temozolomide inhibit regulatory T cells (Treg) activity in a dose-dependent manner [27].

Various animal studies demonstrated a remarkable recovery in the treatment of tumor-bearing mice with OV combined with immune checkpoints inhibitors (ICIs) [51]. ICIs are a relatively new class of immunotherapies that aim to overcome tumor-induced immune suppression and evasion caused by the expression of immune checkpoints. Monoclonal antibodies that inhibit programmed cell death protein 1 (PD-1), its ligand (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4) have demonstrated remarkable responses in melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, bladder cancer, head and neck cancer, Hodgkin lymphoma, Merkel cell carcinoma, and likely other cancers as well [24, 81].

Chimeric antigen receptor-T (CAR-T) therapy has given promising results in blood-related cancers like leukemia and lymphoma but has a limited response in solid tumors, therefore, the combination with OVs is believed to improve the outcome of treated patients. In CAR-T therapy, T cells from patients are genetically modified to express chimeric antigen receptor (CAR) that specifically recognizes a tumor-associated antigen (TAA) then the engineered T cells are transfused back to the patients [48, 79].

Transgene arming

A large number of genes has been used in vitro experiments to change the OV genetic material and improve their therapeutic activity. These genes include regulatory cytokines, proapoptotic genes, extracellular matrix degradation enzymes, immune checkpoints inhibitors monoclonal antibodies and antiangiogenic proteins [32].

The FDA approved HSV talimogene laherparepvec (T-VEC) for the treatment of melanoma was engineered from HSV-1 with the deletion of the ICP34.5 gene involved in virus replication and ICP47 gene in immune evasion. The additional modification was the insertion of GM-CSF, a cytokine and growth factor that stimulates the differentiation and maturation of granulocytes and monocytes [55, 73].

OVs can also be armed with bispecific antibody (BiTE) where one arm of the antibody can bind to a cancer cell via a tumor-specific antigen and the other arm interact with $CD8^+$ T lymphocytes [18, 88].

Safety concerns

Although OVs have proven to have an excellent safety record in the clinic, there remain a number of unique challenges in the clinical development of oncolytic viruses. The ability of OVs to actively replicate raises a number of concerns and therefore requires regulations before being dis-

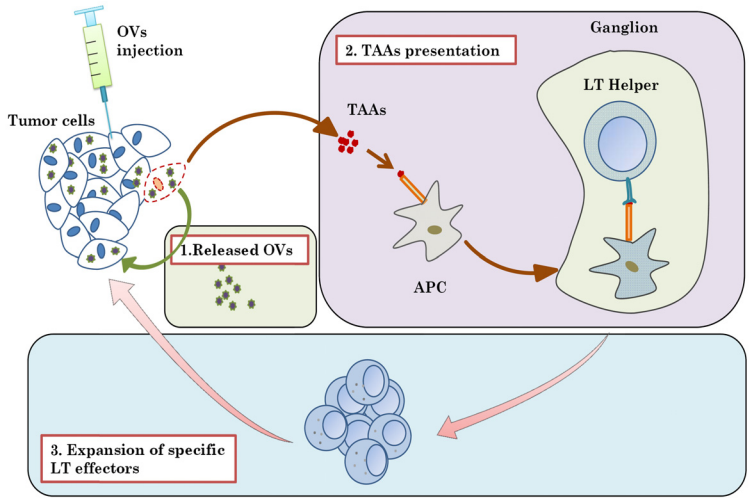

Fig. 3. The induction of immune response by oncolytic viruses. The cell lysis of cancer cells by oncolytic viruses is followed by the release of neo-oncolytic viruses, tumor-associated antigens (TAAs), danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). The new oncolytic viruses can infect other existing cancer cells and continue the cycle of cancer cells elimination. TAAs, DAMPs and PAMPs are processed by antigen presenting cells (APCs) and initiate adaptive immune response by $CD8^+$T lymphocytes against cancer cells.

tributed for treatment. The overall concern in the development of OVs is the environmental shedding of the virus from patients receiving treatment and the risk of transmission to the general population. The shedding from the patient's body through one or all of the following routes: blood, fecal, urine, saliva, or wounds/sores on the skin is taken into consideration. Shedding is a considerable biosafety concern as it raises the possibility of transmission of OV products from treated to untreated individuals [7]. As such, the FDA has established guidelines as to how and when data regarding shedding should be collected during preclinical and clinical development and the way it is to be used to assess the potential for transmission to untreated individuals. Some viruses such as HSV, vesicular stomatitis virus (VSV), and reovirus display minimal shedding, whereas other viruses including adenovirus and VV are known to be more problematic.

OVs in clinical development

Herpes viruses (HSV)

HSV-1, enveloped double-stranded DNA virus of the Herpesviridae family, was the first virus to be genetically modified to treat cancer after the deletion of thymidine kinase (TK). HSV-1 replicates in the nucleus and is highly pathogenic to human as it can affect peripheral nerves through surface nectins (nectin 1 and nectin 2) of neurons. Due to this risk, further engineering modifications resulted in the deletion of the ICP34.5 gene (Table 1) responsible for the neurovirulence and blocks protein kinase R (PKR)-IFN antiviral response. T-VEC is an oncolytic HSV-1 approved for the treatment of melanoma. ICP34.5 was deleted in T-VEC together with US11 which inhibits the phosphorylation of PKR and therefore stops the induction of apoptosis in infected cancer cells [42]. In addition to the deletion, the GM-CSF gene has been inserted in T-VEC which enhance the antitumor immune response. Since the approval of T-VEC by the FDA in 2015, other engineered HSV-1 are being evaluated in clinical studies. Seprehvir (HSV1716), in which ICP34.5 was deleted, is being investigated (Table 1) in patients with hepatocellular carcinoma (HCC), GBM, mesothelioma, and neuroblastoma [54]. G207 contains a deletion of the ICP34.5 gene with disruption of UL39 and is being evaluated in GBM [61]. For OrienX010, in addition to ICP34.5 gene deletion and GM-CSF insertion, ICP47 gene was deleted (Table 1). ICP47 gene blocks the presentation of HSV-1 viral proteins, therefore, its deletion allows the control of the infection [56]. Different from other oncolytic HSV-1 viruses, HF-10 is a natural mutant that conserved both copies of ICP34.5 genes but with the deletion of UL56. HF-10 is currently in clinical trials for breast cancer, melanoma and pancreatic cancer [38].

Measles virus (MV)

MVs, single-stranded RNA viruses of the Paramyxoviridae family, infect cells through the interaction of the envelope protein, hemagglutinin (H) proteins, and the host cellular molecules, CD46 [5]. They initiate fusogenic syncytia that lead to cell death and result in the release of intracellular danger signals to activate the immune system. A sodium/iodide membrane protein (SLC5A5) has been inserted in the measles virus encoding thyroidal sodium iodide symporter (MV-NIS) OV and is currently being investigated in clinical studies (Table 1). I^{131}-label with sodium iodide allows to perform easy monitoring and at the same time allows to conduct radiotherapy [28, 66].

Newcastle disease virus (NDV)

NDVs, double-stranded RNA viruses also of Paramyxoviridae family, are bird viruses that infect cells through hemagglutinin-neuraminidase (HN) protein on the plasma membrane or via direct endocytosis. PV701 and NDV-HUJ OVs from NDV have shown the capacity to selectively multiply in cancer cells and induce immune activation. They are currently in clinical trials (Table 1). Both administrated to patients via IV, PV701 was evaluated in patients with unresponsive solid tumors while NDV-HUJ is being investigated in patients with recurrent GBM [11].

Vesicular stomatitis virus (VSV)

VSV, single-stranded RNA viruses of Rhabdoviridae family, entry cells using low-density lipoprotein (LDL) receptor and are also dependent on the aberrant IFN signaling pathway. The low preexistence of neutralizing antibodies allows the IV delivery of the OVs [6]. In clinical trials, VSV- IFNβ and VSV-IFNβ-NIS after infection produce human IFNβ which protects non-neoplastic cells but increase the immune response towards cancer cells. In addition to IFNβ, VSV-IFNβ-NIS oncolytic virus expresses sodium iodide symporter for tumor-monitoring and for radiotherapy [71, 93].

Table 1 Clinical trials of oncolytic virus

Virus	Genetic modifications	Cancer	Manufacturer
Adenovirus			
H101	E1B deletion, partial E3 deletion	Squamous cell carcinoma, Head and neck cancer [90]	Shanghai Sunwaybio
Onyx-015	Type 2/5 chimaera, E1 deletion	Head and neck [47], pancreatic [35], ovarian [83], colorectal cancers [77]; gliomas [31], lung metastasis [92], liver metastasis [59]	Onyx Pharmaceuticals
DNX-2401	Δ24-RGD insertion	Glioblastoma [50], Ovarian cancer	DNAtrix
Oncos-102	Δ 24-RGD-GM-CSF insertion	Solid tumors [76]	Oncos Therapeutics
CG0070	GM-CSF insertion, E3 deletion	Bladder cancer [74]	Cold Genesys
Vaccinia virus			
JX-594 (Pexa-Vec)	GM-CSF insertion, TK disruption	Melanoma [40], liver cancer [68], colorectal cancer [69], breast cancer, hepatocellular carcinoma [36]	Sillajen
GL-ONC1	TK disruption, haemagglutin disruption, F14.1L disruption	Lung cancer [49], head and neck cancer [63], mesothelioma [52].	Genelux
Herpesvirus			
T-VEC	ICP34.5 deletion, US11 deletion, GM-CSF	Melanoma [3], Head and neck cancer, pancreatic cancer [10]	Amgen
G207	ICP 34.5 deletion, UL39 disruption	Glioblastoma [62]	Medigene
HF10	UL56 deletion, selected for single partial copy of UL52	Breast cancer [65], melanoma [86], pancreatic cancer [64]	Takara Bio
SEPREHVIR	ICP34.5 deletion	Mesothelioma [54], Glioblastoma [15], Neuroblastoma [75]	Virttu Biologics
OrienX010	ICP34.5 deletion, ICP47 deletion, GM-CSF insertion	Melanoma [17], Pancreatic cancer [56]	OrienGene Biotechnology
Reovirus			
Reolysin	None	Glioma [25], sarcomas [37], solid tumors [33], ovarian cancer [16], melanoma [29], pancreatic cancer [8], multiple myeloma [78], head and neck cancer [41].	Oncolytics Biotech
Poliovirus			
PVS-RIPO	IRES from HRV2 insertion	Recurrent glioblastoma [19]	Istari Oncology, Inc.
Coxsackievirus			
Cavatak (CVA21)	None	Melanoma [2], breast cancer, prostate cancer [67].	Viralytics

Adenovirus

Adenoviruses, naked double-stranded DNA viruses of Adenoviridae family, possess a large genome that allows performing numerous modifications. Infection by adenoviruses can occur in both human and animals, therefore, the preexistence of neutralizing antibodies is frequent and limit the efficacy of oncolytic adenovirus. Adenoviruses are one of the most investigated viruses in OV drug development. Adenoviruses infect host cells through coxsackievirus-adenovirus receptor and in the early stages produce E1A and E1B that that specifically target p53 (tumor suppressor) and retinoblastoma protein (pRb). Modifications in adenoviruses

include manipulation of these early genes (E1A and E1B) expression and the insertion transgenes [91].

H101, approved in China for treatment of head and neck cancer, has both genes E1A and E1B deleted. In CG0070, OV investigated for bladder cancer, E1A gene is under the control of E2F-1 promoter which is dependent on Rb. DNX-2401 contains a 24 bp Arg-Gly-Asp (RGD) binding motif in the E1A gene which suppresses the ability to bind to Rb. For ONCOS-12, in addition to the insertion of the RGD motif, GM-CSF was adding for the enhancement of the immune response. DNX-204 is being investigated for glioblastoma (Table 1) and ovarian cancer while clinical trials for Oncos-12 are conducted in solid tumors [14].

Vaccinia viruses (VVs)

VVs, enveloped double-stranded DNA virus of the Poxviridae family, infect host cells by endocytosis and possess a high tropism specific for tumor cells. VVs have already proved to successfully activate immune response during the fight against smallpox which led to the eradication of the disease. In order to increase the cancer cell selectivity, TK gene, B18r, and VGF are usually modified [13]. Currently, three oncolytic VVs are in clinical investigations [12].

JX-594 (PexaVec) is Wyeth strain in which TK was disrupted and GM-CSF was inserted [69, 70]. GL-ONC1 contains the disruption of TK, HA, and F14.5L [63]. In TG6002, an enzyme, FCU1, which can convert a nucleoside analog, 5-flucytosine (5-FC), into a chemotherapeutic drug, 5-fluorouracil (5-FU), was inserted [23]. The combination therapy has proven to improve the antitumor efficacy of VV. The deletion of TK limits the viruses' replication to dividing cells which express high levels of human TK.

Coxsackievirus

Coxsackievirus, naked single-stranded RNA virus of Picornaviridae family, replicates in the cytoplasm and infect cancer cells through intracellular adhesion molecule-1 (ICAM-1) and decay-accelerating factor (DAF). One particular coxsackievirus was developed for the treatment of cancer, it's coxsackievirus A21 (Table 1) also known as Cavatak. Cavatak possesses a natural tropism for cancer cells with ICAM-1 and DAF overexpression such as multiple myeloma, melanoma, and breast cancer. Cavatak doesn't contain any modification and has a natural ability to enhance the immune response by the DAMPs [4]. Cavatak has shown to increase the infiltration of NK cells and CD8+T cells in tumors together with increased levels of IFNs [67].

Reovirus

Reovirus, naked double-stranded RNA virus of Reoviridae family, replicates in the cytoplasm of infected host cells. Cancer cells with mutant Ras pathway are most likely to be infected as the PKR pathway is often blocked. This unique natural tropism led to many clinical investigations in numerous cancers such as gliomas, melanoma, ovarian cancer, pancreatic cancer, multiple myeloma head, and neck cancer and colorectal cancer. The major obstacle for the use of reovirus as an OV is that 100% of participants in clinical trials presented preexistent neutralizing antibody. Reolysin (Table 1) is an oncolytic reovirus with no genetic modification that has proven to be efficient as a monotherapy or in combination with chemotherapy and radiotherapy [57, 58].

Retrovirus

Retrovirus, enveloped single-stranded RNA of Retroviridae family, uses its enzyme, reverse transcriptase, to produce DNA from RNA. Toca-511 is an oncolytic retrovirus in which a gene coding for cytosine deaminase has been inserted. cytosine deaminase can convert 5-FC into a chemotherapeutic drug, 5-FU [72]. Retroviruses are different from other OVs as they do not induce cell lysis but replicate selectively in mitotic cells. In clinical trials, patients with high-grade glioma presented an overall survival of 13.6 months [43].

Poliovirus

Polioviruses, naked single-stranded RNA viruses of Picornaviridae family, are very pathogens to humans but only 1% of infected persons develop poliomyelitis. Polioviruses infect host cells through CD155 and replicate in the cytoplasm [9]. Due to the pathogenic potency, polioviruses have to be attenuated. In PVS-RIPO (Table 1), internal ribosome entry site (IRES) site of polioviruses is replaced with IRES from human rhinovirus type 2 (HRV2). This engineering increases the selectivity of PVS-RIPO for GBM and activates T cells [85].

Conclusion and future perspectives

The approval by the FDA of T-VEC in 2015 triggered a high interest in the development of OV for cancer therapy. Despite decades of investigations, there are a number of ob-

stacles delivery methods due to neutralizing antibodies and to the location of tumors. The delivery system is the main issue as most of the oncolytic viruses today are delivered locally. This system works with skin tumor or accessible tumors in the abdomen but poses a problem in some tumors like brain tumors and blood-related cancer. A second obstacle is that oncolytic virotherapy relies on the activation of innate and adaptive immune responses which are usually absent or suppressed. This activation, though beneficial for specific immune response, contributes to the elimination of OVs, therefore, significant cancer cells lysis. The currently available data about oncolytic virotherapy are just the tip of the iceberg. Despite the existing hurdles, oncolytic viruses are set to be the next generation of drugs in cancer therapy.

Acknowledgement

This work was supported by a research grant of Pukyong National University (2019 year).

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초록 : 종양 용해성 바이러스 - 암 치료에서의 새 시대

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최근 수십 년 간 종양 용해성 바이러스(Oncolytic viruses; OV)는 암 치료제로서의 잠재성에 의해 광범위하게 연구되어왔다. 종양 용해성 바이러스는 두 가지의 독특한 장점을 가지고 있는데, 첫째로 암세포만을 특이적으로 감염시키고 사멸시킬 수 있다는 것이고, 두 번째로는 암이 진행되는 초기 단계에 숨어서 인식되지 않는 상태인 종양 관련 항원들을 인식하는 특정한 적응 면역을 활성화 시키는 것이다. 2015년에는 유전자 변형 종양 용해성 바이러스인 Talminogene laherparepvec (T-VEC)이 미국 식약청(FDA)의 승인을 받았으며, 현재는 다양한 종양 용해성 바이러스들이 단일로 사용되거나 기존의 암 치료 방법인 면역 치료법, 방사선 치료법, 화학 치료법과 함께 사용되어 임상 시험에서 활성이 연구되고 있다. 종양 용해성 바이러스 치료법의 효능은 항 종양 면역 활성과 항바이러스 반응의 균형이 어느 정도인가에 의해 조절되기 때문에, 획기적인 성과에도 불구하고 암 치료를 위한 종양 용해성 바이러스의 개발은 전달 방법, 바이러스를 인식하는 신체 내 항체 및 종양의 복잡성, 가변성, 반응성에 따른 항바이러스의 면역 유도와 같은 다양한 장애물을 극복하여야 하는 문제가 있다. 종양 내에 직접 종양 용해성 바이러스를 투여하는 방법은 눈에 띄는 부작용이 없이 고형 종양을 줄이는 것에 성공하였으나, 아쉽게도 뇌종양 같은 일부 종양에는 사용할 수 없고 전신 투여가 필요한 단점이 존재한다. 이러한 장애물들을 극복하기 위해서 종양 용해성 바이러스의 효능을 높이기 위한 형질 전환 유전자의 삽입 혹은 면역 조절 물질과 바이러스를 조합하는 등의 다양한 전략들이 개발되고 있다.