

An Overview on Oncolytic Viruses as Cancer Therapy

Review Article

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Abstract

The current regimen of cancer therapy (chemotherapy and radiotherapy) suffers with disadvantages such as narrow therapeutic index that further facilitate tumor evolves drug resistance and severe side-effects. Oncolytic viruses are therapeutically useful anticancer viruses that will selectively infect and damage cancerous tissues without causing harm to the normal tissues. Many naturally occurring Oncolytic viruses have a preferential tropism to tumor or associated endothelial cells and others are genetically engineered to change their cellular or organ tropism toward cancer. Antitumor effect of Oncolytic viruses is either by locale cell death or by initiation of the systemic immune response against tumor. Oncolytic Adenovirus, Herpes Simplex Virus, Newcastle Disease Virus, and Reovirus are representative of Oncolytic viruses that have potential to lysis tumor. The effects of the host immune response on the efficacy of Oncolytic viruses are complex. But, using of carrier cells as delivery vehicles could hide the viral antigen from antibodies and complements. Oncolytic viruses have been combined with many cancer therapies to increase response against cancer. Since many forms of canine or feline neoplasms resemble to humane counterpart. So, oncologists believe that Oncolytic virotherapy could soon be a reality in veterinary medicine.

Keywords: Apoptosis; Cancer; Combination Therapy; Host Immune Response; Oncolytic Viruses.

Abbreviations: ADDC: Antibody Dependent Cellular Cytotoxicity; APC: Antigen Presenting Cell; CAR: Cox-sackie Adenovirus Receptor; CD4+: Cluster of Differentiation 4; CD46: Cluster of Differentiation 46; CD8+: Cluster of Differentiation 8; CDV: Canine Distemper Virus; CTL: Cytotoxic T Lymphocyte; DAMPS: Damage Associated Molecular Pattern Molecules; DCs: Dendritic cells; DNA: Dioxo Ribonucleic Acid; dsDNA: Double stranded Dioxo Ribonucleic Acid; dsRNA: Double stranded Ribose Nucleic Acid; E1A: Early gene A E1B Early gene B; GM-CSF: Granulocyte Macrophage –Colony Stimulating Factor; HSPs: Heat Shock Proteins; HSV: Herpes Simplex Virus; IFNS: Interferons; Kb: Kilo bases; mRNA: Messenger Ribose Nucleic Acid; MV: Measles Virus; NDV: Newcastle Disease Virus; NK: Natural Killer Cell; NM: Nano Meter; OVs: Oncolytic Viruses; P53: Tumor suppressor protein 53; PAMPS: Pathogen-Associated Molecular Pattern; PKB: Protein kinase B; PKR: Protein kinase R; PSA: Prostate Specific Antigen; RNA: Ribose Nucleic Acid; SLAM: Signaling Lymphocyte Activation Molecule; TAAS: Tumor Associated Antigens; TLRs: Toll like Receptors; T-VEC: Talimogene laherparevec; UTR UnTranslated Region.

Introduction

Cancer is one of the leading causes of death in worldwide. Despite significant progress made in cancer therapies, but mortality rates for most malignancies remain terrifyingly high. Cancer results either due to decreased cell death or increased cell birth [70]. The inhibition of cancer growth and succession is one of the major

challenges faced by modern medicine [49]. The classical regimen of cancer therapy (chemotherapy and radiotherapy) suffers with disadvantages such as narrow therapeutic index that further facilitate tumor evolves drug resistance and severe side-effects [7].

The current goal for developing new therapies for the treatment of cancer is to design therapeutic agents that have a large therapeutic

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index (i.e. high potency against malignant cells) with little or no toxicities to normal cells. Future treatment modalities need to be more selective and specific which allowing effective drug doses reach to each tumor cell [16].

Oncolytic viruses are therapeutically useful anticancer viruses that will selectively infect and damage cancerous tissues without causing harm to the normal tissues. Each virus has a specific cellular tropism that determines which tissues are preferentially infected. The field of Oncolytic virotherapy began as an observational science more than a century ago, when it was noted that cancer regressions sometimes occurred spontaneously in patients following certain viral infections [55]. Most people think of viruses as pathogenic microorganisms that infect cells, overtake their DNA, RNA and protein synthetic machinery to replicate and then lyse their host cell to spread their progeny, thereby propagating the infection throughout a tissue. Viral infection also results cytopathic effects, such as induction of cell death and dysfunction [41].

With the advent of modern biotechnology tools and better understanding of cancer biology and virology, it has become feasible to engineer viruses with increased tumor selectivity and enhanced oncolytic activity. Naturally occurring lytic viruses have evolved to infect, replicate and lyse cells. It is interesting that the replication cycle of many viruses exploits the cellular pathways that are altered in cancer cells [53].

The anticancer activities of OVs are derived from multimodal cancer killing mechanisms. The first is the direct oncolysis of cancer cells by the virus. The second is apoptotic and necrotic death of uninfected cells induced by anti-angiogenesis and anti-vasculature of the Oncolytic viruses as shown in animals and humans [8]. The last is cytotoxicity to cancer and stromal cells by activated innate and tumor-specific immune cells [65].

Probably the most serious limitation to the successful application of Oncolytic virotherapy has been the limited ability to deliver viruses specifically and efficiently to the tumor, while perhaps its greatest strength has been the ability to achieve selective and efficient amplification of the virus and lysis of the cancer cells. Through extensive investigations in the last few years, a number of novel strategies to achieve tumor-selective replication and potent oncolysis have been developed. In addition, the issue of tumor-selective systemic delivery of OVs via the use of carrier cellular vehicles has been explored [62].

Due to strong similarities between naturally occurring human and pet cancers, Oncolytic virotherapy have been used for canine or feline cancer patients [48].

Therefore, the objectives of this paper are:

- To highlight Oncolytic Virus as cancer therapy,
- To impart professionals with advantage and application of major Oncolytic viruses as future cancer therapy in human and Veterinary medicine

Tumor Selectively Replication of Oncolytic Viruses

Cancer cells have several distinct hallmarks that separate them from normal cells: sustained growth signals, insensitivity to anti-growth signals, evasion of apoptosis, increased angiogenesis, cell immortality, and metastasis [25]. OVs possess the ability to selectively infect and replicate in cancer and associated endothelial cells and kill these cells in cancerous tissues while leaving normal tissues unharmed. Many naturally occurring OVs have a preferential tropism for tumor and associated endothelial cells. Others are genetically engineered to change their cellular or organ tropism to cancer [57].

For instance, constitutively active PKB (Protein kinase B) pathway signaling serves as a sustained growth and survival signal in many different types of cancer. Wang and colleagues demonstrated that the natural tropism of myxoma virus in cancer cells capitalizes on endogenous PKB activity via complex formation between PKB and myxoma viral protein [67]. Cancer cells also have been shown to over express selected surface receptors, which is another mechanism by which viruses may selectively bind to and infect cancer cells. In squamous cell carcinoma, higher expression of the cell surface adhesion molecule nectin-1 correlated with increased HSV-1 infection and cytotoxicity compared to cells that had lower nectin-1 levels. Measles virus has been shown to utilize the surface receptor CD46 for cellular entry, which is over expressed in a variety of human cancers, including hepatocellular carcinoma, colorectal cancer, ovarian cancer, and breast cancer [2].

In addition, OVs can also capitalize on deficient anti-viral defense mechanisms in cancer cells. When normal cells are infected by viruses, release of IFNs and activation of TLRs (Toll like Receptors) by recognition of viral elements activate several downstream pathways, leading to protein kinase R (PKR) activation. Phosphorylated PKR subsequently blocks protein synthesis and prevents viral replication in the cell. Cancer cells have abnormal IFN pathways and abnormal PKR activity, making them more susceptible to viral infection [34].

Also, viral gene inactivation is a commonly used strategy to limit viral infection in cancer cells which often capitalizing the alterations on cellular metabolism and survival pathways of transformed cells. For example, Adenovirus can be used as an Oncolytic virus after genetic modification; the modified version replicates and proliferates only in cancer cells with an abnormal p53 (Tumor suppressor protein 53) mediated cell cycle. The adenovirus E1B gene has been found to inactivate the tumor suppressor protein p53, so that adenovirus with a deleted E1 gene has a relatively high replication rate in cancer cells with deficient p53 because it no longer expresses E1B protein [38].

Transcriptional targeting is another method that is used to produce tissue specific OVs replication by putting viral essential genes under the control of desirable promoters. The adenovirus can design with the E1A viral protein (essential for viral replication) under control of the prostate-specific antigen promoter. Since prostate cancer cells express higher levels of PSA more highly

than normal cells, E1A is selectively expressed in these cells, resulting in viral replication and eventual oncolysis. However, normal cells, which do not express PSA at high levels, will not generate significant amounts of E1A, resulting in defective viral replication and, thus, careful healthy tissue from lysis [13].

Mechanism of Action

Intrinsic Mechanisms

Although the mechanisms of action of Oncolytic viruses are still incompletely understood, but, it appears that the overall antitumor effect induced by Oncolytic viral treatment has two major Components: (1) local cell death of both virally infected and non-infected cancer cells and (2) initiation of the systemic immune response to virally induced cell destruction within the tumor [4].

OVs infection of a cancer cell results in cell death by multiple mechanisms including apoptosis, Pyroptosis, autophagic cell death, and necrosis. Perhaps with the exception of apoptosis, the remaining modalities of cell death listed above are highly immunogenic, leading to activation of both the innate and adaptive immune responses. The cell death of virus infected cancer cells leads to release of TAAs (Tumor Associated Antigens) and other danger signals, including DAMPs and PAMPs molecules [10].

When the host immune system is activated and ready against this substance, antitumor effects due to cytotoxic CD8+ T cell activation can be observed at distant tumor sites that were not locally treated with the virus [19].

Lastly, dying cells also release a variety of cytokines into the local environment, such as interferons, tumor necrosis factor-alpha and interleukins that promote further cell mediated immune response. Taken together, the presence of TAAs, PAMPs, DAMPs and cytokines stimulate APC maturation which, in turn, primes both CD4+ and CD8+ T lymphocytes in the adaptive host immune response by cross presentation [5]. Moreover, type I IFNs and DAMPs can also directly stimulate natural killer (NK) cell response against cancer cells, this is an example of how the innate immune system is also involved in the antitumor response after OVs treatment [34]. Additionally, some types of OVs also target tumor vasculature, leading to death of uninfected tumor cells due to loss of the tumor blood supply [9].

Enhancing Oncolytic Viruses Antitumoral Response

Just as deletion of viral genes has been used to improve tumor selectively, insertion of therapeutic genes via genetic engineering has been employed to enhance OVs antitumoral responses. One major strategy that will be the focus of this section is the expression of immune stimulating molecules including cytokines, molecules that enhance immune system cross-priming and T lymphocyte co-stimulatory molecules [4].

A number of studied OVs expressing cytokines have demonstrated promising results. Several OVs currently in clinical trials express GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor), a cytokine that promotes APC maturation and stimulates cytotoxic T lymphocyte responses against tumors. T-VEC

(Talimogene laherparevec) is the most studied OVs expressing GM-CSF. Analysis of biopsies from melanoma lesions treated by intratumoral T-VEC injection induced both local and systemic T lymphocyte responses [33].

Heat shock proteins (HSPs) are released during oncolysis of OVs infected tumor cells, leading to initiation of chemokine production and activation of dendritic cells via the TLR4 pathway. Given that HSPs release cross-primes the innate and adaptive immune systems, OVs were engineered to over express HSPs, in particular HSP70. Adenoviral vectors expressing HSP70 have demonstrated antitumor effect in patient derived from xenograft models of hepatocellular cancer, as well as in a Phase I trial of solid tumors in humans [27].

Directly targeting T lymphocyte activation by engineering OVs that express T lymphocyte co- stimulatory molecules is another approach aimed to increasing cytotoxic T lymphocyte activation against tumor cells. Professional APCs hold co-stimulatory molecules such as CD40 and CD80. When CD40L, a transmembrane protein expressed on CD4+ T cells, binds to its receptor on an APC, a T-helper response is induced and leads to CTL activation. Along similar lines, binding of CD28 on T lymphocytes to CD80 triggers CTL proliferation and activation. Preclinical models using CD40L- and CD80-armed OVs have shown induction of T-helper response and antitumor effects [47].

Representative Oncolytic Viruses

Adenovirus

Adenovirus has emerged as one of the most potential viral therapeutic agent for cancer therapy in the late 1950. The adenoviral genome consists of linear, dsDNA of 26-45 kb. It is a non-enveloped, icosahedral virus with capsid of 65-80 nm diameters. The structural elements of capsid include penton, hexon and fibre proteins which play a crucial role in virus entry into the cells [49].

Adenovirus entry into the cells occurs by receptor-mediated endocytosis. The capsid structural elements such as penton recognize and bind with the primary receptor, the coxsackie-adenovirus receptor (CAR) resulting in internalization of the virus and endocytosis by clathrin coated pits and subsequent lysis of the endosomes releases virus particles in the infected cells [18]. In this process, a series of viral proteins co-operate to promote efficient replication of the virus and its release. These major viral proteins include E1A, E1B-55kD, E1B-19kD, E3-11.6 KD and other associated proteins. The two genes particularly, E1A and E1B (E1B-55kD) have been the targets of modification in order to create tumor-specific viruses [68].

In normal circumstances, the products of these genes act in concert to force the host cell to enter S phase which is a prerequisite for the viral replication process. Thus, deletion of E1A will make the virus susceptible to the antiviral mechanisms of the retinoblastoma protein (a tumor suppressor protein); specifically by blocking the G1 to S transition. On the other hand, deletion of E1B, allows p53 to induce apoptosis in infected cells, aborting replication and spread of the virus. Most of the cancer cells fulfill these requirements and hence become selective targets

for oncolysis by adenoviral E1-deletion mutants [31].

It was proven that this mutant to be a safe agent for the treatment of patients with squamous cell carcinoma of the head and neck. Oncolytic adenoviruses also have been used in clinical trials for various cancer types such as glioma, ovarian cancer, pancreatic cancer, prostate cancer and colorectal cancer [18].

Herpes Simplex Virus (HSV)

HSV is an enveloped, dsDNA virus with 152 kb long genome. The transcription, replication and packaging of HSV take place in the nuclei of infected cells. In cells permissive for this virus, replication cycle is usually completed within 20 hour, releasing thousands of viral progeny on cell lysis. The virus enters into the cell by fusion of the viral envelope proteins with the host cell plasma membrane. The viral protein gC and gB are required for binding of the virus to host cells receptor whereas gD plays a major role in virus entry [49]. The genome of HSV-1 consists of three major gene regions alpha, beta, and gamma and each of the genes act cooperatively to regulate viral entry, replication and multiplication in host cells. The alpha genes are transcribed in early infection in absence of de novo protein synthesis and these products regulate transcription of beta and gamma genes. The beta genes products are important in viral nucleic acid metabolism and are also required for viral DNA replication [43].

The HSV gamma genes have been divided into two subgroups, gamma 1 and gamma 2, which encode different proteins of each type. The gamma 1 genes are expressed in early infection and do not depend on viral DNA synthesis in contrast to gamma 2 genes that are lately expressed and are dependent on viral DNA synthesis and hence can be blocked by inhibitors of viral DNA synthesis. The HSV cycle is usually completed by assembly of virus followed by their release into extracellular space [44].

The classical method to make HSV Oncolytic is the deletion of the diploid gamma 134.5 gene, which encodes the primary neurovirulence factor. This deletion precludes the ability of the virus to overcome cellular protein kinase R (PKR) which is mediated block of viral protein synthesis, thereby rendering the virus non-replicative in quiescent cells. Tumor cells with defective PKR pathways or activated remain permissive for viral replication [40].

Much of the early interest in HSV has been directed towards their use against brain tumors and this remains an active area of investigation. However, an increasing number of preclinical studies have also shown that HSV can be effective against breast cancer. In some cases, the complete eradication of breast cancer tumors or the inhibition of metastases has been reported (James and Douglas, 2013)30. In October 2015, (HSV-1) expressing GM-CSF named T-VEC became the first OVs approved by the US Food and Drug Administration for the treatment of advanced melanoma [3].

Newcastle Disease Virus (NDV)

Newcastle disease virus (NDV) also known as avian paramyxovirus-1 belongs to the genus Avulavirus of the family *Paramyxoviridae*. The NDV genome has 15,186 nucleotides long single stranded, *negative-sense* RNA which contains six genes

encoding at least eight proteins- six structural (nucleocapsid protein, phosphoprotein, matrix protein, fusion protein, haemagglutinin-neuraminidase, and RNA-dependent RNA polymerase and two non-structural (V and W). NDV binds cells via the haemagglutinin-neuraminidase protein, which attaches to sialic acid containing host cell receptors. Binding is followed by fusion of viral and cell-surface membranes, a process mediated by fusion protein. The viral RNA is then released into the cytoplasm and undergoes replication [49].

NDV is categorized into three pathotypes depending on the severity of the disease that it causes in birds: lentogenic (avirulent), mesogenic (intermediate), or velogenic (virulent). The cleavage site in the fusion protein of the NDV has been shown to be a major determinant of virulence. Pathogenic classification of NDV strains in birds correlates with their oncolytic properties in cancer cells. On the basis of this finding, in human cancers NDV strains have been classified as either lytic or non-lytic, with velogenic and mesogenic viruses being lytic and lentogenic viruses in general being non-lytic [15].

Mechanisms underlying NDV mediated cytotoxicity have been investigated in multiple studies. Experimentations on chicken embryos inoculated with NDV revealed evidence of apoptosis in embryonic tissues. Multiple subsequent studies confirmed the dominant role of apoptosis in NDV-induced cell death. Induction of apoptosis by NDV requires viral entry, replication, de-novo protein synthesis, and activation of caspases. In addition to its direct cytopathic effects, the anti-cancer activity of NDV is associated with the activation of both innate and adaptive immune responses [51].

An attenuated strain of NDV was used in phase I clinical trial and it was shown that when administered intravenously it replicates specifically in tumor cells and causes cytolysis of tumors of epithelial origin (carcinomas including breast, lung, prostate and colon), neuroectodermal (melanomas, glioblastomas and neuroblastomas) and mesenchymal origin (sarcomas). In all the cases, survival rate was encouraging with minimal side effects [37].

Reoviruse

Reoviruses are non-enveloped icosahedral viruses with (dsRNA) genome belong to the family reoviridae. The capsid of reoviruses is composed of an outer and inner shell and the virion has a diameter of approximately 80 nm. Reovirus genome segments have a total size of about 23.5 kb and encode for 12 viral proteins which contains 8 structural (sigma 1, sigma 2, sigma 3, lambda 1, lambda 2, lambda 3, Mu1, and Mu2) which are used for virus replication. The reovirus non- structural proteins include sigma1s, which may have a role in reovirus virulence and sigmaNS, MuNS, and MuNSC which are involved in viral inclusion formation [61].

The reovirus infectious life cycle starts with the binding of the virus particle to the target cell surface via viral protein sigma 1. The binding is initiated with the attachment of the body domain of sigma 1 to the cell surface glycans, its function is as the co receptors by low affinity binding to sigma1, and by enabling the virus particle to diffuse laterally on the cell surface to facilitate the high affinity binding of the sigma 1 head domain to the junctional adhesion molecule-A [6]. After cell attachment, reovirus particles are internalized into cell via cellular transmembrane receptor

beta1 integrin mediated endocytosis. Reovirus replication and virion assembly takes place in viral factories which are formed in the cytoplasm of infected cells and consist of viral dsRNAs, viral proteins, complete and nascent virus particles, cell microtubules, and intermediate filaments [46].

It is important to elucidate the mechanisms of reovirus induced cell death. Many studies have indicated that reovirus replication induces apoptosis in cultured cells and *in vivo*. The transcription factor, nuclear factor kappa B may play a significant role in reovirus induced apoptosis in susceptible host cells. Additionally, the role of interferon regulatory factor-3 is important for efficient induction of apoptosis in reovirus infected cells [26]. Oncolytic reoviruses used against breast, colon, ovarian, lung, neurological, hematological, pancreatic, sarcoma, and bladder neoplasms and show efficient result [1].

Tumor Specific Delivery of Oncolytic Viruses

Oncolytic virotherapy has the greatest potential to be successful in the clinical setting if such therapy can be administered systemically to target the metastatic tumor burden effectively. The effects of the host immune response on the efficacy of Oncolytic viruses are complex. When stimulated, immune cells could result in virus clearance but might also induce specific and non-specific anti-tumoral activities. It appears that the innate immune response plays an important role in virus clearance, whereas T cell-mediated responses are largely responsible for the anti-tumoral effect [69]. For the treatment of metastatic or hematological malignancies, intravenous virus delivery could be hindered by neutralizing antibodies, complement activation, non-specific uptake by other tissues such as the liver and spleen, and as well as poor virus escape from the vascular compartment [39].

Numerous experiments have been done to modify the immune response in favor of virus replication and tumor lysis. One method is by using an immunosuppressive agent, such as cyclophosphamide, that has been shown to improve virus spread and anti-tumoral efficacy [50]. Single doses of the angiostatic and anti-inflammatory cyclic peptide of arginine-glycine-aspartic, given before an oncolytic HSV and resulted in reduced tumor vessel permeability and leukocyte infiltration. Various data suggest that pre-existing antibodies decrease virus spread after intravenous delivery, but have a lesser effect on intratumoral injection [14]. Instead of injecting naked virions, using cells as delivery vehicles could hide the viral antigen from antibodies and complements. This so-called “Trojan horse” strategy involved infecting the body's cells *in vitro* and administering these cells back systemically, which would then carry the oncolytic virus to the tumor environment [24].

Delivery of Oncolytic Viruses via Carrier Cells

Because viruses outside of a host cell are essentially inert particles, they rely on passive targeting to reach a tumor systemically. Vehicles that have endogenous tumor targeting activity could therefore be usefully incorporated to deliver OVs to the tumor tissues *in vivo*, resulting in greater delivery to the tumor and reduced off target toxicities. In this regard, specific autologous cells have been investigated as potential carriers for viral delivery to the tumor where replication and amplification of the virus

should increase the effective local viral dose in the tumor and thus enhance the Oncolytic effects [62].

Chemokines and integrins as carrier cell: In order to develop efficient cellular vehicles for OVs as well as effective cancer immunotherapy, it is extremely important to develop a systematic understanding of the molecular basis of cell trafficking and biodistribution of candidate carrier cells. Two classes of molecules, chemokines and adhesion molecules such as integrins, have been shown to be important for cell trafficking within immune systems and into tumors. Chemokines are generally secreted polypeptides which guide lymphocyte movement throughout the body by controlling integrin avidity and inducing migration. Cancer cells express a number of chemokines which may attract certain types of cells to tumor. Manipulation of the chemokine-chemokine receptor systems may be very useful for efficient trafficking of carrier cells as well as for cancer immunotherapy [17].

Stem cells and progenitor cells as carriers: Mesenchymal progenitor cells possess properties such as simple isolation and propagation procedures, making these cells attractive candidates as cellular vehicles. The recent demonstration that cancer stem cells derived from breast cancer patients can be infected by Oncolytic Adenoviruses, raised the possibility that cancer stem cells could be used as carriers for delivery of OVs to cancer [22].

Immune cells as carriers: A variety of immune cells can respond to “danger signals” released from cancer tissue used to trafficking the cancer sites. These immune cells are used as cellular vehicles for delivery of OVs. The types of cells investigated so far have included T cells and monocytes. In addition, dendritic cells and NK cells may also be useful for this purpose. A potential advantage of using immune cells as cellular vehicles is that it may produce a combined immune virotherapy [28].

Cancer cells as carriers: The idea of using tumor cells as carriers to deliver OVs was first demonstrated in a regional delivery of replication-selective HSV-1 for the intraperitoneal therapy of epithelial ovarian cancer. In later studies, the tumor carrier cells have been inactivated by gamma irradiation after infection, which did not affect the production and release of oncolytic parvovirus. Using a model of spontaneous metastases of human breast cancer, it was shown that intravenous injected tumor cells localized to metastatic lesions, and were able to carry an oncolytic Adenoviruses to the metastases thereby delivering the therapy in a localized and less toxic fashion [52].

Endothelial progenitors and endothelial cells as carriers: Recent studies have also demonstrated that transplanted endothelial progenitor cells can migrate via peripheral blood and home exclusively to the site of tumor neovasculature. Therefore, it has been proposed that endothelial cells may also act as a “Trojan horse” for systemically delivering OVs to metastases. In fact, blood outgrowth endothelial cells have been tested to systemically deliver an Oncolytic measles virus to a human glioma model in mice [12].

Combination Therapies

Chemotherapy and radiotherapy are currently the standard of care for many malignancies, but clinical data shows that combining

OVs with these systemic therapies can increase the response seen with either therapy alone. OVs have been combined with many therapeutic agents in animal models. Any synergistic effect, either immunogenic or cytotoxic, will hopefully lead to increased therapeutic efficacy, including potentially increasing the sensitivity of tumor cells to chemo- or radio-therapy or targeting resistant cell populations [58].

Some chemotherapeutic agents may up regulate cell surface receptors that viruses use to enter and infect tumor cells. For example, MAP kinase (mitogen activated protein kinase) inhibitors have been shown to up regulate coxsackie-adenovirus receptor expression, which enables enhanced adenovirus entry. Other lines of evidence suggest that chemotherapeutic agents can also enhance OVs function by affecting the immune response to infection. Paclitaxel up regulates MHC (Major Histocompatibility Complex) class I molecule expression, leading to enhanced antigen presentation and immune system cross-priming [32]. Also, Drugs that increase activation of the tumor suppressor gene p53 can, for example, increase the sensitivity of cells to reovirus mediated oncolysis [45].

Adenovirus has been given in combination with 5-flurouracil (5-FU) chemotherapy, with evidence of efficacy when given intravenously in an immuno-competent mouse bladder tumor model. Interestingly, the same effect was not seen in nude immuno-suppressed mice, suggesting that T cell-mediated immunity may have a role. Reovirus has been combined with a number of chemotherapeutic agents in prostate cancer cell lines *in vitro*. *In vitro*, decreased tumor growth and increased survival in combination with docetaxel was observed [36]. A parvovirus-cisplatin combination induced higher cytokine release than either agent alone and also resulted in pronounced DC maturation and Cytotoxic T-cell activation [42].

Although the combination of OVs with cytotoxic chemotherapy has potential to the specific immune interactions. There is now increased recognition that chemotherapy agents themselves may have immunomodulatory effects on B cell, macrophage, and NK cell responses and heterogeneous effects on the activity and maturation of DCs. Gemcitabine has been shown to potentiate the oncolytic effect of reovirus through inhibition of myeloid-derived suppressor cells, which can suppress an anti-tumor immune response [21].

OVs combination with radiation has also been shown to improve antitumor response in preclinical models by enhancing apoptosis in the combination therapy. Cellular changes induced by irradiation can enhance the ability of viruses to replicate and spread within a tumor. In a human glioma xenograft model irradiation combined with a modified HSV produced greater tumor reduction than either treatment alone, and an increased viral load was recovered in irradiated grafts [11]. Furthermore, OVs are being engineered with therapeutic genes that improve local radioactive particle delivery, in particular radioactive iodine. Both vaccinia and measles virus have OVs strains developed carrying the human sodium iodide symporter, which allows entry of radioactive iodine into virus infected cells to produce further tumor destruction through local radiation exposure [20].

Additionally, Monoclonal antibodies, such as trastuzumab, act via multiple mechanisms: firstly, by a direct effect on binding to

a target ligand, disrupting intracellular signaling pathways and secondly, via antibody-dependent cellular cytotoxicity (ADCC). Indeed, activation of NK cells with reovirus has been shown to support ADCC. Trastuzumab has also shown potential when combined with reovirus. *In vitro* and *in vivo* models, combination therapy increased the cytotoxic and anti-tumor effects [23].

OVs combined with Anti-Angiogenic Therapy like Sunitinib and sorafenib (small molecule inhibitors of a number of anti-angiogenic proteins) and bevacizumab (an anti-vascular endothelial growth factor monoclonal antibody), have also been investigated with some encouraging results. HSV in combination with bevacizumab, there was evidence of viral distribution to breast cancer cells resulting in decreased tumor size [64].

Application of Oncolytic Virotherapy in Veterinary Medicine

In contrast to the progress of human Oncolytic virotherapy, there are very a few clinical trials using OVs for canine or feline cancer patients [48]. Since many forms of canine or feline neoplasms resemble to their human counterparts in histological appearance, tumor genetics, biologic behavior, pathologic expression, recognized risk factors and response to therapy so it is reasonable to expect that the human clinical protocols will transfer directly for the treatment of pet cancer patients [35].

There are strong similarities between naturally occurring human and canine cancers including colorectal carcinoma, fibrosarcoma, osteosarcoma, soft tissue sarcoma, Burkitt lymphomas and small lymphocytic lymphoma [54]. Several types of feline neoplasms such as squamous cell carcinoma and mammary carcinoma also show similarities in tumor biology, expression patterns and prognosis with human head and neck squamous cell carcinoma and a wide subset of human breast cancers [66].

As OVs show continuous promise in clinical application for treatment of many cancer types in human patients and considering the high similarity and increasing frequency of these cancers in pets, oncologists believe that oncolytic virotherapy could soon be a reality also in veterinary medicine. Moreover the data from canine studies are more reliable and may be helpful in designing human clinical trials. The translation of oncolytic virotherapy from dogs to humans and the reverse could be important for development of drugs. Many oncolytic viruses have been tested as oncolytic agents for treatment of canine or feline cancer. They include human and canine adenoviruses, canine distemper virus, and reovirus [29].

Canine Distemper Virus (CDV)

Canine distemper virus (CDV) is an enveloped virus with a single stranded RNA genome belonging to the genus morbillivirus of the paramyxoviridae family. It is a close relative of measles virus (MV). In fact, both MV and CDV use a similar cellular receptor for entry into cells [59]. Attenuated MV is used for the treatment of human lymphoma and, consequently, measles virus has shown promising anti-tumor activity against a variety of malignant neoplasm in both preclinical and clinical studies. Because of its similarity to MV, CDV was considered for treatment of canine lymphoma [56].

CDV binds to the cellular receptor, the signaling lymphocyte activation molecule (SLAM), which is over-expressed on malignant canine B and T lymphocytes. Attenuated CDV was able to infect canine lymphoma cells in cell culture via binding to SLAM and to induce apoptosis in these cells. While preliminary, these results support the continued evaluation of CDV for the treatment of canine lymphoma [63].

Nevertheless, the most dogs are vaccinated against canine distemper virus and the high prevalence of virus neutralizing antibodies is one major obstacle to the use of CDV in canine clinical trials. The use of vectors of non-canine origin like e.g., MV or removing key neutralizing epitopes on the surface of viral capsid proteins might help to avoid pre-existing immunity. In addition, intratumoral or mucosal virus application or administration of higher virus doses could also be a solution for pre-existing immunity problems [60].

Conclusion and Recommendations

Oncolytic viruses are tumor selective potent anti-cancer agents. Currently in the early stages of their emergence as useful therapy, their promise is yet to be fulfilled. Human tumors are very diverse, and the response to virotherapy is variable. Significant challenges remain to be overcome before Oncolytic viruses can emerge as broadly useful therapy. The anti-viral immune response is a major obstacle to effective virotherapy, although rapid clearance of virus from the bloodstream has limited systemic application. Resistance and overlapping toxicity are the major problem of radiotherapy and chemotherapy in cancer patient. The significant incidence and mortality associated with canine and feline cancers continues to challenge modern veterinary medicine to develop more reliable therapies. One of the most promising novel cancer therapies is Oncolytic virotherapy. Despite this review, it is clear that Oncolytic viruses are moving closer to fulfilling their exciting clinical potential and may become the standard of care for certain cancer scenarios in the future.

So, based on the above facts, the following recommendations are forwarded in order to strength oncolytic virotherapy concept and to realize its benefits:

- Scientists should be providing further study on virotherapy of different tumor as well as on response of host against therapy and systemic delivery mechanism.
- Current cancer therapy (chemotherapy and radiotherapy) should be expanded with combination of virotherapy to lack of cross resistance and toxicity.
- Due to strong similarity between humane and pet cancers veterinarians should focus on investigation of OVs for two-way street development of drugs.
- Universities and research institution should upgrade their laboratory in terms of manpower and facilities for efficient application and distribution of oncolytic virotherapy.

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