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Oncolytic virus immunotherapy for cancer treatment

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Abstract
Cancer is the uncontrolled growth of cells because of mutation that occur in proto-oncogene and tumor suppressor gene. The p53 tumour suppressor gene and gene product are among the most diverse and complex molecule involved in cellular function. Nearly 50-60% of cancer occur due to mutation in p53. Surgery, radiotherapy and chemotherapy could improve the survival of cancers patient, but most patients with advanced cancer usually have a poor survival or could not afford the high cost of chemotherapy. India has the largest pool of patients with cancer. In India, preventive oncology and early detection is much more important than drug discovery. The emergence of oncolytic virus provided a new strategy for us to alleviate or even cure malignant tumors. An oncolytic virus can be described as a genetically engineered or naturally existing that can selectively replicate in cancer cells and kill them without damaging the healthy cells. On the other hands the viral infection will activate virus directed immune responses, and may trigger immune response directed against tumor cells. There have been many kinds of oncolytic viruses such as *Herpes virus*, A*denovirus* and *Coxsackievirus.* In 2004, RIGVIR, a non-pathogenic cytopathic human orphan virus, was approved in Latvia for treatment of melanoma and become the first oncolytic virus approved by regulatory authorities for cancer treatment. Three viruses currently use in clinical uses, RIGVIR, Oncorine and T-VEC have shown satisfactory therapeutic effects. Oncolytic viruses could be the next remarkable wave in cancer immunotherapy.

Keywords: Cancer, Tumor cells, Oncolytic virus, Immunotherapy, RIGVIR, Oncorine and T-VEC

Introduction
Viruses are particles that infect or enter our cells and then use the cell's genetic machinery to make copies of themselves and subsequently spread to surrounding uninfected cells. Infection by certain viruses has been implicated in the development of certain cancers, such as the hepatitis B virus (HBV) in liver cancer and the human papilloma virus (HPV) in cervical cancer and head and neck cancer. More recently, viruses have been used to target and attack tumors that have already formed. These viruses-some, but not all, of which have been modified are known as oncolytic viruses and they represent a promising approach to treating cancer for several reasons; Cancer cells often have impaired antiviral defences that make them susceptible to infection (Cook *et al.* 2020) [2]. These natural viruses can be engineered to give them advantageous properties, including decreasing their ability to infect healthy cells as well as granting them the ability to deliver therapeutic payloads specifically to tumors and produce immune-boosting molecules once they infect tumor cells. After infection, these oncolytic viruses can cause cancer cells to "burst" killing the cancer cells and releasing cancer antigens. These antigens can then stimulate immune responses that can seek out and eliminate any remaining tumor cells nearby and potentially anywhere else in the body.
The Oncolytic Virus field gained considerable attention after positive results from many clinical trials. So far, four OVs have been approved globally. The first OV, a picornavirus called Rigvir, was approved in Latvia to treat melanoma but never achieved widespread use. Secondly, an engineered adenovirus designated H101, was approved in China in 2005 to treat head and neck cancer. Thirdly, in 2015 another OV, an engineered Herpes simplex virus (HSV-1), named *Talimogene Laherparepvec* (T-VEC), was approved in the USA and Europe for the treatment of non-resectable metastatic melanoma. Finally, in 2021 a modified herpes simplex virus, named DELYTACT was approved in Japan for brain cancers such as glioblastoma. Oncolytic virotherapy received even more attention after realizing that the true potential of viruses in cancer therapy lies in the ability to trigger novel cancer-specific acquired immune responses against tumor antigens (Ramelyte *et al.* 2020) [9].

These observations have shifted the application of OVs from purely lytic agents to antitumor immune-activating agents, and the field could now be more correctly called "oncolytic immunotherapy". Another newer aspect of OV is their potential application in combination therapy with traditional and modern cancer treatment modalities, particularly with immune checkpoint inhibitors (ICIs) and T cell-based therapies.

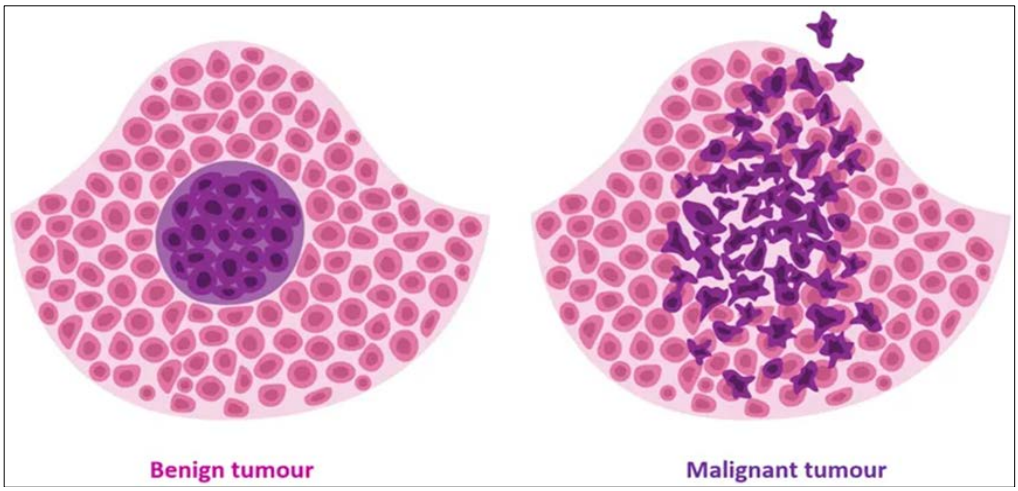

Fig 1: Different types of tumours

Mechanisms of Cancer Cell Tropism of OVs

Oncotropism of OVs generally depends on multiple factors like cell surface receptors necessary for virus binding/entry (for some, but not, all OVs), cellular metabolic status, and the ability of the virus to overcome intracellular innate immune or antiviral signaling pathways within cancer cells (likely applicable for all OVs). The early observations that some OVs exploit unique extracellular molecules expressed on cancer cells for binding and entry led to this field's initial growth. For example, CD46, CD155, and integrin α2β1 molecules are frequently overexpressed in many classes of tumor cells, and can serve as the receptor for measles virus, poliovirus, and echovirus, respectively (Yaqi *et al.* 2021) [10]. However, the same OV might use a different cell surface molecule for different cancer types. Members of oncolytic poxviruses such as VACV and MYXV displayed natural cancer cell tropism and selectively targeted tumors but this specificity is mainly because virus binding and entry is not mediated by selective receptor molecules on the cell surface (and thus virus binding is relatively promiscuous for both normal and cancerous cells), but rather is determined by the innate intracellular environment in cancerous cells being less inhibitory to the virus than in normal primary cells. After binding and entering tumor cells, OVs can exploit multiple lytic mechanisms to kill the infected cancer cells that may or may not be linked to the actual extent of virus replication within the target cells. OVs are thought to mediate antitumor activity through multiple mechanisms: (a) selective virus replication within cancer cells, causing direct cytolytic effects (a mechanism also known as oncolysis). (b) indirect effects of cell death (e.g., apoptosis-like vs. necrosis-like) on both infected and uninfected cancer cells and associated endothelial cells in the tumor-associate vasculature leading to reduced angiogenesis and (c) activation of systemic antitumor (and antiviral) immunity and recruitment of activated immune cells into the TME (Kelly *et al.* 2015) [6]. However, these mechanisms differ widely from virus to virus, the nature and type of cancer cells, and the overall interaction among the OV, TME, and host immune system. Most viruses antagonize the host-induced cell death pathways that get activated upon virus infection. In some cases, virus-encoded proteins are known to target different types of cell death pathways, either as inhibitors or inducers. However, once infected by an OV, the cancer cells will usually die from the induction of cell death pathways and/or cell integrity failure caused by virus-induced cell damage. Additionally, for preferential induction of cell lysis, some OVs have been engineered to specifically activate different types of cancer cell death pathways such as apoptosis, necrosis, autophagy, or pyroptosis.

The advantages of OVs are that they can trigger multi-mechanistic cell death pathways within the tumor bed. Among these, ICD is believed to play a crucial role in promoting acquired anti-tumor immunity. When the replication of OVs in cancer cells induces ICD, this results in the release of tumor-associated antigens (TAAs), damage-associated molecular patterns (DAMPs), OV-derived pathogen-associated molecular patterns (PAMPs), and upregulation of multiple inflammatory cytokines, all of which subsequently activate both innate and adaptive immune responses (Albert *et al.* 2018) [1]. The release of DAMPs such as extracellular ATP and high mobility group box 1 (HMGB1) proteins and those cytoplasmic proteins that become exposed at the cell surface, such as HSP (Heat shock protein) 70, HSP90, and calreticulin (CRT) are all hallmarks of ICD. After secretion, DAMP molecules bind to their receptors CD91 (CRT), P2RX7 (ATP), and TLR4 (HMGB1) on dendritic cells (DCs), which subsequently mature, process antigens, and then educate/activate T cells to enhance antitumor responses. Extracellular ATP and surface-exposed CRT act as 'find me' and 'eat me' signals to phagocytic immune cells. At the molecular level, cGAS, a DNA sensor that responds to cell stress by binding to abnormal cytoplasmic DNA in infected cells and activate STING pathways, trigger innate immunity using type I. (Galanis, *et al.* 2012) [3].

Recent studies have shown that OVs including adenovirus, parvovirus, reovirus, coxsackievirus, VACV, NDV, and HSV all induce varying degrees of ICD. OV-mediated induction of ICD plays a crucial role in converting lymphoid-deficient or low immune sensor expressing tumors (i.e., "cold" tumors) into T cell-inflamed tumors (i.e., "hot" tumors). Apart from ICD, autophagy also can induce antitumor immune responses due to OV infection and replication in cancer cells.

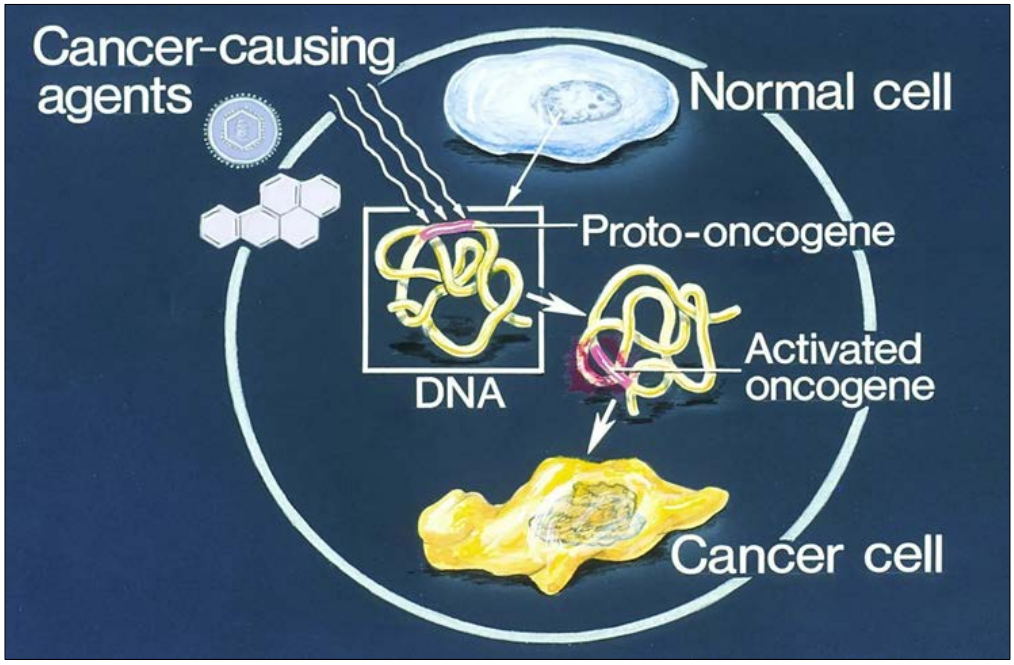

Fig 2: Critical cancer genes in oncolytic immunotherapy

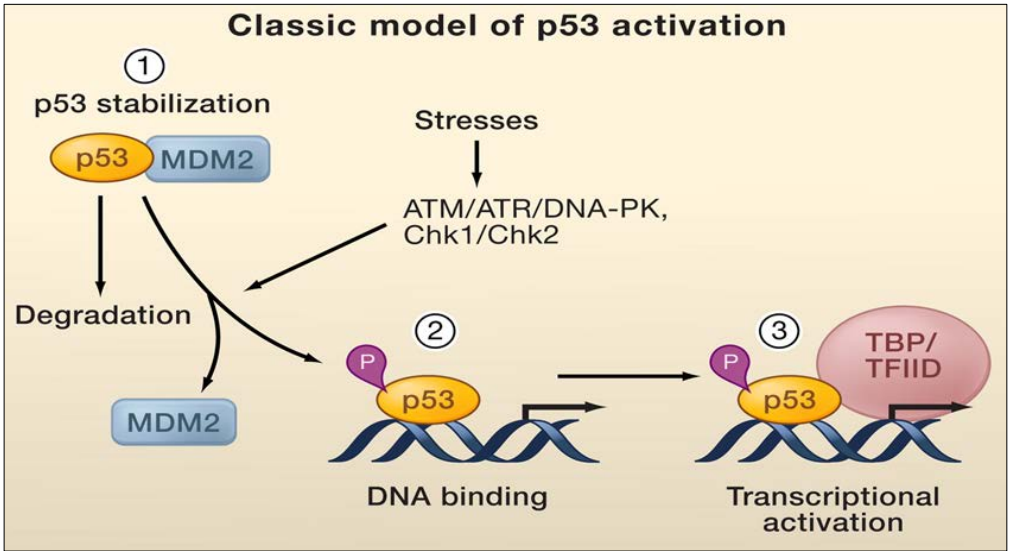

Fig 3: Classic model of p53 activation

The genetic engineering of OVs has now become an integral part of developing safe, cancer-selective, and highly effective OVs against diverse types of cancers. Engineered OVs have overcome some of the challenges that are listed in the above section. Any modification of OV relies heavily on understanding the biology and genetic information of the virus, virus-host interactions, how viruses kill infected cells, and how cells protect themselves from the lytic infection (Gong *et al.* 2016) [4]. Genetic engineering by knockout deletion of certain viral genes can enhance OV tumor cells tropism and reduced toxicity for normal cells; engineering and arming via knockins with different ectopic transgenes has enabled OV application as oncolytic immunotherapy to more broadly activate the anti-tumor immune responses. This field of developing engineered OVs and arming OVs with transgenes is rapidly expanding due to the recent discovery of many new biologics with diverse potential as immunotherapy.

During the past few years, many reviews have been written on this topic and we have briefly highlighted some of the key engineering of OVs that substantially improved application of OV as cancer therapeutics. Based on the purpose and type of transgenes used for OV engineering and modifications, they can be classified into many groups.

Virotherapy is a cancer treatment using a virus to find and destroy a cancerous cell without harming healthy cells. types of virotherapy includes oncolytic virotherapy and viral vectors, which is also called viral gene therapy. Viruses make their way into cancer cells and reproduce rapidly. The rapid viral reproduction ruptures the membranes of cancer cells and destroy them. The destroyed cancer cells release antigens, which are substances more easily recognised as foreign by the body. this stimulates the immune system to attack remaining tumour, too (Rajani *et al.* 2016) [8].

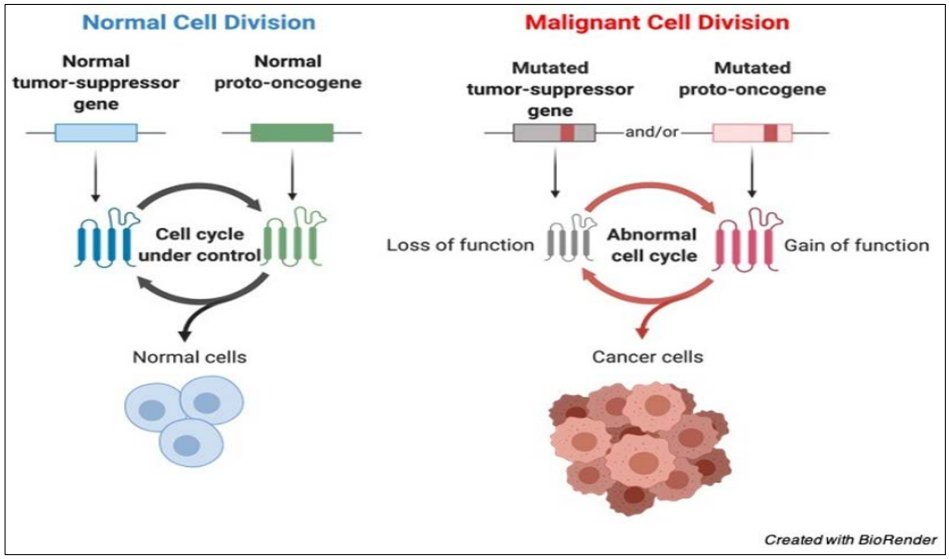

Fig 4: Mechanism of Virotherapy

Combination Therapy with Oncolytic Virus

OVs provide multi-mechanistic therapeutic effects against most types of cancers. However, in clinical trials of monotherapy, OVs with earlier generations of armings (such as GM-CSF) have shown complete response in relatively few patients. Although engineering of OVs with different approaches enhanced oncolytic activity and activated the antitumor immune responses, better therapeutic outcomes were reported when oncolytic viruses were used in combination with other cancer treatment modalities, such as chemotherapy, radiation therapy, immunotherapy, or cell therapy. (Ocean *et al.* 2013) [7]. Traditional therapies such as radiotherapy (RT) and chemotherapy have been used either alone or in combination. Radiotherapy is mostly used for the local control of tumors and displays a wide range of antitumor effects. However, due to OVs limited success, radiotherapy plus OVs have been studied as a combination therapy in preclinical models and a limited number of clinical trials. In these models, OV downregulated DNA damage repair proteins, sensitized tumor cells to the effect of RT, enhanced trafficking of immune cells, and enhanced overall survival of mice. Thus, OV-mediated inhibition of cellular DNA repair pathways can sensitize tumors with RT. Similarly, oncolytic VSV expressing IFNβ (VSV-IFNβ) in combination with RT enhanced antitumor immune response and tumor reduction in syngeneic models (Harrington *et al.* 2020) [5].

Conclusions

In summary, oncolytic viruses (OVs) represent a promising advancement in cancer treatment, utilizing their ability to selectively infect and destroy tumor cells while stimulating immune responses. Engineered to enhance their efficacy and safety, OVs are now being tested in combination with traditional and modern therapies, including chemotherapy and immune checkpoint inhibitors. This approach leverages the dual benefits of direct tumor cell killing and immune system activation, potentially overcoming the limitations of monotherapy. OVs have shown clinical success, with several already approved for use, and ongoing research continues to explore their full therapeutic potential in cancer care.

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