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Armed Oncolytic viruses: An important pioneering tool in cancer therapeutics

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Abstract

Oncolytic viruses (OVs) are emerging tools with unique characteristics that have attracted great interest in developing effective anticancer treatment. At present, the possibility to arm oncolytic viruses with therapeutic payloads is appealing more attention. A broad array of genes is under consideration as therapeutic genes arming OVs. Tumour suppressor genes are intended to counteract its loss and thus induce apoptosis of cancer cells. Cytokines and other immunostimulatory genes are aiming to enhance the systemic immune response and antitumor immunity. Prodrug-activating genes/suicide genes encode for enzymes which convert prodrugs into active form. However, recent advancements in the understanding of OVs are shifting the therapeutic paradigm toward a greater focus on their immunomodulatory role.

Keywords: Oncolytic viruses; tumour suppressor genes; cytokines; prodrug-activating genes

Introduction

Nowadays, cancer is to be considered as an important cause of death in both humans and animals. Earlier, some traditional treatments like surgery, radiotherapy, and chemotherapy have been used as cancer therapeutics. While, currently novel therapeutic strategies such as immunotherapy, hormone therapy, stem cell therapy, chimeric lymphocyte therapy, and oncolytic virotherapy are being developed to fight against neoplasm. [2, 8]. Amongst them, oncolytic virotherapy have aroused great interest in human medicine due to the advancement in biotechnology. Generally, the oncolytic viruses can selectively replicate in tumour cells and destroy them without affecting healthy cells [11, 1]. Additionally, some important cellular

responses like translation suppression and apoptosis are restricted in tumour cells to limit the viral infections. However, the tumour cells have several defence mechanisms against immune recognition which can be responsible for viral tropism towards neoplasm.

Oncolytic viruses have several important properties like selective replication in malignant cells, immunostimulant effect and transgene delivery. Usually, oncolysis causes the virus release from infected host cell and its subsequent spread amongst nearby tumour cells. The replication of oncolytic virus results in release of tumour-specific and virus-specific antigens together with damage-associated molecular pattern molecules (DAMPs). Subsequently, its uptake and presentation by the dendritic cells (DCs) leads to the induction of tumour- and virus-specific T cells. These all event are responsible for the remarkable inflammatory response and chemokines release. Currently, some oncolytic viruses such as adenovirus, herpes virus and vaccinia virus have been genetically modified to carry therapeutic transgene. These transgenes include cytokines, antibodies and pro-drug convertase enzymes. The specific delivery of armed genes in tumour microenvironment is responsible for an effective cancer therapy [4]. In this article we have briefly discussed regarding some available armed oncolytic viruses those are caring various therapeutic transgenes.

Armed oncolytic viruses with tumour suppressor genes

The intension of tumour suppressor gene's arming with oncolytic viruses is to counteract loss of these genes. There are different types of tumour suppressor genes which include p53, Rb, p21 and p27. In 2002, Sauthoff *et al.,* [9] engineered p53 gene into the replicating adenovirus and demonstrated its expression to improve tumour killing activity. Till today, numerous pre-clinical studies have been conducted regarding restoration of tumour suppression function. Currently, the theoretical bases for these virotherapies have been reviewed. The tumour suppressor genes can affect a number of pathways in the cell, which might be indirectly compromised the engineered or endogenous tumour selectivity mechanism of the oncolytic virus.

Armed oncolytic viruses with prodrug converting enzymes

The efficacy of traditional chemotherapies has been hampered by dose -limiting toxicities to normal cells. Prodrug therapies seek to reduce the toxicity by selective generation of chemotherapeutic agent at the target site. Such prodrug - based cancer therapies have two basic components: an inactive, nontoxic prodrug and a prodrug - activating enzyme. The prodrug only becomes cytotoxic when activated by the appropriate enzyme. If the activating enzyme is expressed exclusively in tumour cells, then the prodrug will be activated, or become cytotoxic, only at the site of the target cancer cell [6]. These bystander effects are particularly important to compensate the inefficient infection and transduction of tumour cells.

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Armed oncolytic viruses with antiangiogenic substances

The uncontrolled growth of tumour is depending on an adequate supply of oxygen and nutrients from the blood. When tumour growth exceeds the normal blood supply to a tissue or organ, new blood vessel formation must be stimulated that can be termed as tumour neovascularization [5]. Vascular endothelial growth factor (VEGF) is to be considered as a major mediator of angiogenesis; therefore, several antiangiogenic strategies are based on blocking VEGF. However, the development of these inhibitors as therapeutics has been hampered due to manufacturing difficulties and solubility issues.

Armed oncolytic viruses with cytokines

Cytokines are to be considered as key players in stimulating and regulating antitumor immune responses. The most essential cytokines in the anti-tumour response are IL-12, GM-CSF and IL-2 [10]. Despite of immune modulatory actions, the cytokines have lost popularity due to low objective response rates and non-negligible side effects upon systemic administration. Hence, several viruses have been engineered to express different cytokines or chemokines. The most extensively studied transgene is the cytokine GM-CSF which promotes dendritic cells recruitment and maturation. Currently, GM-CSF has been successfully used to arm Herpes simplex virus (HSV) and this armed virus has been approved by the FDA under the name of T-VEC for treatment of metastatic melanoma patients.

Armed oncolytic viruses with checkpoint inhibitors

One of the most promising immune therapeutics are checkpoint inhibitors. Inhibitory receptors such as CTLA-4 and PD-1 act as checkpoints to avoid over activation and inhibit the T cell activation in the lymph nodes and survival in the TME [7]. Treatment with these inhibitors results in reactivation of the suppressed immune cells. Additionally, variety of other co-inhibitory receptors like lymphocyte activation gene 3 (LAG-3), T cell immunoglobulin and mucin receptor protein 3 (TIM-3) have been recently identified. LAG-3 is normally activated by its ligand MHC-II on APCs and indirectly reduces T cell proliferation.

Armed oncolytic viruses with bispecific T cell engagers

BiTEs (bispecific T cell engagers) are a class of bispecific monoclonal antibodies that have shown promising anti-tumour effects. These antibodies simultaneously bind to CTLs via T cell receptor (TCR) and expressed tumour antigen resulting in bypassing MHC dependent antigen presentation. However, they have a very short half-life and therefore require continuous infusion. Vaccinia virus (VV) armed with BiTE (specific for TCR and TAA) was tested in a xenograft lung cancer mouse model. The study has showed increased tumour cell killing through T cell activation [3].

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Conclusion and future view

Armed oncolytic viruses represent a promising frontier in the battle against cancer. Their unique ability to selectively target and destroy cancer cells, stimulate the immune system, and incorporate therapeutic payloads offers multifaceted benefits in the quest for more effective and personalized cancer treatments. As part of evolving combination therapies and personalized medicine approaches, armed oncolytic viruses hold the potential to transform cancer care. The future of armed oncolytic viruses in cancer treatment is poised to revolutionize the field. With the prospect of improved long-term outcomes, reduced side effects, and broader clinical adoption, these innovative viral therapies hold great promise in shaping the future of cancer therapeutics.

Table 1. Currently developed armed oncolytic viruses

Virus family	Virus name	Armed substances	Route of administration	Phase and type of clinical trail
Herpesviridae	Talimogene laherparepvec	Armed with GM-CSF	Intratumoral	Phase III complete; melanoma
Adenoviridae	CG0070	Armed with GM-CSF	Intravesicular	Phase II and III; bladder cancer
Poxviridae	JX-594 (Pexa-Vec)	Armed with GM-CSF	Intratumoral	Phase IIB; Hepatocellular carcinoma
Paramyxoviridae	MV-NIS	Armed with human NIS	Intravenous	Phase I; myeloma
Rhabdoviridae	VSV-hIFNβ	Armed with human IFNβ	Intratumoral	Phase I; hepatocellular carcinoma
Retroviridae	Toca 511	Armed with cytosine deaminase	Intratumoral Intravenous	Phase I and II; glioma

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