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Oncolytic Viruses in Tumorigenic Pathways

Bharat Mishra*, Joyalyn Joy, Linda Mariya Jose and Prasanth Francis

*Department of Pharmacology, Nirmala College of Pharmacy, Muvattupuzha, Ernakulam, Kerala, Pin code: 686631, India

ABSTRACT

Toxicity remains a major issue with current anticancer agents due to non-selective action. Immunotherapy is a profound development in anti-cancer treatment due to its ability to deliver therapy to specific cellular targets. Cancer immunotherapy is based around the concept of helping the immune system to recognize and attack certain cancer cells. The cancer-killing properties oncolytic viruses are supported by observations that in case of the chickenpox infection which brought back the WBC count and lymph node status in patients with lymphocytic leukemia. Measles improved in the prognosis of leukemia, Hodgkin's, and Burkitt's lymphoma. The viruses kill neoplastic cells as well as trigger already existing but ineffective anti-tumor immune response against the tumor. Virus infection of a tumor cell results in the virus making copies of it until the cell bursts. The dying cancer cell releases materials, such as tumor antigens, that allow the cancer to be recognized, by the immune system. Numbers of researchers are working in this field to utilize virus to bring novel therapeutic options for various cancers. Adenovirus type 5 injection which is the first oncolytic virus-drug named 'ONCORINE' was approved in 2005 for head and neck malignancy. A second one approved by the US FDA in October 2015, Talimogene laherparepvec (T-VEC), a genetically engineered herpes virus, that could treat advanced melanoma. More viruses are under trial for their oncolytic potential. In this article we intend to portray the various altered pathways developed, by which the tumour cells gain the trait to bring about increased viral tropism and tumour toxicity.

Keywords: Toxicity, Oncolytic Virus, Immunotherapy, Tumour Toxicity, Specificity

INTRODUCTION

Cancer, a condition in which cellular changes causes the uncontrolled growth and division of cells, they build up within the body, use oxygen and nutrients that might usually nourish other cells. Tumors grow in an immunosuppressive environment where the immune reactions against cancer cells are silenced by the tumour itself. Cancer treatment includes surgery, chemotherapy and radiation therapy. Immunotoxins like monoclonal antibodies of bacterial or plant protein toxins is also a potential therapy for treating cancer [1]. Surgery is the most common treatment for cancer. It minimises the cancer but cannot completely cure. The process of anticancer drugs used to kill cancer cells is known as chemotherapy. Radiation therapy is additionally one among the method which kills neoplastic cell, by using X-rays, gamma rays and charged particles cancer treatment is done successfully [2]. The inability of chemotherapy and radiotherapy to selectively target cancer cells leads to a very high degree of toxicity [3]. Also, the development of chemo-resistance leads to inappropriate response to chemotherapeutic agents and some of the treatments have side effects like myelosuppression, hypertension, hyper pigmentation, diarrhoea, headache, etc.

*Corresponding Author
bharatekansh[at]gmaildotcom

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Growth Signalling in Cancer Development

Growth factor receptor signalling is intimately related with tumor progression. Genetic changes leading to constitutive activation of protein signaling pathways end in uncontrolled proliferation, differentiation and/or metastasis, and are related to most if not all human cancers. Growth factors (GFs), are regulators of tumor progression, their function including clonal expansion, invasion across tissue barriers, angiogenesis, and colonization of distant niches [4]. Many tumour cells acquire mutations that enable them to escape IFN-mediated signaling pathways that regulate proliferation and apoptosis [5]. Studies revealed that virally transformed cells, chemically transformed cells, as well as cells derived from human tumors, often secrete GFs, which are responsible for self-stimulation (autocrine) of growth [6]. Some of the examples of molecular signalling and their prevalence in cancers are, RAS mutations characterize up to 25% of human cancers, and mutational inactivation of a TGF-β effector, SMAD4/DPC4, is abundant in pancreatic tumors etc [6].

Oncolytic Virus

Oncolytic virus (OV) , are a group of virus that selectively invades cancer cells; as these (cancer cells) die under the viral burden, the released virus particles proceed to infect other cancer cells. Oncolytic viruses are engineered to be able to stimulate the anticancer immune response. Clinically tested oncolytic agents include adenovirus, reovirus, measles, herpes simplex, Newcastle disease virus, and vaccinia virus [7]. The delivery of OVs into the tumor wakes up the immune system in order that it can facilitate a robust and sturdy response against the tumor itself. OVs encoding tumor antigens are often utilized in vaccination strategies. To discover a balance between anti-tumor and anti-viral immunity is, under this new light, a priority for researchers [7].

Oncolytic Virus Tumour Tropism

Tumor cells acquire mutations that allow them to escape IFN-mediated signalling pathways that regulate proliferation and apoptosis, but alteration in IFN signalling cripples the innate antiviral response of tumor cell [8]. The defects in translational control or in other signalling pathways, such as those involving Myc, Ras, Akt, and p53, renders them susceptible to lethal viral infections [9]. Selective tumor cell replication can be attributed to infection of neoplastic cells, which harbor low levels of protein kinase R (PKR) and dysfunctional type I IFN signaling elements. These modifications allow more efficient viral replication, and with deletion of specific viral genes, replication in normal cells with activated PKR is prevented [10].

Mollecular Pathways Involved in the Tumourigenesis Process and Effect Of Viruses

Virus and Ras pathway

The Ras/Raf pathway is one of the crucial cell signaling pathway utilized by eukaryotic cells for growth and proliferation. Mutations during this pathway cause uncontrolled growth and proliferation of cancerous cells, effectively giving them a serious advantage over normally functioning cells. Activation of Ras causes the phosphorylation of the downstream protein referred to as Raf [11]. Activation of Ras causes the synchronizing activity of transcription factors controlling type of genes related to the cell cycle, growth, proliferation, differentiation, and apoptosis [12]. In normal cells, viral protein synthesis is blocked by antiviral mechanisms, but in transformed cells, dysregulated translation and compromised antiviral mechanisms combine to allow successful virus replication [13]. The various viruses affecting the Ras pathway includes HSV-1, VSV, and Reovirus. Action of HSV-1 was studied in NIH-3T3 cells and found that NIH-3T3 cells transformed with the oncogenes such as v-erbB, or activated Ras (all activators of the Ras signalling pathway) become more permissive to HSV-1. Ras pathway Inhibitors as farnesyl transferase inhibitor 1, effectively

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suppressed HSV-1 infection of Ras transformed cells. The farnesyl transferase inhibitor FTI-1, at its effective levels blocked HSV-1 infection in Ras transformed cells by reducing the level of viral protein synthesis. Farnesyl protein transferase inhibitor II (FPTI-II), was also effective in blocking HSV-1 infection in these cells [12]. Inhibition of viral protein synthesis is the principal anti-viral strategy of the host cell, and is usually achieved by phosphorylation of the double-stranded RNA-activated protein kinase (PKR). PKR phosphorylation results in the phosphorylation of the translation initiation factor eIF-2α, which causes the inhibition of translation of the viral transcripts in normal cells. In transformed cells, the PKR phosphorylation is prevented or reversed by activated Ras or one of its downstream elements, causing the viral gene translation to proceed. Elements of the Ras signalling pathway inactivate PKR, resulting in enhanced infection of the transformed cells. Viruses having ineffective anti-PKR mechanism would infect only transformed cells and be potentially Oncolytic [11].

Vesicular stomatitis virus (VSV) had an efficient action on activated Ras pathway which resulted rapid depletion of tumour cells. Vesicular stomatitis virus (VSV) can multiply in malignant cells more efficiently than in normal cells. Although the selective replication appears to be caused by defects within the interferon (IFN) system in malignant cells, cancer cells showed defects in inducing an IFNα-responsive factor, MxA, which is known to stop VSV RNA synthesis, activation of the extracellular signal-regulated protein kinase (ERK) signaling results in the defect in IFNα-mediated upregulation of MxA protein, which facilitates VSV oncolysis. Activated RAS or Raf1 weakened the IFNα-dependent anti-VSV effects. The RAS/Raf1/ MEK/ERK pathway is crucial for VSV-mediated oncolysis. Overexpression of RAS/Raf1 resulted in the negative regulation of the IFNα-induced antiviral responses [9].

In case of reovirus

Reovirus inherently prefers replicating in cells with dysregulated protein signaling cascades that consist of Ras activation. Lack of PKR phosphorylation in reovirus infected Ras-transformed cells suggested that reovirus translation is spared in transformed cells because PKR isn't activated .Ras transformed cells experience an absence of translational suppression molecules like PKR which is augmenting in reoviral replication. In reovirus it was found that activated RA1GEF pathway was used by the virus for infection [13]. RalGEF activity is necessary to render cells permissive to reovirus. Active Rlf acts similarly to Ras to enhance reovirus infection at the extent of translation. RalGEF is necessary for reovirus protein synthesis. Inhibition of Ral signaling inhibits initial stages in replication, namely, viral attachment and process of transcription p38 is an emerging promising candidate downstream molecule in Ras promotion of viral replication. RalGEF is likely to be upstream of p38. Moreover, genetic and chemical inhibition of PKR promotes reovirus protein synthesis. Thus, it is conceivable that Ras suppression of PKR activity promotes viral protein synthesis [14].

Defence response – IFN signalling

Interferons belong to the family of autocrine and paracrine cytokines secreted by host cells in response to pathogens, especially viruses [15]. They are circulating factors that bind to cell surface receptors, activating a signaling cascade, ultimately leading to both an antiviral response and an induction of growth inhibitory and/or apoptotic signals in normal and tumor cells [16]. The main anti-cancer effects of interferon include immunoregulatory effects, suppression of cell growth inhibition of cell migration, promotion of cell death and senescence, and prevention of angiogenesis [15]. Tumor cells, which have lost their interferon responsiveness, become selective targets for the virus. VSV replicates in tumor cells, resulting in cytolysis and spread of the virus to neighbouring tumor cells, [16].

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In case of Talimogene Laherparepvec (T-VEC) can target and propagate in cancer cells by using surface-bound nectins to enter the cell and preferentially replicates in tumor cells by exploiting disrupted oncogenic and antiviral signaling pathways, most notably the protein kinase R(PKR) and type I IFN pathways, [17]. The MAPK kinase (MEK), which plays a key role in the MAPK signaling pathway, suppress the activation of PKR and subsequently promote replication of HSV-1 in tumor cell lines in vitro. T-VEC infection is an enhanced disruption of type I IFN pathway in tumor cells. Type I IFNs mediate both antiviral and antitumor responses by limiting cellular proliferation and promoting viral eradication, [18].

Epigenetic Silencing of IRF7 and/or IRF5 in Lung Cancer Cells Leads to Increased Sensitivity to Oncolytic Viruses and was found that manipulating IFN signaling by altering IRF expression changes the viral susceptibility of these cells. Lung cancer cells are often partially shielded from viral killing using IRF5+IRF7 over expression, whereas IFN pathway disruption by transfection of siRNAs to IRF5+IRF7 increases cell's vulnerability to virus infection. Therefore, IRF5 and IRF7 are key transcription factors in IFN pathway that determine viral sensitivity of carcinoma of lung cells; the epigenetically impaired IFN pathway in carcinoma tissues provides potential biomarkers for a successful selective killing of cancer cells by oncolytic viral therapy [19]. Enhanced expression of IRF5 and/or IRF7 could possibly reactivate IFN related genes, inhibit cell growth, and may also induce senescence. The sensitivity to oncolytic VSV was strongly due to the disruption of the IFN signaling pathway. IRF5 and IRF7 are vital factors in IFN pathway that determine the viral sensitivity of the cells to OVs. IRF5 and IRF7 are the main two fundamental factors in IFN signalling that regulate oncolytic viral sensitivity. Transcription factors IRF5 and IRF7 were found to be the critical regulators of innate immune system and also the useful biomarkers for oncolytic virus susceptibility in lung cancer cells [19]. In addition to VSV, other RNA viruses like NDV and influenza virus have also been demonstrated to possess tumor-selective cytotoxicity using an equivalent mechanism to focus on cells with diminished IFN activity [9]. Cancer selectivity results through IFN-mediated inhibition of replication in normal tissues, whereas replication and oncolysis proceeds unhindered in tumor cells with defects in IFN responses [20].

Virus and p53 pathway

p53 is a tumour suppressive gene that codes for a protein that regulates the cell cycle. p53 has its role in conserving stability by preventing genome mutation, hence it is known as guardian genome. It plays a crucial role in cell cycle control and apoptosis. Defective p53 could allow abnormal cells to proliferate, leading to cancer. Around 50% of all human tumors contain p53 mutants. In normal cells, the p53 protein level is found to be low. DNA damage and other stress signals may trigger the rise of p53 proteins, which have three major functions: growth arrest, DNA repair and apoptosis (cell death). The growth arrest halts the progression of cell cycle, preventing replication of damaged DNA. During the expansion arrest, p53 may activate the transcription of proteins involved in DNA repair [21], [22] ONYX-015 (dl1520, CI-1042) is a modified adenovirus which selectively replicates in p53-deficient cancer cell but not normal cells [23]. It is modified from an epidemic that expresses the first region protein, E1B, which binds to and inactivates p53. P53 suppression is important for the virus to multiply. In the advanced version of the virus E1B was deleted. E1B was found to have other are which vital to the virus. In addition, its specificity was undermined by finding that the virus is able replicate in cells with wild-type p53 [21].

Both reovirus and myxoma virus preferentially infect cancer cells bearing dysfunctional or deleted p53, ATM and Rb tumor suppressor genes. ATM (ataxia telangiectasia mutated) is a serine threonine protein kinase that is activated in response to DNA damage. Loss of p53 activity confers increased susceptibility to reoviral and myxoma viral infectivity, replication and cytolysis. Activity of a minimum of three different tumor suppressor genes (p53, ATM and Rb) can modulate responses to those oncolytic viruses. It was found that a mutant adenovirus that did not express E1B replicated

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and killed p53-dysfunctional human tumor cells. p53 gene contributed to innate immunity by enhancing the interferon-dependent antiviral activity of cells independent of its functions both as a pro-apoptotic and tumor suppressor gene [23].

Virus and the AKT/MTOR pathway

The phosphatidylinositol 3-kinase/protein kinase-B/mammalian target of rapamycin (PI3K/AKT/mTOR), which is associated with the mitogen-activated protein kinase (MAPK) pathway, is a crucial and extensively studied intracellular signaling pathway in tumorigenesis. The Akt pathway, or PI3K-Akt Pathway could also be a signal transduction pathway that promotes survival and growth in response to extracellular signals. The phosphatidylinositol-3-kinase (PI3K) pathway plays an important role in cell growth and survival and is activated in various cancers. PI3K pathway has a crucial role in normal cell growth and in the cellular response to stress [24].

Normal cellular mechanism

Initial stimulation by one among the expansion factors causes activation of a cell surface receptor and phosphorylation of PI3K, leading to activation of Akt. Activated Akt mediates downstream responses, including cell survival, growth, proliferation, cell migration and angiogenesis, by phosphorylating a variety of intracellular proteins. The pathway is present in all cells of higher eukaryotes and is highly conserved [25].

Alteration in tumours

Problems with PI3K-Akt pathway regulation can cause increase in signalling activity. This has been linked to a variety of diseases like cancer and sort II diabetes. A major antagonist of PI3K activity is PTEN (phosphatase and tensin homolog), a tumour suppressor which is usually mutated or lost in cancer cells. Studies have documented gene amplification of the Akt isoforms in various types of cancer, including glioblastoma, ovarian, pancreatic and breast cancers [26]. Akt is also up-regulated in terms of mRNA production in breast and prostate cancer. Hyperactivity of the pathway promotes the epithelial-mesenchymal transition (EMT) and metastasis due to its effects on cell migration [27]. Akt also contributes to angiogenesis by activating endothelial gas synthase (eNOS), which increases production of nitric oxide (NO) [28]. In cancer cells, a rise in Akt signalling correlates with a rise in glucose metabolism, compared to normal cells. Cancer cells favour glycolysis for energy production over mitochondrial organic process, even when oxygen supply isn't limited [29]. High endogenous levels of phosphorylated Akt in human cancer cells indicate susceptibility to myxoma virus infection and that constitutive activation of Akt is required for productive myxoma virus (MV) infection. Evidence of phosphorylated Akt and PTEN mutations in human medulloblastoma samples suggests that constitutive activation of the PI3K/Akt pathway may be a crucial step in medulloblastoma tumorigenesis. Susceptibility of human cancer cells to infection with myxoma virus is directly correlated to levels of activated Akt pathways that lead to activation of its downstream effectors that are involved in myxoma virus replication [30]. Rapamycin has been found to increase both Akt activation and myxoma virus replication in a variety of different cancer cell. Myxoma virus may be a valuable therapeutic option in reovirus-resistant tumors and may address the problem of innate or acquired resistance [30].

Virus and VEGF signalling pathway

Blood vessels can be critical for the expansion of tumors in human hosts. Cancer biologists have observed that blood vessels were essential to support tumor growth beyond the dimensions allowed by oxygen diffusion alone. The vascular endothelial protein (VEGF) family of growth factors consists of mediators of angiogenesis and lymphangiogenesis when looked into the

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context of tumor biology. The several endothelial cell functions regulated by VEGF, include mitogenesis, permeability, vascular tone, and therefore the production of vasoactive molecules. The VEGF family signals predominantly through the receptor tyrosine kinases, along side the co-receptors neuropilin (NP)-1 and NP-2, and, in some cases, other receptors such as integrins [31]. Hematologic malignancies have seen elevated levels of VEGF circulating as well as cellular. Transcription of the VEGF gene is physiologically regulated by hypoxia-mediated control of gene transcription [32]. Tumor neo-vasculature is different in several ways from normal blood vessels as a result of chronic exposure to pro-angiogenic cytokines that are secreted by cancer cell signaling events triggered by vascular endothelial growth factor (VEGF) capable of antagonizing cellular antiviral responses, which causes the tumor endothelial to sensitize their cells to Oncolytic virus infection and destruction [33].

VEGF/VEGFR2 signaling through Erk1/2 and Stat3 causes the up regulation, nuclear localization, and activation of the transcription repressor PRD1-BF1/Blimp1, which are genes involved in type I interferon (IFN)-mediated antiviral signaling. Suppression of the VEGF signalling *in vivo*, decreases PRD1-BF1/Blimp1 expression in tumor vasculature and inhibits intravenously administered oncolytic vaccinia delivery and spread within the tumor. VEGF treatment led to tampering of the type I interferon (IFN) response. In addition to oncolytic vaccinia, other type I IFN-sensitive OV strains, like herpes simplex virus (HSV), lacking one copy of ɣ34.5, the rhabdoviruses VSVD51, and Maraba virus MG1 , demonstrated enhanced infectivity [33]. Tightly associated endothelium of normal blood vessels causes the suppression of VEGF signals and resistance to infection, altered tumor vasculature having excess of VEGF supports oncolytic virus replication and acts as channel for virus spread from the vascular system into the tumor bed [34].

Future Prospective

The Difference in susceptibility of tumor cell types to distinct Oncolytic viruses reflect the differing tropism requirements of a given virus, considering the heterogeneity that is observed in the signaling microenvironments of different tumors. As mentioned, susceptibility to reovirus oncolysis is highly correlated with the presence of activated Ras, whereas myxoma virus requires Akt activation for permittivity [34]. Identification of the signal aberrations in various tumours and administering the susceptible OV for specific oncolysis will see a significant effect in tumour specific treatment. Research into modifying OV to increase their tumour specificity and enhance their safety profile holds for the future development of cancer therapy [35].

Combinatorial therapy with the already existing chemotherapy and radiation therapy could lead to faster tumour regression and prevent relapses. As OVs can be used as vehicles to incorporate genes into tumour cells that activates a harmless prodrug to cause site specific toxic chemotherapy as well as delivery of genes that enable tumour cells to concentrate proteins that are tagged with radioactive iodine so that only micro doses of radiation is required for cancer cell destruction are areas of ongoing research. OVs can also be employed as potential vectors to deliver tumour toxic substances or tumour specific antigens to further enhance anti-tumour efficacy [36].

CONCLUSION

OVs sustain replication in cells containing aberrant signalling pathways (tumour cell lines), induce cell lysis and release of immune stimulators (antigens), triggering the wake-up of the existing cold immune environment against tumour and the virus themselves. Altered signalling pathways induce a decrease in antiviral IFN signalling. Downstream molecules of altered pathways serve as essential components of viral replication. These two events enable targeted viral replication in tumour cells. Excess virus load cause cell lysis and specific immune mediator release that trigger immune response. This could probably suppress unidentified

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metastasis at lower doses of viral treatment. The future effect of the viruses is thanks to this immunological activation. The generated immunological memory may further prevent the relapse of the tumour. Genetically modified OVs confer less injury to normal cells.

ABBREVIATIONS

a) T-VEC - Talimogene laherparepvec
b) SMAD4/DPC4- Signal transduction proteins
c) OV - Oncolytic virus
d) IFN – Interferon
e) HSV-1 – Herpes simplex virus 1
f) VSV – Vascular stomatitis virus
g) NIH 3T3 - Continuous cell line of high contact-inhibition established from NIH Swiss mouse embryo cultures
h) EGFR – Epidermal growth factor receptor
i) PKR – Protein kinase R
j) IRF7/IRF5 – Interferon regulatory factor
k) MV – Mixoma virus
l) VEGF - Vascular endothelial growth factor

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