VIRUSES AND HUMAN CANCER: FROM CAUSALITY TO CURE

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ABSTRACT

The role of viruses in cancer may be viewed as a double-edged sword. It is estimated that about 20% of all cancer cases across the globe are due to persistent viral infections. Oncoviruses can be DNA or RNA viruses that induce mutation in the target host cell, although perseverance of viral infection alone is not adequate for formation of tumors but is one of the steps in the multi-step process of cancer development. The virus-infected host cells after having undergone genetic changes enter cell cycle and produce next progeny of transformed cells which have characteristics of autonomous growth and survival completing their role as oncogenic virus. The traditional chemotherapy and radiotherapy have limited therapeutic index and plethora of treatment related side effects. This situation has provided a thrust for search of novel therapeutic strategies that can selectively destroy tumor cells, leaving the normal cells unharmed. Recent technical advances in the genetic modification of the virus to improve their tumor specificity have led to the transformation of virus as weapon against cancer called as Oncolytic virus. This review attempts to summarize the causative association of virus with cancer and the techniques by which the virus can be metamorphosed as cure that kills tumor cells along with developments made on Oncolytic virotherapy for cancer treatment.


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INTRODUCTION

Cancer is one of the leading causes of death worldwide. Despite of significant progress made in various cancer treatment modalities, mortality rates for most malignancies remain unpleasantly high. Neoplasm progression is one of the major challenges faced by modern medicine. Cancer is the result of decreased cell death or increased cell birth. In other words, decreased tendency for apoptosis contributes to tumor formation. Worldwide estimation is that about 20% of all cancers are due to persistent virus infection [1]. The association of virus with neoplasia was first observed by an Italian physician Sanarelli in 1889 who noted association between myxomatosis of rabbits with poxvirus. Since then, a number of viruses capable of inducing tumors (oncogenic viruses) in experimental animals, and some implicated in humans have been identified [2]. DNA or RNA viruses may induce mutation in the target host cell, although persistence of viral infection alone is insufficient for oncogenesis but is one of the steps in the multi-step process of cancer development. The virus infected host cells after having undergone genetic changes enter cell cycle and produce next generation of transformed cells which have characteristics of autonomous growth and survival completing their role as oncogenic virus [3]. In spite of achieving significant successes in medical sciences in the past few decades, the mortality rates due to cancer remain unchecked. Another major problem of cancer therapy is the incomplete eradication of the invasive primary tumor mass or dissemination of cancerous cells leading to recurrence of disease.

The current goal for developing novel therapies for the treatment of cancer is to design therapeutic agents that have a high therapeutic index (i.e. high potency against malignant cells) with little or no toxicity to normal cells. Recent technical advances in the genetic modification of the virus to improve their tumor specificity have led to the development of new weapons for war against cancer. The classical regimen of cancer therapy (chemotherapy, radiotherapy and immunotherapy) suffers with disadvantages such as narrow therapeutic index that further reduces as tumor evolves drug resistance and severe side-effects. With the advent of better understanding of cancer biology and virology, it has become possible to engineer viruses with increased tumor selectivity and enhanced oncolytic activity. Interestingly the replication cycle of many viruses exploits the same cellular pathways that are altered in cancer cells. Specific targeting of tumor cell can be achieved by taking advantage of the fact that tumor cells have altered microenvironment, display certain tumor specific receptors and modified cellular pathways. Gene therapy and oncolytic virotherapy represent the modern treatment modalities that offer unique opportunities for effective tumor targeting [4]. Many different viruses are used in oncolytic virotherapy but the first virus to enter the clinic was ONYX-015 (an oncolytic adenovirus) that exhibited both the safety and anti-tumor potential of this approach [5]. The results of the early phase II and III clinical trials have allowed the investigators to examine the limitations of these viruses, restrictions in this kind of therapy and also to develop potentially far more effective approaches. In this review, we discuss the various viruses that cause cancer, the challenges in oncolytic virotherapy and the mechanisms how the recent advances from improving virus delivery to altering host immune responses have paved way by overcoming hurdles for the development of safe and effective virotherapy against cancer.

General aspects of viral carcinogenesis

The infectious nature of oncogenic viruses sets them apart from other carcinogenic agents. A thorough study of both the pathogenesis of viral infection and the host response is decisive to a full understanding of the resulting cancers. Human oncogenic viruses belong to different virus families and utilize different strategies to contribute to cancer development; however they share many common attributes. One key attribute is their ability to infect, but not kill, their host cell. Oncogenic viruses have the propensity to establish long-term infection in host cell and consequently, develop strategies for escaping the host immune response, which would otherwise inactivate the virus. Despite the viral etiology of several cancers, it appears that the viruses often are not adequate for, but may contribute to carcinogenesis. The additional co-factors that play an important role in the transformation process are the host immunity, chronic inflammation and additional host cellular mutations. The long-term interactions between virus and host are key features of the oncogenic viruses, as they set the platform for a variety of molecular events that may contribute to eventual virus-mediated tumorigenesis [6].

Human oncogenic viruses

Oncogenic viruses lead to the development of malignant tumours by actively encouraging cell transformation and prompt uncontrollable cell generation. Oncogenic viruses belong to a number of virus families, which includes the DNA virus families (Retroviridae and Flaviviridae) and the DNA virus families (Hepadnaviridae, Herpesviridae, Papillomaviridae) [7]. Studies of the RNA and DNA tumour viruses have led to the discovery of oncogenes and tumour suppressors and have greatly added to our understanding of the etiology of carcinogenesis, both virally and non-virally induced. Virus-promoted malignant transformations in cells are the first step in the complex oncogenesis process [8]. The genes in the viral genome that change host cell proliferation control are called viral oncogenes (v-onc genes) which lead to the synthesis of new proteins, and are responsible for transformation characteristics. Viral oncogenes constantly struggle with tumour suppressor genes, which protect DNA and control cell activities. The tumour suppressor genes lose this struggle or viral oncogenes win this struggle, and it leads to cancer [9].

DNA tumor viruses

DNA tumour viruses have two life forms. The cells which are in permissive state, viral replication causes cell lysis and cell death compared to the non-permissive cells in which the viral DNA is mostly integrated into the different sites of the cell chromosomes. There it encodes binding proteins which inactivates cell growth, regulating proteins like p53 and retinoblastoma. As a result of the expression of the proteins that regulate viral and cellular DNA synthesis the cell gets transformed [9]. Human oncogenic DNA viruses are shown in Table 1[1, 10-12].
Table 1: Human oncogenic DNA viruses.

<table>
<thead>
<tr>
<th>Taxonomic grouping</th>
<th>Examples</th>
<th>Tumour types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoviridae</td>
<td>Adenovirus types 9, 12, 18, 31</td>
<td>Various solid tumours in rodents</td>
</tr>
<tr>
<td>Hepadnaviridae</td>
<td>HBV</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Herpesviridae</td>
<td>EBV, KSHV (HHV-8)</td>
<td>Burkitt’s lymphoma, Nasopharyngeal carcinoma, B-cell lymphoma, Hodgkin’s lymphoma, Kaposis’s sarcoma, MulticentricCastleman’s disease</td>
</tr>
<tr>
<td>Papillomaviridae</td>
<td>HPV types 6, 11, 16, 18, 31, 45</td>
<td>Oral, cervical, and anal cancer</td>
</tr>
<tr>
<td>Polyomaviridae</td>
<td>Merkel cell polyomavirus</td>
<td>Merkel cell carcinoma</td>
</tr>
<tr>
<td>Poxviridae</td>
<td>MCV</td>
<td>Various solid tumours</td>
</tr>
</tbody>
</table>


RNA tumor viruses

All oncogenic RNA viruses are retroviruses. In 1961, it was found that Rous sarcoma virus (RSV) particles contain RNA; therefore, oncogenic retroviruses are called RNA tumor viruses [7]. In retroviruses, more than 30 oncogenes were defined [10]. Retroviruses have 3 basic genes (gag, pol and env), which are utilized for the production of structural proteins, virion-associated enzymes, and envelope glycoproteins [13]. In tumor development, RNA tumor viruses use different oncogenic mechanisms. Some encode oncogenic proteins, which are similar to the cellular proteins in cellular growth control. Overproduction of these oncogenic materials or modification in their functions stimulates cellular proliferation. The RNA tumour viruses upon infection of the permissive cells; releases progeny virus through budding. The permanent genetic mutations transform the infected cell into cancer [9]. Human oncogenic RNA viruses are shown in Table 2[8].

Table 2: Human oncogenic RNA viruses.

<table>
<thead>
<tr>
<th>Taxonomic grouping</th>
<th>Examples</th>
<th>Tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroviridae</td>
<td>HTLV type 1</td>
<td>Adult T-cell leukemia</td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>Hepatitis C virus</td>
<td>Hepatocellular carcinoma</td>
</tr>
</tbody>
</table>

EBV

EBV is a ubiquitous double-stranded DNA virus of the γ herpes virus subfamily of the Lymphocryptovirus (LCV) genus and is also known as human herpes virus 4 (HHV-4). It is one of the most common viruses to be found in humans with more than 95% of world’s population being infected [14]. The majority of the EBV infection occurs in infants without causing observable symptoms [15]. Post-adolescent infection with EBV often results in mononucleosis, a self-limiting lymph proliferative disease. EBV infection is related to various forms of human cancers, including Burkitt’s and Hodgkin’s lymphoma, B-cell lymphoma in immune-compromised patients, gastric carcinoma, nasopharyngeal carcinoma (NPC) and post-transplantation lymph proliferative disease [16, 17]. Though the incidence of EBV infection is high, only a minority of the infected individuals develop cancer [15]. Currently, there is no vaccine to prevent EBV infection.

HTLV-1

HTLV-1 is a delta type complex retrovirus endemic to Japan, South America, Africa, and the Caribbean [18]. It was the first human retrovirus to be discovered and identified in 1977 [19]. Approximately 10% of infected patients are thought to develop primarily adult T-cell leukemia (ATL) and the prognosis remains poor for these individuals. Currently, there is no vaccine to prevent HTLV-1 infection [16]. Retrovir R (generic name Zidovudine; GlaxoSmithKline and Folotyn (Pralatrexate solution; Allos Therapeutics, Inc.) were investigated for preventive measures but; both are directed towards the cancer rather than the virus itself [20].

HPV

HPV is a group of non-enveloped and double-stranded DNA viruses of the Papillomaviridae family. Till date 200 human papillomavirus (HPV) types have been identified; this can cause range of epithelial hyperplastic lesions [21]. They can be classified into two groups: mucosal and cutaneous which are further classified into low- and high-risk groups depending on the associated lesion’s propensity for malignant progression. 10-20% of the infected individuals develop cancer of the cervix, anus, vulva, penis and of the head and neck area and oropharynx. Type 16 and 18 of HPV are associated with 70% of the cervical cancers [22]. Currently vaccines developed are Gardasil R (Merck Sharp &Dohme) and Cervarix R (GlaxoSmithKline) against high-risk HPV types 6, 11, 16 and 18, and types 16 and 18 respectively [23].

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HBV

HBV is a circular and partially double-stranded DNA virus which has a major role in hepatocellular carcinoma (HCC), the fifth most common type of cancer. The replication of HBV is dependent on reverse transcription and majority of the infections are asymptomatic and non-cytopathic [24]. Currently, none of the virally encoded proteins have been directly linked to the acute oncogenic activity due to the lag time between infection and the development of HCC. Rather, persistent infection with HBV is associated with varying degrees of chronic liver disease, progressing to cirrhosis and HCC (16). Presently, vaccines developed to prevent HBV infection are available including Engerix-B R (GlaxoSmithKline), Shanvac-B R (Shantha Biotech) and Genevac BTM (Serum Institute) [25].

HCV

HCV is also linked with chronic hepatic disease and HCC. HCV is a single-stranded RNA virus of the Hepacivirus genus in the Flaviviridae family and is the only positive-stranded RNA virus among the human oncogenic viruses [26]. Nearly 20% of the infected individuals are expected to develop liver complications such as hepatitis, hepatic steatosis and cirrhosis with 4-7% risk to progress to HCC [27]. An effective vaccine for HCV has not been produced till date due to a weak immune response. U.S. Food and Drug Administration have approved protease inhibitors - (Merck Sharp &Dohme) and Incivek (Vertex Pharmaceuticals Inc.) for the treatment of chronic HCV infection [28, 29]

KSHV

KSHV is a double-stranded human rhadinovirus of the γ-herpesvirus subfamily [30] which is associated with all forms of KS, occurring commonly in AIDS and immune-suppressed patients. KSHV is also associated with primary effusion lymphomas (PELs), and MulticentricCastlemann's disease (MCD) [15]. Not all KSHV-infected subjects develop associated diseases, thus implicating other factors such as host immune surveillance failure. Currently, there is no effective vaccine to prevent KSHV infection [31].

MCV

MCV is a double stranded DNA virus which causes Merkel cell carcinoma (MCC) [22]. Nearly 80% of the MCC patients have the MCV integrated in a monoclonal pattern. The causal relationship between MCV and MCC is somewhat contentious as the research towards understanding MCC and MCV is at an early stage [32]. Drugs and vaccines towards the treatment and prevention of MCV infection have not been developed.

Oncolytic virus

Viruses are nature’s nanoparticle with a diameter ranging from 20 to 500 nm. An oncolytic virus (OV) is a virus having the ability to selectively propagate in cancer cells and destroy it, without causing undue damage to normal non-cancerous tissues. Certain viral genes act as tumour destructive agent, and the viral capsid as a nucleic acid delivery vehicle [33]. As the virus starts to replicate at the tumour site, its destructive effect increases, leading to tumour regression. In general, oncolytic viruses derive their specificity by exploiting cell surface receptor or intracellular aberrations in gene expression that arise in malignancies during tumor development. The greatest advantage that the oncolytic virus offers over chemotherapeutic agent is its ability to be engineered by in vitro genetic manipulation in response to preclinical and clinical findings [34]. Oncolytic activity of many viruses including Poliovirus, Adenovirus, and Coxsackie virus was tested in various animal and human models to treat tumours. However, uncontrolled infections and significant morbidity and mortality led to the near abandonment of trials [35].

Thereafter with the advent of modern biotechnology and better understanding of cancer biology, the field of oncolytic virotherapy has gained momentum and it is still evolving as researchers are attempting to generate more efficacious genetically modified existing viruses and new viruses targeted towards the treatment of specific cancers or towards the expression of desired cancer suppressing genes [36]. Currently, pre-clinical studies and phase I–III clinical trials are underway using OVs for the treatment of certain cancers. To date, numerous wild-type and genetically modified viruses have been found to show oncolytic properties (Table 3), such as Vesicular stomatitis virus [37], Polio virus (PV) [38] and Newcastle disease virus [39]. The world’s first oncolytic virus to be approved was a genetically modified adenovirus-H101 type 5 by China’s State Food & Drug Administration in 2005 [33], in which E1B-55 kD and partial E3 genes have been deleted. OncoVEX (Amgen; Thousand Oaks, CA, USA) [40], Reolysin R (Oncolytics Biotech Inc., Calgary, AB, Canada) [41] and JX-594 (Jennerex; San Francisco, CA, USA) have the greatest chance of being approved for clinical use in the coming years [42]. The virus can also be used as a vector to express an enzyme in tumour cells following the administration of a prodrug that combines with the enzyme to generate cytotoxic compounds that destroy the target cell and surrounding cells. Although modifying the genetic stability and specificity of any virus has obvious health and safety implications, the flexibility and specificity of the naturally occurring and genetically modified OVs permits their utilisation, and indeed, their unrealised potential for the treatment of a wide variety of cancers, with minimal immunological side effects. Although both DNA and RNA viruses have been studied for their use in oncolytic virotherapy, DNA viruses being more amenable to genetic manipulation are more frequently used [36].
Table 3: Human oncolytic viruses and their cancer therapeutic target.

<table>
<thead>
<tr>
<th>Oncolytic virus</th>
<th>Genome</th>
<th>Cancer target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesicular stomatitis virus (VSV)</td>
<td>Single-stranded RNA rhabdovirus</td>
<td>Brain tumour, colorectal cancer and nasopharyngeal carcinoma</td>
</tr>
<tr>
<td>Poliovirus 1 (RIPO)</td>
<td>Single-stranded RNA enterovirus</td>
<td>Glioblastoma and Neuroblastoma</td>
</tr>
<tr>
<td>Reovirus (RV)</td>
<td>Double-stranded RNA reovirus</td>
<td>Multiple cancer types</td>
</tr>
<tr>
<td>Newcastle disease virus</td>
<td>Single-stranded RNA avian paramyxoviruses</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Measles vaccine virus</td>
<td>Single-stranded RNA Virus</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Myxoma Virus (MYXV)</td>
<td>Double-stranded DNA virus</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>H101 and Onyx-15</td>
<td>Double-stranded DNA Adenovirus</td>
<td>Head and neck cancer</td>
</tr>
<tr>
<td>OncoVEX</td>
<td>Double-stranded DNA Herpesvirus</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>JX594</td>
<td>Double-stranded DNA vaccinia virus</td>
<td>Liver cancer</td>
</tr>
</tbody>
</table>

Current issues in Oncolytic virotherapy

Gene therapy is the major concept behind Oncolytic virotherapy and the people are aware of the dangers of Gene therapy. The first mishap occurred in September 1999 when Jesse Gelsinger, healthy teenage died due to toxic shock receiving adenovirus vector carrying transgene volunteering for clinical trial for condition Ornithine Transcarbamylase Deficiency. Immune reactions against the vectors introduced and the inappropriate administration of vector and transgene are the main obstacles for this kind of therapy [43]. This includes cytotoxic T-lymphocytes toxicity, low infectivity, agglutination due to antibodies, intracellular inhibition of virus and poor safety and control of oncolytic virotherapy. Many of the obstacles and barriers are actively being resolved now due to the advancement in the molecular biology and biotechnology. An illustration of some obstacles and solutions are described in the figure 1 below.

Figure 1: Overcoming the obstacles of Oncolytic virotherapy.

Frequent inactivation of the virus vector circulating in the blood stream can be stopped by formulating vector in Polyethylene glycol, collagen matrix or liposomes. CTL toxicity causes the reduction of the virus ability to replicate by eliminating the infected cell populations. Immune suppressants along with proper vector engineering can help abate this effect. Poor viral transduction can be resolved by vector modifications, coat protein alterations, or formulating the vector with reagents that enhance infection, such as bidirectional antibodies and liposomes [44]. Inflammatory effects due to viral infections can be resolved by simple immune suppression.
suppressants, anti-inflammatory treatments, such as cortico-steroids, in addition to vectors designed to inhibit initial inflammation cascades. Safety and control concerns mandate that control mechanisms such as genomic degradation mechanisms be engineered into vectors. Strategies for effective tumor targeting and improving efficacy are discussed in detail further [45].

**Strategies for tumor targeting**

Oncolytic Virotherapy using virus vectors is a promising approach against tumors over current available therapies. Along with other pitfalls, one of the major obstacles is the effective delivery of virus vector to the target tissue. Cancer cells have altered cell physiology such as self-sufficiency in growth signals, less sensitive to growth inhibition signals, evasion of apoptosis, uncontrolled replication potential, sustained angiogenesis and metastasis. These altered cellular functions make favourable environment in the host for the viruses, therefore these properties can be harnessed for selective replication of OVs in cancer cells. Selective targeting can be achieved by two general approaches which includes deletion of viral genes required for viral replication in normal cells but dispensable in tumour cells and use of tissue/tumour specific promoters for critical viral genes. Tumour targeting can also be achieved by targeting various molecular steps/regulators of cell cycle. Some of these are discussed below.

**Pro apoptotic targeting**

In order to assist their replication many viruses delay apoptosis of the infected cells. The activity of critical growth regulators of programmed cell death such as p53 and pRb25 are altered by encoding certain proteins. The virus is adapted to disable viral proteins that prevent apoptosis. Normal cells then quickly die upon infection before the progeny viruses are produced. On the other hand the infected cancer cells do not have the ability to undergo apoptosis. Therefore, the virus can generate progeny and spread in cancer cells only. Adenoviral proteins E1A and E1B delay premature apoptosis by inactivating pRb and p53 in normal cells respectively [33]. A virus having deletion in E1 can be rendered tumour specific. ONYX-15 is the type of mutant having mutation in E1B and HB101 by deleting in two viral genes- E1B and E3 respectively [46].

**Translational targeting**

Normal cell upon viral infection, double stranded RNA and lipopolysacharide produce Type I interferon which shuts down the protein synthesis in the neighbouring cell, rendering them unfit for viral replication. Most of the cancer cells have defective interferon signalling pathways; hence one strategy to enhance tumour specificity is to mutate the OVs for induction of more potent interferon response, which will minimize the replication of OVs in the normal cells whereas the cancer cells remain permissive [41]. The virus is adapted to disable viral proteins that antagonize the cellular interferon (IFN) response. Normal cells upon infection release interferon, causing the neighbouring cells to terminate the translation process. Infected cancer cells do not have the ability to release or respond normally to interferon [33].
Transcriptional targeting

Oncolytic viruses can be made selective to tumour cells by placing essential viral gene under the control of tumour specific promoter. Certain tumour specific gene promoters like human telomerase reverse transcriptase (hTERT) and survivin are active in a variety of tumour types while others show specificity for particular tumours, e.g. Prostate specific antigen (PSA) for prostrate and tyrosinase for skin [47]. An essential viral gene is placed under the control of a tumour-specific promoter (some virus promoters are naturally tumour specific). Generally, the selected gene encodes an early viral protein that is essential for successful completion of the virus life cycle. This is applicable only to DNA viruses (excluding poxviruses) and retroviruses [48].

Transductional targeting

Viruses enter into the target cells through a receptor that is expressed in abundance on tumour cells in comparison to the normal cells. Tumour cells express high level of tumour specific receptors, For example, most cancerous cells over express intra cellular adhesion molecule-1 (ICAM-1) and decay accelerating factor (DAF). By the display of single-chain antibodies or other polypeptide binding ligands on the viral surface, the attachment specificity of the virus can be reprogrammed towards the tumour antigens [49].

Targeting strategies based on tumour micro-environment

Tumour cells develop a modified microenvironment such as hypoxia, activation of certain proteases and angiogenesis to support abnormal cell proliferation and tissue invasion. This altered microenvironment can be harnessed for developing tumour targeting strategies [49]. Vesicular stomatitis virus (VSV) is known to have an inherent capacity of replication under hypoxic tumour environment [50].

Targeting tumour using carrier cells as cellular vehicle for oncolytic viruses

Cancer cells releases number of chemokines that helps trafficking of immune cells towards tumour. These immune cells can be used as vehicle for efficient delivery of OVs to cancer cells. Other types of cells such as mesenchymal stem cells and endothelial precursor cells have also been developed as cellular vehicles for selective delivery of OVs to tumour cells. These cellular vehicles not only help in delivering the OVs to the tumour site but also overcome the problem of pre-existing antiviral immunity [50].
Strategies for improving efficacy of Oncolytic Virus

For efficacy, oncolytic viruses must be capable of penetrating host defences to access growing tumours, whether primary or metastatic. They must also be capable of propagating sufficiently at the target site to destroy infected tumours before the infection is controlled and eliminated by the immune system.

Virus delivery via the bloodstream

In the bloodstream viral particles can be neutralized by antibodies and complement system, bound by receptor-positive non-target cells or get phagocytose in the liver and the spleen. Therefore, intravenously administered viruses are eliminated rapidly from the circulation. This process of elimination becomes faster after each subsequent exposure due to increasing antiviral immunity. So formidable are the barriers to efficient and accurate vascular delivery of viruses that agnosticism has been expressed as to whether these agents will ever be exploitable as systemic therapies. However, against this uninformed negativity, the virotherapy research community is developing a broad range of viable solutions to the intravascular (intravenous or intra-arterial) delivery problem [51].

Serotype switching

For many viruses (e.g. adenovirus and VSV), there are many naturally occurring serotypes that are resistant to neutralization by antisera against the other serotypes. One approach to increase the efficacy of OVs is to administer a different viral serotype at each successive treatment cycle. Modification of certain viruses is also possible by engineering or evolving them so that they evade the neutralization step by antibodies raised against the original virus. This serotype-switching approach is not applicable to monotypic viruses such as measles [52].

Polymer coating

Coating of virus with suitable polymer is another approach to block antibody recognition. Near about 90% of the primary amino groups on the surface of adenovirus particles became modified when adenoviruses were mixed with polymer poly [N-(2-hydroxypropyl) methacrylamide] (pHPMA) bearing reactive 4-nitrophenyl (ONp) esters on pendent diglycyl side-chains. This polymer coated viruses showed extended circulation times in vivo but prevented the virus from binding to its cellular receptors. Partial infectivity can be restored by incorporating cell targeting ligands into the polymer coating [53].

Antibody depletion

Reduction of the concentration of the circulating antiviral antibodies before infusing the virus in the patient is another alternative approach towards virus modification. This could be achieved by infusing soluble viral antigens, passing the blood through antigen-loaded columns or immunizing with antiviral antibodies to elicit an anti-idiotypic antibody response that secludes antiviral antibodies and prevents them from interacting with infused viral particles. Another approach for reducing the antiviral antibodies concentration is by destruction of virus specified B lymphocytes or antibody producing plasma cells with steroids, cyclophosphamide or anti B-cell antibodies. However, reductions in the concentration of neutralizing antibodies after terminating their production are very slow because the serum half-life of antiviral IgG is longer than 20 days. Plasmapheresis technique can be used routinely for depletion of IgM antibodies or immune complexes. This approach, being straight forward, is relatively ineffective for depleting circulating IgG [54].

Antibody evasion

Recent data indicate that it could be possible to ‘hide’ a virus so that it cannot be seen or bound to any antiviral antibodies as it passes through the bloodstream towards tumour cell population. This approach is an alternative to changing virus coating and suppressing antibody responses [55]. This can be accomplished either by using virus infected cells as carriers to conceal the virus or by delivering the viral genome to target cells as non-immunogenic infectious nucleic acid. Both of these approaches have the potential to elude phagocytic clearance mechanisms that sequester viruses in the liver and the spleen. These approaches must be used in conjunction with effective targeting strategies to minimize the transduction of non-target tissues [56].

Virus extravasation

Size of the viral particle and the permeability of tumor blood vessels influence the extravasation of intravenously administered viruses into the parenchyma of a tumor. The permeability of blood vessels is greater at the tumor periphery, and OVs extravasate more efficiently at that location. This is demonstrated in mouse xenograft models, and perhaps in some primary and metastatic human cancers [57]. The vascular permeability can be increased by local expression of vascular endothelial growth factor (VEGF) or by local inflammation secondary to treatment with radiotherapy or chemotherapy. Another approach is to engineer the attachment proteins on virus to bind to receptors on tumor blood vessel endothelium for enhancing the viral extravasation from tumor blood vessels. Viruses showing specificity both for neovessel endothelium and antigens expressed on tumor cells are required to ascertain that intratumoral propagation can proceed after the virus has been transported across the endothelial lining of the tumor blood vessels [58].

Intratumoral spread of the virus

The period from infection to target cell death can range from a few hours to few days, and the number of progeny released from single infected cell can range from 1 to 1,00,000 depending on the virus. Therefore, in the absence of an immune system, OVs spread across tumours at widely differing speeds. Antiviral immunity is the major host factor in the presence of an immune system
that serves to modulate the speed of intratumoral virus propagation. Most important in this regard is the cellular arm of the immune system, which controls the spread of infection by destroying infected cells before they have a chance to release their viral progeny [59].

**Immunosuppression**

Immunosuppressive drugs can be used to suppress Antiviral cytotoxic T lymphocyte responses to promote intratumoral spread of an oncolytic virus [60]. Cyclophosphamide is a preferred immunosuppressant drug to use in combination with oncolytic virotherapy because the rapidly dividing lymphocytes are exquisitely sensitive to its cytotoxic actions and it has proven activity as an anti-cancer agent extensively used in treatment of human malignancies. Cyclophosphamide is available at low cost, well tolerated and strongly suppress antiviral immune responses, whether primary or anamnestic, B cell or T cell, when administered at the appropriate dose and time following virus exposure. Hence, cyclophosphamide can greatly increase the efficiency of virus spread and help to limit increases in the antiviral antibody titre between successive viral doses [61].

**CONCLUSION**

Oncovirus infect the host cells; they cause chronic inflammation leading to tumor formation. On the other hand, OV infection of the host cells selectively lyses the tumor cells in the body playing a characteristic role in cancer therapy. Cancer is a complex disease; many cancers can be easily and effectively prevented through vaccination (e.g. HBV and HPV vaccines). Failure in the host immune system, genetic mutations, chronic inflammation and viral infections are widely recognized as the pathological basis for the development of most tumors. An extensive study of the molecular, immunological and oncological pathways underlying viral infection and cancer is expected to develop novel anti-cancer OV therapy. This will have the potential to treat efficiently tumors with less toxic anti-viral compounds and approved OVs. The thorough understanding of the OV functionality can be achieved by the application of the proteomics. Such knowledge is essential for improved vector design and treatment regime. In conclusion, OVs aims to facilitate the next major breakthrough in cancer research through the provision of novel target-based therapeutics.

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