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Review Article

The Role of Viruses in the Development of Cancer

Oluremi B.B.[1] and Omobolade E.S.[2]

[1,2]*Department of Pharmaceutical Microbiology, Faculty of Pharmacy, University of Ibadan, Oyo State, Nigeria*

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Abstract

Cancer continues to be a leading cause of death globally. According to the World Health Organisation, it ranked second most common cause of death globally, claiming millions of lives with millions of new cases diagnosed yearly. Despite recent advances in cancer research and availability of several therapies, severe adverse effects, multi-drug resistance and cost of management are drawbacks of available therapies. Hence, the need for novel approaches that will mitigate the limitations of these conventional treatment options. Cancer has been linked to several factors and while the focus is usually on carcinogenic substances, viruses have been found to account for 15-20% of cancer cases. Oncolytic viruses are viruses that are used in cancer treatment. These viruses have the ability to selectively infect and replicate within tumor cells making them specific in their action against them. This promising approach is also effective when combined with other cancer treatment options such as chemotherapy and radiation.

Key Words: Cancer, Oncogenic viruses, Oncolytic viruses

INTRODUCTION

Cancer

Cancer remains a major source of global health concern, and in spite of great advances in cancer research, researchers are still looking for novel therapeutic approaches to treating cancer (Javid *et al*., 2023). Cancer is a life-threatening disease that is characterized by uncontrollable cell growth and the spread of abnormal cells (Fig.1) which has been linked to several factors such as hormonal imbalance, chemical carcinogens, genetics, lifestyle, environmental, and viruses (Rwazain, 2011). With an estimated 9.6 million deaths worldwide in 2018 and nearly 10 million deaths in 2020, cancer has been ranked as the second most common cause of death globally. Although the precise etiology of cancer remains partly known, several factors have been linked to its development. Recent studies have shown the critical role viruses play in the emergence of several cancers. Studies have also shown that 20% of all cancer cases globally are linked to viral infections (Smith & Smith, 2016). Although there are numerous potential causes of cancer, many people are unaware of another significant etiology – oncoviruses, or viruses that cause cancer. This can be mainly attributed to the cancer prevention strategies now in place which focus more on modifiable lifestyle risk factors, like food and workout. However, oncoviruses are significant despite their low awareness since they account for more than 17% of all cancer cases worldwide. These cancers pose a big threat to public health in developing countries and immunosuppressed populations.

According to Durgalakshmi *et al*., 2021, the eradication of these infectious agents would result in a 23.6% decrease in cancer rates in developing nations and a 7.7% decrease in cancer rates in developed nations. This implies that there will be 390,000 and 1.5 million fewer cases of cancer annually. While the focus is not usually on oncovirus, research has shown them to be the second most significant risk factor for the development of cancer in humans besides tobacco consumption.

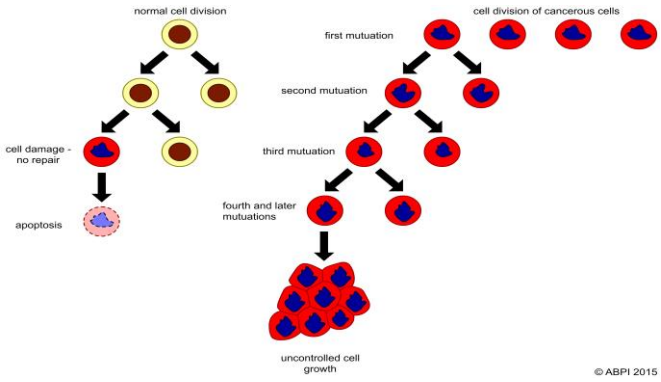

Fig.1: Cancer: Uncontrolled cell growth https://www.abpischools.org.uk/topics/cell-division/mutations-and-cancer/

Role of Viruses in Cancer

The role of viruses in cancer could be both positive and negative. On one hand, some viruses have been implicated in the development of cancer while some show great potential in cancer therapy (Niedźwiedzka-Rystwej *et al*., 2020). The oncogenic viruses have various mechanisms by which they induce tumor proliferation and these are also influenced by factors such as the host's immune response, genetic alterations, environment, and lifestyles.

**Author for Correspondence:* Tel: +2347066414734 E-mail: *bolaji0708@gmail.com*

On the other hand, recent studies (Li *et al*., 2022)) have shown that viruses can also be used for therapeutic purposes. Oncolytic viruses have been gaining attention due to their ability to infect and destroy cancer cells while having no adverse effects on normal cells. Currently, the number of viruses used in the treatment of cancers is still limited and there is a need to study other classes of viruses to explore their potential as therapeutic agents. Furthermore, viruses have shown great potential as a diagnostic tool for cancer and have also been found useful in viral gene therapy and viral immunotherapy. Although the use of oncolytic viruses is still fairly new, there is the need to further explore their uses.

Negative Role of Virus in Cancer Development

Infection-related cancer accounts for 15%-20% of cancer cases worldwide with bacteria and viruses as the leading causes of these infections. While a fraction of these cancer cases are caused by bacteria, viruses have been implicated in the majority accounting for about 10%-15% of all cancers worldwide (Tashiro and Brenner, 2017; Javid *et al*., 2023). Reports have shown that 10%-12% of new cancer cases are caused by viral infections (Plummer *et al*., 2016. However, other studies have shown that viral-induced cancer is a rare occurrence, and though viral infection increases the chances of developing cancer they do not necessarily contribute to cancer progression In any case, the incidence of viral-associated cancer is steadily rising in developed countries due to the rising number of immunosuppressed patients and changes in sexual practices (Tashiro and Brenner, 2017).

Oncogenic Viruses

Oncogenesis is the process by which malignant tumors are formed. There are at least seven viruses that have been implicated as the causes of cancer and this number is projected to increase with time (Tashiro and Brenner, 2017; Latha *et al*., 2023). These viruses produce an oncogenic effect that induces the formation of tumor cells. Viral infection does not always lead to tumor formation, however, the transformation of viral infection to cancer depends on several factors such as cellular mutation, immune complications, chronic inflammation, and environmental mutagens (Tashiro and Brenner, 2017, Latha *et al*., 2023).

Viral-induced oncogenesis is caused by viral interaction with the human immune system which leads to immune suppression (Nimrah *et al*., 2016). Viral oncoprotein (V-onc) plays a role in cellular growth and development. They carry out different functions such as activating cellular signaling pathways, altering transcriptional or post-transcriptional of cellular genes and microRNAs, apoptosis, inactivating tumor suppressor protein, and signal transduction (Guangxiang *et al*., 2015). V-onc can be transformed into oncogenes through mutations, recombination, and chromosomal translocation which eventually lead to the formation of tumors (Murat *et al*., 2012). Viral oncoproteins also deregulate various cellular signaling pathways that are directly linked to the development of oncogenesis, such as Notch signaling, MAPK TLR, JAK/STAT, JNK, Wnt, interferon regulatory factors (IRFs), the ubiquiting-proteasome system, tumor necrosis factor (TNF), and nuclear factor (NF) (Purushothaman *et al*., 2020).

How Viruses Produce Oncogenic Effects

Viruses can exert their oncogenicity in three ways: i) by directly inducing cellular transformation of infected cells, ii) through chronic inflammation, and iii) by inhibiting the host immune system (Tashiro and Brenner, 2017). When a virus directly induces transformation, such viruses are classified as direct carcinogens. Some viruses integrate their genome into the host genome or form a stable episome and can regulate host cell growth. Once the host cell recognizes these foreign genes, it triggers DNA damage response (DDR) leading to an increase in genetic instability thus raising mutation rates. An increase in mutation rate leads to the acquisition and expression of oncogenes which directly contribute to cancer formation. This usually occurs in Human Papilloma Virus, Epstein-Barr Virus, and Kaposi-Sarcoma-associated Herpes Virus related cancers (Moore and Chang, 2010). Viruses can also produce oncogenic effects through chronic infection and inflammation which eventually leads to a carcinogenic transformation thereby aiding cancer formation. These viruses are classified as indirect carcinogens (Mesri *et al*., 2014). A good example is Hepatitis C and Hepatitis B virus induced cancer which occurs after chronic hepatic inflammation causes oxidative DNA damage followed by macronodular cirrhosis which facilitates the formation of hepatocellular cancer (McGivern and Lemon, 2011; Ringhelhan *et al*.; 2015). Whereas viruses like HIV may not be oncogenic, they however, inhibit host immune systems allowing mutation to occur and ultimately results in the formation of malignant tumors (Amsterdam, 2015).

Factors Leading to Viral Transformation of Cells into Tumor Cells

Several factors can lead to the viral transformation of cells into tumor cells. First is the presence of viral oncogenes which when expressed leads to the development of oncogenes. Viral oncogenes are the cellular counterpart of proto-oncogenes found in cells. These oncogenes control several processes such as signal transducers, growth factors apoptosis regulators, transcription, and growth factor receptors which when disrupted can induce oncogenesis (Javid *et al*., 2023).

Another factor is the presence of tumor suppressor genes which prevents malignant transformation of the cells by protecting the cells from unnecessary cell growth or cell division. However, when these tumor suppressor genes are inactivated or suppressed, the cell loses the ability to regulate these actions hence promoting malignant transformation. Viral oncoproteins interfere with tumor suppressor gene function and aid unbridled proliferation. The two proteins involved in the cell growth cycle are the P53 and pRB. The main role of p53 is to prevent abnormal cell growth. HBV encoded hepatitis B X-antigen (HBx) oncoprotein inactivates p53 and blocks p53-mediated apoptosis. Hepatitis C virus (HCV) containing nonstructural protein 5A (NS5A) interferes with the DNA binding activity of p53. The pRB functions as a negative regulatory protein of the cell cycle. The E7-oncoprotein of human papillomavirus (HPV) interferes with its binding to the E2F transcription factor, hence E7 causes several biological effects like increased transcription, autophagy, and inhibition of interferon signaling (Javid *et al*., 2023). Some oncoviruses integrate their genetic material into the host genome causing the expression of the viral genome which triggers mutations, uncontrollable cell division, and cellular transformation.

Another way by which oncoviruses act is by deregulation of cell cycle. Deregulation of the cell cycle interrupts with accurate DNA replication and Chromosomal segregation. Cyclins, cyclin-dependent kinases (CDKs), and their inhibitors regulate cell cycle and homeostasis mechanisms. Apoptosis is another regulatory mechanism in the cell that eliminates damaged cells, thus preventing their further

division, which allows for unlimited proliferation of damaged cells. Studies have shown that molecular alterations of the host genome by oncoviruses lead to deregulation of apoptotic processes and disruption of homeostasis. Viruses have evolved many strategies to overcome the regulatory system of the cell cycle leading to continuous proliferation of the infected cells (Dittme and Krown, 2007).

Types of Oncogenic Virus

The genetic makeup of oncoviruses determines the mechanism by which they cause cancer. Oncoviruses with a DNA genome, such as HPV, EBV, KSHV, and HBV, interfere with the tumour suppressor gene p53 to cause unchecked cell proliferation. Because it regulates the cell cycle, apoptosis, and DNA repair, p53 is commonly referred to as the "guardian of the genome." However, DNA oncovirus-infected cells lack the p53 repair machinery, thereby causing a slow buildup of mutations that impact the cell cycle (Rwazavain., 2011). On the other hand, RNA oncoviruses work by introducing their genetic material into the genome of the infected cell. The viral RNA is transformed into DNA by the enzyme reverse transcriptase and is subsequently integrated into the host's genomic DNA.

DNA Oncoviruses

Epstein-Barr Virus

The Epstein-Barr virus (EBV) is one of the first human cancer viruses to be discovered and has been linked to several cancers such as Burkitt lymphoma (20-95%) (Young *et al*., 2016) and nasopharyngeal cancer (80-100%) (Lin *et al*., 2014). EBV is a gamma herpes virus that affects most human populations with high prevalence in adults. EBV infects the lymphocytes and epithelial cells. Research indicates that 1.8% of all cancer-related deaths are thought to be related to EBV-associated cancers (Khan and Hashim, 2014). Through altering cellular gene transcription and triggering cell signaling pathways, EBV has the capacity for transforming cells in vitro resulting in EBV-encoded latent genes transformation into lymphoblastic cell lines (LCLs).

It is uncommon for the EBV genome to integrate with the host. However, the viral genome is partially deleted as a result of EBV's incorporation into the host genome's weak spots. Additionally, it creates a region in the host DNA that causes instability (Javid *et al*., 2023). At least six viral proteins are involved in the transformation process of the virus, which helps to make B cells immortal. Among these, the trans-activators LMP1 (Latent Membrane Protein 1) and EBNA2 (Nuclear Antigen linked with EBV) are involved in deregulating processes of cellular homeostasis or stimulating the transcription of molecules implicated in B cell activation. Many viral genes that may sustain the virus in the infected cell and imitate the biological signals involved in lymphoid cell proliferation, cycle regulation, or cell death are involved in the immortalization and transformation of extremely complex products (Moukassa *et al*., 2018).

Human Papilloma Viruses (HPV)

Human Papilloma virus (HPV) belongs to the family of Papillomaviridae and infects the epithelial cells. They are non-enveloped viruses and have a genome of double-strand DNA that is roughly 8000 bp in size. Almost a dozen (types 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 62, 66, and 68) types of the more than 100 members of this family that have been reported have been identified as high-risk because of their epidemiological association with cervical and other cancers. The most common HPV subtypes detected in tumors are 16 and 18, with the first being primarily linked to invasive cervical cancer and the latter more commonly occurring in squamous cell carcinoma. Since HPV is spread via skin contact, including genital touch during sexual activity, sexually active people tend to have more cases of HPV infection in their genital area.

The immune system typically controls infection, and HPV only persists in a small percentage of individuals, raising the possibility of developing epithelial lesions (Morale-Sanchez and Fuentes-Panama, 2014). The lack of ability of infected cells to present antigenic epitopes to adaptive immune cells appears to be a major factor in viral persistence; this is often seen in people with changes in the Human Leucocyte Antigen (HLA) presentation pathway. The oncogenes E6 and E7, which are encoded by HPV, are essential to the development of cancer. The disruption of the E2 gene, a negative regulator of E6 and E7 expression, caused by HPV-16 integration into the host genome results in an increased expression of these two oncoproteins, which ultimately results in cancer. E6 oncogenes cause the rapid degradation of p53, a crucial tumor-suppressor protein that also activates human TERT (hTERT) thereby raising the risk of cancer. Furthermore, E7 contributes to the development of cancer by deactivating the tumour suppressor protein pRB that stops uncontrollably growing cells (Javid *et al*., 2023). In addition, other factors like high generation of ROS and repetitive nerve stimulation (RNS) cause breakage of the DNA strand allowing HPV to integrate with the DNA thereby increasing the risk of cancer. Also, high-risk HPV infections that contribute to inflammation-mediated cervical carcinogenesis show evidence of nitrative and oxidative DNA damage (Williams *et al*., 2014).

Hepatitis B Virus (HBV)

Hepatitis B virus is a double-stranded DNA virus that belongs to the family Hepadnaviridae and have been known to increase the risk of hepatocellular carcinoma (HCC). Reports have shown that approximately 80% of HCCs have the HBV genome, and individuals who are chronic HBV carriers have a 5–15-fold increased incidence risk of HCC. Hepatitis B virus can be transferred through sexual contact, contact with blood or other body fluids, or/and vertical transmission from mother to child. HBV infections only need to be initiated with a low titre of virions. As the immune system is still growing during pregnancy, childbirth, or early infancy, the majority of chronic carriers acquire their status during these periods. About 1% to 5% of adults and teenagers who get an infection go on to have a chronic condition (Trepo *et al*., 2014).

Most HCC tumor cells exhibit the HBVX protein (HBx). HBx is a regulatory protein containing 154 amino acids and they play a crucial role in the viral life cycle. The expression of this protein is prolonged in all stages of carcinogenesis. HBx protein inactivates p53 proteins and interacts with the DNA-repairing protein DDB1, potentially influencing repair processes and permitting genetic alterations. HBx affects the mobilization of intracellular calcium by triggering calcium-dependent kinases, which have the ability to influence various cell regulatory pathways. This protein interacts with and inhibits the activity of multiple transcription factors, which may contribute to the progression of HCC. These transcription factors include CREB, ATF, EGR1, OCT1 RXR, and the p53 tumour suppressor protein (Fazlalipour *et al*., 2023).

Kaposi's Sarcoma-associated Herpes Virus (KSHV)

Kaposi's sarcoma-associated herpesvirus (KSHV) is a linear double-stranded DNA herpesvirus that is known to cause Kaposi sarcoma and primary effusion lymphoma associated with AIDS patients (Ethel *et al*., 2019)

Furthermore, this virus is linked to inflammatory cytokine syndrome and multicentric Castleman disease (MCD). The cancer caused by KSHV often appears as reddish-purple or blue-brown tumors that grow slowly under the skin. If KS lesions are found to appear in internal organs such as the lungs, liver, or gastrointestinal tract, they may be very fatal. The oncoprotein latency-associated nuclear antigen 1 which is encoded by the KSHV induces its activity by preventing the tumor suppressive action of p53 and its transcription. (Javid *et al*., 2023)

RNA Viruses

Hepatitis C Virus (HCV)

HCV is a positive-sense single-stranded RNA virus that belongs to the family of Flaviviridae. HCV has been implicated in some HCC and lymphomas. HCV infection can result in chronic inflammation which increases the chances or eventually leads to the development of HCC (El-serag and Rudolf, 2007). Studies have shown that HCV causes dysregulation of glycolysis which is attributed to the NS5A gene, while other studies show that the overexpression of the HCV core protein leads to decreased oxidative phosphorylation and increased oxidative stress all of which raise the development of cancers (Ivanov *et al*., 2017; Smirnova *et al*., 2017). Reactive oxygen species (ROS) can also be increased by HCV infection, and ROS-sensitive transcription factors can be expressed that promote carcinogenesis, cell division, and viral replication (Quarato *et al*., 2013).

Human T-cell Leukemia Virus-1 (HTLV-1)

The human T-cell leukemia virus-1 belongs to the Retroviridae family and are single-stranded RNA of positive sense. Research has shown that HTLV-1 affects 15-25 million people worldwide with the established route of transmission being intravenous, breastfeeding, and sexual contact. The virus proliferates within the dendritic cells, T- and B-lymphocyte cells, and expresses Tax and HTLV-1 basic leucine zipper factor (HBZ), two proteins connected to oncogenesis, which promote the growth of infected T cells. Due to the proliferation of these infected T-cells, numerous infected T-cells have distinct locations for integrating HTLV-1 with the host DNA (Morale-Sanchez and Fuentes-Panama, 2014). Studies have shown that HBZ is in charge of tumor maintenance, while Tax plays a part in tumor initiation. Tax is a 40-kDa trans-regulatory protein crucial in immortalizing infected cells resulting in the development of adult T-cell leukemia. Tax also inhibits the actions of the protein responsible for regulating antitumor responses, allowing the generation of reactive oxygen species which eventually lead to DNA damage thereby facilitating the proliferation of cancer cells (Vandermeulen *et al*., 2021).

Positive Role of Viruses in Cancer

Although extensive studies have been conducted on viruses that cause cancer, researches have recently shown that viruses possess therapeutic properties as evident in virotherapy. These novel research outputs indicate the use of viruses for cancer treatment. The three aspects of virotherapy include oncolytic viruses which is the use of viruses to treat cancer, viral immunotherapy which involves the use of viruses to deliver immune stimulating substances as seen in live attenuated vaccines (Lawler, 2017), and viral vectors which make use of viruses with immunogenic properties to deliver desired genes into the cell so that they will be expressed (Brentville *et al*., 2018).

Oncolytic Viruses

Oncolytic viruses (OV) also known as tumor-selective viruses are viruses that possess anti-cancer activity with promising potential as a cancer therapeutic agent. These viruses possess the ability to selectively infect and lyse tumor cells while also stimulating the body's immune system to attack tumor cells. In recent years, oncolytic viruses have gained more attention due to their advantages (compared to some other cancer therapies) such as their ability to target multiple cancer types, enhance the effectiveness of other cancer therapies and stimulate immune response (Fukura *et al*., 2020; Peer *et al*., 2020). OVs exert their anticancer activity through replication within cancer cells leading to cell lysis, and inducing the release of antigen that helps the immune system to recognize and destroy the cancer cells. The inability of conventional cancer therapies to selectively kill tumor cells without having negative effects on healthy cells is one of their biggest obstacles and oncolytic viruses can be engineered to achieve this (Javid *et al*., 2023). Moreover, throughout the transformation process, cancer cells typically undergo changes such as the loss of innate antiviral response pathways, which makes them more susceptible to viruses compared to their non-transformed cellular counterparts (Lawler *et al*., 2017; Engeland and Bell, 2020). Tumour necrosis factor (TNF) and type I and II interferons (IFNs) are two examples of antiviral responses that have been lost in cancer cells due to transformation.

Riga Virus (RIGVIR), a non-pathogenic intestinal cytopathic human orphan RNA virus, derived from the native of enteric cytopathogenic human orphan virus type 7 (ECHO-7) strain of picornavirus was the first oncolytic virus to be approved by regulatory bodies for the therapy of cancer. It was approved in Latvia for the treatment of melanoma (Kaufman *et al*., 2015). In 2015, the US Food and Drug Administration (FDA) granted the first oncolytic viral immunotherapy license for Talimogene laherparepvec (T-VEC) or imlygic used for treating melanoma (Antdbacker *et al*., 2015). It was approved for specific subgroups of melanoma patients. In T-VEC, a modified herpes simplex virus (HSV), the ICP34.5 and ICP47 neurovirulence genes that obstruct antigen presentation are deleted. Furthermore, the anti-tumor immune response is strengthened when macrophages and dendritic cells infiltrate the infected tumor resulting in the production of immune-stimulating GM-CSF protein in cancer cells and is less likely to infect healthy cells (Rehman *et al*., 2016)). T-VEC destroys cancer by infecting tumor cells and promoting their death. It is used for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after initial surgery. In a 2015 clinical trial conducted with 436 patients comparing intra-tumoral administration of T-VEC to subcutaneous delivery of GM-CSF in patients with stage IIIb to IV melanoma, it was found that 16.3% of T-VEC-treated patients had a durable response to therapy, while 2.1% of patients receiving GM-CSF treatment experienced a durable response (Andtbacker *et al*., 2015). Clinical trials are still being conducted on other oncolytic viral agents.

Types of Oncolytic Viruses

Some viruses possess the innate ability to attack tumor cells while others are engineered to attack them. The Newcastle disease virus (NDV) is a well-known RNA virus that has oncolytic properties and can potently stimulate antitumor immune responses. NDV selectively infects, replicates within, and lyses cancer cells by exploiting defective antiviral defenses in cancer cells (Kan *et al*., 2021; Tian *et al*., 2023). The hepatitis B virus (HBV) is another oncovirus that shows anticancer activity through upregulating the transforming growth factor- beta (TGF-β) and downregulating the intracellular level of tumor suppressor protein p53 while upregulating TERT, MLL4, and CCNE1. Non-engineered oncolytic viruses include autonomous parvovirus, reovirus, and NDV (Javid *et al*., 2023).

Another example of a virus that probably causes cancer is the oncolytic adenovirus, which infects host cells by inserting its own nucleic acid into essential cell processes. Despite its origin, this virus is similar to the NDV in that it is frequently employed in cancer therapy and mostly requires engineering and modification (Ghanaat *et al*., 2021; Tripodi *et al*., 2021). Engineered viruses include adenovirus, herpes simplex, and vaccinia, and they differ in their capacity to lyse cells, trigger the immune system, and transmit genes.

Coxsackievirus A21 (CVA21) used to treat melanoma is another OV used in cancer therapy. Clinical research using CVA21 showed that 19.3% of patients had a durable response and 75.4% of patients survived one year after starting treatment (Andtbacka *et al*., 2015). Research is ongoing on poliovirus (PVSRIPO) harboring the internal ribosome entry site of human rhinovirus type 2 (HRV2) for the treatment of glioblastoma (Dighe *et al*., 2023). Since glioblastoma cells predominantly express the poliovirus receptor, CD155, they are suitable targets for PVSRIPO oncolytic virus therapy (Holl *et al*., 2016).

Mechanisms of Action of Oncolytic viruses

Viruses have been selected as a novel treatment approach because of their ability to recognize and selectively target cancer cells. They have the ability to target particular receptors that are overexpressed on tumor cells, thereby entering those cells. For example, the measles virus can target CD46, which is overexpressed in multiple myeloma cells (Ong *et al*., 2006). Also, tumor cells' uncontrolled metabolism, quick growth and division make them a prime target for many viruses, this is more favorable for their proliferation than normal cells.

There are two major mechanisms by which oncolytic viruses exert their anti-tumor activity. First, they infect tumor cells resulting in the lysing of the infected cells. Secondly, they produce antigens that stimulate the body's anti-tumor immune response following cell lysis (Newman and Zloza., 2017). Oncolytic viral infection is mostly restricted to tumor cells due to defective interferon and toll-like receptor signaling in tumor cells, which aids viral replication. In contrast, non-cancerous cells with functional interferon signaling and other viral recognition pathways successfully thwart viral replication because they are yet to lose their ability to induce antiviral response and can successfully ward off viral infection. If the virus is not removed from the tumor cells, it may trigger necrosis, pyroptosis, or apoptosis, which will cause the tumor cells to lyse (Kohlhapp and Kaufman, 2016). Tumor neoantigens, damage-associated molecular patterns (DAMPs), calreticulin, uric acid, and pattern-associated molecular patterns (PAMPs); (such viral proteins and genomic material) are liberated from the cell after lysis (Kaufman *et al*., 2015). Antigen-presenting cells take up and deliver released antigens, which activate IL-2-Secreting CD4+ T-lymphocytes. Engagement of IL-2 by the IL-2 receptor on cytotoxic T (CD8+) lymphocytes activates CTLs that are reactive to tumor antigens. Released from lysed tumor cells, cytokines like TNF-α, IFN-γ, and IL-12 can bind to cytokine receptors on CD8+ T cells and natural killer (NK) cells, causing tumor cells that downregulate major histocompatibility complex (MHC) antigen-presentation molecules and tumor cells that express neoantigens to be destroyed (Kaufman *et al*., 2015).

Reactive oxygen species (ROS) generation in infected cancer cells is another mechanism of action of oncolytic viruses. ROS are important components in regulating cellular signaling pathways, and high levels of ROS can cause cancer cells to die. ROS generation is induced by oncolytic viruses through a variety of mechanisms, such as mitochondrial dysfunction and activation of the NADPH oxidase pathway. ROS can also positively influence the antitumor immune response by improving antigen presentation and immune cell recognition (Guo *et al*., 2021). Solid tumors are characterized by hypoxia, which is a major cause of resistance to traditional anticancer therapies. Oncolytic viruses can target the hypoxic tumour microenvironment by inducing a state of hypoxia that enhances viral replication and oncolysis. Additionally, the immune response to viral infection can result in the release of proangiogenic factors that may help to normalize the tumour vasculature and alleviate hypoxia (Jing *et al*., 2019). An additional strategy for targeting hypoxia is the inhibition of the hypoxia-inducible factor 1 (HIF-1) pathway, which controls the transcription of genes involved in angiogenesis, metabolism, and survival. Oncolytic viruses can target HIF-1 through a number of mechanisms, including the regulation of downstream signaling pathways and the inhibition of NF-1α receptors.

Benefits of Oncolytic Viruses

The use of oncolytic viruses in cancer therapy has some major benefits over conventional cancer therapies in that they can selectively target cancer cells thereby eliminating the risk to normal cells which is not the case with many conventional therapy options. OVs have been shown to have good clinical tolerability and efficacy in clinical trials. Currently, transmission from patients infected with OV is yet to be seen, even though shedding of the virus in urine and respiratory secretions have been observed. (Zeyaullah *et al*., 2012; Laure Aurelian, 2013) However, how these viruses will be administered is yet to be fully comprehended (Zeyaullah *et al*., 2012). Two recent clinical trials conducted showed evidence of the efficacy of intratumorally administered viruses. One of these trials showed that when patients with metastatic melanoma who received an intratumoral injection of an oncolytic Herpes Simplex virus (OHSV) equipped with the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) known as T-Vex (Talimogene laherparepvec), eight out of fifty treated patients experienced complete regression of the injected and uninjected lesions. Moreover, clinical efficacy was enhanced when oncolytic viruses were used in conjunction with cytotoxic medications or radiation therapy. However, the precise role that the viruses played in addition to the anticancer medications was yet to be understood (Harrington *et al*., 2010). The distinct capability of OVs to specifically target cancers without relying on particular patterns of antigen expression sets them apart from other immunotherapy techniques (Gulley *et al*., 2017). In addition, OVs have the ability to enhance systemic antitumor immunity, rewire the immunosuppressive tumor microenvironment

(TME), and facilitate the recruitment of tumor-infiltrating lymphocytes (TILs) (Russell and Barber, 2018). These characteristics make them excellent prospects against many cancers (Raja *et al*., 2018).

Challenges of Oncolytic Viruses

Even though OVs have a lot of potential, there are still a lot of limitations to be overcome in order to increase their effectiveness in virotherapy. These include elements of viral tropism, viral dissemination, delivery systems, dosage regimens, antiviral immunity, and oncolysis caused by the OVs. In solid tumors, a number of obstacles must be overcome by OVs especially to get to tumor sites. First, viruses need to pass through the endothelium layer in order to reach the target cells and these physical barriers present a significant delivery problem (Kuczynski *et al*., 2019). Furthermore, interstitial hypertension is brought on by abnormal lymphatic networks, vascular hyperpermeability, and the dense extracellular matrix (ECM) of solid tumors, all of which can hinder viral infiltration. Thanks to advancements in science, many of these challenges are already being addressed. Preclinical and early-stage clinical trials are currently looking closely at ways to enhance oncolytic virotherapy (Zheng *et al*., 2019).

Another big obstacle is the route of administration of OVs. The focus in most clinical trials is usually on the viruses' interaction with cells and oftentimes, circulation kinetics, susceptibility to first pass hepatic clearance, and the difficulty of a virus to reach cancer cells are overlooked. Relatively not much research has been done on the instability of therapeutic virus particles in the harsh environment of the human bloodstream. Many workers still describe how viral therapies work in human serum dilutions, but in clinical investigations, the agents must survive in pure human blood if administered intravenously. Moreover, since viruses are often susceptible to innate immune defenses, they may be eliminated before they are chanced to interact with the cancer cells (Syemour and Fisher., 2016). However, in December 2023, the 8th Oncolytic Virotherapy summit was held in Boston to showcase brand new pivotal data to ensure a pathway of success for regulatory approval of OV drugs.

CONCLUSION

Most conventional therapies lack selective toxicity against tumor cells so there has been a need to search for a therapy that can attack cancer cells without having any effect on normal cells. For example, chemotherapy destroys normal cells since they cannot tell the differences between normal and abnormal cells. Other detrimental effects include vomiting, diarrhoea, fatigue, infertility, alopecia, and nausea. Oncolytic viruses have an advantage over conventional cancer therapies in that they are specific towards tumor cells and the tumor microenvironment can aid their growth. Some oncolytic viruses can be designed through genetic engineering and be made to recognize only tumor cells while not affecting normal cells. Also, they can be used in combination therapy with other conventional therapies to reduce their side effects. Although there is still the need to further refine these oncolytic viruses, this new approach is not without its challenges. While it has shown promising potential in clinical trials, there is still the problem of the engineered virus reverting to the wild type or evolving into a more virulent type. Additionally, the effective dose and best route of administration are yet to be properly studied which raises the need to further study the application of these viruses for cancer therapy.

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