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Review Article

Molecular Mechanisms Associated with Virus-induced Oncogenesis and Oncolysis

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Abstract: Cancer is a leading cause of human deaths worldwide. Besides inherited genetic disorders, a diverse range of physical, chemical and biological agents may induce cancer. About 15-20% of cancers are known to be originated due to pathogens. Viruses are considered to be the second (after smoking) most important risk factor in inducing human cancer. Viruses may either harbour a copy of oncogene or have an ability to alter the expression of cellular copy of the oncogenes. Both RNA and DNA viruses are can induce oncogenesis. Most of the DNA tumour viruses either integrate their genome (complete or part of it) into the host genome or express early genes that are required for early event of virus replication. These early genes are responsible for oncogenic transformation of host cells. Based upon the mechanism involved, oncogenic RNA viruses are divided into two groups-transforming and non-transforming RNA viruses. Transforming RNA viruses carry viral oncogenes that are homologous to the host oncogene, their expression in infected cells results in oncogenic transformation of the cell. Non-transforming RNA viruses induce oncogenesis similar to the DNA viruses. Contrary, oncolytic viruses selectively replicate in cancerous cells and induce cell death without any damage to the normal tissues. Typically, oncolytic viruses are nonpathogenic to humans that can naturally replicate in cancer cells by exploiting oncogenic cell signalling pathways. Pathogenic viruses can also be genetically manipulated which allow them to replicate in cancerous but not in normal cells. This review review describes the molecular mechanisms associated with virus induced oncogenesis and oncolysis.

Keywords: Oncogenic, Oncolytic, Virus

1. Introduction

Cancer or oncogenesis is referred to as unrestrained growth of the cells. It is a multi-step process which is usually initiated by mutations in protein-encoding genes that regulate cell division. As a result of these mutations, the cancer cells acquire a selective advantage to multiply more rapidly than the normal cells. When such tumour cells remain at their original location, they are considered benign. They are referred to as malignant if they become invasive/spread from their primary site to a different or secondary site (metastasize) within the host's body, where new tumours may form [1]. Out of approximately 35,000 protein-coding genes in the human genome, only a small number are associated with cancer. These genes which regulate biological changes in transforming cells can be broadly classified into two groups namely, growth stimulatory genes (proto-oncogenes), and growth inhibitory genes (anti-oncogenes or tumour suppresser genes) [2].

The mutated forms of proto-oncogenes which cause cancer are called oncogenes. The mutations in proto-oncogenes always remain in dominant form, therefore, only one copy of the gene needs to be mutated in inducing cancer [3]. There are numerous cellular genes which serve as targets for

oncogenesis, following viral infection. For example, (i) Akt signalling pathway-associated oncogenes such as *Akt* and *PI3K* regulate cell survival by maintaining cytoskeleton integrity and evasion of apoptosis [4]. (ii) Cell cycle control related oncogenes such as *Cyclin* and *Cdk* are associated with advancement of cell cycles from G1 to S/ M phase [5]. (iii) MAPK signalling pathway related genes such as *Ras, RTK*, *Mos, p38, Myc* and *Fos/Jun* regulate cell proliferation and growth [6].

Tumour suppressor genes encode proteins which impair cell divsion or induce apoptosis or programmed cell death. Mutations in tumour suppressor genes are always recessive. Therefore, mutation in both the copies of the gene is required for functional inhibition [7]. Two tumour suppresser genes are known to be directly linked with viral induced oncogenesis (i) Retinoblastoma (RB), which is associated with cell cycle control by binding with E2F transcription factor and (ii) p53 which is associated with apoptosis [8].

The basic cause of cancers is environmental exposure to carcinogens such as cigarette smoking, exposure to UV/nuclear rays, ethidium-bromide, aluminium, arsenic, radon, lead, titanium dioxide, cobalt, tungsten carbide, indium phosphide and welding/mining fumes [9]. A minority of cancers also results due to inherited genetic mutations. Infections with certain viruses, bacteria, and parasites have also been recognized as risk factors for several types of cancer in humans/animals.

About 15-20% of cancers are known to be originated due to pathogens [10]. Both RNA and DNA viruses are associated with cancers. Viruses are considered to be the second (after smoking) most important risk factor in inducing human cancer. Viruses which are involved in oncogenesis either have a copy of one of these genes or may have an ability to alter expression of cellular copy of these oncogenes. In 1908, Oluf Bang and Vilhelm Ellerman were the first to show that avian erythroblastosis (a form of chicken leukemia) is transmitted by cell-free extracts, which was subsequently confirmed for solid tumours in chickens in 1910-1911 [11]. During early 1950s, there were evidences that viruses could incorporate or remove genetic material in cells [12]. The new genes acquired from the viruses could make the cell cancerous. Many of these viral oncogenes have been investigated and shown to induce cancer [12].

Virus-induced tumours can be divided into two classes; acute or slowly transforming. In acutely transforming viruses, the viral particles carry a gene that encodes for an overactive oncogene called viral-oncogene (*v-onc*), and the infected cell is transformed as soon as *v-onc* is expressed [13]. In contrast, in slowly transforming viruses, the integration of viral genome near a proto-oncogene in the host genome is obligatory [14]. The viral promoter or other transcription regulation elements in turn cause over expression of that proto-oncogene, which in turn induces uncontrolled cellular proliferation. Since viral genome insertion is not specific to proto-oncogenes and the chance of insertion near that proto-oncogene is low, slowly transforming viruses have a very long tumour latency compared to acutely transforming viruses [13]. Advances in cancer research lead to development of anti-cancer vaccine. HPV was the first vaccine to be developed to prevent hepatocellular carcinoma [15]. Later on, in 2006 U.S. Food and Drug Administration approved a human papilloma virus vaccine (Gardasil) which protected against four HPV types which cause cervical cancers and genital warts [15].

2. Oncogenic DNA Viruses

Following infection, most of the DNA tumour viruses either integrate their genome (complete or part of it) into the host genome or express early genes that are required for early event of virus replication. These early genes are responsible for oncogenic transformation of host cells by diverse mechanisms (Table 1) explained below.

Table 1. *Oncogenic DNA viruses.*

Virus family	Virus	Animal species	Tumour	References
Papillomaviridae	Bovine papilloma virus 4 (BPV-4)	Cattle	Cancer of the upper gastrointestinal tract	[16, 17]
	BPV-16	Human	Cancer of the upper gastrointestinal tract	
	BPV-1/2/4	Cattle	Cancer of the urinary bladder	
	HPV-16/18	Human	Cancer of the genital tract	
	HPV-16/5	Rabbit	Skin carcinoma	
Polyomaviridae	Simian Viruses 40	Rodents and Human	Brain tumours, bone tumours, mesotheliomas, and non-Hodgkin's lymphomas	[18, 19]
	Mouse polyomavirus	Mice and hamsters	Leukaemia	
	Human polyomavirus 6	Human	HPyV6 associated pruritic and dyskeratotic dermatosis (H6PD)	
	Human polyomavirus 7	Human	HPyV7-related epithelial hyperplasia	
	Merkel cell polyomavirus	Human	Merkel cell cancer	
	BK polyomavirus	Human	Nephropathy; haemorrhagic cystitis	
	JC polyomavirus	Human	Progressive multifocal leukoencephalopathy	
Herpesviridae	Epstein-Barr virus (Human herpes virus 4)	Human	Burkitt's lymphoma, Nasopharyngeal cancer, B cell lymphomas, Hodgkin's lymphoma X-linked lymphoproliferative disease (Duncan's syndrome)	[20, 21]
	Human herpesvirus 8 (HHV-8, Kaposi's Sarcoma herpesvirus)	Human	Effusion lymphoma, Castelman's disease and oral hairy leukoplakia	
	Ovine herpesvirus 1 (OvHV-1)	Sheep	Pulmonary adenomatosis	

Virus family	Virus	Animal species	Tumour	References
	Marek's disease virus	Poultry	Malignant lymphomatosis	
	Herpesvirus saimiri (HVS)	Squirrel and monkeys	Generalized lymphoblast infiltration and leukaemia	
	Herpesvirus sylvilagus	Rabbit	Malignant lymphoma	
Hepadnaviridae	Hepatitis B virus (HBV)	Human	Hepatocellular carcinoma (HCC)	[22]

2.1. Inhibition of Retinoblastoma Protein

Retinoblastoma (RB) protein is known to impair progression of cell cycle from G1 to S phase [23]. The RB phosphorylation is regulated by cyclin D/CDK4/6, a complex critical to entry of the cell into S phase. p16 or $p16^{INK4a}$ is a tumour suppressor protein which plays an important role in cell cycle regulation by disruption of RB (inhibitor of CDK4/6 mediated RB phosphorylation) and thereby decelerating the cell's progression from G1 to S phase [24]. In normal cells, RB remains in hypophosphorylated form during early G phase. In response to growth stimuli, the complexes of D/CDK4/6 phosphorylate RB [23] which result in release of the E2F from RB, eventually leading to transcription activation of genes required to sustain in S-phase (Figure 1).

The DNA tumour viruses disrupt the normal function of RB to induce cancer. For example, E7 protein of papillomavirus [25] and T-antigen of polyomaviruses bind to pRB to facilitate release of E2F protein [17]. Besides, E7 protein of papillomavirus may directly bind to E2F-1, leading to the activation of E2F-1-dependent transcription [25]. Despite the fact that adenoviruses do not cause cancer in humans, E1A protein of adenoviruses disrupts the RB-E2F interactions [26]. However, herpesviruses indirectly inhibit RB by up-regulating cyclin/Cdk complexes.

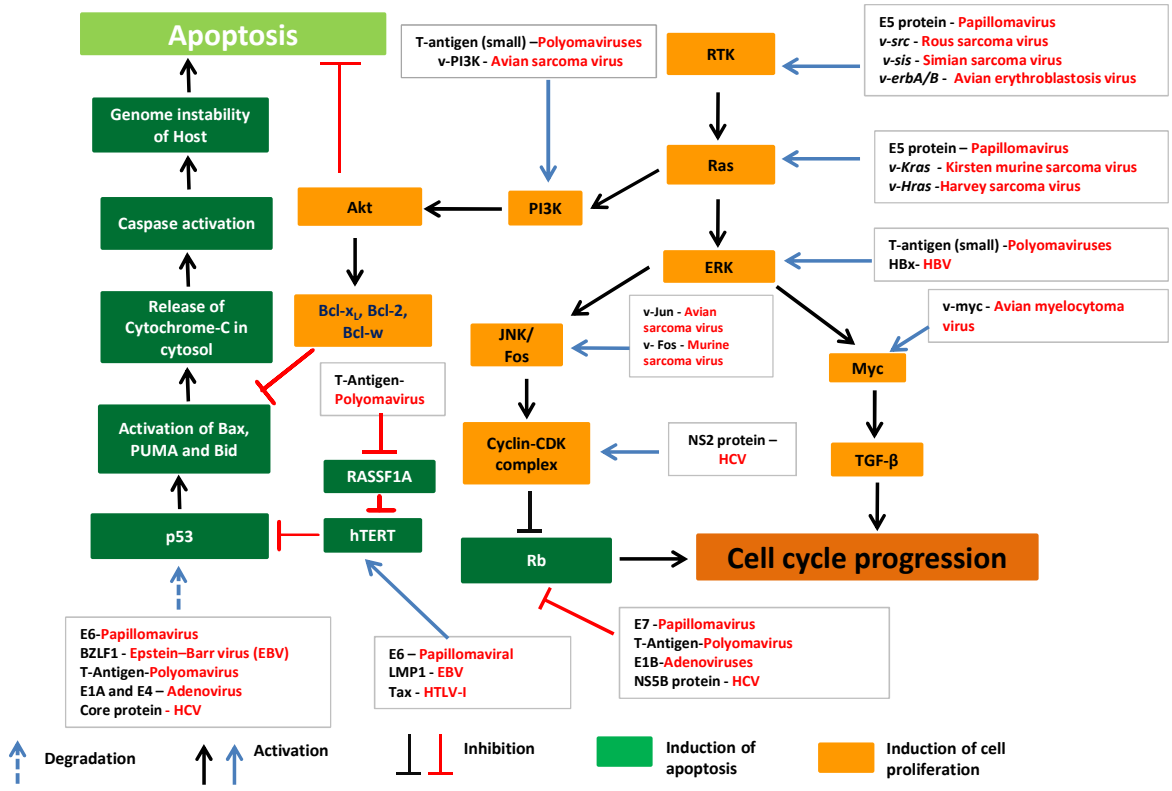

Figure 1. *Mechanisms employed by the viruses in inducing oncogenesis.*

Cell division and apoptosis is regulated by diverse range of signalling pathways. Whereas RTK/Ras/ERK pathways associated with cell cycle progression (growth), PI3K/Akt pathways is associated with cell survival during stress. The cross talk between these pathways establish a balance between cell proliferation and apoptosis. p53 and Retinoblastoma (Rb) are the major proteins associated with apoptosis. Inhibition/degradation of these proteins, results in failure of control on cell cycle, thereby resulting in cell proliferation or oncogenic transformation. Cancer is associated with either the inhibition of apoptotic signalling or hyper activation of growth factors. Viruses have got the capability to usurp these cell signalling pathways with the basic aim of effectively replication them inside the cells. However, these manipulated host factors induces oncogenic transformation of the cell. Viruses like papillomavirus, polyomavirus and HBV induce oncogenic transformation by directly activating the molecules that are associated with cell proliferation (saffron boxes). On the other hand, viruses such as polyomavirus (T-antigen), papillomavirus (E6 protein),

EBV (LMP1/ BZLF1 protein), HTLV (Tax protein), adenoviruses (E1A and E4 protein) and HCV (core protein) induce oncogenic transformation by inhibiting apoptotic signals (green boxes). Some of the viruses like retroviruses contain a copy of cellular oncogene, and upon infection they insert their viral copies of oncogene into host genome near cellular oncogenes. The expression of these viral oncogenes in host cells results in oncogenic transformation of cells.

2.2. Inhibition of p53-mediated Apoptosis

p53 is a tumour suppressor protein which regulates cell growth by inhibiting DNA mismatch repair. The p53 activity is regulated by p14ARF and MDM2 proteins. Under resting stage, p53 protein is maintained in its inactive (nonphosphorylated) form by MDM2. MDM2 induces proteasomal degradation of p53 protein by its ubiquitylation [27]. p14ARF acts as an upstream activator of p53, which itself is induced by E2F upregulation. Under stress such as viral infection, p14ARF binds to MDM2 which results in suppression of p53 ubiquitylation (prevents MDM2 binding) and thereby maintaining it in active (phosphorylated) form. Phosphorylated p53 remains stable and accumulates in the nucleus [28]. Mutations in p14ARF are also a frequent cause of cancer [29]. Upon activation, p53 stimulates two major apoptotic pathways. (i) Intrinsic mitochondrial pathway which is mediated by balance in Bcl-2 family members. The Bcl-2 family encompasses both anti-apoptotic (*Bcl-x_L, Bcl-2, KSHV-Bcl-2, Bcl-w*) and pro-apoptotic (*Bax, PUMA and Bid*) members. p53 up-regulates expression of *Bax, PUMA and Bid* to induce pro-apoptotic members to release of cytochrome-c from the mitochondria and hence ensues caspase-mediated apoptosis [30]. (ii) Extrinsic death receptor pathway wherein p53 triggers the activation of a caspase cascade, through the induction of genes encoding three transmembrane proteins, Fas, DR5 and PERP [31].

Proteins encoded by oncogenic DNA viruses also modulate p53 function to ensure their optimal replication. For example, T-antigen (Large) of SV40 (polyomavirus) [32], E6 protein of papillomavirus [17] and E1B protein of adenoviruses [33] directly bind with p53 and inhibits p53-dependent transcription, eventually resulting in impairment of apoptotic signals. Besides, papillomavirus, adenovirus (Ad) and Epstein–Barr virus can also induce proteasomal degradation of p53 [34] which is mediated via cellular proteins. For example, high risk papillomavirus E6 protein interacts with the host E6AP protein [35], adenoviral E1B-55K and E4orf6 proteins as well as Epstein–Barr viral protein BZLF1 interact with cellular proteins Cullin5/Cullin2 to induce E3 ubiquitin ligase-mediated proteaosomal degradation of p53 [33]. Besides depletion of p53, viruses may also directly target Bcl-2 protein family members, for example, the NS5A protein of HCV can interact with Bax and prevent apoptosis in p53-independent manner [36].

2.3. Modulation of Cell Signalling Pathways

The Ras/MEK/ERK signalling is associated with cell proliferation and growth whereas the Ras/PI3K/Akt signalling is associated with cell survivability. Some DNA viruses directly target these signalling pathways to achieve oncogenic transformation of cells. For example, E5 protein of papillomaviruses stimulates Ras [17] and HBV HBx protein modulate MAPK pathways [37] to induce oncogenesis (Table 1). The T antigen of polyomavirus interacts with cellular phosphatase PP2A and also activates growth factor receptors, such as Met [38], Notch-1 [39] and IGF-1R [40] which eventually result in modulation of Akt and MAPK pathways [32].

2.4. Modulation of Antiviral Pathways

To direct the normal cell towards oncogenic transformation, viruses may modulate antiviral immune responses by directly targeting inflammatory or interferon signalling pathways. For example, latent membrane protein 1 (LMP1) of EBV [41] and Tax protein of HTLV-I [42] target nuclear factor-κB (NF-κB) pathway that subsequently regulates growth and progression of inflammation-induced tumours [43]. Likewise, KSHV ORF K9 inhibit interferon-induced signalling pathways to contribute to host cell transformation [44].

2.5. Miscellaneous Targets of DNA Viruses

In addition to these major targets, several other cellular proteins also serve as targets for oncogenic transformation by viruses, for example, human telomerase reverse transcriptase (hTERT) and RASSF1A. hTERT is catalytic subunit of telomerase which is activated by oncogenes such as *c-Myc, Sp1, HIF-1* and *AP2*. Conversely hTERT activity may be suppressed by p53 [45]. Several oncogenic DNA viruses have shown to activate hTERT in order to induce oncogenic transformation, viz; papillomavirus E6 protein [46], EBV LMP1protein [47] and HTLV-I Tax protein [48].

Tumour suppressor Ras association domain-containing protein 1A (RASSF1A) also serves as a virus-induced target of oncogenesis. Silencing of RASSF1A induces telomerase activity. T-antigen of polyomavirus not only inactivates p53, but also inactivates the RASSF1A gene [49].

Besides, herpesviruses may also transform the cell by site-specific damage of host DNA [50]. In general, herpesviruses maintain their genome as episome (extra-chromosomal circular form) in the nucleus of infected cells, without integration with the host genome [50]. During oncogenic transformation, the virus integrates its genome into specific sites in the host genome thereby inducing breakage/damage that eventually results in oncogenic transformation [20]. Similarly, the E6 and E7 protein of papillomaviruses induce cellular genomic instability and mitotic defects in inducing carcinogenesis [51].

3. Oncogenic RNA Viruses

Based upon the mechanism involved, oncogenic RNA viruses are divided into two groups-transforming and non-transforming RNA viruses. Transforming RNA viruses

carry viral oncogenes that are homologous to the host oncogene, their expression in infected cells results in oncogenic transformation of the cell. Non-transforming RNA viruses induce oncogenesis similar to the DNA viruses.

3.1. Retroviruses

The oncogenic retroviruses may be either transforming or non-transforming in nature. Transforming retroviruses carry certain genes that are non-essential for viral replication and are homologues to host oncogenes. Such viruses integrate their viral copies of oncogene in host genome and upon expression they transform the cell (Table 2). Non-transforming retroviruses lack oncogenes but could achieve oncogenic transformation by proviral insertional mutagenesis (integrating a provirus near normal cellular proto-oncogenes and activating their expression) [52] (Table 2).

Table 2. *Oncogenic RNA viruses.*

RNA viruses	Virus	Viral oncogene	Animal affected	Tumour	References
Tansforming retroviruses	Rous sarcoma virus	*v-src*	Poultry	Sarcoma	[53]
	Simian sarcoma virus	*v-sis*	Monkey	Sarcoma	
	Avian erythroblastosis virus	*v-erbA or v-erbB*	Poultry	Avian erythroblastosis	[54]
	Kirsten murine sarcoma virus	*v-Kras*	*Mice*	*Murine sarcoma*	[52]
	Moloney murine sarcoma virus	*v-mos*	*Mice*	*Murine Leukemia*	[55]
	Harvey sarcoma virus	*v-HRas*	*Mice*	*Leukemia*	[56]
	CT10 avian sarcoma virus	*v-Crk*	Poultry	Avian sarcoma	[52]
	MC29 avian myelocytoma virus	*v-myc*	Poultry	Avian myelocytoma	[57]
	Avian sarcoma virus 16	*v- PI3K*	poultry	Avian sarcoma	[52]
	Avian sarcoma virus 17	*v- Jun*	Poultry	Avian sarcoma	
	Finkel-Biskis-Jinkins murine sarcoma virus	*v-Fos*	Mice	murine sarcoma	[58]
Non transforming retroviruses	Avian leukosis virus	-	Poultry	Avian leucosis complex	[52]
	Mouse mammary tumour virus (MMTV)	-	Mouse	Mammary tumour	
Flaviviruses	Hepatitis C virus	-	Human	Hepatocellular carcinomas	[59]

3.2. Flaviviruses

Flaviviruses achieve oncogenic transformation similar to DNA viruses i.e. by modulating expression of cellular genes that lead to oncogenic transformation. For example, HCV NS5B directly binds with RB to alter its localization and proteosomal degradation. Similarly, NS2 protein activates cyclin/Cdk and core protein directly dysregulates p53 pathway [59]. Besides, HCV can also modulate MAPK and Akt signalling pathways in inducing oncogenic transformation [59].

4. Oncolytic Viruses

Oncolytic viruses selectively replicate in cancerous cells and induce cell death without any damage to the normal tissues. Typically, oncolytic viruses fall into two classes (i) Viruses that are nonpathogenic to humans and have a naturally replicate in cancer cells. For example, H1 autonomous parvoviruses, Newcastle disease virus (NDV), reovirus, mumps virus, moloney leukemia virus and Seneca Valley virus. These viruses are highly dependent on oncogenic signalling pathways for their replication and require higher magnitude of innate antiviral signalling to be effectively eliminated from the infected cells [60]. (ii) Viruses that are genetically manipulated for use as vaccine vectors, viz; measles virus, poliovirus, and vaccinia virus. Genetically-engineered viruses containing mutations which allow them to replicate in cancerous but not in normal cells are also referred as oncolytic viruses, viz; adenovirus, herpes simplex virus, and vesicular stomatitis virus [61].

4.1. Mechanisms Employed by the Oncolytic Viruses to Selectively Grow in Tumour Cells

4.1.1. Upregulation of Tumour-specific Primary Receptor

Viruses use the cell surface proteins as receptors for attachment/entry into the host cell. Some tumour cells naturally express high amount of viral primary receptor proteins to facilitate enhanced receptor-mediated entry of the virus into the tumour cells. For instance, higher expression of Cd155 receptor in malignant glioma cells facilitates entry of polioviruses [62] and enhanced expression of urokinase or CD46 in various malignancies facilitates measles virus entry [63]. Likewise, Nectin-1 expression by squamous cell carcinoma is a predictor of herpesvirus-associated oncolysis [64].

Viruses may also be engineered to target tumour-specific surface markers such as epidermal growth factor receptors (EGFR), human epidermal growth factor receptor 2 (HER2) and somatostatin receptors (SSTR) [65-67] which are upregulated in certain types of tumours. Coating of adenovirus with a dendermeric polymer (targeting EGFR) results in enhanced tropism towards tumour cells with up-regulated EGFR. A genetically engineered single-chain variable fragment (scFv) antibody fused with HSV surface glycoprotein that targets cellular receptors EGFR and HER2 showed enhanced tropism of HSV1 towards tumour cells [65, 66]. Similarly, Oncolytic adenovirus was modified with somatostatin motifs for selective infection of neuroendocrine tumour cells [67].

Despite the fact that the expression of *coxsackievirus*-adenovirus *receptor* (CAR) in various

tumours is variable, the efficiency of adenovirus is very low for cells with low or no CAR receptors [68]. To overcome the issues, Arg-Gly-Asp (RGD) motif was introduced in the surface-exposed loops of adenovirus fibre knob which enabled the adenovirus to bypass CAR and mediate cell entry via RGD binding integrins [69].

4.1.2. Upregulation of Tumour Specific Transcriptase Promoter

Tumour cells are associated with aberrant expression of cellular tumour specific transcriptase promoters that are exploited by oncolytic viruses to induce oncolysis. For example, hTERT and Cyclin E promoters help adenoviruses to selectively replicate in tumour cells [70]. Likewise, engineered adenovirus containing prostate-specific or telomerase-promoter-specific expression of adenoviral E1 and E4 protein renders its replication exclusively in tumour cells [71].

4.1.3. Enhanced Expression of Tumour Specific Proteins

Tumour cells are associated with aberrant expression of specific proteins which may be exploited by oncolytic viruses to ensure their optimum replication and subsequently oncolysis of infected cells. For instance, Thymidine kinase (Tk) and Ras generally remain inactive in normal cells but are activated in tumour cells [72]. Activated Ras/MEK pathway suppresses IFN response that ensures faster replication of the oncolytic viruses, viz; HSV and reoviruses [72]. Besides, activated Ras is also utilized by the oncolytic viruses to induces apoptosis, for example, reovirus induces apoptosis of tumour cells by accumulating Ras in the Golgi complex [73].

ELK is a transcription factor which is expressed in high level by those tumourogenic cells that express enhanced levels of Ras. Infected cell protein-4 (ICP4), an HSV protein necessary for virus replication was expressed under the control of ELK promoter. Since Ras/Elk is likely to express only in tumours, ICP4/HSV exclusively replicates/lyse tumour cells [74].

VGF (vaccinia growth factor) and $\gamma_1$34.5 proteins, respectively in vaccinia virus and HSV-1 are required to activate Ras signalling in normal cell. Activated Ras is in turn required for efficient virus replication. Therefore, VGF and $\gamma_1$34.5 deletion mutants, lacking in capabilities to induce Ras cannot efficiently replicate in normal cells. Conversely, cancerous cells which express high levels of Ras support virus replication [75].

Tk play a key role in DNA synthesis in both prokaryotes and eukaryotes. Viruses such as vaccinia and HSV also encode TK, athough they can exploit cellular TK as well, which is highly expressed in cancerous cells. Therefore, TK deleted vaccinia or HSV mutants which efficiently replicate in cancerous but not in normal cells, may be utilized as an oncolytic agent [76].

4.1.4. Aberrant Expression of miRNA in Tumour Cells

A large number of cancer types are associated with disruption of miRNA homeostasis. The tropism of the virus towards tumour cells can also be manipulated by regulating miRNA expression. For example, genetically engineered adenovirus expressing mir199 which negatively regulates adenoviral E1A gene expression, restricts virus growth in normal cells. However, mir199 is non-functional in tumour cells [77], thereby ensuring virus replication and oncolysis. Similarly, MV-EGFP (mtd), an miRNA sensitive measles virus was engineered to restrict its replication in tumour cells [78].

4.1.5. Lack of IFN and PKR Signalling in Tumour Cells

IFN and protein kinase R (PKR) signalling is required to limit virus replication [79, 80]. Tumour cells lack IFN and PKR signalling machinery, thereby facilitating virus replication. For example, VSV matrix (M) protein inhibits IFN signalling, mutation in which limits the viral growth in normal cells. Due to lack of IFN signalling, VSV-M mutant ensures its replication only in tumour cells [81].

Upon secretion from the virus infected cells, IFN binds to nearby cells and activates STAT (signal transducer and activator of transcription) that serve as transcription factors to up-regulate the expression of antiviral proteins. Viruses are known to inhibit activation of STAT to ensure their replication. For example, measles virus non-structural proteins C and V abrogate IFN signalling by inhibiting STAT phosphorylation [79]. Deletions of these genes restrict measles virus replication in tumour cells due to lack in IFN signaling [82].

The activated PKR is known to phosphorylate eukaryotic initiation factor-2 alpha (eIF-2α) which results in inhibition of viral mRNA transcription. HSV1 ICP34.5 protein binds with protein phosphatase-1 (PP1), which is known to block PKR/eIF2 signalling, thereby facilitating virus replication [80]. Lack of PKR signalling in tumour cells allows selective replication of HSV-1 (ICP34.5) deletion mutant.

4.1.6. Inability to Express MHC-restricted Antigen

HSV-1 α47, ICP34.5 and ICP47 proteins help the virus to evade the immune system by blocking MHC-1-mediated presentation of HSV1 antigens [83, 84]. Cancerous cells usually lack in the capacity to present the MHC-I antigen thereby preventing them from recognition by cytotoxic T cells. Injection of ICP34.5 and ICP47 deletion mutant of HSV-1 directly in tumours leads to cell death (due to HSV replication), though it prevents recognition by the immune system [83, 84].

4.1.7. Deletion Mutation of Viral Anti-apoptotic Factors

Adenoviruses exclusively replicate in host cells during the S phase. Adenovirus E1A and E1B inhibit tumour suppressor proteins RB and p53 respectively, which eventually enable the cell to enter into S phase [85]. Therefore, normal expression of these proteins in infected cells provides suitable environment for viral replication as well as in preventing cell lysis. Cancerous cells are lacking in apoptotic machinery. Adenoviral E1A and E1B deletion mutants restrict viral growth in normal cells. However, the cancerous cells which remain in S phase may ensure selective growth of such adenoviral mutants and the same [(E1A: dl1520 and H101 and E1B: AdΔ19K, dl 922-947 and AdA-24)] have been used in

oncotherapy [63].

Cellular $p16^{Ink4a}$ protein is known to function as an inhibitor of CDK4/6-mediated RB phosphorylation and have been shown to be mutated in most of the human cancers [24]. HSV ICP6 inhibits $p16^{Ink4a}$. Therefore deletion of ICP6 gene restricts HSV growth in tumour cells [86].

4.2. Mechanisms Involved in Destruction of Tumour Cells by Oncolytic Viruses

Some viruses naturally encode proteins that induce cell lysis. However others may be engineered to encode oncolytic proteins (Table 3).

Table 3. *Oncolytic viruses.*

Virus family	Virus	Modifications	Target tumour type	References
Adenovirus	Oncorine (H101)	Deletion of E1B-55k and E3 gene	Liver, lung, head/neck and pancreas	[87]
	Onyx-015	Deletion of E1B-55k or E3B gene	Squamous cell carcinomas of the head and neck and pancreatic cancer	[88]
	CG7060	Regulation of the expression of viral genes by prostate tissue-specific promoters	Prostate cancer	[89]
	CG7870/CV787	Regulation of the expression of viral genes by rat probasin and prostate tissue-specific promoters *(PSA)*	Prostate cancer	[71]
	CG0070	Insertion of E2F-1 and GM-CSF	Non-muscle invasive bladder cancer	[90]
	Ad5-yCD/TKrep	Insertion of yCD and TK fusion gene	Prostate cancer	[91]
	Ad5-yCD/mutTKSR39rep-ADP	Insertion of yCD, TK fusion and ADP gene	Prostate cancer	[92]
	Ad5-yCD/mutTKSR39rep-hIL12	Insertion of yCD, TK fusion and human IL-12 gene	Prostate cancer	[93]
	Telomelysin	Regulation of the expression of viral genes by hTERT promoter	Various solid tumours	[70]
	CGTG-102	Insertion of GM-CSF	Solid tumours	
	Ad5-D24-RGD/DNX-2401	Modification of viral surface by incorporating RGD-fiber	Malignant glioma and brain cancer	[94]
	Ad5-SSTR/TK-RGD	Viral surface modification by incorporating the RGD fiber or SSTR and insertion of TK	Gynecologic cancer	[95]
	INGN-007 (VRX-007	Insertion of ADP gene	Tumour of liver and lungs	
	ColoAd1	Chimeric Ad11p/Ad3	Lymph nodes and normal margins in resected tissues	[96]
	ICOVIR-5	Regulation of the expression of viral genes by E2F1 promoter	Melanoma	[97]
	T-VEC (Onceover)	Insertion of GM-CSF	Melanoma	[98]
Herpesvirus	G207	Deletion of ICP34.5 and ICP6	Human rhabdo-myosarcoma and angiogenesis	
	HSV 1716 (Seprehvir)	Deletion of ICP34.5	Malignant pleural mesothelioma	[80]
	G47Delta	Modified G207 by deletion of *γ34.5*, *ICP6* and *a47*	Nasopharyngeal carcinoma	[86]
	NV1020	Deletion in UL56, UL24 and endogenous tk gene and insertion of an exogenous HSV-1 tk gene	Hepatic malignancy	[99]
	HF10	HSV-1 HF strain	Solid tumours outside the brain.	[100]
Paramyxovirus	Measles virus MV-CEA	Genetically engineered to produce carcino-embryonic antigen (CEA)	Ovarian, peritoneal, myeloma etc.	[101]
	Newcastle disease virus NDV-HUJ	-	Glioblastoma, neuroblastoma, sarcomas	[102]
	MTH-68/H	Newcastle Disease Virus Vaccine	Advanced tumours of the renal, colon and breast	
Reovirus	Reolysin	-	Diverse types of cancer	[103]
	Pelareorep	-	Prostate cancer	
Rhabdovirus	VSV-hIFNβ Vesicular stomatitis virus	Insertion of IFN-β	Hepatocellular carcinoma	[104]
Picornavirus	CAVATAK	-	Melanoma	[94]
	PVS-RIPO	-	Glioblastoma	[62]
Poxvirus	Pexa-Vec/JX-594Vaccinia (Wyeth strain)	Insertion of GM-CSF and deletion of TK	Tumour of liver, colorectal, head/neck tumours	[105]
	GL-ONC1 (GLV-h68) Vaccinia (Lister)	Insertion of expression viral gene marker Renilla Luciferase GFP	Advanced head/neck cancer undergoing standard chemo-radiotherapy	[106]
	vvDD-CDSRVaccinia (Western Reserve	Deletion of TK and VGF and viral surface modification by incorporating CD and Somatostatin R	Advanced solid cancers	[107]

Virus family	Virus	Modifications	Target tumour type	References
Parvovirus	H-1 PV	-	Glioblastoma	
Seneca Valley Virus	NTX-010	-	Neuro-endocrine tumours	[108]
Retrovirus	Toca 511	Viral surface modification by incorporating CD	Gastrointestinal tumours	[109]
Sendai virus	HVJ-E, GEN0101and TSD-0014	Inactivated Sendai virus particles	Prostate cancer and melanoma	[110]

4.2.1. Activation of Viral Anti-tumour Protein in Cancerous Cells

Some viruses encode oncolytic proteins which specifically kill cancerous cells. For instance, in normal cells, VP3 (apoptin) protein of chicken*anaemia virus (CAV) is* localized in the cytoplasm wherein it remains inactive (nonphosphorylated) and can be readily neutralized. In tumour cells, Akt-associated increased microtubule activity allows its localization into the nucleus. In the nucleus, apoptin is phosphorylated by CDK2 that subsequently results in induction of p53-independent apoptosis by activating *caspase-3 pathway [111]*.

Newcastle disease virus (NDV) have the natural potential to infect cancerous cells and lyse them by nucleoprotein and hemagglutinin protein-associated triggering of p53-mediated cell death [112].

4.2.2. Development of Anti-tumour Immunity

Infection of some oncolytic viruses induce development of anti-tumour immunity, the mechanism of which is not fully understood. It is believed that such viruses upregulate the production of pro-inflammatory cytokines and tumour neo-antigen in the infected cells to directly stimulate APCs and cytotoxic T cells. For instance, parvovirus infection induces release of pro-inflammatory cytokines which results in activation of APCs and cytotoxic T cells [113]. Besides, the virus also down-regulates expression of oncogen *c-Myc* and induces cathepsin-mediated (p53-independent) apoptosis of tumour cells [112].

4.2.3. Immune-stimulatory Gene

The viruses can be mutated by introducing some of the immune-stimulatory genes (interleukin family of genes). For instance, Talimogenelaherparepvec (T-VEC) HSV was engineered to express human granulocyte–macrophage colony-stimulating factor (GM-CSF). GM-CSF expressing T-VEC-HSV enhances capabilities of the APCs so as to efficiently present cancer antigens which eventually results in activation of NK cells and tumour antigen-specific T cells, thereby causing cell lysis [98]. By employing these concepts, vaccinia virus was engineered to express IL-10 and GM-CSF gene [105], adenovirus was engineered to express pro-apoptotic transgene TRAIL (tumour-necrosis-factor-related apoptosis-inducing ligand), GM-CSF and ADP [114]. Similarly, oncolytic potentiality of measles virus was enhanced by insertion of immunomodulatory neutrophil-activating protein [115]. Likewise, NDV oncolytic potential was enhanced by insertion of IL-2, TRAIL and GM-CSF [116].

4.2.4. RNAi

RNAi represents a promising novel therapeutic option for treating cancer. Viruses may be armed with RNAi for selective silencing of the genes associated with oncogenesis. For instance, Ad-TERTp-E1A-1504 is an engineered adenovirus that induces silencing of tumour-promoting EphA3 (inhibit Akt/mTOR pathways) gene [117]. Similarly, Ad-DeltaE1-shVEGF and AAV-ARHP8 were engineered for RNAi-mediated silencing of VEGF [118] and androgen receptor (AR) genes respectively [119].

4.2.5. Converting Pro-drug into Active Toxic Compound

The viruses which have the ability to selectively grow in tumour cells can be modulated by introducing selective gene(s) that have the ability to convert nontoxic pro-drug into toxic compounds. In quiescent cells, a cellular form of viral TK is not expressed but is up-regulated only in actively dividing tumour cells (during the G1 and S phases of the cell cycle-generating dNTPs required for DNA synthesis). The activated TK causes the conversion of the Ganciclovir (GCV) into Ganciclovir triphosphate (GCV-TP) that induces tumour cell death. Tk-expressing adenovirus and herpes simplex virus have been shown to trigger the susceptibility of tumour cells against Ganciclovir [91, 99].

5. Controversial Virus–tumour Associations

Viruses are believed to be co-evolved with their main hosts. Therefore their detections in the animal tissues must not be an unprecedented event. Likewise, detection of the viruses from tissues from tumour must not always be explained as the causative agent of the cancer. Therefore, numerous reports on virus–tumour associations have been controversial; the presence of the virus has been merely considered as contamination.

During the 1970s, HSV2, which causes genital herpes, was believed to be the causative agent for cervical carcinoma. Later on HPV was established as the causative agent of the cervical carcinoma [120]. Now, in the era of next generation sequencing (NGS), it has been confirmed that more than 90% of cervical carcinomas express high levels of high-risk HPV without any HSV2 sequences [121].

Viruses such as HPV, MMTV (mouse mammary tumour virus) and Epstein-Barr virus (EBV) were initially implicated in breast cancer [122]. However, transcriptomic data of more than 800 specimens demonstrated no association of these viruses in inducing breast cancer [122]. A small number of

NGS reads (9 out of >1.5 billion) were seen in theses specimens but that were suggestive of contamination [123].

The role of cytomegalovirus (CMV) in inducing human cancer is also controversial. Initially, CMV DNA and protein were detected in majority of gliomas [124]. However, later on, CMV was shown to be associated with a wide variety of other cancers. Likewise, CMV was proposed as a causative agent of most types of brain tumours, though this has been contested in other reports. Screening of over 700 glioma materials by NGS concluded absence of CMV RNA. Further, analysis of deep sequencing data from 34 glioblastoma tumours failed to see the presence of CMV [125].

HPV16 is usually detected in head, neck and cervical tumours. Few studies have shown its detection outside of its primary detection i.e. in lung and bladder carcinoma. Further, a recent NGS-based study reported HPV16 detection in gliomas [121].

EBV is implicated in a wide range of cancers including Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma and gastric adenocarcinoma. Additionally, transcriptomic analysis recently revealed EBV in 2 out of 105 diffuse large B-cell lymphomas [126]. Two tumours were also positive for HHV6 in this cohort (99 and 19 ppm), in one case coinciding with EBV infection. Analysis of viral gene expression patterns further supported a causative role for EBV, while HHV6 was suggested to be due to disease-related immunosuppression.

BK polyomavirus (BKV) was shown to be associated with urothelial carcinoma [123]. However earlier findings about its association in bladder carcinoma are contrasting, probably due to the fact that polyomaviruses often cause asymptomatic infections and are ubiquitous in humans.

Xenotropic murine leukemia virus-related virus (XMRV) was discovered in 2006 in patients with prostate cancer [127]. Later on, conflicting reports emerged about causation of prostate cancer by XMRV. It was reported that XMRV was generated due to recombination event in a laboratory mouse [128]. The virus was propagated via cell culture derived from a tumour present in this mouse and spread through contamination of laboratory samples. Further experiments demonstrated that XMRV detection was due to contaminated samples and was not associated in inducing prostate cancer.

The initial reports on virus-tumour associations were based on traditional viral detection/diagnosis technique such as PCR, in situ hybridization, western blotting and immunohistochemistry, all of which are prone to false positive detections. NGS is a powerful technique to explore the genome-wide changes in gene expression between cell lineages from diverse tissues or in diverse environments. Genomic and transcriptomic analysis of large number of tumours/virus in an unbiased manner (advance genomic tools/ NGS), is likely to explain clarity to some of these proposed virus-cancer associations.

6. Conclusions

Viruses are one of the leading causes of cancer. Both RNA as well as DNA viruses are able to induce cancer. With the advent of NGS, novel viruses are being identified which are associated with cancer. Understanding the mechanisms by which they induce cancer is likely to provide insights into the development of novel anticancer drugs. Ever since the completion of human genome project in 2001, ~520 kinases (kinome) were identified. Most of the cancers are associated with dysregulation of the kinome. Likewise, kinases are essentially required for virus replication in the target cells. Therefore, kinome may serve as fascinating targets for development of antiviral and anticancer drugs. Conversely, several non-pathogenic (human) viruses have a natural tendency to selectively replicate and kill cancer cells. Some other viruses have been genetically engineered to selectively kill the target cells. Further exploration of virus-host interaction is likely to provide insights for the development of better oncolytic viral agents. However some of the virus-tumour association are controversial which. The NGS-based approaches have great potential to solve the debated virus–tumour associations.

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References

[1] Wittekind C, Neid M. 2005. Cancer invasion and metastasis. Oncology 69 Suppl 1: 14-16.

[2] Sever R, Brugge JS. 2015. Signal transduction in cancer. Cold Spring Harbor Perspectives in Medicine 5.

[3] Cantley LC, Auger KR, Carpenter C, Duckworth B, Graziani A, Kapeller R, Soltoff S. 1991. Oncogenes and signal transduction. Cell 64: 281-302.

[4] Qin J, Xie LP, Zheng XY, Wang YB, Bai Y, Shen HF, Li LC, Dahiya R. 2007. A component of green tea, (-)-epigallocatechin-3-gallate, promotes apoptosis in T24 human bladder cancer cells via modulation of the PI3K/Akt pathway and Bcl-2 family proteins. Biochemical and Biophysical Research Communications 354: 852-857.

[5] Ingraham BA, Bragdon B, Nohe A. 2008. Molecular basis of the potential of vitamin D to prevent cancer. Current Medical Research and Opinion 24: 139-149.

[6] Zhang XK, Huang DP, Chiu DK, Chiu JF. 1987. The expression of oncogenes in human developing liver and hepatomas. Biochemical and Biophysical Research Communications 142: 932-938.

[7] Miyashita T, Krajewski S, Krajewska M, Wang HG, Lin HK, Liebermann DA, Hoffman B, Reed JC. 1994. Tumor suppressor p53 is a regulator of bcl-2 and bax gene expression in vitro and in vivo. Oncogene 9: 1799-1805.

[8] Szekely L, Selivanova G, Magnusson KP, Klein G, Wiman KG. 1993. EBNA-5, an Epstein-Barr virus-encoded nuclear antigen, binds to the retinoblastoma and p53 proteins. Proceedings of the National Academy of Sciences of the United States of America 90: 5455-5459.

[9] Parsa N. 2012. Environmental factors inducing human cancers. Iranian journal of public health 41: 1-9.

[10] De Flora S, La Maestra S. 2015. Epidemiology of cancers of infectious origin and prevention strategies. Journal of Preventive Medicine and Hygiene 56: E15-20.

[11] Justice Jt, Beemon KL. 2013. Avian retroviral replication. Current Opinion in Virology 3: 664-669.

[12] Moore PS, Chang Y. 2010. Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nature reviews. Cancer 10: 878-889.

[13] Butel JS. 2000. Viral carcinogenesis: revelation of molecular mechanisms and etiology of human disease. Carcinogenesis 21: 405-426.

[14] Luo GG, Ou JH. 2015. Oncogenic viruses and cancer. Virologica Sinica 30: 83-84.

[15] Ljubojevic S. 2006. The human papillomavirus vaccines. Acta Dermatovenerologica Croatica: ADC 14: 208.

[16] Chan PK, Chang AR, Cheung JL, Chan DP, Xu LY, Tang NL, Cheng AF. 2002. Determinants of cervical human papillomavirus infection: differences between high- and low-oncogenic risk types. The Journal of Infectious Diseases 185: 28-35.

[17] Campo MS. 2003. Papillomavirus and disease in humans and animals. Veterinary and Comparative Oncology 1: 3-14.

[18] Nguyen KD, Lee EE, Yue Y, Stork J, Pock L, North JP, Vandergriff T, Cockerell C, Hosler GA, Pastrana DV, Buck CB, Wang RC. 2017. Human polyomavirus 6 and 7 are associated with pruritic and dyskeratotic dermatoses. Journal of the American Academy of Dermatology 76: 932-940 e933.

[19] Ali N, Shaikh MU, Hasan S. 2011. BK Virus Associated Late Onset Haemorrhagic Cystitis After Allogeneic Peripheral Blood Stem Cell Transplant. Indian journal of hematology & blood transfusion: An Official Journal of Indian Society of Hematology and Blood Transfusion 27: 177-179.

[20] Elgui de Oliveira D. 2007. DNA viruses in human cancer: an integrated overview on fundamental mechanisms of viral carcinogenesis. Cancer Letters 247: 182-196.

[21] Hinze HC. 1971. Induction of lymphoid hyperplasia and lymphoma-like disease in rabbits by Herpesvirus sylvilagus. International Journal of Cancer 8: 514-522.

[22] Mathew S, Ali A, Abdel-Hafiz H, Fatima K, Suhail M, Archunan G, Begum N, Jahangir S, Ilyas M, Chaudhary AG, Al Qahtani M, Mohamad Bazarah S, Qadri I. 2014. Biomarkers for virus-induced hepatocellular carcinoma (HCC). Infection, genetics and evolution: Journal of Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases 26: 327-339.

[23] Giacinti C, Giordano A. 2006. RB and cell cycle progression. Oncogene 25: 5220-5227.

[24] Ohtani N, Yamakoshi K, Takahashi A, Hara E. 2004. The p16INK4a-RB pathway: molecular link between cellular senescence and tumor suppression. The Journal of Medical Investigation: JMI 51: 146-153.

[25] Hwang SG, Lee D, Kim J, Seo T, Choe J. 2002. Human papillomavirus type 16 E7 binds to E2F1 and activates E2F1-driven transcription in a retinoblastoma protein-independent manner. The Journal of Biological Chemistry 277: 2923-2930.

[26] Seifried LA, Talluri S, Cecchini M, Julian LM, Mymryk JS, Dick FA. 2008. pRB-E2F1 complexes are resistant to adenovirus E1A-mediated disruption. Journal of Virology 82: 4511-4520.

[27] Brooks CL, Gu W. 2006. p53 ubiquitination: Mdm2 and beyond. Molecular Cell 21: 307-315.

[28] Amaral JD, Xavier JM, Steer CJ, Rodrigues CM. 2010. The role of p53 in apoptosis. Discovery Medicine 9: 145-152.

[29] Brown VL, Harwood CA, Crook T, Cronin JG, Kelsell DP, Proby CM. 2004. p16INK4a and p14ARF tumor suppressor genes are commonly inactivated in cutaneous squamous cell carcinoma. The Journal of Investigative Dermatology 122: 1284-1292.

[30] Cory S, Adams JM. 2002. The Bcl2 family: regulators of the cellular life-or-death switch. Nature reviews. Cancer 2: 647-656.

[31] Haupt S, Berger M, Goldberg Z, Haupt Y. 2003. Apoptosis - the p53 network. Journal of Cell Science 116: 4077-4085.

[32] White MK, Khalili K. 2004. Polyomaviruses and human cancer: molecular mechanisms underlying patterns of tumorigenesis. Virology 324: 1-16.

[33] Querido E, Blanchette P, Yan Q, Kamura T, Morrison M, Boivin D, Kaelin WG, Conaway RC, Conaway JW, Branton PE. 2001. Degradation of p53 by adenovirus E4orf6 and E1B55K proteins occurs via a novel mechanism involving a Cullin-containing complex. Genes and Development 15: 3104-3117.

[34] Scheffner M, Werness BA, Huibregtse JM, Levine AJ, Howley PM. 1990. The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. Cell 63: 1129-1136.

[35] Scheffner M, Huibregtse JM, Vierstra RD, Howley PM. 1993. The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. Cell 75: 495-505.

[36] Chen Y, Williams V, Filippova M, Filippov V, Duerksen-Hughes P. 2014. Viral carcinogenesis: factors inducing DNA damage and virus integration. Cancers 6: 2155-2186.

[37] Kim CM, Koike K, Saito I, Miyamura T, Jay G. 1991. HBx gene of hepatitis B virus induces liver cancer in transgenic mice. Nature 351: 317-320.

[38] Cacciotti P, Libener R, Betta P, Martini F, Porta C, Procopio A, Strizzi L, Penengo L, Tognon M, Mutti L, Gaudino G. 2001. SV40 replication in human mesothelial cells induces HGF/Met receptor activation: a model for viral-related carcinogenesis of human malignant mesothelioma. Proceedings of the National Academy of Sciences of the United States of America 98: 12032-12037.

[39] Bocchetta M, Miele L, Pass HI, Carbone M. 2003. Notch-1 induction, a novel activity of SV40 required for growth of SV40-transformed human mesothelial cells. Oncogene 22: 81-89.

[40] Pass HI, Mew DJ, Carbone M, Matthews WA, Donington JS, Baserga R, Walker CL, Resnicoff M, Steinberg SM. 1996. Inhibition of hamster mesothelioma tumorigenesis by an antisense expression plasmid to the insulin-like growth factor-1 receptor. Cancer Research 56: 4044-4048.

[41] Mosialos G, Birkenbach M, Yalamanchili R, VanArsdale T, Ware C, Kieff E. 1995. The Epstein-Barr virus transforming protein LMP1 engages signaling proteins for the tumor necrosis factor receptor family. Cell 80: 389-399.

[42] Yasunaga J, Matsuoka M. 2007. Leukaemogenic mechanism of human T-cell leukaemia virus type I. Reviews in Medical Virology 17: 301-311.

[43] Karin M, Greten FR. 2005. NF-kappaB: linking inflammation and immunity to cancer development and progression. Nature Reviews. Immunology 5: 749-759.

[44] Moore PS, Chang Y. 1998. Antiviral activity of tumor-suppressor pathways: clues from molecular piracy by KSHV. Trends in Genetics: TIG 14: 144-150.

[45] Jin X, Beck S, Sohn YW, Kim JK, Kim SH, Yin J, Pian X, Kim SC, Choi YJ, Kim H. 2010. Human telomerase catalytic subunit (hTERT) suppresses p53-mediated anti-apoptotic response via induction of basic fibroblast growth factor. Experimental and Molecular Medicine 42: 574-582.

[46] Veldman T, Horikawa I, Barrett JC, Schlegel R. 2001. Transcriptional activation of the telomerase hTERT gene by human papillomavirus type 16 E6 oncoprotein. Journal of Virology 75: 4467-4472.

[47] Terrin L, Dal Col J, Rampazzo E, Zancai P, Pedrotti M, Ammirabile G, Bergamin S, Rizzo S, Dolcetti R, De Rossi A. 2008. Latent membrane protein 1 of Epstein-Barr virus activates the hTERT promoter and enhances telomerase activity in B lymphocytes. Journal of Virology 82: 10175-10187.

[48] Gabet AS, Mortreux F, Charneau P, Riou P, Duc-Dodon M, Wu Y, Jeang KT, Wattel E. 2003. Inactivation of hTERT transcription by Tax. Oncogene 22: 3734-3741.

[49] Toyooka S, Carbone M, Toyooka KO, Bocchetta M, Shivapurkar N, Minna JD, Gazdar AF. 2002. Progressive aberrant methylation of the RASSF1A gene in simian virus 40 infected human mesothelial cells. Oncogene 21: 4340-4344.

[50] De Bolle L, Naesens L, De Clercq E. 2005. Update on human herpesvirus 6 biology, clinical features, and therapy. Clinical Microbiology Reviews 18: 217-245.

[51] Duensing S, Lee LY, Duensing A, Basile J, Piboonniyom S, Gonzalez S, Crum CP, Munger K. 2000. The human papillomavirus type 16 E6 and E7 oncoproteins cooperate to induce mitotic defects and genomic instability by uncoupling centrosome duplication from the cell division cycle. Proceedings of the National Academy of Sciences of the United States of America 97: 10002-10007.

[52] Butel JS. 2000. Viral carcinogenesis: revelation of molecular mechanisms and etiology of human disease. Carcinogenesis 21: 405-426.

[53] Iba H, Takeya T, Cross FR, Hanafusa T, Hanafusa H. 1984. Rous sarcoma virus variants that carry the cellular src gene instead of the viral src gene cannot transform chicken embryo fibroblasts. Proceedings of the National Academy of Sciences of the United States of America 81: 4424-4428.

[54] Graf T, Beug H. 1983. Role of the v-erbA and v-erbB oncogenes of avian erythroblastosis virus in erythroid cell transformation. Cell 34: 7-9.

[55] Gojobori T, Yokoyama S. 1985. Rates of evolution of the retroviral oncogene of Moloney murine sarcoma virus and of its cellular homologues. Proceedings of the National Academy of Sciences of the United States of America 82: 4198-4201.

[56] Manly KF, Anderson GR, Stoler DL. 1988. Harvey sarcoma virus genome contains no extensive sequences unrelated to those of other retroviruses except ras. Journal of Virology 62: 3540-3543.

[57] Enrietto PJ, Payne LN, Hayman MJ. 1983. A recovered avian myelocytomatosis virus that induces lymphomas in chickens: pathogenic properties and their molecular basis. Cell 35: 369-379.

[58] Vogt PK. 2012. Retroviral oncogenes: a historical primer. Nature reviews. Cancer 12: 639-648.

[59] Vescovo T, Refolo G, Vitagliano G, Fimia GM, Piacentini M. 2016. Molecular mechanisms of hepatitis C virus-induced hepatocellular carcinoma. Clinical microbiology and infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases 22: 853-861.

[60] Watanabe H, Saitoh K, Kameda T, Murakami M, Niikura Y, Okazaki S, Morishita Y, Mori S, Yokouchi Y, Kuroiwa A, Iba H. 1997. Chondrocytes as a specific target of ectopic Fos expression in early development. Proceedings of the National Academy of Sciences of the United States of America 94: 3994-3999.

[61] Russell SJ, Peng KW, Bell JC. 2012. Oncolytic virotherapy. Nature Biotechnology 30: 658-670.

[62] Merrill MK, Bernhardt G, Sampson JH, Wikstrand CJ, Bigner DD, Gromeier M. 2004. Poliovirus receptor CD155-targeted oncolysis of glioma. Neuro-oncology 6: 208-217.

[63] Singh PK, Doley J, Kumar GR, Sahoo AP, Tiwari AK. 2012. Oncolytic viruses & their specific targeting to tumour cells. The Indian Journal of Medical Research 136: 571-584.

[64] Yu Z, Adusumilli PS, Eisenberg DP, Darr E, Ghossein RA, Li S, Liu S, Singh B, Shah JP, Fong Y, Wong RJ. 2007. Nectin-1 expression by squamous cell carcinoma is a predictor of herpes oncolytic sensitivity. Molecular Therapy: The Journal of the American Society of Gene Therapy 15: 103-113.

[65] Grunwald GK, Vetter A, Klutz K, Willhauck MJ, Schwenk N, Senekowitsch-Schmidtke R, Schwaiger M, Zach C, Wagner E, Goke B, Holm PS, Ogris M, Spitzweg C. 2013. EGFR-Targeted Adenovirus Dendrimer Coating for Improved Systemic Delivery of the Theranostic NIS Gene. Molecular Therapy. Nucleic Acids 2: e131.

[66] Petrovic B, Gianni T, Gatta V, Campadelli-Fiume G. 2017. Insertion of a ligand to HER2 in gB retargets HSV tropism and obviates the need for activation of the other entry glycoproteins. PLoS Pathogens 13: e1006352.

[67] Leja J, Yu D, Nilsson B, Gedda L, Zieba A, Hakkarainen T, Akerstrom G, Oberg K, Giandomenico V, Essand M. 2011. Oncolytic adenovirus modified with somatostatin motifs for selective infection of neuroendocrine tumor cells. Gene Therapy 18: 1052-1062.

[68] Jiang H, Gomez-Manzano C, Lang FF, Alemany R, Fueyo J. 2009. Oncolytic adenovirus: preclinical and clinical studies in patients with human malignant gliomas. Current Gene Therapy 9: 422-427.

[69] Sengupta S, Ulasov IV, Thaci B, Ahmed AU, Lesniak MS. 2011. Enhanced transduction and replication of RGD-fiber modified adenovirus in primary T cells. PloS One 6: e18091.

[70] Fujiwara T, Tanaka N. 2007. [Theranostic application of telomerase-specific oncolytic adenovirus for human cancer]. Nihon rinsho. Japanese Journal of Clinical Medicine 65: 1913-1922.

[71] Small EJ, Carducci MA, Burke JM, Rodriguez R, Fong L, van Ummersen L, Yu DC, Aimi J, Ando D, Working P, Kirn D, Wilding G. 2006. A phase I trial of intravenous CG7870, a replication-selective, prostate-specific antigen-targeted oncolytic adenovirus, for the treatment of hormone-refractory, metastatic prostate cancer. Molecular Therapy: The Journal of the American Society of Gene Therapy 14: 107-117.

[72] Balachandran S, Porosnicu M, Barber GN. 2001. Oncolytic activity of vesicular stomatitis virus is effective against tumors exhibiting aberrant p53, Ras, or myc function and involves the induction of apoptosis. Journal of Virology 75: 3474-3479.

[73] Garant KA, Shmulevitz M, Pan L, Daigle RM, Ahn DG, Gujar SA, Lee PW. 2016. Oncolytic reovirus induces intracellular redistribution of Ras to promote apoptosis and progeny virus release. Oncogene 35: 771-782.

[74] Pan W, Bodempudi V, Esfandyari T, Farassati F. 2009. Utilizing ras signaling pathway to direct selective replication of herpes simplex virus-1. PloS One 4: e6514.

[75] McCart JA, Ward JM, Lee J, Hu Y, Alexander HR, Libutti SK, Moss B, Bartlett DL. 2001. Systemic cancer therapy with a tumor-selective vaccinia virus mutant lacking thymidine kinase and vaccinia growth factor genes. Cancer Research 61: 8751-8757.

[76] Puhlmann M, Brown CK, Gnant M, Huang J, Libutti SK, Alexander HR, Bartlett DL. 2000. Vaccinia as a vector for tumor-directed gene therapy: biodistribution of a thymidine kinase-deleted mutant. Cancer Gene Therapy 7: 66-73.

[77] Callegari E, Elamin BK, D'Abundo L, Falzoni S, Donvito G, Moshiri F, Milazzo M, Altavilla G, Giacomelli L, Fornari F, Hemminki A, Di Virgilio F, Gramantieri L, Negrini M, Sabbioni S. 2013. Anti-tumor activity of a miR-199-dependent oncolytic adenovirus. PloS One 8: e73964.

[78] Baertsch MA, Leber MF, Bossow S, Singh M, Engeland CE, Albert J, Grossardt C, Jager D, von Kalle C, Ungerechts G. 2014. MicroRNA-mediated multi-tissue detargeting of oncolytic measles virus. Cancer Gene Therapy 21: 373-380.

[79] Palosaari H, Parisien JP, Rodriguez JJ, Ulane CM, Horvath CM. 2003. STAT protein interference and suppression of cytokine signal transduction by measles virus V protein. Journal of Virology 77: 7635-7644.

[80] Learmonth K, Braidwood L, Woll P, Conner J. 2015. Immune responses following intrapleural administration of oncolytic SEPREHVIR in patients with malignant pleural mesothelioma. Journal for Immunotherapy of Cancer 3: P335-P335.

[81] Stojdl DF, Lichty BD, tenOever BR, Paterson JM, Power AT, Knowles S, Marius R, Reynard J, Poliquin L, Atkins H, Brown EG, Durbin RK, Durbin JE, Hiscott J, Bell JC. 2003. VSV strains with defects in their ability to shutdown innate immunity are potent systemic anti-cancer agents. Cancer Cell 4: 263-275.

[82] Takeuchi K, Kadota SI, Takeda M, Miyajima N, Nagata K. 2003. Measles virus V protein blocks interferon (IFN)-alpha/beta but not IFN-gamma signaling by inhibiting STAT1 and STAT2 phosphorylation. FEBS Letters 545: 177-182.

[83] Liu BL, Robinson M, Han ZQ, Branston RH, English C, Reay P, McGrath Y, Thomas SK, Thornton M, Bullock P, Love CA, Coffin RS. 2003. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. Gene Therapy 10: 292-303.

[84] Goldsmith K, Chen W, Johnson DC, Hendricks RL. 1998. Infected cell protein (ICP) 47 enhances herpes simplex virus neurovirulence by blocking the CD8+ T cell response. The Journal of Experimental Medicine 187: 341-348.

[85] Gonzalez R, Huang W, Finnen R, Bragg C, Flint SJ. 2006. Adenovirus E1B 55-kilodalton protein is required for both regulation of mRNA export and efficient entry into the late phase of infection in normal human fibroblasts. Journal of Virology 80: 964-974.

[86] Wang JN, Hu P, Zeng MS, Liu RB. 2011. Anti-tumor effect of oncolytic herpes simplex virus G47delta on human nasopharyngeal carcinoma. Chinese Journal of Cancer 30: 831-841.

[87] Liang M. 2018. Oncorine, the World First Oncolytic Virus Medicine and its Update in China. Current Cancer Drug Targets 18: 171-176.

[88] Ries S, Korn WM. 2002. ONYX-015: mechanisms of action and clinical potential of a replication-selective adenovirus. British Journal of Cancer 86: 5-11.

[89] DeWeese TL, van der Poel H, Li S, Mikhak B, Drew R, Goemann M, Hamper U, DeJong R, Detorie N, Rodriguez R, Haulk T, DeMarzo AM, Piantadosi S, Yu DC, Chen Y, Henderson DR, Carducci MA, Nelson WG, Simons JW. 2001. A phase I trial of CV706, a replication-competent, PSA selective oncolytic adenovirus, for the treatment of locally recurrent prostate cancer following radiation therapy. Cancer Research 61: 7464-7472.

[90] Burke JM, Lamm DL, Meng MV, Nemunaitis JJ, Stephenson JJ, Arseneau JC, Aimi J, Lerner S, Yeung AW, Kazarian T, Maslyar DJ, McKiernan JM. 2012. A first in human phase 1 study of CG0070, a GM-CSF expressing oncolytic adenovirus, for the treatment of nonmuscle invasive bladder cancer. The Journal of Urology 188: 2391-2397.

[91] Freytag SO, Stricker H, Pegg J, Paielli D, Pradhan DG, Peabody J, DePeralta-Venturina M, Xia X, Brown S, Lu M, Kim JH. 2003. Phase I study of replication-competent adenovirus-mediated double-suicide gene therapy in combination with conventional-dose three-dimensional conformal radiation therapy for the treatment of newly diagnosed, intermediate- to high-risk prostate cancer. Cancer Research 63: 7497-7506.

[92] Freytag SO, Stricker H, Lu M, Elshaikh M, Aref I, Pradhan D, Levin K, Kim JH, Peabody J, Siddiqui F, Barton K, Pegg J, Zhang Y, Cheng J, Oja-Tebbe N, Bourgeois R, Gupta N, Lane Z, Rodriguez R, DeWeese T, Movsas B. 2014. Prospective randomized phase 2 trial of intensity modulated radiation therapy with or without oncolytic adenovirus-mediated cytotoxic gene therapy in intermediate-risk prostate cancer. International Journal of Radiation Oncology, Biology, Physics 89: 268-276.

[93] Pol J, Buque A, Aranda F, Bloy N, Cremer I, Eggermont A, Erbs P, Fucikova J, Galon J, Limacher JM, Preville X, Sautes-Fridman C, Spisek R, Zitvogel L, Kroemer G, Galluzzi L. 2016. Trial Watch-Oncolytic viruses and cancer therapy. Oncoimmunology 5: e1117740.

[94] Lin CZ, Xiang GL, Zhu XH, Xiu LL, Sun JX, Zhang XY. 2018. Advances in the mechanisms of action of cancer-targeting oncolytic viruses. Oncology Letters 15: 4053-4060.

[95] Kim KH, Dmitriev I, O'Malley JP, Wang M, Saddekni S, You Z, Preuss MA, Harris RD, Aurigemma R, Siegal GP, Zinn KR, Curiel DT, Alvarez RD. 2012. A phase I clinical trial of Ad5.SSTR/TK.RGD, a novel infectivity-enhanced bicistronic adenovirus, in patients with recurrent gynecologic cancer. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 18: 3440-3451.

[96] Dhar D, Spencer JF, Toth K, Wold WS. 2009. Effect of preexisting immunity on oncolytic adenovirus vector INGN 007 antitumor efficacy in immunocompetent and immunosuppressed Syrian hamsters. Journal of Virology 83: 2130-2139.

[97] Alonso MM, Gomez-Manzano C, Jiang H, Bekele NB, Piao Y, Yung WK, Alemany R, Fueyo J. 2007. Combination of the oncolytic adenovirus ICOVIR-5 with chemotherapy provides enhanced anti-glioma effect in vivo. Cancer Gene Therapy 14: 756-761.

[98] Andtbacka RH, Ross M, Puzanov I, Milhem M, Collichio F, Delman KA, Amatruda T, Zager JS, Cranmer L, Hsueh E, Chen L, Shilkrut M, Kaufman HL. 2016. Patterns of Clinical Response with Talimogene Laherparepvec (T-VEC) in Patients with Melanoma Treated in the OPTiM Phase III Clinical Trial. Annals of Surgical Oncology 23: 4169-4177.

[99] Kelly KJ, Wong J, Fong Y. 2008. Herpes simplex virus NV1020 as a novel and promising therapy for hepatic malignancy. Expert Opinion on Investigational Drugs 17: 1105-1113.

[100] Nawa A, Luo C, Zhang L, Ushjima Y, Ishida D, Kamakura M, Fujimoto Y, Goshima F, Kikkawa F, Nishiyama Y. 2008. Non-engineered, naturally oncolytic herpes simplex virus HSV1 HF-10: applications for cancer gene therapy. Current Gene Therapy 8: 208-221.

[101] Nakamura T, Peng KW, Harvey M, Greiner S, Lorimer IA, James CD, Russell SJ. 2005. Rescue and propagation of fully retargeted oncolytic measles viruses. Nature Biotechnology 23: 209-214.

[102] Csatary LK, Moss RW, Beuth J, Torocsik B, Szeberenyi J, Bakacs T. 1999. Beneficial treatment of patients with advanced cancer using a Newcastle disease virus vaccine (MTH-68/H). Anticancer Research 19: 635-638.

[103] Gollamudi R, Ghalib MH, Desai KK, Chaudhary I, Wong B, Einstein M, Coffey M, Gill GM, Mettinger K, Mariadason JM, Mani S, Goel S. 2010. Intravenous administration of Reolysin, a live replication competent RNA virus is safe in patients with advanced solid tumors. Investigational New Drugs 28: 641-649.

[104] Diaz RM, Galivo F, Kottke T, Wongthida P, Qiao J, Thompson J, Valdes M, Barber G, Vile RG. 2007. Oncolytic immunovirotherapy for melanoma using vesicular stomatitis virus. Cancer Research 67: 2840-2848.

[105] Bell J, McFadden G. 2014. Viruses for tumor therapy. Cell Host and Microbe 15: 260-265.

[106] Mell LK, Brumund KT, Daniels GA, Advani SJ, Zakeri K, Wright ME, Onyeama SJ, Weisman RA, Sanghvi PR, Martin PJ, Szalay AA. 2017. Phase I Trial of Intravenous Oncolytic Vaccinia Virus (GL-ONC1) with Cisplatin and Radiotherapy in Patients with Locoregionally Advanced Head and Neck Carcinoma. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 23: 5696-5702.

[107] Downs-Canner S, Guo ZS, Ravindranathan R, Breitbach CJ, O'Malley ME, Jones HL, Moon A, McCart JA, Shuai Y, Zeh HJ, Bartlett DL. 2016. Phase 1 Study of Intravenous Oncolytic Poxvirus (vvDD) in Patients With Advanced Solid Cancers. Molecular Therapy: the Journal of the American Society of Gene Therapy 24: 1492-1501.

[108] Burke MJ, Ahern C, Weigel BJ, Poirier JT, Rudin CM, Chen Y, Cripe TP, Bernhardt MB, Blaney SM. 2015. Phase I trial of Seneca Valley Virus (NTX-010) in children with relapsed/refractory solid tumors: a report of the Children's Oncology Group. Pediatric Blood and Cancer 62: 743-750.

[109] Merchan JR, Ostertag D, Jolly DJ, Tejera D, Gruber HE, Shorr J. 2018. Toca 511 and Toca FC in patients with gastrointestinal tumors in the Toca 6 study. Journal of Clinical Oncology 36: TPS880-TPS880.

[110] Nakajima TI, Toshimitsu & Wada, Hiroshi & Yamauchi, Toshie & Kiyohara, Eiji & Kane, Yasufumi.. 2013. A Novel Therapy for Melanoma and Prostate Cancer Using a Non-Replicating Sendai Virus Particle (HVJ-E)

[111] Danen-van Oorschot AA, van Der Eb AJ, Noteborn MH. 2000. The chicken anemia virus-derived protein apoptin requires activation of caspases for induction of apoptosis in human tumor cells. Journal of Virology 74: 7072-7078.

[112] Jhawar SR, Thandoni A, Bommareddy PK, Hassan S, Kohlhapp FJ, Goyal S, Schenkel JM, Silk AW, Zloza A. 2017. Oncolytic Viruses-Natural and Genetically Engineered Cancer Immunotherapies. Frontiers in Oncology 7: 202.

[113] Moehler MH, Zeidler M, Wilsberg V, Cornelis JJ, Woelfel T, Rommelaere J, Galle PR, Heike M. 2005. Parvovirus H-1-induced tumor cell death enhances human immune response in vitro via increased phagocytosis, maturation, and cross-presentation by dendritic cells. Human Gene Therapy 16: 996-1005.

[114] Cattaneo R, Miest T, Shashkova EV, Barry MA. 2008. Reprogrammed viruses as cancer therapeutics: targeted, armed and shielded. Nature reviews. Microbiology 6: 529-540.

[115] Iankov ID, Allen C, Federspiel MJ, Myers RM, Peng KW, Ingle JN, Russell SJ, Galanis E. 2012. Expression of immunomodulatory neutrophil-activating protein of Helicobacter pylori enhances the antitumor activity of oncolytic measles virus. Molecular Therapy: The Journal of the American Society of Gene Therapy 20: 1139-1147.

[116] Howells A, Marelli G, Lemoine NR, Wang Y. 2017. Oncolytic Viruses-Interaction of Virus and Tumor Cells in the Battle to Eliminate Cancer. Frontiers in Oncology 7: 195.

[117] Zhao Y, Li H, Wu R, Li S, Wang P, Wang H, Wang J, Zhou J. 2015. Antitumor Effects of Oncolytic Adenovirus-Carrying siRNA Targeting Potential Oncogene EphA3. PloS One 10: e0126726.

[118] Yoo JY, Kim JH, Kwon YG, Kim EC, Kim NK, Choi HJ, Yun CO. 2007. VEGF-specific short hairpin RNA-expressing oncolytic adenovirus elicits potent inhibition of angiogenesis and tumor growth. Molecular Therapy: The Journal of the American Society of Gene Therapy 15: 295-302.

[119] Sun A, Tang J, Terranova PF, Zhang X, Thrasher JB, Li B. 2010. Adeno-associated virus-delivered short hairpin-structured RNA for androgen receptor gene silencing induces tumor eradication of prostate cancer xenografts in nude mice: a preclinical study. International Journal of Cancer 126: 764-774.

[120] Smith JS, Herrero R, Bosetti C, Munoz N, Bosch FX, Eluf-Neto J, Castellsague X, Meijer CJ, Van den Brule AJ, Franceschi S, Ashley R, International Agency for Research on Cancer Multicentric Cervical Cancer Study G. 2002. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. Journal of the National Cancer Institute 94: 1604-1613.

[121] Cao S, Wendl MC, Wyczalkowski MA, Wylie K, Ye K, Jayasinghe R, Xie M, Wu S, Niu B, Grubb R, 3rd, Johnson KJ, Gay H, Chen K, Rader JS, Dipersio JF, Chen F, Ding L. 2016. Divergent viral presentation among human tumors and adjacent normal tissues. Scientific Reports 6: 28294.

[122] Salmons B, Gunzburg WH. 2013. Revisiting a role for a mammary tumor retrovirus in human breast cancer. International Journal of Cancer 133: 1530-1535.

[123] Tang KW, Alaei-Mahabadi B, Samuelsson T, Lindh M, Larsson E. 2013. The landscape of viral expression and host gene fusion and adaptation in human cancer. Nature Communications 4: 2513.

[124] Cobbs CS, Harkins L, Samanta M, Gillespie GY, Bharara S, King PH, Nabors LB, Cobbs CG, Britt WJ. 2002. Human cytomegalovirus infection and expression in human malignant glioma. Cancer Research 62: 3347-3350.

[125] Tang KW, Hellstrand K, Larsson E. 2015. Absence of cytomegalovirus in high-coverage DNA sequencing of human glioblastoma multiforme. International Journal of Cancer 136: 977-981.

[126] Strong MJ, O'Grady T, Lin Z, Xu G, Baddoo M, Parsons C, Zhang K, Taylor CM, Flemington EK. 2013. Epstein-Barr virus and human herpesvirus 6 detection in a non-Hodgkin's diffuse large B-cell lymphoma cohort by using RNA sequencing. Journal of Virology 87: 13059-13062.

[127] Urisman A, Molinaro RJ, Fischer N, Plummer SJ, Casey G, Klein EA, Malathi K, Magi-Galluzzi C, Tubbs RR, Ganem D, Silverman RH, DeRisi JL. 2006. Identification of a novel Gammaretrovirus in prostate tumors of patients homozygous for R462Q RNASEL variant. PLoS Pathogens 2: e25.

[128] Johnson AD, Cohn CS. 2016. Xenotropic Murine Leukemia Virus-Related Virus (XMRV) and the Safety of the Blood Supply. Clinical Microbiology Reviews 29: 749-757.