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THE ROLE OF RNA VIRUSES IN HUMAN CANCERS

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Abstract. Many RNA viruses have been reported to be oncogenic (or carcinogenic) in a variety of animal and human cancers. The increase in the incidence and prevalence of cancer-causing viruses in human populations can be known as a key precursor to the development of various cancers. The retrovirus family and Hepatitis C virus (HCV) are also reported to cause cancer. Viral oncoproteins such as Tax of HTLV 1 interacts with cellular ubiquitination complex such as cyclindromatosis tumor suppressor, ubiquitin-specific proteases 7, 11, 15 and 20, A-20 and signal-transducing adaptor molecule binding protein-like-1 in order to improve the cellular signaling pathways. The viral oncoproteins binding to DUB, leading to proliferation of virus-infected cells and cell transformation. Proto-oncogenes (c-onc genes) are the cellular form of v-onc genes. The activation of c-onc genes leads to cell growth. C-onc genes are transformed into an oncogenic form by viral infection. C-onc genes play some roles such as protein kinases, growth factors, growth factor receptors, and DNA binding proteins. The study of transforming retroviruses and their oncogenes and the multiple mechanisms deployed by other RNA viruses to use the growth-suppressive and proapoptotic function of tumor suppressor genes has been added to our current understanding of cancer biology. Oncogenic RNA viruses are important experimental models to study molecular investigation such as cellular networks, including the discovery of oncogenes and tumor suppressors. Understanding of different strategies of RNA viruses as well as the function of their proteins helps to make more extensive plans regarding the adoption of follow-up, prevention and treatment strategies in cancer patients caused by viral origin.

Key words: *RNA virus, cancer, oncogenesis, tumor, carcinogen, Iran.*

РОЛЬ РНК-ВИРУСОВ В ОНКОГЕНЕЗЕ ЧЕЛОВЕКА

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Резюме. Известно, что многие РНК-вирусы являются онкогенными (или канцерогенными) при различных видах рака у животных и человека. Увеличение заболеваемости и распространенности вирусов, вызывающих рак, в человеческой популяции можно расценивать как ключевой предшественник развития различных видов рака. Семейство ретровирусов и вирус гепатита С (ВГС) также вызывают рак. Вирусные онкопротеины, такие как Tax Т-лимфотропного вируса человека (HTLV-1), взаимодействуют с клеточным комплексом убиквитинирования, таким как супрессор опухоли цилиндроматоза, убиквитин-специфические протеазы 7, 11, 15 и 20, A-20 и STAMBPL1 для усиления клеточных сигнальных путей. Вирусные онкопротеины связываются с деубиквитиназой, что приводит к пролиферации инфицированных клеток и клеточной трансформации. Протоонкогены (гены c-onc) представляют собой клеточную форму генов v-onc. Активация генов c-onc при-

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водит к росту клеток. Гены c-onc трансформируются в онкогенную форму при вирусной инфекции могут выступать в качестве протеинкиназ, факторов роста, рецепторов факторов роста и ДНК-связывающих белков. Изучение трансформирующих ретровирусов и их онкогенов, а также разных механизмов, используемых другими РНК-вирусами для подавления роста и проапоптотической функции генов-супрессоров опухолей привносит новые данные в понимание биологии рака. Онкогенные РНК-вирусы являются важными экспериментальными молекулярными моделями по изучению клеточных сетей, включая открытие онкогенов и супрессоров опухолей. Понимание различных стратегий РНК-вирусов, а также функций их белков помогает расширить стратегии для последующего наблюдения, профилактики и лечения больных раком, обусловленного различными вирусами.

Ключевые слова: *РНК-вирус, рак, онкогенез, опухоль, канцероген, Иран.*

Introduction

Cancer is a main disease affecting individuals and health care systems. Generally, carcinogenesis plays a complex, multistep process, and it has been represented that several viruses play significant roles in different stages and development of human neoplasm. The association of a virus with cancer has been proved and the study of oncogenic viruses is important to the discovery of cellular pathways.

M'Fadyan and Hobday described the cell-free transmission of oral dog warts in 1898, and in 1907 Ciuffo published similar transmission studies with human warts [76, 133]. In 1908, Ellermann and Bang showed that leukemia in birds could be transmitted from animal to animal via leukemic cells or serum [87]. Peyton Rous in 1911 produced solid tumors in chickens using cell free extracts from a transplantable sarcoma [9]. In 1966, Rous was awarded the Nobel Prize for his pioneering work over two decades on animal oncogenic viruses [28]. The cancer virology studies began one hundred years ago with the discovery of avian sarcoma and acute leukemia viruses. In 1970, the discovery of reverse transcriptase in retroviruses also accelerated research on these viruses [120].

After the successes of the animal tumor virus field, search for human tumor viruses became important. In 1964, the discovery of Epstein–Barr virus (EBV) from Burkitt's lymphoma (BL) and in 1970, the discovery of hepatitis B virus (HBV) in human sera, proved the roles of viruses in human cancer. Additionally, a broad epidemiological study provided a link between persistent HBV infection and liver carcinogenesis [5, 34, 113].

In 1984, human papillomavirus (HPV) 16 and 18 were isolated from human cervical cancer [18].

The third major discovery was the isolation of the human T-cell leukemia virus (HTLV-I) from T-cell lymphoma/leukemia patients, hepatitis C virus (HCV) and human herpes virus 8 (HHV8)/Kaposi's sarcoma herpesvirus (KSHV).

General aspects of viral carcinogenesis

The nature of oncogenic viruses sets them apart from other carcinogenic agents and this understanding has increased our knowledge of cellular pathways involved in growth and differentiation and neoplasia. Human oncogenic viruses belong to different virus families and an important feature of them is their ability to infect, but not kill, their host cell. These viruses have evolved strategies for evading the host's immune response.

These viruses contribute to carcinogenesis but the majority of tumor virus-infected patients do not develop cancer, and in those the development of cancer prolongs many years, passing between initial infection and tumor appearance.

The co-factors, such as host immunity and chronic inflammation and host cellular mutations play an important role in the transformation process.

The geographical distribution of many virus-associated cancers and geographical restriction of the virus or access to essential co-factors, have proved the role of viruses in cancer. Thus, the contribution of virus-mediated tumorigenesis to molecular events in cells and long-term interactions between virus and host are features of viral oncogenesis [8].

Human oncogenic viruses

Human tumor viruses belong to a number of virus families, including the RNA virus families such as *Retroviridae* and *Flaviviridae* and the DNA virus families such as *Hepadnaviridae, Herpesviridae,* and *Papillomaviridae*. Viruses that are compellingly associated with human malignancies include; (1) HTLV-1 (adult T-cell leukemia (ATL)), (2) HPV (cervical cancer, skin cancer in patients with epidermodysplasia verruciformis (EV), head and neck cancers, and other anogenital cancers) (3) HHV-8 (Kaposi's sarcoma (KS), primary effusion lymphoma, and Castleman's disease) (4) EBV (Burkitt's Lymphoma (BL), nasopharyngeal carcinoma (NPC), post-transplant lymphomas, Hodgkin's disease and (5) HBV and HCV (hepatocellular carcinoma (HCC)) [34].

Viruses with potential roles in human malignancies include; (1) simian vacuolating virus 40 (SV40) (brain cancer, bone cancer, and mesothelioma); (2) BK virus (BKV) (prostate cancer) (3) JC virus (JCV) (brain cancer) (4) human endogenous retroviruses (HERVs) (germ cell tumors, breast cancer, ovarian-cancer, and melanoma) (5) human mammary tumor

virus (HMTV) (breast cancer) and (6) Torque teno virus (TTV) (gastrointestinal cancer, lung cancer, breast cancer, and myeloma). Studies of RNA tumor viruses have led to the discovery of oncogenes, tumor suppressors and our understanding of the etiology of carcinogenesis, both virally and non-virally induced [50, 64].

Ubiquitination

Ubiquitin is a 76-amino acid polypeptide encoded by at least four different genes in mammalian cells; UBA52, UBB, UBC and RPS27a. The UBB and UBC genes code for poly-ubiquitin precursors, but the UBA52 and RPS27A genes encode fusion proteins L40 and S27a, respectively. These precursor proteins are processed by the cellular endopeptidases [48].

Ubiquitination has different effects on cellular processes such as protein turnover, transcription, cell cycle progression, host defense, signal transduction pathways, receptor recycling, endocytosis, chromatin remodeling, angiogenesis, apoptosis, nuclear export of mRNA, DNA repair and also ubiquitination of proteins could affect their stability, conformation, intracellular localization, protein-protein interaction.

E1 is a universal ubiquitin activating enzyme, E2 is an ubiquitin conjugating enzyme and E3 is an ubiquitin ligase. The E4 ubiquitin ligase acts in association with the E3 ubiquitin ligase.

Ubiquitination involves monoubiquitin or polyubiquitin chains on single or multiple lysine residues in which ubiquitination at Lysine 11 (K-11), Lysine 48 (K-48) and lysine 63 (K-63) are the most studied ubiquitination.

The K-11 and K-48 are involved in the degradation of proteins and the K-63 regulates the intracellular localization and their activity [86].

The process of ubiquitination can be corrupted by proteases called deubiquitinases or DUBs. The human genome encodes for at least 98 known DUBs which have been classified into 6 different families (1) ubiquitin-specific proteases (USPs), (2) ubiquitin carboxyterminal hydrolases (UCHs), (3) ovarian-tumor proteases (OTUs), (4) Machado–Joseph disease protein domain proteases (MJD), (5) Jab1/Mov34/Mpr1 (JAMM) metalloprotease deubiquitinase and (6) monocyte chemotactic protein-induced protein (MCPIP) family [82, 115].

These proteases play a key role in maintenance of the free ubiquitin pool, histone modification, protein stability, vesicular trafficking, and receptor recycling. DUBs can modulate cell signaling, DNA damage repair, cell cycle progression, immune responses and apoptosis. Mutations or altered expression levels of DUBs in signaling pathways, Chromatin remodeling, immune response, angiogenesis, cell cycle progression, apoptosis and stress response cause the development of cancers and disorders in humans [24].

DUBs are reported to play in important role in the life cycle of many human oncogenic viruses. These viruses not only engage cellular DUBs but encode their own DUBs to support virus invasion, replication, and persistence or to destroy host immune responses [103].

Many USPs are reported to play a role in carcinogenesis. Some OTUs are regulated in tumorigenesis and constitute a 15 member strong family of proteases in humans. Apart from the ovarian tumor domain, the members also have UIMs, UAD and Zn fingers. The MCPIP family of DUBs has seven members which are reported to play a role in cancer-related pathways. USP6 was the first DUB to be identified as an oncoprotein that has function as both, an oncoprotein or a tumor suppressor and can also interact with a viral oncoprotein to drive oncogenesis. Interestingly, viral DUBs have also been implicated as mediators of oncogenesis [103] (Fig. 1).

Growth factors

Growth factors are polypeptides that stimulate the proliferation in target cells caring receptors to be able to respond to growth factors. For example, platelet-derived growth factor (PDGF), composed of 2 polypeptide chains, induces the proliferation of fibroblasts [62].

The relation between growth factors and retroviral oncogenes was clarified by sis oncogene studies on the simian sarcoma virus, which was the first retrovirus isolated from monkey fibrosarcoma [125].

The sis gene encodes the PDGFs beta chain and showed that growth factors that are inappropriately expressed have functions similar to oncogenes. Studies revealed that expression of the sis gene product (PDGF-β) leads to significant neoplastic transformation in fibroblasts, but this transformation was not in cells without the PDGF receptor. Therefore, sis transformation needs interaction between the sis gene product and the PDGF receptor [72].

Growth factor receptors such as erb B, erb B-2, fms, kit, met, ret, ros, and trk have protein structure with 3 parts: the extracellular ligand-binding area, the transmembrane, and the intracellular tyrosine kinase catalytic ones. These receptors can enable one-way passage of information from the cell membrane. The mutation and abnormal expression in growth factor receptors cause transformation into oncogenes [106].

Mitogenic signals are transmitted from growth factor receptors to the cell nucleus by signal transduction. Signal transducers are composed of 2 main groups: nonreceptor protein kinases and guanosine triphosphate (GTP)-binding proteins. The nonreceptor protein kinases are divided into subgroups: tyrosine kinases (abl, lck, and src) and serine/threonine kinases (raf-1, mos, and pim-1). GTP-binding proteins with GTPase activity are divided into monomeric (H-ras, K-ras, and N-ras) and heterotrimeric

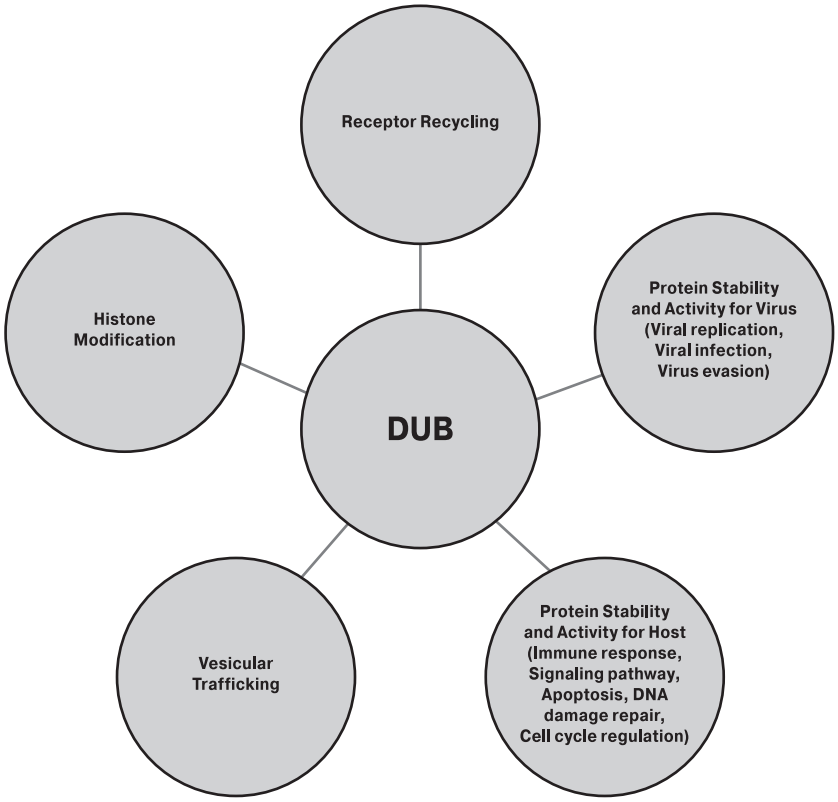

Figure 1. Multiple roles of DUBs in Viral and Host systems

(gsp and gip) groups. Signal transducers are transformed into oncogenes by mutations that lead to activities, frequently causing uncontrollable cellular proliferation [121].

Transcription factors

Transcription factors are nuclear proteins and their regulation is induced by binding to specific DNA sequences located above the target genes or heterodimeric complex proteins.

Transcription factors can modulate extracellular signals into modulated changes in gene expression. Many c-onc genes are transcription factors and have homology with protooncogenes. Some examples of these factors are erb A, ets, fos, jun, myb, and c-myc. C-onc genes as a transcription factors are activated with chromosomal translocations in hematologic and solid neoplasms [106].

Uncontrollable cell proliferation has been shown in cancer cells and programmed cell death leads to neoplasia and failure in anticancer treatments. In chromosomal translocations in human lymphoma, Bcl-2, was discovered and shown as a protooncogene that regulates programmed cell death [23].

Tumor suppressor genes

Tumor suppressor genes function in the prevention and regulation of cell growth. When these genes lose their alleles, they fail to regulate and prevent cell growth. Mutations can be passed on to the next generation and individuals with mutations malignancy development. The retinoblastoma gene (Rb) and p53 are the most studied tumor suppressor genes [126].

Other tumor suppressor genes are the VHL gene in Von Hippel–Lindau syndrome, Wilms tumor gene (WTI), NF1 and NF2 genes in neurofibromatosis, and APC and DCC genes in familial adenomatous polyposis [30, 66, 84].

Oncogenesis

Viruses encourage hematopoietic tumors, sarcomas and carcinomas. Oncogenesis is a cytological, genetic, and cellular transformation process that results in malignant tumors. The discovery of viral oncogenes are derived from cellular genes called protooncogenes led to the understanding the roles of c-onc genes in different tumor types. The activation of oncogenes requires genetic changes in cellular protooncogenes. Oncogenes are activated by mutation, gene amplification and chromosome rearrangements [65, 77].

Expression of the neoplastic phenotype includes the capacity for metastasis and usually requires a combination of protooncogene activation and tumor suppressor gene loss or inactivation.

The roles of c-onc genes in tumor formation were strengthened with studies of oncogenic retroviruses without v-onc genes, which integrate near the c-onc

genes and activate their expression. The c-myc gene has been detected in some avian retroviruses (MC29, OK-10, and MH2). It is activated via insertional mutagenesis in lymphomas stimulated by avian leukosis virus (ALV), Moloney murine leukemia virus (Mo-MLV), and various other viruses that do not carry v-onc genes [81, 106].

Direct stimulation of growth

In viral entry, the surface (SU) proteins can bind to growth factor receptors on the cell surface and stimulate growth signals by imitating normal ligand receptor interaction. These interactions arouse viral replication by the interaction of SU protein with a surface receptor that induces growth and makes cells susceptible to infection. This growth can also increase the number of appropriate target cells and the number of infected cells increases the amount of viral replication.

Erythroleukemia, caused by a polycythemic strain of the Friend virus, can set an example for tumor induction resulting from stimulation of growth receptors by Env proteins. This virus diffuses erythroid proliferation, which causes splenomegaly [106].

RNA tumor viruses

Although the Retroviridae family has been associated with many animal tumors, only one human retrovirus, HTLV-1, has been related to human cancers. Studies with animal retroviruses can be helpful in establishing the concept of oncogenic viruses and the discovery of oncogenesis, and also may give more information about tumor suppressors and regulators of cellular signal transduction pathways [63].

The development of an *in vitro* transformation assay for Rous sarcoma virus (RSV) helped us with the genetic analysis of the retroviral life cycle and retrovirus-induced transformation in cell culture [116]. After infection, the viral RNA genome is reverse-transcribed by the viral reverse transcriptase into a double-stranded DNA. Then it integrates into the host chromosome and is expressed under the control of viral transcriptional regulatory factors [107].

As a result of integration, retroviruses acquire and transduce cellular genetic material to activate or inactivate cellular genes via provirus insertion [125]. The transducing retroviruses that led to RSV transforming gene, v-src, hybridized into cellular sequences; ultimately [125]. The transducing retroviruses, that led to RSV transforming gene, v-src, hybridized to cellular sequences; ultimately this finding led to the discovery of proto-oncogenes, a group of cellular genes that mediate viral carcinogenesis and have important roles in the control of cell growth and differentiation [75]. The viral oncogenes (v-onc genes) can alter host cell proliferation control, leading. The viral oncogenes (v-onc genes) can alters host cell proliferation control, leads to the synthesis of new proteins, and are responsible for transformation characteristics. Protooncogenes (c-onc genes) can be classified into different groups in terms of their protein products, such as protein kinases, growth factors, growth factor receptors, and DNA binding proteins. There are also genes that prevent malignant transformation, which are the cellular equivalents of v-onc genes. The activation of c-onc genes with mutation leads to uncontrolled cell growth [7].

C-onc genes are transformed into an oncogenic form by point mutation, amplification, deletion, or chromosomal translocation. They are called antioncogenes (tumor suppressor genes) and unpreventable growth occurs when these genes lose their suppressive effects. Oncogenes are firmly struggling with tumor suppressor genes, which protect DNA and control cell activities [7].

Three basic genes (gag, pol, and env) of Retroviruses are used for the synthesis of structural proteins, virion-associated enzymes, and envelope glycoproteins [59]. Lentiviruses have an extra nonstructural gene (v-onc) that transforms host cells. In 1961, it was found that Rous sarcoma virus (RSV) contains RNA and then the fourth gene in the RSV, v-scr (sarcoma) gene, was discovered [117].

Some RNA tumor viruses can encode oncogenic proteins (like cellular proteins involved in cellular growth control) that cause tumor development.

The second group of retroviruses can cause cell transformation by integration of their promoters and viral enhancers near the cellular growth-stimulating gene.

The third group encodes a protein tax that transactivates the expression of cellular genes [106].

Some retroviruses, called exogenous, show a horizontal spread and their genes only exist in infected cells, whereas endogenous retrovirus gene sequences are localized to the chromosomes of all cells.

Most exogenous retroviruses are oncogenic and some of them can lead to the development of lymphoma, leukemia and carcinoma.

Retroviruses are divided into acute transforming retroviruses which can rapidly cause tumors within days after injection. These retroviruses also transform cell cultures into neoplastic phenotypes. Chronic transforming retroviruses can cause tumors in experimental animals after a period of many months [32].

Numerous animal retroviruses with oncogenic properties have been discovered. Related to Scr, the transduced retroviral oncogenesis is derived from cellular sequences and is not necessary for viral replication. The recombination events that allow obtaining of host cell derived coding sequences often leave viral genomes mutated and the virus defective for replication. These viruses are dependent on replication helper viruses to provide the replication factors [71].

Cellular transcriptional and translation are lost and the over-expression of a proto-oncogene under the control of viral promoters can cause malignant transformation.

The acquired proto-oncogene is not necessary for viral replication but is replicated as the viral genome, acquiring frequent mutations in infected cells. Such oncogene transducing retroviruses efficiently transform cells and cause tumors in experimental animals. Mutations in cellular oncogenes that arise in human tumors as a consequence of mutagenics are discovered in transducing carcinogenic retroviruses [101].

Human RNA viruses that cause cancer include the retrovirus Human T-cell Leukemia virus type I (HTLV-I) and hepatitis C virus (HCV) [80].

Other RNA viruses

The cis-acting retroviruses do not contain host cell derived sequences but transform cells by integrating a near cellular proto-oncogene or tumor suppressor and retain all of their viral genes and so replicate without helper virus [17].

These viruses cause malignancy in some infected animals after a longer latency period, and they generally do not efficiently transform cells in culture.

Moreover, the Friend murine leukemia virus had integrated into both alleles of the p53 gene in an erythroleukemic cell line, providing evidence that p53 was a tumor suppressor rather than an oncogene. Friend murine leukemia virus (F-MuLV) can cause leukemogensis consisting of an acute transforming virus spleen focus-forming virus (SFFV) as well as a helper virus (F-MuLV). Friend SFFV oncogene is a deleted version of a retroviral envelope protein that is a recombinant between F-MuLV and an endogenous MuLV-related provirus [90].

The SFFV env protein activates signal transduction pathways. The Friend virus complex has a role in insertional oncogenesis, including inactivation of the p53 tumor suppressor gene. Proto-oncogenes activation and mammary carcinogenesis induced by Mouse mammary tumor virus (MMTV) infection in the immune system (dendritic cells, T and B lymphocytes) before trafficking to the mammary gland [31, 98].

MMTV also encodes additional proteins (besides the standard retroviral Gag, Pol and Env proteins), including a viral super antigen (Sag) and a small regulatory protein Rem that are both important for replication *in vivo* [14]. Jaagsiekte sheep retrovirus JSRV (like MMTV) is a beta retrovirus, and it induces lung cancer in sheep [49]. While JSRV does not carry cellular proto-oncogene, the envelope protein of this virus also functions as an oncogene. The JSRV Env protein induces oncogenic transformation [55].

Like MMTV, JSRV also encodes a small regulatory protein Rej that is necessary for unspliced viral RNA translation. Epsilonretroviruses, in particular walleye dermal sarcoma virus (WDSV) causes dermal sarcomas in walleye pike. WDSV encodes viral cyclin which has functions as both a repressor of viral transcription and an oncogene [13]. Delta retroviruses and HTLV-I encode a series of proteins derived by alternate splicing into the X region of the genome [1] (Table 1).

Table 1. The animal oncogenic RNA viruses

Taxonomic grouping	Examples	Tumor Types
Alpharetrovirus	AEV	Erythroblastosis, Carcinoma, Sarcoma
	ALV	
	ASV	
Deltaretrovirus	BLV	Lymphoma
Gammaretrovirus	Ab-MLV	Lymphoma
	FeLV	
	FeSV	
	Mo-MLV	
	MSV	

Note. AEV: Avian erythroblastosis virus, ALV: Avian leukosis virus, ASV: Avian sarcoma virus, BLV: Bovine leukemia virus, Ab-MLV: Abelson murine leukemia virus, FeLV: Feline leukemia virus, FeSV: Feline sarcoma virus, Mo-MLV: Moloney murine leukemia virus, MSV: Murine sarcoma virus

Nontransforming retroviruses activate cellular protooncogenes

Many retroviruses do not have viral oncogenes, like ALV and mouse mammary tumor viruses. They encourage tumor formation by integrating a provirus into normal cellular protooncogenes and inducing their expression through insertional mutagenesis by addition of the provirus presenting strong promoter and enhancer sequences in the gene locus [106]. More than 70 proto-oncogenes have been determined that are activated by proviral insertion of a non-transforming retrovirus [32]. The replication of these viruses without oncogenes does not transform cells in culture and make tumors *in vivo* with long latent periods. Most of the infected cells proliferate, and changes in the cell and infected tissue morphology are significant. A widespread viral replication is seen in the latent period or preleukemic stage of the disease. In infected cells with ALV, malignant disease is significant in the bursa [99]. During lymphoma development in mice, proliferative changes have been determined in the thymus. Proliferative changes and preleukemic cells can be clearly detected in the bone marrow and spleen before thymic lymphoma develops. Avian leukosis virus with c-myc and mouse mammary tumor virus with fibroblast growth factor Int-2 or Wnt-1 do proviral insertional mutagenesis [32]. In rodent, feline, and avian retroviruses, such as avian leukosis virus and mouse mammary tumor virus (MMTV), insertional mutagenesis is observed [10]. There is no evidence to show this mechanism significantly contributes to human carcinogenesis, cloning of affected genes

led to the discovery of numerous oncogenes, such as int-1,int-2, Pim-1, bmi-1, Tpl-1, and Tpl-2, that contribute to the development of human neoplasms [76].

Role of the long terminal repeat in oncogenesis

Long terminal repeat (LTR) sequences have effects on the types of tumors and found one of the main factors for distinguishing oncogenic and nononcogenic murine leukemia viruses (MLVs) and ALVs. Simple retrovirus expression is controlled by LTR. LTR has a U3 region, which contains promoter and enhancer attachment motifs that restrain the expression of sequences placed under their control. These factors affect the virus replication cycle. High levels of replication increase recombinant oncogenic potential [58].

The influence of the viral long terminal repeats (LTRs) on the proto-oncogenes LTR is activation of proto-oncogenes. Some changes in the 5'-LTR, such as deletions or hypermethylation, are common in Adult T-cell leukemia/lymphoma (ATL or ATLL) cells. As a result, the transcription of viral genes encoded on the plus strand is blocked but the 3'-LTR is conserved and hypomethylated in all ATLs [83, 119] (Table 2).

Human T-cell leukemia virus (HTLV-1)

In 1977, HTLV-1 was discovered as the first human oncogenic retrovirus by Takatsuki and colleagues who studied a particular leukemia termed adult T-cell leukemia (ATL) in Japan [38].

In 1980, Robert Gallo identified a novel retrovirus in cultured human T-cell lymphoma cells, which was named the human T-cell lymphotropic virus (HTLV-1) [20].

HTLV-1 is a single-stranded RNA retrovirus with a diploid genome which is a delta type complex retrovirus and is the agent of ATL and tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM). Approximately 10% of infected patients are thought to develop cancer, primarily adult T-cell leukemia (ATL) [78, 79, 127].

It is estimated that about 20 million people worldwide are infected with HTLV-1 and it is endemic to Japan, South America, Africa, and the Caribbean [4]. HLTV-1 does not have a classical oncogene, but the virus can cause expression of cellular protooncogenes. In non-endemic regions like the USA, England, and in the Caribbean Islands, parts of South America and Africa, the virus is also associated with ATL as well as some T-cell lymphomas and forms of mycosis fungoides [42].

The virus is transmitted from mother to child via breast milk or transplacentally. All ways such sexual and intravenous transmission happend by infected T cells, not free virus, which probably is due to its low levels of transmission to contacts [96].

Table 2. Human oncogenic RNA viruses

Taxonomic grouping	Examples	Tumor types
Retroviridae	HTLV type 1	Adult T cell leukemia
Flaviviridae	Hepatitis C virus	Hepatocellular carcinoma

Note. HTLV: Human T-cell leukemia virus.

People who are at low risk of blood-borne infections tend to show HTLV-1 infection rates below 1%, while those at high risk (such as injection users) can have much higher rates [60].

A second retrovirus, HTLV-2, was isolated from a case of hairy-cell leukemia, but the virus has remained an agent without an established disease association [74].

The HTLV-1 itself, in contrast to HIV, is genetically stable because the HTLV-1 proviral genomes are replicated in their host by cellular polymerase not by reverse transcriptase, which is error-prone, and is used for replication of virus. There is no vaccine available for this virus and treatment is restricted to management of the opportunistic infections resulting from the immunosuppression caused by ATL [85].

Oncogenic properties and mechanism of oncogenesis

HTLV-1 can transform CD4 and CD8 positive T cells. HTLV-1 also infects B and T lymphocytes, dendritic cells, fibroblasts and rodent cells. 1–5 percent of mononuclear cells integrate proviral DNA in peripheral blood in asymptomatic carriers. The viral genome persists as a DNA copy or proviral genome in $CD4^+$ T cells [43, 57].

After infection, the viral reverse Transcriptase (RT) using viral RNA as, template, synthesizes proviral DNA that is integrated into the host cell genome by virally encoded integrase. Viral replication is directed from these integrated viral genomes. The U3 region of the 5'-LTR serves as the viral promoter and is instrumental in determining whether an infected cell is permissive for viral replication [73].

Typical retroviral genes (gag, pro, pol, env and IN) are encoded by the genome, but there are six proteins encoded within the px region of the genome. HTLV-1 proviral DNA integrates into chromosomal sites in all ATL cells in patients producing a state of "clonal integration" [21, 46].

Unlike many other retroviruses, but like bovine leukemia virus, HTLV-1 does not have an oncogene derived from a cellular protooncogene [29].

The viral accessory protein Tax, is the major transforming protein of HTLV-1 which modulates expression of viral genes like long terminal repeats (LTRs), and also dysregulates multiple cellular transcriptional signaling pathways including nuclear factor kappa B (NF-κB), serum responsive factor

(SRF), cyclic AMP response element-binding protein (CREB), and activator protein 1 (AP-1) [29, 52].

Tax binds directly to promoter or enhancer sequences and also interacts with cellular transcriptional co-activators such as p300/CBP, and P/CAF. In addition, Tax is also able to inactivate p53, p16INK4A, and the mitotic checkpoint protein, mitotic arrest deficient (MAD) 1 [109]. Moreover, the C-terminal PDZ domain-binding motif of Tax interacts with the tumor suppressor hDLG, which is important for transformation of rat fibroblasts and inducing interleukin-2 independent growth of mouse T-cells [19].

Tax proteins are found in only 40% of ATLs, suggesting that Tax may be necessary to initiate transformation, but may not be needed for maintenance of the transformed phenotype. Tax is the main aim of the host's cytotoxic T lymphocyte (CTL) response; therefore, the reduction of Tax expression allows infected cells to evade immune surveillance and allows for progression of ATL [130].

There are several mechanisms by which ATL cells lose Tax expression, such as the loss of the viral promoter for tax transcription, the 5'-LTR, mutation of the tax gene, and epigenetic changes in the 5'-LTR [83].

It has been shown that HTLV-1 Tax expression causes multipolar mitoses, from which aneuploidy can arise. So Tax targets the cellular TAX-1 BP2 protein, which normally hinders centriole replication, thus, making numerical centrosome aberrations. Tax engages RAN-BP1 during mitosis and fragments spindle poles, thereby provoking multipolar, asymmetrical chromosome segregation. Such mechanisms help the long-standing observations of aneuploidy and multipolar spindles in ATL cells ("flower cells") [91].

In addition, it has been demonstrated in ATL cell lines to lack an intact mitotic spindle assembly checkpoint, which may be associated with binding to MAD1. Tax may act as a mitotic mutator gene, increasing the incidence of mitotic abnormalities by binding and activating the anaphase promoting complex/cyclosome (APC/C), thereby promotes premature securin reduction and mitotic exit, thus leading to aneuploidy [76].

Tax (trans-acting factor) encoded by the px region is necessary for cellular transformation and interacts with specific sets of cellular genes.

Tax activates the IL-2 receptor and several cytokines involved in T-cell growth by destabilizing I-κB and activating NF-κB. Tax also blocks cellular gene expression through CREB/CRE. Tax can induce Bcl-XL and resistance to apoptosis. Tax interferes with the DNA polymerase and DNA repair mechanisms and inactivates p16 INK4A, an inhibitor of cyclin-dependent kinases 4–6. Tax can miss the mitotic checkpoint by causing mislocation of hsMAD1 and hsMAD2 [40].

In all ATL cells, the HBZ mRNA is transcribed from the 3'-LTR. Suppression of HBZ gene transcription inhibits the proliferation of ATL cells. HBZ gene expression induces the proliferation of a human T-cell line. HBZ may have a function at the mRNA and protein levels, as the RNA form of HBZ supports T-cell proliferation through regulation of the E2F1 pathway, whereas HBZ protein suppresses Tax-mediated viral transcription through the 5'-LTR [102, 112].

HTLV-1 and STAMBPL1

The Tax oncoprotein of HTLV-1 is known to shuttle across nuclear-cytoplasmic compartments and Tax activates the host NF-κB pathway and engages the host transcriptional machinery to drive viral gene expression [36].

The K-63 ubiquitinated Tax (by UbC13) interacts with Ikkγ to activate the Ikk. Signal transducing adaptor molecule binding protein-like 1 (STAMBPL1) is a DUB from the JAMM metalloprotease deubiquitinase family which acts as a partner to Tax [103].

STAMBPL1 acts on the K-63 linked ubiquitin and plays a role in cell surface receptor recycling. In ATL cases, STAMBPL1 cooperates with Tax and leads its translocation from the nucleus to the cytoplasm. This move defends Tax from its K-48 linked ubiquitination and proteasomal degradation inside the nucleus. Thus, STAMBPL1 protection for Tax and its movement to the cytoplasm is responsible for the activation of Ikk and NF-κB by Tax and potentiating of T-cell transformation by HTLV-1 [22].

HTLV-1 and CYLD

The active CYLD is able to K-63 deubiquitinating Tax oncoprotein in the nucleus. This deubiquitinated Tax is unable to activate Ikk but not Tak1 (an activator of Ikk-β). So, IκBa and NF-κB inhibitors are stabilized. The HTLV-1 transforms T-cells constitutively phosphorylate CYLD to make it catalytically compromised. Thus, the virus overcomes the CYLD-mediated NF-κB in activation, which is helpful for the proliferation of virus infected host cell [22, 45].

HTLV-1 and USP20

The cellular USP20 is able to subvert the activity of Tax oncoprotein. USP20 can deubiquitinate TRAF-6 and inactivate it or can deubiquitinate the K-63 polyubiquitinated Tax to prevent its association with Ikk-γ for its activation. So USP20 can be detrimental to the NF-κB signaling stimulated propagation of HTLV infected cells. This strategy causes unchecked proliferation and transformation of the HTLV-infected cells [22, 45] (Fig. 2).

Human immunodeficiency virus (HIV)

The human immunodeficiency virus (HIV) is a Lentivirus of the Retroviridae family, as an enveloped RNA virus that includes some of the most influential viruses on in human populations, such as leukemia viruses. In fact, the Human Immunodeficiency Virus (HIV) causes worldwide Acquired Immunodeficiency Syndrome (AIDS) pandemic and is behind the millions of deaths the worldwide and suffering [16].

The viral genome is a dimmer of linear RNA with each strand being 7 to 15 kilobases in length. There are generally three large genes, which are gag, for group specific antigen (structural proteins); pol, for polymerase (variety of enzymes); and env, for envelope proteins [37].

HIV is transmitted by unprotected sex, injections with needles used by an HIV-infected person, prenatal or perinatal exposure of infants from infected mothers, transfusion of blood products containing HIV, organ transplants from an infected person and needle sticks from health care workers [105].

HIV enters the host cell via the CD4 molecule and chemokine receptor as receptors. HIV infects human immune system cells such as helper T cells (specifically $CD4^+$ T cells), macrophages, and dendritic cells [41]. HIV causes low levels of $CD4^+$ T cells through a number of mechanisms, including apoptosis of uninfected bystander cells, direct killing of infected cells by viruses and killing of $CD4^+$ T cells by CD8 cytotoxic lymphocytes. When the $CD4^+$ T cell drops below a critical level, the body becomes more susceptible to opportunistic infections [124].

Acquired immune deficiency syndrome (AIDS) caused by HIV, does not lead to cancers directly, but the infection can increase a person's risk of getting several types of cancer.

As a matter of fact, the immune system destroys cancer cells, so a weak immune system lets cancer cells survive to grow into a tumor.

HIV infection may be linked to Kaposi sarcoma and cervical cancer. It's also related to non-Hodgkin lymphoma, lymphoma, and central nervous system lymphoma [108].

Anal cancer, lung cancer, cancers of the mouth and throat, Hodgkin lymphoma, skin cancers (basal cell, squamous cell, and Merkel cell) and liver cancer are other types of cancer that may be more likely to develop in people with HIV infection [44].

Many people infected with HIV are also infected with other viruses that cause certain cancers. HIV infection causes weakness in the immune system and reduces the body's ability to fight infections that may cause cancer.

The highly active antiretroviral therapy (HAART) greatly reduced the incidence of Kaposi sarcoma and non-Hodgkin lymphoma among people infected with HIV. HAART reduces the amount of HIV in the blood and restores immune system function.

Although, the risk of these cancers is still much higher among people infected with HIV. This high risk may be due However, to the fact that immune system function remains substantially impaired in people treated with HAART. In addition, over time, HIV can develop resistance to the drugs used in HAART [26].

Human endogenous retroviruses (HERVs)

HERVs are sequences that resemble infectious retroviruses that result from exogenous retroviral infections that have become incorporated into the germ line DNA. HERVs comprise 8% of the genome and have a similar genomic organization to exogenous complex retroviruses such as Human Immunodeficiency virus (HIV) and HTLV [39].

Recent evidence suggests that some HERVs may have both physiological and pathological roles in human malignancy. Some HERVs have a role in human malignancy, due to the increased expression of the HERV mRNA functional protein and retrovirus-like particles in certain cancers.

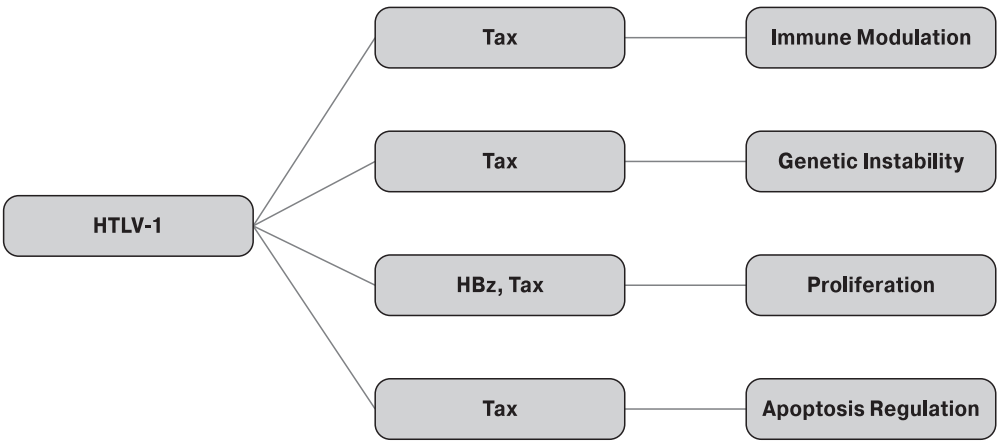

Figure 2. Schematic depiction of the major biological activities that contribute to the transforming activities of HTLV-1

HERVs may be associated with the generation of new promoters or the activation of protooncogenes [25].

The association of HERV-K with cancers, breast cancer, including germ cell tumors, myeloproliferative disease, ovarian cancer, melanoma and prostate cancer has been proved. The HERV-K proteins Rec and Np9 can bind the promyelocytic leukemia zinc finger (PLZF) protein and suggest that HERV-encoded proteins may cause carcinogenic process [111].

The recurrent chromosomal translocations contribute to the development of human solid tumors and these translocations result in HERV-K regulatory sequences being placed upstream of the coding sequences of ETS transcription factor family members. These translocations are similar to insertional mutagenesis, where retroviruses contribute to carcinogenesis by integrating in the cellular protooncogenes and causing their aberrant expression [101].

Mouse and Human mammary tumour virus (HMTV)

Mouse mammary tumor virus (MMTV) is a retrovirus which belongs to the genus Betaretrovirus. Since 1943, the role of HMTV in human breast cancers has been determined, when a mouse mammary tumor virus (MMTV) was shown to cause mammary cancers in mice [98].

Several investigations established that MMTV-like sequences were present in human breast cancer, but not present in normal tissues. MMTV also encodes additional proteins (besides the standard retroviral gag, pol and env proteins), including a viral super antigen (Sag) and a small regulatory protein Rem that are both important for replication *in vivo* [31].

In mice, HMTV increases tumor formation through the insertion mutagenesis of Wnt oncogenes [2].

It has been reported that env is absent in normal tissues and present in breast cancer tissues in both mice and human samples. The common integration MMTV sites is in loci 35, which contains regions of the Fgf and Rspo genes. The Phf19 gene increases cell invasion and Fox1 promotes anchorage colony formation of infected cells [2].

Infected cells with MMTV have active Src kinase and escape from apoptosis by activation of tyrosine kinase-based activation motif-mediated Src tyrosine kinase signaling pathways [2].

In human breast tumors, approximately 20 common HMTV insertion sites are mutated for env, gag, and sag in patients with carcinoma and hyperplasia. 78% of MMTV genes are found in many human breast cancers. The presence of these viruses in breast cancer is associated with an increased grade of breast cancer [12].

A number of studies have suggested that an MMTV-related virus, human mammary tumor virus (HMTV), may be associated with human breast cancers.

A 660bp sequence similar to the MMTV env gene was detected in American women's breast cancers [12]. Moreover, integrated env and LTR HMTV genes of MMTV into several chromosomes stimulates oncogenesis via insertional mutagenesis.

The HMTV particles with morphogenic and molecular characteristics similar to MMTV were found in primary breast cancer cells (replicates successfully in human breast cancer cells) [128].

Xenotropic murine leukemia virus (XMRV)

In 1990, Xenotropic murine leukemia virus (XMRV) was discovered as a Gammaretrovirus (*Retroviridae* family) that arose from the recombination of two endogenous mouse retroviruses, and in 2006 an apparently novel retrovirus and potential human pathogen was introduced [93]. XMRV is a murine leukemia virus (MLV) that formed through the recombination of the genomes of two parent MLVs known as preXMRV-1 and preXMRV-2 [56].

In some studies on XMRV, the virus was detected in cancerous prostate tissues [104]. The data indicated the presence of a gammaretrovirus-like sequence in seven of eleven tumors homozygous for the R462Q mutation [123]. A 2009 study reported evidence of XMRV infection in 23% of subjects independent of the RNase L gene variation, and detection of XMRV was again reported in a 2010 article [88].

The causal role of XMRV in cancer and direct cell transforming has not been established. In prostate cancer, XMRV protein has been found in tumor-associated but nonmalignant stromal cells [110].

Xenotropic murine leukemia virus-related virus (XMRV) was reported in patients with prostate cancer with a mutation in RNase L [94].

In familial prostate cancer, susceptibility locus Hpc1 is linked to mutations in the structural gene for RNase L which is a factor in the interferon induced innate viral response. The inherited defects in RNase L might cause infection with an oncogenic virus, thus causing the development of prostate cancer. XMRV protein was found in the hematopoietic and stromal cells of the prostate tumors [11].

Rous sarcoma virus (RSV)

Rous sarcoma virus (RSV) is an Alpharetrovirus, and it causes sarcoma in chickens. Harry Rubin and Howard Temin in 1958 reported that chicken embryo fibroblasts could be altered morphologically by RSV infection [100, 129]. It is known that the src gene is responsible for morphological transformation in healthy cells. Src is a tyrosine kinase which plays roles in the regulation of cell growth and differentiation. It has an SH2 and SH3 domain, which are responsible for its activation and deactivation [97].

The src gene is not necessary for RSV proliferation, but it increases virulence when present. The src

gene leads to uncontrolled growth in abnormal host cells. RSV takes up the src gene and incorporates it into its genome, conferring it with the advantage of being able to stimulate uncontrolled mitosis of host cells [51]. RSV has one glycoprotein, env, is made up of gp85 and gp37. The function of env is to bind RSV to the host cell receptor and induce fusion with the target cell. Gag proteins (Pr76) are necessary for virion assembly and mature virus infection of the host cell [51].

Hepatitis C virus (HCV)

HCV is a single-stranded RNA virus of the Hepacivirus genus in the *Flaviviridae* family [95]. More than one-third of liver cancers are linked to HCV infection in the United States and other countries, where both viral hepatitis and liver cancer are more common [27]. HCV is transferred from person to person through sharing needles, unprotected sex, or childbirth and this virus can also pass on through blood transfusions [3, 61]. The 9.6 kb genome has one open reading frame (ORF) and a 3000 amino acid residue polyprotein precursor cleaved by cellular and viral proteases into three structural proteins (core, E1, E2) and seven nonstructural proteins (p7, NS2, NS3, NS4a, NS4B, NS5A, and NS5B) [35, 89].

Persistent infection with HCV is associated with hepatitis, cirrhosis, hepatic steatosis, and hepatocellular carcinoma (HCC) [54]. In most infected patients, HCV prolongs a persistent and life-long infection via viral immune evasion strategies. The intermediated double-stranded RNA (dsRNA) during HCV genome replication stimulates cellular dsRNA-sensing machinery, which leads to the activation of proteins involved in antiviral response, including interferons (IFNs), interferon regulatory factors (IRFs), signal transducers and activators of transcription (STATs), interferon stimulated genes (ISGs) and NF-κB [15].

From HCV proteins, NS5A and E2 mediated suppression of dsRNA-activated kinase PKR. HCV is also very effective in corrupting T-cell mediated adaptive immunity [92].

NS5A as a nonstructural protein has been implicated in conferring resistance to interferon and altering cellular signaling pathways [53]. Analysis of NS5a sequence from interferon resistant patients showed a sequence diversity that localized to a region of the NS5a gene. This region is called interferon sensitivity determining region (ISDR) [118].

This region was necessary for NS5a interaction with PKR (protein kinase, a mediator of apoptosis in response to certain types of cellular stress) induced by interferon that suppresses viral translation and interferon's antiviral effects [122].

The persistence of HCV infection causes quasispecies in which viruses escape the host immune system [33].

Quasi-species and persistent HCV infection are likely to be of the central importance to the development of HCC, whether transformation is induced by immune-mediated turnover of infected cells or caused by viral gene products.

HCV has used different mechanisms to cause persistent infections and evade the host immune response [70]. The generation of viral quasi-species resulted by error-prone replication, selects the virus to replicate in the presence of an immune response. Infection with HCV causes active inflammation and fibrosis, which can lead to cirrhosis and ultimately to tumor development [67].

Numerous co-factors such as coinfection with HBV and alcohol consumption are helpful for the development of HCV [131]. Viral Core, NS3, NS4B, and NS5A have been shown to be transforming in murine fibroblasts and transgenic mice expressing HCV core protein develop HCC. The HCV core protein can modify intracellular signaling pathways which inhibit immune-mediated cell killing. HCV core blocks TNFα-mediated apoptosis through interactions with the TNFα and their receptor [6, 69].

TNFα is an inflammatory cytokine secreted by activated macrophages and T-cells, which play in important role in acute infections. TNFα induces FAS-mediated apoptosis and helps to clear infected cells. HCV core binds to the cytoplasmic domains of tumor necrosis factor receptor 1 (TNFR1), lymphotoxin b, and gC1q receptors and stops FAS/TNFα receptor signaling. Corruption of TNFα mediated signaling helps in the survival of infected hepatocytes and promotes persistent HCV infection [114, 132].

Expression of HCV core activates NF-κB, a transcription factor involved in regulating the immune response. There are elevated levels of NF-κB protein and increased NF-κB DNA binding activity in chronic infected HCV hepatocytes. The core has been shown to adjust the activity of transcription factors and cytokines that could promote cellular transformation and HCC [6, 47].

Hindering interferon action promotes persistent infection and may evade from cellular signaling pathways that could ultimately lead to cellular transformation. In addition, HCV proteins activate cellular oncoproteins and inactivate tumor suppressors, such as p53, CREB2/LZIP, and the retinoblastoma protein (pRB) [6, 68] (Fig. 3 and 4).

Conclusion

Several viruses with oncogenic ability, with different mechanisms depending on different host factors, induce cell proliferation and lead to tumors in animals and humans.

The oncogenic RNA viruses encode transforming proteins to stimulate tumor formation. The small viral genomes are integrated into host cell chro-

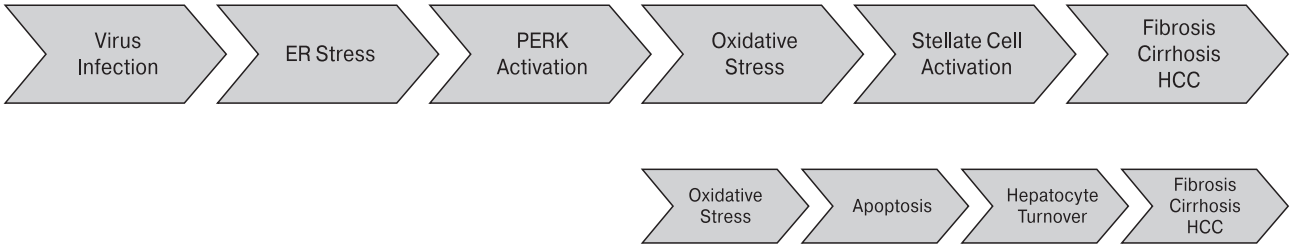

Figure 3. Chronic virus infection and cell stress. Sequential steps from virus infection through cell stress and leading to liver injury and HCC are shown

mosomes and cause mutations and chromosomal rearrangements that cause cancer. Both the epidemiology of cancer and the biology of RNA viruses show the role of any agent being thought as a factor. Although RNA viruses can transform cells *in vitro* or even in animals, the condition in humans is likely to be much more complex. Viruses as direct transforming agents and cofactors are certainly important in most common cancers. Probably, most mechanisms of carcinogenesis may involve a combination of genetic alterations, immune system dysfunctions, and viral infections. The review in this article emphasizes the importance of RNA viruses and their mechanisms that can lead to cancer.

More investigation of the role of RNA viruses in cancer may result in new approaches that could lead to better diagnosis, prevention, and treatment of these cancers. The antiviral agents in cancer therapy should be considered, as they are in other infection-associated cancer types such as hepatocellular carcinoma, brain tumors, sarcoma, nasopharyngeal and some hematopoietic cancers.

Obviously, the study of how RNA viruses interrupt cell cycle regulatory and intercellular signaling mechanisms to achieve their replicative success continues to reach a novel insight into multiple human diseases, including cancer.

Ubiquitination is a post-translational modification which influences protein structure, cellular localization and activity. Many viral proteins have also evolved to play DUB like roles. Many oncogenic viruses interrupt the host deubiquitinase function or exploit their own DUBs to drive cellular transformation.

Seven cellular DUBs-CYLD, USP7, USP11, USP15, USP20, A20 and STAMBPL1 (AMSH-LP) out of 100 DUBs have been related to viral oncoproteins. Cancer associated DUBs (CADs)-DUBs with altered expression or inherent mutation and Cancer related redundant pathway associated DUBs (CRRPADs) are 2 main groups of DUBs. Out of 52 DUBs implicated in cancer, only 7 have been reported as interacting partners for viral oncoproteins. Based on the importance of neoviral DUBs in cellular transformation, an intensive search for specific inhibitors for viral DUBs is important. DUBs in cancer-related pathways would establish them as the cancer chemotherapeutic target for the UPS which has been targeted by drugs. Human RNA viruses that cause cancer include the retrovirus Human T-cell Leukemia virus type I (HTLV-I) and hepatitis C virus (HCV). In addition, AIDS is caused by retrovirus (HIV-1 and -2), developing complications of the immunodeficiency characteristic cancers such as sarcoma in AIDS pa-

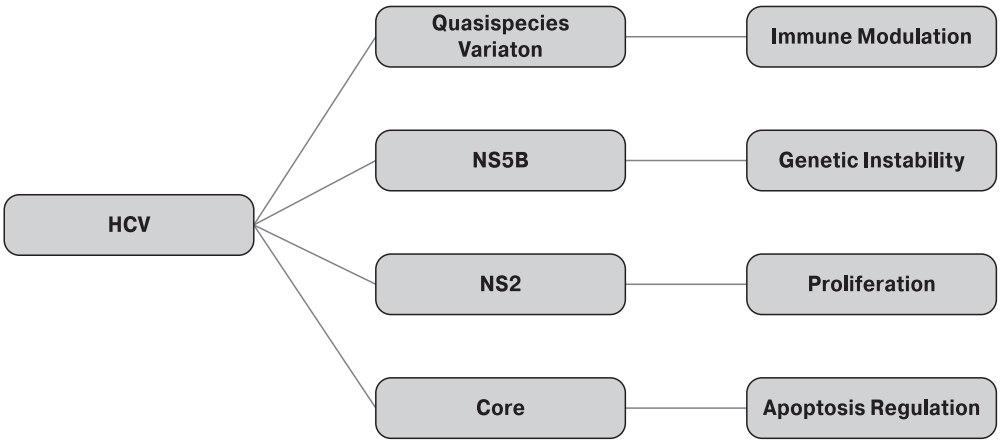

Figure 4. Schematic depiction of the major biological activities that contribute to the transforming activities of HCV

tients. The persistent infection can lead to chronic liver damage and the development of hepatocellular carcinoma is associated with an RNA virus called hepatitis C virus (HCV).

In our article, the roles of some HCV viral proteins in causing cellular damage leading to tumorigenesis in persistently infected patients is described. Moreover, causing malignant hepatocyte transformation by indirect and extra virological factors such as inducing hepatocyte regeneration leading to virological damage or immunological attack and mediators of mutation must be considered. All these interactions between virus and host added to time and environmental factors, determine the ultimate clinical outcome.

HCV infection contributes to HCC by causing chronic inflammation. HTLV-1 starts pro-proliferative and immunomodulating signals through the activation of NF-κB and its transcriptional regulatory program.

The angioproliferative disease is an excellent example of how cells express distinct gene programs can cooperate in tumor initiation, maintenance and dissemination and also reveal the existence of a virally initiated process of paracrine transformation. Intercellular cooperation is not limited to viral associated tumors but occurs in some aggressive human neoplasia.

The knowledge of retroviral integration sites and transmitted transforming genes can increase the data about oncogenes and tumor suppressors that are found in human malignancies.

The main difference between transforming animal retroviruses and human tumor viruses is that oncogenes of human tumor viruses are viral genes, rather than mutated versions of cellular genes.

Retroviruses that have v-onc genes cause malignancies, including sarcomas and hematopoietic cell tumors, in a short period of time.

Many retroviruses do not have viral oncogenes, but they integrate their genome into protooncogenes which activate their expression by proviral insertional mutagenesis, leading to growth and differentiation of the host cells. Based on findings of HLTV1 in leukemic cells in ATL, it seemed to be necessary to find a relationship between virus and disease even before showing the transforming ability of the virus.

In our article, the identification of RNA virus oncogenes and cellular proto-oncogenes, induction of signal transduction pathways, and characterization of tumor suppressor genes were discussed. The discovery of avian sarcoma and acute leukemia viruses as RNA-containing viruses in the retroviridae family was the origin of cancer virology that started one hundred years ago. Laboratory studies on RNA tumor viruses (many of them animal viruses) are highly relevant to human cancer and many of the viral oncogenesis explained by these studies are suitable for human cancers, including those that are not caused by viruses.

Acute transforming viruses that have viral oncogenes inducing tumors rapidly and non-acute retroviruses not carrying oncogenes inducing tumors more slowly, are two groups of oncogenic retroviruses. The Rous sarcoma virus (RSV) is a prototypic acute transforming retrovirus that has v-src derived from the cellular proto-oncogene c-src.

Non-acute retroviruses typically induce tumors by the influence of the viral long terminal repeats (LTRs). Transforming virus SFFV as well as a helper virus (F-MuLV) makes leukemogensis by the Friend MuLV complex by recombinant between F-MuLV and an endogenous MuLV-related provirus. MMTV initially infects cells of the immune system by insertional activation of proto-oncogenes and carcinogenesis occurs. The roles of the viral Tax protein and alternative splicing in the X region of the HTLV-I genome and their potential roles in oncogenesis are described.

Tumors often have a large population of proliferative cells and might be permissive for viral replication. The discovery of virus sequences in tumors could represent a major challenge for the future.

The presence of the viral gene products in cancer may be exploited in novel therapies that distinguish these cells from normal cells. Targeting cancer cells would have more advantages than traditional modalities such as chemotherapy and radiation, including significant toxicities. Useful strategies for vaccine design to hinder primary infection and targeted therapies for the treatment of disease must be carefully considered in the future.

Additional information

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References

1. Ajiro M., Zheng Z.M. Oncogenes and RNA splicing of human tumor viruses. *Emerg. Microbes Infect., 2014, vol. 3, no. 9: e63. doi: 10.1038/emi.2014.62*
2. Alibek K., Kakpenova A., Mussabekova A., Sypabekova M., Karatayeva N. Role of viruses in the development of breast cancer. *Infect. Agent Cancer, 2013, no. 8: 32. doi: 10.1186/1750-9378-8-32*
3. Alter M.J. Prevention of spread of hepatitis C. *Hepatology, 2002, vol. 36, no. 5, suppl. 1, pp. S93–S98. doi: 10.1053/jhep.2002.36389*
4. Amano M., Setoyama M., Grant A., Kerdel F.A. Human T-lymphotropic virus 1 (HTLV-1) infection — dermatological implications. *Int. J. Dermatol., 2011, vol. 50, no. 8, pp. 915–20. doi: 10.1111/j.1365-4632.2011.04882.x*

5. Andersson J. An Overview of Epstein-Barr Virus: from Discovery to Future Directions for Treatment and Prevention. *Herpes, 2000, vol. 7, no. 3, pp. 76–82*
6. Banerjee A., Ray R.B., Ray R. Oncogenic potential of hepatitis C virus proteins. *Viruses, 2010, vol. 2, no. 9, pp. 2108–2133. doi: 10.3390/v2092108*
7. Batra N., Ghag I., Babu K., Divanji T. Reviewing Oncogenes and Proto-Oncogenes. *International Journal of Scientific Research in Science and Technology, 2021, vol. 8, iss. 3, pp. 458–479. doi: 10.32628/IJSRST2183100*
8. Cancer a Comprehensive Treatise 2: Etiology: Viral Carcinogenesis. Ed. Becker F. *Springer, 2013. 455 p.*
9. Becsei-Kilborn E. Scientific discovery and scientific reputation: the reception of Peyton Rous' discovery of the chicken sarcoma virus. *J. Hist. Biol., 2010, vol. 43, no. 1, pp. 111–157. doi: 10.1007/s10739-008-9171-y*
10. Beemon K., Rosenberg N. Mechanisms of Oncogenesis by Avian and Murine Retroviruses. *Cancer Associated Viruses, 2011, pp. 677–704.*
11. Beuten J., Gelfond J.A., Franke J.L., Shook S., Johnson-Pais T.L., Thompson I.M., Leach R.J. Single and multivariate associations of MSR1, ELAC2, and RNASEL with prostate cancer in an ethnic diverse cohort of men. *Cancer Epidemiol Biomarkers Prev., 2010, vol. 19, no. 2, pp. 588–599. doi: 10.1158/1055-9965.EPI-09-0864*
12. Bevilacqua G. The Viral Origin of Human Breast Cancer: From the Mouse Mammary Tumor Virus (MMTV) to the Human Betaretrovirus (HBRV). *Viruses, 2022, vol. 14, no. 8: 1704. doi: 10.3390/v14081704*
13. Birkenheuer C.H., Brewster C.D., Quackenbush S.L., Rovnak J. Retroviral cyclin controls cyclin-dependent kinase 8-mediated transcription elongation and reinitiation. *J. Virol., 2015, vol. 89, no. 10, pp. 5450–5461. doi: 10.1128/JVI.00464-15*
14. Boeras I., Sakalian M., West J.T. Translation of MMTV Gag requires nuclear events involving splicing motifs in addition to the viral Rem protein and RmRE. *Retrovirology, 2012, no. 9: 8. doi: 10.1186/1742-4690-9-8*
15. Brownell J., Bruckner J., Wagoner J., Thomas E., Loo Y.M., Gale M Jr, Liang T.J., Polyak S.J. Direct, interferon-independent activation of the CXCL10 promoter by NF-κB and interferon regulatory factor 3 during hepatitis C virus infection. *J. Virol., 2014, vol. 88, no. 3, pp. 1582–1590. doi: 10.1128/JVI.02007-13*
16. Campbell-Yesufu O.T., Gandhi R.T. Update on human immunodeficiency virus (HIV)-2 infection. *Clin. Infect. Dis., 2011, vol. 52, no. 6, pp. 780–787. doi: 10.1093/cid/ciq248*
17. Chamanian M., Purzycka K.J., Wille P.T., Ha J.S., McDonald D., Gao Y., Le Grice S.F., Arts E.J. A cis-acting element in retroviral genomic RNA links Gag-Pol ribosomal frameshifting to selective viral RNA encapsidation. *Cell Host Microbe, 2013, vol. 13, no. 2, pp. 181–192. doi: 10.1016/j.chom.2013.01.007*
18. Chen A.A., Gheit T., Franceschi S., Tommasino M., Clifford G.M.; IARC HPV Variant Study Group. Human Papillomavirus 18 Genetic Variation and Cervical Cancer Risk Worldwide. *J. Virol., 2015, vol. 89, no. 20, pp. 10680–10687. doi: 10.1128/JVI.01747-15*
19. Cherian M.A., Baydoun H.H., Al-Saleem J., Shkriabai N., Kvaratskhelia M., Green P., Ratner L. Akt Pathway Activation by Human T-cell Leukemia Virus Type 1 Tax Oncoprotein. *J. Biol. Chem., 2015, vol. 290, no. 43, pp. 26270–26281. doi: 10.1074/jbc.M115.684746*
20. Coffin J.M. The discovery of HTLV-1, the first pathogenic human retrovirus. *Proc. Natl Acad. Sci. USA, 2015, vol. 112, no. 51, pp. 15525–15529. doi: 10.1073/pnas.1521629112*
21. Cook L.B., Elemans M., Rowan A.G., Asquith B. HTLV-1: persistence and pathogenesis. *Virology, 2013, vol. 435, no. 1, pp. 131–140. doi: 10.1016/j.virol.2012.09.028*
22. Currer R., Van Duyne R., Jaworski E., Guendel I., Sampey G., Das R., Narayanan A., Kashanchi F. HTLV tax: a fascinating multifunctional co-regulator of viral and cellular pathways. *Front. Microbiol., 2012, no. 3: 406. doi: 10.3389/fmicb.2012.00406*
23. Delbridge A.R., Grabow S., Strasser A., Vaux D.L. Thirty years of BCL-2: translating cell death discoveries into novel cancer therapies. *Nat. Rev. Cancer, 2016, vol. 16, no. 2, pp. 99–109. doi: 10.1038/nrc.2015.17*
24. Deng L., Meng T., Chen L., Wei W., Wang P. The role of ubiquitination in tumorigenesis and targeted drug discovery. *Signal Transduct. Target. Ther., 2020, vol. 5, no. 1: 11. doi: 10.1038/s41392-020-0107-0*
25. Downey R.F., Sullivan F.J., Wang-Johanning F., Ambs S., Giles F.J., Glynn S.A. Human endogenous retrovirus K and cancer: Innocent bystander or tumorigenic accomplice? *Int. J. Cancer, 2015, vol. 137, no. 6, pp. 1249–1257. doi: 10.1002/ijc.29003*
26. Eggleton J.S., Nagalli S. Highly Active Antiretroviral Therapy (HAART), 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–.
27. El-Serag H.B., Mason A.C. Risk factors for the rising rates of primary liver cancer in the United States. *Arch. Intern. Med., 2000, vol. 160, no. 21, pp. 3227–3230. doi: 10.1001/archinte.160.21.3227*
28. Elemento O. The road from Rous sarcoma virus to precision medicine. *J. Exp. Med., 2021, vol. 218, no. 4: e20201754. doi: 10.1084/jem.20201754*
29. Ernzen K.J., Panfil A.R. Regulation of HTLV-1 transformation. *Biosci. Rep., 2022, vol. 42, no. 3: BSR20211921. doi: 10.1042/BSR20211921*
30. Eshghifar N., Farrokhi N., Naji T., Zali M. Tumor suppressor genes in familial adenomatous polyposis. *Gastroenterol. Hepatol. Bed. Bench., 2017, vol. 10, no. 1, pp. 3–13.*
31. Fan H. Cell transformation by RNA viruses: an overview. *Viruses, 2011, vol. 3, no. 6, pp. 858–860. doi: 10.3390/v3060858*
32. Fan H., Johnson C. Insertional oncogenesis by non-acute retroviruses: implications for gene therapy. *Viruses, 2011, vol. 3, no. 4, pp. 398–422. doi: 10.3390/v3040398*
33. Farci P. New insights into the HCV quasispecies and compartmentalization. *Semin. Liver Dis., 2011, vol. 31, no. 4, pp. 356–374. doi: 10.1055/s-0031-1297925*
34. Ghoreshi Z.A., Molaei H.R., Arefinia N. The Role of DNA Viruses in Human Cancer. *Cancer Inform., 2023, no. 22: 11769351231154186. doi: 10.1177/11769351231154186*
35. Fazlalipour M., Keyvani H., Monavari S.H., Mollaie H.R. Expression, Purification and Immunogenic Description of a Hepatitis C Virus Recombinant CoreE1E2 Protein Expressed by Yeast Pichia pastoris. *Jundishapur J. Microbiol., 2015, vol. 8, no. 4: e17157. doi: 10.5812/jjm.8(4)2015.17157*

36. Fochi S., Mutascio S., Bertazzoni U., Zipeto D., Romanelli M.G. HTLV Deregulation of the NF-κB Pathway: An Update on Tax and Antisense Proteins Role. *Front. Microbiol., 2018, no. 9: 285. doi: 10.3389/fmicb.2018.00285*
37. Freed E.O. HIV-1 replication. *Somat. Cell. Mol. Genet., 2001, vol. 26, no. 1-6, pp. 13–33. doi: 10.1023/a:1021070512287*
38. Gallo R.C. Research and discovery of the first human cancer virus, HTLV-1. *Best Pract. Res. Clin. Haematol., 2011, vol. 24, no. 4, pp. 559–565. doi: 10.1016/j.beha.2011.09.012*
39. Garcia-Montojo M., Doucet-O'Hare T., Henderson L., Nath A. Human endogenous retrovirus-K (HML-2): a comprehensive review. *Crit. Rev. Microbiol., 2018, vol. 44, no. 6, pp. 715–738. doi: 10.1080/1040841X.2018.1501345*
40. Gatza M.L., Watt J.C., Marriott S.J. Cellular transformation by the HTLV-I Tax protein, a jack-of-all-trades. *Oncogene, 2003, vol. 22, no. 33, pp. 5141–5149. doi: 10.1038/sj.onc.1206549*
41. Geijtenbeek T.B., Kwon D.S., Torensma R., van Vliet S.J., van Duijnhoven G.C., Middel J., Cornelissen I.L., Nottet H.S., KewalRamani V.N., Littman D.R., Figdor C.G., van Kooyk Y. DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. *Cell, 2000, vol. 100, no. 5, pp. 587–597. doi: 10.1016/s0092-8674(00)80694-7*
42. Gessain A., Mahieux R. Tropical spastic paraparesis and HTLV-1 associated myelopathy: clinical, epidemiological, virological and therapeutic aspects. *Rev. Neurol. (Paris), 2012, vol. 168, no. 3, pp. 257–269. doi: 10.1016/j.neurol.2011.12.006*
43. Gillet N.A., Malani N., Melamed A., Gormley N., Carter R., Bentley D., Berry C., Bushman F.D., Taylor G.P., Bangham C.R. The host genomic environment of the provirus determines the abundance of HTLV-1-infected T-cell clones. *Blood, 2011, vol. 117, no. 11, pp. 3113–3122. doi: 10.1182/blood-2010-10-312926*
44. Grulich A.E., Vajdic C.M. The epidemiology of cancers in human immunodeficiency virus infection and after organ transplantation. *Semin. Oncol., 2015, vol. 42, no. 2, pp. 247–257. doi: 10.1053/j.seminoncol.2014.12.029*
45. Harhaj E.W., Giam C.Z. NF-κB signaling mechanisms in HTLV-1-induced adult T-cell leukemia/lymphoma. *FEBS J., 2018, vol. 285, no. 18, pp. 3324–3336. doi: 10.1111/febs.14492*
46. Hashikura Y., Umeki K., Umekita K., Nomura H., Yamamoto I., Hasegawa H., Yanagihara K., Okayama A. The diversity of the structure and genomic integration sites of HTLV-1 provirus in MT-2 cell lines. *Hum. Cell, 2016, vol. 29, no. 3, pp. 122–129. doi: 10.1007/s13577-016-0136-8*
47. Hassan M., Selimovic D., Ghozlan H., Abdel-Kader O. Induction of high-molecular-weight (HMW) tumor necrosis factor(TNF) alpha by hepatitis C virus (HCV) non-structural protein 3 (NS3) in liver cells is AP-1 and NF-kappaB-dependent activation. *Cell. Signal., 2007, vol. 19, no. 2, pp. 301–311. doi: 10.1016/j.cellsig.2006.07.002*
48. Heride C., Urbé S., Clague M.J. Ubiquitin code assembly and disassembly. *Curr. Biol., 2014, vol. 24, no. 6, pp. R215–R220. doi: 10.1016/j.cub.2014.02.002*
49. Hofacre A., Fan H. Jaagsiekte sheep retrovirus biology and oncogenesis. *Viruses, 2010, vol. 2, no. 12, pp. 2618–2648. doi: 10.3390/v2122618*
50. Howley P.M., Knipe D.M., Cohen J.L., Damania B.A. Fields Virology: DNA Viruses. *Lippincott Williams & Wilkins, 2021.*
51. Hu W.Y., Myers C.P., Kilzer J.M., Pfaff S.L., Bushman F.D. Inhibition of retroviral pathogenesis by RNA interference. *Curr. Biol., 2002, vol. 12, no. 15, pp. 1301–1311. doi: 10.1016/s0960-9822(02)00975-2*
52. Huang Q., Niu Z., Han J., Liu X., Lv Z., Li H., Yuan L., Li X., Sun S., Wang H., Huang X. HTLV-1 Tax upregulates early growth response protein 1 through nuclear factor-κB signaling. *Oncotarget, 2017, vol. 8, no. 31, pp. 51123–51133. doi: 10.18632/oncotarget.17699*
53. Huang Y., Staschke K., De Francesco R., Tan S.L. Phosphorylation of hepatitis C virus NS5A nonstructural protein: a new paradigm for phosphorylation-dependent viral RNA replication? *Virology, 2007, vol. 364, no. 1, pp. 1–9. doi: 10.1016/j.virol.2007.01.042*
54. Irshad M., Gupta P., Irshad K. Molecular basis of hepatocellular carcinoma induced by hepatitis C virus infection. *World J. Hepatol., 2017, vol. 9, no. 36, pp. 1305–1314. doi: 10.4254/wjh.v9.i36.1305*
55. Johnson C., Hung F. Jaagsiekte Sheep Retrovirus and Lung Cancer. In: Cancer Associated Viruses. *Springer, 2011, pp. 755–791.*
56. Kakisi O.K., Robinson M.J., Tettmar K.I., Tedder R.S. The rise and fall of XMRV. *Transfus. Med., 2013, vol. 23, no. 3, pp. 142–151. doi: 10.1111/tme.12049*
57. Kannian P., Yin H., Doueiri R., Lairmore M.D., Fernandez S., Green P.L. Distinct transformation tropism exhibited by human T lymphotropic virus type 1 (HTLV-1) and HTLV-2 is the result of postinfection T cell clonal expansion. *J. Virol., 2012, vol. 86, no. 7, pp. 3757–3766. doi: 10.1128/JVI.06900-11*
58. Katoh I., Kurata S. Association of endogenous retroviruses and long terminal repeats with human disorders. *Front. Oncol., 2013, no. 3: 234. doi: 10.3389/fonc.2013.00234*
59. Katsura Y., Asai S. Evolutionary Medicine of Retroviruses in the Human Genome. *Am. J. Med. Sci., 2019, vol. 358, no. 6, pp. 384–388. doi: 10.1016/j.amjms.2019.09.007*
60. Kengne M., Tsata D.C.W., Ndomgue T., Nwobegahay J.M. Prevalence and risk factors of HTLV-1/2 and other blood borne infectious diseases among blood donors in Yaounde Central Hospital, Cameroon. *Pan. Afr. Med. J., 2018, no. 30: 125. doi: 10.11604/pamj.2018.30.125.14802*
61. Keyvani H., Fazlalipour M., Monavari S.H., Mollaie H.R. Hepatitis C virus — proteins, diagnosis, treatment and new approaches for vaccine development. *Asian Pac. J. Cancer Prev., 2012, vol. 13, no. 12, pp. 5931–5949.*
62. Kim S.G., Zhou J., Solomon C., Zheng Y., Suzuki T., Chen M., Song S., Jiang N., Cho S., Mao J.J. Effects of growth factors on dental stem/progenitor cells. *Dent. Clin. North Am., 2012, vol. 56, no. 3, pp. 563–575. doi: 10.1016/j.cden.2012.05.001*
63. Klein G. Perspectives in studies of human tumor viruses. *Front. Biosci., 2002, vol. 7, pp. d268–d274. doi: 10.2741/A726*
64. Knipe D., Howley P., Griffin D., Lamb R., Martin M., Roizman B., Straus S. Fields Virology. Vol. 1 and 2. Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2013.
65. Kontomanolis E.N., Koutras A., Syllaios A., Schizas D., Mastoraki A., Garmpis N., Diakosavvas M., Angelou K., Tsatsaris G., Pagkalos A., Ntounis T., Fasoulakis Z. Role of Oncogenes and Tumor-suppressor Genes in Carcinogenesis: A Review. *Anticancer Res., 2020, vol. 40, no. 11, pp. 6009–6015. doi: 10.21873/anticanres.14622*
66. Korf B.R. Neurofibromatosis. *Handb. Clin. Neurol., 2013, vol. 111, pp. 333–340. doi: 10.1016/B978-0-444-52891-9.00039-7*

67. Lin M.V., King L.Y., Chung R.T. Hepatitis C virus-associated cancer. *Annu. Rev. Pathol., 2015, vol. 10, pp. 345–370. doi: 10.1146/annurev-pathol-012414-040323*
68. Machida K., Liu J.C., McNamara G., Levine A., Duan L., Lai M.M. Hepatitis C virus causes uncoupling of mitotic checkpoint and chromosomal polyploidy through the Rb pathway. *J. Virol., 2009, vol. 83, no. 23, pp. 12590–12600. doi: 10.1128/JVI.02643-08*
69. Malekshahi, A., Alamdary, A., Safarzadeh, A., Khavandegar, A., Nikoo, H. R., Safavi, M., Ajorloo, M. Potential Roles of Core and Core+1 Proteins During the Chronic Phase of Hepatitis C Virus Infection. *Future Virology, 2023, vol. 18, no. 3, pp. 193–207. doi: 10.2217/fvl-2022-0117*
70. Manns M.P., Buti M., Gane E., Pawlotsky J.M., Razavi H., Terrault N., Younossi Z. Hepatitis C virus infection. *Nat. Rev. Dis. Primers, 2017, no. 3: 17006. doi: 10.1038/nrdp.2017.6*
71. Marriott A.C., Dimmock N.J. Defective interfering viruses and their potential as antiviral agents. *Rev. Med. Virol., 2010, vol. 20, no. 1, pp. 51–62. doi: 10.1002/rmv.641*
72. Martin I.V., Borkham-Kamphorst E., Zok S., van Roeyen C.R., Eriksson U., Boor P., Hittatiya K., Fischer H.P., Wasmuth H.E., Weiskirchen R., Eitner F., Floege J., Ostendorf T. Platelet-derived growth factor (PDGF)-C neutralization reveals differential roles of PDGF receptors in liver and kidney fibrosis. *Am. J. Pathol., 2013, vol. 182, no. 1, pp. 107–117. doi: 10.1016/j.ajpath.2012.09.006*
73. Martin J.L., Maldonado J.O., Mueller J.D., Zhang W., Mansky L.M. Molecular Studies of HTLV-1 Replication: An Update. *Viruses, 2016, vol. 8, no. 2: 31. doi: 10.3390/v8020031*
74. Martinez M.P., Al-Saleem J., Green P.L. Comparative virology of HTLV-1 and HTLV-2. *Retrovirology, 2019, vol. 16, no. 1: 21. doi: 10.1186/s12977-019-0483-0*
75. Maślikowski B.M., Néel B.D., Wu Y., Wang L., Rodrigues N.A., Gillet G., Bédard P.A. Cellular processes of v-Src transformation revealed by gene profiling of primary cells — implications for human cancer. *BMC Cancer, 2010, no. 10: 41. doi: 10.1186/1471-2407-10-41*
76. McLaughlin-Drubin M.E., Munger K. Viruses associated with human cancer. *Biochim. Biophys Acta, 2008, vol. 1782, no. 3, pp. 127–150. doi: 10.1016/j.bbadis.2007.12.005*
77. Mesri E.A., Feitelson M.A., Munger K. Human viral oncogenesis: a cancer hallmarks analysis. *Cell. Host Microbe, 2014, vol. 15, no. 3, pp. 266–282. doi: 10.1016/j.chom.2014.02.011*
78. Monavari S.H., Keyvani H., Mollaie H., Fazlalipour M., Salehi-Vaziri M., Bokharaei-Salim F., Mollaie R., Sadeghi F. Detection of human T-cell lymphotropic virus Type-1 among patients with malignant hematological diseases in Capital of Iran, Tehran. *J. Gen. Mol. Virol., 2011, vol. 3, no. 5, pp. 67–70.*
79. Montanheiro P., Vergara M.P., Smid J., da Silva Duarte A.J., de Oliveira A.C., Casseb J. High production of RANTES and MIP-1alpha in the tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM). *J. Neuroimmunol., 2007, vol. 188, no. 1–2, pp. 138–142. doi: 10.1016/j.jneuroim.2007.05.015*
80. Moore P.S., Chang Y. Why do viruses cause cancer? Highlights of the first century of human tumour virology. *Nat. Rev. Cancer., 2010, vol. 10, no. 12, pp. 878–889. doi: 10.1038/nrc2961*
81. Morse H.C. 3rd, Hartley J.W., Fredrickson T.N., Yetter R.A., Majumdar C., Cleveland J.L., Rapp U.R. Recombinant murine retroviruses containing avian v-myc induce a wide spectrum of neoplasms in newborn mice. *Proc. Natl Acad. Sci. USA, 1986, vol. 83, no. 18, pp. 6868–6872. doi: 10.1073/pnas.83.18.6868*
82. Neutzner M., Neutzner A. Enzymes of ubiquitination and deubiquitination. *Essays Biochem., 2012, vol. 52, pp. 37–50. doi: 10.1042/bse0520037*
83. Nosaka K., Matsuoka M. Adult T-cell leukemia-lymphoma as a viral disease: subtypes based on viral aspects. *Cancer Sci., 2021, vol. 112, no. 5, pp. 1688–1694. doi: 10.1111/cas.14869*
84. Olah E. Cancer Susceptibility Genes in Heritable Cancer Syndromes. *Nőgyógyászati Onkológia, 1997, vol. 2, pp. 119–128.*
85. Overbaugh J., Bangham C.R. Selection forces and constraints on retroviral sequence variation. *Science, 2001, vol. 292, no. 5519, pp. 1106–1109. doi: 10.1126/science.1059128*
86. Panasenko O.O. Identification of ubiquitinated proteins. *Materials and Methods, 2014, 25 p. doi: 10.13070/mm.en.4.827*
87. Payne L.N. Retrovirus-induced disease in poultry. *Poult. Sci., 1998, vol. 77, no. 8, pp. 1204–1212. doi: 10.1093/ps/77.8.1204*
88. Payton S. XMRV in prostate cancer. *Nat. Rev. Urol., 2010, vol. 7, p. 3. doi: 10.1038/nrurol.2009.240*
89. Penin F., Dubuisson J., Rey F.A., Moradpour D., Pawlotsky J.M. Structural biology of hepatitis C virus. *Hepatology, 2004, vol. 39, no. 1, pp. 5–19. doi: 10.1002/hep.20032*
90. Podschwadt P., Malyshkina A., Windmann S., Werner T., Hansen W., Bayer W. A detailed analysis of F-MuLV- and SFFV-infected cells in Friend virus-infected mice reveals the contribution of both F-MuLV- and SFFV-infected cells to the interleukin-10 host response. *Retrovirology, 2022, vol. 19, no. 1: 29. doi: 10.1186/s12977-022-00613-4*
91. Pujari R., Hunte R., Thomas R., van der Weyden L., Rauch D., Ratner L., Nyborg J.K., Ramos J.C., Takai Y., Shembade N. Human T-cell leukemia virus type 1 (HTLV-1) tax requires CADM1/TSLC1 for inactivation of the NF-κB inhibitor A20 and constitutive NF-κB signaling. *PLoS Pathog., 2015, vol. 11, no. 3: e1004721. doi: 10.1371/journal.ppat.1004721*
92. Reyes G.R. The nonstructural NS5A protein of hepatitis C virus: an expanding, multifunctional role in enhancing hepatitis C virus pathogenesis. *J. Biomed. Sci., 2002, vol. 9, no. 3, pp. 187–197. doi: 10.1007/BF02256065*
93. Robinson M.J., Erlwein O., McClure M.O. Xenotropic murine leukaemia virus-related virus (XMRV) does not cause chronic fatigue. *Trends Microbiol., 2011, vol. 19, no. 11, pp. 525–529. doi: 10.1016/j.tim.2011.08.005*
94. Rodriguez J.J., Goff S.P. Xenotropic murine leukemia virus-related virus establishes an efficient spreading infection and exhibits enhanced transcriptional activity in prostate carcinoma cells. *J. Virol., 2010, vol. 84, no. 5, pp. 2556–2562. doi: 10.1128/JVI.01969-09*
95. Rogo L.D., Akogwu S., Umar U.Z., Aliyu A.M., Aminu B.M. The genetic and molecular studies of hepatitis C virus: a review. *Bayero Journal of Pure and Applied Sciences, 2011, vol. 4, no. 1, pp. 72–74.*
96. Rosadas C., Taylor G.P. Mother-to-Child HTLV-1 Transmission: Unmet Research Needs. *Front. Microbiol., 2019, no. 10: 999. doi: 10.3389/fmicb.2019.00999*

97. Roskoski R. Jr. Src protein-tyrosine kinase structure and regulation. *Biochem. Biophys. Res. Commun., 2004, vol. 324, no. 4, pp. 1155–1164. doi: 10.1016/j.bbrc.2004.09.171*
98. Ross S.R. Mouse mammary tumor virus molecular biology and oncogenesis. *Viruses, 2010, vol. 2, no. 9, pp. 2000–2012. doi: 10.3390/v2092000*
99. Roy S., Bondada M.S., Zhang Y., Moffat K., Nair V., Yao Y. Proviral ALV-LTR Sequence Is Essential for Continued Proliferation of the ALV-Transformed B Cell Line. *Int. J. Mol. Sci., 2022, vol. 23, no. 19: 11263. doi: 10.3390/ijms231911263*
100. Rubin H. The early history of tumor virology: Rous, RIF, and RAV. *Proc. Natl Acad. Sci. USA, 2011, vol. 108, no. 35, pp. 14389–14396. doi: 10.1073/pnas.1108655108*
101. Salavatiha Z., Soleimani-Jelodar R., Jalilvand S. The role of endogenous retroviruses-K in human cancer. *Rev. Med. Virol., 2020, vol. 30, no. 6, pp. 1–13. doi: 10.1002/rmv.2142*
102. Satou Y., Yasunaga J., Yoshida M., Matsuoka M. HTLV-I basic leucine zipper factor gene mRNA supports proliferation of adult T cell leukemia cells. *Proc. Natl Acad. Sci. USA, 2006, vol. 103, no. 3, pp. 720–725. doi: 10.1073/pnas.0507631103*
103. Saxena N., Kumar V. Oncogenic viruses: DUBbing their way to cancer. *Virol. Discov., 2013, vol. 1: 1. doi: 10.7243/2052-6202-1-5*
104. Schlaberg R., Choe D.J., Brown K.R., Thaker H.M., Singh I.R. XMRV is present in malignant prostatic epithelium and is associated with prostate cancer, especially high-grade tumors. *Proc. Natl Acad. Sci. USA, 2009, vol. 106, no. 38, pp. 16351–16356. doi: 10.1073/pnas.0906922106*
105. Sethi A.K., Celentano D.D., Gange S.J., Gallant J.E., Vlahov D., Farzadegan H. High-risk behavior and potential transmission of drug-resistant HIV among injection drug users. *J. Acquir. Immune Defic. Syndr., 2004, vol. 35, no. 5, pp. 503–510. doi: 10.1097/00126334-200404150-00008*
106. Şevik M. Oncogenic viruses and mechanisms of oncogenesis. *Turkish Journal of Veterinary & Animal Sciences, 2012, vol. 36, no. 4, pp. 323–329.*
107. Shi K., Pandey K.K., Bera S., Vora A.C., Grandgenett D.P., Aihara H. A possible role for the asymmetric C-terminal domain dimer of Rous sarcoma virus integrase in viral DNA binding. *PLoS One, 2013, vol. 8, no. 2: e56892. doi: 10.1371/journal.pone.0056892*
108. Shiels M.S., Pfeiffer R.M., Hall H.I., Li J., Goedert J.J., Morton L.M., Hartge P., Engels E.A. Proportions of Kaposi sarcoma, selected non-Hodgkin lymphomas, and cervical cancer in the United States occurring in persons with AIDS, 1980-2007. *JAMA, 2011, vol. 305, no. 14, pp. 1450–1459. doi: 10.1001/jama.2011.396*
109. Shukrun M., Jabareen A., Abou-Kandil A., Chamias R., Aboud M., Huleihel M. HTLV-1 Tax oncoprotein inhibits the estrogen-induced-ER α-Mediated BRCA1 expression by interaction with CBP/p300 cofactors. *PLoS One, 2014, vol. 9, no. 2: e89390. doi: 10.1371/journal.pone.0089390*
110. Silverman R.H., Nguyen C., Weight C.J., Klein E.A. The human retrovirus XMRV in prostate cancer and chronic fatigue syndrome. *Nat. Rev. Urol., 2010, vol. 7, no. 7, pp. 392–402. doi: 10.1038/nrurol.2010.77*
111. Simmons W. The role of human endogenous retroviruses (HERV-K) in the pathogenesis of human cancers. *Mol. Biol., 2016, vol. 5, no. 169: 2.*
112. Sugata K., Yasunaga J., Kinosada H., Mitobe Y., Furuta R., Mahgoub M., Onishi C., Nakashima K., Ohshima K., Matsuoka M. HTLV-1 Viral Factor HBZ Induces CCR4 to Promote T-cell Migration and Proliferation. *Cancer Res., 2016, vol. 76, no. 17, pp. 5068–5079. doi: 10.1158/0008-5472.CAN-16-0361*
113. Lok A.S. Hepatitis B: 50 years after the discovery of Australia antigen. *J. Viral. Hepat., 2016, vol. 23, no. 1, pp. 5–14. doi: 10.1111/jvh.12444*
114. Sun J., Bodola F., Fan X., Irshad H., Soong L., Lemon S.M., Chan T.S. Hepatitis C virus core and envelope proteins do not suppress the host's ability to clear a hepatic viral infection. *J. Virol., 2001, vol. 75, no. 24, pp. 11992–11998. doi: 10.1128/JVI.75.24.11992-11998.2001*
115. Sun T., Liu Z., Yang Q. The role of ubiquitination and deubiquitination in cancer metabolism. *Mol. Cancer, 2020, vol. 19, no. 1: 146. doi: 10.1186/s12943-020-01262-x*
116. Svoboda J. Cell Association in Rous Sarcoma Virus (RSV) Rescue and Cell Infection. *Folia Biol. (Praha), 2015, vol. 61, no. 5, pp. 161–167.*
117. Svoboda J. Rous sarcoma virus centennial in Folia Biologica. *Folia Biol. (Praha), 2013, vol. 59, no. 3, pp. 103–104.*
118. Taguchi T., Nagano-Fujii M., Akutsu M., Kadoya H., Ohgimoto S., Ishido S., Hotta H. Hepatitis C virus NS5A protein interacts with 2',5'-oligoadenylate synthetase and inhibits antiviral activity of IFN in an IFN sensitivity-determining region-independent manner. *J. Gen. Virol., 2004, vol. 85, pt 4, pp. 959–969. doi: 10.1099/vir.0.19513-0*
119. Taylor G.P., Matsuoka M. Natural history of adult T-cell leukemia/lymphoma and approaches to therapy. *Oncogene, 2005, vol. 24, no. 39, pp. 6047–6057. doi: 10.1038/sj.onc.1208979*
120. Telesnitsky A., Goff S.P. Reverse Transcriptase and the Generation of Retroviral DNA. In: Retroviruses. Eds: Coffin J.M., Hughes S.H., Varmus H.E. *Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press, 1997.*
121. Tidyman W.E., Rauen K.A. Pathogenetics of the RASopathies. *Hum. Mol. Genet., 2016, vol. 25, no. R2, pp. R123–R132. doi: 10.1093/hmg/ddw191*
122. Toroney R., Nallagatla S.R., Boyer J.A., Cameron C.E., Bevilacqua P.C. Regulation of PKR by HCV IRES RNA: importance of domain II and NS5A. *J. Mol. Biol., 2010, vol. 400, no. 3, pp. 393–412. doi: 10.1016/j.jmb.2010.04.059*
123. Urisman A., Molinaro R.J., Fischer N., Plummer S.J., Casey G., Klein E.A., Malathi K., Magi-Galluzzi C., Tubbs R.R., Ganem D., Silverman R.H., DeRisi J.L. Identification of a novel Gammaretrovirus in prostate tumors of patients homozygous for R462Q RNASEL variant. *PLoS Pathog., 2006, vol. 2, no. 3: e25. doi: 10.1371/journal.ppat.0020025*
124. Vidya Vijayan K.K., Karthigeyan K.P., Tripathi S.P., Hanna L.E. Pathophysiology of CD4+ T-Cell Depletion in HIV-1 and HIV-2 Infections. *Front. Immunol., 2017, no. 8: 580. doi: 10.3389/fimmu.2017.00580*
125. Vogt P.K. Retroviral oncogenes: a historical primer. *Nat. Rev. Cancer, 2012, vol. 12, no. 9, pp. 639–648. doi: 10.1038/nrc3320*
126. Vurusaner B., Poli G., Basaga H. Tumor suppressor genes and ROS: complex networks of interactions. *Free Radic. Biol. Med., 2012, vol. 52, no. 1, pp. 7–18. doi: 10.1016/j.freeradbiomed.2011.09.035*

127. Watanabe T. Adult T-cell leukemia: molecular basis for clonal expansion and transformation of HTLV-1-infected T cells. *Blood, 2017, vol. 129, no. 9, pp. 1071–1081. doi: 10.1182/blood-2016-09-692574*
128. Welsh J. Modeling Breast Cancer in Animals — Considerations for Prevention and Treatment Studies. *Animal Models for the Study of Human Disease. Academic Press, 2017, pp. 925–948.*
129. Withers J.B., Beemon K.L. The structure and function of the rous sarcoma virus RNA stability element. *J. Cell. Biochem., 2011, vol. 112, no. 11, pp. 3085–3092. doi: 10.1002/jcb.23272*
130. Yasunaga J.I. Viral, genetic, and immune factors in the oncogenesis of adult T-cell leukemia/lymphoma. *Int. J. Hematol., 2023, vol. 117, no. 4, pp. 504–511. doi: 10.1007/s12185-023-03547-5*
131. Zampino R., Pisaturo M.A., Cirillo G., Marrone A., Macera M., Rinaldi L., Stanzione M., Durante-Mangoni E., Gentile I., Sagnelli E., Signoriello G., Miraglia Del Giudice E., Adinolfi L.E., Coppola N. Hepatocellular carcinoma in chronic HBV-HCV co-infection is correlated to fibrosis and disease duration. *Ann. Hepatol., 2015, vol. 14, no. 1, pp. 75–82.*
132. Zhu N., Ware C.F., Lai M.M. Hepatitis C virus core protein enhances FADD-mediated apoptosis and suppresses TRADD signaling of tumor necrosis factor receptor. *Virology, 2001, vol. 283, no. 2, pp. 178–187. doi: 10.1006/viro.2001.0896*
133. Zur Hausen H. Papillomaviruses in human cancers. *Proc. Assoc. Am. Physicians, 1999, vol. 111, no. 6, pp. 581–587. doi: 10.1046/j.1525-1381.1999.99723.x*

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