*Review Article*

# Tumorigenesis related to retroviral infections

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**Abstract**
Retroviral infections are considered important risk factors for cancer development in humans since approximately 15-20% of cancer worldwide is caused by an infectious agent. This report discusses the most established oncogenic retroviruses, including human immunodeficiency virus (HIV), human T-cell leukemia virus (HTLV-1 and -2), Rous sarcoma virus (RSV), Abelson murine leukemia virus (A-MuLV), Moloney murine leukemia virus (M-MuLV), murine mammary tumor virus (MMTV), bovine leukemia virus, (BLV), Jaagsiekte sheep retrovirus (JSRV), and Friend spleen focus-forming virus (SFFV). The role of retroviruses as inducers of carcinogenesis, the mechanisms underlying oncogenic transformation, and the routes of transmission of several cancer-related retroviral infections are also described. Finally, the impact of cancer-related retroviral infections in the developing world is addressed. This review is an update of carcinogenesis caused by retroviral infections.

**Key words:** cancer; retroviruses; retrovirus oncogenesis; transmission; HIV; HTLV

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## Introduction

Infectious agents are considered to play a vital role in the development of cancer. The vast majority of several common malignancies worldwide are believed to be due to viral infections; however, the role of infections as cancer contributors is a matter of intense debate and controversy [1]. Since 1990, the number of scientific publications dealing with viral, bacterial, parasitic, and protozoan infections contributing to cancer has increased significantly. These rates could be doubled if cases are included where there is a presumptive link, and viral infections are confirmed to have a distinct etiological role in the development of cancer. Several reports might be accidental, likely due to lack of obvious scientific criteria; however, others are clearly based on research related to the carcinogenic activity and synergy in cancer progression.

The current view is that tumor viruses could cause carcinogenesis. Tumor viruses can be classified into two groups according to their genetic material: DNA tumor viruses and RNA tumor viruses. The current review is focused on RNA tumor retroviruses and will discuss the cancer-related retroviral infections and the mechanisms underlying retroviral transformation.

Normal cells are transformed into tumor cells by genetic modifications resulting from mutations within specific genes: oncogenes and silence tumor suppressor genes or from chromosomal rearrangements [2,3]. Oncogene-bearing retroviruses normally cause tumors with a short latent period, whereas oncogenic retroviruses that lack oncogenes induce tumors with a much longer latent period [4]. The chronic persistence of tumor virus infection can lead to oncogenesis [5].

## Retroviruses

Most retroviruses are RNA viruses that can cause either leukemia (malignancy of lymphoblasts, myeloblasts, or erythroblasts) or sarcoma (solid tumors that can metastasize in any organ of the body) and are also known as leukoviruses or leukemia sarcoma viruses. Retroviruses are divided into two subfamilies: the *Spumaretrovirinae* and the *Orthoretrovirinae*, according to disparities in morphology, gene expression and viral protein processing. The common feature among the genus of

**Table 1.** Description of retroviruses

| Genera | Species |
|---|---|
| **Alpharetroviruses** | Avian sarcoma-leukosis virus, Rous sarcoma virus |
| **Betaretroviruses** | Mouse mammary tumor virus |
| **Gammaretroviruses** | Murine leukemia virus, Feline leukemia virus |
| **Deltaretroviruses** | Human T-lymphotrophic virus, Bovine leukemia virus |
| **Epsilonretroviruses** | Walleye dermal sarcoma virus |
| **Lentiviruses** | Human immunodeficiency viruses (HIV-1 and HIV-2), Simian immunodeficiency virus, Feline immunodeficiency virus |
| **Spumaviruses** | Boviny foamy virus, Simian foamy virus |

*Spumaretrovirinae* is that their virions are composed of large amounts of reverse transcribed DNA. All oncogenic retroviruses are members of the *Orthoretrovirinae* genus, which is further subdivided into seven genera according to genome complexity and virion morphology. These include: a) simple retroviruses such as alpharetroviruses, betaretroviruses and gammaretroviruses; and b) complex retroviruses including deltaretroviruses, epsilonretroviruses, lentiviruses and spumaviruses [6] (Table 1).

The genomes of simple retroviruses encode the virion capsid/nucleocapsid (Gag) proteins, the enzymes needed for genome replication (reverse transcriptase and integrase; Pol/In), and the envelope proteins (Env) that bind the cell surface molecules used for virus entry [7]. In some instances, simple viruses carry an oncogene or the superantigen gene (*Sag*) of murine mammary tumor virus (MMTV) [4]. Conversely, the genomes of complex retroviruses encode non-structural proteins that facilitate virus replication or that counteract intrinsic, innate, or adaptive immune responses during *in vivo* infection [7].

In alpharetroviruses and gammaretroviruses, *env* genes demonstrate a notable variability reflecting adaptation to a variety of receptors and hosts without greatly affecting antigenicity. Nevertheless, in primate lentiviruses, primary receptor usage remains constant while antigenicity and co-receptor usage are significantly modified [8].

It is believed that up to 8% of the human genome consists of human endogenous retrovirus sequences [9]. Human endogenous retroviruses (HERVs) are vertically transmitted as stable Mendelian genes in the germline of most eukaryotes. They derive from the integration of exogenous, infectiously transmitted retroviruses in the host genomes and are followed by genetic stabilization through accumulation of mutations [4,10]. Under normal circumstances, HERVs are functionally defective or controlled by host factors [9-11]. Several types of HERVs belong to the betaretroviruses and gammaretroviruses genera [4].

*Retroviral mechanisms underlying oncogenesis*

The mechanisms by which oncogenic retroviruses induce malignancies vary. Oncogenic retroviruses are classified into two groups based on the mechanism underlying the disease. Acute-transforming retroviruses are typically replication defective and they rapidly induce tumors because of the viral oncogenes that they carry (proto-oncogenes) [12]. They form polyclonal tumors with a short latency after infection of the host, usually within two to three weeks. This could be attributed to their high transformation capacity [13,14]. Transformation is mediated by the expression of viral oncogenes including *v-Abl* in the Abelson Murine leukemia virus (A-MuLV), which are virally encoded oncogenenic versions of normal cellular genes [13].

**Table 2.** HIV associated malignancies

| |
|---|
| 1. Kaposi's sarcoma |
| 2. Cervical carcinoma |
| 3. Hodgkin's lymphoma |
| 4. Non Hodgkin's lymphoma |
| 5. Squamous cell carcinoma |
| 6. Plasmacytomas |
| 7. Primary CNS lymphoma |
| 8. Burkitt's lymphoma |
| 9. Pediatric leiomyosarcoma |
| 10 Immunoblastic lymphoma |
| 11. Anal canal carcinoma |

Once captured by the virus, protooncogenes undergo mutations that lead to uncontrolled cell proliferation [10]. It is important to note that activation of cellular proto-oncogenes has been discovered in human cancers. This can result from up-regulation of proto-oncogene products by gene amplification or chromosomal translocation, or activation of proto-oncogene proteins by point mutations [15].

Unlike acute-transforming retroviruses, non-acute or slow-transforming viruses are considered replication competent and do not carry oncogenes. Tumorigenesis results from mutations caused by either promoter/enhancer insertion or by insertional mutagenesis [12-16]. During the promoter/enhancer insertion non-acute transforming viruses can activate cellular proto-oncogenes by inserting a viral long terminal repeat (LTR) close to the proto-oncogenes to induce tumors [17]. Insertional mutagenesis is a common mechanism in rodent, feline, and avian retroviruses, where the retrovirus integrates into the host genome and affects the transcription of the neighboring genes [18]. In general, non-acute-transforming retroviruses induce tumors with a prolonged latent period [12].

Oncogenic retroviruses could also cause cancer by the expression of auxiliary viral oncogenes including the *tax* gene of the human T-cell leukemia virus (HTLV-1) [19]. The HTLV-1 oncogenic retrovirus does not contain viral homologues of cellular proto-oncogenes and does not integrate into specific sites of the human genome to disrupt proto-oncogenes [20]. The transforming entity of HTLV-1 has been attributed to the virally encoded oncoprotein Tax that promotes transcription and cell cycle progression. It is believed that Tax acts in *trans* to activate LTR and a set of cellular genes, including proto-oncogenes that drive cell division, thereby creating a cellular environment favoring aneuploidy and DNA damage. The HTLV-1 infection also leads to chromosomal instability caused by Tax [4,21,23].

Another mechanism of transformation by which retroviruses induce cancer includes several retroviral envelope (Env) proteins [12]. For example, Jaagsiekte sheep retrovirus (JSRV) is a simple retrovirus that does not express any recognized oncogenes but still can cause a contagious lung cancer in sheep and goats, known as ovine pulmonary adenocarcinoma (OPA). It is now well-established that Env is oncogenic. One mechanism of transformation involves activation of phosphoinositide-3-OH kinase (P13K)/Akt and mitogen-activated protein kinase (MAPK) signaling cascades. Another potential mechanism involves Env binding to Hyaluronidase 2 (Hyal2), Hyal2 degradation, and activation of the RON receptor tyrosine kinase that is normally suppressed by Hyal2 [10, 19, 24]. Another example of retroviral Env proteins inducing transformation comprises the Env protein (gp55) that is the oncogene of Friend spleen focus-forming virus (SFFV) that induces erythroleukemia in mice [12]; furthermore, the MMTV Env protein has been implicated in mammary tumorigenesis [7]. The Env proteins might reveal other cellular pathways involved in oncogenic transformation [12].

**Table 3.** Summary of retroviral associated malignancies

| Virus | Malignancy |
|---|---|
| HTLV-1 | T-cell leukemia/lymphoma in humans |
| HTLV-2 | Hairy cell leukemia in humans |
| RSV | Fibrosarcoma and sarcoma in chickens |
| A-MULV | B-cell lymphoma in young animals |
| M-MULV | T-lymphoma |
| MMTV | Breast, ovarian, prostate, endometrial cancers and skin malignancies in humans |
| BLV | Lymphomas in cattle |
| JSRV | Ovine pulmonary adenocarcinoma in sheep and goats |
| SFFV | Erythroleukemia in mice |

HTLV; human T-cell leukemia virus, RSV; Rous sarcoma virus**,** A-MuLV; Abelson murine leukemia virus**,** M-MuLV; Moloney murine leukemia virus, MMTV; murine mammary tumor virus, BLV; bovine leukemia virus**,** JSRV; Jaagsiekte sheep retrovirus, SFFV; Friend spleen focus-forming virus

*Retroviruses-related cancer*

Retroviruses have been associated with a variety of diseases that include an array of malignancies [25]. They were first associated with malignant disease in animals [4]. The first retrovirus described as oncogenic was Rous sarcoma virus (RSV) in 1911, which caused sarcomas in chickens [26]. There is a growing body of evidence that this group of viruses comprise a model representing the retroviruses' group that is capable of actually causing tumors in mammals [26]. RSV has been linked in several malignant transformations including fibrosarcoma and sarcoma in chickens. In young inoculated chickens, the tumors can develop rapidly, within two to three days in multiple locations. Moreover, increasing the age of the tested animal may automatically reduce these tumors. This decreased oncogenic capacity in mammals is due to the inability of most RSV strains to replicate in mammalian cells *in vivo*. They efficiently infect only cells that have divided and can be used for gene transfer in both *in vivo* and *in vitro* experiments. The viral *src* oncogene is an activated and over-expressed protein-tyrosine kinase responsible for a number of molecular events [27]. Its increased activity, which has been observed in various human malignancies including breast, ovary, lung, pancreatic, stomach, and colon carcinomas, might represent a promising target for drug therapy interventions [28].

The primate T cell lymphoma/leukemia viruses (PTLV) comprise another oncogenenic genus of retroviruses, in which five human species have been identified: HTLV-1, -2, -3, -4, and -5 [29,30]. HTLV-1 retrovirus was first isolated in 1980 from peripheral blood of patients diagnosed with cutaneous T cell lymphoma and is considered the causative agent of T cell origin of leukemia/lymphoma present in adults and several chronic inflammatory diseases in the eyes, lungs, skeletal muscles, or central nervous system (HTLV-1 associated myelopathy/tropical spastic paraparesis: HAM/TSP) [20, 31]. HTLV-1 infections are endemic in southwest Japan, the Caribbean basin, and South Africa [20]. HTLV-1 virus can be transferred via various routes including sexual intercourse, blood transfusion, breastfeeding, or transplacentally [20,21,32].

Apart from the common structural genes, *gag*, *pol*, and *env*, which are found in retroviruses, HTLV-1 contains several open reading frames in a pX region at the 3' end of its genome. They have the potential to encode essential regulatory proteins (Tax) and three accessory proteins (p12, p13, and p30) that are important for viral infectivity and replication by influencing cellular signaling and gene expression [33]. The Tax protein is considered a strong enhancer of viral gene expression and malignant transformation leading to the progress of adult T-cell leukemia [34]. It binds to host transcription factors,

promoting efficient transcription of the virus. Tax protein appears to be predominantly important for the virus's oncogenic potential and pathogenesis by stimulating continuous proliferation of infected cells and immortality of cells *in vitro* [20,35]. It is important to note that HTLV-1 virus is considered genetically stable because the HTLV-1 proviral genomes are replicated by cellular polymerase α and not by reverse transcriptase, which is error prone and used for virus replication [21].

Another retrovirus putatively associated with human cancers is HTLV-2, which has been linked to hairy cell leukemia; however, the etiological role remains poorly established. HTLV-3 and -4 have been discovered in Central Africa, whereas HTLV-5 has been reported in the past in a cutaneous T cell lymphoma case; however, the disease associations of all three viruses remain unconfirmed due to the limited number of cases in which they have been identified [20,29,30].

The genetic composition of HIV-1 is more complex than that of other retroviruses and resembles the genome of HTLV-1 in several aspects. It contains two copies of single-stranded RNA, approximately 9.3 kD in size. At both ends of the genome, there are two identical regions known as the long terminal regions that enclose the regulation and expression genes of the virus. In the remainder of the genome, there are three major sections that involve the GAG, POL, and ENV regions. The regulatory proteins of the HIV-1 are involved in several processes including transactivation, viral mRNA expression, RNA replication, reverse transcription, and RNA release, among others. In general, the genome of HIV consists of nine genes [36].

There is an extensive list of cancers associated with HIV-positive individuals (Table 2) [37,38]. These tumors are a result of either the lack of the appropriate immune response or the reactivation of etiological agents associated with tumors in immunosuppressed HIV-infected individuals [39]. Cancers associated with acquired immunodeficiency syndrome (AIDS) are usually reported in the advanced stages of HIV infection [40,41]. The most common HIV-associated cancers include Kaposi's sarcoma, which is a mesenchymal tumor originating from lymphatic endothelial cells; non-Hodgkin's lymphoma; and cervical cancer. Both HIV-1 and HIV-2 have been associated with an increased risk of cervical cancer [42]; moreover, Burkitt lymphoma is a highly aggressive tumor that contains one of the cancer subtypes highly affecting HIV-infected patients [40,43]. Current studies suggest that lung cancer risk is higher in HIV-infected patients than in uninfected persons [44,45]. It is important to note that although Hodgkin's lymphoma has been repeatedly associated with AIDS, the Centers of Disease Control and Prevention (CDC) do not consider it as an AIDS-defining illness [42,46]. All AIDS-associating diseases, including cancers, occur at exceptionally high incidence [39,42].

Moloney murine leukemia virus (M-MuLV) can cause T cell-lymphoma with a significant latency by insertional activation of several oncogenes and by inducing events before outgrowth of the tumor cells and events involved in tumor progression [47]. The A-MuLV is a transformation-defective retrovirus derived from M-MuLV [43]. The life cycle of this virus is more atypical than other retroviruses, such as RSV, because the replication of A-MuLV is defective [45]. The A-MuLV was originally observed in transgenic mice (nude mice with no thymus and T cells) treated with prednisolone. The A-MuLV can infect and transform several target cells *in vivo* and *in vitro*. The A-MuLV can cause B cell origin lymphoma in most young animals through co-infection by another virus (helper virus) while the adult animals seem to resist tumor growth. Recent evidence indicates that overexpression of the moloney leukemia virus 10 (MOV10) protein in the virus producer cells inhibits HIV-1, simian immunodeficiency virus, and murine leukemia virus replication. This observation emphasizes its wide antiretroviral activity that is involved in host defense against retroviral infection [48,49]. Although MOV10 can potentially inhibit HIV-1 replication at multiple stages [50], Wang *et al*. [49] also demonstrated that HIV-1 could suppress MOV10 protein expression to counteract the cellular resistance.

The MMTV is an interesting betaretrovirus genus, first described in 1936, in the milk of a strain of mice exhibiting an elevated incidence of mammary carcinomas [7]. It is a non-defective virus expressing all viral genes required for replication; however, additional genetic and hormonal factors regulate the expression of the MMTV provirus. Normally, MMTV infects approximately 80% of the breast epithelial cells of the experimental animal. Previous reports suggested the involvement of MMTV in neoplastic mammary glands of cats and dogs. Companion animals might contribute to the transmission of MMTV between mouse and man [51]. MMTV-like virus DNA has been detected in

several human cancers including breast, liver, ovarian, prostate, endometrial, and skin malignancies [52,53]. There is increased speculation that a human relative of MMTV (HMTV) might be involved in human carcinogenesis; however, this is not yet confirmed [12]. A summary of retroviral associated malignancies is provided in Table 3.

## Transmissible cancer

Although cancer is commonly regarded as non-transmissible, there has been strong evidence suggesting transmissible malignancies from one host to another. As a consequence, the notion that cancer is not contagious might need reconsideration. The possibility of a contagious cancer has been reported in various case studies [54,55]. An estimated 15% of all cancers worldwide are due to infectious etiologies with the vast majority of them (11%) due to viral infections [30].

Transmission of animal retroviruses has been demonstrated for oncogenic retroviruses [32]. Several leukemia-related retroviruses are transmitted via infected cells [56]. For example, bovine leukemia virus (BLV) that causes enzootic bovine leucosis, characterized by lymphosarcoma in cattle [57], can be transmitted by different routes including oral inoculation of BLV infected cells [32], vertical transmission, or insect bites [58].

Direct transmissions of malignancies are not restricted to animals [30]. Although rare, human-to-human transmissions have also been reported. A physiological route for tumor cell transmission in humans is through transplacental transmission from mother to fetus, or organ transplantation [2]. It is noteworthy that HTLV-1 infected mothers are normally advised against breast-feeding [32]. Precise cases of human contagious cancer documented include reports on colonic adenocarcinoma transmission via needle stick [54] and a pancreatic adenocarcinoma through renal transplantation [55]. It is important to note that hematological malignancies have also been observed in approximately 0.06% of hematopoietic stem cell transplants [30].

## Impact on the developing world

In developing countries, there is a high prevalence of cancer-related retroviral infections, the implications of which are of significant concern. Cancer causes increasing morbidity and mortality, particularly in the developing world. The HIV epidemic is contributing to this increased epidemic of many cancers [59]. It is estimated that the incidence of HIV-related cervical cancer in developing and low-income countries is likely large, although limited, in the developed world [60]. There is an increasing incidence of AIDS-related diseases in countries where antiretroviral medications are not yet widely available [39,60]. Moreover, BLV-associated lymphomas in cattle create another issue that has a great economic impact on the livestock sector for many countries, especially in low-income regions [58]. Although the prevalence of non-Hodgkin lymphoma is higher in developed countries, the ratios of mortality-to-incidence rates are higher in the low- and middle-income countries [61].

The importance of cancer-related retroviral infections lies not only in the high incidence reported in developing regions, but also in its potential to be transmissible; therefore, there are devastating economic and social consequences owing to contagious cancer for the prevention of emerging malignancies.

Since retroviral infections lead to human malignancy, ongoing research should focus on understanding the molecular biology of the cancer-related infection in order to halt cancer progression. Immunizations and other high-control measures against cancer-related infections could play a pivotal role in the decline of morbidity and mortality worldwide and especially in developing regions where the incidence of viral infections is at peak and individuals remain in the disease's deadly trails. The priority of medical research should involve health delivery strategies for low-income countries and control of the disease.

## Conclusion

It is currently plausible that tumorigenesis could be attributed to the involvement of several viruses that express oncogenes and are therefore capable of transforming normal cells into malignant cells. Testing this hypothesis could provide insights into new possibilities regarding the elimination of the prevalence of cancer and perhaps progressively enhance cancer prevention and therapy strategies. Further research on the possible correlation between infections and the risk of tumorigenesis are vital for accurate conclusions.

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