

Oncogenic viruses and mechanisms of oncogenesis

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Abstract: In this article, current information about oncogenic DNA and RNA viruses and their oncogenesis mechanisms that cause tumors and cancers in animals and humans is presented.

Key words: Oncogenic viruses, oncogenesis, tumor, DNA, RNA

Introduction

Oncogenic viruses are significant pathogens for humans, farm animals, and pets. These pathogens are classified into different virus families such as Hepadnaviridae, Flaviviridae, and Retroviridae (1).

Oncogenic viruses (tumor viruses) consist of both DNA and RNA viruses (2). Unlike RNA tumor viruses, DNA tumor virus oncogenes encode viral proteins necessary for viral replication. RNA tumor viruses carry changed variants of normal host cell genes, which are not necessary for viral replication (3).

Oncogenic viruses promote cell transformation, prompt uncontrollable cell generation, and lead to the development of malignant tumors (4). All malignant tumors are called cancer (5). Oncogenic abnormalities are seen in pediatric leukemias, lymphomas, and various solid tumors (6).

Virus-promoted malignant transformations in cells are the first step in the complex oncogenesis process (4). The genes in the viral genome that change host cell proliferation control, lead to the synthesis of

new proteins, and are responsible for transformation characteristics are called viral oncogenes (v-onc genes) (3).

Protooncogenes (c-onc genes) are the cellular counterparts of v-onc genes. Their functions are cellular growth and development. The activation of c-onc genes with mutation leads to uncontrolled cell growth (6). C-onc genes are transformed into oncogenic form by amplification, point mutation, deletion, or chromosomal translocation (7). 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. They are called antioncogenes (tumor suppressor genes). When these genes lose their suppressive effects, unpreventable growth occurs (6).

Oncogenes are constantly struggling with tumor suppressor genes, which protect DNA and control cell activities. There are many studies that indicate

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that tumor suppressor genes lose this struggle or that oncogenes win this struggle, which leads to cancer (8).

Classification of oncogenes

Oncogenes can be categorized into 5 groups in terms of the biochemical and functional properties of protein products of protooncogenes. These groups are growth factors, growth factor receptors, signal transducers, transcription factors, and others (9).

Growth factors

Growth factors are secreted polypeptides that stimulate the proliferation of target cells and have extracellular signal functions. Target cells must have a specific receptor to be able to respond to a specific type of growth factor. As an example of growth factors, platelet-derived growth factor (PDGF), which is composed of 2 polypeptide chains, induces the proliferation of fibroblasts.

The relation between growth factors and retroviral oncogenes was revealed with *sis* oncogene studies on the simian sarcoma virus, which was the first retrovirus isolated from monkey fibrosarcoma. Sequence analysis showed that *sis* encodes PDGF's beta chain. This exploration pointed out the principle that growth factors that are inappropriately expressed have functions similar to oncogenes. Studies showed that incessant expression of the *sis* gene product (PDGF- β) leads to significant neoplastic transformation in fibroblasts, but this transformation did not occur in cells without the PDGF receptor. Therefore, *sis* transformation requires interaction between the *sis* gene product and the PDGF receptor (9).

Growth factor receptors

Some viral oncogenes are modified versions of normal growth factors that have intrinsic tyrosine kinase activity. Growth factor receptors have a characteristic protein structure that has 3 main parts: the extracellular ligand-binding area, the transmembrane, and the intracellular tyrosine kinase catalytic areas. Growth factor receptors are molecular tools that enable one-way passage of information from the cell membrane. Growth factor receptors play a role in the regulation of normal cell growth. Some examples of growth factor receptors are *erb B*,

erb B-2, *fms*, *kit*, *met*, *ret*, *ros*, and *trk*. Their mutation and abnormal expression cause their transformation into oncogenes (9).

Signal transducers

Mitogenic signals are transmitted from growth factor receptors on the cell surface to the cell nucleus through a series of interconnected complex processes called the signal transduction path. This regulator information is completed with the gradual phosphorylation of proteins that interact with each other in the cytosol. 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 (e.g., *abl*, *lck*, and *src*) and serine/threonine kinases (e.g., *raf-1*, *mos*, and *pim-1*). GTP-binding proteins with intrinsic GTPase activity are further divided into monomeric (e.g., *H-ras*, *K-ras*, and *N-ras*) and heterotrimeric (e.g., *gsp* and *gip*) groups. Signal transducers are transformed into oncogenes by mutations that lead to irregular activities, frequently causing uncontrollable cellular proliferation (9).

Transcription factors

Transcription factors are nuclear proteins. They regulate the expression of target genes or gene families. Transcriptional regulation is induced by the binding of protein to specific DNA sequences or DNA structural motifs that are located above the target genes. Transcription factors can also bind to other proteins like heterodimeric complexes. Transcription factors are the final step of the signal transducer process that changes extracellular signals into modulated changes in gene expression. Many c-onc genes are transcription factors and they were discovered by studies on retroviruses that have homology with protooncogenes. Some examples of these factors are *erb A*, *ets*, *fos*, *jun*, *myb*, and *c-myc*. C-onc genes that function as transcription factors are generally activated with chromosomal translocations in hematologic and solid neoplasms (9).

Others

In mature tissues, a different cell death program, which is called apoptosis, has been described. In mature cells, apoptosis can be induced with

external stimulations like steroids and radiation. Cancer cell studies have shown that uncontrollable cell proliferation and irregularly programmed cell death leads to neoplasia and failure in anticancer treatments. *Bcl-2*, which was discovered during the studies of chromosomal translocations in human lymphoma, is the only protooncogene that regulates programmed cell death (9).

Tumor suppressor genes

Tumor suppressor genes show antipathy to oncogenes. Their normal functions are to prevent and regulate cell growth. When they lose both of their alleles, they generally lead to failure of regulation and prevention of cell growth. Mutations in one allele are recessive and can be passed on to the next generation. Individuals with a mutation in one allele carry great risk for malignancy development. Among tumor suppressor genes, the retinoblastoma gene (Rb) and p53 are the most studied. Other tumor suppressor genes are the Wilms tumor gene (WT1), the VHL gene in Von-Hippel Lindau syndrome, the NF1 and NF2 genes in neurofibromatosis, and the APC and DCC genes in familial adenomatous polyposis (10).

Oncogenesis

Oncogenesis is a cytological, genetic, and cellular transformation process that results in malignant tumors. Viruses extensively encourage hematopoietic tumors and sarcomas and, more rarely, carcinomas. The discovery of viral oncogenes and the realization that they are derived from cellular genes called protooncogenes led to the understanding that c-onc genes have roles in different tumor types. Assumptions about 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, a protooncogene, 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. This gene is also activated by chromosomal translocation and mutation in Burkitt's lymphoma, a human tumor that is not associated with retroviruses (11).

Mechanisms of oncogene activation

The activation of oncogenes requires genetic changes in cellular protooncogenes. Oncogenes are activated by 3 genetic mechanisms:

- a) Mutation
- b) Gene amplification
- c) Chromosome rearrangements

These mechanisms result in either an increase in protooncogene expression or a change in protooncogene structure. Neoplasia is a multistep process; therefore, more than one of these mechanisms contribute to the formation of tumors. 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 (9).

Nontransforming retroviruses activate cellular protooncogenes

Many retroviruses do not have viral oncogenes, like ALV and mouse mammary tumor virus, but they can encourage tumor formation. They achieve this by integrating a provirus next to normal cellular protooncogenes and activating their expression through a mechanism known as proviral insertional mutagenesis. The addition of the provirus presents strong promoter and enhancer sequences in the gene locus and these changes modify gene expression. It has been determined that more than 70 protooncogenes are activated with proviral insertion of a nontransforming retrovirus. The replication capability of these viruses without oncogenes does not transform cells in culture and stimulates tumors in vivo with long latent periods (12).

In most of the viruses in this group, a widespread replication is seen in the latent period or preleukemic stage of the disease. Most of the infected cells proliferate, and changes in the cell composition and infected tissue morphology are significant. For example, the follicles of cells infected with ALV are significant in the bursa before malignant disease develops. During lymphoma development in mice, proliferative changes have been determined in the thymus. These preleukemic changes do not only occur in tissues where the tumor develops. Proliferative changes and preleukemic cells can

be clearly detected in the bone marrow and spleen before thymic lymphoma develops (11).

Direct stimulation of growth

Other than their classic roles in mediating viral entry, some surface (SU) proteins can bind to growth factor receptors on the cell surface and trigger growth-stimulating signals by imitating normal ligand receptor interaction. This interaction extends to the appropriate target pool and stimulates viral replication in 3 ways. First, the interaction of SU protein with a surface receptor that stimulates growth can make cells susceptible to infection, and retroviruses can lead to infection in the cell; second, stimulation of growth can increase the number of appropriate target cells; and third, an increase in the number of infected cells increases the amount of viral replication. The combination of these effects has a significant influence on tumor development. Erythroleukemia, stimulated by a polycythemic strain of the Friend virus, can set an example for tumor induction resulting from stimulation of growth receptor by *Env* proteins. This virus stimulates diffuse erythroid proliferation, which causes splenomegaly (11).

Role of the long terminal repeat in oncogenesis

The significance of the long terminal repeat (LTR) in oncogenesis modulation was first determined in experiments comparing LTR sequences of viruses with different oncogenic potential. Through analyses of chimeric viruses, it was found that these sequences are one of the major determinants for distinguishing oncogenic and nononcogenic ALVs and murine leukemia viruses (MLVs). LTR sequences also have effects on the types of tumors. Simple retrovirus expression is controlled by the LTR. LTR has a U3 region, which contains promoter and enhancer attachment motifs that mediate the expression of sequences placed under their control. These elements affect the virus replication cycle. High levels of replication increase recombinant oncogenic potential (11).

Common topics in oncogenesis

In spite of the differences among oncogenic retroviruses, tumor induction by these agents includes some common biological themes. The first is that tumor induction is a multistage process. In spite of the stunning differences in the latent period,

which distinguish tumors stimulated by viruses with *v-onc* genes and those without *v-onc* genes, the dominant growth signals provided by *v-onc* gene products are not adequate to completely transform cells into tumor cells. The second characteristic is that there is cooperation between different oncogenes. Cooperating genes may exist in a retrovirus that contains a single *v-onc* gene and may be activated as a result of spontaneous mutation. Finally, virus-cell interactions in all oncogenic retroviruses indicate that a certain virus stimulates a specific type of tumor (11).

Oncogenic viruses

Oncogenic viruses can be divided into 2 groups, based on their genetic material, as DNA and RNA tumor viruses (13).

DNA tumor viruses

DNA tumor viruses have 2 life forms. In permissive cells, viral replication causes cell lysis and cell death. In nonpermissive cells, viral DNA is mostly integrated into the different sites of cell chromosomes. It encodes binding proteins and inactivates cell growth, regulating proteins like p53 and retinoblastoma. The cell is transformed as a result of the expression of proteins that control viral and cellular DNA synthesis (3,4). Animal and human oncogenic DNA viruses are shown in Table 1 (12,14-16) and Table 2 (12,13,17,18), respectively.

RNA tumor viruses

All oncogenic RNA viruses are retroviruses (2). In 1961, it was found that Rous sarcoma virus (RSV) particles contain RNA; thus, oncogenic retroviruses were called RNA tumor viruses (19). In retroviruses, more than 30 oncogenes were defined (12).

Retroviruses have 3 basic genes (*gag*, *pol*, and *env*), which are used for the synthesis of structural proteins, virion-associated enzymes, and envelope glycoproteins (20). Complex retroviruses such as lentiviruses have an extra nonstructural gene (*v-onc*) that allows them to transform the cell (21). For example, this fourth gene in the RSV is the *v-scr* (sarcoma) gene. RSV gains this cellular origin gene after infecting cells (9).

In tumor development, RNA tumor viruses use different oncogenic mechanisms. Some encode

Table 1. Animal oncogenic DNA viruses.

Taxonomic grouping	Examples	Tumor types
Adenoviridae	BAV type 3	Various solid tumors
Hepadnaviridae	GSHV, WHV	Hepatocellular carcinoma
Herpesviridae	MDV, HVS	Lymphoma, carcinoma
Papillomaviridae	BPV types 1, 2, 4 CRPV	Papilloma, carcinoma, sarcoma, lymphoma
Polyomaviridae	MPYV, SV40	Various solid tumors
Poxviridae	FIBV, MYXV, RFV, SQFV	Myxoma, fibroma

BAV: Bovine adenovirus, GSHV: Ground squirrel hepatitis virus, WHV: Woodchuck hepatitis virus, MDV: Marek disease virus, HVS: Herpesvirus saimiri, BPV: Bovine papilloma virus, CRPV: Cottontail rabbit papillomavirus, MPYV: Murine polyomavirus, SV40: Simian virus 40, FIBV: Hare fibroma virus, MYXV: Myxoma virus, RFV: Rabbit fibroma virus, SQFV: Squirrel fibroma virus.

Table 2. Human oncogenic DNA viruses.

Taxonomic grouping	Examples	Tumor types
Adenoviridae	Adenovirus types 9, 12, 18, 31	Various solid tumors in rodents
Hepadnaviridae	HBV	Hepatocellular carcinoma
Herpesviridae	EBV	Burkitt's lymphoma Nasopharyngeal carcinoma B-cell lymphoma Hodgkin's lymphoma
	KSHV (HHV-8)	Kaposi's sarcoma Primary effusion lymphoma Multicentric Castleman's disease
Papillomaviridae	HPV types 6, 11, 16, 18, 31, 45	Oral, cervical, and anal cancer
Polyomaviridae	Merkel cell polyomavirus BK virus, JC virus	Merkel cell carcinoma Solid tumors in rodents
Poxviridae	MCV	Various solid tumors

HBV: Hepatitis B virus, EBV: Epstein-Barr virus, KSHV: Kaposi's sarcoma-associated herpesvirus, HHV: Human herpes virus, HPV: Human papillomavirus, MCV: Molluscum contagiosum virus

oncogenic proteins, which are similar to the cellular proteins in cellular growth control. Overproduction of these oncogenic materials or modification in their functions stimulates cellular proliferation. These RNA viruses can cause rapid tumor development. The second group of retroviruses integrates their promoter sequences and viral enhancers near the cellular growth-stimulating gene and initiates cell transformation. The third group of RNA tumor viruses encodes a protein tax that transactivates the expression of cellular genes (4).

The infection of permissive cells with RNA tumor viruses causes the release of progeny virus from the cell surface through budding, and permanent genetic mutations transform the infected cell into cancer (3).

When the virus is integrated into the cell chromosome, it falls under the control of the cell's regulator genes and can remain in the cell without causing any harmful effects. Such retroviruses are called endogenous retroviruses. If cells that carry such a virus are exposed to various mutagenic or cancerogenic factors (irradiation, mutagenic, or

cancerogenic chemicals; hormonal or immunological stimulations; etc.), the virus is activated and starts to proliferate (22-24).

On the contrary, some retroviruses have an infectious character and show a horizontal spread. These retroviruses are called exogenous retroviruses and they also may occur as a result of the mutation or recombination that results from exposure to various environmental conditions (22). Exogenous retrovirus gene sequences only exist in infected cells, whereas endogenous retrovirus gene sequences are localized in the chromosomes of all cells (19,25). The majority of exogenous retroviruses are oncogenic and some can characteristically lead to the development of lymphoma and leukemia, while some others can lead

to carcinoma. Although some exogenic retroviruses carry rapid oncogenic characteristics, some show very slow oncogenic activity in cells (22).

Retroviruses are divided into 2 different classes in terms of the duration of tumor formation in experimental animals. Acute transforming retroviruses can rapidly cause tumors within days after injection. These retroviruses also transform cell cultures into neoplastic phenotypes. Chronic transforming retroviruses can cause tissue-specific tumors in susceptible experimental animals after a period of many months (9). Animal and human oncogenic RNA viruses are shown in Table 3 (11,12) and Table 4 (13), respectively.

Table 3. Animal oncogenic RNA viruses.

Taxonomic grouping	Examples	Tumor types
Alpharetrovirus	AEV ALV ASV	Erythroblastosis, carcinoma, sarcoma
Deltaretrovirus	BLV	Lymphoma
Gammaretrovirus	Ab-MLV FeLV FeSV Mo-MLV MSV	Lymphoma

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.

Table 4. Human oncogenic RNA viruses.

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

HTLV: Human T-cell leukemia virus.

Conclusion

Globally, almost 20% of cancers are related to infection agents (26). Several viruses with oncogenic potential stimulate cell proliferation and cause tumors and cancer in animals and humans. They act

with different mechanisms depending on different host factors.

The tumor viruses with small genomes integrate into host cell chromosomal DNA and cause mutations and chromosomal rearrangements that predispose to

cancer. The oncogenic DNA and RNA viruses that are carrying oncogenes encode transforming proteins to stimulate tumor formation.

Many retroviruses do not have viral oncogenes. They integrate near some of the protooncogenes,

activate their expression by proviral insertional mutagenesis, and modulate growth and differentiation of the host cells (27). Retroviruses that carry v-onc genes induce a wide range of malignancies, including sarcomas and hematopoietic cell tumors, in a short period of time (11).

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