

Role of Virus in Oncogenesis – A Systemic Review

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ABSTRACT

Introduction: Viral infection contributes significantly to the global cancer burden. Cancer is a disease that has a molecular basis. The first regulatory factors in this biological process are proto-oncogenes. They act as growth factors by transmitting signals. Changes to these genes, known as oncogenes, result in the appearance of cancer cells. Chromosomal translocation, point mutation, and gene amplification are the activation processes that lead to proto-oncogenes. The path from basic viral infection to tumorigenesis is complicated by factors such as immune complications, cellular mutations, and exposure to other cancerous agents. Hepatitis B virus (HBV), Hepatitis C virus (HCV), Epstein-Barr virus (EBV), Human papillomavirus (HPV), Kaposi's sarcoma herpes virus (KSHV), and Human T lymphotropic virus 1 are the viruses involved in the development of human cancer (HTLV-1).

Materials and Methods: Scientific databases were searched for the literature and relevant articles were selected for review.

Conclusion: This review article summarises knowledge about human oncogenic viruses and the molecular mechanisms that lead to tumorigenesis in humans, cancer hallmarks, host and environmental co-factors that contribute to the biology of multistep oncogenesis mediated by established human oncoviruses, and oncogenic DNA and RNA viruses.

Keywords: Chromosomes, Tumors, Mutations, DNA, RNA, Genetics

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INTRODUCTION

Oncogenesis, the process by which malignant tumours form, is a genetic, cytological, and cellular change. These viruses, which can be either DNA or RNA viruses, do not always cause tumours; other factors such as chronic inflammation, environmental mutagens, and immunosuppression are also involved.

However, changing traditional scientific thinking to accept the involvement of infectious agents in cancer was difficult, owing to the biological processes involved not conforming to Koch's causation dogmatic principles.¹ Because cancer is multifactorial and tumorigenic viruses are generally present in a large portion of the population without causing disease, Koch's original observations about the transmission of acute infectious agents are difficult to apply to cancer. Sir Austin Bradford Hill's epidemiologic causation criteria, which were originally proposed to establish a causal relationship between smoking and lung cancer, are better suited as a foundation for inferring a causal relationship between a viral infection and cancer.²

Viral 'oncoproteins' can activate cellular signalling pathways, alter transcriptional or post-transcriptional expression of cellular genes and microRNAs, and destabilise or inactivate tumour suppressor proteins and proteins that regulate cell polarity, signal transduction, immune response, and apoptosis.³ Oncogenic initiation is caused by viral interactions with the human immune system and ultimately by immune suppression.⁴ The cellular counterparts of v-onc

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genes are proto-oncogenes (c-onc genes). Their roles include cellular growth and development. Proto-oncogenes are cellular counterparts of viral oncogenes that are converted to an oncogenic state by viral oncogenes through mutations, amplifications, deletions, or chromosomal translocations. Oncogenes are constantly battling tumour suppressor genes, which protect DNA and regulate cell activity. Many studies show that tumour suppressor genes lose this battle or that

oncogenes win this battle, resulting in cancer.^{5,6}

Classification of Oncogenes

- Growth Factors
- Growth Factor Receptors
- Signal Transducers
- Transcription Factors
- Others (Apoptosis) And Tumor Suppressor Genes.⁵

Growth Factors: Growth factors are polypeptides that are released and have extracellular signalling properties that promote the growth of target cells. Platelet-derived growth factor (PDGF), a type of growth factor composed of two polypeptide chains, stimulates fibroblast growth.⁵

Growth Factor Receptors: Growth factor receptors are molecular devices that allow information to travel only in one direction from the cell membrane. Growth factor receptors play a role in regulating healthy cell growth. Two examples are the growth factor receptors *ros* (reactive oxygen species) and *trk* (tropomyosin receptor kinase) and they become oncogenes due to mutation and abnormal expression.⁵

Signal Transducers: Mitogenic signals are transmitted from growth factor receptors on the cell surface to the nucleus via the signal transduction path, which is a series of interconnected complex processes. This regulatory information is completed by the gradual phosphorylation of proteins in the cytosol that interact with one another. Signal transducers are classified into two types: Guanosine triphosphate (GTP)-binding proteins Non-receptor protein kinases. There are two types of nonreceptor protein kinases: tyrosine kinases and serine/threonine kinases.⁵

Transcription Factors: Transcription factors are nuclear proteins that regulate the expression of specific genes or families of genes. Regulation is caused by protein binding to specific DNA sequences or DNA structural motifs located above the target genes. Transcription factors can also interact with other proteins to form heterodimeric complexes. These factors bring the signal transducer process to a close, converting extracellular signals into modulated changes in gene expression.⁵

Others (Apoptosis): External stimuli such as steroids and radiation can cause mature cells to die. Uncontrollable cell proliferation and irregularly programmed cell death result in neoplasia and treatment failure, according to cancer cell studies.⁵

Tumor Suppressor Genes: Tumor suppressor genes are anti-oncogene. Their normal functions include cell growth prevention and regulation. When they lose both of their alleles, they generally fail to regulate and prevent cell growth. Recessive mutations in one allele can be passed down from generation to generation.⁷

History of Tumor Virology: The notion that viruses play a role in cancer aetiology stems from research published in 1911 by Peyton Rous, who discovered a filterable agent (Rous sarcoma virus [RSV]) in cell extracts from a chicken tumour. In the 1930's, two tumour viruses were described in mammals, implying that viruses may play a similar causal role in human cancers. Mouse mammary tumour virus (MMTV) is a cancerous agent, or "milk factor," that is transmitted by mothers to young mice in their milk, and mouse leukaemia virus was discovered in

the 1950's. The first human tumour viruses were discovered in the 1960's and 1970's. The first detection of Epstein-Barr virus (EBV) by electron microscopy in cells cultured from Burkitt's lymphoma marked the beginning of human tumour virology. In the 1970's, zur Hausen proposed that HPV played a role in the aetiology of cervical carcinoma, and in the 1980's, HPV16 and HPV18 were found in cervical carcinoma. In the 1990's, epidemiological studies linked "high-risk" HPV infections to cervical carcinoma.

Finally, recent molecular biology advances have resulted in the discovery of two new human oncoviruses. Moritz Kaposi's sarcoma is a rare skin tumour described by Moritz Kaposi in 1872 that rose to prominence in the early 1980s as an AIDS-defining disease caused by KSHV (Kaposi sarcoma associated herpes virus), also known as human herpesvirus 8.⁵

Signalling Pathways Manipulated by Oncogenic Viruses Pi3k-aKt-mTOR Signalling Pathway: The phosphatidylinositol 3-kinase-aKt-mechanistic target of rapamycin (Pi3K-aKt-mTOR) pathway is activated when a diverse group of growth factor receptors are stimulated by various stimuli. Pi3K activation phosphorylates phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 3,4,5-trisphosphate, which activates aKt further. aKt then causes the phosphorylation and activation of a variety of downstream effectors, including mTOR.¹⁷

MAPK Signalling Pathway: Cell surface receptor kinases activate a mitogen-activated protein kinase (MAPK) cascade in response to extracellular signals (for example, growth factors) or stress stimuli (for example, osmotic stress, heat shock, ultraviolet irradiation, and oxidative stress), ultimately regulating the transcription of diverse genes involved in cell cycle progression, growth, differentiation, programmed cell death, and the antiviral immune response. Extracellular signal-regulated kinases (erKs), JUN N-terminal kinases (JNKs), and p38 enzymes are the three best-studied subfamilies of MAPKs.¹⁷

Notch Signalling Pathway: The Notch signalling pathway is found in a wide range of cell types. Notch ligand binding promotes notch receptor proteolysis and translocation of the receptor's intracellular domain to the nucleus, where it activates transcription of downstream genes such as HES1, CCND1, MYC, and BCL2.¹⁷

WNT/B-Catenin Signalling Pathway: WNT ligands activate the frizzled family cell surface receptors in this pathway, preventing -catenin degradation and allowing stabilised -catenin to engage DNA bound transcription factors and stimulate transcription of downstream target genes that control many important biological processes such as cellular proliferation, stem cell renewal, embryonic development, and tissue regeneration. In human skin, for example, WNT ligands released by basal epidermal keratinocytes promote dermal fibroblast proliferation.¹⁷

NF-KB Signalling Pathway: Nuclear factor-B (NF-B), a key transcription factor family, is normally found in the cytoplasm in an inactive form in complex with members of the NF-B inhibitors (iB) family of proteins. Extracellular signals, such as infectious agents, inflammatory cytokines, and other pathogenic insults, stimulate the NF-B signalling pathway, resulting in a cascade of orderly responses culminating in the activation of the iB kinase (iKK) complex. In turn, activated iKK



causes phosphorylation and degradation of I κ B. The NF- κ B that is released can translocate into the nucleus and coordinate the expression of many genes involved in inflammation, immunity, cell death, and proliferation.¹⁷

DNA Damage Response: This signalling network's main components are ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) kinases. The ATM kinase pathway is activated primarily by double-stranded DNA breaks, whereas the ATR kinase pathway is activated primarily by single-stranded breaks. These pathways can also induce senescence or apoptosis, depending on the severity of the damage.¹⁷

Oncogenesis: Oncogenesis is the process of cytological, genetic, and cellular transformation that results in malignant tumours. Viruses promote hematopoietic tumours, sarcomas, and, in rare cases, carcinomas. The discovery of viral oncogenes and the realisation that they are derived from cellular genes known as protooncogenes led to the realisation that c-onc genes play different roles in different types of tumours. Studies of oncogenic retroviruses without v-onc genes, which integrate near the c-onc genes and activate their expression, bolstered assumptions about the roles of c-onc genes in tumour formation. The protooncogene c-myc has been found in some avian retroviruses (MC29, OK-10, and MH2). It is activated through insertional mutagenesis in lymphomas induced by avian leukaemia virus (ALV), Moloney murine leukaemia virus (Mo-MLV), and other viruses lacking v-onc genes. This gene is also activated by chromosomal translocation and mutation in Burkitt's lymphoma, a non-retroviral human tumor.⁵

Mechanisms of Oncogene Activation: The activation of oncogenes requires genetic changes in cellular proto-oncogenes: Oncogenes are activated by 3 genetic mechanisms:

- Mutation
- Gene amplification
- Chromosome rearrangements.⁸

Direct Stimulation of Growth: Aside from their traditional roles in viral entry, some surface (SU) proteins can bind to growth factor receptors on the cell surface and stimulate growth by mimicking normal ligand receptor interaction. This interaction extends to the appropriate target pool and stimulates viral replication in three ways: first, the interaction of SU protein with a surface receptor that stimulates growth can make cells susceptible to infection, and retroviruses can infect the cell; second, growth stimulation can increase the number of appropriate target cells; and third, an increase in the number of infected cells increases the amount of viral replication.⁸

Role of the Long Terminal Repeat in Oncogenesis: The role of the long terminal repeat (LTR) in oncogenesis modulation was first discovered in experiments that compared LTR sequences from viruses with varying oncogenic potential. These sequences were discovered to be one of the major determinants for distinguishing oncogenic and non-oncogenic ALVs and murine leukaemia viruses through analyses of chimeric viruses (MLVs). LTR sequences also influence the types of tumours.⁸

General Mechanisms of Viral Oncogenes: Cancer development is a complex multistep process involving complex events that transform a normal cell into a cancerous cell. The

majority of human tumour viruses encode oncogenic proteins that specifically target cellular proteins, such as p53 (a tumour suppressor gene that controls cell cycle progression and apoptosis) and retinoblastoma (pRb), which play a significant role in tumour suppression loss, which leads to cancer development. Viral oncogenesis is caused by the presence of viral oncogenes (v-onc), activation of cellular proto-oncogenes, cellular transformations, a disrupted cell cycle, and tumour suppressor inactivation.⁹

CAUSES OF VIRAL ONCOGENESIS

- Presence of viral oncogenes (v-onc)
- Cellular transformations
- Deregulated cell cycle
- Inactivation of tumor suppressors

Presence of Viral Oncogenes (V-ONC): Viral oncogenes are the offspring of cellular proto-oncogenes. Oncogene products include growth factors, growth factor receptors, transcription factors, signal transducers, and apoptosis regulators. Both viral and cellular oncogenes play important roles in cancer development, and cancer can be caused solely by cellular oncogenes.⁴

Cellular Transformations: Tumour viruses incorporate their genetic material into the host cell genome, which is required for cellular transformations, mutations, chromosomal rearrangements, and uncontrollable cell divisions by interfering with the mitogenic signalling pathway and cell cycle processes. DNA viruses directly insert genetic material into the host genome, causing neoplasia, whereas RNA viruses must reverse transcribe RNA to DNA before inserting into the host genome. Thus, the major cause of host cellular transformation is disrupted regulation of cellular metabolism due to insertion of viral genome into the host cellular genome.¹⁰

Cell Cycle Deregulation: Cell cycle regulates accurate DNA replication and chromosomal segregation. Cyclins, cyclin-dependent kinases (CDKs), and their inhibitors regulate cell cycle and homeostasis mechanism. Apoptosis is a regulatory procedure for the homeostatic balance of human body and its deregulation leads to unlimited proliferation of transformed cells. It is noted that molecular alterations of host genome by oncoviruses lead to deregulated apoptotic processes and disrupted homeostasis. Viruses have evolved many strategies to overcome the regulatory system of cell cycle leading to continuous proliferation of the infected cells. Viral oncogenes increase or decrease the effects of specific cell cycle regulatory proteins and arrest the mutated cells in the synthetic phase of cell cycle that leads to the induction of transcriptional phosphorylation and DNA replication.¹¹

Inactivation of Tumor Suppressors: Tumor suppressor genes protect the cells from malignant transformations by instructing the cells to prevent cell growth and division. Viral oncoproteins interfere with tumor suppressor genes function causing deregulated cell growth and uncontrolled cell proliferation. The p53 plays a major role in eliminating or inhibiting abnormal cell proliferation. Hepatitis B (HBV)-encoded hepatitis B X-antigen (HBx) oncoprotein inactivates p53 and blocks p53-mediated apoptosis. Hepatitis C (HCV) containing nonstructural protein 5A (NS5A) interferes with the DNA binding activity of p53. The pRb is a negative regulatory protein of cell cycle. The E7



oncoprotein of human papilloma virus (HPV) interferes with its binding to E2F transcription factor. Thus E7 causes several biological effects like increased transcription, autophagy, and inhibition of interferon signalling. Cancer-causing viruses have got a significant role in the advancement of research related to cancer biology.¹²

Oncogenic Mechanisms of Some Major DNA and RNA viruses

DNA Oncoviruses and their Targets: DNA tumor-generating viruses include EBV, HPV, Kaposi's sarcoma herpes virus (KSHV), HBV, and MCV. These oncogenic viruses act in two ways; in permissive cells, viral replication causes cell lysis and death, while in nonpermissive cells, viral DNA is integrated into the host genome. The integrated DNA encodes binding proteins to arrest normal cell growth by acting on regulatory proteins; p53 and pRb. Cellular proteins p53 and pRb are the central targets of oncogenic viruses. Thus, the host cell is transformed to express proteins that facilitate both viral and cellular DNA synthesis.¹⁴ Tumor necrosis-associated factors (TRAFs) and Nuclear Factor kappa-light-chain enhancer of activated B cells (NK-kB) are the main target factors for viral oncogenes. Hypophosphorylated Rb negatively regulates G1 phase of cell cycle to S phase (synthesis phase) and further blocks the E2F activity (transcriptional factor of eukaryotes), a transcriptional factor that is involved in DNA replication.¹⁵ Viral oncoproteins bind specifically to Rb and inactivate its hypophosphorylated form leading to the production of free E2 that further causes uncontrolled proliferation of transformed cells.¹³

RNA Oncoviruses and Their Targets: Among RNA viruses, HCV and HTLV-1 are linked to human cancers. Both viruses use distinct oncogenic mechanisms. Overproduction of oncogenic materials stimulates cellular proliferation in some cases, while viruses integrate their genomes near cellular growth stimulating genes to initiate cellular transformations in others. Tax protein, found in some RNA viruses, activates the expression of cellular genes. Taxation promotes malignant transformations by disrupting the host cell cycle and causing uncontrollable divisions. HTLV basic leucine zipper protein (HBZ) stimulates cell proliferation while inhibiting Tax-mediated transactivation. The host cellular targets for RNA viruses are MHC-1, STAT-5 (signal transducer and activator of transcription), and hTERT (human telomerase reverse transcriptase).¹⁶

CONCLUSION

Onco-viruses are responsible for approximately 20% of all human cancers, according to history. Viruses are regarded as a primary source of cancer growth and must not be overlooked; otherwise, progress in cancer treatment would be impossible. There are viruses that are suspected of causing cancer in humans, but there is insufficient data to reach a consensus on their etiological role in cancer development. There is a need to develop preventive measures, vaccines, and drugs to combat viruses. Oncogenic mechanisms of some major viruses

have been well described. Oncoviruses act in different ways depending upon the factors of host. Some small genomic viruses act by integrating in the host cell genome and causing mutations in it. Some retroviruses activate the expressions of proto-oncogenes inducing several different malignancies. Viruses are considered a primary source of cancer growth and must not be ignored; otherwise, advancement in proper treatment against cancers would be no more possible. There are viruses that are addressed to be cancer causing for humans, but still there is no sufficient data to create a consensus regarding their etiological role in cancer development. Further studies on the viral oncogenic mechanisms on the basis of their cellular and molecular roles may be helpful in designing effective cancer therapeutics.

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