

## VIRUSES AND CANCER – AN OVERVIEW

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### ABSTRACT

Viruses were initially seen as unusual agents that caused cancer in animals but were of no relevance to humans. They are now accepted as bonafide aetiologic factors of human cancers. Carcinogenesis is a multistep process and in virally associated human cancers, the viruses appear to be necessary but are not sufficient for tumour development. Viruses possess genes with potential to modulate host responses and through this means, they evade detection and recognition by the immune system. The mechanism of transformation of a normal cell into a neoplastic cell can either be direct or indirect. Better understanding of the role of viruses in human cancer will have therapeutic implication as control can be instituted.

### INTRODUCTION

Viruses are now accepted as bonafide aetiologic factors of human cancer.(1) Cancer is seen as accidental side effect of viral replication strategies as the tumour viruses establish long term persistent infections in humans.(1)

The viruses were initially seen as unusual agents that caused cancer in animals but were of no particular relevance to humans.(1) They have however revealed the functional foundations of the genetic basis of cancer and have provided a conceptual framework applicable not only to cancer induced viruses.(1) It is estimated that 15% of all human tumours worldwide are caused by viruses.(2) The percentage of virus-

related cancers is approximately 3 fold higher in developing countries than in developed countries.(1)

Some viruses are associated with a single tumour type e.g. hepatitis B virus (HBV) while others e.g. Epstein Barr virus (EBV), are associated with multiple tumour types.(1)

A tumour-causing virus may produce non-neoplastic disease in some hosts.(3) For example, EBV causes infectious mononucleosis in some young adults undergoing primary infection, while human papillomaviruses (HPV) cause a variety of benign hyperplasia and both HBV and hepatitis C virus (HCV) cause hepatitis This article seeks to review the molecular relationship between viruses and human cancers

## **CARCINOGENESIS AS A MULTISTEP PROCESS**

Carcinogenesis occurs in a stepwise fashion and a series of discrete complimentary events must occur to convert a normal cell to a cancer cell.(4,5)

In those cancers with viral aetiology, the virus appears to be necessary but not sufficient for tumour development.(1) Additional changes must accumulate to complement those mediated by viral functions, in order to disable the multiple regulatory pathways and checkpoints in normal cells and to allow a cell to be completely transformed.(1)

### **MODULATION OF HOST RESPONSES**

Viruses may contain genes that have the potential to modulate host responses.(6) Different viral strategies exist for evasion of detection and recognition by the immune system.(1) These include (i) restricted expression of viral genes and proteins that makes the infected nearly invisible to the host e.g. EBV in B-cells (ii) infection of sites that are relatively inaccessible to immune responses e.g. JC virus and herpes simplex virus in the central nervous system; HPV in the epidermis (iii) variation in viral antigens that allows escape from antibody and T cell recognition e.g. human immunodeficiency virus (HIV) and influenza virus (iv) downregulation of expression of host MHC class I molecules in infected cells (v) inhibition of antigen processing and MHC class I restricted presentation (vi) infection of essential immune cells .(7-9) Despite these elaborate viral evasion mechanisms, the immune system usually prevails e.g. prevalence of HPV may be as high as 50% among young women, but declines with age.(10,11)

Genetic alterations in p53 gene are now recognized as the most common mutations in human cancers, occurring in over 50% of all tumours.(12,13) Cellular endonucleases induced as part of the apoptotic response to damage inflicted by viral infections could degrade replicating viral DNA and block virus replication.(14) Therefore, some viruses are known to encode proteins which suppress or delay apoptosis long

enough to allow for production of progeny virus.(14) For example, adenovirus E1B-19K protein, which is functionally similar to the Bcl-2 family of cellular proteins, blocks p53-dependent apoptosis.(15)

## **CANCERS ASSOCIATED WITH VIRUSES**

Viruses are associated with a variety of types of human malignancies. HBV and HCV cause hepatocellular carcinoma.(16,17) EBV is linked to Burkitt lymphoma, nasopharyngeal carcinoma, post-transplant lymphoma and Hodgkin disease.(18-20) HPV causes cervical cancer, skin cancers in patients with epidermodysplasia verruciformis and possibly head and neck cancers and other anogenital cancers.(10,11,21,22) Human T-lymphocyte virus-1(HTLV-1) induces adult T-cell leukaemia.(3,23) Human herpesvirus-8 (HHV-8), otherwise known as Kaposi sarcoma herpesvirus (KSHV) is related to Kaposi sarcoma and primary effusion lymphoma.(24,25) Simian virus 40 (SV 40) is associated with brain tumours, osteosarcomas and mesotheliomas.(26,27)

## **MECHANISMS OF TRANSFORMATION**

Human tumours display different mechanisms of cell transformation and fall into both direct- and indirect-acting categories.(1) The direct-acting viruses carry 1 or more viral oncogenes, whereas the indirect acting agents do not possess an oncogene.(1)

## **HUMAN PAPILLOMAVIRUS**

DNA sequence of HPV 16 and 18 and less commonly HPV 31, 33, 35 and 51 are found in approximately 85% of invasive squamous cell cancers and their precursors.(28) The HPV viral DNA is usually integrated in to the host genome in cancer, suggesting that integration of viral DNA is important in malignant transformation.(28) The papillomaviruses encode E6 protein, E7 protein and an early protein designated E5.(1) In HPV-induced tumours, p53 mutations are extremely

uncommon, presumably because loss of p53 function is accomplished by binding to the E6 oncoprotein.(28) The E6 oncoprotein also mediates the degradation of BAX, a proapoptotic member of the BCL-2 and it inactivates telomerase.(28) The E7 protein binds to the retinoblastoma (Rb) protein and displaces the E2F transcription factors that are normally sequestered by Rb protein.(28) E7 oncoprotein also inactivates the Cyclin Dependent Kinases Inhibitors (CDKIs) CDKNI A/p2 and p27. The E5 protein complexes with Platelet Derived Growth Factor (PDGF)  $\beta$ -receptor and activates it in a ligand-independent fashion to mediate a sustained mitogenic signal.(28)

### **EPSTEIN BARR VIRUS**

EBV is another direct-acting tumour virus that encode a viral oncoprotein LMP-1 that resembles a cell surface receptor.(1) LMP-1 mimics an activated growth factor receptor and mediates its proliferative signals.(29) It binds to and activate a signalling molecule that is normally activated by the CD 40 receptor in B cell, which is the key recipient of helper T-cell signals.(30) LMP-1 activates NFkB and JAK/STAT signalling pathways and promotes B-cell survival and proliferation, thus efficiently co-opting a normal B-cell activation in order to increase the number of cells the virus can infect and inhabit.(31) Several of the EBV-encoded Nuclear Antigens (EBNAs) are necessary for immortalization of B-cells.(32) EBNA-1 expressed consistently in Burkitt lymphoma has been shown to be oncogenic in transgenic mice.(32) EBNA-2 gene transactivates several host genes, including cyclin D and members of the src family, thereby promoting the transition of resting B-cells from  $G_0$  to  $G_1$ .(33) EBNA-2 also activates the transcription of LMP-1 and is a key regulator of viral gene expression.(3)

(1)

(2)

### **HEPATITIS B VIRUS**

Despite compelling epidemiologic and experimental evidence, the precise role of HBV in the causation of human liver cancer is not clear.(3) It is likely that the effect of HBV is indirect and possibly multifactorial.(34) Chronic liver injury secondary to persistent viral infections leads to necrosis, inflammation and liver regeneration which over time results in cirrhosis, with hepatocellular carcinoma arising out of this background.(35) HBV transactivator protein, the x-protein (HBx) contributes indirectly to liver carcinogenesis by activating the Ras-Raf-mitogen-activated protein kinase signalling cascade.(36) HBx can also bind to p53 and it appears to interfere with its growth-suppressing activities.(37-40)

### **HEPATITIS C VIRUS**

HCV does not carry a classical oncogene but it has been reported that viral non-structural protein NS3 can transform NIH 3T3 and can bind p53.(41-42)

### **HUMAN T-LYMPHOCYTE VIRUS-1**

HTLV-1 is the only retrovirus accepted as having an aetiologic role in a specific human cancer and it appears to act indirectly in the development of acute T-cell leukaemia.(1) Similar to the AIDS virus, HTLV-1 has tropism for CD 4+ T-cells and hence this subset of T-cells is the major target for neoplastic transformation.(28) It seems the secrets of the transforming activity of the HTLV-1 are found in the TAX gene.(43) The product of the TAX gene can activate the transcription of several host cell genes involved in proliferation and differentiation of T-cells, including c-fos, genes encoding interleukin-2 (IL-2) and its receptor and GM-CSF.(43) TAX protein also dysregulate the cell cycle by inactivating the cell cycle inhibitor p16INK4a and enhancing cyclin D activation.(43) TAX also contributes to malignant

transformation by interfering with DNA repair functions and inhibiting ATM-mediated cell cycle checkpoints activated by DNA damage.(44)

### HUMAN IMMUNODEFICIENCY VIRUS

The role of HIV in carcinogenesis is probably even more indirect.(45) Immunosuppression to HIV infection predisposes those individuals to certain cancers, especially EBV-positive lymphomas, HHV-8 (KSHV)-positive Kaposi sarcoma and HPV-positive tumours.(1) A more direct role of HIV in the genesis of Kaposi sarcoma has been proposed, involving a cellular growth-promoting effect by the HIV tat protein.(46)

### HUMAN HERPESVIRUS TYPE 8

The HHV-8 (KSHV) genome possesses a number of cellular regulatory gene homologues, including genes related to chemokines, cellular proliferation factors, intercellular signalling components and inhibitors of apoptosis.(24, 25, 47)

### CONCLUSION

The role of viruses in the spontaneous and experimental induction of cancer is well established. The study of the role of these viruses has historically provided an appropriate background for understanding the role of oncogenes in carcinogenesis. The number of human cancers associated with viral infections is limited. Better understanding of the role of these viruses in the causation human cancer will have therapeutic implication as control can be instituted.

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