

ONCOGENIC DNA AND RNA VIRUSES CAUSING THE CANCER PATHOGENESIS

Govind Pandey^{1*} and Madhuri S.²

¹Ex-Professor / Principal Scientist & Head of Pharmacology (Pharmacy); presently, Officer-In-Charge of Rinder Pest (Animal Husbandry Department, Govt. of MP), Jabalpur Division, Jabalpur, MP, India.

²Department of Zoology, Govt. MH College of Home Science & Science for Women, Jabalpur, MP, India.

*Corresponding author's E-mail: drgovindpandey@rediffmail.com

Received on: 04-10-2010; Finalized on: 20-12-2010.

ABSTRACT

The present paper explore out the better-characterized and most intensively studied oncogenic viruses of humans and animals. Many DNA and RNA viruses have been proved to be oncogenic (or carcinogenic) in a variety of animals, ranging from amphibia to primates, and evidence grows stronger that certain forms of human cancer are of viral origin. Several DNA viruses have been associated with the causation of cancer in animals. Adenoviruses cause tumours in laboratory animals, while bovine papillomaviruses cause both types of tumours (neoplasm), i.e., benign neoplasm as well as malignant neoplasm (cancer) in their hosts. Of the various human DNA viruses, human papillomaviruses (HPV), Hepatitis B virus (HBV), Epstein-Barr virus (EBV) and Kaposi sarcoma herpes virus have been reported to cause cancer in humans. The human 'T' cell leukemia virus type 1 (HTLV1) and Hepatitis C virus (HCV) of RNA type are also reported to cause cancer. HPV have been implicated in the development of many cancers, e.g., squamous cell carcinoma of cervix, oral cancer and laryngeal cancer. Bovine papillomavirus (BPV) is known to cause epithelial and mucosal tumours in cattle. HBV and HCB viruses may be the primary cause of hepatocellular carcinoma (HCC). EBV (a member of herpes family) has been reported to cause lymphomas and nasopharyngeal carcinomas.

Keywords: Cancer, Humans and animals, Oncogenic (or carcinogenic) DNA and RNA viruses.

INTRODUCTION

Cancer is an abnormal growth and proliferation of cells. It is a frightful disease which is uncontrollable and incurable, and may occur at any time at any age in any part of the body. Cancer is caused by a complex, poorly understood interplay of genetic and several environmental factors. It represents the largest cause of mortality in the world and claims over 6 millions. Many studies showed that several environmental factors, including air, water and industrial pollutants, environmental chemicals and radiations, etc. may cause various cancers¹⁻². The environmental factors may also be different microbes, including viruses. Many DNA and RNA viruses have been proved to be oncogenic in a variety of animals, ranging from amphibia to primates, and evidence shows that certain human cancers are of viral origin. Hence, considering the virus as one of the important aetiological agents of cancer, this review has been presented to discuss some better-characterized and most intensively studied oncogenic DNA and RNA viruses.

EBV, a herpes virus, was discovered from a Burkitt lymphoma cell line in 1963³. It was the first virus identified from a human neoplastic cell, followed by HPV, HBV, HCV, HTLV1 and human herpes type 8 (HHV8)⁴. The RNA and DNA oncogenic viruses have made fundamental contributions to the areas of cancer research. Transforming retroviruses carry oncogenes derived from cellular genes that are involved in mitogenic signalling and growth control. Viruses are now accepted as bonafide aetiologic factors of human cancer; these include HBV, EBV, HPV, HTLV1 and HCV, and several

candidate human cancer viruses. It has been estimated that 15% of all human tumours (or neoplasms, cancers) worldwide are caused by viruses. The infectious nature of viruses distinguishes them from all other cancer-causing factors; cancer viruses establish long-term persistent infections in humans, with cancer an accidental side effect of viral replication strategies. Viruses are usually not complete carcinogens, and the known human cancer viruses display different roles in transformation. Many years may pass between initial infection and tumour appearance, and most infected individuals do not develop cancer, although immunocompromised individuals are at elevated risk of viral-associated cancers⁵.

The genomes of oncogenic DNA viruses integrate into and form stable associations with host cell genome. The virus is unstable to complete its replicative cycle because the viral genes essential for completion of replication are interrupted during integration of viral DNA. Thus, the virus can remain in a latent state for years. Those viral genes that are transcribed early in the viral life cycle (early genes) are important for transformation, and are expressed in transformed cells⁶. The 'T' antigen proteins encoded by DNA tumour virus early genes are involved in the transformation of normal cells to immortalized neoplastic cells that may or may not be tumorigenic in immunocompetent animals. Studies have been made of the tumorigenicity of DNA virus-transformed cells and the interactions of these cells *in vivo* and *in vitro* with immunologically nonspecific host effector cells such as natural killer (NK) cells and macrophages. The results imply that the 'T' proteins determine the capacity of



transformed cells to induce tumours by governing the level of susceptibility that transformed cells express to destruction by such host cellular defenses⁷. An *in vitro* system to study the carcinogen-induced amplification in simian virus 40 (SV40)-transformed Chinese hamster (CO60) cells has been described⁸. DNA amplification of helper-dependent parvovirus AAV (adeno-associated virus) can be induced by a variety of genotoxic agents in the absence of co-infecting helper virus. The results, including electron microscopic examination, suggest that the AAV origin / terminal repeat structure is recognized by the cellular DNA replicative machinery induced or modulated by carcinogen treatment in the absence of parvoviral gene products⁹.

Some scientific reports on oncogenic DNA viruses

Several DNA viruses have been associated with the causation of cancer in humans and animals. Adenoviruses can cause tumours in laboratory animals, while BPV cause benign as well as malignant neoplasms in their hosts⁶. BPV has been reported¹⁰ to cause epithelial and mucosal tumours in cattle. Followings are the important oncogenic DNA viruses:

1. Human Papilloma Viruses (HPV)

The HPV are small DNA tumour viruses, belonging to the family of Papovaviridae. About 70 genetically distinct types of HPV have been identified. HPV have been implicated in the development of many cancers, e.g., squamous cell carcinoma of cervix, oral cancer and laryngeal cancer⁶. The incidence of cervical carcinoma worldwide is estimated as high as 400,000 diagnosed per year. More than 90% of high-grade cervical dysplasias and invasive cervical cancers have been associated with 10 to 15 high-risk HPV viral types¹¹. Epidemiologic studies

suggest that carcinoma of cervix is caused by a sexually transmitted agent and HPV is the culprit. DNA sequences of HPV 16 and 18 and less commonly, HPV 31, 33, 35 and 51 are found in about 85% of invasive squamous cell cancers. In cancer, the viral DNA is usually integrated into the host cell genome. The oncogenic potential of HPV 16 and 18 can be related to viral E6 and E7 early viral gene products, which act in conjunction to immortalize and transform cells¹². The replication of DNA viruses is dependent on the replication machinery of the host cells, and E6 and E7 act to overcome the activity of cell cycle inhibitors. E6 and E7 enhance p53 degradation, causing a block in apoptosis and decreased activity of p21 cell cycle inhibitor. E7 associates with p21 and prevents its inhibition of the cyclin D/CDK4 complex; E7 can bind to RB, removing cell cycle restriction. The net effect of HPV E6 and E7 proteins is to block apoptosis and remove the restraints to cell proliferation (Figure 1)^{6,13}.

Figure 1: Effect of Human Papilloma Virus (HPV) proteins E6 and E7 on the cell cycle

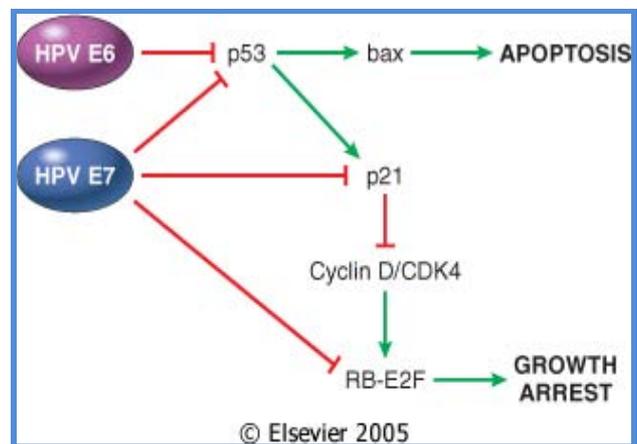
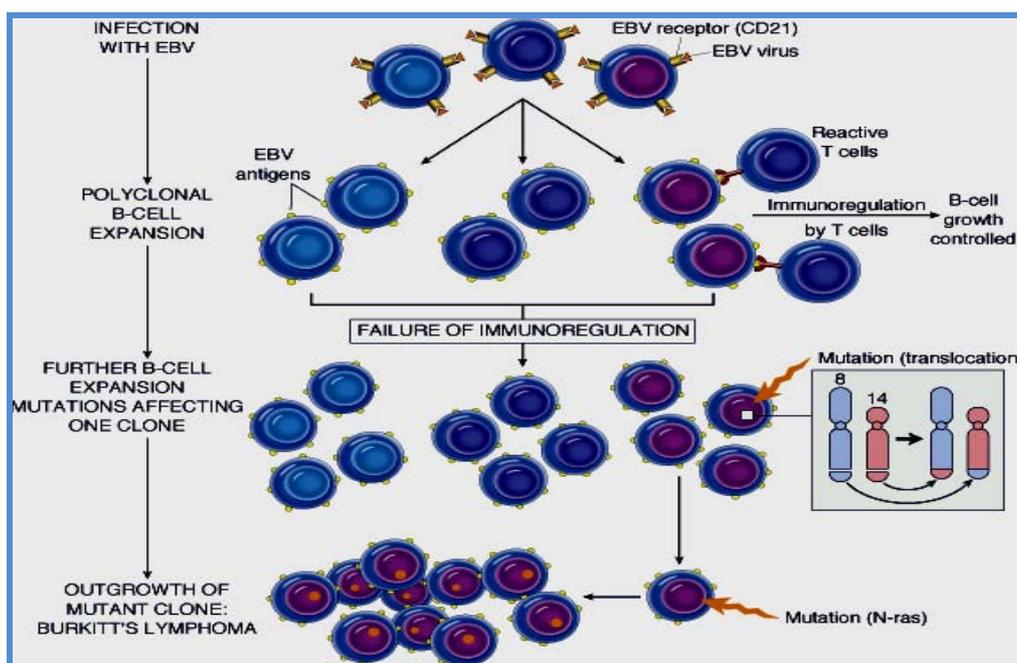


Figure 2: Epstein-Barr Virus (EBV) in the development of Burkitt lymphoma



2. Epstein-Barr Virus (EBV)

The EBV, a member of herpes family, has been found to cause the pathogenesis of four types of human tumours, i.e., the African form of Burkitt lymphoma, B cell lymphoma in immunosuppressed individuals, some cases of Hodgkins's lymphoma and nasopharyngeal carcinomas¹⁴. EBV infects epithelial cells oropharynx and B lymphocytes. Within B lymphocytes, the linear genome of EBV circularizes to form an episome in the cell nucleus. The infection of B cell latent, i.e., there is no replicaion of virus and the cells are not killed, but the latently infected B cells are immortalized and acquire the ability to propagate indefinitely in vitro. The molecular basis of B cell immortalization by EBV is complex. It appears that EBV serves as one factor in the multistep development of Burkitt lymphoma (Figure 2). Subsequent studies have demonstrated two important facts in EBV-associated malignant neoplasms. First, more than 90% of the world population is infected with EBV before adolescence, but EBV-associated malignant neoplasms develop in a limited number of patients in an endemic or non-endemic manner. Secondly, EBV is associated with the transformation of various types of cells such as lymphoid, dendritic, smooth muscle and epithelial cells. EBV-associated gastric carcinoma (GC) is the monoclonal growth of EBV-infected epithelial cells. EBV-associated GC is distributed worldwide and more than 90,000 patients are estimated to develop GC annually in association with EBV (10% of total GC). It occurs in two forms in terms of the histological features, i.e., lymphoepithelioma-like GC and ordinary type of GC. Both share characteristic clinicopathological features such as the preferential occurrence as multiple cancer and remnant stomach cancer. EBV-associated GC shows gastric cell phenotype, resistance to apoptosis, and the production of immunomodulator molecules⁴.

3. Hepatitis B Virus (HBV)

The HBV is a small enveloped DNA virus which primarily infects hepatocytes and causes acute and persistent liver disease. Chronic HBV infection is a major risk factor for the development of HCC. The HBV is endemic in countries of the Far East and Africa; these areas have the highest incidence of HCC. Studies in experimental animals also support a role for HBV in the development of liver cancer. In virtually all cases of HBV-related liver cell cancer, the viral DNA is integrated in to the host cell genome, and as with HPV, the tumours are clonal with respect to these insertions⁶. The role of HBV in carcinogenesis appears to be complex, and may involve both direct and indirect mechanisms. Chronic liver inflammation and hepatic regeneration induced by cellular immune responses may favour the accumulation of genetic alterations. Also that the HBV DNA may disrupt or promote the expression of cellular genes, which are important in cell growth and differentiation. Recent genetic studies have provided insight into the mechanisms underlying viral associated hepatocarcinogenesis, showing that the rate of chromosomal alterations is significantly increased in HBV-

related tumours compared with tumours associated with other risk factors. HBV might, therefore, play a role in enhancing genomic instability. These data also suggest that the chronic HBV infection triggers oncogenic pathways, thus playing a role beyond stimulation of host immune responses and chronic necroinflammatory liver disease¹⁵. Persistence of high HBV DNA concentration suggested an increased risk of carcinogenesis⁶.

Some scientific reports on oncogenic RNA viruses

The RNA viruses have also been found to cause various cancers, some of which are as under:

1. Hepatitis C Virus (HCV)

The HCV is an emerging infection in India which causes liver disease. This is a RNA virus that belongs to the Flaviviridae family and genus hepacivirus¹⁶. HCV is also strongly linked to the pathogenesis of HCC. The role of this virus seems to be related to its ability to cause chronic liver cell injury and inflammation that is accompanied by liver regeneration. Mitotically active hepatocytes, surrounded by an altered environment, are prone to genetic instability and cancer development⁵. Few studies from India have also corroborated the association between HCV and HCC; the earliest report from Delhi noted that 15% of patient with HCC were positive for antibody to HCV¹⁷.

2. Human T-Cell Leukemia Virus Type 1 (HTLV1)

Only one human retrovirus, HTLV1 is firmly implicated in the causation of cancer. HTLV1 is associated with a form of 'T' cell leukemia / lymphoma that is endemic in certain parts of Japan and the Caribbean basin, but is found sporadically elsewhere, including the United States. Similar to the AIDS virus, infection of HTLV1 in human requires transformation of infected 'T' cells via sexual intercourse, blood products or breast-feeding. Leukemia develops in only 3-5% of the infected individuals after a long latent period of 40-60 years⁶.

REFERENCES

1. Pandey Govind, Madhuri S. Global scenario of radiation in cancer risk: A review. *Int J Pharmaceu Biol Arch* 1(3):2010,195-198.
2. Madhuri S. Studies on oestrogen induced uterine and ovarian carcinogenesis and effect of ProlImmu in rats. PhD thesis, Rani Durgavati Vishwa Vidyalyaya, Jabalpur, MP, India: 2008.
3. Epstein MA. Reflections on Epstein-Barr virus: some recently resolved old uncertainties. *J Infect* 43:2001,111-115.
4. Uozaki H, Fukayama M. Epstein-Barr Virus and gastric carcinoma- Viral carcinogenesis through epigenetic mechanisms. *Int J Clin Exp Pathol* 1:2008,198-216.



5. Butel JS. Viral carcinogenesis: revelation of molecular mechanisms and etiology of human disease. *Carcinogenesis* 21(3):2000,405-426.
6. Kumar V, Abbas AK, Fausto N. Neoplasia. In: *Pathologic Basis of Disease*, 7th Edn. Saunders, Elsevier India Pvt Ltd, New Delhi: 2006, p. 269-342.
7. Lewis AM Jr, Cook JL. A new role for DNA virus early proteins in viral carcinogenesis. *Science* 227(4682):1985,15-20.
8. Berko-Flint Y, Karby S, Hassin D, Lavi S. Carcinogen-induced DNA amplification in vitro: Overreplication of the simian virus 40 origin region in extracts from carcinogen-treated CO60 cells. *Mol Cell Biol* 10(1):1990,75-83.
9. Yalkinoglu AO, Zentgraf H, Hubscher U. Origin of adeno-associated virus DNA replication is a target of carcinogen-inducible DNA amplification. *J Virol* 65(6):1991,3175-3184.
10. Campo MS. Bovine papillomavirus and cancer. *Vet J* 154(3):1997,175.
11. Steigme CK. The HPV DNA virus hybrid capture assay: What is it--and where do we go from here? (Cover Story). *Medical Laboratory Observer, AllBusiness.com*: 2003.
12. Munger K. Disruption of oncogene / tumour suppressor networks during human carcinogenesis. *Cancer Invest* 20:2002,71.
13. Helt AM, Galloway DA. Mechanism by which DNA tumour virus oncoproteins target the Rb family of pocket proteins. *Carcinogenesis* 24:2003,159.
14. Dolcetti R, Masucci MG. Epstein-Barr Virus: Induction and control of cell transformation. *J Cell Physiol* 196:2003,207.
15. Cougot D, Buendia M, Neuveut C. Carcinogenesis induced by Hepatitis B virus. *Human Cancer Viruses* 1:2008,108-136.
16. Mukhopadhyaya A. Hepatitis C in India. *Journal of Biosciences* 33(4):2008,465-473.
17. Ramesh RMA, Panda SK. Prevalence of Hepatitis C virus antibodies in chronic liver diseases and hepatocellular carcinoma patients in India. *J Gastroenterol Hepatol* 7:1992,393-395.

About Corresponding Author: Dr. Govind Pandey



Dr. Govind Pandey, PhD Hons. (Pharmacology) with more than 30 years of experience is enriched with multifarious personality. He is an able academician, educationalist, scientist, researcher, teacher, administrative officer, advisor, social worker, a Hindi literalist and eloquent speaker endowed with strong writing flair. He is probably the 'First Person in MP' and 'First Veterinarian in India' with maximum academic qualifications (about 20 degrees/diplomas/ certificates). His 'Biography' has been included in one of the world's famous books, 'Who's Who in the World' published from America. He has been Professor/Principal Scientist & Head of Pharmacology (Pharmacy). He has published more than 175 scientific papers and received 29 'Awards/Honours/Recognitions /Fellowships' (including 5 'Awards', etc. in Hindi literature). Dr. Pandey has also published 5 books in Hindi literature.