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Oncogenesis: The Role of Virus

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Review Article

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Abstract: Oncogenesis is a very complex and multistep process with many factors involved. Among the various cancers viral oncogenesis constitutes about 12%. The human population has been plaqued by viruses particularly viruses with oncogenic potential. Worldwide, viruses cause numerous miseries ranging from flu to complex cancers. A noteworthy few among them are caused by oncoviruses such as Human papilloma virus, Hepatitis B, Hepatitis C, HTLV-1, EBV. Among these viruses Human papilloma virus and Human T Lymphocyte virus have direct oncogenic potential whereas HIV, EBV, Hepatitis B and Hepatitis C have indirect oncogenic potential. In this review, we aim to discuss briefly about the pathogenesis of the most commonly 6 occuring oncoviruses and their oncogenic potential.

Keywords: Viral Oncogenesis; HIV; HTLV; EBV; HPV; HEPATITIS B; HEPATITIS C.

INTRODUCTION

Viruses are the main cause of the development of several human cancers. Viral oncogenesis is a multistep process, only a small percentage of the infected individuals develop cancer often taking many years to decades for forming a full blown event after initial infection which reflects host genetic variability and the fact that viruses contribute to only a portion of the oncogenic events [1]. Virus Pathogenic mechanisms include entry of the virus at a body site (the portal of entry), replication at that site, and then spread to and multiplication within sites (target organs) where disease or shedding of virus into the environment occurs [2].

To cause disease, the infecting virus must be able to overcome physical barriers, distance, host defenses, and differing cellular susceptibilities to infection. Viruses rely on the host cell for these functions as they cannot synthesize their genetic and structural components. The virus replication robs the host cell of energy and macromolecular components, and therefore severely impairing the function and often resulting in cell death and disease. Approximately 12% of human cancers worldwide are caused by oncovirus infection with more than 80% of cases occurring in the developing world [1]. Oncoviruses are rarely fully oncogenic and appears to be necessary but not sufficient to cause cancer. This review aims to project the oncogenic potential of various viruses especially in the South East Asian region in a comprehensive manner.

HUMAN IMMUNO DEFICIENCY VIRUS (HIV)

HIV is a single stranded RNA virus which causes Acquired immunodeficiency syndrome (AIDS). The infection leads to depletion of CD4+ T cells and immunosupression leading to oppourtunistic infection, secondary neoplasm and neurological manifestations [5]. 95% of HIV infections are in developing countries such as Africa, Thailand, India, and Indonesia with an estimated 5 millon infections each year. Sexual transmission, parenteral and mother-to- infant transmission are major routes of HIV infection [5].

The entry of HIV into cell require CD4 molecule, which acts as high affinity receptor for virus. The virus binds to CD4 along with HIV envelope Glycoprotein (gp120) must bind to cell surface molecule (CCR4 AND CXCR4) to facilitate cell entry [11]. HIV envelope gp 120 binds initially to CD4 which exposes new site on gp 120 for CXCR4 and CCR5 coreceptors [5]. The transmembrane protein gp 41 undergoes transformational change and get inserted into target membrane facilitating fusion of virus with the cell which leads to entry of HIV genome into the cytoplasm of cell[11]. The HIV strains R5 (macrophage tropic) which uses CCR5 as coreceptor and infects monocytes and T-cells, whereas X4(T cell tropic) uses CXCR4 coreceptor and infects activated T cells[10]. Initially the infection are transmitted by R5 strain but during the course of infection R5 evolve into X4 strain, as a result of gp 120 gene mutation[5]. Viral genome undergoes reverse transcription, leading to formation of

cDNA which remains in episomal form in cytoplasm, in dividing T cells; the cDNA enters the nucleus and gets integrated into host genome.

By 2016, 37 million people were infected with HIV globally, but the infection rate has been reported to be decreased to 1.8 million per year because of increased number of infected people on antiretroviral therapy.

HUMAN T-CELL LEUKEMIA VIRUS-1 (HTLV)

Human T Cell Leukemia virus 1 is a retro virus with a unique potential to be the cause for Leukemia. This virus spreads specifically infects T cells through sexual contacts and through blood products. This infection has been reported predominantly in the East specifically in Japan and other areas such as Caribbean, South and Central America [6]. The infected persons could develop Leukemia after a long latent period of approximately 20 to 50 years.

The extended latency period of HTLV could be the reason behind its multistep process where many mutations subsequently accumulate. The primary factor responsible is a unique area in the genome called pX which encodes a unique gene called TAX. This protein is ideally responsible for tranactivation of cytokines and their receptors (IL-2, IL-2R,IL-15,IL-15R) through NF-κB this pathway occurs through an autocrine signalling loop[5].

The other paracrine signalling system activates granulocyte macrophages colony stimulating factor which also stimulates the neighbouring macrophages to produce the mitogens for T cell [5]. Thus, this multistep process explains the unique potential of HTLV to cause leukemia after a prolonged latency period.

EPSTEIN BARR VIRUS (EBV)

EBV is a main causative agent of B-cell tumors such as burkitt lymphoma and some B-cell lymphomas [9]. This virus is predominantly reported in parts of Africa. EBV uses CD21 JAK/STAT pathways, via B-cell surface molecule CD40 [9]. EBNA-2 encoded gene receptor to attach and infect B cells [5]. EBV has encoded genes such as LMP-1, a primary transforming oncogene which promotes B-cell proliferation by activating NF-κB and transactivates cyclin D and SRC family genes. EBV genome contains vIL-10 cytokine which prevents macrophages and monocytes from activating T-cells and is required for EBV dependent B-cell transformation.

In immunologically normal individuals, the polyclonal B-cell proliferation, is asymptomatic or develops episodes of infectious mononucleosis [5]. LMP-1 is major antigen which is recognized by the immune system. Additional mutation, such as t(8:14), leading to activation of MYC gene, which substitutes LMP-1 signaling and evades immune system. In immunosupressed individuals there is B-cell proliferation with expression of LMP-1 gene producing lymphoblastoid like cells [5].

HUMAN PAPILLOMA VIRUS (HPV)

Human papilloma virus is a epitheliotropic non-enveloped virus with double stranded circular DNA genome, causing infection of skin and mucous membrane [1]. HPV is predominantly reported in western countries [5]. It spreads through sexual contact and infects cervix, vagina, anus, in oral cavity it effects through tonsillar crypts and oro pharynx[4]. High risk HPVs such as16 and 18 have been implicated in genesis of cancer, particularly squamous cell carcinoma of cervix. Low risk HPVs such as 6 and 11 cause low malignant potential genital warts [5].

E6 and E7 are oncogenes of HPV, which interact with growth regulating factor and tumor suppressor gene. The E7 protein promotes cell cycle progression by binding with retinoblastoma (RB) protein and displacing E2F transcription factor, it also inactivates CDKIs and activates cyclins E and A [4]. The degradation of p53 and BAX is mediated by E6 protein, which activates telomerase [5]. The HPV genome in benign warts is in non-integrated form, while in cancers it is randomly integrated in to host genome, resulting in over expression of E6 and E7[5]. Genomic instability is induced by E6 and E7 oncoproteins, thus accelerating the expansion of cells with tumor promoting host cell mutations [1].

The anti HPV vaccine has been proven to give complete protection from HPV causing cervical cancer [5].

HEPATITIS B VIRUS (HBV)

Hepatitis B is a DNA virus causing acute and chronic hepatitis. HBV induced chronic liver disease is important precursor of hepatocellular carcinoma [7]. This virus can survive high temperature. The regions such as; southeast asia, china ,south America have high endemicity with vertical transmission from mother to child as the main mode of transmission, where as in developed countries there is low prevelance of HBV, where virus is transmitted via blood products, dialysis, IV drug abuse and sexual intercourse[5]. Virus can also spread through body secretion such as semen, saliva, sweat, breast milk. The virus has an incubation period of 45- 160 days, followed by a period of acute disease lasting for several weeks.

Translation of C gene in core and precore region produces HBcAg, which is present in infected hepatocyte and HBeAg which is secreted into blood that establish persistent infection [7]. DNA polymerase with reverse transcriptase generates mutant viral genes [5]. HBVx protein can activate signal transduction pathways that contribute to carcinogenesis; it also helps in DNA repair and inhibition of protein degeneration [7]. The

activated immune cells produce mediators that are mutagenic and genotoxic, which activates NF-κB pathway with in hepatocytes blocking apoptosis, allowing dividing hepatocytes to accumulate mutation causing the viral induced hepatocellular carcinoma [1].

The hepatitis vaccine could give protective response in 95% of children and growing adults [5].

HEPATITIS C VIRUS (HCV)

HCV is a single stranded RNA Virus. HCV is the main cause of chronic liver disease in the western world, predominatly in north america, western Europe, central and southeast asia, with worldwide carrier rate of 175 million persons [8]. The incubation period of the virus is 150-160 days leading to acute illness which is mild in nature, which further progress to chronic hepatitis with some developing cirrhosis and hepatocellular carcinoma. The major route of transmission of infection is through blood inoculation. Immunocomprised patients, injectable drugabusers, transplant recipients are at high risk[5].

HCV encodes core gene, NS3 and NS5A genes promote liver cell proliferation via the β-catenin pathway. HCV core and NS3 activate multiple signal transduction pathways promoting cell growth and inactivate multiple tumor suppressor gene. HCV core avoid immune destruction by blocking apoptosis and promotes cyclin E and CDK2 expression [1]. HCV infection triggers innate immunity, but viral proteins block the signalling that triggers interferon beta (IFNβ) as well as IFN alpha signalling by targeting JAK/STAT. NS5A gene binds to cellular signalling molecules suppresses immune responses, tumor suppressors, and apoptosis[1]. Thus resulting in hepatocellular carcinoma.

Prolonged treatment with interferon alpha with combination of antiviral drug have been reported to be useful in some cases[8].

CONCLUSION

Cancer is the consequence of infections with virus which persist and replicate in the host through oncogenic pathways giving the cancer characteristic to infected cell. Environmental and other cofactor such as immunosuppression and genetic predisposition could accelerate the development of cancer. The long incubation period of virus provides an opportunity for prevention and clinical intervention.

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