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DNA Oncogenic Virus Leading To Cancer- A Review

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Abstract

Oral cancers are the sixth most common cancer worldwide. These diseases have high mortality rate and is growing high in the developing countries. Although oral cancers can occur due to alcohol consumption, pan chewing, smokeless tobacco, tobacco chewing etc., viruses like DNA oncogenic and RNA oncogenic viruses (Human Papilloma virus, Human Polyoma virus,SV-40 virus, Epstein Barr virus, Human Herpes virus, Hepatitis virus ets) can also be an etiological agent in causing cancer.

Keywords: Human Papilloma virus, Human Polyoma virus,SV-40 virus, Epstein Barr virus, Human Herpes virus, Hepatitis virus.

Introduction

Oral cancer is a serious and growing problem in many parts of the globe. Oral and pharyngeal cancer together is the sixth most common cancer in the world. The annual estimated incidence is around 2,75,000 for oral and 1,30,300 for pharyngeal cancer excluding nasopharynx, two-thirds of these cases occurring in developing countries.[1] Oral squamous cell carcinoma spreads locally involving perioral structures and metastasizes to local regional lymph nodes. The disfigurement consequential of the disease and treatment is permanent affecting the quality of life. This chronic disease is a public health problem both in developing as well as developed countries. The burden of Oral squamous cell carcinoma is great because of the associated high cost of treatment, permanent impairment and high mortality. The prevalence of oral squamous cell carcinoma is high in Asian countries especially Southeast Asia[2]. Considering all the age groups, men are more affected than women.

Although it has been suggested that habit history like tobacco chewing or alcohol consumption might cause carcinogenesis but it is always not considered to be true. Various chemical or virus carcinogen might cause carcinogenesis. Both DNA and RNA oncogenic virus are involved in causing cancer. DNA oncogenic viruses such as Papavovirus, Herpesvirus, Adenovirus, Poxvirus, Hepadnavirus can cause Squamous Cell Carcinoma, Papillomas, Burkitts Lymphoma, Kaposi Sarcoma, Hepatocellular carcinoma while RNA oncogenic viruses like Acute Transforming virus, Slow Transforming virus, Human T-cell Lymphotropic virus, Hepatitis virus can cause leukemia and sarcomas.[3]

DNA oncogenic virus include

- Various types of Papavovirus are Human Papilloma Virus, Polyoma Virus and SV-40 virus.
- Various types of Herpesvirus are Epstein Barr Virus, Human Herpes Virus 8, Lucke's frog virus.
- Hepadna Virus include Hepatitis B virus.

RNA oncogenic virus include:

Human T-cell Lymphotropic Virus like HTLV1 AND HTLV2.

Brief Note about All Viruses

1. Human Papilloma Virus: Papillomaviruses are members of the papovaviridae family, which also included the vacuolating viruses (SV40) and polyoma viruses. The papillomaviruses are non-enveloped, circular, double‑stranded DNA viruses with a genome of about 8 kb.[1]

Classification

Papillomaviruses are classified according to their host range and the relatedness of their nucleic acids:

- Papillomavirus was first named according to its natural host, e.g. cottontail rabbit (Shope)papillomavirus, bovine papillomavirus, deer papillomavirus, HPV, etc.
- Based on clinical prognosis of their associated lesion they can be: Low‑risk HPVs, which cause benign epithelial hyperplasia, and high‑risk HPVs, e.g. HPV‑16 and ‑18 infected lesions have high propensity for malignant transformation
- According to the International Agency for Research on Cancer:
- Group 1: HPV‑16 and ‑18 as carcinogenic in humans
- Group 2A: HPV 31 and 33 as probably carcinogenic in humans
- Group 2B: Remaining HPVs as possibly Carcinogenic[1]

2. Human Polyoma Virus: Human polyomaviruses were originally grouped in the family Papovaviridae because of their similarity in morphology and genome organization but are now classified in the separate families of Polyomaviridae and Papillomaviridae, respectively.[4]

Classification

Two rare human polyomaviruses were isolated in 1971 and are known as BK virus and JC virus. Infection with BK virus may cause mild respiratory disease, whereas infection with JC virus can affect the respiratory system, the kidneys, or the brain. JC virus is responsible for causing progressive multifocal leukoencephalopathy (PMLE) in immunocompromised people. [4]

3. SV-Virus: It is a kind of polyoma virus and it is present in kidney cell cultures. It is used to prepare both the inactivated and live attenuated vaccine.[5]
4. Epstein Barr Virus: Family: Herpesviridae, Subfamily: Gammaherpesvirinae (EBV); Genus: Lymphocryptovirus (EBV). It is enveloped, icosadeltahedral nucleocapsid symmetry, spherical to pleomorphic particle, 120-220 nm in diameter. Between the capsid and the envelope is an amorphous layer of proteins termed the tegument. The nucleic acid is Linear, double-stranded DNA about 184 kbp in length.The physicochemical properties: Nonionic detergents solubilize the envelope; virus inactivated by standard disinfectants, UV light, and gamma-irradiation; infectivity sensitive to acid pH and high temperatures. The virus is stable at low temperatures, especially at -60°C or below which is inactivated by heat (50-60°C for at least 30 min).

Classification

Two major EBV types have been detected in humans: EBV-1 and EBV-2 (also known as types A and B). EBV-1 and EBV-2 differ in the sequence of the genes that code for the EBV nuclear antigens (EBNA-2, EBNA-3A/3, EBNA-3B/4, and EBNA-3C/6).[6]

5. Hepatitis B virus: HBV, a member of the Hepadnaviridae family, is a small DNA virus with unusual features similar to retroviruses. HBV replicates through an RNA intermediate and can integrate into the host genome. The unique features of the HBV replication cycle confer a distinct ability of the virus to persist in infected cells. It is if 8 typical types.[7]

Carcinogenic Potential

DNA Oncogenic Group I- Papavovirus

a) Human Papilloma Virus : A short brief about mechanism of HPV invading the host cells. HPV enters the host cell by binding to cell surface receptors. The virions bind initially to the basement membrane before entering the basal keratinocyte cell surface. With the help of the receptors HPV undergoes a process known as Internalization and gains entry towards the host cells to invade. Once HPV infects the host tissue, its genome is integrated into the host genome and two products are formed – 'E6 protein' and 'E7 protein' which suppresses the tumor suppressor gene and finally leads to the increase of DNA synthesis.[7] HPV is correlated with Oral Squamous cell carcinoma(OSCC) is as follows- HPV can cause OSCC and it is dependent on many factors whereas some authors state that HPV has no correlation with habits, site of tumor, age and gender while others states that alcohol consumption and tobacco habits have a synergistic effects on causing OSCC.

b) Human Polyoma Virus: A short brief about mechanism of Polyoma Virus invading the host cells. Polyoma virus mostly causes Merkel Cell Carcinoma. Merkel cells are located at the basal layer of the epithelia of the skin and oral mucosa and are in direct contact with the tactile neural discs, to which these cells transmit mechanical information. However, in the epithelium of the mouth, the format and function of these cells increase in complexity and this can be detected by special markers like cytokeratin 20 and CD56. After primary infection, the virus may establish persistent infection in uroepithelial cells, oligodendrocytes and mononuclear cells from the blood.[8] In a great majority of the cases, the infection is asymptomatic, and the virus can be detected in the urine.

c) SV-40 Virus: SV40 DNA has been sporadically detected in human tumors. SV40 has been detected predominantly in samples from mesotheliomas, brain tumors, and osteosarcomas and has been detected most frequently in mesotheliomas, choroid plexus tumors, and ependymomas, although with wide variations.[9]

DNA Oncogenic Group II- Herpesvirus

a) Epstein Barr Virus: The oral cavity is a primary site for transmission and persistence of EBV. EBV disseminates to other anatomical sites, and is found in blood circulating B cells in healthy carriers at a frequency of 1–50 in 10^6 B lymphocytes .EBV is periodically shed in the saliva throughout the lifetime of infected individuals and can be transmitted to naïve individuals . Lifelong carriage of EBV is achieved by the biphasic nature of the viral life cycle. Transmission via the oral cavity targets epithelial cells and naïve B lymphocytes for infection. Lymphoid-rich regions in the oral cavity such as tonsils and adenoids

that constitute Waldeyer's ring juxtapose epithelial and B lymphocytes for efficient entry and egress of the virus. Entry into naïve B lymphocytes and epithelial cells is mediated by engagement of viral glycoproteins on the viral envelope with cellular receptors on the cell's plasma membrane . The virus enters cells by either endocytosis in B lymphocytes or direct fusion of the viral envelope with the plasma membrane of epithelial cells. Inside the virion, the linear EBV genome carries few epigenetic marks being mostly devoid of DNA methylation or histones .Following entry, the virus delivers its linear genome to the nucleus where the genome undergoes a circularization event through recombination of terminal repeats present at the ends of the linear DNA Each circularization event results in a fused terminal repeat fragment that has a unique number of repeats, and is used as a marker for viral clonality .Furthermore, the EBV genome in cells is replicated and maintained as an extrachromosomal episome.[10] EBV virus causes Hodgkin's lymphoma, natural killer/T-cell lymphoma, nasopharyngeal carcinoma (NPC), gastric carcinoma, and oropharyngeal squamous cell carcinoma (OSCC).

b) Human Herpes Virus 8: HHV-8 infection of cells results in one of two discrete viral programs, latency and lytic replication. During latent infection, few viral genes are expressed and the HHV-8 genome is maintained as an episome. The HHV-8 gene products that are expressed in latently infected KS tumor ("spindle") cells. Although spindle cells in KS lesions are predominately (~99%) latently infected with HHV-8, but a proportion undergoes lytic replication and produce virions.[11]

All the other groups of DNA and RNA oncogenic viruses does not have any relevant significant correlations with oral cancer.

Chronicle of cancer immunotheraphy according to Tarro et al,

(a) 1890s - Mixtures of dead bacteria were injected by William B. Coley into cancer patients to stimulate the immune system.

(b) 1909 - According to Paul Ehrlich the immune system may suppress tumor development.

(c) 1960s – Both in animals and men neoplastic cell antigens stimulate the onset of specific humoral and cellular antibodies

(d) 1972 - Immunogenecity of a soluble transplantation antigen from adenovirus 12 - induced tumor cells demostrated in inbred hamsters .

(e) 1975 – Discovery of Monoclonal Antibodies, highly specific immunological tools.

(f) 1980 – Mass-production of interferon, the immune-stimulating molecule, after inserting its coding gene into bacteria. Therapeutic Vaccine Strategies (A) Tumor cells are removed from a patient and treated biochemically or irradiated. Then the extracts of the dead cancer cells are reinjected, boosting the immune system to attack the tumor cell.

(g) 1983 – Tumor liberated protein (TLP) boosts the immune system's cancer responsive capabilities. G.

(h) 1986 – Interferon is approved by the Food and Drug Administration (FDA) for the treatment of hairy cell leukemia.

(i)1991 – TLP may have the potential to greatly improve the cure rate and/or serve as a lung cancer vaccine [14].

(j)1997 – The FDA okays the first monoclonal antibody (MA) treatment against cancer (for non-Hodgkin's lymphoma).

(k) 1998 – The FDA approves the MA Herceptin for the treatment of metastatic breast cancer.

(l) 2002 – National Cancer Institute researchers prove that two kinds of immune cell – CD4+ T cells and CD8+ T cells-are required for the treatment against cancer .

(m) 2002 – Detection of lower levels of TLP/antiTLP may be of clinical relevance (Tarro and Esposito). TLP as candidate marker for the early detection of NSCL cancer . Therapeutic Vaccine Strategies (B). Tumor – associated antigens resulting from protein bits, or from synthesized peptides specific for the cancer tissue, can be used successfully as vaccine to mount a vigorous antitumor attack.

(n) 2009 – Development of a vaccine approach for therapeutical and preventive application . Basic Cellular Immune Response to Cancer. The dendritic cell is an immune cell that presents specific antigens taken from a tumor cell to two other immune cells, the CD4+ and CD8+ cells. The CD4+ cell releases cytokine molecules that help to activate the CD8+ cells, prompting them to attack other cells with the same antigen . Therapeutic Vaccine Strategies (C). The dendritic cells of a cancer patient are removed and loaded with antigens from the tumor . The dendritic cells grow outside the body and then are reinjected, triggering a powerful response by the T cells 2010 – The FDA approves the first therapeutic cancer vaccine for advanced prostate cancer (Provenge).[12]

Anti cancer vaccine ---Tumor liberated protein (TLP), a tumor-associated antigen (complex) first described by Tarro et al., is present in the sera from lung cancer patients mainly at early stage disease. Since early detection clearly improves overall survival in lung cancer, identification of early screening biomarkers for patients at risk for the development of this disease represents an area of intense investigation.

Genetic Markers

1. HPV molecular marker : p21 and pRB[13]
2. Human Polyoma Virus: Cytokeratin 20,56[14]
3. Epstein Barr Virus : CD21 and CD35[15]
4. Human Herpes virus 8: CD31, CD34[16]

Anticaries Vaccine Of Individual Virus

1. HPV: Gardasil is a quadrivalent vaccine against HPV types 6, 11, 16, and 18 and Cervarix is a bivalent vaccine approved for the prevention of cervical cancer and precancerous lesions caused by HPV 16 and 18.[17]
2. EBV: Vaccinia-gp350, Recombinant gp350, EBNA-3A peptide[18]
3. Human Herpes Virus 8: KSHV vaccine[19]

Conclusion

Viruses are the most important etiological agent in causing cancer. Both the DNA and RNA oncogenic virus can lead to carcinoma but the prevalence of DNA oncogenic virus is very high. While diagnosing carcinoma cases, apart from the habits, virus also has become as an important aetiopathogenesis. Certain vaccines, radiotherapy are also available in treating viral oncogenesis. Moreover, among all the viruses discussed so far HPV virus has the maximum carcinogenic potential. Minute traces occurs in RNA oncogenic viruses according to Pandey et al.

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