

Viruses in Oral Squamous Cell Carcinoma : A Review

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Abstract:

Oral cancers are one of the most commonly occurring neoplasm in the world. These conditions have a high mortality rate which is rapidly increasing. Factors like tobacco consumption, alcohol, genetics, etc., play a role in etiopathogenesis of these lesions, currently there is a lot of growing interest in role of viruses like Epstein–Bar virus, human papilloma virus, herpes simplex virus, hepatitis C virus etc., in oral carcinogenesis. Viruses can induce cancers through various methods. Thus knowing the exact role of viruses in cancers can affect the treatment plans and prognosis of the treatment.

Keywords: Carcinogenesis, oral cancer, viruses.

Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most common malignancy world wide and accounts for approximately 5% of malignant tumors in developed countries. Prevalence and anatomic distribution of these lesions are associated with habits like tobacco, smoking, alcohol, etc., Thus the use of tobacco and alcohol are considered as a risk factors for OSCC, but it does not always show a positive correlation. Individual that develops the OSCC without past habit history suggests that others factors can play a role in head and neck carcinogenesis.[1]

It has been suggested that habit as well as chemical carcinogens, radiation energy, chronic irritation, and viruses play an important role in their etiology.[2] Viruses such as herpes simplex virus (HSV), human papilloma viruses (HPV), hepatitis C, Epstein– Barr viruses (EBVs) have shown close association with the development of premalignant lesions/conditions and OSCC.[3]

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Oral squamous cell carcinoma and viruses

OSCC usually originates from the stratified squamous epithelium. The etiology of OSCC is complex and involves many factors. As it has been proved that betel quid, and alcohol consumption are the major risk factors for developing OSCC, However, additional factors such as genetic predisposition, diet or oncogenic viruses causes impairment of physiological mechanisms of cellular proliferation control.[4]

The viruses are classified under two categories: Viruses *strongly associated* with oral squamous cell carcinoma i.e. Human Papilloma Virus, Herpes Simplex Virus (HSV) and viruses *less frequently* associated with oral squamous cell carcinoma are Epstein barr virus (EBV) and Hepatitis C virus (HCV).

A. Human Papilloma virus

The exact role of HPV in the development OSCC is still unknown. Papilloma viruses are members of the papovaviridae family, which also includes other viruses like polyoma viruses. The papilloma viruses are nonenveloped, circular, double-stranded DNA viruses.

Classification

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

- i. Papilloma virus was first named according to its natural host, e.g. cotton tail rabbit papilloma virus, bovine papilloma virus etc.

- ii. 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 rate of malignant transformation
- iii. 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.[3]

Carcinogenic potential of human papillomaviruses

Studies have shown that almost 100 distinct types of HPV have been identified. However, not all types are associated with OSCC. High prevalence of HPV-16 and HPV-18 with OSCC is seen in Indian betel quid chewers. The constant detection of the HPV in OSCC patients who do not habitually use tobacco or consume alcohol has also indicated the close association of HPV with OSCC. Among various strains of HPV, HPV-16 is most commonly associated in these patients.[4]

DNA is the genetic constituent of HPV. When the host tissues get infected with HPV, E6 protein and E7 protein are formed following complete degradation of host genome. E6 protein forms a complex that causes degradation of p53 gene by inhibiting apoptosis while E7 protein causes an increase in DNA synthesis and proliferation which leads to disturbance in the retinoblastoma tumor suppressor gene.

Basal keratinocytes are the target cells for HPV where new virions are produced and released subsequently when the superficial cells flake off. These HPV altered keratinocyte as well as koilocytes are also found in patients with OSCC.[5]

B. Herpes Simplex virus

HSV is a double-stranded DNA virus that is enveloped. The two most common forms are HSV 1 and HSV 2. Both viruses have similar structures. HSV 1 mainly causes oral and ocular infections while HSV 2 causes genital infection. They have a difference in the ability to transform cells. The transforming region of HSV 1 is located in the left third of the genome. It is also known as minimum transforming region (mtr) 1, while in HSV 2, mtr 2, mtr 3 are close to the center of the genome.[6]

Herpes Simplex Virus and Oral Squamous Cell Carcinoma

The association between oral cancer and HSV is still a topic of debate except for the fact that HSV can transform some animal cells to a malignant phenotype in vitro. Actually HSV has shown cocarcinogenic activity in combination with chemicals in vivo. But it is difficult to study, because cells that are transformed by HSV do not express specific virus antigens or retain any specific genes of the virus. Instead it seems likely that the transformation is due to the virus acting as a mutagen, and a region of the viral genome has been isolated, which raises the mutation frequency in cultured cells. This results in features of malignancy. Also the mutations and the phenotypic changes are not sufficiently specific to act as markers by which a herpes-induced malignancy could be diagnosed.[7]

Herpes Simplex Virus In Cell Transformation

The transforming mechanisms of HSV 1 and 2 remain unclear. The viruses have not been shown to encode an oncogene or related gene and furthermore the transforming regions of the genome are not retained in transformed cells. Few other mechanisms that are proposed in cell transformations of HSV are induction of cellular proteins, host cell shut off process, stimulation of other viruses by HSV, chromosomes as targets.

C. Epstein-Bar virus

It is one of the most common viruses in humans. It is enveloped double-stranded DNA and also known as human herpes virus-4. EBV is named after Michael Anthony Epstein and Yvonne Barr, who discovered and documented the virus in 1964. It belongs to the genus Lymphocryptoviridae and a gamma 1 subtype of the subfamily Gamma herpesviridae. EBV is commonly associated with a number of malignancies such as Burkitt's lymphoma, Hodgkin's disease, stomach carcinomas, and nasopharyngeal carcinoma.[7]

Epstein-Bar virus and carcinogenesis

First stage in the mechanisms of EBV tumorigenesis is establishment of a persistent infection. The primary infection starts within the oropharyngeal epithelial cells with viruses subsequently passing to subepithelial B-cells through direct contact. The invasion of the immune system by EBV stimulates CD8 T-cell response. The development of a virus-specific adaptive immune response reduces the number of EBV-infected B-cells subsequently leads to the elimination of EBV infection. This elimination

of infection remains as a latent infection after incompletely persistent EBV infection in peripheral blood lymphocytes and/or as a lytic infection in the oral cavity. It leads to shedding of infectious viruses via oral secretions. EBV infects B-cells and converts them to lymphoblastoid cells which have tendency to proliferate continuously. They express nine latency-associated viral proteins which includes six nuclear antigens (Epstein-Barr nuclear antigen [EBNA] - 1, 2, 3A, 3B, 3C and leader protein [LP]) and three membrane proteins (latent membrane protein (LMP) - 1, 2A and 2B).[8]

Genomic instability is a hallmark of malignant transformation and is frequently associated with chromosomal aberrations such as reciprocal translocations, deletions, inversions, and duplications. They deregulate the expression of oncogenes or tumor suppressor genes. It has been demonstrated that the EBV nuclear antigens (EBNA 1 and EBNA 3C, and the LMP 1) promotes genomic instability, breaking of DNA and phosphorylation of histone H2AX.[9]

EBNA causes DNA damage by inducing reactive oxygen species and also there is inhibition of DNA repair in LMP 1 expressing cells through down regulation of the DNA damage-sensing kinase, reduction of phosphorylation of its downstream targets Chk2 and inactivation of the G2 checkpoint. EBNA 3C enhances the propagation of damaged DNA. Thus, it has been postulated that EBV independently targets multiple cellular functions involved in the maintenance of genome integrity which causes genomic instability which considered as a critical event in viral oncogenesis. Also role of EBV in neoplastic transformation in oral cancers is indicated by a positive correlation between different grades of OSCC and EBV DNA positivity. A percentage positivity of EBV DNA increases from well differentiated OSCC to poorly differentiated OSCC.[9]

D. Hepatitis C virus

It is an enveloped single-stranded positive sense RNA virus belongs to genus (hepacivirus) within the Flaviviridae family. It is an etiological agent for most cases of non-a, non-b hepatitis, liver cirrhosis, and hepatocellular carcinoma. The oral cavity is frequently exposed to HCV viruses, thereby causing an increase in the risk of genetic instability in the cells. In HCV-positive patients, the squamous cells of oral cavity are continuously exposed to HCV from saliva as well as from serum. This might leads to the development of OSCC. Anti-HCV antibodies

were also detected in patients with OSCC, but the exact mechanism is unclear.[10]

Conclusion

Viruses are important risk factors for oral cancerous. While diagnosing these lesions one should always consider the possible role of viruses in their etiopathogenesis which can alter treatment plan for the patients. Recently, vaccines against HPV for prevention of cervical cancer has been invented. Similarly, future research should be carried out to develop a vaccine against these viruses in order to prevent the occurrence of oral malignancies.

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