Oncogenic Viruses and Mechanisms in Oral Squamous Cell Carcinoma: A Mini Review

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is a common epithelial malignancy with varied etiology. The traditional risk factors are the usage of tobacco and tobacco products. About 15-20% of the population exists with oral squamous cell carcinoma without being exposed to these carcinogenic products. The other factors which may influence the disease process are environmental factors, genetic alterations and viruses. Some oncogenic DNA viruses are strongly associated with OSCC while other viruses are little expressed. While diagnosing OSCC one should always consider the possible role of viruses in their etiopathogenesis as it is crucial for diagnosis and successful treatment. Screening of the oncogenic viruses at an early stage may also aid in the prognosis of oral squamous cell carcinoma. The current review focuses on the possible mechanisms of the oncogenic viruses in the etiopathogenesis of OSCC.

Key Words: Oncogenesis, Epstein - Barr virus, Human papilloma virus, Human simplex virus, mechanisms, Cancer

INTRODUCTION

Worldwide, cancer of the oral cavity ranks sixth, and it is the most common malignancy burden worldwide, which accounts for 5% in developed countries with a survival rate of 5 years (1). Tobacco, betel quid, alcohol usage plays a major role in emergence of Oral Squamous Cell Carcinoma (OSCC) (2). But still, some may develop OSCC without the consumption of tobacco products. Lifestyle, environmental factors, diet, and viral carcinogens also pose a risk to development of OSCC (3). Peyton Rous, 100 years ago experimentally proved chicken sarcomas could be caused by a virus called Rous Sarcoma Virus. In 1930's, it became further evident that tumors in rabbits could be caused by a virus called Shope Papillomavirus (4). Many epidemiological as well as molecular data depict that members of the Herpes viridae family, such as Epstein Barr virus (EBV) and human herpes simplex virus (HSV) and certain types of human papilloma viruses (HPV) have an oncogenic capability for OSCC (5). Co-infection by two or more virus species has also been proposed as a risk factor for increased cancer development (6). Evans and Mueller guidelines and Hill's Criteria clearly define the relationship between oncogenic viruses and human cancers (7).This short review will attempt to reveal the mechanisms of oncogenic viruses in oral squamous cell carcinoma.

Epstein Barr Virus (EBV)

Epstein-Barr virus (EBV) was the first human virus to be directly associated with human malignancies. Epstein-Barr virus (EBV) is the name coined after M. Anthony Epstein and Yvonne Barr, who had discovered the virus. Also known as Human Herpes Virus 4 (HHV-4), it is a virus of the Herpes family. Epstein-Barr virus consists of a linear double-stranded DNA core surrounded by a nucleocapsid and envelope (8).

EBV is usually transmitted from person to person via saliva. Two subtypes of EBV are evident to infect humans: EBV-1 and EBV-2. The virus utilizes

complement receptor CD21 to attach and bind with infected B cells particularly in the oropharynx. In acutely infected B lymphocytes, EBV expresses proteins which cause cell proliferation (9). EBV infection of B cell usually starts with the attachment of the viral membrane glycoprotein to the CD21 receptor molecule on the lymphocytes (10).After binding to CD21, EBV immediately activates Lymphocyte Cell-specific Protein-Tyrosine Kinase (lck) and mobilizes calcium (11).Followed by, there is an increase in mRNA synthesis, homotypic cell adhesion, blast transformation, surface CD23 expression (a characteristic surface marker for activated B cells), and interleukin (IL)-6 production. Then this viral genome becomes uncoated and enters into the nucleus where it immediately circularizes. The process of circularization involves recombination between repeat units on the opposing termini and the number of terminal repeats used to form CCC (Covalently Closed Circular Episome) (12). Circularization leads to the expression of all of the EBNA proteins and the two latent membrane proteins [LMPs] (13).

Latent Membrane Protein -1 (LMP-1) enhances oncogenesis by virtue of its ability to recruit the cellular genes. It also inhibits apoptosis by elevating the levels of Bcl-2, matrix metalloproteinase-9 (MMP-9), and fibroblast growth factor-2 (FGF-2) (14). In immunocompromised individuals, infected cells become increased in number. B cell growth control pathways are activated by inducing transformation and leading to malignancies such as nasopharyngeal carcinoma, Burkitt's lymphoma, post-transplant lymphomas and gastric carcinomas (15).

Human Papilloma Virus (HPV)

The human papilloma viruses (HPV) are DNA viruses. Its family consists of more than 200 genotypes which are classified according to the ability to infect and transform epithelial cells. It belongs to the family called Papova viridae. These are small non-envelope dicosahedral viruses with an 8kbp long double stranded circular DNA genome (16). Its genotype includes HPV1 which infect epidermal cells and HPV6, HPV 11, HPV 16 and HPV 18 which infects epithelial cells of the oral cavity and other mucosal surfaces. The Human papilloma virus genome comprises early and late genes which encodes the early proteins as [E1–E7] and late proteins as [L1-L2] (17).

The E1-E7 early proteins are non-structural proteins. E1–E5 early proteins are involved in replication and transcription of the genome. E6 and E7 early proteins are involved in host cell tumoral transformation whereas L1, L2are code for the structural capsid proteins which are activated during the final stages of the viral cycle. E1 – E6 early protein genes and two L1, L2 late protein genes can be detected in HPV infection. The oncogenic properties of HPV can be expressed by the activities of the two viral genes encoding E6 and E7 (18).

Role of HPV E6

The E6 proteins binds and mediates the p53 degradation and also stimulate Telomerase Reverse Transcriptase [TERT], the catalytic subunit of Telomerase enzyme which leads to tumor development by enhancing cell survival or proliferation and by impairment of cellular differentiation. It also enhances angiogenesis for tumor development by increasing vascular endothelial growth factor (VEGF) and anti-apoptotic bcl-2 and also by suppressing Tumor Suppressor Protein 1 [TSP-1] (19).

Role of HPV E7

The HPV E7 proteins interact with cellular factors which controls the cell cycle including Activator Protein- 1 (AP-1) transcription complex, Cyclin Dependent Kinase [CDK] inhibitors, p21 and p27 and histone deacetylases. E7 protein in High risk HPV 16 and HPV 18 can decrease the expression of Major Histocompatibility Complex (MHC) Class I molecules thereby interfering with MHC class I antigen presentation. This further leads to down-regulation of cellular immune responses allowing HPV to be persistent in infected epithelial cells. High-riskE7 oncoprotein of HPV can induce chromosome duplication errors which lead to dysregulation of mitotic spindle formation, contributing to the genomic instability of the cell and resulting in tumor development and progression (20). When the E7 protein binds to the cellular Retinoblastoma (Rb) protein it releases E2F, a family of transcription factors which becomes unbound and free to induce cell cycle activation and proliferation (21).

Herpes Simplex Virus (HSV)

Herpes Simplex Virus is a double-stranded DNA virus. These viruses are in two forms, known as HSV 1 and HSV 2. Herpes Simplex Virus (HSV) 1 causes

oral and ocular infections, whereas Herpes Simplex Virus (HSV) 2 causes genital infections. HSV-1 and HSV-2 viruses are encoded by identical regions of the viral genome. Each virus will cause a severe primary infection which is followed by a latent infection and later by recurrent infections (22).

The following are the various mechanisms involved in cell transformation:

Stress or Heat shock Proteins: Infection by HSV 1 influences the expression of "stress" or "heat shock" proteins. Activation of stress protein genes primarily causes dramatic increase in the rate of RNA synthesis, followed by changes in chromatin structure. So the stress response clearly represents a major, physiologic alteration in cellular metabolic state which in turn causes malignant transformation (23).

Virus act as a mutagen: The association between OSCC and HSV is not clearly defined because the transformed cells of HSV do not express virus specific antigens. Rather, the transformation is because of the mutagenic effect of the virus and the viral genome raises the mutation frequency in cultured cells (24).

Host cell shutoff is identified as an important event during infection of cells by HSV and it's a multistep process depending on the viral activity. The DNA fragment which transfers the ability of the cell to shut off host protein synthesis was also capable of transferring the function affecting the physical integrity of host mRNA. In vitro, this finding suggests that the shutoff of host protein synthesis is mechanistically linked to the physical degradation of host mRNA. So the infected cell fails to secrete cellular proteins further promoting RNA degradation quickly resulting in malignant transformation (25).

Stimulation of other viruses by HSV

In cervical carcinogenesis, HSV and HPV may act as co-carcinogens, with HSV as an initiator and HPV as a promoter. Therefore HSV may have a role in stimulation of replication of other viruses (26).

Chromosomes as targets

When the cells are infected by HSV there is a chromosomal damage which is first restricted to a chromosome 1q andto some extent on chromosome 3, 9 and 16. Damage to a particular chromosomal site might be another possible mechanism of cell transformation by HSV (27).

Hepatitis C Virus (HCV)

Hepatitis C virus is a single-stranded positive-sense RNA virus which is enveloped, and isolated in 1989by Choo et al, from a chronically infected chimpanzee (28). HCV contains six genotypes and 100 subtypes. The envelope consists of two glycoproteins namely E1 and E2, which forms heterodimers at the virion surface. The gene which coded for RNA gets translated into a viral polyprotein which further is cleaved by cellular proteases to produce the capsid protein. For viral RNA replication, HCV requires viral proteases NS2 and NS3 and nonstructural proteins NS4A and NS 5A and 5B (29).

The exact mechanism of HCV in OSCC is undefined, but it was found that the squamous cells of the oral cavity are frequently exposed to HCV from the saliva and serum of HCV positive patients. When the oral cavity is continuously exposed to HCV, it can lead to the risk of genetic instability resulting in the development of OSCC (30).

CONCLUSION

Viruses account for about 20% of total human cancer cases. The most common mechanisms of viral oncogenesis are multifarious and may involve the initiation of chronic inflammation, upheaval of host genetic integrity and homeostasis, interference with cellular DNA repair mechanisms and cell cycle dysregulation. Understanding the principles of viral oncogenesis may enable the identification of infectious etiology of cancer and development of therapeutic or preventive strategies for virus-associated cancers.

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