Molecular Pathogenesis Oral Squamous Cell Carcinoma – Implication for Therapy

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Abstract

Background Oral squamous cell carcinoma is the most common subtype of head and neck carcinoma. The development of oral squamous cell carcinoma (OSCC) is a multistep process requiring the accumulation of multiple genetic alterations, influenced by a patient's genetic predisposition as well as by environmental influences, including tobacco, alcohol, chronic inflammation, and viral infection.

Discussion Tumorigenic genetic alterations consist of two major types, tumor suppressor genes, which promote tumor development when inactivated and oncogenes, which promote tumor development when activated. Tumor suppressor genes can be inactivated through genetic events such as mutation, loss of heterozygosity, or deletion, or by epigenetic modifications such as DNA methylation or chromatin remodeling. Oncogenes can be activated through overexpression due to gene

amplification, increased transcription, or changes in structure due to mutations that lead to increased transforming activity. These events result in the increased production of growth factors or cell-surface receptors and the activation of intracellular messenger signaling, leading to autonomous growth of tumor cells without extracellular growth stimuli. Along with evasion of growth-inhibitory signals by the inactivation of tumor suppressors and the inhibition of apoptosis, leads normal oral epithelial cells to acquire the malignant phenotype. As OSCCs grow, invade, and metastasize, new blood vessel formation is critical and OSCCs, like most tumors, are able to create a blood supply by stimulating endothelial cell proliferation and new blood vessel formation.

Conclusion The understanding of the molecular alterations contributing to the development of OSCC is leading to improvements in the early diagnosis of tumors and the refinement of biologic treatments individualized to the specific characteristics of a patient's tumor.

KEY WORDS: oral squamous cell carcinoma, multistep carcinogenesis, oncogene, tumor suppressor gene.

Introduction

Cancers, including oral squamous cell carcinoma (OSCC), emerge from the accumulation of genetic changes and epigenetic anomalies in the signaling pathways that are associated with cancer, resulting in phenotypes that facilitate OSCC development.

OSCC is a malignant neoplasm derived from the stratified squamous epithelium of the oral mucosa. The development of oral squamous cell carcinoma (OSCC) is a multistep process requiring the accumulation of multiple genetic alterations (Figure 1).

Its pathogenesis is multifactorial, associated with cigarette smoke, alcohol and snuff, as well as the papilloma virus, among others. The malignant neoplasm occurs at various sites of the mouth, the most frequent being the lip, lateral edges of the tongue and floor of the oral cavity. The incidence of OSCC increases with age, with the majority of OSCC occur in mid-age patients.[1]

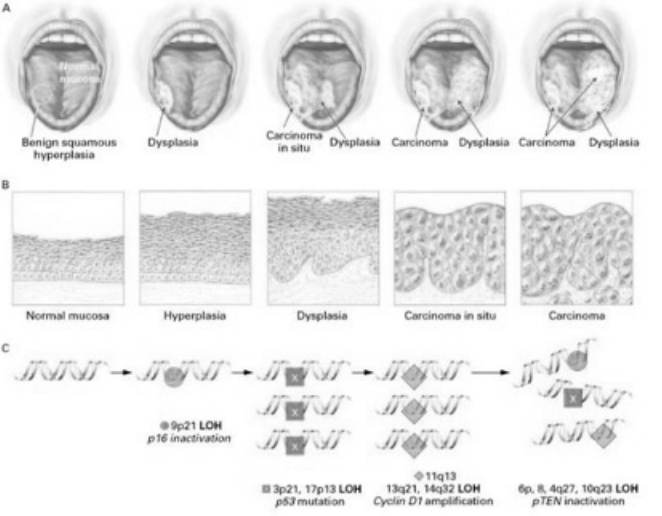

Figure 1. Multi-stage evolution of cancer [1]

OSCC is characterized by histopathological and clinical manifestations. All carcinogenesis evolves from initial oral squamous cell carcinoma is the most common subtype of head and neck carcinoma. More than 95% of the carcinomas of the oral cavity are of squamous cell type, in nature. OSCC constitute a major health problem in developing countries, representing a leading cause of death of patients. The survival index continues to be small (50%), as compared to the progress in diagnosis and treatment of other malignant tumors.

According to World Health Organization, carcinoma of oral cavity in males in developing countries, is the sixth commonest cancer after lung, prostrate, colorectal, stomach and bladder cancer, while in females, it is the tenth commonest site of cancer after breast, colorectal, lung, stomach, uterus, cervix, ovary, bladder and liver. As the gateway to the alimentary and respiratory tract, the oral cavity has repeated exposure to many carcinogenic agents, specifically tobacco, alcohol, betel nut and Human Papillomavirus (HPV). Worldwide, approximately 275,000 oral cavity malignancies are diagnosed each year and the predominant malignancy is squamous cell carcinoma. In Sri Lanka, India, Pakistan and Bangladesh, nearly a quarter of total cancer diagnoses are oral cavity squamous cell carcinoma. In western countries, oral cavity squamous cell carcinoma represents approximately 3% of new cancer diagnoses annually. Globally, oral cavity squamous cell carcinoma primarily affects males (1.5:1); however, in regions where female tobacco and betel nut consumption is common, the gender difference normalizes. Worldwide the mortality

rate is estimated to be nearly 50%.[2,3]

Since, the oral cavity is more accessible to complete examination, it could be used in early detection of precancerous and cancerous lesions. But either due to ignorance or inaccessibility of medical care, the disease gets detected in the later stages. Thus, there is a need for improvement in early detection of oral carcinomas, because in the initial stages, treatment is more effective and the morbidity is minimal. Most invasive oral carcinomas are preceded by a pre invasive stage, that may last for many years.

Tumor progression in epithelial has been classified as normal, hyperplastic (non-dysplastic), dysplastic carcinoma in situ and invasive carcinoma. The majority of the initial alterations of precancerous and cancerous oral lesions are not readily recognizable, on clinical or histopathological examination. The basic biology of initiation and progression of these tumors is still obscure.[2]

The risk factors include tobacco associated intra-oral carcinogens, which may play a synergistic role in oral tumorigenesis. From relative risk factors of alcohol and tobacco, it has been estimated, that 75% of all oral cancers are preventable. In the remaining 25% of patients who are not exposed to these substances, the cause/s of their tumors remains unknown. The disproportionately higher incidence of carcinoma of the head-neck in relation to other malignancies, may be due to use of tobacco in various forms, consumption of alcohol, low socioeconomic condition related to poor hygiene, poor diet and rampant viral infections.[2,4]

Discussion

In adult tissues, the growth of cell is determined by the rates of cell proliferation, differentiation, and death by apoptosis that happened in cell cycle. There is a large number of known polypeptide growth factors, some of which act on many cell types, and others have restricted cellular targets. In addition to stimulating cell proliferation, growth factors may also have effects on cell locomotion, contractility, differentiation, and angiogenesis, activities that may be as important as their growth promoting effects [1-3].

Cell differentiation occur in cell cycle, so any mutations or defects allow the replication of cells with DNA strand breaks and chromosome abnormalities that may cause tissue alterations and neoplasia. The cell cycle between normal cell and cancer cell showed in figure 2.[5]

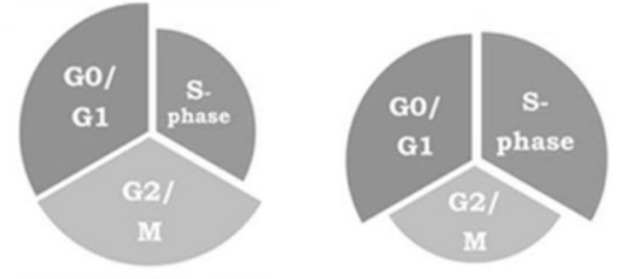

Figure 2. Cell differentiation occur in normal and cancer cell cycle[5].
Cancer cell (left), Normal cell (right)

Seven fundamental changes in cell physiology that together determine malignant phenotype: Self-sufficiency in growth signals, insensitivity to growth-

inhibitory signals, evasion of apoptosis, defects in DNA repair, limitless replicative potential, sustained angiogenesis and ability to invade and metastasize.[5]

Oral carcinogenesis like any other cancer is a progressive disease and normal epithelium passes through stages starting from dysplasia to finally transforming into invasive phenotypes. Although all types of carcinomas are seen in oral cavity, the most common form of OSCC is squamous cell carcinoma. Use of genetic and proteomic approach in recent years have revealed the molecular pathological picture of OSCC.[6]

Tumorigenic genetic alterations consist of two major types, tumor suppressor genes, which promote tumor development when inactivated and oncogenes, which promote tumor development when activated. Tumor suppressor genes can be inactivated through genetic events such as mutation, loss of heterozygosity, or deletion, or by epigenetic modifications such as DNA methylation or chromatin remodeling. Oncogenes can be activated through overexpression due to gene amplification, increased transcription, or changes in structure due to mutations that lead to increased transforming activity. These events result in the increased production of growth factors or cell-surface receptors and the activation of intracellular messenger signaling, leading to autonomous growth of tumor cells without extracellular growth stimuli. Along with evasion of growth-inhibitory signals by the inactivation of tumor suppressors and the inhibition of apoptosis, leads normal oral epithelial cells to acquire the malignant phenotype. As OSCCs grow, invade, and metastasize, new blood vessel

formation is critical and OSCCs, like most tumors, are able to create a blood supply by stimulating endothelial cell proliferation and new blood vessel formation (Figure 3) [5,7].

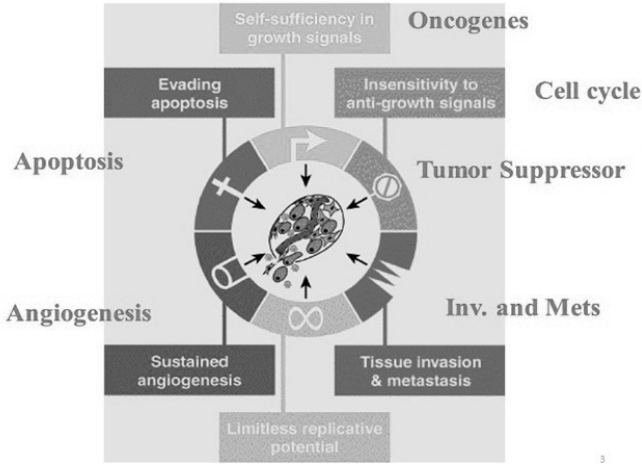

Figure 3. Role of genes mutation in SCC cascade

There is active search to identify genetic alterations in oncogenes or tumor suppressor genes, role of genomic instability and epigenetic modifications and to generate a gene expression profile in oral oncogenesis. Understanding these genetic changes and gene expression patterns are keys to the understanding of molecular pathogenesis of OSCC.

Though, there are some significant leads achieved, the complete understanding of molecular pathology of OSCC and its association with causative agent will require another decade of intensive research [5,6,7].

Proto-oncogenes, Oncogenes, and Genetic Alterations

Oncogenes can be classified according to the roles of their normal counterparts (proto oncogenes) in the biochemical pathways that regulate growth and differentiation. These include the following: Growth factors (TGF, FGF, PDGF), Cell surface receptors (EGFR, FGFR), Intracellular signal transduction pathways (RAS), DNA binding nuclear proteins transcription factors (MYC, FOS, JUN), Cell cycle proteins (cyclins and cyclin dependent protein kinases), Inhibitors of apoptosis (bcl2) Genetic alterations define molecular basis of carcinogenesis which includes point mutations, amplifications, rearrangements, and deletions.

Several oncogenes have also been implicated in oral carcinogenesis. A few proto oncogenes encode growth factors that stimulate tumor cell growth. In some instances a growth factor acts upon the same cell that produces it (autocrine stimulation). Other growth factors act upon the receptors of neighboring cells (paracrine stimulation). Examples of growth factors involved in neoplastic transformation include platelet derived growth factor (PDGF) and fibroblast growth factor (FGF).

Aberrant expression of epidermal growth factor receptor (EGFR), K-ras, c-myc, int-2, Parathyroid adenomatosis 1 (PRAD-1) and B-cell lymphoma (bcl) like oncogenes have been reported in OSCC development. Over expression and amplification of cellular oncogene EGFR have been reported in a 7,12-Dimethylbenz(a)anthracene (DMBA) induced hamster cheek pouch malignant OSCC model. Transforming growth factor-alpha (TGF-a) is known to promote neovascularization and mitogenesis.

It has been shown to be aberrantly expressed in human OSCC and in hamster oral tumor. [5,8]

Tumor Suppressor Genes

Oncogenes alone are not sufficient to cause oral cancer and appear to be initiators of the process. The crucial event in the transformation of a premalignant cell to a malignant cell is inactivation of cellular negative regulators tumor suppressor genes and is regarded to be a major event leading to the development of malignancy.

Tumor suppressor genes are most often inactivated by point mutations, deletions, and rearrangements in both gene copies. More than 50% of all primary OSCC harbor p53 mutation. Inactivation of p53 represents the most common genetic change in all human cancers. The most commonly deleted region in HNC is located at chromosome 9p21–22. Loss of chromosome 9p21 Occurs in the majority of invasive tumors in head and neck cancer. Homozygous deletions in this region are frequent and represent one of the most common genetic changes identified. p16 (CDKN2) present in this deleted region, is a potent inhibitor of cyclin D1. Loss of p16 protein has been observed in most advanced pre-malignant lesions also. Mayo et al. have identified an alternative RNA transcript for p16 termed as Alternative Rating Frame (ARF; or p16b). Introduction of p16 or p16ARF into HNC cell lines result in potent growth suppression. Loss of chromosome 17p is also frequent in most human cancer including OSCC. It is seen in approximately 60% of invasive lesions. Although p53 inactivation correlates closely with loss of 17p in invasive lesions, p53 mutations are quite rare in