The Human Oral Cancer and Molecular Biology

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Quick Response Code

doi: 10.5866/2014.631620

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Article Info:

Received: April 14, 2014

Review Completed: May 12, 2014

Accepted: June 10, 2014

Available Online: October, 2014 (www.nacd.in)

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ABSTRACT:

The molecular biology and its application in the study of cancer have significantly advanced the field of human cancer research. Two classes of highly conserved cellular genes in the malignant transformation process include oncogenes and tumor suppressor genes were demonstrated. This review provides an attempt to assess the current status of the molecular biology of human oral cancer.

Key words: Molecular biology, Oral cancer.

INTRODUCTION:

The ICD defines oral cancer as cancer of the oral cavity and pharynx. Cancer of the oral cavity includes cancer of the lip, tongue, salivary glands, gum & floor. Pharyngeal cancer of the mouth includes oropharynx, nasopharynx, hypopharynx and other buccal areas. Oral cancer is the sixth most common cancer for both gender in the general population and the third most common cancer in developing nations. Cancer prevalence in India is estimated to be around 2.5 million, with over 8,00,000 new cases and 5,50,000 deaths occurring

each year due to this disease. Different cancers occur in different states of our country. Oesophageal cancers: Southern states of India like Karnataka and Tamil Nadu and also in Maharashtra and Gujarat. Stomach cancers: Southern India with the highest incidence in Chennai. Oral cancers: Kerala (South India) Pharyngeal cancers: Mumbai (Western India). Thyroid cancers occur among women: Kerala. Gall bladder cancer: Northern India, particularly in Delhi and West Bengal.^{1, 2}

Tobacco and alcohol remain the most important risk factors for squamous cell carcinomas of the oral

cavity. Viruses, most notably the human papillomavirus also have long been linked to human oral carcinogenesis.^{3, 4}

Molecular Basis and Biology of Human Oral Cancer:

Carcinogenesis is a complex, multi-step process in which genetic events within signal transduction pathways governing normal cellular physiology are quantitatively or qualitatively altered. There are two mechanisms by which proto-oncogenes can be converted to cellular oncogenes:⁵

- **Quantitative:** Tumour formation induced by increase in the absolute number of proto-oncogene products or by its production in inappropriate cell types.
- **Qualitative:** Conversion from proto-oncogene to transforming gene includes changes in the nucleotide sequence and acquisition of the new properties.

Under normal conditions the regulatory pathways controls functions such as cell division, differentiation and adhesion. These signals either directly alter cell function or stimulate the transcription of genes, whose proteins effect the change (signals and cell function are depicted in the picture below). Cell function can be demonstrated by two appropriate terms such as Senescence and Ageing. Senescence refers to a post maturational process that leads to diminished homeostasis and increased vulnerability of organism to death. Ageing in contrast refers to any time related process and is a continuous process that starts at conception and continues until death.^{6, 7}

Cancer is the result of an accumulation of changes in the excitatory and inhibitory cellular pathways occur at any level of given pathway. Generally 3-6 mutations are needed to transform a normal cell to malignant counterpart.²

CYTOGENETICS OF HUMAN ORAL CANCER:

In almost two-thirds of all head and neck cancer cells are deleted in the region located in chromosome 9p21-22, suggesting a gene in this region is mutated early in oral carcinogenesis, similarly pl6, 3p and 13q also.⁸

Essential Alterations for Malignant Transformation

- Self sufficiency of growth signals: Tumors have capacity to proliferate without external stimuli, as a consequence of oncogene activation.
- Insensitivity to growth inhibitory signals: Tumors may not respond to inhibitory molecules such as transforming growth factor (TGF- α), cyclin dependent kinase (CDK) inhibitors
- Evasion of apoptosis: Tumors become resistant to programmed cell death, due to inactivation of p53.
- Defects in DNA Repair: Tumors fail to repair DNA damage, due to loss of function of p53.
- Limitless replicative potential: Tumor cell have unrestricted proliferative capacity & associated with maintenance of telomere length & function.
- Sustained angiogenesis: Genetic abnormalities that dysregulate the growth can lead to sustained angiogenesis. Tumors can't enlarge beyond 1 - 2 mm in diameter, unless they are vascularized. This vascularization can be induced by various factors: importantly vascular endothelial growth factors (VEGF).
- Ability to invade and metastasis: Biologic hallmark of malignant neoplasm for invasion and metastasis are integrins & matrix metalloproteins (MMP's).⁹⁻¹¹

Genetic damage in oral cancer cells can be divided into two categories:-

1. Dominant changes: Those occur in proto-oncogenes and certain tumour suppressor genes (TSGs) resulting in gain of function.
2. Recessive changes- Those occur in growth-inhibitory pathway genes or commonly in tumor suppressor genes causing loss of function.¹³

Oncogenes Implicated In Human Oral Cancer

Epidermal growth factor receptor (EGFR)/ c-erb 1, members of the ras family, cmyc, bcl-1, c-erb B1, transforming growth factor-alpha (TGF α).

Flow Chart: Depicting Simplified Scheme of Molecular Basis of Cancer

Selected Oncogenes

Growth Factors: PDGF- α chain, Fibroblast growth factors, TGF α , HGF

Growth Factor Receptors: EGF-receptor family, CSF-1 receptor, Receptor for neurotrophic factors, PDGF receptor, Receptor for stem cell (steel) factor

Proteins Involved in Signal Transduction: GTP-binding K-RAS, H-RAS, N-RAS, Nonreceptor tyrosine kinase ABL, RAS signal transduction, BRAF, WNT signal transduction β -catenin.

Nuclear Regulatory Proteins: Transcriptional activators C-MYC, N-MYC, L-MYC

Cell-Cycle Regulators: Cyclins CYCLIN D, CYCLIN E, Cyclin-dependent kinase CDK4

Growth factors

Early in oral carcinogenesis TGF- α is overexpressed by hyperplastic epithelium and later by inflammatory infiltrate, particularly eosinophils - surrounding the invading oral epithelium.²

Anti tumour and tumour progression role of Eosinophils: Anti tumor effect:- Eosinophils (EOS) is associated with the release of cytotoxic proteins, including eosinophil cationic protein(ECP), major basic protein (MBP), eosinophil peroxidase (EPO) and eosinophil-derived neurotoxin (EDN), which has been linked to tumour cell apoptosis. EOS is thought to be recruited to tumours, by selective EOS chemoattractant eotaxin, which binds to CCR3 receptor on these cells.¹⁴

Tumour progression role:- Eosinophils promote angiogenesis, release pro-angiogenic factors like basic-fibroblast growth factor (b-FGF), interleukin IL-6, IL-8, granulocyte macrophage colony stimulating factor (GM-CSF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF- β) and matrix metalloproteinase-9 (MMP-9) on stimulation by TNF- α .

EOS can synthesise and release many others growth factors like vascular endothelial growth factors (VEGF).¹⁴

Cell-surface receptors

EGFR, the biological receptor of EGF and TGF- α , is a 170,000-dalton phosphoglycoprotein frequently found to be over expressed in human oral cancers.

Three mechanisms are postulated to activate the EGFR gene in carcinogenesis:

- (1) Deletions or mutations in the ligand-binding domain
- (2) Over expression of the EGFR gene and
- (3) Deletion in the intracellular domain of receptor¹⁵

Intracellular messengers

Of all the members of the intracellular signalling pathway, only members of the ras gene family encode for the related protein P²¹ localized to the cytoplasmic side of the cellular membrane. ras proteins transmit mitogenic signals by binding GTP. Hydrolysis of GTP to GDP ends the signal.¹⁶

Transcription factors

Transcription factors are proteins that regulate the expression of other genes are altered in oral cancer. Modulation of gene expression is an important outcome in the alteration of the intracellular pathways. c-myc, regulate cell proliferation and differentiation, frequently over expressed in oral cancers. cyclin D1, cell cycle promoter also amplified in head and neck Cancers.¹³

Tumor Suppressor Genes (TSGs)

Tumor suppressor genes or anti-oncogenes are lost due to chromosomal alterations during tumor

formation. Functional loss of multiple tumor suppressor genes leads to the development of malignancy. oncogenes, effect cellular change through mutation of only one of the two gene copies. Tumor suppressor genes are inactivated by point mutations, deletions, and rearrangements in both gene copies in a "two-hit" fashion. Therefore, the loss of function of tumor suppressor genes, are difficult to achieve. The role of TGF β in epithelial malignancy has been controversial for some time, but it is now recognized that TGF acts as a potent tumor suppressor in the early stages of tumour progression, while later functioning more to enhance the malignant phenotype. Tumour-suppressor activities have been attributed to growth inhibition and the stimulation of apoptosis. More recently, the maintenance of genomic stability and the induction of replicative senescence together with the suppression of telomerase activity have been suggested as additional tumour-suppressor effects of TGF β .^{17, 18}

P53

The tumour suppressor gene p53 - mutated approximately in 70% of adult solid tumours. In normal cell biology, p53 acts as a regulator of DNA synthesis. If genomic DNA damaged, p53 produced to block cell division at the G1-S boundary and stimulate DNA repair. p53 also activate apoptosis. Mutation of p53 allows tumours G1-S boundary, propagate genetic alterations which can lead to other activated oncogenes or inactivated tumor suppressor genes. Alteration of the p53 gene occurs as point mutations and deletions.¹⁹

The E6 and E7 oncoproteins are normally under control of E2 and E1 inhibitory genes. These genes can be deleted or altered upon integration, leading to unchecked transcription of E6 and E7. These proteins are then able to disrupt the function of Rb and p53, known tumor suppressor genes. p53 has been implicated in a wide variety of cancers and is known to be the target of many different viral particles. p53 and Rb are tumor suppressor genes, they regulate cell-cycle checkpoints at the G1 phase. If inactivated, cells are more prone to push through division and replication, even in the setting of harmful gene mutations, which can lead to malignancy.

The E6 gene is able to inactivate p53 through association with E6 associated protein. This complex then interacts with p53 and undergoes ubiquitin-dependent degradation of p53. E7 is able to bind and interact with the Rb gene product. E7 has the ability to phosphorylate the Rb proteins, leading to degradation by ubiquitination. This subsequently leads to E2F activation, which produces a family of transcription factors leading to cell proliferation.¹⁹

E-cadherin - cell-cell adhesion molecule associated with both invasion and metastasis, is down-regulated in oral cancers

Deleted in colon cancer (DCC) is a N-CAM-like molecule important for cell - cell contact inhibitor, mutated during oral cancer development.

Growth suppressor intracellular messengers include the adenomatous polyposis coli (APC) gene, a G like Protein frequently mutated in certain familial colorectal cancers. The transcription factor Rb, a known tumor suppressor gene, reduced expression in a small percentage of oral tumours. Retinoic acid receptor-beta also down-regulated in head and neck cancers.^{20, 21}

Conclusion

Research on oral cancer lags behind when compared to cancer from other sites. However, efforts are intensifying through research aiming to expand the knowledge on base of human oral cancer. Hope to master all modes of investigation, which include modern molecular biology, somatic cell genetic technologies, sophisticated and novel cell-culture techniques, molecular epidemiology analysis, and the treatment of oral cancer patients with biologically based therapy, including gene therapy in the next coming decades.

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