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GENES AND ORAL CANCER: A REVIEW

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ABSTRACT

Carcinogenesis is a complex, multistep process in which genetic events within cell transduction pathways governing normal cellular physiology are quantitatively or qualitatively altered. It is a multistage process involving gene, or epigenetic damage in susceptible cells that gain a selective growth advantage and undergo clonal expansion as a result of activation of proto oncogene or inactivation of tumor suppressor gene or both. Multiple genetic events culminate in carcinogenesis, however, not all genetic events occur in all squamous oral carcinomas and similar genetic alterations may occur at different times in the process of carcinogenesis.

KEYWORDS: Carcinogenesis; Genes; Oral cancer.

1. INTRODUCTION

Carcinogenesis is a complex, multistep process in which genetic events within cell transduction pathways governing normal cellular physiology are quantitatively or qualitatively altered.[1]

The process of carcinogenesis involves seven fundamental changes in cell physiology that determines malignant phenotype. These includes 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. Another important hallmark identified for tumor development is the acquired capacity of developing tumors to escape immune control of the body. This formed the basis of immunoediting hypothesis of tumor development.[1]

2. Multistage carcinogenesis

It is a multistage process involving gene, or epigenetic damage in susceptible cells that gain a selective growth advantage and undergo clonal expansion as a result of activation of proto oncogene or inactivation of tumor suppressor gene or both.[2]

The first stage of the carcinogenic process, tumor initiation, involves exposure of normal cells to chemical, physical, or microbial carcinogens that cause a genetic change(s) providing the initiated cells with both an altered responsiveness to their microenvironment and moreover exerts a selective clonal expansion advantage when compared to the surrounding normal cells. The initiated cells may have decreased responsiveness to the inter- and intracellular signals that maintain normal tissue architecture and regulate the homeostatic growth and maturation of cells. For example, initiated cells may be less responsive to negative growth factors, inducers of terminal cell differentiation and/or programmed cell death.[3]

Tumor promotion results in proliferation and/or survival of the initiated cells to a greater extent than normal cells and enhances the probability of additional genetic damage including endogenous mutations accumulating in the expanding population of these cells. The probability of a subpopulation of initiated cells converting to malignancy can be substantially increased by their further exposure to DNA-damaging agents that may activate protooncogenes and/or inactivate tumor suppressor genes. Malignant cells continue to exhibit progressive phenotypic changes during tumor progression and may exhibit intrinsic genomic instability that is manifested by the abnormal number and structure of chromosomes, gene amplification, and altered gene expression.[3]

This classical view of two stage Carcinogenesis involving a mutation, tumor initiation, and an epigenetic change, tumor promotion, has been conceptually important but is also considered to be simplistic in that the number of independent genetic and epigenetic events may be 6 or more in certain types of cancer.[3]

3. Theories of carcinogenesis

3.1 Gene mutation theory

This is the most widely accepted theory, supported by a large volume of experimental data. This theory maintains that somatic gene mutations form the basis of neoplastic transformation and their clonal expansion leads to carcinogenesis. However, it does not explain tumor heterogeneity and aneuploidy and also does not provide explanation for long latent periods between exposure to carcinogens and the development of tumors.[4]

3.2 Aneuploidy theory

According to this hypothesis, a carcinogen initiates carcinogenesis by a preneoplastic aneuploidy, which destabilizes mitosis. This initiates an autocatalytic karyotype evolution that generates new chromosomal variants, including rare neoplastic aneuploidy. This theory provides a plausible explanation for the long latent periods from carcinogen treatment to cancer development and the clonality.[4]

3.3 Epigenetic theory

It has been recognized that non-mutational stable changes occur in cellular genome, which can contribute to carcinogenesis. Such events are broadly termed epigenetic and are thought to involve DNA methylation, genome imprinting and changes in DNA - nucleoprotein structure. Increased levels of methylated cytosine (one of the pyrimidine bases in DNA) results in the elevation of spontaneous mutation rates in the affected genome.[4]

4. Oral carcinogenesis

Oral carcinogenesis is a molecular and histological multistage process featuring genetic and phenotypic markers for each stage, which involves enhanced function of several oncogenes and /or the deactivation of tumour suppressor genes, resulting in the loss of cell cycle checkpoints.[5] It is a highly complex multifocal process that takes place when squamous epithelium is affected by several genetic alterations.[6] It is the progression from a normal healthy cell to a pre-malignant or a potentially malignant cell- characterized by an ability to proliferate autonomously.

According to International Classification of Diseases (ICD version 9, categories: 140-146, 149), oral cancer refers to a subgroup of head and neck malignancies that develop at the lips, tongue, salivary glands, gingiva, floor of the mouth, oropharynx, buccal surfaces and other intraoral locations.[7] The term is synonymous to squamous cell carcinoma (SCC) of oral mucosal origin that accounts for more than 90% of all malignant presentations at the aforementioned anatomical sites.[8]

Oral cancer is estimated by the WHO to be the eighth most common cancer worldwide. However, the incidence of oral cancer has a significant local variation and is increasing in some parts of the world. In India and other Asian countries, oral and oropharyngeal carcinomas (OCs) comprise up to half of all malignancies, with this particularly high prevalence being attributed to the influence of carcinogens and region-specific epidemiological factors, especially tobacco and betel quid chewing.[8]

5. Gene classes involved in carcinogenesis

5.1 Oncogenes

Oncogenes are altered growth-promoting regulatory genes, or proto-oncogenes, that govern the cell's signal transduction pathways, and mutation of these genes leads to either overproduction or increased function of the excitatory proteins. Although oncogenes alone are not sufficient to transform epithelial cells, they appear to be important initiators of the process, and are known to cause cellular changes through mutation of only one gene copy.[9]

5.1.a Oncogenes implicated in oral carcinogenesis

i. Transforming growth factor α (TGF-α)

Aberrant expression of transforming growth factor α (TGF-α) is reported to occur early in oral carcinogenesis, first in hyperplastic epithelium, and later in the carcinoma within the inflammatory cell infiltrate, especially the eosinophils, surrounding the infiltrating epithelium. TGF-α stimulates cell proliferation by binding to EGFR in an autocrine and paracrine fashion. TGF-α is believed to stimulate angiogenesis and has been reported to be found in "normal" oral mucosa in patients who subsequently develop a second primary carcinoma.[9]

ii. Epidermal growth factor receptor (EGFR)

EGFR, the biological receptor of EGF and TGF-á is frequently overexpressed in oral cancers and this was found to be the result of EGFR gene amplification in 30% of oral cancers. It has been suggested that overexpression of the EGF receptor is often accompanied by the production of its ligands, TGF-α and EGF. The interaction of the receptor and its ligands initiates a cascade of events, translating extracellular signals through the cell membrane and triggering intrinsic tyrosine kinase activity. Mutations of genes encoding growth factor receptors can result in an increased number of receptors, or the production of a continuous ligand independent mitogenic signal. Gene amplification and increased numbers of EGF receptors in oral cancers are associated with the degree of differentation and aggressiveness of the tumours.[9]

iii. RAS family

Members of the ras family (H-ras, K-ras, and N-ras) are overexpressed in oral cancers. Loss of control of N-ras might be an early step in carcinogenesis in oral cancers, with increased expression occurring early in dysplastic lesions, ras mutations are uncommon in the progression of oral cancers in the Western world, occurring in less than 5% of all cases. In contrast, 55% of lip cancers have H-ras mutation and H-ras mutation occurs in 35% of oral cancers in the Asian population, where it is especially associated with betel nut chewing.[9]

iv. c- myc gene

c- myc is frequently overexpressed in oral cancers as a result of gene amplification. c-Myc induces both cell proliferation and apoptosis. It requires p53 to induce apoptosis. Retinoblastoma tumour suppressor gene Rb-1 nuclear protein pR6 interacts with the c-myc gene, preventing its transcription, and thus inhibiting cell proliferation.[9]

v. PRAD-1 gene

The PRAD-1 gene located on 11q13 encodes cyclin D which ogether with the Rb gene product controls the G1 to S transition of the cell cycle. The PRAD-1gene is amplified in 30–50% of head and neck cancers. Amplification of this gene is correlated with cytological grade, infiltrative growth pattern, and metastases.[9]

vi. hst-1/ int- 2 gene

The hst-1/int-2 gene encodes a protein that is homologous to fibroblast growth factor, and which in oral cancers has been shown to be involved in tumour growth, and to have angiogenic activity. This gene maps to human chromosome 11q13.3. It is coamplified with int-2 in some cancers. Coamplification of the int-2 and hst-1 genes has also been reported in oral squamous carcinomas.[9]

vii. PTEN

In oral cancer, genetic alterations in PTEN (located at 10q23.3) occur in 5-10% of oral squamous cell carcinoma lesions, but, remarkably, loss of PTEN expression has been observed in upto 29% oral squamous cell carcinoma of tongue.[5]

5.2 Tumour suppressor genes

The crucial event in the transformation of a premalignant cell to a malignant cell is inactivation of cellular negative regulators— tumour suppressor genes—and is regarded to be a major event leading to the development of malignancy. Tumour suppressor genes are most often inactivated by point mutations, deletions, and rearrangements in both gene copies.[9]

i. P53

In normal cell biology, p53 acts as regulator of DNA synthesis. When genomic DNA is damaged, p53 is produced to block cell division at G_1-S boundary and stimulate DNA repair. P53 also activate pathways leading to apoptosis. Mutations of p53 allows tumours to pass through G_1-S boundary and propagate the genetic alterations that lead to other activated oncogenes or inactivated TSGs. P53 has been shown to interact with oncogenic protein E6 of HPV and results in rapid degradation of p53 protein by ubiquitin mediated proteolysis system. Smoking and tobacco use have been associated with mutation of p53 gene in SCC of head and neck.[10]

ii. doc-1 gene

doc-1 gene is mutated in malignant oral keratinocytes leading to a reduction of expression and protein production. Re- expression of doc-1 gene in malignant oral keratinocytes results in reversion of many malignant phenotypes back to normal, rendering the doc-1-transfected oral cancer cell to look and act like normal counterpart.[10]

iii. Thrombospondin 1 (TSP-1)

TSP-1, an extracellular glycoprotein, downregulated in oral cancer cells, has been shown to suppress the ability of malignant oral keratinocytes to induce angiogenesis in vitro. Therefore, loss of TSP-1 function may be a critical event in tumour neovascularization.[11]

5.3 Metastasis genes

Malignant cells, which leave the primary tumor and colonies distant sites, are the major cause of death in patients with solid tumor. The complexity of the metastases process suggests that it may be under genetic control. Genes involved in metastasis are nm23-H1 (NME1) and nm23-H2 (NME2). A combined loss of chromosomes 11p and 17 p is associated with a significantly higher incidence of metastasis in regional lymph nodes of breast cancer. Angiogenesis is required for expansion of the primary tumor, and new blood vessels penetrating the tumor are frequent sites for entry of tumor cells into the circulatory system. Cell must first detach themselves from the primary tumor and it has been suggested that malignant cells have a reduced ability to adhere to each other.[12]

5.4 Apoptosis genes

The production of tumors includes disturbances of the mechanism that control cell death by apoptosis since cells escape normal ageing and death. It is the myc gene that acts as a bivalent regulator of both cell proliferation and apoptosis depending on the availability of growth factors. The normal p53 protein appears to be involved in the induction of apoptosis in susceptible cells. Activated ras, bcl-2 or p53 oncogenes may rescue cells from susceptibility to apoptosis, leading to population expansion.[12]

5.5 DNA repair genes

Mutation in DNA repair genes are known to lead some cancers. Failure of repair has been associated with Xeroderma pigmentosum, Ataxia telangiectasia, Fanconi's anemia, Bloom's syndrome, and Cockayne's syndrome.[12]

6. CONCLUSION

Multiple genetic events that culminate in carcinogenesis include the activation of oncogenes and inactivation of tumour suppressor genes. However, not all genetic events occur in all squamous oral carcinomas and similar genetic alterations may occur at different times in the process of carcinogenisis. This may account for the different clinical behaviour of tumours classified as the

same TNM stage. This may increase our understanding of the molecular basis of these lesions and establish whether different cancer subtypes show different growth characteristics. This approach could ultimately lead to appropriate gene therapy.

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