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Molecular Pathology And Genetics Of Oral Carcinogenesis

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Abstract
Oral carcinogenesis is a multifactorial process involving multitudinous inheritable events that alter normal functions of oncogenes and tumor suppressor genes. Modern research has unveiled a new mutational landscape of oral cancer and factor contributing to the therapeutic resistance. It may be a realistic expectation that early prevention of oral cancer will be possible and this approach may lead to development of target dependent tumor specific drugs and appropriate gene therapy.

Keywords: Carcinogenesis, methylation, leukemia, oncogenes, cytogenetics

Introduction

Oral carcinogenesis is a multifactorial process involving multitudinous inheritable events that alter normal functions of oncogenes and tumour suppressor genes. The prevalence of oral cancer remains high in both Asian and Western countries. [1]

Several threat factors associated with development of oral cancer are now well- known including tobacco chewing, Smoking and Alcohol consumption. [2]

The primary treatment option for oral cancer remains surgery but it's associated with massive defect, incapability to carry out normal oral function. psycho-social stress and complete rehabilitation. Other treatment options alike as chemotherapy and radiotherapy have their own limitations in terms of toxin, intolerants and remedial resistance. [3]

The extent of oral cancer spread is estimated by staging the cancer. The commonly used staging system of oral cancer in TNM system, where T (for tumour) defines size of primary tumours (1- 4) N for lymph nodes) shows extend of cancer spread to lymph nodes in vicinity of organ (N0- N3) M (for metastasis) describes spread of cancer to other region of body vis lymph or blood (M0- M1). The goal is to describe recent advances in our understanding to molecular control of the in numerous pathways related to these processes. [4]

Aetiology and risk factors of oral squamous cell carcinoma

1)Chemical factors

Tobacco

Many reports suggest that tobacco in various forms, including smoking, chewing and in betel quid etc., have carcinogenic potential in oral cavity. The various forms in which tobacco are cigarettes, cigars, pipe and bidi etc. Hookah or chillum are other common forms of smoking in some countries like India. [5]

Tobacco use causes many types of cancer, including cancer of the lung, larynx, mouth, oesophagus, throat,

bladder, kidney, liver, stomach, pancreas, colon and rectum, and cervix, as well as acute myeloid leukaemia. People who use snuff or chewing tobacco have increased risks of cancers of the mouth, oesophagus, and pancreas.[6]

Alcohol

Alcohol is also found to be a major risk factor of OC. Alcohol may have addictive effect and aids in entry of carcinogens into the exposed cells, changing the metabolism of oral mucosal cells. Recent studies depict pure ethanol does not cause the development of OC [7].

Drinking alcohol can cause cancer of the mouth, throat, oesophagus, larynx, liver, and breast.

2) Biological Factors

A) Viruses

Viruses can destroy host cellular apparatus and modifying DNA and the chromosomal structures inducing proliferative alterations in the cells. HPV [8] and HSV have been established in current years as causative agents of OC. The commonly detected HPV in head and neck squamous cell carcinoma is HPV-16, followed by HPV-18, HPV-31, and HPV-33.

HSV-1 is associated with sores around the mouth and lip and is suggested to be a causative organism of OC [9]. Risk of oral cavity and pharyngeal cancer is high among human immunodeficiency virus patients indicating a link between HIV and OSCC. Certain viruses like Epstein Barr Virus, human herpesvirus-8 and cytomegalovirus are also reported as risk factors of OSCC in certain studies.[5]

B) Syphilis

The data on association between syphilis and OC is weak. There are reports of 19 and 6% serological positive cases for syphilis among tongue cancer patients.[5]

C) Candida

Candida plays a role in initiation of OC. Clinical studies have reported that nodular leukoplasia infected with Candida has a tendency for high rate of dysplasia and malignant transformation. [10]

3) Dental Hygiene and Related Factors

There is inverse association between oral hygiene and OC. Poor oral hygiene and chronic irritation from sharp teeth also play a possible role in the development of OC. There are several scattered evidences on the role of Oro-dental factors in the causation of OC. [5]

4) Nutritional factors

Dietary deficiencies are also reported to play a role in the development of OC. This requires more clinical and experimental evidence for establishment with development of OC. Higher intake of fruits and vegetables lowers the risk of oc. [11]

Molecular Pathogenesis

1)Oncogenes and protooncogenes

Oncogenes are growth regulating and promoting genes that control transduction pathways of cell signals. Therefore, a mutation of these genes can lead to overproduction in the function of the stimulatory proteins [12]

These genes were initially discovered in retroviruses which causes cancers in birds and cats by virtue of a highly tumorigenic ‘molecular hitchhiker’, a mutated gene(oncogene) not native to the virus but picked up from a homologue in the eukaryotic genome.[13]

Aberrant expression of several oncogenes: tumour suppressor gene and proto-oncogenes such as epidermal growth factor receptor (EGFR/c-erb 1), members of the ras gene family, c-myc, int-2, hst-1, PRAD-1, and bcl-1 play a key role in cancer progression [14]

Some well-known oncogenes and their encoded proteins: [2].

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Table I. *Common genetic alterations in Head and Neck Carcinoma (HNC) (Modified from Kim and Califano, 2004).*

Location and/or gene	Type of alteration and frequency	Reference
9p21-22/ $p16^{INK4a}/p14^{ARF}$	Loss of heterozygosity (LOH) in 70%	Califano, 1996 (11); El Naggar, 1995 (14)
3p21/ *RASSF1A*	30% LOH in precancerous lesions	Kim and Califano, 2004 (13)
11q13/*(PRAD-1/Cyclin D1/hst-1/int-2)*	Amplification in >33% of HNCs	Kim and Califano, 2004 (13); Balz, 2003 (16)
9p21/p15	Hypermethylation in 30% of OSCCs	Shaw, 2006 (22)
9p21/p16 (CDKN2A)	Hypermethylation in 76% of OSCCs	Sanchez-Cespedes, 2000 (33); Ha and Califano, 2006 (30)
EGFR	Alteration of pathway by overexpression or other mechanism in 90%	Grandis, 1993 (41)
	Amplification in 30% of OSCCs	Scully, 1993 (42)
H-ras	Mutation in 55% of lip cancers	Milasin, 1994 (45)
	Mutation in 35% of OSCCs	Kuo, 1994 (46)
17p13/*p53*	Mutation in 79% of HNCs	Balz, 2003 (16)
	Overexpression in 47% of precancerous lesions	Warnakulasuriya, 1998 (7)
19q34/*DAPK*	Hypermethylation in 27% of sera from HNC patients	Sanchez-Cespedes, 2000 (33)
10q26/*MGMT*	Hypermethylation in 56% of saliva samples	López, 2003 (34)
	Hypermethylation in 7- 68% of primary tumours	Ha and Califano, 2006 (30)

HNC: Head and neck carcinoma; RASSF1A: Ras association domain family 1A.

Overexpression and amplification of cellular oncogene EGFR have been reported in a 7,12-Dimethylbenz(a)anthracene (DMBA) induced hamster cheek pouch malignant OC model Transforming growth factor-alpha (TGF-α) is known to promote neovascularization and mitogenesis. It has been shown to be aberrantly expressed in human OC and in hamster oral tumour [5]

2) Genetic Alterations

Genetic alterations define molecular basis of carcinogenesis which includes point mutations, amplifications, rearrangements, and deletions. [5]

The major epigenetic modification in tumours is methylation. Alterations in the methylation patterns can play an important role in tumorigenesis. Epigenetic modifications are frequently connected with the loss of genetic expression and important for the multiple indispensable genetic events during carcinogenesis. Malignant progression takes place because these alterations can inactivate DNA repairing genes.

Methylation patterns of p16, methylguanine- DNA methyltransferase (MGMT) and Death- associated protein kinase (DAP- K) genes in smears of cases suffering from head and neck cancer showed abnormal hypermethylation patterns by a methylation specific polymerase chain response (PCR).[15]

3)Tp53 Gene

The p53 gene, frequently referred to as the" guardian of the genome," is a critical tumour suppressor gene that plays an elemental part in regulating cell growth, precluding cancer, and maintaining genomic stability. TP53 is a tumour suppressor gene which prevents carcinogenesis by instigating G1 cell cycle arrest. triggered p53 (protein product of TP53) is a DNA-binding transcript factor that targets different proteins that are involved in apoptosis (e.g., Bad, Puma, Apaf1) induction of cell cycle arrest (e.g., BTG2, CDNK1, GADD45) and activation of DNA repair mechanisms (e.g., p48) after exposure to UV light or other DNA damaging agents [4]. Inactivation of p53 leads to inheritable change which represents the most in all mortal cancers [5]. variation of the p53 gene occurs as point mutations and deletions. Point mutations result in a structurally altered protein that sequesters the wild- type protein, which inactivates it in a" dominant-negative" fashion. Deletions also

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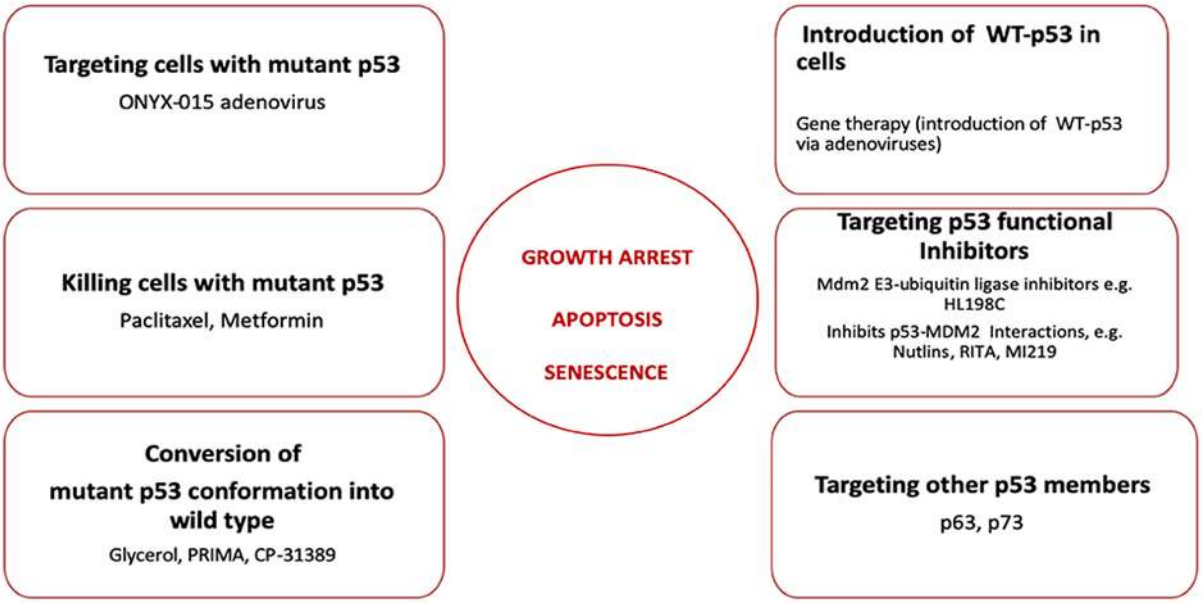
leads to a reduction and loss of p53 expression and protein function [3]. TP53 mutations can be segregated into disruptive or non-disruptive groups. Disruptive mutations due to presence of early stop codon irregularities in the DNA binding areas occurs and induce substantial loss of function. It results in, restriction of apoptosis or cell- cycle arrest leading to neoplasm cell survival and treatment failures. Disruptive and non-disruptive mutations are linked with resistance to standard anticancer medicines similar as Cisplatin, anthracyclines and antimetabolites. P53 also stimulates transcript of MDM2, hence they're balanced via negative feedback process. The discovery of p53 homologs, p63 and p73, has opened new areas of cancer exploration. Treatment Strategies Targeting p53 have been developed to restore the function of mutant p53 in oral cancers.[4] .

They’re epitomized as follows:



In gene therapeutic viruses are genetically manipulated into vectors similar as adenovirus which has extraordinary partiality for cells lining the upper aerodigestive tract, to deliver a gene not causing any complication by themselves [16]. The taxane medicines(paclitaxel) are extensively used to kill the cancer cells as it inhibits microtubule polymerization only in cells containing mutant p53. Another medicine metformin, which is used to enhance the insulin perceptivity in type II diabetic cases, can widely induce apoptosis in cells devoid of active p53.

4)Cytogenetic of oral cancer.

Oral carcinogenesis is a multistep process in which genetic events lead to the disruption of the normal regulatory pathways that control basic cellular functions including cell division, differentiation, and cell death. Several studies have shown that there is a genetic component in the developed of carcinoma. These include reports of the Occurrence of familial aggregations of cancer, involving oral cancer, with carcinoma developing at a younger age.

Whether patients develop single site oral cancer or multiple site oral cancer, much evidence has accumulated to suggest that multiple genetic events lead to oral cancer.

Genetic alterations known to occur during carcinogenesis including point mutation, amplifications, rearrangements, and deletion. Point mutations (single base changes) can lead to overactivity or inactivity of gene products. Several studies have identified specific genetic alteration in oral carcinomas and in premalignant lesions of the oral cavity.

Loss of heterozygosity (LOH) was reported at 9p21-p22 in 72% of tumours. These authors also identified significantly greater allelic imbalance in patients with TNM stage 4 disease compared with stages 1-3.[17] More recently, these researchers reported allelic loss

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in 77% of premalignant lesions similar to that found in oral carcinomas, with 55% of cases showing microsatellite instability. & These patients carried a 73% probability of developing oral squamous carcinoma within five years.

Approximately two thirds of all head and neck cancers contain a deleted region in chromosome 9p21-22. [18] Gain of DNA content by aneuploidy may also be a predictor of cancer in precancerous lesion. Oral leucoplakia lesions show higher rates of malignant progression.[19]

Genetic damage in oral cancer cells can be divided into two categories. Dominant changes, most frequently occurring in proto-oncogenes but also in certain TSGs, result in gain of function. Recessive changes, mutations most frequently noted in growth-inhibitory pathway genes or commonly in tumour suppressor genes, cause loss of function. [20]

4)Tumour suppressor gene

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. Tumour suppressor genes and is regarded to be a major event back leading to the development of malignancy

Mutation of p53 occurs either as a point mutation, which results in a structurally altered protein that sequesters the wild-type protein, thereby inactivating its suppressor activity, or by deletion, which leads to a reduction or loss of p53 expression and protein function. [17]

This overexpression is related to the cell proliferation index and mdm2 expression but is independent of p53 protein alteration71.

Another suppressor gene is INK4-ARF, whose product, pl6 protein, acts as powerful inhibitor of cyclin-dependent kinases (CDK4 and CDK6). Thus, inhibition of this factor, along with overexpression of cyclin D1, increases CDK4/6 activity and stimulates cell proliferation. [21]

Using IHC in 220 OSCC samples and 90 premalignant lesions (38 with dysplasia), Soni et al. found dysregulation of the pl6/pRb/D 1 cyclin pathway to be an initial event in the onset of epithelial dysplasia. Thus, 90% of OSCCs and 83% of premalignant lesions showed altered expression of some protein of the pRb pathway. Moreover, simultaneous alteration of the pRb pathway and p53 was related to malignant transformation and a worse prognosis.[22]

5)Cell adhesion molecule

Cell surface molecules might also be inhibiting oral keratinocyte proliferation. primary oral squamous cell carcinomas and concurrent metastatic disease, P-cadherin is consistently up regulated, and localisation of the catenin associated with E-cadherin is altered.

Although the exact genetic events that result in degradation of the E-cadherin -catenin complex in oral carcinogenesis is not understood, mutations of E-cadherin, a-catenin, and ß-catenin in other tumours have been described. At present, it is unknown whether APC controls the E-cadherin-catenin complex in oral carcinoma. Other cell adhesion molecules include the cation dependent, heterodimeric family of integrins, which mediate cell-cell and cell-matrix interactions and play a role in the maintenance of tissue integrity and in the regulation of cell proliferation, growth, differentiation and mutation.

The localisation and the quantity of the x6 chain has been shown to be altered, with high levels of x6 in contrast to B4, both in premalignant and malignant oral mucosa. This suggests that this might be an early but non-specific marker of oral malignancy, and that abnormal extracellular signals might be involved.

This integrin might be important in oral neoplasia because in vitro studies suggest that negative malignant cell lines can be reversed after transfection of the integrin. [17]

Conclusion

Oral cancer is a heterogeneous, aggressive entity. There is a great need for improved diagnosis and management of precancerous epithelium. The spectrum of research activities aimed at reducing the incidence and increasing the early diagnosis and treatment of oral cancer ranges from basic science laboratory research to human clinical trial. [3]

Despite major advances in molecular pathology of HNC and oral cancer. There remain numerous gaps in lur knowledge of molecular markers involved in oral carcinogenesis. Other molecular pathology

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approaches are emerging including assessment of hypermethylation of promoter regions of certain genes (e.g., p16INK4a, MGMT, DAPK1) and tumour stroma interactions, which could provide new and promising data.[1]

Modern research has unveiled a new mutational landscape of oral cancer and factor contributing to the therapeutic resistance. [4] It may be a realistic expectation that early prevention of oral cancer will be possible, and this approach may lead to development of target dependent tumour specific drugs and appropriate gene therapy.[2]

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