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Novel Tumour Suppressor Genes Associated With Oral Cancer

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Abstract:
The cancer of oral cavity is the most prevalent with a recorded incidence rate higher in male than in females. In India, oral and nasopharyngeal carcinomas comprise upto half of all malignancies. The influence of carcinogens and region specific epidemiological factors like tobacco, betel leaf and quid chiming, makes it more aggressive and resistant to treatment. Tumour suppressor genes (TSG's) are genes that prevent cells from acquiring malignant characteristics. The aim of this study is to give a brief review on the novel tumour suppressor genes implicated in oral cancer in the last decade. A review with recent information about tumour suppressor genes in oral cancer and its role from various search engines like medline, google scholar, BiORXIV, medRXIV, Chem RXIV, MESH, cochrane etc. Novel genes and signalling pathways have been implicated in the process of tumorigenesis in the last few years. The reports and studies discussed in this review helps in gaining knowledge about the role of tumor suppressor genes in oral cancer. A most comprehensive knowledge on the pathways will enable us to choose candidate genes as targets of therapy.

Keywords: Genetic predisposition, oral cancer, prevalence, tumour suppressor genes, tumorigenesis
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I. INTRODUCTION

The incidence of oral cancer is rising in most countries. In the general male population, oral cancer is the 6th most frequent cancer (Scully et al., 2001). SCC (Squamous Cell Carcinoma) accounts for most of the oral cancers and is associated with avoidable etiological factors. (Scully et al., 2011). It affects the tissue lining of the mouth which is perfectly visible for dentists during examination. Dentists being the first to encounter such changes in oral cavity have the responsibility to counsel and effectively treat the disease tumor suppressor genes are genes which prevent cells from acquiring malignant characteristics. The loss of these genes may even be more important than proto Oncogene / oncogene activation for the formation of human cancer cells (Rivelin et al.,2011). A tumor suppressor gene also known as an antioncogene, is a gene that protects a cell from one step on the way to cancer. When the mutation occurs, it leads to a loss or reduction in its function, the cell can progress to cancer, usually in combination with other genetic changes. The loss of these genes may be even more important than proto-oncogene activation for the formation of many types of human cancer cells. TSGs can be grouped into various categories such as caretaker genes, landscaper genes and gatekeeper genes (Rivelin et al., 2011). TSGs in oral cancer have been analyzed a lot in many studies. The aim of this review is to highlight the importance of TSGs in oral cancer and provide an outline on a brief understanding of tumour suppressor genes. Previously our team had conducted numerous studies (Ashwin et al., 2015, Smiline et al., 2019, Renuka et al., 2017, Shahana et al., 1993, Marickar et al., 2014, Ashwatha et al., 2017, Vaishali et al., 2018) and lab studies (Aafreen et al., 2019; Girija et al., 2019, Smiline et al 2018, Girija et al., 2018) and *in vitro* studies (Paramasivam et al., 2020, Vijayashree et al., 2018,Vijayashree et al., 2018) over the past 5 years. The idea for this review stemmed from the current interest in the community.

II. ORAL CANCER PREVALENCE

Oral cancer accounts for 10.4% of all cancers worldwide (GLOBOCAN 2018 report). Oral cancer is a major public health problem in the Indian subcontinent, where it ranks among the top three types of cancer in the country. The difference in incidence and partner of oral cancer can be due to an overall effect of ageing of population as well as some regional differences in the prevalence of specific risk factors. The common etiological factors include consumption of tobacco, heavy alcohol, smokeless tobacco are the main reasons (Warnakulasuriya et al., 2009). A variety of suspected risk factors may include chronic isoutation, poor oral hygiene, viral infection, occupational exposure, malnutrition etc. Oral cancer refers to a subgroup of malignancies of head and neck that develop at the lips, tongue, oropharynx, buccal surface salivary glands, floor of the mouth and other intra oral locations which is according to International Classification of diseases. The term is synonymous to squamous cell carcinoma that accounts for almost all the malignancies at the aforementioned anatomical sites (Shah et al., 2003). In India oral and oropharyngeal carcinomas comprise hay of all malignancies due to influence of carcinogens and region specific epidemiological factors and tobacco and betel quid chewing (Jemal et al., 2005). Tumour suppressor genes are genes which prevent cells from malignant characteristics.

III. RISK FACTORS:

The most important risk factor for the development of oral cancer is tobacco and alcohol consumption (Black et al., 1993). Several studies have supported a significant familial component in the development of oral cancer. The estimates of risk in first degree relatives of oral cancer patients vary widely and have been reported to be 1.7, 9.25, 103. 511 or 3.812 in various studies, although it should be noted that some of these studies refer to head and neck cancer in general (Ogden et al., 2005). Oral cancer patients whose relatives have upper respiratory and digestive tract tumours are also more likely to develop a second primary tumour, an important cause of treatment failure. Genetic aggregation of oral cancer, mostly with an autosomal dominant mode of inheritance was reported in a small percentage of oral cancer patients (Nair et al., 2004). The genetics for oral cancer could be as a result of imitating high risk habits within the

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family, such as smoking and genetic traits (Gupta et al., 2003). Individuals who carry the fast metabolizing alcohol dehydrogenase type 3 allele can be vulnerable to chronic alcohol consumption could develop oral cancer. A recent review suggests that a single nucleotide polymorphism in the *CCND1* gene encodes cyclin D which has been associated with oral cancer susceptibility (Goldstein et al., 1994).

IV. TUMOUR SUPPRESSOR GENES:

The proto-oncogenes that encode proteins promote cell growth. The genes that encode proteins apply brakes to cell proliferation and are called growth regulatory genes, recessive oncogenes, or antioncogenes, but they are most commonly referred to as tumour suppressor genes. In contracting to oncogenes that can affect a cellular change by mutation of only one of the two copies of gene, these genes are inactivated by deletions, point mutations and rearrangements in both of the gene copies in a "two-hit" fashion. Hence, there is a transformation to malignancy of oral keratinocytes (Jemal et al., 2005).

Many TSGs that were initially identified in pediatric tumors that formed early in life because one mutated TSG had already been inherited (Jemal et al.,2005) e.g., the first and prototypic cancer suppressor gene to be discovered was the retinoblastoma (Rb) gene, the discovery of which was accomplished by the study of a rare disease, the retinoblastoma (an uncommon childhood tumor) (Warnakulasuriya et al., 2009). However, identification of TSGs occurred a decade behind the isolation of the first oncogenes, because in cancer cells, TSGs are a "negative phenotype" or an event no longer present within the cell. Knudson predicted that the inactivation of both copies of TSGs occurs in a "two-hit" fashion through mathematical models analyzing genetic pedigrees of pediatric tumor patients. Harris et al. carried out fusion of malignant cells with normal cells in culture and found that malignant phenotype was suppressed in the hybrid cells. This was attributed to the action of TSGs in the normal cells. The loss of this tumor suppressor activity leads to malignancy. The same experiments have been performed with normal and malignant oral keratinocytes to show that TSG loss is necessary for oral carcinogenesis (Jemal et al., 2005).

Mutations and subsequent inactivation of a TSG cause so-called "loss of function," whereas inactivation of an oncogene gives "gain of function." TSGs are, however, most commonly recessive to the normal allele, meaning that if one allele is mutated its phenotype is not expressed as long as the other allele's nature is of a wild type (Ogden et al., 2005). Commonly, one allele of a TSG sustains a mutation (heterozygosity) which inactivates the function of its protein and then the second allele is lost via deletion or gene conversion, resulting either in a loss of heterozygosity (LOH) or a reduction to homozygosity at the locus in the cells of the tumor (Nair et al., 2004). LOH appears to represent the second genetic inactivation step in the complete loss of a TSG locus (Gupta et al., 2003). The TSGs p53 and Rb have been the most extensively studied genes.

p53 GENE

The TSG p53 is known to be mutated in approximately 70% of all known adult tumors. In squamous cell carcinoma of head and neck region (SCCHN) 40–50% of the tumors studied had mutations in this gene. The p53 gene, so-called because it produces a 53 kDa nuclear phosphoprotein (wild type or normal p53 protein) is located on the short arm (p) of chromosome 17 (Ogden et al., 2005). In normal cell, p53 acts as a regulator of DNA synthesis. The wild type (normal) p53, is essential for normal cell growth and the eventual suppression of the malignant phenotype. Inactivation of p53 induces the development of malignancy. Thus, normal p53 acts as a "molecular guard," monitoring the integrity of the genome, usually residing in the nucleus. It is present at a very low concentration in all normal cells and tissues. It has a very short half-life (6–20 min).

p63 GENE

The p63 gene is located on chromosome 3q27–29 and expresses at least six different transcripts. The molecular weights of the p63 protein range from 44 to 72 kDa. A direct role of p63 in tumorigenesis has not been demonstrated to date, though amplification of the 3q27 region has been detected in a number of tumors including squamous cell carcinoma (Shah et al., 2003).

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This is suggestive of a putative role of p63 as an oncogene rather than as a TSG.

p73 GENE

The p73 gene has been considered a candidate TSG because of: (i) its location in a region on chromosome 1p36.6 frequently deleted in certain tumors; (ii) its structural and functional homology with p53; (iii) its imprinting status; and (iv) its reduced expression in some tumors. However, its frequent mutation, biallelic expression and over expression in other tumor types contraindicate this hypothesis (Nair et al., 2004). So far the well-characterized transcripts are p73α and p73β. When p73 protein is overproduced, it can activate transcription of p53-responsive genes and also induce apoptosis. El-Naggar et al., in their study showed infrequent molecular alterations of the p73 gene in SCCHN and that this gene plays a minor role in a subset of these tumors (Williams et al., 2000).

V. RETINOBLASTOMA GENE

Rb is a human childhood disease, involving a tumor of the retina. It occurs both as a heritable trait and sporadically (by somatic mutation). The Rb gene is mapped on chromosome 13q14 (Shah et al., 2003). Rb arises when both copies of the Rb gene are activated. In the familial form of disease, one parental chromosome carries an alteration in this particular region. A somatic event in retinal cells causes a loss of the other copy in the Rb gene that in turn causes a tumor. In the sporadic form of the disease, the parental chromosomes are normal; both of the alleles of retinoblastoma are lost by individual somatic events. The cause of Rb is therefore loss of protein function, usually resulting from mutations that prevent gene expression (as opposed to point mutations that affect the function of the protein product) loss of Rb is involved also in other forms of cancer, including osteosarcomas and small lung cancers (Shah et al., 2003).

Although Rb, and cyclin kinase inhibitors p16, p21, and p27 play a role in the cycle of a proliferating cell, the role that is relevant for tumorigenesis is more probably their function in the quiescent (G0) state. Loss of the Rb gene was said to be uncommon in HNSCC and oral carcinomas (Rayband-Diogene et al., 1996). However, in some reports lack of pRb expression has been observed in 66% of oral squamous cell carcinomas (OSCCs) and 64% of premalignant lesions. p16 expression is absent in 63% of OSCCs and 59% of the premalignant lesion (Scully et al., 2004). Alteration in pRb/p16 expression is an early event in oral tumorigenesis and might be involved in the development of betel and tobacco related malignancies (Todd et al., 1997). In contrast to this, it was also observed that pRb is strongly expressed in OSCCs, irrespective of differentiation (Scully et al., 2004). More studies are clearly necessary to elucidate its role in oral carcinogenesis.

Doc-1 GENE

In malignant oral keratinocytes, doc-1 gene is mutated, thus leading to a reduction of expression and function of protein. Re-expression of doc-1 in malignant oral keratinocytes results in the reversion of many malignant phenotypes back to normal, rendering the doc-1-transfected oral cancer cell to look like and act like its normal counterpart. The precise function of doc-1 is normal oral keratinocyte biology is unclear. An 87 amino acid polypeptide that doc-1 shows a significant homology to a gene product induced in mouse fibroblasts by tumor necrosis factor–alpha (TNF-α). TNF-α decreases proliferation and increases differentiation. TNF-α is responsible for antiproliferative activity in human OSCC cell lines alone or in combination with interferon-α or -γ. It has been proposed that doc-1 may be an important regulator of TNF-α-induced keratinocyte differentiation/apoptosis (Scully et al., 2011).

VI. CYCLIN DEPENDENT KINASE GENES

The existence of p16 first became apparent from analysis of G1 cyclin-CDK immunoprecipitated, where it is found to be associated principally with cyclin D-CDK4. The localisation of *CDKN2A* TSG is on chromosome 9p21. The p16 has been designated as "multiple tumor suppressor 1", as it is mutated in many forms of cancers (Lewin et al., 2003). Genetic alterations involving the 9p21–22 region are common in human cancer, and the *CDKN2A* gene is considered to be the target in this region. Germline *CDKN2A*

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mutations have been shown to predispose to familial melanoma. SCCHN has also been in individuals from melanoma prone kindreds and germline *CDKN2A* mutations have been found. Somatic mutations of *CDKN2A* occur in 10% of HNSCC, and homozygous deletions occur in approximately 50% of cases. Methylation of *CDKN2A* is another important mechanism causing inactivation of this gene in SCCHN. It is thought that loss of 9p is an early event in the development of SCCHN and high frequencies of LOH at 9p21–22 are reported in dysplasia, carcinoma in situ, and SCCHN (Rayband-Diogene et al., 1996).

p27 GENE

The gene p27, a CDKI maps to chromosomes 12p12–12p13.1. Reduced levels of p27Kip1 protein have been identified in a number of human cancers, and in some cases reduced p27Kip1 expression is associated with an increased proliferative fraction. A study by (Jordan et al., 2003), observed that p27Kip1 protein was significantly reduced in oral dysplasias and carcinomas as compared with the normal epithelial controls. In addition, there was a significant reduction in p27Kip protein expression between low- and high-grade dysplasias, suggesting that changes in p27Kip expression may be an early event in oral carcinogenesis. (Rayband-Diogene et al., 1996)

VII. FRAGILE HISTIDINE TRIAD GENE

Fragile histidine triad (FHIT) is a TSG mapped to chromosome 3p14.2. It encodes the FHIT protein which has a dinucleoside triphosphate hydrolase activity. Various investigators have suggested that the FHIT gene is altered in HNSCC with decreased or aberrant protein but no mutations or deletions (Gupta et al., 2003). Loss of function of the protein may be important in the development and/or progression of head and neck cancer (Rayband-Diogene et al., 1996). In the absence of the FHIT protein, di-adenosine-tetraphosphate may accumulate, leading to DNA synthesis and cell replication (Weinberg et al., 2014).

VIII. E-CADHERIN GENE

E-cadherin is one of the most important molecules in cell-cell adhesion in epithelial tissues. It is localized on the surface of epithelial cells in regions of cell-cell contact known as adherens junction. Classical cadherins, E, and N-cadherins being the best characterized play important roles in the formation of tissues during gastrulation, neurulation, and organogenesis. (Williams et al.,2000). The human epithelial (E)-cadherin gene maps to chromosome 16q 22.1. It encodes a 120 kDa glycoprotein with a large extracellular domain, a single transmembrane segment and a short cytoplasmic domain, which interacts with the actin cytoskeleton through linker molecules, α-, β-, and γ-catenins.

IX. CONCLUSION

Novel genes and signalling pathways have been identified in the process of tumorigenesis in the last few decades. A more comprehensive knowledge on the pathways will enable us to choose candidate genes as targets of therapy. In the near future, as a realistic expectation, early prevention of cancer will be possible as this approach may lead to development of target dependent drugs and appropriate gene therapy.

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XI. CONFLICT OF INTEREST:

None

XII. REFERENCES:

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