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Novel Tumour Suppressor Genes Implicated In 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 association with oral cancer and its role was derived from various sources such as Medline, Google scholar, 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 would help in gaining knowledge about the role of tumor suppressor genes in oral cancer. A more comprehensive knowledge on the pathways will enable us to choose candidate genes as targets of therapy.

Keywords: Genetic predisposition, innovative technique, oral cancer, prevalence, tumour suppressor genes, tumorigenesis

INTRODUCTION

Cancer is a multifactorial disease caused by both environmental and genetic factors. The defect in a single gene might not always be responsible for the development and progression of cancer. Instead, accumulation of mutations in vital genes drives the transformation of normal to malignant cells. Tumor suppressor genes are a group of genes which is involved in the suppression of cancerous growth and development. The name "anti-oncogenes" have been used synonymously to indicate these crucial checkpoint genes which suffered loss of function mutations (Figure 1). It has been evidenced that a "two-hit" process works in most cases wherein, both the copies experience mutations resulting in the functional loss of the product. One of the most popular tumor suppressor genes is p53 whose loss has been documented in several types of cancer. The major consequence of this ablation is uncontrolled proliferation of the cells due to the loss of control over DNA repair process, cell cycle arrest and apoptosis. Previously our team had conducted numerous in silico studies pertaining to molecular genetics[1-2], herbal studies[3-9], microbial genetics[10-12] and other in vitro studies[13-16] over the past 5 years. Our department is passionate about research we have published numerous high quality articles in this domain over the past years ((Kavitha et al., 2014) , (Praveen et al., 2001),(Devi and Gnanavel, 2014), (Putchala et al., 2013), (Vijayakumar et al., 2010), (Lekha et al., 2014a, 2014b) (Danda, 2010) (Danda, 2010) (Parthasarathy et al., 2016) (Gopalakannan, Senthilvelan and Ranganathan, 2012), (Rajendran et al., 2019), (Govindaraju, Neelakantan and Gutmann, 2017), (P. Neelakantan et al., 2015), (PradeepKumar et al., 2016), (Sajan et al., 2011), (Lekha et al., 2014a), (Neelakantan, Grotra and Sharma, 2013), , (Jeevanandan and Govindaraju, 2018), (Abdul Wahab et al., 2017), (Eapen, Baig and Avinash, 2017), (Menon et al., 2018), (Wahab et al., 2018), (Vishnu Prasad et al., 2018), (Uthrakumar et al., 2010), (Ashok, Ajith and Sivanesan, 2017), (Prasanna Neelakantan et al., 2015). The idea for this review stemmed from the current interest in the community.

Novel tumor suppressor genes

TFPI2 (Tissue factor pathway inhibitor 2)

The TFPI2 gene codes for a member of the serine proteinase inhibitor family. The protein encoded is found to inhibit several serine proteases such as trypsin, chymotrypsin, kallikrein, plasmin etc., A recent study by Kim et al[17], identified that the expression of TFPI2 was low owing to the hypermethylation of the promoter regions. The consequence of which led to transcriptional silencing of the associated gene, as observed in the OSCC cell lines. Also, the in vitro study was replicated in 33 OSCC tissues from patients, accounting for a majority (97%) of hypermethylation in the TFPI2 gene. Earlier Wang[18] et al, reported the TFPI2 gene was inactive in the nasopharyngeal carcinoma cell line (NPC). Abnormal methylation was observed in 66.7% of NPC cell lines and more than 80% in primary NPC tumors in comparison to normal epithelial cells of the nasopharyngeal region. The ectopic expression of TFPI-2 gene product resulted in apoptosis, inhibition of cell proliferation, cell migration etc.,

p63 and p73 genes

The p63 or TP63 gene belongs to the p53 and p73 family, playing a very important role in the process of carcinogenesis. Lo Muzio et al,[19] investigated the role of p63 in tumorigenesis to reveal its biological function as a potential prognostic marker in oral cancer. Immuno-histochemistry was applied to demonstrate the expression of p63 in oral squamous cell carcinoma tissues alongside with normal mucosa. The p63 was found to be over-expressed or amplified in poorly differentiated tumors. Furthermore, they reported that patients with increased expression of p63 suffered poorer survival rates when compared to those with reduced p63 expression. A diffused expression correlated with aggressive and poorly differentiated tumor associated with poor prognosis. Although considered as oncogene in some instances, p63 as tumor suppressor has been demonstrated in several other studies. The role of p63 in oral cancer is yet to be explored. A closely related member is the p73 protein, which functions by suppressing the epithelial-mesenchymal transition.[20] In vitro experiments designed to demonstrate the anti-cancer property of Abrus agglutinin (AGG) resulted in upregulation of p73. Moreover, the knockdown of p73 decreased AGG-induced apoptosis.[21]

KRT84 (Keratin 84) gene

A very recent study by Liu and colleagues[22] identified KRT84 as a novel tumor suppressor gene implicated in OSCC. The in vitro analysis of gene and protein expression in HSC-3 and normal human oral gingival epithelial cell line HOEC were assessed using quantitative real-time PCR and Western blot analysis respectively. Interestingly, the mRNA levels in HSC-3 cells were found to be significantly lower than in the HOEC cells. The protein expression correlated well with the mRNA expression. Immunohistochemistry based analysis revealed a decreasing trend in the intensity of protein encoded by KRT84 gene in OSCC samples from stage I to IV.

SOX7 gene

SOX7 (Sex Determining Region Y-Box 7), is a transcription factor belonging to the SOX family of genes. The protein is involved in the regulation of embryonic development and determination of the cell fate. SOX7, acts as a transcriptional regulator by forming a protein complex. They are reported to play a vital role in tumorigenesis. Oh and team[23] investigated the effects of SOX7 gene product on the proliferation, colony forming ability and invasive property of OSCC cells. Experimental evidence demonstrated the biological role of SOX7 in OSCC cases. The silencing of SOX7 by using small interfering RNA conferred the ability of cell proliferation and invasion upon SCC-4 cells. The treatment of SCC-9 and SCC-25 cells with SOX7 peptide, restored the tumor suppressing effect, wherein a marked decline in cell proliferation, colony formation and invasion was observed. Tissue level expression analysis also revealed a significant decrease in the levels of SOX7 when compared to normal oral mucosal cells. The decreased expression was also associated with advanced TNM stage, lymph node metastasis and poor prognosis.

Per2 gene

Period Circadian Regulator 2, encoded by Per2 gene is a transcriptional repressor which forms the prime factor in regulating the circardian rhythm. These proteins are involved in a wide array of functions including metabolism, cardiovascular, renal and endocrine functions. The dysregulation of this protein is implicated in sleep disorders and several types of cancer. The clock gene Per2 serves as a tumor suppressor and is expressed at lower levels in tumor tissues. Liu and team[24] investigated the biological functions of Per2 by inducing stable overexpression or silencing of the gene. It was found that Per2 expression was diminished in OSCC cells. The overexpression of Per2 was found to promote autophagy and apoptosis in OSCC cells, thereby inhibiting cell proliferation. In contrast, the OSCC cells with a silenced Per2 demonstrated increased expression of PIK3CA, p-AKT, p-mTOR, p62 and Beclin1, eventually leading to the inhibition of apoptosis. It was concluded that Per2 suppressed OSCC progression by inducing autophagy and promoting apoptosis in a PI3K/AKT/mTOR pathway dependent manner.

microRNAs as tumor suppressors

microRNA-486-3p

MicroRNAs are known to regulate gene expression by inhibiting translation or causing degradation of mRNA. Discoidin domain receptor-1 (DD1) is a signal transduction protein which undergoes autophosphorylation at tyrosine residues. The expression of DDR1 has been reported in several cancer types including lung, breast, brain, oral, liver cancer etc., A very recent study by Chou et al[25], identified microRNA-486-3p as an upstream regulator of DDR1. The consequence of which is known to influence proliferation of cells and anti-apoptotic nature. Experimental evidence showed that microRNA-486-3p bound to 3'-UTR of DDR1 resulted in the downregulation of DDR1. The microRNA-486-3p was co-regulated along with the gene ANK1 through epigenetic processes. It was also proposed that arecoline, the alkaloid present in betel nut resulted in aberrant methylation leading to inhibition of microRNA-486-3p which eventually leads to over-expression of DDR1.

microRNA-367

Phosphoinositide-3-Kinase Regulatory Subunit 3 (PIK3R3), serve as second messengers in growth signaling pathways. Dysregulation of this protein has been observed in asbestos-related lung carcinoma and cervical non-keratinizing squamous cell carcinoma. Sun et al., reported that the regulation of PIK3R3 is regulated by miR-367 in OSCC. The study demonstrated a dramatic decrease in the levels of miR-367 in OSCC tissues and cell lines which correlated with an increase in the expression of PIK3R3. The knockdown of PIK3R3 resulted in the inhibition of cellular proliferation and invasion of OSCC cells, thus demonstrating the role of PIK3R3 in the process of tumorigenesis. Interestingly, the PIK3R3 was targeted by miR-367, thereby exerting a partial control over the proliferation and invasion of cells.[26]

microRNA-106a

LIMK1 (LIM Domain Kinase 1) is a serine/threonine kinase that regulates actin polymerization via phosphorylation. The protein is expressed ubiquitously during the development process. They also play an important role in many cellular processes associated with cytoskeletal structure. Increased expression of LIMK1 has been documented in many cancer types. The microRNA-106a has been found to influence the expression of LIMK1, which was reported recently by Shi et al. The expression of LIMK1 was inversely related to the expression of miR-106a in OSCC cells. In silico analysis has also predicted miR-106a potentially targets LIMK1. Introduction of miR-106a into OSCC cells mimicked the effects produced upon silencing of LIMK1. In contrast, LIMK1 overexpression reversed the effect of miR-106a.[27]

microRNA-205

Kim and colleagues demonstrated the function of miR-205 in KB oral cancer cells. As with all the tumor suppressor components the expression of miR-205 was much lower in KB cells when compared to normal oral keratinocytes. The induced overexpression of miR-205 resulted in the increase of cell cytotoxicity and induction of apoptosis through caspase activation. The induction of cytokine IL-24 was strongly affected soon after the transfection of miR-205 into KB cells. The IL-24 component acts as an anti-angiogenic, immunostimulatory and inducer of apoptosis. Thus, the above report provides substantial evidence on the restoration of tumor suppressor activity upon targeting with miRNAs.[28]

microRNA-769-5p

The miR-769-5p is yet another microRNA which is shown to be downregulated in tissues and blood of patients suffering from OSCC. In vitro and in vivo experiments revealed that miR-769-5p suppressed cell proliferation, invasion and metastasis, with marked increase in the apoptosis process. The miR-769-5p targets JAK1/STAT3 pathway providing a clue towards therapeutic target development.[29]

microRNA-139-5p

HOXA9 (Homeobox Protein Hox-A9) belongs to a class of transcription factors called the homeobox genes. These factors regulate gene expression, morphogenesis and differentiation by acting as DNA binding transcription factors. A translocation in this gene is known to produce a fusion product between this gene and NUP98, which is known to be associated with myeloid leukemogenesis. A study conducted by Wang and team demonstrated the effect of miR-139-5p as a tumor suppressor in OSCC. The miR-139-5p levels were low with a concomitant increase in the levels of HOXA9. The ability of proliferation, invasion and migration was significantly diminished in miR-139-5p mimic group compared to the control group, thus providing evidence on the targeted effect of the microRNA studied.

The novel tumor suppressor genes and microRNAs identified in recent years are of great value since they can be used as prognostic markers. Various studies pertaining to identification of key targets or genes involved directly or indirectly in the process of molecular carcinogenesis has paved the way for creation of a hub of genes intended for screening and early detection of oral cancer.[1,2] A more exhaustive knowledge on these markers could also aid in designing therapeutic targets intended to target the tumor cells.

CONCLUSION

Novel genes and signalling pathways have been implicated 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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Conflict of Interest

None

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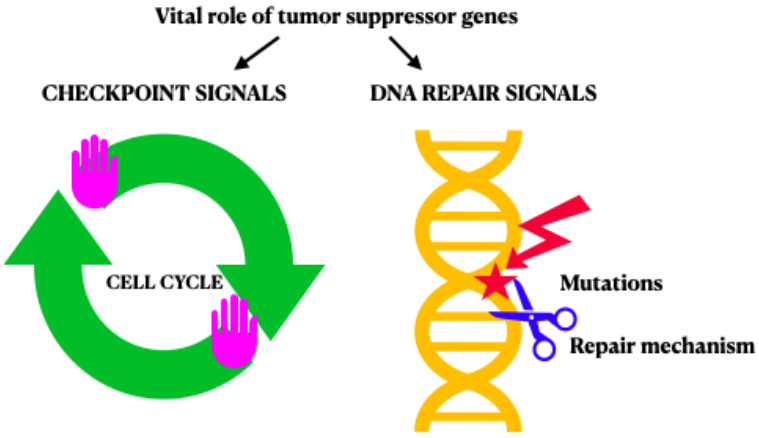

Fig.1: Diagramatic representation of the functions of tumor suppressor genes