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Review Article

Development and Progression of Oral Cancer: The Role of Proteins

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ABSTRACT

Oral cancer is the most common and vigorous type of cancer. It is one of the major problems in India. High pervasiveness, hindered diagnosis and limited access to healthcare systems contribute to high mortality rate. This review explores the etiologic and pathophysiologic nature of oral cancer, the role of major proteins such as tumour suppressor proteins, oncogenes, cell adhesion molecules and salivary protein biomarkers for early detection, therapeutic targets and the role of pharmacogenomics which can reduce the risk present in treatment approaches. This review showcases the important roles these factors play in the diagnosis, prediction, protection and treatment planning for oral cancer, with the intention to improve clinical outcomes and promote earlier intervention plans.

INTRODUCTION

Oral cancer is one of the critical health issues in India and other South-east Asian countries where it ranks among the top three types of cancer in the country. [33] The rates of oral cancer in India are escalating, affecting approximately 20 people per 1,00,000 individuals representing greater than 30 percent of all cancers in the country within the age group above 35 years. [34] The difference in occurrence and pattern of the disease can likely be due to the synergistic effect of ageing and regional differences in disease-specific risk factors. [35] It is a serious public health concern in India. Firstly, it is diagnosed before or at the last stages, which results in low medication opportunities and increased cost to the patients who typically cannot afford this type of medication. [36] Secondly, rural areas in low-income countries also have limited access to healthcare services. As a result, postponing the medications has also been greatly associated with advancement in the stages of oral cancer. [37] Thirdly, oral cancer likely affects the underprivileged people as they have higher exposure to risk factors such as the use of tobacco. [38] The early detection and prevention of oral cancer reduces this concerning health burden. In light of this, we focus on oral cancer, etiology, pathophysiology, the major roles of proteins in the formation, detection and the role of

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pharmacogenomics in the treatment plan for the management of oral cancer.

WHAT IS ORAL CANCER?

Oral cancer (mouth cancer/ oral cavity cancer) is the abnormal and uncontrollable growth of the epithelial cells present in the lining of the lips, mouth, and the upper throat. [1] Generally, it starts as an ulcer that thickens over time and grows continuously. The formation of a lump takes place, which is known as a Tumour. [2] The symptoms may include red or white patches in the mouth lasting for more than 2 weeks, ulceration, bumps in the neck, pain, difficulty in swallowing, loose teeth, etc. [3]

ETIOLOGY

1) Tobacco smoking – The greatest risk of all is found in certain isolated Indian and South American cultures where the practice of reverse smoking takes place, in which the burning end of the cigar/cigarette is placed in the mouth. Around 50% of the oral malignancies caused by smoking are due to reverse smoking. [4] The aromatic hydrocarbon benz-pyrene and nitrosamines present in the tobacco are the important carcinogens that causes oral cancer induced by tobacco smoking. Their metabolites bind with DNA to form adducts, which are responsible for critical mutations during DNA replication. [5]

2) Betel quid – In recent research, the ability to develop carcinoma, mutations and genotoxic potential of betel quid ingredients like areca nut and tobacco was found. [6] The studies on oral mucosal fibroblasts using cell proliferation assays have proven that a few ingredients present in the betel quid can activate carcinoma and cell proliferation in squamous cells present in the oral cavity. It has been shown that DNA damage occurred due to methylation-inducing agents and reactive oxygen species, which were produced as intermediates during the metabolism of betel quid in our bodies. [7]

3) Micronutrient - Vitamin E has been shown to prevent tumour formation in Hamsters and this has been attributed to the stimulation of a potent immune response by vitamin E. It also has the capability to minimize the formation of hydroxyl radicals, which in turn reduces the oxidative stress present on the cells. Clinical testing with α-tocopherol, which is an antioxidant, has been shown to be more effective in the treatment of oral squamous cell carcinoma. Although it has beneficial use in the treatment of oral cancer, the treatment testing must be done with caution as increased levels of Vitamin E have been indicated to trigger skin tumour conformation. [8]

4) Viral infection – Human papilloma virus (HPV) is the most common virus that causes the formation of carcinoma in the oral cavity. They contain DNA as the main infecting part and have the tendency to move towards epithelial tissue, specifically to squamous epithelium. They induce cancer progression by using their gene products that are capable of interrupting the cell cycle process. The tumour suppressor genes like p53 and Rb get bonded to the viral proteins such as E6 and E7, respectively, causing disturbance in the cell cycle, promoting uncontrollable growth and triggers inflammation. [9]

5) Genetic factors – Alterations in genes play a major role in the formation and advancement of oral carcinoma. The mutations in tumour suppressor genes disturbs the cell cycle regulations and cause genomic instability. Amplification of oncogenes leads to uncontrolled cell proliferation and initiates tumour growth. Abnormalities in chromosomes such as gain of 11q3 and loss of 3p, 9p and 17p also leads to malignancy. [12,51 and 52]

PATHOPHYSIOLOGY OF ORAL CANCER

It develops through a multistep process involving the genetic, epigenetic, environmental and immune–related factors. Chronic exposure to carcinogens induces compounds like nitrosamines and acetaldehyde, which cause DNA damage in the oral epithelium. [10] It progresses from normal epithelium to dysplasia and eventually leads to invasion of carcinoma by accumulation of genetic alterations, including the mutation of TP53, PIK3CA and CASP8. [11] Simultaneously, chronic inflammation mediated by cytokines like IL-6 and TNF–α creates a tumour-promoting environment. The activation of signalling pathways such as EGFR/AKT promotes uncontrolled proliferation and survival. The hyper methylation silences the tumour suppressor gene and causes genomic instability. [12] The infected cells activate the telomerase enzyme, which provides replicative immortality. The hypoxia stimulates the production of Vascular Endothelial Growth Factor, leading to angiogenesis. The loss of E–cadherin and increased metalloproteinase allows cancer cells to invade the surrounding tissues and undergo metastasis. Resistance to apoptosis is achieved through mutation. The microenvironment achieves an immunosuppressive nature through the triggering of T regulatory cells. [13] Ultimately, this leads to repeated malignant transformation, progression and resistance to the therapy of oral cancer.

WHAT ARE PROTEINS?

Proteins are complex macromolecules that are composed of numerous amino acids linked by peptide bonds. It is important for various biological processes. They act as enzymes, structural components, signalling molecules and transporters within the cell. The specific arrangement of the amino acids determines their unique three-dimensional structure and functions. [14] They are synthesized through the translation process, where the ribosomes decode the messenger RNA (mRNA) to connect the amino acids in the correct order. [15] Their various functions are necessary for the maintenance of the cell structure, communication, metabolism, and immune responses. Abnormalities in the protein structure or expression can cause diseases like cancer.

Major role of proteins in oral cancer

1) Tumour suppressor protein – it is a gene that protects a cell from the occurrence of cancer. The inactivation or mutation of these can progress to carcinoma. This can occur due to a combination of other genetic changes. The inactivation is done by point mutation, deletions and rearrangement of the gene copies. [16] Few tumour suppressive genes are:

a) p53 gene – it is known to be mutated in approximately 70% of all known adult tumours. It regulates the DNA repair, cell cycle suppression and apoptosis. Its dysfunction leads to genomic instability and accumulation of mutations. Overexpression of the mutated gene indicates an advanced tumour stage. [17]

b) p27 gene - it is a protein which are found to be in reduced amounts in majority of the carcinogenic patients. In some cases, the reduced protein levels are associated with excessive proliferation of the tumour cells. It is predicted that the changes in gene expression might be an event in the early stage of oral cancer. [18,19,20]

2) Oncogenes – these become activated when proto-oncogenes are overexpressed by carcinogenic agents. Activation of oncogene might be due to chromosomal translocation, gene amplification, point mutation or deletion. This causes dysregulation of major pathways that control the growth and differentiation of cells. [21]

a) EGFR (Epidermal Growth Factor)– It is present at increased levels in many solid tumours due to focal gene amplification or genomic copy number gain. In a few cases, up-regulation and triggering of EGFR in oral carcinoma is caused by somatic mutation of the receptor. [22] These mutations transmit important tyrosine kinase activity to the mutant receptor, which leads to uninterrupted activation of subsequent oncogenic pathways. [23]

3) Cell adhesion molecule – These are very essential for maintaining the stable structure of the squamous epithelium present in the oral cavity. In normal epithelium, keratinocytes are attached to each other. [24]

a) E–cadherin – It is one of the most important molecules that has adhesive properties. Its main function is to keep the basement membrane intact. It is present on the surface of epithelial cells, specifically in the regions of the cell-cell adhering junction. It also plays a role in the development of tissues during organ formation. Suppression of E-cadherin is the main step that causes the disintegration of tumour cells from the epithelial layer. Therefore, this promotes invasiveness and metastasis of the tumour. [25]

4) Salivary biomarkers – The saliva contains many proteins and polypeptides, which are present in large proportions and play a major role in the identification of carcinogens. There are more than 100 biomarkers that are reported in the saliva using various techniques like Protein biomarker– High performance liquid chromatography, Enzyme linked immunosorbent assay, Two dimensional gel electrophoresis, etc. [26]

a) Interleukin-6 (IL-6) – It is a pro-inflammatory protein which plays a major role in the immune cell response, triggering of inflammation and cancer development. In saliva, an increased level of IL-6 has been identified as a biomarker for early detection of oral cancer as a non-invasive biomarker. Increased levels of IL-6 are related to inflammation and growth of the tumours by activating STAT3 signals, which leads to proliferation, formation of new blood vessels and immune invasion. [49 and 50]

5) Innate host defence protein – These are the proteins that are present in the host immune system, which responds to a microbial attack. Almost every tissue takes part in innate host defence as a barrier surface like, mucosal epithelia in the oral cavity and gastrointestinal tract. [39] Pathogens are detected by pattern recognition receptors. Innate immune system reacts to the microbial attack quickly through cytotoxicity, phagocytosis and secretion of antimicrobial polypeptide (AMPs-proteins). The AMPs acts as a link between the microbial infection and the formation of a tumour in the oral cavity. [40,41 and 42]

a) S100 proteins – It is a type of AMP which are involved in proliferation, differentiation, timed cell death, invasion and initiating inflammation. Gene expression of various S100 proteins depends on various cellular factors. Despite having structural similarities, they show a variety of different functions inside and outside of the cell. [43 and 44] For example, S100A7 is overexpressed in oral carcinoma, leading to the advancement of proliferation and concomitant suppression of differentiating tumour cells. The level of expression correlates with the stage of malignancy. [45,46,47 and 48]

6) Therapeutic targets - They have shown their usefulness in managing various carcinogens, mostly because of their ability to reduce toxicity by several folds when compared with chemotherapeutic drugs. The resistance to targeted cancer therapies is due to the emergence of various genetic and non-genetic mechanisms. [28 and 29]

a) VEGF (Vascular Endothelial Growth Factor) - It is easy to access as it circulates in the blood and directly acts on endothelial cells; therefore, it is used as one of the therapeutic targets. Carcinogenic blood vessels that are formed due to this factor are disorganised, twisted and contains high interstitial pressure. These factors significantly reduce access to chemotherapy. The major approaches are VEGF receptor targeted treatment that includes the inhibition of VEGF, which causes the reduction of blood vessel abnormalities. [30]

7) Prognostic indicator – These are the measurable variables that provide information about the progression of a disease condition, regardless of treatment. [31] These factors help to estimate the outcomes like survival, disease recurrence, complications, patient counselling or design and interpret clinical trials. [32]

a) Cyclin d1 – The crucial role of cyclin-dependent kinase in the cell cycle is to perform the phosphorylation of retinoblastoma protein. Prevention of cells from replicating is achieved by decreased phosphorylation of retinoblastoma protein, which forms a tough complex with the transcription factor and can cause the inhibition of E_2F, leading to dysregulation of cell proliferation, therefore contributing to oncogenesis that acts as a prognostic indicator of oral carcinoma. [27]

ROLE OF PHARMACOGENOMICS IN THE TREATMENT OF ORAL CANCER

It improves the treatment for oral cancer by utilizing the patient's information regarding their genetics which helps in the management of chemotherapy choice, especially with the drugs like fluoropyrimidine (5-FU) where in the variations in DPYD gene decreases the activity of dihydrpyrimidine dehydrogenase, an enzyme that is responsible for metabolizing the 5- FU, elevating severe toxicities such as decreased white blood cell count, inflammation of mucosal membrane and diarrhoea in heterozygous carriers. [53] Similar conditions can be analysed using pharmacogenomics and provide an effective treatment that has high efficacy and reduced adverse effects, therefore adapting from trial and error chemotherapy to accurate and patient-focused care. [54]

CONCLUSION

Oral cancer is a critical public health concern in some developing countries like India, due to its high pervasiveness, hindered diagnosis and limited access to healthcare systems. The development and mutation of oral carcinoma is complex; it involves many risk factors such as tobacco use, betel quid, micronutrients and viral infections. There are various proteins that play critical roles in tumour suppression, oncogenesis, cell adhesion, and metastasis processes. Tumour suppressor proteins like p53 and p27, oncogenes such as EGFR, and molecules like E–Cadherin and VEGF not only plays a key role in oral carcinogenesis but also are a potential diagnostic and therapeutic targets. Additionally, salivary protein biomarkers help in the early detection of carcinoma with the non-intrusive tools present in the saliva. Acquiring more knowledge about the molecular pathways and the various roles of proteins in the development and diagnosis can lead to improvised diagnostic methods, more efficient treatment and improved patient care outcomes.

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