Oncogenes Associated with Oral Cancer - An Update

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Abstract

Oral cancer and oropharyngeal cancer represent a large group disorder that falls into the head and neck category and is considered as the most leading cause of death in developing countries. The prime reason for the high mortality rate of patients suffering from oral cancer is the delay in the diagnosis of the type and grade of oral cancer and also in the offering of prompt treatment. A report from India demonstrated that 35% of oral squamous carcinoma contains H-ras gene mutations which are an oncogene. Advances in the field of oncogenes have created an instrument to examine the various phases of carcinogenesis, including progress from premalignant to metastatic stages. These systems have direct importance to oral malignancy where the precancerous stage is very much characterized. Primer investigations into the articulation and capacity of oncogenes recommend anomalies including the individual proliferation of at least three kinds of these oncogenes. Some of the oncogenes associated with oral cancer are studied in this article and the factors contributing to its molecular basis like chromosome instability and telomerase activity are also discussed briefly. There are many risk factors and other predisposing factors that may affect the diagnosis, prognosis, and progression of oral cancer and are also discussed in this article.

Keywords: *Proto-oncogenes; Oncogenes; Oral cancer.*

Introduction

Oral cancer is considered to be the most common form of cancer affecting males with a greater prevalence in the Asian-population. Around 90% of head and neck cancer are typed as oral squamous cell carcinoma (OSCC)[1]. OSCC is the 6th most common type of cancer with poor clinical indications which needs to be surpassed with advancements in its molecular basis. Oncogenes are capable of inducing cell transformation and is hence implicated in the molecular basis for cancer[2, 3]. The gain of function mutations in oncogenes are considered to be the prime etiological factors influencing the transformation of a proto-oncogene into an oncogene[4]. Prevailing changes most often happening in proto-oncogenes in addition to certain tumor silencing genes (TSGs) bring about an increase in the magnitude of the disease. Environmental exposure to pro-carcinogens, along with habits such as pan, gutka, and tobacco usage also increases the transformation and progression of the disease.

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Oncogenes

Proto-oncogenes assume a significant role in controlling cell division and apoptosis during development and improvement. In such a situation when a proto-oncogene becomes mutated, or the cell makes additional duplicates of the proto-oncogene, the gene becomes hyperactive and leads to uncontrolled cell division, eventually leading to the advancement of a malignant growth cell from an ordinary cell. When a proto-oncogene is actuated by a transformation, we at that point allude to it as an oncogene. So it's the

initiation of oncogenes that is one of the processes that add to the formation of a tumor. Proto-oncogenes transform to oncogenes which are an essential part of cancer progression[5]. Point mutations in proto-oncogene results in a constitutively active protein[6] which is the result of localized gene amplification of a DNA strand containing proto-oncogenes.[7] There are many types of oncogenes involved in the progression of oral cancer some of which are discussed.

RISK FACTORS ASSOCIATED WITH ORAL CANCER

The use of smoking and smokeless tobacco such as pan, gutka, etc., seems to be the principal risk factor associated with oral cancer in Asian subcontinent[8]. Other habits, occupations, environmental exposure, sharp tooth, etc may be responsible for the increased vulnerability of the patient towards oval cancer. Some or all of these factors may contribute to the prognosis of the patient and if identified as a precancerous or cancer-prone condition may even to its early diagnosis. There is a low prevalence of screening and poor awareness of oral cancer and precursor lesions[9]. The risk of oral cancer in smokers is more than the non-smokers' population. Even passion smoking is associated with some risk. The danger of creating oral malignant growth relies upon the term and recurrence of tobacco use. Smoking may prompt malignant growth in the mouth or throat, and oral tobacco items are related to disease in the cheeks, gums, and internal surface of the lips.

Virus

Viruses may also be responsible for the development of cancer[10] some of the strongly associated viruses with oral cancer are Epstein Barr virus (EBV), human papillomavirus (HPV 16 and HPV 18)[11] and herpes simplex virus[12]. Other lifestyle choices may also have an impact on the procurement of oral cancer and its progression like occupation, frequency of exposure and so on. Be that as it may, no persuading proof exists that they are a hazardous factor in OSCC. In this manner more investigations are required so as to explain the various parts of infection contribution. So preventive measures against viral agents like vaccinations play an essential role[13] acquisition of a virus that may also serve as a prelude to cancer.

MOLECULAR BASIS

Carcinogenesis is a complex, multistep process with altered signal transduction pathways in case of oral cancer[14]. Dysplasia may be due to premalignant lesions such as leukoplakia, erythroplakia, lichen planus and so on[15]. The state of dysplasia when discovered early could aid in identifying the specific treatment modality.[16] One of the crucial segments of oral cancer is the transformation of proto-oncogenes into oncogenes. Chromosomal instability is a common feature of solid tumours[17], which is responsible for cancer development and progression. Malignant cells consistently contain unusual quantities of chromosomes, called the aneuploid state, which prompts modified measurements and articulation of the entirety of the functions carried on a given chromosome. As malignant cells quickly develop and isolate, they don't adapt well to additional chromosomes, which prompts anomalous chromosome isolation and extra changes in chromosome number as the cells keep on separating. This property of cancer cells is named chromosomal instability.

Telomerase activity was detected in 89% of malignant and 5% of normal oral mucosal tissue[18] which indicates that activation of telomerase is frequent in oral squamous cell carcinoma. This is also clinically useful marker for prognosis of oral cancer. Cell cycle regulation is important in the progression of oral cancer. The overexpression of cycle regulators promote oral cancer progression by enhancing cell proliferation with prevention of GI phase arrest[19] There is a strong relationship between oral squamous cell carcinoma and DNA repair genes[20]. The x-ray repair cross complementing group seems to be a risk factor for predisposition of oral squamous cell carcinoma. Understanding the molecular basis is important because it helps in the development of gene therapies[21] that target specific genes.

Type of Oncogenes

Nuclear Transcription Regulators

They are present in the nucleus and give rise to encoded proteins that are transcription factors. Though they contain many subdivisions, the most involved genes with oral cancer are jun and fos[22]. The most commonly found complex in cancer tissues was the c-fos-Jun D

complex. The current discoveries demonstrate that c-Jun; the significant part of the AP-1 transcription factor is modified in dysplastic epithelium and oral SCC. The overexpression of c-Jun reveals its job in early carcinogenesis. Henceforth, c-Jun may act in various instrumental ways and pathways that lead to a harmful change in oral cells.

Intracellular Signal Transducers

Ras and raf are the most involved genes with oral cancer. The Ras gene gives rise to protein serine kinase and the raf gene generates GTP/GDP binding protein[23]. The H-Ras protein was fundamentally overexpressed in oral carcinoma[24,25]. The vast majority of the OSCC cases indicated positive recoloring with moderate articulation. Most of H-Ras positive cases were found in people with numerous hazard propensities including tobacco usage in some form. H-Ras expression expanded in cases influenced with buccal mucosa site and higher evaluation of carcinoma. Relative mRNA level of H-Ras was essentially raised in oral carcinoma. Protein and mRNA levels of H-Ras were ineffective in relation.

Apoptosis Inhibitors

Numerous genes viz., Bcl-2, Bcl-x, Bcl-xL, Bcl-2-related protein A1, BAG-1, and survivin have been found to be associated with oral cancer. The process of mitochondrial apoptosis is regulated by pro and anti-apoptotic proteins that belong to the BCL-2 family. A balance between the pro and anti-apoptotic protein ensures proper regulation of the programmed cell death which influences the development of an organism. Any dysregulation in the BCL-2 pathway can prevent the process of apoptosis eventually leading to the uncontrolled proliferation of cells facilitating tumor development, progression, and resistance to cancer therapy[26].

Cell Growth Proteins

In case of cancer, growth factors are deregulated. There is over-expression of transforming growth factor x by autocrine mechanism. Thus there is alteration of mutation of the all surface receptor genes there by producing a ligand-independent mitogenic signal[27]. The G-protein coupled receptors are the surface receptors most associated with turnover growth and metastasis and are involved in signal transmission.

DIAGNOSTIC PROPERTY

Oncogenes serve as poor prognostic markers[28] as their presence suggests the initiation or progression of cancer. Oncogenes can serve as diagnostic markers and help in the early diagnosis for example to detect precancerous lesions and mutated oncogenes are distinguished from proto-oncogenes[29]. Confined, community oriented systematic research will help the study of oncogenes in oral cancer reach new heights like advancements in the diagnostic methods and targeted therapy. Some of the microbial infections may also predispose to many future complications in chronic presentations and drug resistance may also play a role [30, 31, 32, 33] which also include cancer and other iatrogenic diseases as well. So knowledge of the properties of potential natural medicaments may prove useful to prevent the chronic persistence of these infections [34, 35] without any drugs but just by incorporating them into our lifestyle. Some of the microbes for example like *Acinetobacter baumannii* is a recently identified orodental pathogen and gene studies [36,37,38,39] pertaining to this may prove imperial in understanding its pathogenesis and so on. Many contemporary medications[40] against these microbes as well as others and preventive measures[41,42] are also being studied through further research.

Conclusion

Cancer is a complex genetic disorder which involves abnormalities in multiple genes which are implicated in one or more biological processes including cell cycle regulation, DNA repair, replication, regulation of gene expression etc. The review highlights the common genes involved in the development and progression of oral cancer. Epigenetic mechanisms also work simultaneously to modify the gene expression of proto-oncogenes. Further research on these epigenetic controllers would aid in deriving strongest association between these oncogenes and oral cancer.

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