Review Article

Genes and oral cancer

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Oral cancers have been one of the leading causes of deaths particularly in the developing countries. Prime reason for this high mortality and morbidity is attributed to the delay in diagnosis and prompt treatment. Relentless research in the field of oncology has led to the advent of novel procedures for the early detection of oral cancers. Molecular biology is highly promising in this regard. It is a procedure that detects alterations at a molecular level much before they are seen under a microscope and much before clinical changes occur. Molecular studies serve as the basis by which we will eventually be able not only to augment clinical assessment and classification of oral lesions but also predict malignant potential of oral lesions, thus reducing the incidence and increasing the scope for early diagnosis and treatment of oral cancers. However, making such sophisticated tools available for the common man in developing countries is one of the most important challenges faced today.

Key words: Cytogenetics, intracellular messengers, oncogenes, oral cancer, transcriptional factors, tumor suppression gene

Introduction

Carcinogenesis is a complex, multi-process in which genetic events within signal transduction pathways governing normal cellular physiology are quantitatively altered.[1] The genetic basis of cancer is now well-established. Under normal conditions, these tightly controlled excitatory and inhibitory pathways regulate oral keratinocyte biology. Basic cellular functions under these controls include cell division, differentiation, senescence and adhesion. These regulatory pathways are composed of extra cellular ligands which bind to cell-surface receptors to generate intracellular signals sent through secondary messengers. These signals either directly alter cell function or stimulate the transcription of genes whose proteins effect changes.[2] Cancer is the result of an accumulation of changes in the excitatory and inhibitory cellular pathways, which may occur at any level of a given pathway. It has been estimated that from three to six somatic mutations are needed transform a normal cell into its malignant counterpart.[1] As the cell accumulates these alterations or mutations, it becomes functionally independent from the surrounding oral epithelium made up of normal cellular functions tightly controlled by these regulatory pathways are subverted in tumor cells, thus enhancing the ability to proliferate, stimulate neo-vascularization and grow by invading locally or metastasizing to distant sites.[3] The histologic progression of oral carcinogenesis is believed to reflect the accumulation of these changes.[4,5]

Genetic damage in oral cancer cells can be divided into 2 categories. Dominant changes most frequently occurring in proto-oncogenes but also in certain tumor suppressor genes (TSGs) result in gain of function. Recessive changes, mutations most frequently noted in the growth-inhibitory pathway genes or commonly in TSGs, cause loss of function.[2]

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Cytogenetics of Human Oral Cancer

For human oral cancer more than 63 karyotypes have been described. Among them recurrent loss

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of chromosome 9, 13, 18 and Y deletions are more commonly reported than others. Among other notable cytogenetic alterations cellular oncogenes B-cell lymphoma-1, int-2 and hst which have been mapped to chromosome Iq, are important as lead to activation of the oncogenes located in these bands and is associated with carcinogenesis.

Approximately two-third of all head and neck cancer cells contain a deleted region located in chromosome 9p21-22,[6,7] which appears in dysplastic and carcinoma-*in-situ* lesions, thereby suggesting that gene in this region is knocked out early in carcinogenesis.[8] Chromosomal region in 3p and 13q also contain regions frequently deleted and may yield new TSGs or oral carcinogenesis.[9]

Oncogenes Implicated in Human Oral Cancer

Oncogenes, gain of functions mutations of highly regulated normal cellular counter parts (proto-oncogenes), are likely involved in the initiation and progression of oral neoplasia.[5] Cellular oncogenes were initially discovered by the ability of tumor cell deoxyribonucleic acid (DNA) to induce transformation in gene transfer assays.[10] These experiments have led to the identification of more than 60 cellular oncogenes.[11] Mechanism of activation of these cellular oncogenes includes point mutations and DNA rearrangements. Several of these cellular oncogenes are homologous of retroviral oncogenes (e.g. the ras gene); others are new oncogenes. Several oncogenes have been implicated in oral carcinogenesis.[5] Aberrant expression of the proto-oncogene epidermal growth factor receptor (EGFRI c-erb 1) members of the ras family, as well as c-myc, int-2, hst-1, PRAD-l and bel, is believed to contribute to oral cancer development.[9,12,13]

Growth Factors

Growth factors can stimulate oral keratinocyte proliferation.[14,15] During oral carcinogenesis, growth factors are deregulated through increased production and autocrine stimulation.[16-18] Transforming growth factor-alpha (TGF-alpha) is over expressed early in oral carcinogenesis by hyperplastic epithelium and later by inflammatory infiltrate, particularly the eosinophills, surrounding the oral epithelium.[18,19] In addition, TGF-alpha likely serves a tumor promoting the role in epithelial carcinogenesis.[20,21] In the head and neck cancer patients who later develop second primary cancer, “normal” oral mucosa over secretes TGF-alpha, suggesting a “premalignant: State of rapid proliferation and genetic instability of the epithelium.[22] Concomitant expression of TGF-alpha and EGFR may indicate more aggressive tumors than those over expressing EGFR alone.[15]

Cell Surface Receptors

Ligand receptor binding activates a cascade of intracellular biochemical steps.[14] Regulation of protein phosphorylation is an important event in cellular function and gene expression. Mutation of genes encoding cell surface receptors can result in an increased number of receptors or production of a constituent ligand-independent mitogenic signal.[2,23,24]

EGFR, the biological receptor of EGF and TGF-alpha, is a 1,70,000 Dalton phosphoglycoprotein frequently found to be over expressed in human oral cancer. Malignant oral keratinocytes possess from 5 to 50 times more EGFR than their normal counter parts.[25] Currently, 3 mechanisms have been postulated to activate the EGFR genes in carcinogenesis:

- Deletions or mutations in the N-terminal ligand binding domain such as those occurring in the viral oncogene verb B;[26,27]
- Over expression of the EGFR gene concurrent with the continuous presence of EGF and/or TGF-alpha;[28,29]
- Deletion in the C-terminus of the receptor, which prevents down regulation of the receptor after ligand binding.[30,31] However, which of these mechanisms are responsible for the oral malignancies are not fully understood. Oral tumors over expressing EGFR exhibit a higher proportion of complete responses to chemotherapy than tumors to low level EGFR expression. Over expression of EGFR presumably due to higher intrinsic proliferative activity could result in higher sensitivity to drug therapy cytotoxic to cells undergoing mitogenesis.[32]

Intracellular Messengers

Intracellular messengers can also be intrinsically activated thereby delivering a continuous rather than a ligand-regulated signal.[24] Of all the members of the intracellular signaling pathway only members of the ras gene family (H-ras, K-ras and N-ras) have been examined in human oral cancer. Of importance, is the realization that the ras binds the guanine nucleotides (guanosine diphosphate and guanosine triphosphate) with high affinity and specificity. They were eventually shown to be analogous to the G-proteins in coupling receptors to the intracellular secondary messenger.[10] However, the role of mutated ras genes in human oral carcinogenesis is presently not clear. A report from India demonstrated that 35% of oral squamous cell carcinoma contains H-ras mutations.[33]

However, studies form the western world has shown that the H-ras mutations are found in fewer than 5% of head and neck cancers.[34]

Transcriptional Factors

Transcriptional factors, or proteins that regulate the expression of other genes, are also altered in oral cancer. Modulation of gene expressions is an important outcome in the alteration of the intracellular pathways.[2] The transcription factor c-myc, which helps to regulate cell proliferation and differentiation, is frequently over expressed in oral cancer.[5] Over expression due to gene amplification of c-myc is most frequently associated with poorly differentiated tumors and with poor prognosis.[35] The genes whose expression is stimulated by c-myc and their significance to oral carcinogenesis are poorly understood. Another transcription factors, the cell-cycle promoter PRADI (also CCNDI or cyclin DI), is a cell-cycle promoter that is also amplified in the head and neck cancer. While cyclin DI is an important promoter of cell proliferation, its importance to oral cancer development is under investigation.

TSGs

TSGs or anti-oncogenes have been documented to confer negative regulatory controls which are lost due to chromosomal alterations during tumor formation. Functional loss of multiple TSGs is believed to be the major event leading to the development of malignancies.[36,37] Unlike oncogenes, which can effect a cellular change through mutation of only one of the 2 gene copies, TSGs are most often inactivated by point mutations, deletions and rearrangements in both gene copies in a "two-hit" fashion. Therefore, the critical events for the malignant transformation of oral keratinocyte, i.e. the loss of function of TSGs are difficult to achieve. This may account, in part, for the length of time required for the formation of adult solid tumors, such as oral cancers.

Many TSGs were initially identified in pediatric tumors that formed early in life because one mutated TSG had been inherited. However, identification of these genes lagged a decayed behind the first oncogene, because, in cancer cell, TSGs are negative phenotypes-an event no longer presents within the tumor cells. Through mathematical models analyzing genetic pedigrees of pediatric tumor patients, Knudson predicted that the inactivation of the both copies of TSG occurs in two-hit fashion.[38] Experimental evidence followed with the observation that normal tumor hybrids demonstrated normal phenotypes, which suggested that normal cells contain the suppressor of the tumor phenotype. These same experiments have been performed with normal and malignant oral keratinocytes.[39] Only after extensive "chromosomal walking" analysis of pediatric tumor with large chromosomal alterations were the first TSGs isolated.[40] Therefore, whole the identification of these "cancer genes" is one of the primary focus of the tumor biologist today, far less is known about TSGs. Until, only three genes-p53, deleted in oral cancer (DOC-1) and thrombospondin I - have exhibited tumor suppressor activity in malignant oral keratinocytes.[41]

P53

The TSG p53 is known to be mutated in approximately 70% of adult solid tumors.[42] Identifications of members of its suppressor pathway, which themselves may be altered, may prove the importance of p53 to a higher percentage of cancers.[35] In normal cell biology p53 acts as a regulator of DNA synthesis. When genomic DNA is damaged p53 is produced to block the cell division at

the GI-S boundary and stimulate DNA repair.[43] P53 also activates pathways leading to apoptosis. Mutation of p53 allows the tumor to pass through G1-S boundary and propagate genetic alteration that lead to other activated oncogenes or inactivated TSGs. The p53 gene appears to be mutated at the transition of superficial to invasive carcinoma.[44] Alteration of p53 genes occurs as the point mutation and deletions.

Point mutations result in structurally altered proteins that sequester the wild type proteins, thereby, inactivating it in a "dominant-negative fashion." Deletion lead to a reduction and loss of p53 expression and protein functions. Not only has p53 has been demonstrated to be functionally in activated in oral tumors, but also restoration of p53 function in oral cancer cell lines and in oral tumors induced in animal models results in the reversion of the malignant phenotype, thereby turning back oral carcinogenesis.[35]

It should be noted that p53 has been shown to interact with the oncogenic protein E6 of the human papilloma virus (HPV), which results in the rapid degradation of the p53 protein by the ubiquitin mediated proteolysis system.[45,46] Similar interaction has been shown for the HPV E7 protein with pRY,[47] which interferes with the regulation of the activity of the E2F transcription factor family, a phenomenon that has profound consequences for the proliferative pattern of the affected cells.

Given the overwhelming body both epidemiologic and laboratory evidence of an association between HPV infection and cervical cancer, HPV can now be considered causal in the etiology of the cervical cancer. Similar mechanism may be involved oral carcinogenesis. Smoking and tobacco use has been associated with the mutation of the p53 gene in squamous cell carcinoma of the head and neck. By immunohistochemistry p53 expression has been shown in oral tumors from patients who were heavy smokers and drinkers.[48]

These authors suggest that the alteration in the p53 gene may be one of the sites of genetic damage in oral cancer. Polymerase chain reaction has been used recently to show an association between a history of tobacco and alcohol use in the high frequency of p53 mutations in patients with SCC of the head and neck.[49]

Dool

Using the Hamster oral cancer model it has been identified and cloned a novel oral TSG named DOC-1. Mutation of these genes in oral keratinocytes leads to a reduction of expression and protein production.[41] Re-expression of DOC-1 in malignant oral keratinocytes results in reversion of many malignant phenotypes to normal, thus causing the DOC-1 transfected oral cancer cells to look and act like its normal counterpart. The precise function of DOC-1 in normal oral keratinocyte biology is presently unclear. However, GenBank sequence search, we have matched the Hamster DOC-1 gene to a gene induced by tumor necrosis factor alpha (TNF-alpha) in normal murine fibroblasts,[50] thereby establishing a linkage of a tumoricidal cytokine to a TSG and suggesting DOC-1 to be a down-stream mediator of TNF-alpha biological action, such as apoptosis. Experiments are currently in progress to test this hypothesis.

Thrombospondin 1 (TSP1)

A series of elegant studies from the laboratories of Noel Bouck and Peter Polverini has linked suppression of tumor induced angiogenesis with TSP1.[51] Using Hamster cheek pouch oral cancer model, Moroco *et al*. has shown that the control of angiogenesis was lost during oral carcinogenesis.[39] This loss regulation of the angiogenic phenotype in the malignant keratinocytes was correlated with a reduction of TSPI in the conditioned media[51] with the oral growth-suppressors and the signal transduction pathway.

Cell surface molecules may also be important in inhibiting oral keratinocyte proliferation. E-cadheren, a cell to cell adhesion molecule associated with both division and metastasis, is down regulated in oral cancers. DOC is an N-Cam-like molecule believed to be an important cell-to-cell contact inhibitor that is mutated during oral cancer development.[52]

Growth suppressor intracellular messengers may include the adenomatous polyposis coli (APC) gene, a G-like protein frequently mutated in certain familial colorectal cancers.[53] Recent evidence suggests that the APC gene may be altered in the premalignant oral lesions.[54] The transcription factor RB a known TSG,

has been shown to have reduced expression in a small percentage of oral tumors but has yet to exhibit any tumor suppressor activity in oral cancer cells.[52]

Retinoic acid receptor-beta (RAR-b) is down regulated in the head and neck cancer.[55] Retinoids are currently under investigation for prevention and reversion of oral premalignant lesions.[56]

Conclusion

It is clear from this and another recent review that research on oral cancer lacks behind that of cancer from other sites. However, efforts are intensifying through research aiming to expand the knowledge base of human oral cancer; there is a great need of improved diagnosis and management of precancerous epithelium. The spectrum of research activity aimed at reducing the incidence and increasing the early diagnosis and treatment of oral cancer ranges from basic science laboratory research to human clinical trials. Today, no single laboratory can hope to master all modes of investigation which include modem molecular biology, somatic cell genetic technologies, sophisticated and novel cell culture techniques, molecular epidemiology analysis and treatment of oral cancer patients with biologically based therapy, including gene therapy. A successful oral cancer research program must therefore integrate these diverse but intimately related scientific disciplines into a planned and focus program that binds together their strengths and guides them to a mutually accepted goals. It is now essential to create a localized, collaborative network of scientist from different specialties, each with new or established interest in oral cancer, for scientific vigor and rapid progress in investigative oral cancer research.

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