Review Article

Current Molecular Concept of Oral Carcinogenesis and Invasion.

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Abstract:

Oral cancer is the commonest cancer in the South East Asia. Approximately 20-30% suffer from oral caner in out of all cancer patients diagnosed each year in this subcontinent. In Bangladesh the chronic use of betel quid and chewing tobacco in the mouth has been strongly associated with an increased risk for oral cancer. The last two-decade has been enormous advances in our understanding of cancer at molecular level. This review will give a out line of current knowledge of oral cancer, including basic over view of genetic mechanism involving regulation of cell and producing cancer. It is generally accepted that neoplasm arises from series of genetic alteration that lead to cellular proliferation & differentiation. In this review article here is brief discussion of important gene responsible for oral cancer, role of oncogenic viruses & molecular aspect of oral cancer progression, invasion & metastasis.

Key words: *Oral Cancer, invasion and molecular concept.*

Introduction:

Oral cancer is the sixth most common malignancy and is a major cause of cancer morbidity and mortality worldwide[1] and also a major health problem in this subcontinent. Around 400,000 new cases of oral cancer annually detected worldwide[2]. Oral cancer is the commonest cancer in the South East Asia[3] and in India oral cancer comprises 32%-40% of total malignancy where in western countries it is only 3%-5% of total cancers [4-5]. In some parts of India, Srilanka and south East Asia, 40% of all malignancy is oral in origin, a situation that is attributable to the indigenous habit of chewing a mixture of tobacco, areca nut, lime, betel leaf, and spices in a variety of combinations[2]. In Bangladesh it is also one of the most frequent malignant neoplasms and chewing betel quid is thought to be the cause of this disease. A large percentage of people have the common habit of chewing a mixture of betel nut, tobacco leaf, betel quid and scaled lime6. Betel quid may contain some chemical genotoxin reagent that is able to mutate tumor suppressor gene.p53 gene could be one of the specific targets for some betel quid ingredients and betel quid chewing may be a critical environmental factor in the development of oral squamous cell carcinoma[7]. In addition to exposure to tobacco-associated carcinogens, several additional factors and viruses mainly Human Papilloma

Virus (HPV) may play a synergistic role in oral tumorigenesis[5].

So, oral cancer is clearly a multi step process with a multifactoral etiology involving especially tobacco and alcohol use and various genetic changes. Advances in understanding of mechanisms of oral carcinogenesis likely will be necessary to improve survival curves, which, despite better early detection of oral cancer, have plateauted over the past two decades and remain among the worst of all cancer sites[8]. This review is to give a basic out line of current knowledge of genetics to oral cancer formation, its invasion &metastasis. This molecular based understanding can reveal new targets to identify both early &late events in carcinogenic process &thus offer opportunities for treatment &for prevention of oral cancer.

Basic Genetic Mechanism:

All cells contain Genes, which are composed of deoxyribonucleic acid (DNA); a double-stranded coiled molecule. Which located within the nucleus as 23 pairs of chromosome of eukaryotic cells. Proteins are the effectors molecules of all cells, and their formation is dependent on the nucleotides sequences contained in the DNA of a cell[9]. Oral carcinogenesis is a complex, multi step process in which genetic events within signal transuduction pathways governing normal cellular physiology are quantitatively or qualitatively altered[10,11,12]. Under normal conditions, these tightly controlled excitatory and inhibitory pathways regulate oral epithelial cell biology. Basic cellular functions under these controls include cell division, differentiation, and cell death (Apoptosis). An extra cellular ligand, such as a growth factor, binds to a cell surface receptor. The receptor- ligand complex generates excitatory or inhibitory signals sent through intracellular and nuclear messengers that can either alter cell function by changing the effect of proteins[13].

Pathways to cancer:

It now seems clear that random mutations in the genes, which control proliferation or apoptosis, are responsible for cancer. The vast majority of mutations that give rise to cancer are not inherited, but arise spontaneously as a consequence of chemical damage to DNA resulting in altered function of crucial genes[14].

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Epithelium which line the oral cavity give rise to more than 90% of cancer. They are a constantly renewing cell population in health, where the rate of production of new cells is exactly matched by loss of cells through two mechanism: shedding or desquamation of cells from the surface, and programmed cell death- a process called apoptosis. Thus the balance between proliferation and apoptosis is critical, and it is the accumulation of defects in these pathways, which give rise to cancer. The regulation of apoptosis and cell proliferation is control by oncogenes, tumor suppressor genes, and growth factors in oral squamous cell carcinoma. Precise regulation of all this positive and negative signaling is essential to maintain normal cell growth, and disturbance of such regulation can lead to neoplasia [15]

External growth signals and cancer cell:

Normal cells proliferate in response to an array of external, mostly locally produced, growth factors produced by one cell type to activate other cells. These external growth factors include, epidermal growth factor (EGF), fibroblast growth factor (FGF), tumor growth factor alpha (TGF-a) and platelet derived growth factor (PDGF). These growth factors exert their proliferative action after binding to appropriate receptor of target cells Tumor cells have found mechanisms to enable constant activation of these proliferative signals. These mechanisms differ from cancer to cancer depending upon cell type, and within a specific tumor type by pure chance, but the end result is continued mitogenic stimulation[14].

Proto-oncogene/oncogene and Tumour suppressor gene:

Proto-oncogenes code for proteins that regulate the many functions of the normal cell. Proto-oncogenes act in a dominant fashion to positively regulate cell growth and differentiation[16]. When proto-oncogenes are altered, a modified gene called an oncogene is formed. These genes have been described as fundamental components of multistep tumorigenesis. A number of mechanism by which oncogenes are activated have been described. Known mechanisms include point mutations of the gene, gene amplification, and gene overexpression. Precise regulation of all this positive and negative signaling is essential to maintain normal cell growth, and disturbance of such regulation can lead to neoplasia (Fig-A).Mutation in the ras gene family have been shown to play an important role in the development of a number of human cancers. In India, 35% of oral squamous cell carcinomas were shown to have a H-ras mutation[17], whereas in western Europe and in the USA have shown that ras mutations are found in less than 5%. In India the prevalent use of betel quid chewing and reverse smoking, are probably initiating agents in oral cancer these agents may be responsible for the high incidence of ras mutations in the Indian population compared with western Europe[18]. p53 is well established tumor suppressor gene. Alteration of p53 tumour suppressor gene constitutes one of the most common genetic aberrations in a broad spectrum of human cancers[19]. p53 mutation at particular hot spots have been indicated in tobacco chewing associated oral squamous cell carcinoma from India and Pakistan[20]. So,p53 alterations may be useful early bio markers in chewing tobacco associated oral malignancies,further implications in selection and monitoring of patients in chemo prevention trials,and may have implications in probablep53 gene therapy[21]. The genetic damage found in cancer cells is of two sorts: the dominant damage of proto-oncogene, which causes a gain of function whereas recessive lesions of tumor suppressor genes, growth suppressor genes,which cause loss of function[18].

Oncogenic virus:

Human Papilloma Virus (HPV):

Oral Cavity harbors a variety of different HPVs. These viruses in conjunction with carcinogens present in tobacco could contribute to carcinogenesis[22]. Presence of HPV- 16 and 18 in malignant lesions suggests its importance as high risk factor for oral carcinogenesis[23].HPV is detected with increased frequency in oral carcinomatous epithelium in comparison with normal oral mucosa[24].There is significant relationship between HPV-16 and p53 mutation suggesting that HPV-16 infection has strong mutagenic effect on p53 gene, which causes OSCC[25].The E-6 protein of HPV binds with p53 protein and inactivate the tumor suppressor activity by promoting p53 degradation[26].How ever, a geographical difference in HPV infection exists.Difference in life styles contribute to the discrepancy in HPV detection rate[27]. It is conceivable that viruses might contribute aetiologically in some cases of oral carcinoma[28].

Epstein-Barr viruses (EBV):

EBV has been strongly associated with African Burkitt's lymphoma &naso pharyngeal carcinoma[29].EBV DNA &antigens have not been demonstrated in oral carcinoma tissue or cell lines.

Cytomegalo virus and Vericella Zoster Virus (VZV):

There is at least on serological evidence on association between them and oral cancer. But no reliable data yet available.

Human herpes viruses (HHV):

There is high prevalence of serum anti bodies in a higher prevalence of serum anti bodies to HHV-6 in patients with oral carcinoma. But the findings are certainly not specific[28]. A recent population based case-control study of Herpes Simplex Virus(HSV) & infections in oral cancer has indicated an association with HPV and apossible increased risk with HSV[30].

Carcinogenesis:

The multistep process of carcinogenesis is driven in large part by anomalies of proto-oncogenes (mutation,

amplification, protein over expression) and inactivation of tumor suppressor gen. The process of carcinogenesis can be divided into the three stages of initiation, promotion, and progression based on evidence from experimental models[31].Clinically, human tumors can be divided into three groups; premalignant lesions, primary tumors, and metastasis. In certain tumors, premalignant lesions are difficult to be detected at this time. Thus, two types tumor progression pathways can be drawn as shown in Fig-B. Premalignant lesions include dysplasia, hyperplasia, leukoplakia, and adenoma. Cells in the premalignant lesions (initiated cells) are clonally expanded because of the acquisition of selective growth advantage by genetic alteration (or alterations) that occurred in the cells. The initiated cells may be less responsive to negative growth regulators and cell differentiation inducers. The initiated cells or normal cells convert to malignant cells (converted cells) by additional or multiple genetic alterations and produce primary tumors. The converted cells may not be responsive to any of the negative growth regulators, so they continue to expand by pushing surrounding tissue away. During expansion of the converted cells in the primary site, new clones with more malignant phenotypes appear through further accumulation of genetic alterations in some of the converted cells. New clones (Progressed cells) may be more invasive and highly metastatic, and thus metastatic nodules are produced by highly selected and progressed cells, which bear all the genetic alterations necessary to maintain malignant phenotypes acquired during progression [32].(Fig-C)

Invasion & metastasis:

The major characteristic of oral cancer cells is their ability to invade foreign tissues and form metastatic foci at distant locations in the body. At the early stage of invasion the tumor cells become detached from the primary tumor and start migration into adjacent tissue, probably by getting other extra cellular signals or guided by group of chemotactic factors. In most cases the invading cells reach lymphatic or blood vessels (angiogenesis) from where they can spread throughout the body, extravasate and initiate metastasis. Once the tumor cells have spread throughout the body the process may become a hopeless task to control. Therefore, one major focus of cancer research has been the molecular mechanisms behind the development of metastasis.

The process of metastasis is an extremely complicated mechanism that involves a series of sequential steps, many of which can now be explored in detail at the protein or gene level. One of those events is the removal of the extra cellular matrix to allow the spreading of tumor cells. But how these matrices are destroyed to facilitate the migration and proliferation of tumor cells has been the subject of intensive research in recent years.

It has become well established that removal of extra cellular matrix in tumor invasion occurs through the action of a variety of degradation enzymes produced either by the tumor cells themselves or cells of the host tissue[33,34].Matrixmetalloproteinase expression has a potential role in helping oral squamous cell carcinoma cells to invade through the extra cellular matrix (Fig-D). All these observations add evidence that degradative enzymes have a key role in paving the way for invading tumor cells. Thus, there is an urgent need to understand the molecular mechanism(s) which underlie the local and regional spread of this disease.

It is widely accepted that breach of the basement membrane, which separates the epithelial and mesenchymal compartments, represents the first step in tumor cell invasion. This structure is comprised of several components including type four collagen, laminin and proteoglycans and its destruction, as evident in squamous cell carcinoma of the head and neck, permits the local and regional movement of the tumor cells35. In our previous study, we already have been concluded that degradation of MMP play vital role in oral cancer invasion.[36, 37]

Conclusion

The development of molecular biology techniques over the past 20 years has opened up a whole new dimension in our understanding of cancer. This understanding has revealed large numbers of exciting new targets for the development of effective therapies. Some of which have already entered clinical practice as gene therapy, which will be the pioneer of all treatment option in coming decade.

But in this twenty first century Bangladesh is in far back ward position. In our neighboring countries like India & Srilanka there are several studies on oral cancer. Bangladesh is also in same danger zone of oral cancer, as we have the same oral habits. But the magnitude of oral cancer is largely unexplored here though there is high incidence of oral cancer in this country. Most of our people get very minimum dental health facilities and deprived of a balanced diet. They are not aware regarding oral hygiene and bad oral habits, which can cause carcinoma. There is no significant epidemiological study or basic clinical research on oral cancer till now. Most of our doctors or scientists are not interested for such basic research. This may be we doesn't have proper lab facilities, more over our government is not concern about this subject.

This review article highlighted about different molecular mechanism occur in oral cancer, invasion, metastasis, its prevention, early diagnosis, and treatment of cancer by gene therapy. By allowing the direct targeting of the genetic defects that are responsible for malignancy, it is a realistic expectation that early prevention of cancer will be possible and tumor-specific drugs will soon be available which will spare normal cells from the devastating effects of conventional cytotoxic agents. Bangladesh should also share with these enormous advances in gene therapy. We

should enrich our cancer research at molecular level that can give us a whole new dimension for prevention and treatment of oral cancer.

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