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PATHOGENESIS OF ORAL CANCER

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Abstract

The purposes of this study are to study the pathogenesis of oral cancer and to see the role play of oncogenes, onco-suppressor genes in cancer growth and their mutation type. There are many predisposing factors which may influence the development of cancer. The factors are divided intrinsic (hereditary) and extrinsic factors (bacteria, viruses, fungi, chemical, drugs, radiation, trauma, heat, cold and nutrition). These agents may act individually, in combination with other carcinogen (co-carcinogen) or in combination with other agents that do not in themselves causes cancer (promoters), but that help the carcinogens to mutate or depress cells, but in the mechanism still enigma. Oncogenes onco-suppressor genes are normal genes in human. Oncogenes functions are as growth factor (e.g. sis), growth factor receptor (e.g. erbB1), signal transducer (e.g. ras) or nuclear factor (e.g. myc, jun). Tumor (oral cancer) will be arises if oncogenes and onco-suppressor genes function are disturbed by some carcinogen and these genes have mutation, deletion, amplification or translocation. That was also related to the loss or inactivation of onco-suppressor genes such as p53, so that causes the loss of the normal growth regulation/strait control that associated with tumorigenesis.

Introduction

Cancer of oral cavity is one of the numbers cancer in the body and Oral Squamous Cell Carcinoma (OSCC) accounts for more than 95% of all cancer in the oral cavity (Saku T, 2008) and most of oral cancers arise in the tongue which majority of oral cancer present at an advanced stage III or IV. Epidemiological study and experimental evidence indicate a

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causal relationship between some carcinogenic with oral cancer such as chewing tobacco, betel quid chewing, smoking and drinking. [1-4], but the exact cause of cancer is unknown.

There are many predisposing factors, which may influence the development of cancer. These factors are divided into intrinsic (hereditary,developmental factors) and extrinsic factors (bacteria, viruses, fungi, chemical, drugs, radiation, trauma, heat, cold and nutrition).[5,6] These agents may act individually, in combination with other carcinogen (co-carcino gen) or in combination with other agents that do not in themselves cause cancer (promoters), but that help the carcinogens to mutate or depress cells.[6]

According to Reksoprawiro (2008) report the incidence of oral cancer in DR. Soetomo hospital Surabaya, Indonesia from 1998-2007 was 184 cases, which sex ratio between male and female was 50% to 50% and the high frequency in age distribution was female was 41 to 50 year old and male was 51 to 60 year old (Fig. 1).

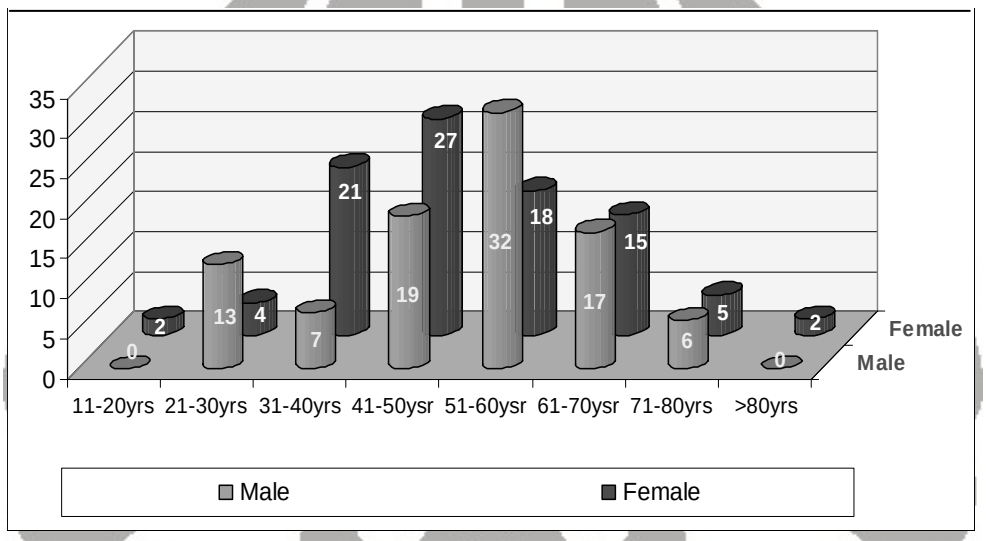

Figure 1: Sex and age distributions of oral cancer patients at DR. Soetomo Hospital, Surabaya, Indonesia in year 1997-2007. (Source: Reksoprawiro S. Surgery in locally advanced oral cancer. 2008)

It is amazing that not all of carcinogens cause cancer, when we consider the numerous carcinogens encountered daily. There might be certain internal mechanisms that either afford protection to humans or make the susceptible. One of these internal mechanisms may be genetic susceptibility or resistance.[7,8] However, the molecular basis of oral cancer is still enigma.

Oncogenes are genes present in human cells, but were originally identified in retroviruses, hence the nomenclature v-onc. They have mutated to produce abnormal products. Onco-suppressor (tumor suppressor) genes are normal genes that its function as depressor of cancer development. *Carcinogenesis* is a sequence of cancer formation process. The purpose of this study of pathogenesis of oral cancer and to see the role play of oncogenes in cancer growth.

Literature Review Pathogenesis Of Oral Cancer

It has been know for a long time that cancer has a multifactorial etiology and is a multi step process involving initiation, promotion and tumor progression [9,10]. *Oncogenes* have been implied to play a critical role in various stages of human tumors. The proto-oncogenes in normal cells may be activated and contribute to neoplastic transformation through point mutations, translocation, deletions, amplification or other genetic mechanism.[11] The common mechanism

for cancer initiation appears to be through damage to DNA resulting in uncontrolled cell proliferation.

There are several gene classes involved in carcinogenesis, which is effected by genetic changes. They are Oncogenes, Tumor suppressor genes, metastasis genes and DNA repair genes.[12]

Oncogenes

Oncogenes are important cellular genes which, in general, act in a positive way in the normal growth regulatory pathway of the cell. Oncogenes can act as growth factors, growth factor receptors, signal transducers and nuclear factor (Figure 2 & 3). Oncogenes are very closely related to proto-oncogenes, but they have mutated to produce abnormal products, or control mechanism have altered to allow gene-expression and thus they have lost the normal activity.

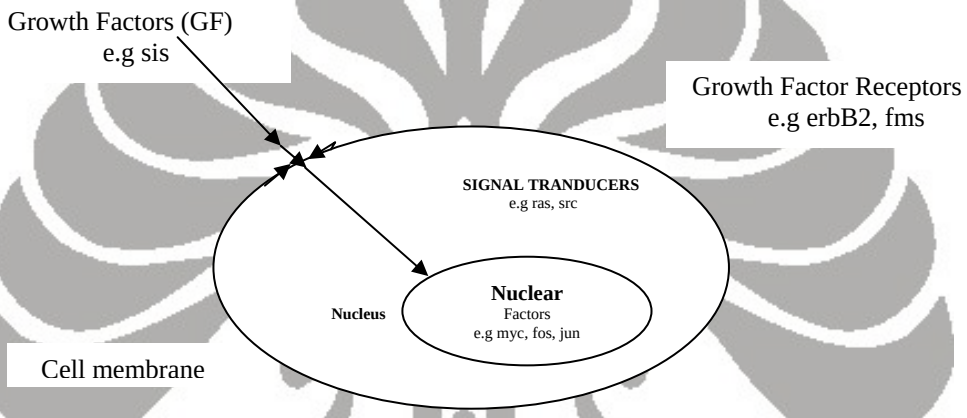

Figure 2. Involvement of Oncogenes in normal growth signal pathway
(Source: Quirke P and Cawkwell L. Molecular Genetics of Cancers)

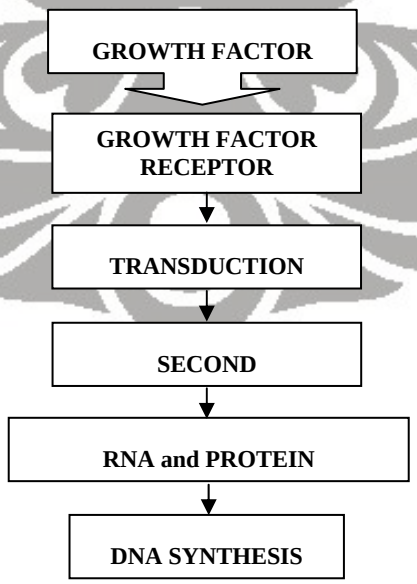

Figure 3: Roles of various proto-oncogenes at several of transmission of growth signal (Source: Scully C. Oncogenes, onco-suppressor, carcinogenesis and oral cancer. 1992)

Several oncogenes and their association with various malignancies are shown in Table 1.

Table 1. Oncogenes association with various malignant neoplasms

Oncogene	Associated neoplasm	Mechanism of activation
Abl	Chronic myelogenous Leukemia	Translocation
ErbB1	Squamous carcinoma Glioblastoma	Amplification
ErbB2	Adenocarcinoma of breast and ovary	Amplification
Myc	Burkitts lymphoma	Translocation
	Small cell carcinoma of lung	
	Carcinoma breast and cervix	Amplification
L-myc	Small cell carcinoma of lung	Amplification
N-myc	Neuroblastoma	Amplification
	Retinoblastoma	
	Small cell carcinoma of lung	
K-ras	Carcinoma of colon, lung and pancreas	Amplification and Point mutation
N-ras	Acute myelogenous and Lymphoblastic leukemia some carcinomas	Point mutation
H-ras	Carcinomas of genitourinary tract and thyroid	Point mutation
Bcl-1	B cell lymphoma	Translocation
Bcl- 2	Follicular lymphoma	Translocation
P53	Head and Neck Cancer	Amplification and Point mutation, deletion

(Sources: Scully C. Oncogenes, onco-suppressor, carcinogenesis and oral cancer. 1992)

Oncogenes may be associated with carcinogenesis, but this is not sufficient for tumor formation. Some carcinogenic agents such as viruses can affect proto-oncogenes by stealing genes, by inducing translocations, or by inserting their oncogenes into host DNA. Other viruses can affect tumor suppressor genes such as p53 gene [13]. Chemical carcinogens or ionizing radiation can also produce similar effects on proto-oncogenes [10,13]. Proto-oncogenes can be activated by a number of oncogenic agents acting in one of 4 main ways [10]:

1. Point mutations. For example, mutations are found in some colon, breast, and oral cancer (Fig. 4).
2. Transduction and insert ional mutagenesis. For example, some retroviruses can cause DNA damage, or can integrate next to a proto-oncogenes and active transcription.
3. Chromosomal rearrangements and chromosome translocation. For example, many hematological malignancies such as Burkitt's lymphoma result from translocation.
4. Amplification, producing many extra copies of the proto-oncogene. For example c-myc and erbB are amplified in some breast and oral carcinomas and then often accompanied by karyotypic abnormalities, poor prognosis, and resistance to cytotoxic drugs.

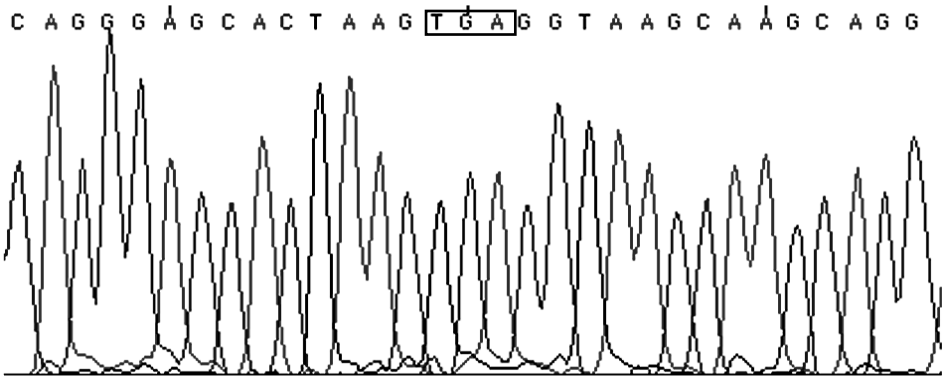

Figure 4. Point mutations of p53 gene found in oral cancer (oral Squamous Cell Carcinoma) which CGA (arginine) to TGA (stop codon). (Source: Syafriadi and Saku. 2007)

Saranath et. al., (1989), found that there was amplification of several oncogenes, including c-myc, N-myc, Ki-ras, in squamous cell carcinoma of oral cavity. They had suggested that these oncogenes may be alternatively or simultaneously activated in oral carcinogenesis.

Amplified oncogene N-myc has been identified also in 89 cases of neuroblastomas, the frequency and degree of amplification in primary neuroblastomas varied greatly about three and 300 copies in 34 out 89 tumors. [14]

Tumor Suppressor Genes

Tumor suppressor gene products are involved in the negative control of cell proliferation and differentiation for example is p53. The loss or inactivation of these genes is associated with tumorigenesis by the loss of the normal growth regulation/restrain control or apoptosis. Inactive of tumor suppressor genes caused by mutation and loss of heterozygosity or DNA metylation. There are many tumor suppressor genes as follow: p53 at chromosome 17p, 'mutated in colorectal cancer' (MCC) gene at 5q, 'dilated in colorectal cancer' (DCC) gene located on 18q21, prohibition gene at 17q21, krev-1/rap 1A located at 1p13-p12, Gas-1 (growth arrest specific) genes have been identified that are expressed especially in cells in resting stage (Go). [9]

Metastasis Genes

Malignant cells, which leave the primary tumor and colonies distant sites, are the major cause of death in patients with solid tumor. The complexity of the metastases process suggests that it may be under genetic control. Genes involved in metastasis are nm23-H1 (NME1) and nm23-H2 (NME2). A combined loss of chromosomes 11p and 17 p was associated with a significantly higher incidence of metastasis in regional lymph nodes of breast cancer. [15]

Angiogenesis is required for expansion of the primary tumor, and new blood vessels penetrating the tumor are frequent sites for entry of tumor cells into the circulatory system. Cell must first detach them selves from the primary tumor and it has been suggested that malignant cells have a reduced ability to adhere to each other. [12]

Apoptosis Genes

The production of tumors includes disturbances of the mechanism that control cell death by apoptosis since cells escape normal ageing and death. It is the myc gene that acts as a bivalent regulator of both cell proliferation and apoptosis depending on the availability of growth factors. The normal p53 protein appears to be involved in the induction of apoptosis in

susceptible cells. Activated ras, bcl-2 or p53 oncogenes may rescue cells from susceptibility to apoptosis, leading to population expansion. (16,17)

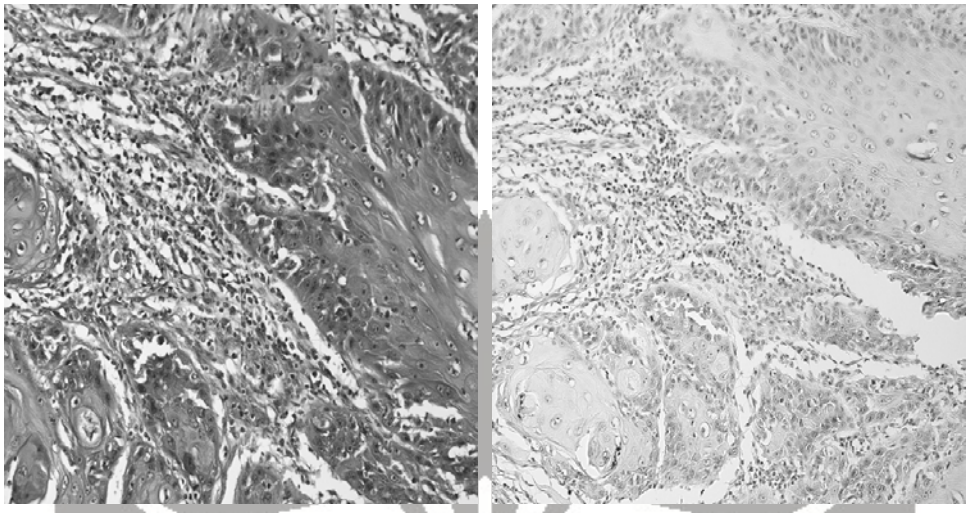

Figure 5. Oral Squamous Cell Carcinoma (A). Tunel staining showed no apoptotic cell in tumor nests of oral SCC (B). p53 gene analysis showed there was point mutation found

DNA Repair Genes

Mutation in DNA repair genes are known to lead some cancers. Failure of repair has been associated with Xeroderma pigmentosum, Ataxia telangiectasia, Fanconi's anemia, Bloom's syndrome, and Cockayne's syndrome. (12)

deletion, amplification, translocations or inserting near or within proto-oncogenes and thereby influence their activity. That was also related with loss or inactivation of tumor suppressor genes such as p53 so that causes loss of the normal growth regulation/restraint controls that associated with tumorigenesis.

Conclusion

Each chromosome has some oncogenes and onco suppressor genes. Oncogenes are important cellular genes which, in general, act in a positive way in the normal growth regulatory pathway of the cell. Recently, more than 50 oncogenes have been identified ; their associations with neoplasm are various. For example, e-myc, L-myc, N-myc, ki-ras and N-ras. All of this oncogene was found related with squamous cell carcinoma of the oral cavity.

Alteration of some carcinogenic such as bacteria, viruses, fungi, chemical, drugs, radiation, trauma, heat could in these genes may disrupt normal cell functions through damaging DNA. Some carcinogenic agents such as viruses can affect proto-oncogenes by point mutations,

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