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*Review Article*

# Head and Neck Cancer Biology - An Overview

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## ABSTRACT

'Every hour hurts, the last one kills'. That is an old saying about getting old. Cancer in general is responsible for about 20% of all deaths in high income countries and 10% in low income countries. Head and neck cancer being more deadly than breast cancer, cervical cancer, and prostate cancer, it has been estimated that it kills one person every hour worldwide. Human head and neck cancer is highly heterogeneous. Understanding the biology of such a heterogeneous disease and its progression is necessary for the development of novel approaches for its prevention, early detection, and treatment. The present review aims at analyzing the current knowledge of the molecular biology and other biological factors in head and neck cancer, and explores the future directions where the field of cancer biology is venturing.

***Key words:*** head and neck cancer, carcinogenesis, genes, biological, molecular.

## INTRODUCTION

Head and neck cancers (HNCs) account for approximately 3% of all malignancies, of which more than 90% are squamous cell carcinomas (SCC), which is associated with low life expectancy rates and high morbidity rates when diagnosed in advanced stages. [1]

The term head and neck cancer (HNC) generally refers to cancers that arise from the structures like skin, nasal cavity, paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, esophagus, thyroid gland and salivary glands. [2] All these cancers have diverse clinical course and outcomes and represent a major health problem. These HNCs are highly heterogeneous in nature with relatively lowest survival rates among the major cancers. Several studies in America suggest that HNCs, particularly tongue cancer, is increasing in young adults both nationally and internationally. [3] Here an attempt is made to discuss the HNC biology at the molecular level.

### Carcinogenesis

Carcinogenesis (oncogenesis) is the progression from a normal cell to a pre-malignant or a potentially malignant cell-characterized by an ability to proliferate autonomously. Oncogenesis involves a series of genetic steps and also epigenetic-outside the gene-changes (**Figure 1**). [4] Cancer cells override these controlling

mechanisms and follow their own internal program for timing their reproduction. These cells usually grow in an unrestricted manner, and over the time, cancer cells can escape cell senescence and death programs thereby becoming immortal. This enhances their supply of oxygen and nutrients by promoting the formation of new blood vessels, and metastasizes to distant anatomical sites. [5] These progressive changes in cellular behavior, from slightly deregulated proliferation to full malignancy, are a result of the accumulation of genetic and epigenetic changes in a limited set of genes. [6]

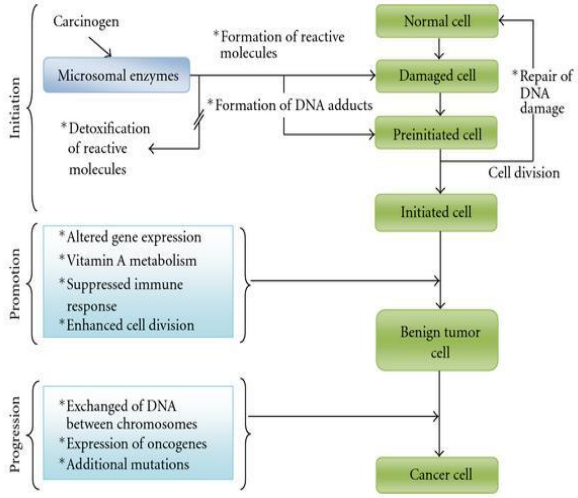


**Figure 1. Stages of carcinogenesis. (Courtesy from intranet.edu.ua)**

## Predisposing Factors Associated With Head And Neck Cancer (HNC)

DNA mutation occurs spontaneously, especially via damage by oxidation and chemical free radicals. The rate of DNA mutations however, is vastly increased by the various exogenous risk factors for cancers, such as tobacco, alcohol, betel nut, chemicals, radiation (sunlight, ionizing), diet, infections and immunocompromised state and low fruits and vegetable consumption and high fat and sugar intake. [4,7] Shillitoe [8] discusses fully the role of HPV and some herpes viruses. Other infections such as candidosis and syphilis have also been implicated. More recently the role of bacterial oral flora with poor oral hygiene is implicated as risk factor for the development of head and neck, and esophageal cancer. [9] Periodontal diseases or tooth loss have also been associated with oral, lung and pancreatic cancer. [10] Other factors implemented in HNC are drugs such as marijuana and diseases such as Fanconi anemia, dyskeratosis congenita, xeroderma pigmentosum, Li Fraumeni syndrome, discoid lupus erythematosus, diabetes and scleroderma. [9]

## Environmental And Genetic Factors

Environmental and genetic factors may also play a role to varying degrees. For example, ionizing radiation from natural or therapeutic sources or nuclear accidents may contribute (e.g. the Chernobyl accident) for HNC. [4,10]

Genetic variation in mechanism protective against cancer may be implicated. Such protective mechanism that may fail and predispose to cancer includes the gene for the liver enzymes (xenobiotic metabolizing enzymes; XME) that degrade chemical carcinogens (cancer causing chemicals); genes that result in the ability to repair DNA mutations (DNA repair genes); oncogenes; tumor suppressor genes (TSGs); and genes related to immune protection [11,12] Most people however, will have their cancer risks greatly increased by exposure to tobacco and / or alcohol. [4]

HNC may be preceded by premalignant lesions such as leukoplakia, erythroplakia, sub-mucous fibrosis, chronic hyperplastic candidosis, and erosive lichen planus. For instant loss of chromosomal material is thought to result in changes leading to dysplasia (9p21, 3p21, 17p13), carcinoma in situ (11q13, 13q21, 14q31), invasive tumors (4q26-286p, 8p, 8q). The studies that suggest role of p16 (9p21) with mutation 70%, APC (adenomatoid polyposis

coli which locus on 5q21-22) with mutation 50% and p53 (17p13) with mutation 40% in all head and neck cancers. [13]

Tobacco:

The genetic alteration associated with HNC is mainly due to a lifetime exposure of environmental factors such as tobacco and alcohol. There are two forms of tobacco, smokeless and smoking form of tobacco of tobacco. Tobacco generates carcinogens (cancer- causing chemicles), such as the tobacco-specific nittrosamines – TSNAs like 4-methylnitrosamino 1, 3, pyridil-1-butanon (NNK); N-nitrosonornicotine (NNN); nitrosodiethanolamine; nitrosopyrrolidin (NPYR); nitrosopiperidine; nitrosobutylamine and nitrosopropylamine. All these forms act as carcinogens in the development of HNC. [4,7]

Betel Nut:

Betel nut use is a habit of approximately 20% of the world's population especially in Asian communities. The International Agency for Research on Cancer long ago recognized areca nut (betel) as carcinogenic in humans. Areca nut contains alkaloids like arecoline, arecadine, arecalidine, guvacoline, guvacine, tanic acid. Arecoline and arecaidine stimulate proliferation and collagen synthesis in a dose-dependent manner, higher concentrations being cytotoxic. Flavonoids, catechins, and tannins in areca nuts cause collagen fibers to crosslink, making them less susceptible to collagenase. Furthermore, the extracts of areca nut and its components have been shown to be crucial in the pathogenesis of HNC by differentially inducing the dysregulation of cell cycle control mitochondrial membrane potential, depletion of cellular glutathione, and intracellular $H_2O_2$ production. [7,14]

Alcohol:

Alcohol (ethanol) use is widespread in most of communities worldwide. Alcohol may be carcinogenic via various mechanisms but an important mechanism is by its oxidation to acetyldehyde (a carcinogen) by enzymes (alcohol dehydrogenases; ADHs). Acetyldehyde is then degraded to acetate by aldehyde dehydrogenases (ALDH). Genetic variations in the activities of these enzymes (ADH and ALDH) may influence the outcome of exposure to alcohol, and its carcinogenicity. Tobacco and alcohol use have an additive carcinogenic effect, and these lifestyle habits often co-exist. [15]

**Carcinogenesis At Molecular Level**

The cancer is mainly developed by the clonal expansion of single precursor cell that has incurred genetic damage. Cancer stem cells are the self sustaining cells, which arise from normal stem cells by mutation of genes that render the stem cells cancerous. [4] Normal cell proliferate only when needed, as a result of delicate balance between growth promoting and growth inhibiting factors under the influence of biochemical cues provided by neighboring cells and circulating factors. [5]

There are four classes of normal regulatory genes, these are - the growth promoting proto-oncogenes, the growth-inhibiting tumor suppressor genes (TSGs), genes that regulates the programmed cell death (apoptosis), and genes involved in DNA repair. [16] Most of the cancers are monoclonal in origin and it has been estimated that five events in humans are required to transform a normal cell into a cancer cell. The stem cells have the ability to accumulate the number of necessary genetic hits which will result in the formation of cancer. [17] The stem cell which is genetically damaged, carry the clonal unit of mutated cells and transforms this mutation to its daughter cells. As a result of subsequent genetic alteration the stem cell escapes control and gains excessive and autonomous growth advantage. With further

clonal expansion and a specific genetic hit leads to loss of heterozygosity (LOH) and a general 'genetic instability' leading to cancer. [18]

Carcinogenesis is a multistep process resulting from accumulation of multiple mutations. Mutation at molecular level includes many steps such as, self sufficiency in growth signals, insensitivity growth inhibitory signals, evasion of apoptosis or resistance to programmed cell death, limitless replicative potential, sustained angiogenesis, defect in DNA repair and ability to invade and metastasize. [5,8] There are two main cell cycle check points, one at the G1/S transition and other at G2/M transition. These checkpoints check for DNA damage; if damage is present, the DNA- repair machinery and mechanisms that arrest cell cycle are put in motion. If the damage is not repairable, apoptotic pathways are activated to kill the cell, so any defect in these checkpoint give rise to chromosomal abnormality. The progressive changes in cellular behavior, from slightly deregulated proliferation to full malignancy, are the result of accumulation of the mutations in a limited set of genes. Among them two classes of genes, oncogenes and tumor suppressor genes play a major role in triggering and promoting cancerous growth. [19]

The molecular alterations observed in HNC are mainly due to oncogenes activation and tumor suppressor genes inactivation, leading to deregulation of cell proliferation. The protein products of these genes affect a variety of intracellular signaling pathways. Activated oncogenes promote cell proliferation, where as TSGs inhibit cell growth and contribute to the carcinogenic process when inactivated by mutations or by genetic and /or epigenetic events. [20]

**Oncogenes**

Overexpession of proto oncogenes- such as epidermal growth factor receptor (EGFR), RAS (signal transducing protein) and MYC genes- can promote the growth, survival and spread of cells- leading to development of cancer (**Figure 2**).

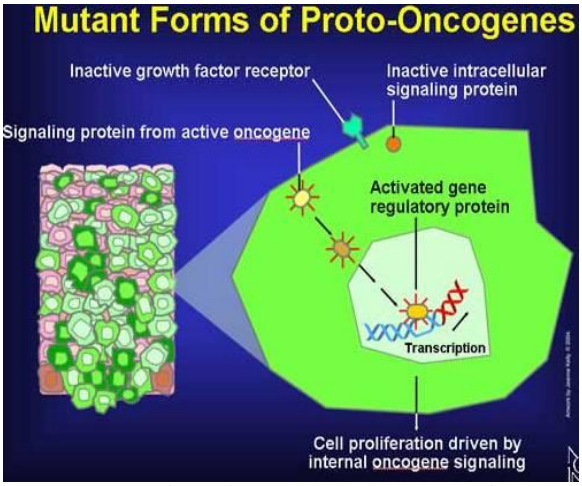


**Figure 2. Mutant form of Proto-oncogene. (Courtesy from www.web.books.com)**

Epidermal Growth Factor Receptor (EGFR)

Over expression of the oncogenes that promote the growth, survival rate, and spread of cells, can lead to the development of cancer. One of more studied gene in HNC is epidermal growth factor receptor (EGFR). It has been over expressed in a majority of HNC. [4] Elevated level of EGFR expression leads to the activation of their kinase (tyrosine kinase cascade) activity by spontaneous dimerization. EGFR activates the ratinoblastoma (RB) / RAF / mitogen activated protein kinase (MAPK) signaling route, the transcription factor signal transducer and activator transcription (STAT), and contribute to the aberrant cell growth. [5,4]

The RAS Oncogene (RAS family of guanine triphoshpate – binding protien)

Members of RAS (signal transducing oncoprotein) family (H-ras, K-ras, N-ras) are some of the most frequently mutated oncogenes in human cancer. RAS plays an important role in signaling cascades

downstream of growth receptors, resulting in mitogenesis. A high incidence of RAS mutation has been found in oral cancer, mainly in Asian populations, where it has been associated with areca nut chewing. [5]

MYC oncogene

Transcription factors contain specific amino acid sequences or motifs that allow them to bind DNA or to dimerize for DNA binding. MYC oncogene act as transcription factor that regulate the expression of the growth promoting genes and it is the most commonly involved oncogene in human cancers. Persistent or overexpression contributes to sustained proliferation of cancer cells. [17]

**Tumor Suppressor Genes (TSGs)**

Tumor suppressor genes (TSGs) are genes that normally function as Brake pedal in growth control- by regulating the cell cycle, programmed cell death (apoptosis), cell adhesion, and DNA repair. TSG (**Figure 3**) function can be disturbed by aberrations such as deletions or mutations in TSGs, or by TSG silencing from hypermethylation, and any of these changes can lead to unchecked cell division and cancer formation. [4]

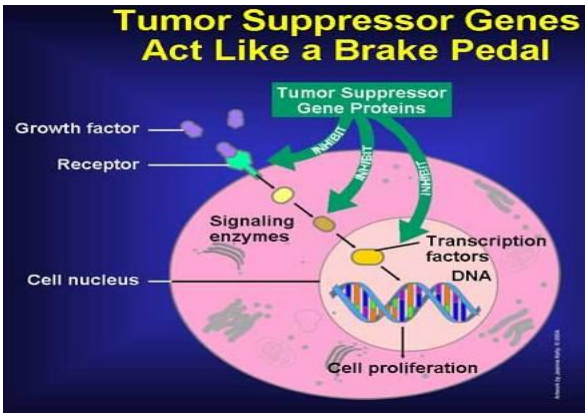


**Figure 3. Tumor suppressor genes. (Courtesy from www.web.books.com)**

TP53 gene

TP53 gene is located on 17p13.1, homozygous activity of TP53 gene actively occurs in HNC. This gene acts as critical gate keeper against the formation of cancer. The functions of TP53 gene (**Figure 4**) are cell cycle regulation and initiation of apoptosis in response to DNA damage. TP53 is called as guardian of the genome. It assists in DNA repair by causing G1 arrest and inducing DNA repair genes. A cell with damaged DNA that cannot be repaired is directed by TP53 to undergo apoptosis. Most of the time, the inactivation of the TP53 pathway results from a loss of function of the tp53 protein, secondary to mutation and/or deletion of the TP53 gene. The silencing of this gene most often through various point mutations leads to the tumor formation. [8,21] There is high incidence of loss of heterozygocity (LOH) at the 9p21 locus and cytogenic abnormality at this site is observed in HNC. The CDKN2a locus codes for both p16 and p14 (ARF), which are putative TSGs that regulate the cell cycle and stabilize TP53 through MDM respectively. [22]

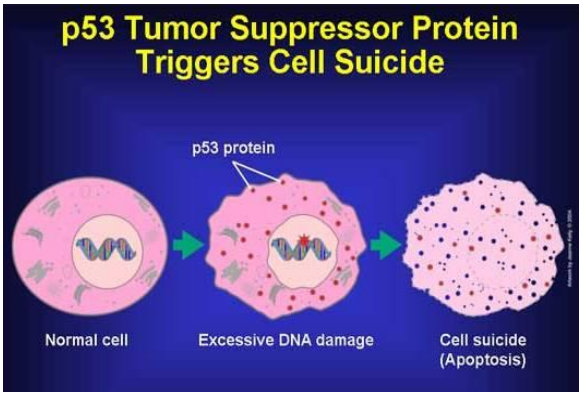


**Figure 4. p53 Tumor suppressor gene. (Courtesy from www.web.books.com)**

Retinoblastoma gene (RB gene)

TSGs apply brakes to cell proliferation by forming the network of checkpoints which prevent uncontrolled growth. RB (retinoblastoma) gene located on chromosome 13q14 and RB protein is the product of RB gene, which plays a key role in regulating cell cycle hypophosphorylated state. Mutation in other genes that control

RB phosphorylation can lead to RB gene loss. Mutational activation of cyclin D or CDK4 would favor cell proliferation by facilitating RB phosphorylation. RB protein is functionally inactivated by binding with a viral protein especially HPV E7 (human papilloma viraus E7) which inactivates RB gene. [17,23 ,24]

Cycline dependent kinase inhibitor P16INK4A gene

Another most important tumor suppressor gene is P16, this gene also act as check point. The CDKN2a locus codes for both p16 and P14(ARF) – putative TSGs; p16 regulate the cell cycle (by blocking cyclin-bound cyclin –dependent kinases [CDKs] CDK4 and CDK6) and p14(ARF) stabilizes TP53 through MDM2. P16 is often inactivated in HNC through homozygous deletion, by promoter methylation, and less commonly by point mutation. [9]

Transforming Growth Factor - β (TGF- β)

TGF-β behaves as potent tumor suppressor and inhibitor of cell proliferation in epithelial cells. The available evidence of TGF-β supports a dual role in carcinogenesis. It acts as a potent tumor suppressor during the early stages of carcinogenesis while promoting tumor progression at later stages. [25]

**Alteration Of Other Genes In HNC**

CYPs and GSTs genes expression in HNC

The two important enzymes which are involved in the process of biometabolization of chemical compounds of tobacco and alcohol are cytochrome P-450 superfamily (CYPs) and glutathione S-transferases (GSTs). CYPs enzyme convert many compounds into highly reactive metabolites and GSTs enzymes are involved in the biosynthesis and metabolism of many substances, including detoxification of exogenous chemical carcinogens, such as aromatic polycyclic hydrocarbons present in the tobacco. Polymorphism in genes that codify the CYPs and GSTs may alter their expression or function and result in activation or detoxification of carcinogenic compounds. [26]

Human Leukocyte antigen (HLA-A Alleles)

Loss or downregulation of human leukocyte antigen (HLA) class I expression has been reported in oral SCC. HLA class I heavy chain of B/C locus and A locus and beta (2-) microglobulin were obviously lost or down regulated in primary oral SCC with the percentage of 31, 55 and 35% respectively. [27,28]

CDKN2B ($p15^{INK4b}$) and CDKN2A ($p14^{ARF}$, $p16^{INK4a}$)

The cyclin-dependent kinase 2A (*CDKN2A*) and *CDKN2B* genes map to 9p21locus. The *CDKN2A* locus controls the RB pathway (which regulates G1/S-phase transition) and the p53 pathway (which induces growth arrest or apoptosis in response to either DNA damage or inappropriate mitogenic stimuli by generating 2 gene products).This regulatory function is achieved through the p16 protein product, which functions upstream of RB, and the p14 protein, which blocks MDM2 inhibition of p53 activity, preventing p53 degradation, and thus permitting p53-induced apoptosis or growth arrest. Genetic alterations at the 9p21 locus have been linked to malignant progression in HNC. [29]

Transcription factor kappa B (NFkB)

In HNC the expression and activity of transcription factor kappa B (NFkB) is often upregulated, and its protein level increases gradually from premalignant lesion to invasive cancer, which suggests that NFkB signaling may play an important role at the early stages of carcinogenesis. [30]

Cyclin D1

Amplification of 11q13 and overexpression of cyclin D1 is seen in 30-60% of HNC. Cyclin D1 induces phoshorylation of RB, thus enabling progression from G1 to S phase.

Amplification of cyclin D1 and inactivation of P16, result in increased phosphorylation of RB gene and has been described in up to 40% of cases of in HNC. [31]

MicroRNA (mir)

MicroRNA (mir) molecules are small ~22- nucleotide, non coding RNA molecules that have been shown to regulate post-transcriptional gene expression in HNC (**Figure 5**). [32]

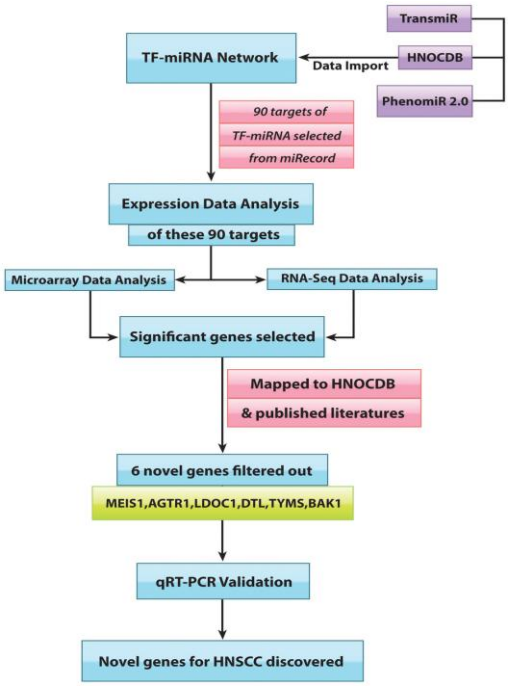


**Figure 5. Role of microRNA in HNC. (Courtesy from www.nature.com)**

Phoshatidylinositol 3-kinase /v –akt murine thymima viral oncogenes homologue (P13K/AKT) pathway and phosphatase and tensin homologue (PTEN)

P13K/AKT pathway is an important intracellular signaling pathway and most frequently activated and proliferation and survival pathway in cancer. This pathway is able to control the major cellular functions such as proliferation, cell growth, apoptosis and malignant transformation. Upon growth factor binding to receptors tyrosine kinase, P13K generate the second messenger phoshatidylinositol 3, 4, 5 triphosphate (PIP3) which induces downstream phosphorylation and activation of survival kinase AKT. PENT a tumor suppressor protein, is an inhibitor of this pathway. Mutation in one or another P13K component accounts for up to 30% of all human cancer, resulting in the deregulation of cellular growth control and survival. [5,33]

**Role Of Matrix Metalloproteinases (MMPs) In HNC**

MMPs are a family of genes thought to be involved in cell adhesion, proliferation, and migration. MMP7 gene expression was associated with a risk of early HNC and MMP2 was found to be related to lymph node metastasis. MMP9 and other MMPs were related to infiltrative growth and lymph node involvement. [34,35]

**Mitochondrial Mutations**

Mitochondria are self contained organelles with a separate genome and even possess a unique genetic code. There is an accumulation of mitochondrial mutations in HNC, as evidenced by the increased mitochondrial DNA content seen as progress from pre-malignant to malignant HNC. [36] One study observed that point mutation in the ATP subunit 6 may have an antiapoptotic effect in cancer cell line. [37]

**Aberrant Protein Expression In HNC**

Proteins identified include a significant number of cytokeratins and other inter mediatory filament proteins, as well as differentiation markers, signal transduction and cell cycle regulatory molecules, growth and angiogenic factors, and matrix degrading proteases. [5]

Signal Transducer and Activator of Transcription (STAT) proteins

To date, seven STAT family member have been identified, STATs 1, 2, 3, 4, 5a, 5b and 6, which participate in the transcription of the gene involved in immune responses, growth, and cell fate decision. Activation or gain of function of

STAT is often associated with cellular transformation and oncogenic potential. Cytokines and growth promoter factors stimulate STAT proteins by acting on their cognate receptors, which leads to the recruitment and phosphorylation of Janu kinade 1 and 2 (JAK-1 and JAK-2) that in turn phosphorylate STAT proteins at specific tyrosine residues, thus promoting their homo- and heterodimerization. [5,38]

**Chemical, physical and viral carcinogens in HNC**

Cancer is a disease primarily caused by cytogenetic changes that progress through a series of sequential somatic mutations in specific genes resulting in uncontrolled cellular proliferation. It may be caused by exposure to any one or more of a variety of chemical or physical agents, by random error of genetic replication. Mutation may be acquired by the action of environmental agents such as chemicals, radiation, viruses, or it may be inherited in the germ line. Agents which can induce cancer are called as carcinogen. [20] These chemicals such as phorbol esters, hormones, phenols, and drugs like alkylating agents and acylating agents can induce cellular transformation hence act as carcinogens. [39,40] Ultraviolet light (UV) and ionizing radiation may directly alter the DNA damage, or results in formation of highly reactive radicals and thereby causing DNA mutagenesis which causes chromosomal breakage, translocation, or point mutation. [41] High risk oncogenic human papilloma virus (HPVs) such as HPV- 16 and HPPV-18 are etiologically related to a subset of HNC. There is substantial epidemiological and molecular pathology evidence indicating that HPV16 is associated with a subset of oropharyngeal cancers.. TheE6 and E7 oncoproteins binds and degrade the host p53 and RB tumor suppressor proteins. The E7 protein binds to RB family members and disrupts their ability to form complexes with E2F, resulting in increased expression of E2F-responsive genes, many of which are required for cell cycle progression. E2 mediated E6 and E7 gene expression resulted in activation of the p53 and RB pathways, inhibition of telomerase activity, and cellular growth arrest and senescence. [42,43]

## CONCLUSION

HNC continues to be a devastating disease, with high mortality and morbidity rates. During the past decade, there has been a significant increase in knowledge regarding the molecular biology of HNC. Here we have made an attempt to review HNC biology. HNC is multifactorial in origin and the risk is increased by exposure to various risk factors like use of tobacco and alcohol. Genetic and epigenetic changes leading to overexpression of oncogenes and silencing of TSGs are also equally important. Certain chemical, physical agents and viruses have also proved to be etiologic agents in HNC.

As the survival rate of treated HNC is low, one needs to concentrate on preventive aspects. The basic objective of our article was to discuss this HNC biology which will definitely help the reader to plan various preventive strategies to reduce the incidence of the cancer in head and neck region.

## REFERENCES


1. Chmitz S, Machiels JP. Molecular biology of squamous cell carcinoma of the head and neck: relevancew and therapeutic implication. Expert Revu Anticancer Ther 2010;10: 1471-1484.
2. Patel SG, Shah JP. TNM Staging of cancer of the head and neck: striving for uniformity among diversity. CA Cancer J Clin 2005;55:242-258.

3. Messadi DV, Smith PW, Wolinsky L. Improving Oral Cancer Survival: The Role of Dental Providers. J of Calif Dent Assoc 2009;37:789-798.
4. Scully C, Petti S. Overview of cancer for healthcare team: Aetiopathogenesis and early diagnosis. Oral Oncol 2010;46:402-406.
5. Gutkind J S, Molinolo A A, Amornphimoltham P, Squarize CH, Castilho RM, Patel V, *et al*. Dysregulated Molecular Networks In Head And Neck Carcinogenesis. Oral Oncol 2009;45:324-334.
6. Hanahan D, Wenberg R A. The hallmark of cancer. Cell 2000;100: 57-70.
7. Pitti S. Lifestyle risk factors for oral cancer. Oral Oncol 2009;4:340-350.
8. Shillitoe EJ. The role of viruses in squamous cell carcinoma of the oropharyngeal mucosa. Oral Oncol 2009,45:351-355.
9. Scully C, Bagan J. Oral squamous cell carcinoma overviev. Oral Oncol 2009;45:301-308.
10. Guha N, Boffetta P, Filho V W, Neto JE, Shangina O, Zaridze D, *et al*. Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: result of two multicentric case-control studies. Am J Epidemol 2007;166:1159-1173.
11. Scully C, Field JK, Tanzawa H. Genetic aberration in oral or head and neck squamous cell carcinoma (SCCHN): 1. Carcinogen metabolism, DNA repair and cell cycle control. Oral Oncol 2000;36: 256-263.
12. Scully C, Field JK, Tanzawa H. Genetic aberration in oral or head and neck squamous cell carcinoma (SCCHN): 3. Clinic-pathological application. Oral Oncol 2000;36: 311-327.
13. Patel V, Leethanakul C, Gutkind JS. New approaches to the understanding of the molecular basis of oral cancer. Cri Rev Oral Biol Med 2000;12:56-63.
14. Cogliano V, Straif K, Baan R, Grosse Y, Secretan B, Ghissassi FE, *et al*. Smokless tobacco and tobacco-related nitrosamines. Lancet Oncol 2004;5:708.
15. Trizna Z, Schantz S P. Hereditary and environmental factors associated with risk and progression of head and neck cancer. Otolaryngol Clin Nort Am 1992;25:1089-1103.
16. Braakhauis BJM, Leemans CR, Brakenhoff RH. A genetic progression model of oral cancer: current evidence and clinical implications. J Oral Pathol Med 2004; 33:317-322.
17. Crowe DL, Hacia JG, Hsieh CL, Sinha UK, Rice H. *et al*. Molecular pathology of head and neck cancer. Histol Histopathol 2002;17:909-914.
18. Hann WC, Weinberg RA. Mechanism of disease: rules for making human tumor cells. N Engl J Med 2002;347:1593-1603.
19. Barket J, Lukas J. Mammalian G1- and S- phase checkpoints in response to DNA damage. Curr Opin Cell Biol 2001;13:738-743.
20. Hardisson D. Molecular pathogenesis of head and neck squamous cell carcinoma. Eur Arch Otolaryngol 2003;260:502-508.
21. Ha PK, Chang SS, Glazer CA, Califona JA, Sidransky D. Molecular techniques and genetic alteration in head and neck cancer. Oral Oncol 2009;45:335-339.
22. Boyel JO, Hakim J, Koch W, van der Riet P, Hruban RH, Roa RA. The

incidence of p53 mutations increases with progression of head and neck cancer. Cancer Res 1993;53:4477-4480.
23. Pietruszewska W, Durko M, Kobos J. Alteration of cell cycle regulating proteins: Rb, p21, and p16 in laryngeal cancer. Otolaryngol Pol 2007;61:951-957.
24. Lim KP, Hamid S, Lau SH, Teo SH, Cheong SC. HPV infection and the alterations of the Prb pathway in oral carcinogenesis. Oncol Rep 2007;17: 1321-1326.
25. Prim SS, Davis M, Paterson IC. The role of TGF- β in epithelial malignanvy and its relevance to pathogenesis of oral cancer. Cri Rev Oral Biol Med 2004;15:337-347.
26. Doraddo lame CV, Raposo LS, Ruiz MT, Biselli JM, Silva Galbiatti AL, Maniglia JV, *et al*. GSTM1 and GSTT1 genes analysis in Head and Neck Cancer Patients. Rev Assoc Med Bras 2010;56:299-303.
27. Tang Q, Zhang J, Qi B *et al*. Downregulation of HLA class I molecules in primary oral squamous cell carcinomas and cell lines. Arch Med Res 2010;40:256-263.
28. Eura M, Katsura F, Oiso M, Obata A, Nakano K, Masuyama K. Frequency of HLA-A alleles in Japanese patients with head and neck cancer. Jpn J Clin Oncol 1999;29: 535-540.
29. Worsham MJ, Chen KM, Tiwari N, Schouten JP, Benninger MS. Fine – Mapping Loss of Gene Architecture at the CDKN2B ($p15^{INK4b}$), CDKN2A ($p14^{ARF}$, $p16^{INK4a}$), and MTAP Genes IN Head and Neck Squamous Cell Carcinoma. *Arch Otolaryngol Head Neck Surg* 2006;132:409-415.
30. Bindu OS, Ramadas K, Sebastian P *et al*. High expression level of nuclear factor kappa B and gilatinases in the tumorigenesis of oral squamous cell carcinoma. Head Neck 2006;28:916-925.
31. Ordonez BP, Beauchemin M, Jordan RCK, Pillai MR. Molecular Biology Of Squamous Cell Carcinoma Of Head And Neck. J Clin Pathol 2000; 59:445-453.
32. Lee R C, Feinbaum R L, Ambros V. The Celegans heterochronic gene lin-4 encodes small RNAs with antisense copmlementarity to lin-14. Cell 1993;75:843-854.
33. Hafner C, Landthaler M, Voqt T. Activation of the P13K.AKT signalling pathway in non-melanoma skin cancer is not mediated by oncogenic PIK3CA and AKT1 hostspot mutations. Experimental Dermatology 2010;19:e222-e227.
34. Franchi A, Santucci M, Masini E, Sardi I, Paglerani M, Gallo O. Expression of matrixmetalloproteinase 1, matrixmetalloproteinase 2, and matrixmetalloproteinase 9 in carcinoma of head and neck. Cancer 2002;95:1902-1910.
35. Liu SY, Liu YC, Huang WT, Huang GC, Su HJ, Lin MH. Requirement of MMP-3 in anchorage – independent growth of oral squamous cell carcinoma. J Oral Pathol Med 2007; 36:430-435.
36. Shidara. Y, Yamagata K, Kanamori T, Nakano K, Kwong JQ, Manfredi G.. Positive contribution of pathogenic mutations in the mitochondrial genome to the promotion of cancer by prevention from apoptosis. Cancer Res 2005; 65:1655-1663.

37. Selak M A, Armour S M, Mackenzie E D *et al.* Succinate links TCA cycledysfunction to oncogenesis by inhibitibg HIF- alpha prolyl hydroxylase. Cancer Cell 2005;7:77-85.
38. O'Shea J J, Gadina M, Scheiber R D *et al.* Cytokine signaling in 2002: new surprise in the Jak/Stat pathway. Cell 2002;109:S121-S131.
39. Chimeno Zoth S A, Collet A M, Heber E *et al*. Early detection of alterations associated to oral cancer. Acta Odontol Latinoam 2000;13: 100-112.
40. Tarvainen L, Kyyronen P, Kauppinen T *et al.* Cancer of the mouth and pharynx, occupation and exposure to chemical agents in Finland. Int J Cancer 2008;123:653-659.
41. William D. Radiation carcinogenesis: lessons from Chernobyl. Oncogene 2008;27 Suppl 2:S9-18.
42. Ordonez B P, Beauchemin M, Jordan R C K. Molecular Biology Of Squamous Cell Carcinoma Of Head And Neck. J Clin Pathol 2000;59: 445-453.
43. Rampias T, Sasaki C, Weinberger P *et al.* E6 and E7 Gene Silencing and Transformed Phenotype of Human Papillomavirus 16-Positive Oropharyngeal Cancer Cells. J Natl Cancer Inst 2009;101:412-423.

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