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Chapter

Molecular Pathogenesis of Oral Squamous Cell Carcinoma

Anshi Jain

Abstract

Oral carcinogenesis is a molecular and histological multistage process featuring genetic and phenotypic molecular markers which involves enhanced function of several protooncogenes, oncogenes and/or the deactivation of tumor suppressor genes, resulting in the over activity of growth factors and its cell surface receptors, which could enhance messenger signaling intracellularly, and/or leads to the increased production of transcription factors. Alone oncogenes are not responsible for carcinogenesis, genes having tumor suppressor activity, leads to a phenotypic change in cell which is responsible for increased cell proliferation, loss of cellular cohesion, and the ability to infiltrate local tissue and spread to distant sites. Understanding the molecular interplay of both onco and tumor genes will allow more accurate diagnosis and assessment of prognosis, which might lead the way for novel approaches to treatment.

Keywords: carcinogenesis, protooncogene, oncogene, tumor suppressor gene, intercellular signaling, cell surface receptors, growth factors

1. Introduction

According to the literature and current scenario it's a well-known fact that environmental and genetic factors modulate the multistep process of carcinogenesis. Genetic events lead to the disruption of normal regulatory mechanism that control basic cellular function of the body including cell division, differentiation and cell death [1]. Boyd and Reade (1988) described the mechanisms involved in carcinogenesis of the oral mucosa and distinguished between three major groups: chemical mechanisms, physical mechanisms, and viral mechanisms. Later Hanahan and Weinberg (2000) described six hallmarks of cancer (hallmarks I): acquisition of growth signaling autonomy (oncogenes), growth-inhibitory signals (tumor suppressor genes), evasion of apoptosis, cellular immortalization, angiogenesis, and finally, invasion and metastasis [2]. A decade later, an updating review (henceforth termed hallmarks II) added two emerging hallmarks: reprogramming energy metabolism and evading immune response, and two enabling traits: genome instability and mutation, and tumor-promoting inflammation [3].

Oral squamous carcinogenesis is the sixth most common cancer worldwide and commonest cancer in India, accounting for 50–70% of total cancer mortality rate. It predominantly affects anterior tongue, cheek, floor of mouth, retro molar area, gingiva or the buccal mucosa [4]. In carcinogenesis multiple genetic events alter the normal functions of both oncogenes and tumor suppressor genes. However, the importance of both the known gene alterations is unidentified and is still not fully understood. The histologic progression of oral carcinogenesis from hyperplasia to

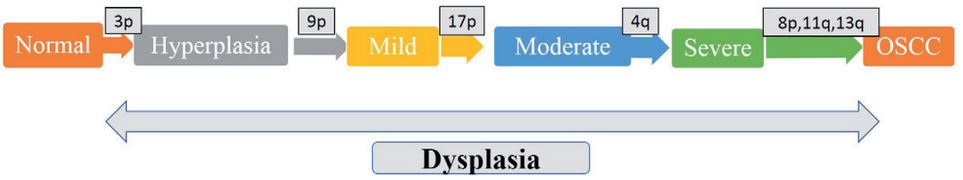

Figure 1.
Molecular model of oral carcinogenesis. The diagram shows the genetic progression from dysplasia to oral squamous cell carcinoma (OSCC), through changes in the p or q arm of chromosomes 3, 4, 8, 9, 11, 13, and 17 [2].

dysplasia, followed by severe dysplasia and eventual invasion and metastases, are believed to reflect the accumulation of these changes [5, 6] (**Figure 1**). Genetic alterations occurring during the carcinogenesis may present in the form of point mutations, amplifications, rearrangements, and deletions [5].

2. The genetic theory of cancer

2.1 Alteration of regulatory pathways during cancer development

Oral carcinogenesis is a complex, multistep process in which genetic events within signal transduction pathways governing normal cellular physiology are quantitatively or qualitatively altered.

Under normal conditions, cell biology of oral epithelia is tightly controlled by excitatory and inhibitory pathways which include cell division, differentiation, and senescence [1]. Cellular pathways of the oral keratinocyte may be diverse and contain the same fundamental elements. Binding of an extracellular ligand to a cell surface receptor forms a receptor-ligand complex that generates excitatory or inhibitory signals which are transferred intracellularly and further nuclear messengers can either directly alter cell function or can stimulate the transcription of genes which can affect protein synthesis [1] (**Figure 2**).

On contrary, oral cancer is the result of an accumulation of changes in these excitatory and inhibitory cellular signals that can occur at any level of a given pathway. Oral epithelial cells collect these alterations or mutations from cellular signals and become functionally independent from the surrounding oral epithelium made up of normal oral keratinocyte neighbors. These tumor cell divide more rapidly, sequester blood vessels to feed that growth, delete or amplify signals to produce abnormal structural or functional changes, and start invading normal tissue at local or distant sites [6].

Oncogenes and tumor suppressor genes constitute the cellular growth-regulatory genes which are widely expressed in normal cells and their protein products are required for cell to work normally. Any alteration or inappropriate expression of these genes can induce neoplasia [7].

The genetic damage of these genes found in cancer cells is of two sorts:

1. Dominant type: proto-oncogenes and oncogenes.

2. Recessive type: tumor suppressor genes, growth suppressor genes, recessive oncogenes, or anti-oncogenes.

The Former typically results in a gain of function, whereas latter causes loss of function [8].

The hallmark of cancer is rapid and uncontrolled growth. Cell cycle regulatory molecules (cyclin-CDK complex and retinoblastoma protein RB) play a key role

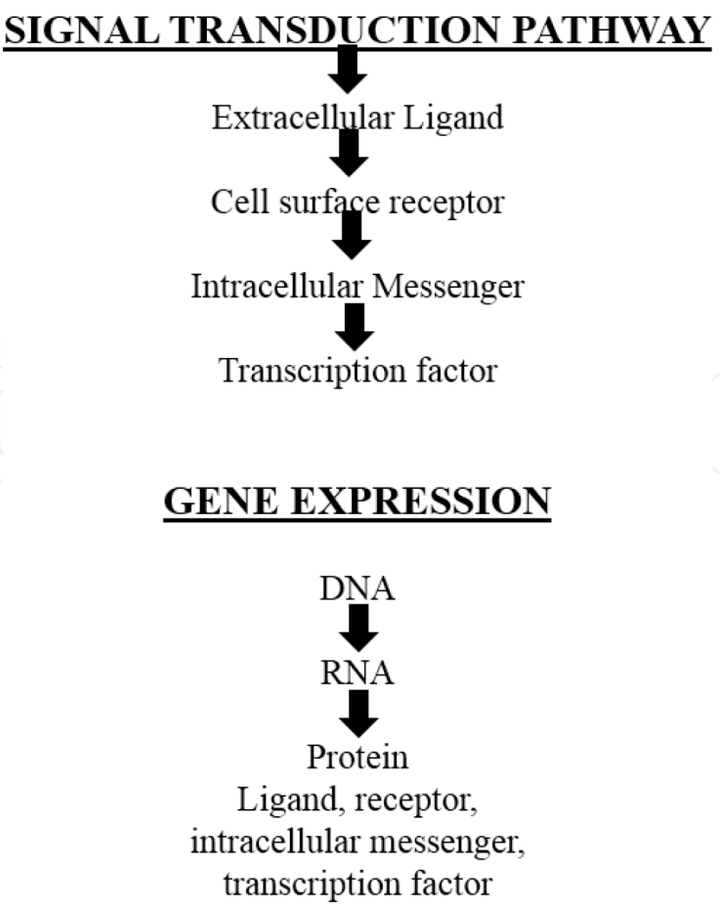

Figure 2.
Signal—transduction pathway.

in pathogenesis of head and neck cancers. Phosphorylation of RB by the cyclin/CDK there is a release of E2F, which transcribe the necessary components of the cell to continue through the G1/S transition. Specifically, RB function is mediated by cyclin E/CDK2 activity. In contrast, CDK4 and CDK6 act upstream of RB and inhibit RB function by phosphorylation [5]. In head and Neck cancers, both up and down regulation of RB function has been observed conferring a greater degree of malignancy and aggressiveness, dependent upon cellular context. Downregulation of RB function—cell cycle to remain unchecked and leads to continual cell division and cell proliferation; up-regulation of RB leading to a decrease in pro-apoptotic signals that are triggered during the cell cycle. In either case, changes in the RB pathway alter cell-cycle transition and allow for greater cancer cell survival [1].

3. Oncogenes and oncoprotein

Oncogenes can be classified according to the roles of their normal counterparts (protooncogenes) in the biochemical pathways that regulate growth and differentiation. These include the following

1. Growth factors (TGF, FGF, PDGF)

2. Cell surface receptors (EGFR, FGFR)

3. Intracellular signal transduction pathways (RAS)

4. DNA binding nuclear proteins transcription factors (MYC, FOS, JUN)

5. Cell cycle proteins (cyclins and cyclin dependent protein kinases)

6. Inhibitors of apoptosis (bcl-2)

Oncogenes are defined as "altered growth-promoting regulatory genes, or proto-oncogenes that govern the cell's signal transduction pathways" [5]. These genes were initially discovered in retroviruses which cause cancers in birds and cats by virtue of a highly tumorigenic 'molecular hitchhiker', a mutated gene (oncogene) not native to the virus but picked up from a homologue in the eukaryotic genome. Alteration or mutation of these proto-oncogenes results in either an overproduction or a "gain-of-function" alteration in these excitatory proteins. Although oncogenes alone are not sufficient to transform a normal oral keratinocyte to a malignant one, they are initiators of the process [6].

Aberrant expression of several oncogenes play a crucial role in development of oral carcinogenesis which includes proto-oncogene epidermal growth factor receptor (EGFR/c-erb 1), members of the ras gene family, c-myc, int-2, hst-1, PRAD-1, and bcl-1 (**Figure 3**) [6].

The potential of proto-oncogenes to participate in tumorigenesis arises from the fact that their protein products are relays in the elaborate biochemical circuitry that governs the phenotype of vertebrate cells polypeptide hormones that act on the surface of the cell, receptors for these hormones, proteins convey signals from the receptors to the deeper cell machinery, and nuclear functions that orchestrate the genetic response to afferent commands [5].

Three biochemical mechanisms which proto-oncogenes act are [8]:

1. The first mechanism is phosphorylation of proteins, with serine, threonine, and tyrosine as substrates.

2. The second mechanism by which the genes act is transmission of signals by GTPases. The role of these signaling devices in tumorigenesis was first

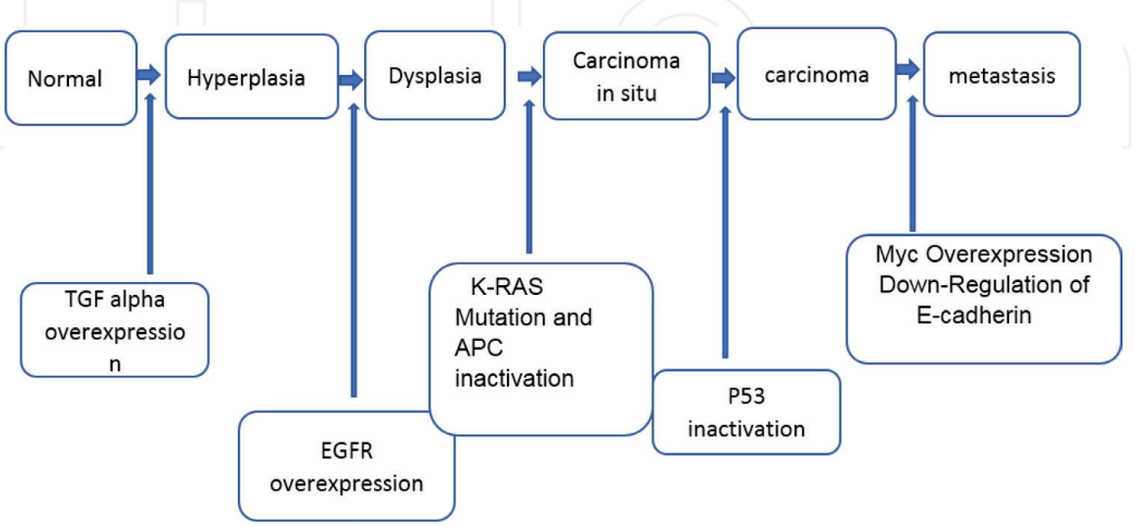

Figure 3.
Oral cancer progression model. The histopathologic progression of normal oral mucosa from hyperplasia to malignancy and metastasis appears driven by interplay of activation of oncogenes in early cellular transformation and inactivation of tumor suppressor genes closer to the initiation of malignancy and metastasis.

appreciated through the discovery of RAS oncogenes, which encode a previously unknown variety of GTPase.

3. The third mechanism consists of control of transcription from DNA. A still growing variety of transcription factors (FOS and MYC) are encoded by proto-oncogenes which may also participate directly in the replication of DNA.

3.1 Growth factor receptors and mechanisms

Activation of growth factor receptors in human tumors include mutations, gene rearrangements, and overexpression. Signaling pathways involved in the development of both cancer and stem cells are: the JAK/STAT pathway, NOTCH signaling pathway, the MAP-Kinase/ERK pathway, the PI3K/AKT pathway, the NFkB pathway, the Wnt pathway and the TGFβ pathways.

In the normal forms of growth factor receptors, the kinase is transiently activated by binding of the growth factors ligand to receptor, leads to rapid receptor dimerization and tyrosine phosphorylation of several substrates that are a part of the signaling cascade. The oncogenic growth factor receptors cause dimerization and activation without binding to the specific growth factor ligand. Hence, the mutant receptors deliver continuous mitogenic signals to the cell [1].

In oral carcinogenesis deregulation of growth factors receptors occurs through increased production and autocrine stimulation. Aberrant expression of transforming growth factor alpha (TGF-α) and beta (TGF-β) occur in carcinogenesis. TGF-α work in association with EGFR and TGF-β follows a pathway along with SMAD2 and 3.

TGF-α is reported to occur early in oral carcinogenesis, following the histological progression of hyperplastic epithelium first, and later in the invasive carcinoma within the inflammatory cell infiltrate, especially the eosinophils, surrounding the infiltrating epithelium. TGF-α stimulates cell proliferation by binding to EGFR and stimulates angiogenesis and has been reported to be found in "normal" oral mucosa in patients who subsequently develop a second primary carcinoma.

Microscopically "normal" oral mucosa of head and neck cancer patients who later develop second primary carcinomas overexpresses TGF-α suggesting a 'premalignant" lesion having rapid proliferation and genetic instability of the epithelium. Prognostically patients with oral tumors overexpressing TGF-α along with EGFR have been shown to have a significantly shorter survival than patients overexpressing EGFR alone [6].

TGFβ1 signals through the TGFβ receptors and these transduce the signal by phosphorylating SMAD2 and SMAD3, which, together with SMAD4, regulate the transcription of target genes.

Recently, a connection of TGFβ signalling pathway and nuclear factor-κB (NF-κB)99 has been studied, it's a transcription factor that provides an important survival signal to cells. Cohen et al. showed that abrogation of the TGF-β pathway was associated with activation of NF-κB, and this intriguing finding suggests that decreased TGFβ signalling is linked to NF-κB activation [9].

3.2 Cell surface receptors

Binding of cell surface receptor with ligands translates signals which are present extracellularly through the cell membrane by activating a cascade of biochemical reactions. Mutations or amplifications of genes encoding growth factor receptors can result in an increased number of receptors or production of continuous ligand-independent mitogenic signals.

EGFR, a 170,000-Da phosphoglycoprotein, is believed to be an important oncoprotein in oral cancer. Currently, three mechanisms have been postulated to activate the EGFR gene in carcinogenesis:

1. Deletion or mutations in the N-terminal ligand-binding domain.

2. Overexpression of the EGFR gene concurrent with the continuous presence of EGF or TGF-α.

3. Deletion in the C-terminus of the receptor that prevents downregulation of the receptor after ligand binding.

In human oral carcinogenesis EGFR is overexpressed as this gene is amplified. Therefore, it has been identified that in comparison to the normal counterpart, malignant oral keratinocytes possess 5–50 times more EGF receptor. Moreover, in oral carcinogenesis the mechanism of signal transduction is either because of overexpression of normal receptors due to mutated gene or because of the formation of many new receptors is not understood yet. Henceforth, oral tumors, having EGFR overexpression, have been shown to exhibit a higher response to chemotherapy than EGFR-negative tumors, presumably because of higher intrinsic proliferative activity leading to higher sensitivity to cytotoxic drugs [6].

3.3 Intracellular signal transduction pathways (RAS)

Like growth factor receptors, intracellular messengers can be intrinsically activated, thereby delivering a continuous rather than a ligand-regulated signal [6]. An oncogene can be activated either by gene amplification and/or mutation. In OSCC, the ras is one of the most frequently genetically altered oncogene. The mutations of three isoforms of ras gene such as Hras, Kras and Nras produce the same phenotype in the in vitro transformation assays. Mutations of the Hras appear to be highly prevalent in OSCC when compared to the Kras and Nras have been reported approximately from 0 to 55%.

3.3.1 Mechanism of ras activation

These genes encode closely related proteins that are located on the cytoplasmic side of the cell membrane and transmit messages from the cell surface receptors to intracellular regulatory enzymes [6].

RAS present on the cytoplasmic side of cell membrane get activated by growth factors through enhanced exchange of guanine nucleotide by forming Grb2 SOS complex. The molecular mechanism underlying in the functions activation of ras depends on the whole super family of small G-proteins because there exist a switch between GTP bound active and GDP-bound inactive state [10].

In normal human cell, an equilibrium is strictly maintained by the activity of GAPs (GTPase activating proteins) and GEFs (Guanine nucleotide exchange factors) between the active and inactive state because ras proteins have a minimal and a measurable activity on their own. The GAPs accelerate the GTP hydrolysis of ras and the antagonist GEFs such as ras-GRFs and ras-GRPs catalyze and weakens the GDP replacing with GTP. In a cell where ras is mutated, the equilibrium between the GTP and GDP-bound state is impaired. The ras is mutated predominantly at codon G12, G13 and Q61. In K-RAS and H-RAS because of point mutations GAP catalyzed hydrolysis of GTP to GDP, thereby generate constantly active ras and is responsible for the activation of downstream effectors whereby cell undergoes aberrant malfunctioning leading to malignancy (**Figure 4**) [10].

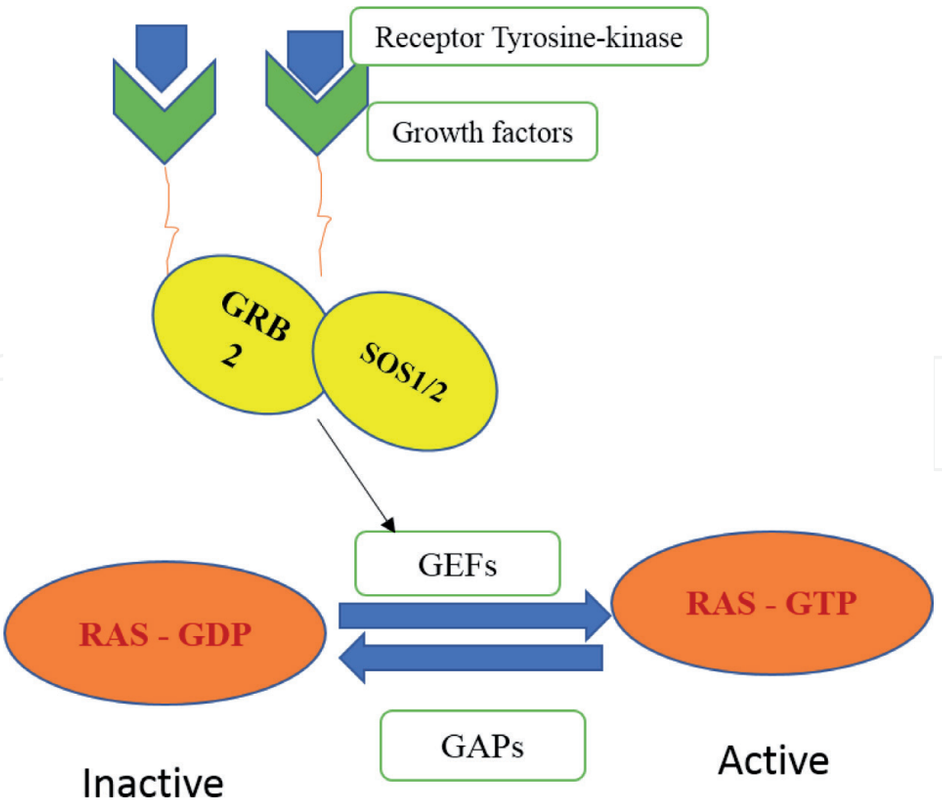

Figure 4.
Mechanisms of the ras activation.

3.3.2 Ras and its major signaling pathways

The ras oncogenes are associated with proteins that are involved in the transduction of extracellular growth, differentiation and survival signals. Ras activate receptor tyrosine kinases (RTKs), which further activate two key signal transduction components:

1. Small GTPase

2. Lipid kinase PI(3)K.

The activated ras stimulates mitogen-activated protein kinase (MAPK) and the phosphatidylinositol-3-kinase (PI3K)/Akt pathways. The key downstream steps involve phosphorylation by RAF1 kinase on two distinct serine residues MEK1/2. The MEK1/2 further phosphorylates specific threonine and tyrosine residues in the activation loops of ERK1/2 and leads to growth and differentiation. On the other hand ras transduces PI3K/Akt signaling pathway which lead to cell cycle proliferation and survival [10].

3.4 DNA binding nuclear proteins transcription factors (MYC, FOS, JUN)

Transcription factors, or proteins that stimulate other genes to be activated, are also altered in oral cancer. A growing number of the known proto-oncogenes encode nuclear proteins. These nuclear proteins are further regulated by receptor activated second messenger pathways. Neutralization of these encoded genes result in cell cycle arrest which prevents mitogenic and differentiation responses to growth factors. C-myc is a gene which helps regulate cell proliferation and apoptosis and is frequently overexpressed in oral cancers as a result of gene amplification.

C-myc is often overexpressed in poorly differentiated tumors, although more recently c-myc has been shown to be overexpressed in moderate and well differentiated oral carcinomas, in which cell proliferation far outweighed the number of apoptotic cells present. For apoptosis, c-myc requires p53 for regulating cell proliferation. c-Myc interacts with retinoblastoma tumor suppressor gene Rb-1 nuclear protein pR6, preventing its transcription, and thus inhibiting cell proliferation. However, on phosphorylation of pR6, c-Myc is increased and cell proliferation proceeds. Another transcription factor which is also amplified in head and neck cancers is PRADl (also CCNDl or cyclin Dl) which acts too as a cell cycle promoter [5–6, 8].

Particular order of oncogene activation has not been shown in oral cancers; instead the accumulation of activated oncogenes should be of primary importance. The importance of the currently identified oncoproteins to oral carcinogenesis is under investigation. Other oncogenes linked to oral cancer development are hst-1, k-2, bcl-1, sea, men-1, and eM1s-1.3.4. Oncogenes alone, however. Not sufficient to result in oral cancer but appear to be initiators of the process and should work along with the inactivation of tumor suppressor genes. The critical event in the transformation of a "premalignant" cell to a malignant cell is the inactivation of cellular negative regulators, tumor suppressor genes.

3.5 Cell cycle proteins (cyclins and cyclin dependent protein kinases)

The cell cycle is a mammalian cells proliferation regulation process and has 4 functional phases:

a. S phase (DNA replication)

b. G2 phase (cells prepare for mitosis)

c. M phase (DNA and cellular components division into two daughter cells)

d. G1 phase (cells commit and prepare for another round of replication).

S and M phases are the major and common process in all cell cycles for replication of cells. It requires interplay of expression of cyclins and cyclin dependent kinases in response to growth factors.

3.5.1 Cdks, the cell cycle

Cdk2 and cdk1, together, direct S and G2 phase transit, while cdk1 governs the G2/M transition and mitotic progression. Cdks can be divided into two groups:

a. 'Cell cycle' cdks, which orchestrate cell cycle progression.

b. 'Transcriptional' cdks, which contribute to mRNA synthesis and processing.

The first group encompasses cyclin D-cdk4 and 6, as well as cyclin E-cdk2 complexes, which sequentially phosphorylate the retinoblastoma protein (RB), to facilitate the G1/S transition. Cyclin A-cdk 2 and 1 are required for orderly S phase progression, whereas cyclin B-cdk1 complexes control the G2/M transition and participate in mitotic progression [11].

The second group includes cyclin H-cdk7 and cyclin T-cdk9 (pTEFb). It phosphorylates the carboxy-terminal domain of RNA polymerase II to promote elongation of mRNA transcription. Cyclin T-cdk9 also regulates mRNA processing [12].

3.5.2 Cdk's and cancer

CDK's and cyclins are the biochemicals play a pivotal role in cell cycle progression and transcription. Errors and dysregulation like amplification, mutation, deletion and hypermethylation of cyclins and its cdk partners activity results in loss of cell cycle check points and apoptotic activity which is a major cause for proliferative disorders such as cancer and which has been directly linked to the molecular pathology of cancer [11].

Cell cycle progression through the G1 phase is regulated by the action of cyclin D-cdk4, cyclin D-cdk6, and cyclin E-cdk2. This transition is mediated through the RB, which is regulated through sequential phosphorylations by CDK. Various genetic and epigenetic alterations in human cancer including mutations and amplification of Cdk and positive regulatory Cyclin subunits, lead to a hyperactivation of Cdk regulatory pathways. Henceforth, alteration in cell cycle checkpoints causes abnormal cell proliferation and results in tumor progression. Although mutations of cdk genes in tumor cells are rather infrequent with the exception of Cdk4 and Cdk6 amplification, overexpression or hyperactivation of basic cell cycle regulators is a general feature of human tumors like leukemia or carcinomas and were associated with poor prognosis [11].

3.6 Inhibitors of apoptosis (Bcl-2)

Apoptosis "programmed cell death'—is a physiologic process of cell to undergo death following sequence of events once the function is over. Any alterations in the mechanism of cell undergoing apoptosis not only contribute to abnormal proliferation of cell but also enhance resistance to anticancer therapies, such as radiation and cytotoxic agents. One of the suggested mechanisms for developing resistance to cytotoxic antineoplastic drugs is the alteration in expression of B-cell lymphoma-2 (Bcl-2) family members.

A balance between newly forming cells and old dying cells is maintained by Bcl-2 family of proteins which consists of 25 pro- and anti-apoptotic members. When there is alteration or disbalance in ratio of distribution of pro and anti-apoptotic proteins resulting in the overexpression of anti-apoptotic Bcl-2 family members, apoptotic cell death can be prevented. Targeting the anti-apoptotic Bcl-2 family of proteins can improve apoptosis and thus overcome drug resistance to cancer chemotherapy [6].

Two major pathways of apoptosis are the intrinsic and extrinsic cell-death pathways.

The intrinsic cell death pathway/mitochondrial apoptotic pathway: mainly triggers apoptosis in response to internal stimuli and is activated by a wide range of signals, including radiation, cytotoxic drugs, cellular stress, DNA damage and growth factor withdrawal. This mechanism involves the release of proteins cytochrome *c* from the mitochondrial membrane space which in turn activates pro caspase-9 and induces apoptosis.

The extrinsic cell-death pathway: pathway functions independently of mitochondria and executes cascade activation of caspases. Activation of cell-surface death receptors, such as Fas and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors, directly activate the caspase cascade via an "initiator" caspase (caspase-8) the role of which is to cleave other pro-caspases into active "executioner" caspases which induces degradation of cytoskeleton and nucleus [13].

3.6.1 Role of Bcl-2 in oral carcinogenesis

Bcl-2 family members can be divided into three subfamilies based on structural and functional features [13].

1. **Bcl-2 homology**—the anti-apoptotic subfamily contains the Bcl-2, Bcl-XL, Bcl-w, Mcl-1, Bfl1/A-1, and Bcl-B proteins, which suppress apoptosis and contain all four Bcl-2 homology domains.

2. **Multidomain proteins**—some pro-apoptotic proteins, such as Bax, Bak, and Bok, contain Bcl-2 homology domains.

3. **BH3-only proteins**—pro-apoptotic proteins, such as Bim, Bad, and Bid, contain only the BH3 domain.

Recent studies have shown that Bcl-2 expression is upregulated in oral SCC. Bcl-2 inhibits cell death via inhibiting apoptosis. Hence, Bcl-2-mediated inhibition of apoptosis may be an important factor in the pathogenesis of oral SCC. Bax forms heterodimers with Bcl-2 and when present in excess, Bax overrides the anti-apoptotic activity of Bcl-2.

P53 tumor-suppressor protein is a direct transcriptional activator of the human Bax gene suggesting that p53 may, in some instances, induce apoptosis via Bax-mediated suppression of Bcl-2 activity. In mutagenesis experiments, single amino acid substitutions in Bcl-2 homology domains disrupted Bcl-2-Bax heterodimers. The Bcl-2 mutants that failed to complex with Bax could no longer inhibit apoptosis. According to the study done by Oltvai et al. (1993) it was suggested that anti-apoptotic activity of Bcl-2 was inhibited by Bax, whereas the findings of Yin et al. (1994) is converse to that of the previous findings, i.e. that the function of Bcl-2 is to inhibit the apoptotic activity of Bax. But it was further hypothesized that the possible mechanism was the formation of Bcl-2-Bax heterodimers which inhibits both apoptotic and anti-apoptotic activity and is only seen when there is a functional excess of Bax or Bcl-2, respectively.

Bcl-x and Bcl-2 form heterodimers with Bad. This dimerization displaces Bax from Bcl-x, and Bcl-2 thereby enhances apoptosis. Therefore, the Bcl-2 family of related proteins (as with the Myc family) functions in part through protein-protein interactions.

In conclusion, Bcl-2-mediated inhibition of apoptosis may be an important factor in the pathogenesis of oral SCC. Furthermore, by blocking apoptosis, Bcl-2 can increase tumor cell resistance to anti-neoplastic drugs.

4. Tumor suppressor genes

Genes that encode the proteins for negative signal transduction pathways and modulate excitatory pathways and negate their effect in a "checks and balances" have been called as growth regulatory genes, recessive oncogenes or anti-oncogenes, but they are most often referred to as tumor suppressor genes. Negative regulatory pathways allow the cell to perform its function in the face of changing internal and external stresses [1, 14].

As been mentioned earlier in the chapter "Oncogenes alone are not sufficient to cause oral cancer and appear to be initiators of the process".

The transformation of a premalignant cell to a malignant cell is due to the inactivation of tumor suppressor gene which is a major event leading to the development of malignancy.

This mechanism of inactivation is may be due to point mutations, deletions, hypermethylation and rearrangements in gene copies. It was identified that many tumor suppressor genes were initially identified in pediatric tumors that formed early in life because one mutated tumor suppressor gene was inherited [1].

This mechanism led the evolution of "Knudson two hit hypothesis" This theory suggested a genetic model for retinoblastoma development. According to this RB gene mutation is inherited is described as the first hit and the tumor-restricted mutation as the second hit. This model further includes genetic aberrations, such as inactivation of a tumor suppressor and activation of an oncogene, as hits. Currently an extensive research on "chromosomal walking" is highlighted in pediatric tumors were the first tumor suppressor genes isolated with large chromosomal alterations. Therefore, although the identification of these "cancer genes" is one of the primary focuses of molecular biologists today, still far less is known about tumor suppressor genes [1].

4.1 Function of p53 as a tumor suppressor gene

The many roles of p53 as a tumor suppressor include the ability to induce cell cycle arrest, DNA repair, senescence, and apoptosis. Due to many genotoxic or chemical insults when genomic DNA damage is being identified, p53 gene activated and stop cell to divide further at the G1-S boundary and it repairs rather than replicates the error in the genetic code. If the chromosomal damage is too great, p53 gene activate apoptotic pathways [15].

4.2 Mutant form of p53

Mutation of p53 allows tumors to pass through the G1-S boundary and propagate the genetic alterations that may lead to other activated oncogenes or inactivated tumor suppressor genes. In addition to the loss of function that a mutation in TP53 may cause, many p53 mutants are able to actively promote tumor development by other means like:

1. Dominant negative manner

2. Gain of function

4.2.1 Dominant negative manner

In a heterozygous situation, where both wildtype (WT) and mutant alleles exist, mutant p53 can antagonize the activity of WT p53 tumor suppressor functions in a dominant negative (DN) manner. The transcriptional activity of WT p53 depends on forming tetramer where mutant p53 interfered in DNA binding activity of WT p53. However, such a heterozygous state is often transient, as TP53 mutations are frequently followed by loss of heterozygosity (LOH) during cancer progression as WT p53 allele is either deleted or mutated [14].

4.2.2 Gain of function

This term refers to the acquisition of oncogenic properties by the mutant form of p53 protein, compared with the mere inactivation of the protein. During tumorigenesis both the dominant negative and GOF effects may play a significant role in missense mutations of TP53 protein [15].

4.3 Mechanistic views of how mutant p53 exerts its function

Various mechanisms by which mutant p53 works in tumor progression:

1. GOF properties acquired by mutant p53 drive cells toward migration, invasion, and metastasis. Recent work demonstrates that mutant p53 can augment

cell migration and invasion. It was studied that "oncogenic" Ras and "Tumor Suppressor" mutant p53 activities occurs in early neoplasms to promote growth and survival, they play an equally important role at late stages of tumor progression in empowering TGFβ-induced metastasis.

2. EMT—metastasis follow the properties of epithelial to-mesenchymal transition (EMT), including loss of cell-cell adhesion and an increase in cell motility., Mutant p53 was found to promote EMT by facilitating the function of the key transcriptional regulators of this process, TWIST1 and SLUG whereas WT p53 was shown to inhibit EMT mechanism.

3. Tp63—an additional mechanism through which mutant p53 was shown to augment cell invasion is via the inhibition of transcriptional activity of TAp63α, but is unable to inhibit this function of TAp63γ indicating a protooncogenic activity of TP 53 [14].

It appears that in certain cancers, p53 is mutated late in the tumorigenesis process or plays a significant role in those advanced stages, whereas other studies indicates its expression in early stages of tumor progression. Therefore, it was hypothesized that TP53 mutations at early stages of tumorigenesis results in uncontrolled proliferation, a feature of both benign and malignant tumors, whereas mutations at later stages synergize with additional oncogenic events to drive invasion and metastasis, the hallmark of malignant tumors. p53 inactivation as a single event results in the high proliferation rate. Inactivation of p53 in conjunction with oncogenic H-Ras expression activates the expression of a large set of chemokines and interleukins reported to promote angiogenesis, invasion, and metastasis.

In general, tumor suppressor genes are thought to act recessively so that both copies of the gene must be inactivated for malignancy to occur. LOH and p53 mutations have been reported in several tumors. There is also controversy about the relation between mutated p53 and detection of its expression by immunohistochemistry. Some authors have commented on high correlation between p53 expression and point missense mutation, whereas others have reported discrepancy in oral cancer and lack of expression of p53 as immunocytochemistry have been attributed to insensitive methods of detecting p53 mutation. In Li-Fraumeni syndrome, mutant p53 is unstable, like the wild-type p53 protein, which suggests that some other event may be necessary for stability, and that stability of p53 is not intrinsic to the mutant p53 structure but might vary in different cell backgrounds. This mechanism can be highlighted by p53 and mdm2 relation because when normal p53 is bound to mdm2 it is targeted for destruction by the ubiquitin dependent pathway. However, it appears that mutant p53 fails to stimulate transcription of mdm2 and therefore mutant p53 is not degraded. Another mechanism tells that if E6 protein forms complexes with wild-type p53 and promotes p53 degradation this could account for the lack of concordance between p53 mutation frequency and LOH [16].

Other tumor suppressor genes include doc-1, the retinoblastoma gene, and APC.

5. Role of HPV in pathogenesis of OSCC

The role of HPV in pathogenesis of human malignancies has become convincingly established. HPV is a strictly epitheliotropic, circular double-stranded DNA virus that is known to be the primary cause of cervical cancer and currently establishing important role in oral carcinogenesis. There are more than 100 subtypes of HPV, some of which are involved in oral carcinogenesis and have been designated as

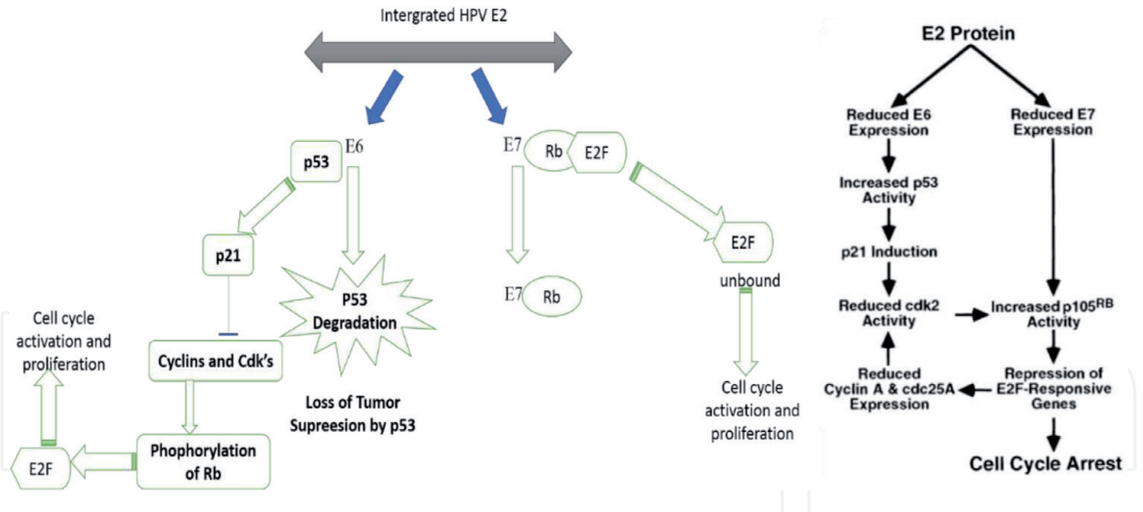

Figure 5.
Cell cycle deregulation by human papilloma virus activated by E6 and E7.

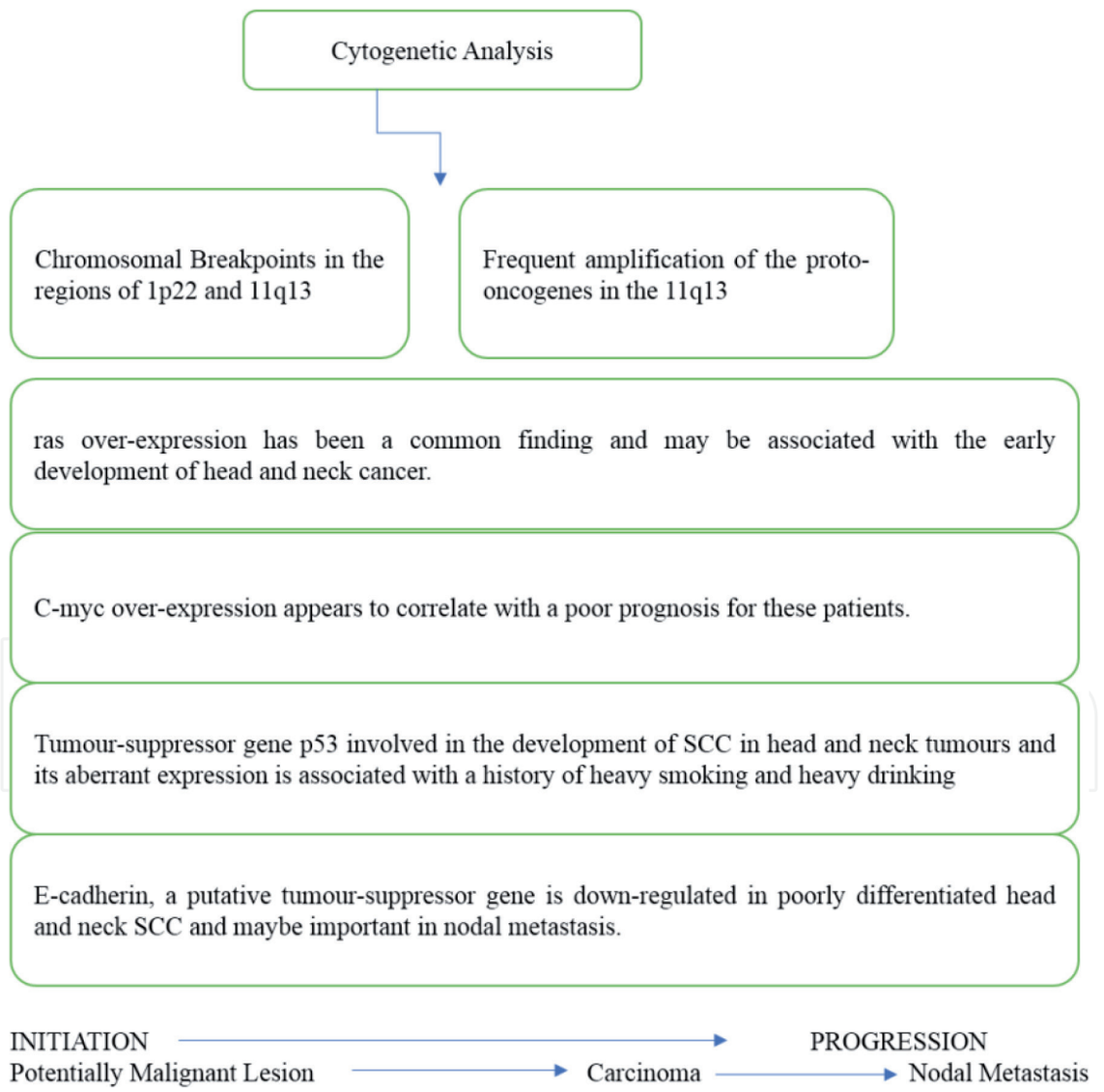

Figure 6.
Proposed molecular model for the genetic events in squamous cell carcinoma of the head and neck [19, 20].

high-risk HPVs. Approximately 85% of squamous cell carcinoma patients. The viral DNA gets incorporated into the host genome and is responsible for malignant transformation. The virus contains two oncogenes, E6 and E7, E1 and E2 open reading

frames will be interrupted and can lead to overexpression of E6 and E7 proteins. This E7 protein binds to underphosphorylated form of retinoblastoma results in the enhanced phosphorylation and degradation. Degraded form of pRb displaces E2F form of transcription factor and subsequent activation of gene promoting cell proliferation. E6 protein degrades p53 protein causing perturbation of cell cycle regulation in the infected cells which is considered to be the onset of HPV-mediated carcinogenesis. The virus is not easily cultured, therefore determining the role of virus in pathogenesis of OSCC is usually determined by detection of the viral DNA genome or expression of the viral genes using PCR methods. E6 and E7 have a crucial role in cervical cancer were also involved in HPV mediated carcinogenesis of the upper aerodigestive tract (**Figures 5** and **6**) [9, 17, 18].

6. Conclusions

Cellular signaling pathways are not isolated from each other but are interconnected to form complex signaling networks. Any change or diversification in this cellular signaling network such as increased production of growth factor or cell surface receptors, increase transcription or translation or intracellular messenger levels will give rise to abnormal proliferation of cell and is one of the reason for multifactorial oral carcinogenesis These changes can, in turn, cause a activation of protooncogene or loss of tumor suppressor activity which give rise to a phenotype capable of increasing cellular proliferation, weakening cell cohesion, and causing local infiltration and metastasis.

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