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JOURNAL OF APPLIED DENTAL AND MEDICAL SCIENCES

VOL . 1 ISSUE 1 APR-JUN 2015

REVIEW ARTICLE

Cell Signaling Pathways in Oral Cancer: A Review

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ARTICLE INFO

Article history:
Received 9th May 2015
Received in revised form 2nd June 2015
Accepted 5th June 2015

Keywords:
Cell Signaling, Oral Cancer, Cell Cycle, Oncogene

ABSTRACT

Oral carcinogenesis is a multistep process in which genetic events lead to the disruption of the normal regulatory pathways that control basic cellular functions including cell division, differentiation, and cell death. Several studies have shown that there is a genetic component in the development of carcinoma. These include reports of the occurrence of familial aggregations of cancer, including oral cancer, with carcinomas developing at a younger age.

INTRODUCTION

In adult tissues, the growth of cell is determined by the rates of cell proliferation, differentiation, and death by apoptosis. There is a large number of known polypeptide growth factors, some of which act on many cell types, and others have restricted cellular targets. In addition to stimulating cell proliferation, growth factors may also have effects on cell locomotion, contractility, differentiation, and angiogenesis, activities that may be as important as their growth promoting effects[1-3]. Cell differentiation occur in cell cycle, so any mutations or defects allow the replication of cells with DNA strand breaks and chromosome abnormalities that may cause tissue alterations and neoplasia[4].

Neoplastic tumor can be a benign tumor or malignant tumor depending on various characteristics as differentiation and anaplasia, rate of growth, local invasion and metastasis. Seven fundamental changes in cell physiology that together determine malignant phenotype :

1. Self-sufficiency in growth signals
2. Insensitivity to growth-inhibitory signals
3. Evasion of apoptosis
4. Defects in DNA repair
5. Limitless replicative potential
6. Sustained angiogenesis
7. Ability to invade and metastasize

In this article we will be discussing the molecular regulation of the cell cycle, since cell cycle abnormalities are fundamental to cancer growth and many of the genes that cause cancer perturb the cell cycle. This is followed by seven biologic alterations which are listed above, since dysregulation of genes contribute to the origin or progression of these biologic alterations.

ALTERED CELL CYCLE

The hallmark of cancer is rapid and uncontrolled growth (Fig. 1). In head and neck cancers, several key cell-cycle regulatory molecules have been implicated in its pathogenesis. An essential component in cell-cycle transition is the cyclin-CDK complex and Retinoblastoma Protein (RB). Upon RB phosphorylation by the cyclin/CDK complexes on RB, there is a release of E2F, subsequently allowing E2F to transcribe the necessary components for the cell to continue through the G1/S transition. Specifically, RB function is

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mediated by cyclin E/CDK2 activity through E2F transcriptionally regulating cyclin E. In contrast, CDK4 and CDK6 act upstream of RB, and they inhibit RB function by phosphorylation[5].

Loss of RB function has mainly been implicated in retinoblastomas; however, both down- and up-regulation of RB function has been observed in head and neck cancer, conferring a greater degree of malignancy and aggressiveness, dependent upon cellular context[5,6]. Downregulation of RB function obviously allows the cell cycle to remain unchecked and leads to continual cell division and cell proliferation; however, up-regulation may also be detrimental, 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. Alteration of these cyclins and CDKs has been observed in head and neck cancers as well[5].

PROTO-ONCOGENES, 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 (bcl2)

The binding of soluble extracellular growth factors to their specific surface Receptors initiates signalling cascades that eventuate in entry of the cell into the mitotic cycle. A few protooncogenes encode growth factors that stimulate tumor cell growth. In some instances a growth factor acts upon the same cell that produces it (autocrine stimulation). Other growth factors act upon the receptors of neighboring cells (paracrine stimulation). Examples of growth factors involved in neoplastic transformation include platelet derived growth factor (PDGF) and fibroblast growth factor(FGF).

GROWTH FACTOR RECEPTOR AND MECHANISM

Growth factor receptors are activated in human tumors by several mechanisms (Fig. 2). These include mutations, gene rearrangements, and overexpression. From the nine main signaling pathways involved in embryonic development and cancer, seven of them have been implicated in both cancer and stem cells. These 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[8].

In the normal forms of growth factor receptors, the kinase is transiently activated by binding of the specific growth factors, followed rapidly by receptor dimerization and tyrosine phosphorylation of several substrates that are a part of the signaling cascade. The oncogenic versions of these receptors are associated with constitutive dimerization and activation without binding *to the* growth factor. Hence, the mutant receptors deliver continuous mitogenic signals to the cell[4].

TRANSCRIPTION FACTORS

Many of the signal transduction systems used by growth factors transfer information to the nucleus and modulate gene transcription through the activity of transcription Factors. Transcription factors have a modular design and contain domains for DNA binding and for transcriptional regulation. The DNA-binding domain permits binding to short sequence motifs of DNA, which may be unique to a particular target gene or may be present in many genes. In general, cellular events requiring rapid responses do not rely on new synthesis of transcription factors but depend on post-translational modifications that cause transcription factor activation and migration into the nucleus. These modifications include heterodimerizatioN, phosphorylation of available factors, and release of inhibition to permit nuclear migration (NFKB)[4].

TUMOR SUPPRESSOR GENES

Oncogenes alone are not sufficient to cause oral cancer and appear to be initiators of the process. The crucial event in the transformation of a premalignant cell to a malignant cell is inactivation of cellular negative regulators tumour suppressor genes and is regarded to be a major event leading to the development of malignancy. Tumour suppressor genes are most often inactivated by point mutations, deletions, and rearrangements in both gene copies.

There has been much research on the tumour suppressor gene p53. The p53 protein blocks cell division at the G1 to S boundary, stimulates DNA repair after DNA damage, and also induces apoptosis[1,8,9,10]. The p53 protein transcriptionally activates the production of the p21 protein, encoded by the WAF1/CIP gene, p21 being an inhibitor of cyclin and cyclin dependant kinase complexes [1,11].

Mutation of p53 occurs either as a point mutation, which results in a structurally altered protein that sequesters the wild-type protein, thereby inactivating its suppressor activity, or by deletion, which leads to a reduction or loss of p53 expression and protein function. The tumour suppressor gene p53 is known to be mutated in approximately 70% of adult solid tumours[1,12].

EVASION OF APOPTOSIS

Cell growth is regulated by growth-promoting and growth-inhibiting genes, cell survival is conditioned by genes that promote and inhibit apoptosis. Therefore, the accumulation of neoplastic cells may occur not only by the activation of oncogenes or inactivation of tumor suppressor genes, but also by mutations in the genes that regulate apoptosis.

Apoptosis is regulated by an interplay of a variety of gene products that can either act as inducers or inhibitors of this process. Following the discovery of the Bcl-2 gene, several mammalian and viral homologues of this gene and its protein have been identified. Current mammalian homologues include Bax, Bcl-X, Mcl-1, Al, Bad, and Bak. Bcl-2, Mcl-1, and A1 have been shown to antagonize the cell death pathway, while Bax, Bak, and Bad act as dominant promoters of programmed cell death[4].

DNA REPAIR, DEFECTS AND GENOMIC INSTABILITY

DNA damage can occur from environmental agents and also the DNA of normal dividing cells is susceptible to alterations resulting from errors that occur spontaneously during DNA replication. Such mistakes, if not repaired promptly, can also push the cells along the slippery slope of neoplastic transformation[4].

Defects in repair mechanisms are present in sporadic human cancers. DNA repair genes themselves are not oncogenic, but their abnormalities allow mutations in other genes during the process of normal cell division. Typically, genomic instability occurs when both copies of these genes are lost. Thus, in this respect they resemble tumor suppressor genes. Defects in three types of DNA repair systems, namely, mismatch repair, nucleotide excision repair, and recombination repair[4].

TELOMERASE ACTIVITY

Telomeres are protein-DNA structures at the ends of eukaryotic chromosomes. Telomerase circumvents the problem of end replication by using RNA to template the synthesis of telomeric DNA.[13,14] Recent studies, using the telomeric repeat amplification protocol (TRAP), have shown that telomerase is activated in most human cancer tissues, but not in most normal tissues or benign tumors.[13,15] In addition, the previous studies have shown that the lack of telomerase activity correlates critically with shortened telomeres and frequent spontaneous cancer remission.[13,16] Thus, the expression of telomerase is important, and it may be a rate-limiting step in tumor progression[13,15] (Fig. 3).

ANGIOGENESIS DEVELOPMENT

Cancer progression requires consecutive transformation events through which tumor cells escape proliferative checkpoint controls and regulatory cues from the extracellular milieu. In this process, tumor cells also acquire the ability to shape the tumor microenvironment for their survival advantage. Virtually, all clinically relevant carcinomas have undergone the "angiogenic switch" , i.e., developed mechanisms to sustain an appropriate blood supply for further tumor expansion.[17,18].

In principle, tumor cells utilize the same programs of angiogenesis that restore organ function after ischemic, mechanical, or microbial injury. Whereas regenerative angiogenesis typically progresses to restore a functional, organ-specific hierarchical vascular bed, tumor vessels retain various degrees of immaturity and tortuous architecture. Thus, tumor vessels have inconsistent directions of flow, imperfect vessel wall architecture including abnormal pericyte recruitment, and—most importantly for the current review—increased permeability and extravasation of blood plasma components.[17]

As vascular endothelial growth factor (VEGF) is considered as the most potent candidate for the induction of angiogenesis in tumor growth, it has naturally received attention as a potential agent for therapeutic angiogenesis [19,20].

INVASION AND METASTASIS

Toward the end of the nineteenth century, Dr. Stephen Paget, a British surgeon, proposed the "seed and soil" hypothesis of cancer metastasis, wherein he postulated that cancer cells are the "seeds" that have variant capacity to escape from primary tumor, spread to, and implant in a distant tissue and that specific qualities of the recipient tissues determine the condition of "the soil," which enables a metastasis to proliferate, survive, and progress in that tissue.[21]

HNSCC development, progression, and metastasis involve the accumulation of genetic mutations and epigenetic changes in the multiple pathways regulating cell growth, proliferation, and death. Initiating mutations occur early in tumorigenesis and allow epithelial cells to escape growth arrest and develop a clonal population of abnormally proliferating cells. With additional mutations, these hyperproliferative cells develop a more malignant phenotype by escaping apoptosis, undergoing epithelial-to-mesenchymal transition (EMT), and invading through the basement membrane. To metastasize, malignant cells must further acquire the ability to dissolve adherens junctions, activate matrix metalloproteinases (MMPs), promote angiogenesis, and evade immune surveillance. Transforming growth factor beta (TGFb) signaling impacts HSNCC development and metastases by affecting virtually all of the aforementioned biological processes.[21]

Many stages of the metastatic cascade depend upon adhesive interactions between tumour cells and other tumour cells, normal host cells, basement membrane components and the components that comprise the extracellular matrix (Fig. 4). A wide range of cell surface adhesion molecules facilitates these interactions, each with their own ligand specificity. These adhesion molecules can be generally separated into four families: the cadherins, the immunoglobulin superfamily, the integrins and the selectins.[22]

CONCLUSION

Cellular signalling pathways are not isolated from each other but are interconnected to form complex signalling networks. Cells receive information from many different growth factor receptors and from cell-matrix and cell-cell contacts. They must then integrate this information to regulate diverse processes, such as protein synthesis and cell growth, motility, cell architecture and polarity, differentiation, and programmed cell death. The same signalling molecules are used to control different processes within different signalling complexes or at different intracellular locations. Moreover, signalling pathways are subject to developmental regulation and generate different outcomes in different cell types; the activation of a signalling molecule may have distinct consequences, depending on the cellular context.[23]

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How to cite this article: Shah S, Pathak P, Gulati N. Cell Signaling Pathways in Oral Cancer: A Review. *J App. Dent. Med. Sci. 2015; 1(1):69-74.*

Source of Support: Nil Conflict of Interest: None declared.

FIGURES

Fig. 1: Multi-stage evolution of cancer

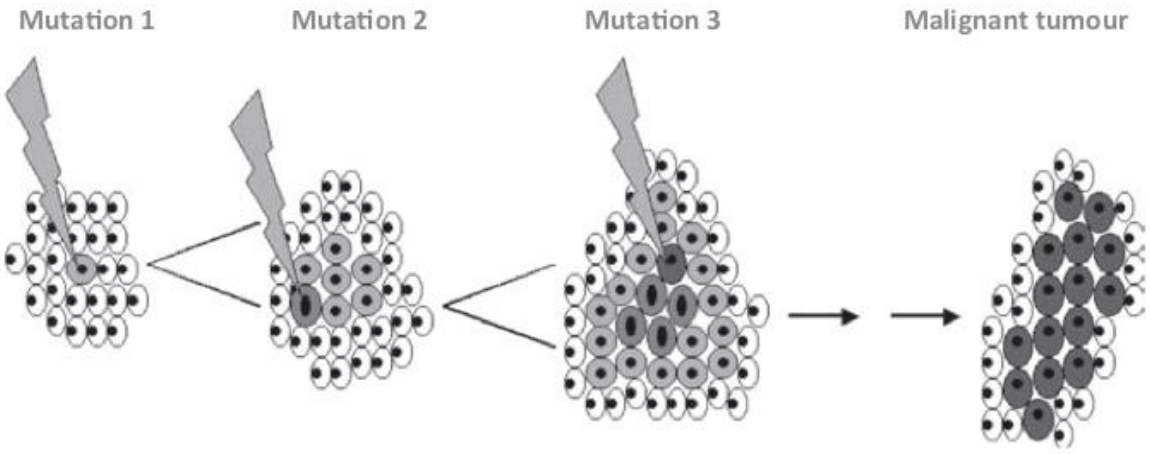

Fig. 2: Subcellular localization and functions of major classes of cancer-associated genes

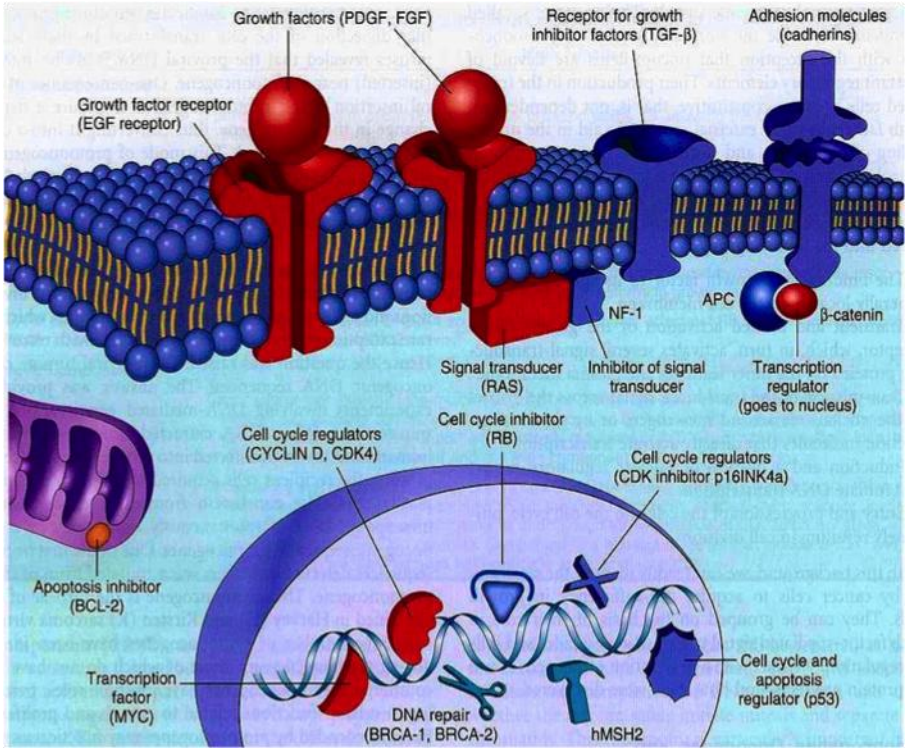

Fig. 3: Cellular responses to telomere shortening

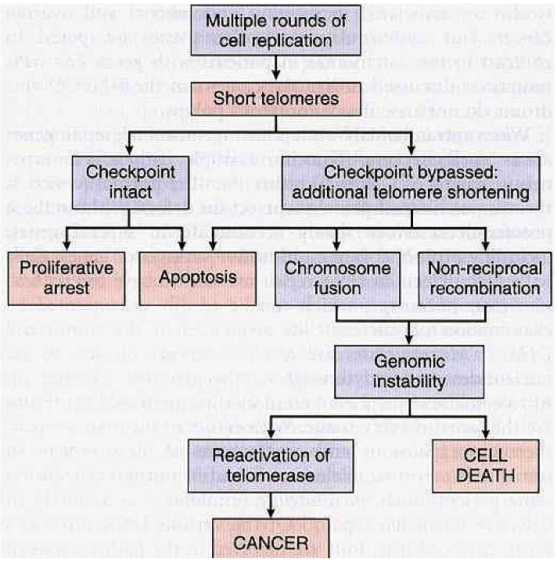

Fig. 4: Roles of proteases in the metastatic cascade