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An Insight on Important Oncogenes –A Review.

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ABSTRACT

Non-lethal genetic damage or mutation to important proto-oncogenes and some tumor suppressor genes can cause uncontrolled cellular proliferation. Such mutant alleles of proto-oncogenes are called oncogenes. When mutation is seen in tumor suppressor genes they are called recessive oncogenes. Such mutation can occur in genes involved in various stages of cell proliferation. Mutation can occur in genes regulating growth factor receptors like epidermal growth factor receptor , signal transduction proteins mainly RAS, nuclear transcription proteins like MYC, MYB, cell cycle promoters like CDKs Cyclin-D and cell-cycle inhibitors. An overview of important oncogenes is dealt in this article.

Key Words: Mutation, Proto-oncogenes, Oncogene.

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INTRODUCTION

Malignancies occur because of the non-lethal genetic damage or mutation that can be acquired due to germ-line mutation or environmental factors like chemicals, viruses , continued irritation and so on. Genes that are principle targets for genetic damage are normal regulatory proto-oncogenes, tumor suppressor genes, genes regulating programmed cell death and genes involved in DNA repair [1]. When proto-oncogenes or tumor suppressor genes gets mutated, the altered gene is called oncogene. Many such mutations are identified in the recent years. Some important extensively studied oncogenes are described here [1, 14].

Proto-Oncogenes

Proto-oncogenes are the ones that code for proteins and regulate the normal cell function. They act in a dominant fashion and regulate cell growth and differentiation in a positive manner. When they get altered, modified gene formed is called an oncogene. In other way mutant alleles of proto-oncogenes are oncogenes. Mutation in proto-oncogenes is considered to be dominant because even mutation in single-allele can cause cellular transformation .Proto-oncogenes can thus be called dominant oncogenes [1, 2].

Tumor Suppressor Genes

Tumor suppressor genes function as promoters or caretakers. They act as brakes in cell cycle. When any mutant gene is encountered, they are either repaired or go for apoptosis. Most important among them is p53 and RB gene. When mutation occurs in single allele there is no malignant transformation. Only is both alleles are mutated they can command cellular proliferation. Thus, they are called recessive oncogenes. But some studies show that even single allele mutation in this gene is enough to cause cellular proliferation [4, 5]. Oncogenes act heterogeneously modulating various stages of cell cycle and promote tumorogenesis and progression.

Growth Factor Receptor Protiens

Normal cell undergo proliferation only when it is stimulated by growth factors either in autocrine or paracrine fashion. Cancer cells proliferate by producing their own growth factors and expressing its specific receptor in autocrine fashion. Many oncogenes that form as a consequence of overexpression or mutation of growth factor receptors are recognized. Such mutant receptor proteins provide uninterrupted mitogenic signals to cells, even if the growth factor in is not expressed [1, 3].

Epidermal growth factor receptor (EGFR) also called as erbb1- EGFR can regulate cell growth when activated by EGF and transforming growth factor. It stimulates epithelial cell proliferation. Overexpression of EGFR is considered an important prognostic marker of survival in betel quid chewers [6]. Fibroblast growth factor (FGF), Platelet derived growth factors (PDGF) are some growth factors produced by cancer cells.

Erbb2 , a related receptor also known as Her-2 or Neu –can exert transforming effects. These tumors are highly sensitive to the mitogenic effects of even insignificant amounts of growth factors [7]. High level of HER2/NEU protein is an indication of poor prognosis mainly in breast cancer. Its amplification has been found in oral cancer specimens, high levels of erbb2 may be associated with worse prognosis in non-dysplastic oral leukoplakia[2].It is seen amplified in 25% to 30% of adenocarcinomas of salivary glands.

Genes Involved In Signal Tranduction

Cancer cells can also acquire unlimited growth potential if there is mutation in genes that codes for various pathways of the signaling transduction from growth factor receptors on cell membrane to the nucleus. They link growth factor receptors to their targets inside the nucleus. Such signaling proteins can act through second messengers or through phosphorylation cascade activate signal transduction molecules. Most important ones are RAS and ABL.

RAS is one of the mutated proto-oncogene in human tumors. In about 30% of tumors RAS mutated versions are noticed more commonly in adenocarcinomas. RAS comes under the Family of G proteins .They bind to guanosine diphosphate [GDP] and guanosine triphosphate [GTP]. Normal RAS proteins change from an excited state to a quiescent state and flip back after completing its task. When bound to GDP they are inactive and when stimulated by growth factors ,phosphorylation occurs and GTP is formed from GDP and successive structural changes occurs and active RAS is generated. This activated RAS then excites down-stream regulators of cellular proliferation like RAF-mitogen-activated protein (MAP) kinase mitogenic cascade. Nucleus is then flooded with signals for proliferation of the cell. This excited active stage of the RAS protein is short-lived in normal conditions. This is because RAS gene have intrinsic guanosine triphosphatase (GTPase) activity which hydrolyzes GTP to GDP and return to the inactive quiescent state inactive after releasing a phosphate group. The family of GTPase-activating proteins, thus act as molecular brakes and inhibit unrestrained RAS activation by supporting hydrolysis of GTP to GDP [1,5].

Most common mutation occurring in RAS gene is point mutations. On molecular analyses three hot spots were revealed. These spots correspond to the GTP-binding pocket or regions where GTP hydrolysis takes place. RAS gets stuck in activated GTP-bound form and the cell is compelled to proliferate continuously. It is commonly associated with familial neurofibromatosis type 1.

Several non-receptor-associated tyrosine kinases also function as signal transduction molecules. ABL is the important one among them .The ABL proto-oncogene function in internal negative regulatory domains through their tyrosine kinase activity. ABL translocate from chromosome 9 to 22 and fuse with part of the breakpoint cluster region (BCR) gene. It is reported in chronic myeloid leukemia and in some acute leukemia's. The trans located genes bears potent unregulated tyrosine kinase activity which in turn activates RAS-RAF cascade and others. Normal ABL protein which is inside the nucleus can promote apoptosis of cells when

there is DNA damage. This is similar to that of p53 gene. The BCR-ABL gene could not complete this function, since it is in the cytoplasm and does not enter the nucleus due to abnormal tyrosine kinase activity. BCR-ABL fusion gene deregulates cell proliferation by incorrect tyrosine kinase activity which gives autonomy and by impaired apoptosis [1-3,5] .

Patients with chronic myeloid leukemia showed dramatic clinical response when treated with an inhibitor of the BCR-ABL fusion kinase .Thus knowledge on the molecular basis of cancer helped drug designing.

Genes Involved In Nuclear Transcription

Eventually, all signal transduction paths go into the nucleus and act on a large panel of responder genes that coordinate the cells' and methodically advance them through the mitotic cycle. A crowd of oncoproteins, containing products of the MYB, MYC, REL, FOS and JUN oncogenes act as transcription factors that control the growth-promoting genes expression such as cyclins.

The most important is MYC gene .All cells express MYC proto-oncogene when resting cells take a signal to divide. Normally MYC levels drops to normal when the cell cycle begins. Oncogenic varieties of the MYC gene are expressed indeterminably or is overexpressed, thus there is sustained cellular proliferation [1].

The MYC protein can stimulate or suppress the transcription of other genes. Numerous growth-promoting genes like cyclin-dependent kinases (CDKs) are stimulated by MYC. They are then driven into the cell cycle. CDK inhibitors (CDKIs) are supressed by MYC. MYC, thus promotes tumorigenesis activating genes responsible for cell proliferation and repressing genes that thwart progression through the cell cycle. MYC gene dysregulation in Burkitt lymphoma's due to 8;14 translocation.

Genes Regulating Cell Cycle

The cyclin family of proteins regulates cell cycle progression. Growth-promoting stimuli finally send the quiescent cells to cell cycle. Cancers can become autonomous, if the regulating genes of cell cycle gets amplified or mutated. Cell cycle is coordinated by Cyclin D Kinases[CDKs]. CDKs gets activated when they bind to cyclins. The CDK-cyclin complexes phosphorylate essential target proteins that make the cell run through the cell cycle. After completing the job, cyclin levels drops rapidly[8- 10, , 14]. About 15 Cyclins are identified. Cyclins D, E, A, and B work successively all through the cell cycle and act on one or more CDK. The cell cycle thus act like relay race regulated by a separate set of cyclins .When one cyclin leaves the field, the next one starts its role. When expression of cyclin D or CDKs is misrelated , there can be neoplastic transformation. Over expression of cyclin D genes is reported in lymphomas , breast cancers and in some other tumors. CDK4 gene amplification occurs in sarcomas, melanomas, and glioblastomas[10,11].

The D-type cyclins are able to initiate the G–S transition by phosphorylating the retinoblastoma protein in response to mitogenic signals. Increased cyclin D expressions is a noticed in some oral cancer and pre-malignant lesions. Cyclin D overexpression specifically, CCND1 gene amplification may indicate worse prognosis and a they are at a high risk of occult cervical lymph node metastasis in low stage tumors [9].Cyclin A overexpression indicates cells are in S-phase- indicates the advanced tumor stage. Cyclin B is overexpressed in oral and tongue cancers [4].

Group of genes called Cyclin D Kinase Inhibitors [CDKIs] play negative control in the cell cycle. Some of them are p21 [CDKN1A], p27 [CDKN1B], and p57 [CDKN1C]. They inhibit CDKs largely. Some others have selective action on particular cyclins. Down regulation of these inhibitors promote the uncontrolled progression of the cell cycle. Some of them act as tumor suppressors and if deletion occurs in this locus it affects e RB and p53 pathways. Thus CDKIs mutation is reported in many human malignancies [1].

Other proto-oncogenes include VEGF (vascular endothelial growth factor) which controls angiogenesis and is important for tumor growth, progression and metastasis. It promotes the progression of OSCC by up regulating microvessel density [12,15].Matrix metalloproteinases (MMP) are zinc metalloenzymes with the ability to degrade the components of the ECM (extracellular matrix) enabling local invasion. Tissue inhibitors of metalloproteinases (TIMPS) bind to the MMPs and inhibit their action. TIMP-2 expression correlates with local recurrence and poor prognosis [5].

CONCLUSION

Oncogenes are mutant allele of proto-oncogens. They form when there is mutation of genes in different areas of cell cycle beginning from genes regulating growth factor receptors (like EGF, PDGF, FGF), signal transduction proteins (RAS,ABL) nuclear transcription proteins (MYC, MYB, FOS), cell cycle promoters (CDKs Cyclin-D), cell-cycle inhibitors (CDKIs).World of oncogenes is still expanding as numerous new genes are identified.

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