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Cancer and Oncogenes - An Overview

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Abstract: Cancer results from many factors such as environmental, toxic chemicals, viruses, life style, epi-genetic and genetic. In genetic level, cancer is caused by oncogene, tumor suppressor gene and miRNA. These genes are required for normal cell proliferation and differentiation, where aberrant expression leads to abnormal cell proliferation. The gene level changes include mutation, translocation, DNA rearrangement in the genes results in activation and formation of tumour. Ras and p53 are the paradigms for oncogenes and tumor suppressor genes respectively. The products of oncogenes include growth factors, growth factor receptors, signal transducers and nuclear transcription factors, where antibodies against oncogene products are the current anti-cancer drugs. MicroRNA, which are the next targets for cancer drug research has gained significant attention, has also proved for its potential to be used in disease prognosis and diagnosis.

Key words: Cancer · Oncogenes · Tumour suppressor genes · miRNA · Cancer therapeutics

INTRODUCTION

Cancer and its Causes: Cancer is currently the cause of 12% of all deaths worldwide. In 2008 approximately 12.7 million cancers occurred and 7.6 million people died of cancer worldwide [1]. This makes it the leading cause of death in the developed world and the second leading cause of death in the developing world. Cancer prevalence in India is estimated to be around 2.5 million, with over 8, 00,000 new cases and 5, 50,000 deaths occurring each year due to this disease in the country [2]. The common sites for cancer in India are oral cavity, lungs, oesophagus and stomach in males and cervix, breast and oral cavity among females.

Cancer is caused by a combination of environmental and genetic factors. Cancer is influenced by environment, lifestyle and diet on one hand, heredity and spontaneous mutations on the other. In normal cell growth there is a finely controlled balance between growth-promoting and growth-restraining signals such that proliferation occurs only when required [3].

Tumor Types: Tumors can be divided into two main groups, benign or malignant. Benign tumors are rarely life threatening, grow within a well-defined capsule which limits their size and maintain the characteristics of the cell of origin and are thus usually well differentiated. Malignant tumors invade surrounding tissues and spread to different areas of the body to generate further growths or metastases. It is this process which is often the most life threatening [4].

The Multistage Nature of Cancer Development: Armitage and Doll [5] concluded that carcinogenesis as a six or seven-stage process. Tumors tend to acquire more aggressive characteristics as they develop and in 1957 Foulds [6] pointed out that tumor progression occurred in a stepwise fashion, each step determined by the activation, mutation or loss of specific genes. The evidence suggested that, in the majority of cases, cancers arise from a single cell which has acquired some heritable form of growth advantage [6]. This initiation step is believed to be caused frequently by some form of genotoxic agent such as radiation or a chemical carcinogen. The cells at this stage, although altered at the DNA level, are phenotypically normal.

Further mutational events involving genes responsible for control of cell growth lead to the emergence of clones with additional properties associated with tumor cell progression. Finally, additional changes allow the outgrowth of clones with metastatic potential. Each of these successive events is likely to make the cell

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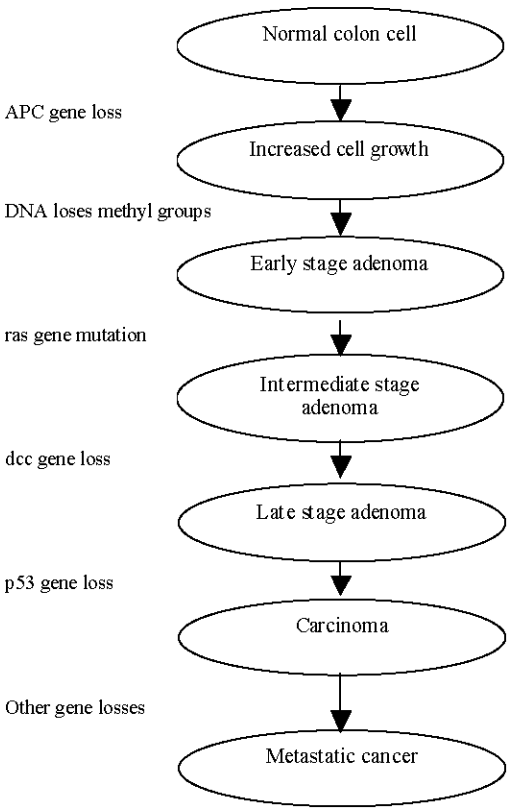

Fig. 1: Stages of Metastasis

more unstable so that the risk of subsequent changes increases. Animal models of carcinogenesis, primarily based on models of skin cancer development in mice, have enabled these steps to be divided into initiation events, promotion, malignant transformation and metastasis [7]. Although it is clear that multiple changes are necessary for tumor development, it is not clear whether the order in which the changes occur is critical.

The following Figure 1 shows the various stages of cancer in development of metagenesis cancer formation.

The following Table 1 shows the differences of cancer cell from a normal cell.

Classification of Cancer: As has become appreciated over the years, cancer is not a single disease, but a whole collection of disorders that constitute at least 300 different histological types. On the basis of embryological origin of the initial tumor cells, cancer cells are classified as follows.

- Carcinomas are epithelial in origin (ectodermal and endodermal).
- Sarcomas are derived from connective tissue (mesodermal).
- Leukemias are from blood-forming cells.
- Melanomas derive from pigment cells (melanocytes).
- Teratomas arise from germ cells or gonadal tissue.

Cancers can also be classified into four main groups on the basis of the genetic defect:

- The majority of cancers are sporadic and are caused by environmental factors such as chemicals and radiation. Mutations in these tumors are found only in the cancer tissue itself.
- These cancers have apparent clustering of cancers in families due to the shared environment of family members rather than because of a genetic defect.
- A small proportion of cancers have a clearly defined genetic cause. In addition, the genes involved have a wider importance as the genes which cause the inherited form of the disease are often the same as those which are implicated in the sporadic form of the disease. The classic example of this is the *APC* gene which is responsible for the inherited condition familial adenomatous polyposis (FAP) and which is also the earliest gene to be mutated in the development of sporadic colorectal cancer. The main exception to this principle is familial breast cancer which is caused by defects in the *BRCA1* and *BRCA2* genes. Defects in these genes have not so far

Table 1: Differences b/w tumour and normal cell

Character	Normal cell	Tumour cell
Morphology	Normal	Cellular and nuclear pleomorphism
Growth factors	Dependent	Independent
Motility	Normal	Increased Motility
Anchorage (Contact with extracellular environment)	Dependent	Independent
Adhesiveness	More	Less
Contact inhibition	Yes	No
Proliferation	limited after reaching certain density	Continued

been observed in sporadic breast cancer. In cancers with a true genetic basis, the causative mutation is found in all the cells of the body. This group can be recognized by an earlier age of onset, multiple cancers in individuals and by segregation of the disease through the family in a Mendelian manner.

- Individuals with some conditions, generally termed chromosome breakage syndromes because of the increased chromosome fragility seen in cultured cells, for example those from xeroderma pigmentosum and ataxia telangiectasia, have an increased risk of cancers although the incidence of cancers is not close to the levels seen in patients in group 3.

Environmental and Epigenetic Factors: Cancers are clearly not just spontaneous changes in the genetic makeup of cells which cause them to run wild. Extra-genomic factors also are important contributors such as smoking (lung cancer), several environmental mutagens having a potential carcinogenic activity (agents able to increase the frequency of cancer), dietary fat (colon cancer). Besides environmental components, other epigenetic factors are known to effect cancer rates [8]. For example, a number of different types of carcinomas express the gene for the protein alpha-fetal-protein (AFP). This gene is normally expressed during the early stages of embryogenesis and not after. This then represents a case where a gene is expressed in the wrong place and at the wrong time. When the AFP gene is examined it is found to completely normal. The signals being sent to the gene are what are aberrant. In another example, some patients with small lung cell carcinomas develop retinal degeneracy. The reason turns out to be that the carcinoma cells begin to display an antigen on their surfaces that is a normal differentiation antigen on retinal cells during development. When the immune system sees the antigen on these cells at the wrong time and in the wrong place it makes antibodies against it. Some number of the tumor cells is destroyed by the antibodies but so is the retina. Therefore, many of the pathophysiological effects of cancer are the result of inappropriate signals being sent and received by the tumors [9]. Cancer, in fact, has been referred to as a "progressive disorder in signal transduction" [10].

Genetic Basis of Cancer: Cancer is caused by alterations in oncogenes, tumor-suppressor genes and microRNA genes. Of the 50,000- 100.000 genes in our genome, about 100 have been identified thus far as proto-oncogenes and about a dozen as tumor suppressor genes [11]. The recognizition that the majority of known oncogenes and tumor suppressors are components of a few common signaling pathways that control the cell cycle, apoptosis, genome integrity, morphogenetic reactions and cell differentiation has widen the scope for discovery of new targets for cancer disease.

Tumor Suppressor Genes: The second group of genes that plays an important role in tumorigenesis are the tumor suppressor genes (anti-oncogenes, recessive tumor genes) are cellular genes. These genes are involved in the control of abnormal cell proliferation and whose loss or inactivation leads to cancer. They act therefore by effectively inhibiting or putting the brake on cell growth and cell cycling. These genes are recessive at the level of the cell although they show dominant inheritance when associated with a familiar cancer syndrome. Both copies of the gene have to be mutated before tumors develop.

Tumor suppressor genes are more difficult to identify than oncogenes. Several dozen tumor suppressor genes have now been identified associated with human tumors, the important noted genes include TP53 (Brain, Breast, colorectal and many type of cancer), APC (adenomatous polyposis coli), BRCA1 and 2 (Familial breast/ovarian cancer), RB1 (Retinoblastoma), *WT1 (*Wilms' tumor), NF1 (Neurofibromatosis1), TSC1 and 75C2 (Tuberous sclerosis), PTCH (Gorlin syndrome or basal cell navus syndrome). A number of tumor suppressor genes such as *p53, APC* and *PTEN* exert tumor suppressor activity by inducing apoptosis with loss of suppressor function leading to reduced apoptosis and tumor growth [12]. *p53* acts by driving cells with damaged DNA along the apoptotic pathway rather than allowing them to continue through the cell cycle [13, 14]. Apoptotic regulators lying downstream of *p53,* such as *BAX, FAS/po1* and *BCL2,* have been shown to be critical to the function of *p53* in suppression of tumors [13, 15]. Both *MYC* and *p53* play a role in the induction of apoptosis. Another proto-oncogene, the *BCL2* gene, acts to block apoptosis specifically, whose gene deregulation, promotes tumor formation. BCL2 belongs to a large family of related proteins, some of which (e.g. BCL2, BCLXL, BCLW and MCL1) suppress apoptosis whereas others (e.g. BAX, BAK, BAD, BIK, BID and BCLXS) act to antagonize the anti-apoptotic properties of the others.

MicroRNA Genes: MicroRNAs (miRNAs) are evolutionarily conserved small noncoding RNAs, also known as micromanagers of gene expression. MicroRNA genes, unlike other genes involved in cancer, do not

encode proteins. Instead, the products of these genes consist of a single RNA strand of about 21 to 23 nucleotides. MicroRNA molecule can anneal to a messenger RNA (mRNA) containing a nucleotide sequence that complements the sequence of the microRNA by blocking protein translation and transcription, thus regulating gene expression. Examples are *miR-15a* and *miR-16-1*, involved in chronic lymphocytic leukemia, suggesting an early event in the pathogenesis of this disease [16].

The regions of the genome that are consistently involved in chromosomal rearrangements in cancer cells but lacking oncogenes or tumor-suppressor genes appear to harbour microRNA genes. Polymorphisms and expression profiling [17-19] in the miRNA pathway (miR-polymorphisms) are emerging as powerful tools to study the biology of a disease since they give signatures of the genes associated with various cancers. Also with wide application of using miRNA microarrays have enabled the identification of a number of miRNAs as potential biomarkers for cancer. Many miRNAs have been identified to act as oncogenes, tumor suppressors, or even modulators of cancer stem cells and metastasis. Thus miRNA have been a potential to be used in disease prognosis and diagnosis.

Oncogenes: An oncogene is a eukaryotic gene coding for a protein, preserved in evolution and presumably fulfills an essential physiological function in the normal cell, which in future has a potential to be an oncogenic determinant [20]. Oncogene was first discovered from the Avian Sarcoma Virus, called src and this form of an oncogene is called a v-oncogene (v-onc). J. Michael Bishop and Harold Varmus of UCSF were awarded the 1989 Nobel Prize in Medicine for the discovery of the cellular origin of the viral oncogenes.

The normal nononcogenic alleles of such genes are often designated as protooncogenes and the mutant alleles as active oncogenes [21]. Since protooncogenes are expressed in normal cells and hence are active genes, the term active oncogene refers to activation of oncogenic function. Oncogenes are cellular or viral (i.e., inserted into the cell by a virus) genes; their expression can cause the development of a neoplasm.

Viruses and Cancer: Viruses are infectious agents that must replicate inside a host cell. Here examples of some of the viruses which promote cancer in humans are given in Table 2.

Methods of Oncogene Identification: The methods used are amplification (Eg. ERBB2, MYCL, MYCN), chromosomal translocation (ABL, BCL1, BCL2, MYC), Homology to retroviruses (HRAS, KRAS, SRC), insertional mutagenesis (EVl, INT1) and transfection assay (MAS, MET, MYC, RAS, TRK) [22].

Activation of Proto-Oncogenes: The following Table 3 shows the various means of proto-oncogene activation for formation of tumours [23, 24].

Table 2: Viruses associated with human cancers

Virus	Associated tumours
DNA viruses	Burkitt's lymphoma
Epstein-Barr	Nasopharyngeal cancer
Hepatitis B	Liver cancer
Papilloma virus	Benign warts, Cervical cancer
RNA viruses	
Human immunodeficiency virus (HIV-1)	Kaposi's sarcoma
Human T-cell leukemia virus type I (HTLV-I)	Adult T-Cell leukemia
HTLV-2	Hairy cell leukemia
HTLV-5	Cutaneous T-cell leukemia

Table 3: Activation of proto-oncogenes

Activation mediated through	Mechanism
RNA virus	Retroviral transduction
	Promote/enhancer insertion
	Trans-activation
Non-viral	Amplification
	Point mutation
	Chromosomal translocation
DNA virus	Altering activity/ expression of host-related genes through protein-protein interaction

Products of Oncogenes: Proto-oncogenes encourage cell growth and division. They code for four classes of oncoproteins that stimulate cell division.

Growth Factors The growth factors include platelet-derived growth factor (PDGF), Epidermal growth factor (EGF), Fibroblast growth factor 1-7 (FGF 1-7), Insulin-like growth factor 1 and 2 (IGF1 and 2), Transforming growth factor α and β (TGF α and β) [25].

Growth Factor Receptors It includes the epidermal growth factor family of receptors ([EGFR] erbB-2, erbB-3 and erbB-4), also known as HER1–4, Platelet-derived growth factor receptor (PDGF-R) and the angiotensin receptors, are examples of the second class of oncoproteins. An antibody to HER2 (Herceptin) has been widely evaluated for the treatment of breast cancer [26]. Two classes of clinically active anti-EGFR agents have been developed: a monoclonal antibody against the extracellular domain of the receptor (cetuximab) and competitive inhibitors of the tyrosine kinase activity of the receptor (e.g., erlotinib and gefitinib). Bevacizumab is a monoclonal anti-VEGF antibody and SU5412, a small molecule, binds the receptor tyrosine kinases of VEGFR1 and VEGFR2 as well as the kinases of the PDGF receptor and KIT. In addition to inhibiting the ABL kinase, imatinib also inhibits the PDGF and KIT receptor kinases. Gastrointestinal stromal tumors that carry activating mutations of KIT [27, 28] respond to imatinib or other inhibitors of these receptor kinases.

Transforming growth factor receptors are serine/threonine kinases rather than tyrosine kinases [29]. The receptor tyrosine kinases possess an extracellular ligand-binding domain, a transmembrane domain and one or two intracellular catalytic kinase domains responsible for transducing the mitogenic signal [30].

Signal Transducers: Many oncogenes encode members of signaltransduction pathways. They fall into two main groups: nonreceptor protein kinases and guanosine-triphosphate-binding proteins [31]. The nonreceptor protein kinases are of two types: tyrosine kinases (e.g., ABL, LCK and SRC) and serine and threonine kinases (e.g., AKT, RAF1, MOS and PIM1). The membrane-associated/guanine nucleotide-binding proteins include RAS, GAS, GIP. The membrane-associated/cytoplasmic protein tyrosine kinases include ABL, SRC, FES, FGR, SYN and LCK. The cytoplasmic protein serine-threonine kinases include RAF, MOS and COT.

Many of the receptors described above utilize common signalling pathways through which they can transmit their signals and although a variety of intracellular signal transduction pathways exist, three major pathways are recognized [32]. These are the PI3-kinase (PI3-K)/AKT pathway, the RAS/mitogen-activated protein kinase (MAPK) pathway and the JAK/signal transducers and activators of transcription (STATs) pathway. Proteins involved in signal transduction become oncogenic if they bear activating mutations.

Nuclear Transcription Factors: The signals emanating from the cytoplasmic signalling molecules ultimately activate the transcription factors. Transcription factors bind DNA and initiate transcription of downstream genes. Transcription factor oncogenes usually are not found to be mutated but are overexpressed in human cancers. For example, the proto-oncogene c-myc, the oncogene is from chicken myelocytomatosis [34] virus, is translocated to the transcription control sequences of IgGin B cells in Burkitt's lymphoma. Because IgG is highly expressed in B cells, this translocation results in tremendous overexpression of c-myc, which drives tumorigenesis [34, 35].

Also transcription factors are often members of multigene families that share common structural domains. For example, the Fos transcription protein dimerizes with the Jun transcription factor to form the AP1 transcription factor and this complex increases the expression of several genes that control cell division [36, 37]. The other transcription proteins acting in the nucleus and transcription factors include MYC, FOS, JUN, MYB, SK1, EV11 and REL. These factors on activation often by phosphorylation, increase the expression of target genes by binding to DNA and activating transcription. Ultimately, the activation of these genes provides the resources and fuel for cancer cell to grow and divide. The Table 4 shows the oncogenes involved in human cancer and their mode of activation.

Oncogenes as Targets: In the past, genes involved in human tumorigenesis were identified because of their homology to known oncogenes. Due to advancements in molecular biology, tumorigenesis-related genes were isolated and expressed in non transformed cells. In vitro assays on the cells expressing the genes were done to determine motility, invasion and anchorage-independent growth; all of these phenotypes are hallmarks of transformed cells. These processes were tedious as only one gene could be analyzed at once.

Table 4: Oncogenes associated with human cancer and their mode of activation

Oncogene	Types of cancer	Activation mutation
abl	Chronic myelogenous leukemia, Acute lymphocytic leukemia	Translocation
bcl-2	Follicular B-cell lymphoma	Translocation
e2a/pbx1	Acute lymphocytic leukemia	Translocation
gip	Adrenal cortical and ovarian cancer	Point mutation
gli	Glioblastoma	Amplification
gsp	Pituitary and thyroid cancer	Point mutation
hox-11	Acute T-cell leukemia	Translocation
lyl	Acute T-cell leukemia	Translocation
c-myc	Burkitt's lymphoma, carcinoma	Translocation, amplification
l-myc	Lung carcinoma	Amplification
n-myc	Neuroblastoma	Amplification
pml/ra/rol	Acute promyelocytic leukemia	Translocation
prad1	Parathyroid adenoma, breast adenoma	Translocation and amplification
ras H	Thyroid carcinoma	Point mutation
ras K	Colon, lung, pancreatic and thyroid	Point mutation
ras N	Acute myelogenous and lymphocytic leukemia, thyroid carcinoma	Point mutation
ret	Thyroid carcinoma	DNA rearrangement

Table 5: Anticancer drugs and their targets to various cancer.

Anticancer drug	Target	Disease
Small molecules Imatinib	ABL,PDGFR,KIT	Chronic myelogenous leukemia, gastrointestinal stromal tumours, chordoma
Gefitinib	EFGR	Non-small-cell lung cancer
Erlotinib	EFGR	Non-small-cell lung cancer
Sorafenib	VEGFR, PDGFR, FLT3	Renal cell carcinoma
Sunitinib	VEGFR, PDGFR, FLT3	Gastrointestianl stromal tumours, renal-cell carcinoma
Monoclonal antibodies Trastuzumab	ERBB2	Breast cancer
Cetuximab	EGFR	Colorectal cancer
Bevacizumab	VEGF	Colorectal cancer, non-small-cell lung cancer
Panitumumab	EGFR	Colorectal cancer
Matuzumab	EGFR	Colorectal cancer
Lapatinib	EFGR/HER-2	Colorectal cancer

Today, multiple genes have been easily analysed through the method of expression cloning, the genes expressed from cancer cells are cloned into viruses, checked for their properties, the gene responsible is then isolated [38]. Another multigene approach is microarrays. In this technique, expressed RNA is isolated from a normal cell and a cancer cell, labelled different colors and used to probe a glass slide (a chip) that contains fragments of as many as 64,000 genes. The intensity of the different colors or of a combined color indicates whether a gene is over expressed or under expressed in the cancer cells. Recently, protein microarrays have been developed where antibodies are spotted on a glass slide and proteins from normal and tumor cells are labeled. Again, color intensity indicates which proteins are over expressed or under expressed in the cancer cells. This technique is advantageous as it is less time consuming also multiple genes can be identified at once. The microarrays can also yield tumor signatures: groups of genes that are over expressed in certain subsets of tumors. In the future, these tumor signatures will be used to identify cancers that will likely respond to one drug or another, providing individualized, specific treatments for the cancer patient.

Cancer Therapeutics Through Oncogenes: A significant increase in potential molecular targets in cancer has occurred with the modern screening methods of gene analysis involved in cancer. Due to the advancements in study of oncogenes, the percentage of new agents that proceeded to phase I trials and were later Food and Drug Administration (FDA) approved has increased from just

8% between 1978 and 1983 to 61% between 1996 and 2001 [39]. Many of the newer molecular targeted drugs are antibodies that block the activation of transforming proteins (Table 5). In addition, monoclonal antibodies are large and may not arrive at the tumor site or may not be able to penetrate past the outer layers of tumor. The small-molecule inhibitors are the newest class of drug to enter trials. These drugs inhibit a molecule thought to be a causative agent in tumorigenesis by inhibiting kinase activities, fatty acid additions, growth factor actions, DNA unwinding, proteosome degradation, mitosis, or other enzymatic activities. There are several drugs that have been approved recently by the FDA, including the EGFR kinase inhibitors Tarceva and Eribitux.

CONCLUSION

The identification of oncogenes involved in the initiation and progression of tumors has been powerful targets for the development of new anticancer drugs. Several new drugs, small molecules and monoclonal antibodies directly affecting oncogene products have been developed. Considerable progress has been made in producing small molecules capable of inhibiting the enzymatic activity of ABL, KIT, EGFR and ERBB2. The advantage of targeted therapy is the dependency of cancer cells on the oncogene product for growth and survival. Thus, cancer cells are more sensitive to the treatment than are normal cells. It is possible to foresee the development of multiple drugs that have multiple targets involved in the development of cancer.

Expression profiling of oncogenes, microRNA genes has revealed signatures associated with tumor classification, diagnosis, staging and progression, as well as prognosis and response to treatment. The discovery of the involvement of microRNAs in the initiation and progression of human cancer may provide additional targets for anticancer treatments.

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