

Review Article

Oncogene: The Dominant Evil**RM. Thorat^{1*}, DD. Gaikwad², SL. Jadhav² and ST. Kokate²**¹Vishal Junnar Seva Mandal Institute of Pharmacy, A/P Ale, Tal-Junnar, Dis-Pune, Maharashtra, India.²Vishal Institute of Pharmaceutical Education And Research, A/P Ale, Tal-Junnar, Dis-Pune, Maharashtra, India.**ABSTRACT**

Oncogene is a dominant mutant allele of a cellular gene (a proto-oncogene) that disrupts cell growth and division and is capable of transforming a normal cell into a cancerous cell. When an oncogene infects any cell, that cell loses its control over its cell cycle and undergoes uncontrolled growth and division leading to formation of tumor or cancerous growth. In most cases, the environmental triggers as well as genetic triggers causes a particular proto-oncogene to change into an oncogene. The activities of activated proto-oncogenes i.e. oncogenes are one of the key mechanisms involved in the malignant transformations of cells and development of tumor cell. Activated oncogenes transforms the cell by taking over the role of growth factors, hormone receptors, G-proteins, intracellular effector system and transcription factors and expresses their functions in an uncontrolled manner. Because of crucial role of oncogenes in development of cancer, oncogenes are topic of interest and also are considered as targets for cancer treatment.

Keywords: Cancer, Oncogene, Proto-oncogene.**INTRODUCTION**

Cancers are characterized by uncontrolled growth and spread of abnormal cells. The most fundamental characteristic of cells is their ability to reproduce themselves. They do this simply by dividing. One cell becomes two, the two become four, and so on. The division of normal cells occurs in a regulated fashion. In most parts of the body, the cells continually divide and form new cells to supply the material for growth or to replace worn-out or injured cells. For example, when you cut your finger, certain cells divide rapidly until the tissue is healed and the skin is repaired. They will then go back to their normal rate of division. In contrast, cancer cells divide in a haphazard manner. The result is that they typically pile up into a non-structured mass or tumor. Cancer is caused by alterations in oncogenes, tumor-suppressor genes, and

microRNA genes. These alterations are usually somatic events, although germ-line mutations can predispose a person to heritable or familial cancer. A single genetic change is rarely sufficient for the development of a malignant tumor. Most evidence points to a multistep process of sequential alterations in several, often many, oncogenes, tumor-suppressor genes, or microRNA genes in cancer cells¹.

GENES AND CANCER

A gene encodes information for the production of a specific protein molecule. It is made up of a nucleotide sequence on a section of chromosomal DNA. When the gene sequence is altered (mutated), it may produce an abnormal protein. Cell division is regulated by a network of proteins. If one or more of these proteins become abnormal, a cell may continue to divide when it should stop.

The genes implicated in cancer development are classified into three types :

1. Oncogenes - which stimulate cell division excessively. They are mutated from normal genes called proto-oncogenes that encode components of the cell's normal growth, such as growth factors.

2. Tumor Suppressor Genes - which inhibit cell division and/or cause apoptosis (cell suicide). Mutations in tumor suppressor genes would promote cell division or allow genetically damaged cell to grow out of control.

3. DNA Repair Genes - which correct the mutations of a gene. Mutations in DNA repair genes can lead to a failure in repair, which would allow other mutated genes to remain abnormal¹.

ONCOGENES

Synonyms : Oncogene; Tropomyosin 4; Tropomyosin 4²

It is a sequence of DNA that has been altered or mutated from its original form, the proto-oncogene.

Oncogenes arise from mutations in genes (proto-oncogenes) found in all normal cells. In their mutated form, they are found in tumour cells and in viruses that are capable of transforming normal cells to tumour cells. Such viruses are able to insert their oncogenes into the host cell's DNA, causing it to divide uncontrollably. More than one oncogene may be necessary to transform a cell in this way³. Some retroviruses rapidly induce tumors when inoculated into animals and can transform cells in vitro. Oncogenes were detected initially as retroviral genes directly responsible for the immortalisation of eukaryotic cells and malignant transformation both in vitro and in vivo. Many of the viral oncogenes (general abbr. v-*onc*) have homologous cellular counterparts (general abbr. c-*onc*) known as proto-oncogenes. Evidence indicates that viral oncogenes originated from cellular genes by recombination between

a parent non-transforming virus and host cellular DNA. Their gene products are generally referred to as oncoproteins. Proto-oncogenes are evolutionary highly conserved genes required for normal cell functions including proliferation and differentiation⁴.

Many abnormal cells normally undergo a programmed form of death (apoptosis). Activated oncogenes can cause those cells to survive and proliferate instead. Most oncogenes require an additional step, such as mutations in another gene, or environmental factors, such as viral infection, to cause cancer. Since the 1970s, dozens of oncogenes have been identified in human cancer.

Most oncogenes are mutations of certain normal genes called proto-oncogenes. Proto-oncogenes are the "good" genes that normally control what kind of cell it is and how often it divides. When a proto-oncogene mutates (changes) into an oncogene, it becomes a "bad" gene that can become permanently turned on or activated when it is not supposed to be. When this happens, the cell grows out of control, which can lead to cancer.

In a cell with normal control regulation (non-cancerous), genes produce proteins that provide regulated cell division. Cancer is the disease caused by cells that have lost their ability to control their regulation. The abnormal proteins allowing the non-regulated cancerous state are produced by genes known as oncogenes. The normal gene from which the oncogene evolved is called a proto-oncogene.

In short, Oncogenes are the genes that are carried in the genomes of cancer cells and are responsible for producing their malignant properties⁵.

Oncogenes differ from normal genes in following aspects,

1. Mutation in the structure of gene;
2. Lacking the normal growth-promoting signals of proto-oncogenes.
3. They act by over-expression to promote autonomus and excessive cellular proliferation⁶

HISTORY

The word oncogene comes from the Greek term oncos, which means tumor. Oncogenes were originally discovered in certain types of animal viruses that were capable of inducing tumors in the animals they infected. These viral oncogenes, called v-onc, were later found in human tumors, although most human cancers do not appear to be caused by viruses. Since their original discovery, hundreds of oncogenes have been found but only a small number of them are known to affect humans. Although different oncogenes have different functions, they are all somehow involved in the process of transformation (change) of normal cells to cancerous cells⁷.

The first oncogene was discovered in 1970 and was termed src (pronounced sarc as in sarcoma). Src was in fact first discovered as an oncogene in a chicken retrovirus. Experiments performed by Dr G. Steve Martin of the University of California, Berkeley demonstrated that the SRC was indeed the oncogene of the virus.

In 1976 Drs. J. Michael Bishop and Harold E. Varmus of the University of California, San Francisco demonstrated that oncogenes were defective proto-oncogenes, found in many organisms including humans. For this discovery Bishop and Varmus were awarded the Nobel Prize for Physiology or Medicine for their concept of oncogenes, although credit for the discovery was claimed by a French cancer specialist, Dominique Stehelin⁸.

Then the next oncogene was discovered in 1982 by Robert Weinberg, a founding member of Whitehead Institute for Biomedical Research and professor of biology at Massachusetts Institute of Technology.

At present approximately 80 oncogenes are known but it is expected that their number is on the order of 200-300⁴.

Research into the structure and function of oncogenes has been a major endeavor for many years.

DEFINITIONS OF ONCOGENE

As Oncogene is a topic of interest all over the world due to its significant role in development of cancer, many definitions of oncogene exists. Not all, but some of them are mentioned here.

The various definitions of oncogene are as follows :

a. Gene that induces a cell to divide abnormally, giving rise to a cancer³.

b. A gene that causes the transformation of normal cells into cancerous tumor cells, especially a viral gene that transforms a host cell into a tumor cell⁸.

c. An oncogene is a gene that, when mutated or expressed at high levels, helps turn a normal cell into a tumor cell⁸.

d. An oncogene is a modified gene that increases the malignancy of a tumor cell⁹.

e. Oncogene A dominant mutant allele of a cellular gene (a proto-oncogene) that disrupts cell growth and division and is capable of transforming a normal cell into a cancerous cell¹⁰.

f. Oncogenes are mutated genes that contribute to cancer development by disrupting a cell's ability to control its own growth and DNA repair mechanisms¹¹

g. Oncogene is a dominantly acting altered genes that are capable of inducing malignant transformations¹².

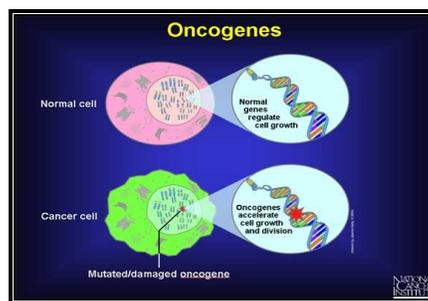


Fig. 1: Concept of Oncogene induced Cancer development

NOMENCLATURE OF ONCOGENES

Oncogenes are generally named after the mammalian species in which retrovirus introduced tumours were first reported. Oncogenes are known by three abbreviations. The names reflect their origin and / or the type of tumour with which they are associated. Each oncogene

receives a three letter italicized code name, that usually gives some hint about their properties. E.g. src

oncogene was derived from the virus including sarcoma¹³. It is well explained on following table:

Table 1: Nomenclature of Oncogenes ¹

S.No.	Virus	Species	Oncogene
1	Rous sarcoma	Chicken	src
2	Avian erythroblastosis	Chicken	Erb-B
3	Avian myeloblastosis	Chicken	myb
4	Avian myelocytomatosis	Chicken	myc
5	Simian sarcoma	Monkey	Sis
6	Abelson Leukemia	Mouse	abl
7	Moloney Murine Sarcoma	Mouse	mos
8	Harvey Murine Sarcoma	Rat	Ha-ras
9	Kirsten Murine Sarcoma	Rat	Ki-ras

Classification of Oncogene⁸⁻⁹

There are several systems for classifying Oncogenes. But there is not yet a widely accepted standard. They are sometimes grouped both spatially (moving from outside the

cell inwards) and chronologically (paralleling the "normal" process of signal transduction). There are several categories that are commonly used:

Table 2: Classification of oncogenes

Category	Examples	Description
Growth factors, or mitogens	c-Sis	Usually secreted by specialized cells to induce cell proliferation in themselves, nearby cells, or distant cells. It induce its own uncontrolled proliferation (autocriueloop), and proliferation of neighboring cells. It also cause production of growth hormones in other parts of the body.
Receptor tyrosine kinases	epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR), HER2/neu	Kinases add phosphate groups to other proteins to turn them on or off. Receptor kinases add phosphate groups to receptor proteins at the surface of the cell. Tyrosine kinases add phosphate groups to the amino acid tyrosine in the target protein. They can cause cancer by turning the receptor permanently on
Cytoplasmic tyrosine kinases	Src-family, Syk-ZAP-70 family, and BTK family of tyrosine kinases, the Abl gene in CML - Philadelphia chromosome	-
Cytoplasmic Serine/threonine kinases and their regulatory subunits	Raf kinase, and cyclin-dependent kinases (through overexpression).	-
Regulatory GTPases	Ras protein	Ras is a small GTPase which hydrolyses GTP into GDP and phosphate. Ras is activated by growth factor signaling and acting like a binary switch in growth signaling pathways.
Transcription factors	myc gene	-

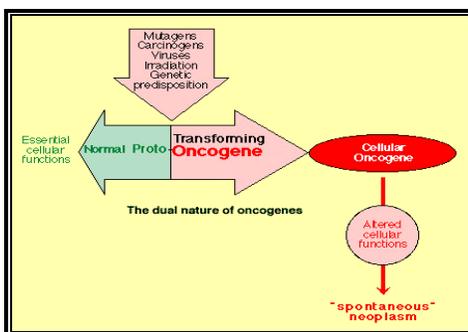


Fig. 2: The dual nature of oncogenes⁴

ONCOGENES IN CANCER INITIATION AND PROGRESSION

The process by which normal cells are transformed into cancerous cells is a complex, multi-step process involving a breakdown in the normal cell cycle. Normally, a somatic cell goes through a growth cycle in which it produces new cells. The two main stages of this cycle are interphase (genetic material in the cell duplicates) and mitosis (the cell divides to produce two other identical cells). The process of cell division is necessary for the growth of tissues and organs of the body and for the replacement of damaged cells. Normal cells have a limited life span and only go through the cell cycle a limited number of times.

Different cell types are produced by the regulation of which genes in a given cell are allowed to be expressed. One way cancer is caused, is by de-regulation of those genes related to control of the cell cycle; the development of oncogenes. If the oncogene is present in a skin cell, the patient will have skin cancer; in a breast cell, breast cancer will result, and so on. Cells that lose control of their cell cycle and replicate out of control are called cancer cells. Cancer cells undergo many cell divisions often at a quicker rate than normal cells and do not have a limited life span. This allows them to eventually overwhelm the body with a large number of abnormal cells and eventually affect the functioning of the normal cells.

A cell becomes cancerous only after changes occur in a number of genes that are involved in the regulation of its cell cycle. A change in a regulatory gene can

cause it to stop producing a normal regulatory protein or can produce an abnormal protein that does not regulate the cell in a normal manner. When changes occur in one regulatory gene this often causes changes in other regulatory genes. Cancers in different types of cells can be caused by changes in different types of regulatory genes. Proto-oncogenes and tumor-suppressor genes are the two most common genes involved in regulating the cell cycle.

Proto-oncogenes and tumor-suppressor genes have different functions in the cell cycle. Tumor-suppressor genes produce proteins that are involved in prevention of uncontrolled cell growth and division. Since two of each type of gene are inherited, two of each type of tumor-suppressor gene are also inherited. Both tumor suppressor genes of a pair need to be changed in order for the protein produced to stop functioning as a tumor suppressor. Mutated tumor-suppressor genes therefore act in an autosomal recessive manner.

Proto-oncogenes produce proteins that are largely involved in stimulating the growth and division of cells in a controlled manner. Each proto-oncogene produces a different protein that has a unique role in regulating the cell cycles of particular types of cells. We inherit two of each type of proto-oncogene. A change in only one proto-oncogene of a pair converts it into an oncogene. The oncogene produces an abnormal protein, which is somehow involved in stimulating uncontrolled cell growth. An oncogene acts in an autosomal dominant manner since only

one proto-oncogene of a pair needs to be changed in the formation of an oncogene. In short, aberrant expression of an oncogene in Factor-dependent cell lines frequently short-circuits factor dependencies and creates cells that can survive and grow in the absence of the growth factor. Under normal circumstances the activity of proto-oncogenes does not cause cell transformation. Genetic alterations including deletions, insertions, point mutations and translocations can activate cellular proto-oncogenes into oncogenes with transforming potential. In this way, a normal cell is converted into a cancer cell with uncontrolled growth & proliferation. Oncogene activation, macrophage infiltration or hypoxia/reoxygenation in tumors induce the generation of reactive oxygen species (ROS). These ROS have roles in mediating cell proliferation, genomic instability, cell motility and angiogenesis and thus can contribute to tumorigenesis, but also can induce cell cycle arrest, senescence and cell death and thus attenuate tumor growth¹⁴

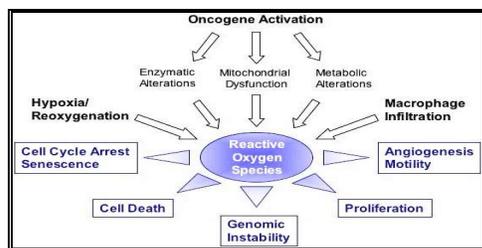


Fig. 3: Scheme showing the generation and effects of reactive oxygen species in tumor progression¹⁵

PROTO-ONCOGENE

A proto-oncogene is a normal gene that can become an oncogene, either after mutation or increased expression. They code for proteins that help to regulate cell growth and differentiation. Proto-oncogenes are often involved in signal transduction and execution of mitogenic signals, usually through its protein product. Upon activation, it (or its product)

becomes a tumor inducing agent, an oncogene.⁶

Proto-oncogenes are evolutionary highly conserved genes required for normal cell functions including proliferation and differentiation. Products displaying homologies to some cellular proto-oncogenes are communication genes encoding growth factors. Other cellular proto-oncogenes encode growth factor receptors. Yet other cellular proto-oncogenes are involved in different ways in signal transduction mechanisms associated with binding of growth factors to their receptor. Her distinction between the terms proto-oncogene and oncogene relates to the activity of the protein product of the gene.

A proto-oncogene is a gene whose protein product has the capacity to induce cellular transformation given it sustains some genetic insult. An oncogene is a gene that has sustained some genetic damage and, therefore, produces a protein capable of cellular transformation.

Proto-oncogenes produce proteins that are largely involved in stimulating the growth and division of cells in a controlled manner. Each proto-oncogene produces a different protein that has a unique role in regulating the cell cycles of particular types of cells. We inherit two of each type of proto-oncogene. A change in only one proto-oncogene of a pair converts it into an oncogene⁸⁻⁹.

CLASSES OF PROTO-ONCOGENE

Proto-oncogenes can be classified into many different groups based upon their normal function within cells or based upon sequence homology to other known proteins. The list of proto-oncogenes identified to date is too lengthy to include here, therefore, only those genes that have been highly characterized are described.

There are five major classes of proto-oncogene/oncogenes

1. Growth factors,
2. Growth factor receptors,
3. Signal transducers
4. Transcription factors, and
5. Programmed cell death regulators.

1. Growth factors

Some proto-oncogenes produce proteins, called growth factors, which indirectly stimulate growth of the cell by activating receptors on the surface of the cell. Different growth factors activate different receptors, found on different cells of the body. Mutations in growth factor proto-oncogene result in oncogenes that promote uncontrolled growth in cells for which they have a receptor. For example, platelet-derived growth factor (PDGF) is a proto-oncogene that helps to promote wound healing by stimulating the growth of cells around a wound. PDGF can be mutated into an oncogene called v-sis (PDGFB) which is often present in connective-tissue tumors.

2. Growth factor receptors

Growth factor receptors are found on the surface of cells and are activated by growth factors. Growth factors send signals to the center of the cell (nucleus) and stimulate cells that are at rest to enter the cell cycle. Different cells have different growth factors receptors. Mutations in a proto-oncogene that are growth factor receptors can result in oncogenes that produce receptors that do not require growth factors to stimulate cell growth. Overstimulation of cells to enter the cell cycle can result and promote uncontrolled cell growth. Most proto-oncogene growth factor receptors are called tyrosine kinases and are very involved in controlling cell shape and growth. One example of a tyrosine kinase is called GDFNR. The RET (rearranged during transfection) oncogene is a mutated form of GDFNR and is commonly found in cancerous thyroid cells. Growth factor receptors are of several different types dependent upon whether or not they exhibit intrinsic enzymatic activity upon growth factor binding and what type of intrinsic activity is associated with the receptor. Numerous growth factor receptors exhibit intrinsic tyrosine kinase activity and many receptors in this class

have been shown to have oncogenic potential.

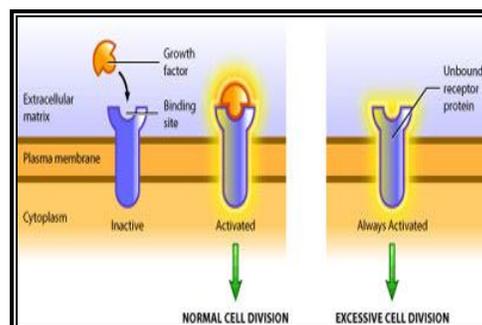


Fig. 4: A modification of Growth factor receptor leading to Cancer development¹

Under normal circumstances membrane-bound receptors require the binding of their ligand to be in an activated state. In contrast, receptors encoded by oncogenes do not require the regulatory step of ligand binding to be active.

3. Signal transducer

Signal transducers are proteins that relay cell cycle stimulation signals, from growth factor receptors to proteins in the nucleus of the cell. The transfer of signals to the nucleus is a stepwise process that involves a large number of proto-oncogenes and is often called the signal transduction cascade. Mutations in proto-oncogene involved in this cascade can cause unregulated activity, which can result in abnormal cell proliferation. Signal transducer oncogenes are the largest class of oncogenes. The RAS family is a group of 50 related signal transducer oncogenes that are found in approximately 20% of tumors.

4. Transcription

Transcription factors are proteins found in the nucleus of the cell which ultimately receive the signals from the growth factor receptors. Transcription factors directly control the expression of genes that are involved in the growth and

proliferation of cells. Transcription factors produced by oncogenes typically do not require growth factor receptor stimulation and thus can result in uncontrolled cell proliferation. Transcription factor proto-oncogenes are often changed into oncogenes by chromosomal translocations in leukemias, lymphomas, and solid tumors. C-myc is a common transcription factor oncogene that results from a chromosomal translocation and is often found in leukemias and lymphomas.

5. Programmed cell death regulators

Normal cells have a predetermined life span and different genes regulate their growth and death. Cells that have been damaged or have an abnormal cell cycle may develop into cancer cells. Usually these cells are destroyed through a process called programmed cell death (apoptosis). Cells that have developed into cancer cells, however, do not undergo apoptosis. Mutated proto-oncogenes may inhibit the death of abnormal cells, which can lead to the formation and spread of cancer. The bcl-2 oncogene, for example, inhibits cell death in cancerous cells of the immune system.

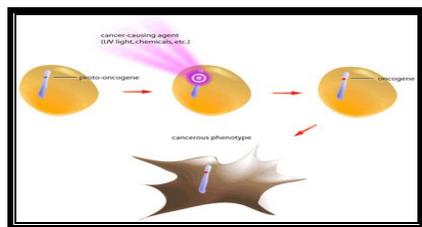


Fig. 5: How Proto-oncogenes can become oncogenes¹¹

Proto-oncogenes encode for normal cellular proteins involved in growth signaling pathways. When these genes become mutated as a result of exposure to chemicals, radiation, or

other carcinogens, these genes are called oncogene^{3, 16}

MECHANISMS OF TRANSFORMATION OF PROTO-ONCOGENE INTO ONCOGENES

The proto-oncogene can become an oncogene by a relatively small modification of its original function. It is not known in most cases what triggers a particular proto-oncogene to change into an oncogene. There appear to be environmental triggers such as exposure to toxic chemicals. There also appear to be genetic triggers since changes in other genes in a particular cell can trigger changes in proto-oncogenes.³

There are two mechanisms by which proto-oncogenes can be converted to cellular oncogenes:

1. Quantitative

Tumor formation is induced by an increase in the absolute number of proto-oncogene products or by its production in inappropriate cell types.

2. Qualitative

Conversion from proto-oncogene to transforming gene (c-onc) with changes in the nucleotide sequence which are responsible for the acquisition of the new properties. The qualitative mechanisms through which proto-oncogenes are changed into oncogenes are, however, better understood. Proto-oncogenes are transformed into oncogenes through:

1. Mutation
2. Chromosomal translocation
3. Gene amplification.
4. Actions of specific tumor viruses.
 - A. Transduction
 - B. Transcription

1. Mutation

A tiny change, called a mutation, in a proto-oncogene can convert it into an oncogene. The mutation results in an oncogene that produces a protein with an abnormal structure.

These mutations often make the protein resistant to regulation and cause uncontrolled and continuous activity of the protein. The RAS family of oncogenes, found in approximately 20% of tumors, are examples of oncogenes caused by mutations.

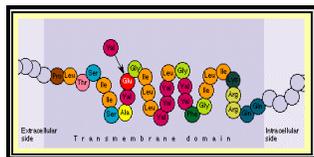


Fig. 6: Activating point mutation in the neu oncogene⁹

A single mutation within the transmembrane region of the protein leading to a glutamine residue in place of a valine residue results in an activated oncogene.

Mutations in these genes tend to relax control mechanisms and accelerate cell division, leading to the cell proliferation that is characteristic of cancer. Some oncogenic mutations cause inhibition of programmed cell death (apoptosis), so that cancerous cells are less likely to be destroyed by the body's defences. Certain oncogenes of vertebrates are derived from viruses (see oncogenic). Compare tumour-suppressor gene.

CAUSES OF GENE MUTATION

Abnormal genes may be inherited at the birth or acquired after birth. The normal operation of our physiological system continuously produces free radicals, which could damage DNA, thereby resulting in gene mutations. DNA may also be damaged by exposure to radiation or chemicals (carcinogens).

Generally, the mutations are of following two types;

- a. Inherited mutations
- b. Acquired mutations

a. Inherited mutations of oncogenes

A few cancer syndromes are caused by inherited mutations of proto-oncogenes that cause the oncogene to be turned on (activated). For example, multiple

endocrine neoplasia type 2 is caused by an inherited mutation in the gene called RET. People affected by this syndrome often develop an uncommon thyroid cancer called medullary cancer of the thyroid. They also develop other tumors, including pheochromocytoma and nerve tumors. Inherited mutations in the gene called KIT cause hereditary gastrointestinal stromal tumors (GIST). Acquired mutations in this same gene cause most cases of GIST. And inherited mutations in the gene called MET cause hereditary papillary renal cancer.

b. Acquired mutations of oncogenes

Most cancer causing mutations involving oncogenes are acquired, not inherited. They generally activate oncogenes by chromosome rearrangements, gene duplication, or mutation. For example, a chromosome rearrangement leads to formation of the gene called BCR-ABL. This leads to the disease chronic myeloid leukemia (CML).

2. Chromosomal translocations

These result from errors in mitosis, have also been implicated in the transformation of proto-oncogene into oncogenes. Chromosomal translocations result in the transfer of a proto-oncogene from its normal location on a chromosome to a different location on another chromosome. Sometimes this translocation results in the transfer of a proto-oncogene next to a gene involved in the immune system. This results in an oncogene that is controlled by the immune system gene and as a result becomes deregulated. One example of this mechanism is the transfer of the c-myc proto-oncogene from its normal location on chromosome-8 to a location near an immune system gene on chromosome-14. This translocation results in the deregulation of c-myc and is involved in the development of Burkitt's lymphoma. The translocated c-myc proto-oncogene is found in the cancer cells of approximately 85% of people with Burkitt's lymphoma.

In other cases, the translocation results in the fusion of a proto-oncogene with

another gene. The resulting oncogene produces an unregulated protein that is involved in stimulating uncontrolled cell proliferation. The first discovered fusion oncogene resulted from a Philadelphia chromosome translocation. This type of translocation is found in the leukemia cells of greater than 95% of patients with a chronic form of leukemia. The Philadelphia chromosome translocation results in the fusion of the c-abl proto-oncogene, normally found on chromosome 9 to the bcr gene found on chromosome-22. The fused gene produces an unregulated transcription factor protein that has a different structure than the normal protein. It is not known how this protein contributes to the formation of cancer cells.

Chromosomal translocations can produce oncogenes in several ways. Firstly, the fusion of one chromosome to another can result in a strong promoter being placed upstream of a gene that would normally be either absent or present only in very low quantities. This has the effect of increasing the intracellular concentrations and activating pathways that would normally be silenced.

Secondly, chromosomal translocations can result in fusion proteins, or proteins that are the product of two separate genes that have been joined.

3. Gene amplification

Some oncogenes result when multiple copies of a proto-oncogene are created (gene amplification). Gene amplification often results in hundreds of copies of a gene, which results in increased production of proteins and increased cell growth. Multiple copies of proto-oncogenes are found in many tumors. Sometimes amplified genes form separate chromosomes called double minute chromosomes and sometimes they are found within normal chromosomes.

4. Actions of specific tumor viruses

Tumor cells also can arise by non-genetic means through the actions of specific tumor viruses. Tumor viruses are of two distinct types. There are viruses with DNA

genomes (e.g. papilloma and adenoviruses) and those with RNA genomes (termed retroviruses). RNA tumor viruses are common in chickens, mice and cats but rare in humans. The only currently known human retroviruses are the human T-cell leukemia viruses (HTLVs) and the related retrovirus, human immunodeficiency virus (HIV). Oncogenic viruses enter cells and addition of DNA or RNA to the cell nucleus causes mutation. The mutant cell may be malignant.

There are two mechanisms through which, tumour viruses can convert a normal gene (proto oncogene) into oncogene:

A. Transduction

B. Transcription

A. Transduction

Retroviruses can induce the transformed state within the cells they infect by two mechanisms. Both of these mechanisms are related to the life cycle of these viruses. When a retrovirus infects a cell its RNA genome is converted into DNA by the viral encoded RNA-dependent DNA polymerase (reverse transcriptase). The DNA then integrates into the genome of the host cell where it can remain being copied as the host genome is duplicated during the process of cellular division. Contained within the sequences at the ends of the retroviral genome are powerful transcriptional promoter sequences termed Long Terminal Repeats (LTRs). The LTRs promote the transcription of the viral DNA leading to the production of new virus particles.

At some frequency the integration process leads to rearrangement of the viral genome and the consequent incorporation of a portion of the host genome into the viral genome. This process is termed transduction. Occasionally this transduction process leads to the virus acquiring a gene from the host that is normally involved in cellular growth control. Because of the alteration of the host gene during the transduction process as well as the gene being transcribed at a higher rate due to its association with the retroviral LTRs the transduced gene

confers a growth advantage to the infected cell. The end result of this process is unrestricted cellular proliferation leading to tumorigenesis. The transduced genes are termed oncogenes. The normal cellular gene in its unmodified, non-transduced form is termed a proto-oncogene since it has the capacity to transform cells if altered in some way or expressed in an uncontrolled manner. Numerous oncogenes have been discovered in the genomes of transforming retroviruses.

B. Transcription

The second mechanism by which retroviruses can transform cells relates to the powerful transcription promoting effect of the LTRs. When a retrovirus genome integrates into a host genome it does so randomly. At some frequency this integration process leads to the placement of the LTRs close to a gene that encodes a growth regulating protein. If the protein is expressed at an abnormally elevated level it can result in cellular transformation. This is termed retroviral integration induced transformation. It has recently been shown that HIV induces certain forms of cancers in infected individuals by this integration induced transformation process¹⁶.

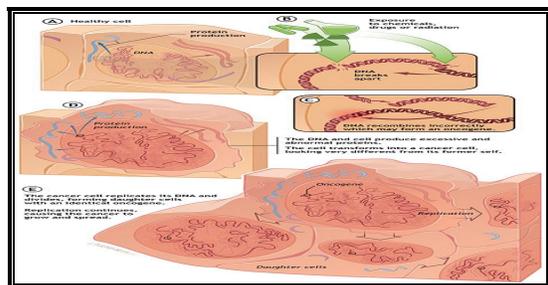


Fig. 7: The Oncogene: A Key Factor in the Development of Cancer¹⁷

FUNCTIONAL PROPERTIES OF ONCOGENES

Historically, transformation events in cancer have been defined as initiation events (contributing to the early stages of neoplastic transition) or progression events (referring to subsequent transformative processes). Oncogenes

encode proteins that control cell proliferation, apoptosis, or both. They can be activated by structural alterations resulting from mutation or gene fusion, by juxtaposition to enhancer elements, or by amplification. Translocations and mutations can occur as initiating events or during tumor progression, whereas amplification usually occurs during progression.

The products of oncogenes can be classified into six broad groups:

1. Transcription factors,
2. Chromatin remodelers,
3. Growth factors,
4. Growth factor receptors,
5. Signal transducers, and
6. Apoptosis regulators.

The activities of activated proto-oncogenes are one of the key mechanisms involved in the malignant transformation of cells and the development of malignant cells that have escaped the constraints of normal regulated cell growth and differentiation. Activated oncogenes are involved in different phases of the initiation, progression, and/or metastasis of tumor cells. Most oncogenes transform cells by taking over the roles of growth factors, hormone receptors, G-proteins, intracellular effector systems, and transcription factors and expressing these functions in an uncontrolled manner.

The activated forms of proto-oncogenes encoding growth factor receptors are altered frequently in a way that allows them to initiate intracellular signal transduction pathways, which would normally be expressed transiently following ligand binding to the receptor. Malignant cells then frequently show an ability to regulate their own growth by the release of autocrine growth modulatory substances.

Most important, the growth of certain malignant cell types has been shown to depend on such autocrine growth circuits. Information is rapidly emerging concerning autocrine growth modulators in selected human malignancies and strategies allowing such circuits to be broken. Several oncogenes are competence

genes involved in cell activation that are expressed in target cells encountering a cytokine.

The so-called Anti-oncogene or tumor suppressor genes are oncogenes involved in negative growth control. These genes may encode growth factors that inhibit the growth of tumor cells or they may interact in a number of different ways with the regulation of growth factor expression and function¹.

INHERITED ONCOGENES

In most cases, oncogenes result from changes in proto-oncogenes in select somatic cells and are not passed on to future generations. People with an inherited oncogene, however, do exist. They possess one changed proto-oncogene (oncogene) and one unchanged proto-oncogene in all of their somatic cells. The somatic cells have two of each chromosome and therefore two of each gene since one of each type of chromosome is inherited from the mother in the egg cell and one of each is inherited from the father in the sperm cell. The egg and sperm cells have undergone a number of divisions in their cell cycle and therefore only contain one of each type of chromosome and one of each type of gene. A person with an inherited oncogene has a changed proto-oncogene in approximately 50% of their egg or sperm cells and an unchanged proto-oncogene in the other 50% of their egg or sperm cells and therefore has a 50% chance of passing this oncogene on to their children.

A person only has to inherit a change in one proto-oncogene of a pair to have an increased risk of cancer. This is called autosomal dominant inheritance. Not all people with an inherited oncogene develop cancer, since mutations in other genes that regulate the cell cycle need to occur in a cell for it to be transformed into a cancerous cell.

The presence of an oncogene in a cell does, however, make it more likely that changes will occur in other regulatory genes. The degree of cancer risk depends on the type of oncogene inherited as well as other genetic factors and

environmental exposures. The type of cancers that are likely to develop depend on the type of oncogene that has been inherited. Multiple endocrine neoplasia type II (MENII) is one example of a condition caused by an inherited oncogene. People with MENII have usually inherited the RET oncogene. They have approximately a 70% chance of developing thyroid cancer, a 50% chance of developing a tumor of the adrenal glands (pheochromocytoma) and about a 5-10% chance of developing symptomatic para-thyroid disease³.

ONCOGENES AS THERAPEUTIC TARGETS

The discovery of oncogenes approximately 20 years ago has played an important role in developing an understanding of cancer. Oncogenes promise to play an even greater role in development of improved cancer therapies since oncogenes may be important targets for drugs that are used for the treatment of cancer.³

The identification of oncogenes involved in the initiation and progression of tumors has generated targets for the development of new anticancer drugs. Several new drugs, small molecules, and monoclonal antibodies directly affecting oncogene products have been developed, and more will follow.¹⁸

The goal of these therapies is to selectively destroy cancer cells while leaving normal cells intact. Many anti-cancer therapies currently under development are designed to interfere with oncogenic signal transducer proteins which relay the signals involved in triggering the abnormal growth of tumor cells. Other therapies hope to trigger specific oncogenes to cause programmed cell death in cancer cells. Whatever the mechanism by which they operate, it is hoped that these experimental therapies will

offer a great improvement over current cancer treatments.¹⁹

Oncogenic proteins in cancer cells can be targeted by small molecules and, when the oncogenic protein is expressed on the cell surface, by

monoclonal antibodies. contains a summary of the targets and drugs (small molecules and monoclonal antibodies) being used in the treatment of a variety of human cancers.³

Table 1. Cancer Therapies That Target Oncogenic Proteins.*

Anticancer Drug	Target	Disease
Monoclonal antibodies		
Trastuzumab (Herceptin, Genentech)	ERBB2	Breast cancer
Cetuximab (Erbix, ImClone)	EGFR	Colorectal cancer
Bevacizumab (Avastin, Genentech)	VEGF	Colorectal cancer, non-small-cell lung cancer
Small molecules		
Imatinib (Gleevec, Novartis)	ABL, PDGFR, KIT	Chronic myelogenous leukemia, gastrointestinal stromal tumors, chordoma
Gefitinib (Iressa, AstraZeneca)	EGFR	Non-small-cell lung cancer
Erlotinib (Tarceva, Genentech)	EGFR	Non-small-cell lung cancer
Sorafenib (Nexavar, Bayer/Onyx)	VEGFR, PDGFR, FLT3	Renal-cell carcinoma
Sunitinib (Sutent, Pfizer)	VEGFR, PDGFR, FLT3	Gastrointestinal stromal tumors, renal-cell carcinoma

* EGFR denotes epidermal growth factor receptor, FLT3 FMS-like tyrosine kinase 3, PDGFR platelet-derived growth factor receptor, and VEGF vascular endothelial growth factor.

Table 3: Cancer Therapies that target Oncogenic Proteins

Biotechnological processes are having a major impact on many industrial sectors, including the pharmaceutical industry. The contributions of recombinant DNA and hybridoma technologies to modern therapeutics include production of natural and unnatural peptides, subunit vaccines, monoclonal antibodies and nucleic acid hybridization probes for in vitro and in vivo diagnostics and biological imaging, therapeutic monoclonal antibodies as tissue-specific delivery systems or as agents to confer passive immunity, production of therapeutic targets for rational drug design, and the use of cloned enzymes as stereospecific catalysts in large-scale production of small medicinal molecules. Biotechnological advances have led to the identification of a discrete set of genes, oncogenes, which may be essential contributing factors for a great variety and number of human cancers. In addition, biotechnological innovations are fostering the exploitation of oncogenes as novel therapeutic targets for cancer diagnosis, prognosis, and treatment. Because oncogenes are activated in

transformation by either qualitative or quantitative mechanisms, however, different biotechnology-based therapeutic approaches are required for each class¹⁵.

Oncogene –Transgenic Animals

One particularly valuable tool for studying the effects and consequences of oncogene expression are transgenic animals. In spite of the potentially lethal effects of untimely and/or unregulated oncogene expression such genes can be studied, for example, if the expression is restricted to a specific tissue, which can be achieved by choosing suitable regulatory elements.

The use of oncogene-transgenic animals allows the spectrum of tissues susceptible to the transforming activity of an oncogene, the relation between multistep oncogenesis and the co-operativity of oncogenes, and the effect of oncogenes on growth and differentiation to be studied in great

detail during normal and malignant development. Viral oncogenes such as the large T antigen gene of SV40 virus, polyoma virus large and middle T genes, bovine papilloma virus, human JC and BK viruses, human T-cell leukemia virus tat oncogene, the LTR sequence of Rous sarcoma virus, and human hepatitis B virus have been used for generating transgenic mice. Cellular oncogenes used to establish transgenic mice include fos, fms, myc, ras, neu, and mos oncogenes and various others⁴.

CONCLUSION

The Oncogene acts as a key factor in development of Cancer and is gaining lot of importance worldwide in Cancer research. Many researchers are very optimistic about the future of cancer therapies using oncogenes and tumor suppressor genes and this remains a very active area of research. There are many clinical trials underway today that could lead to better treatments for many types of cancer. In short, it can be said that, Oncogene resembles to A DOMINANT EVIL which makes a person to suffer from Cancer which is still considered as a dangerous disease all over the world.

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