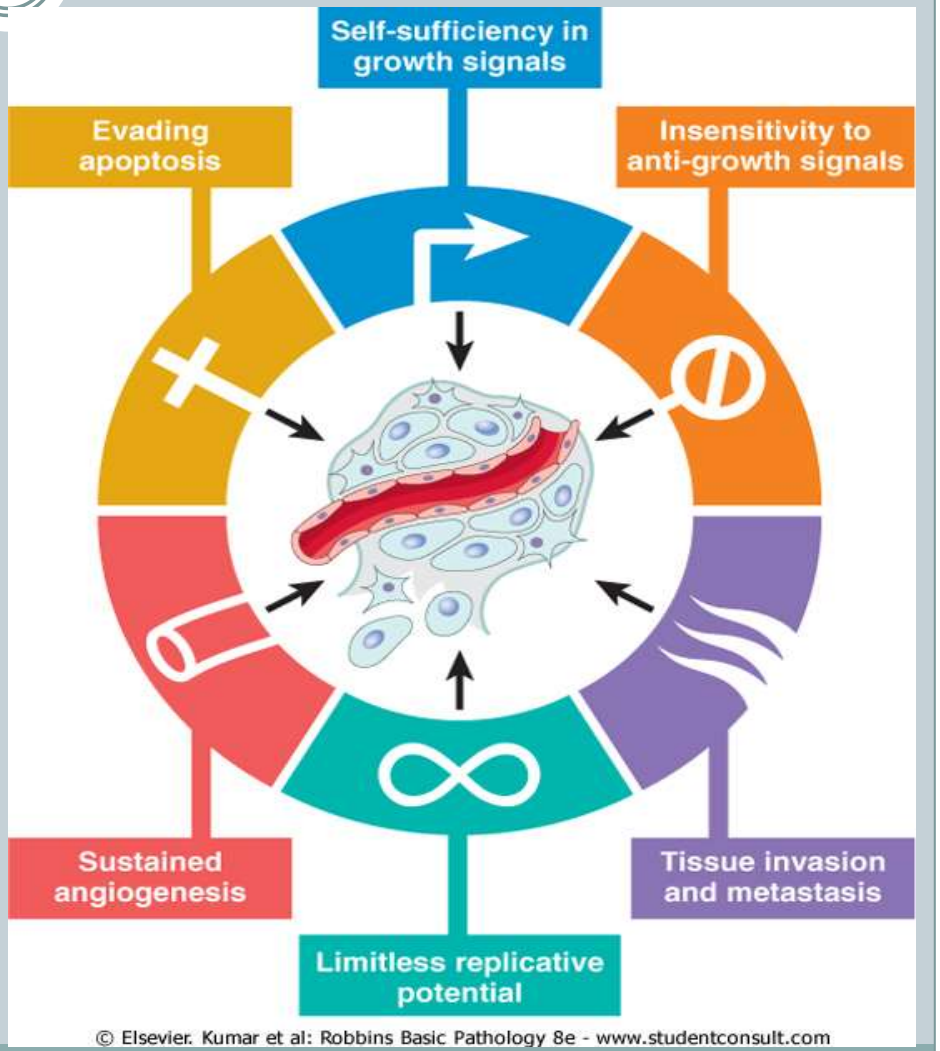
The genetic nature of Cancer

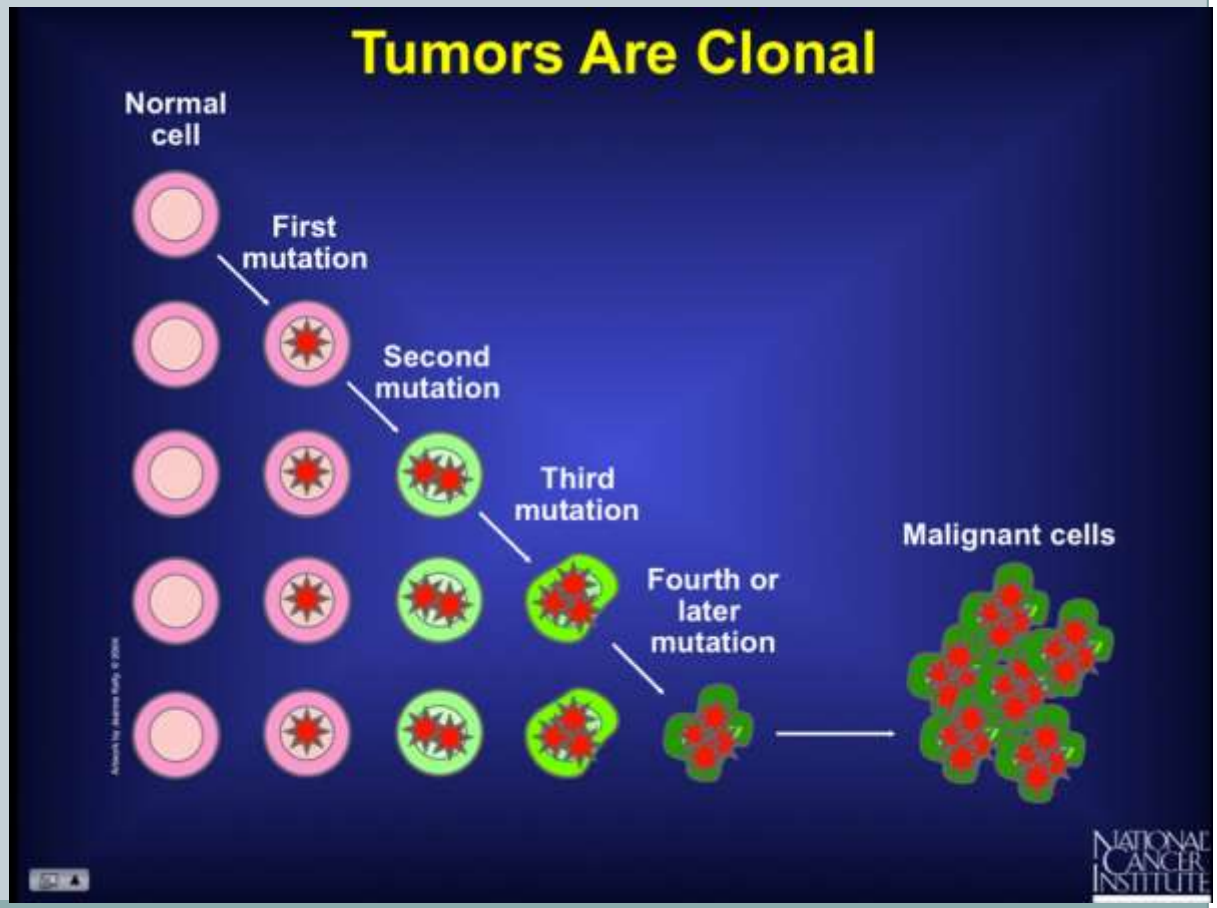
- Cancer is a complex disease that result from the basic process of uncontrolled growth. Cell proliferation results in a mass that invades neighboring tissues and may metastasize to more distant sites.
- In order for a normal cell to transform into a cancer cell, genes which regulate cell growth and differentiation must be altered. When normal regulation is altered, uncontrolled growth is initiated and a malignant tumor develop.
- Genetic changes can occur at many levels, from gain or loss of entire chromosomes to a mutation affecting a single DNA nucleotide.

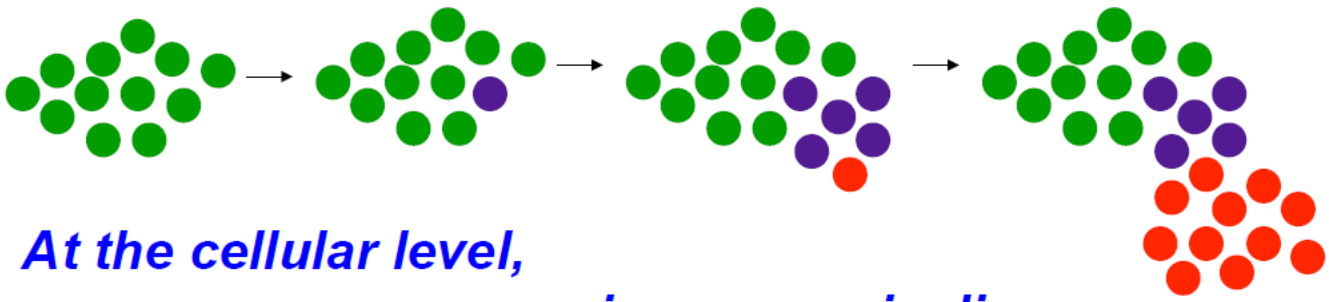
Carcinogenesis

- Carcinogenesis is a multistep process at both the phenotypic & genetic levels, resulting from the accumulation of multiple mutation.



A tumor is formed by the clonal expansion of a precursor cell that has incured genetic damage. Even though most malignant tumors are monoclonal in origin, by the time they become clinically evident their constituent cells are heterogenous.



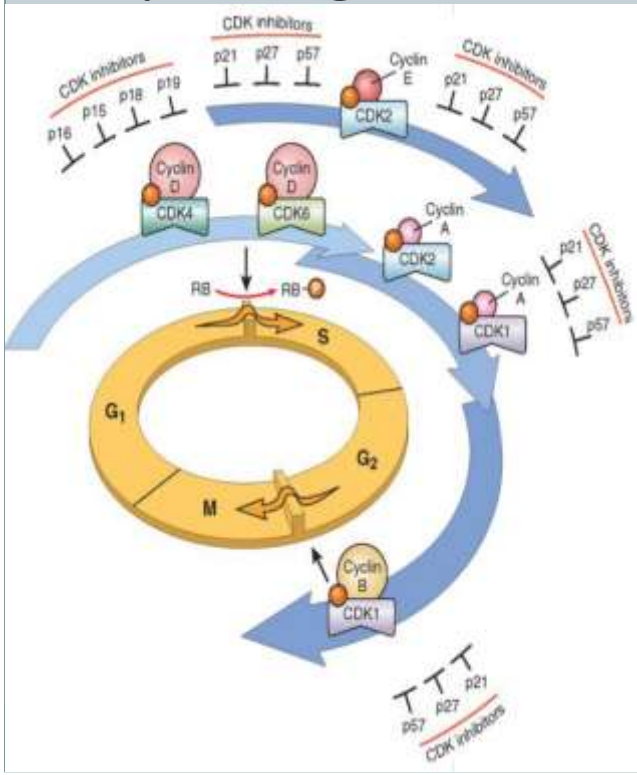


At the cellular level,
cancer is a genomic disease

- Cancer arises from the accumulation of genetic aberrations in somatic cells
- These aberrations consist of mutations and chromosome defects
- Epigenetic aberrations are also present
- Together, they lead to **altered gene expression**
- Over 500 genes are now known to be involved in cancer development

Controls or check points of Cell cycle

The orderly progression of cells through the various phases of cell cycle is regulated by cyclins & their cyclin-dependent kinases (CDKs).mutation of genes that encode these cell cycle regulators have been found in several human cancer.



Cell Cycle Component	Main Function
CYCLIN-DEPENDENT KINASES	
CDK4	Forms a complex with cyclin D that phosphorylates RB, allowing the cell to progress through the G_1 restriction point.
CDK2	Forms a complex with cyclin E in late G_1, which is involved in G_1/S transition. Forms a complex with cyclin A at the S phase that facilitates G_2/M transition.
CDK1	Forms a complex with cyclin B that facilitates G_2/M transition.
INHIBITORS	
CIP/KIP family: p21, p27 (CDKN2A-C)	Block the cell cycle by binding to cyclin-CDK complexes; p21 is induced by the tumor suppressor p53; p27 responds to growth suppressors such as TGF-β.
INK4/ARF family (CDKN1A-D)	p16/INK4a binds to cyclin D–CDK4 and promotes the inhibitory effects of RB; p14/ARF increases p53 levels by inhibiting MDM2 activity.

Mutation

- The basic mechanism in all cancer is mutation. Mutation is change in DNA sequence.
- Rate in humans ~5x10-9 /nucleotide / generation = 25 mutations /cell /generation

Carcinogenic agents are involved through causing mutation. It may be-

- **Germline mutation**s are responsible for 5% to 10% of cancer cases. This is also called familial cancer. These mutations are present in every cell of the body and are passed from parent to child.
- **Sporadic cancer or somatic mutation** are caused by tobacco, over-exposure to UV radiation, and other toxins and chemicals. These mutations are not in every cell of the body and are not passed from parent to child.

Chromosome defects

- ***STRUCTURAL***
- translocation
- inversion
- insertion
- duplication
- amplification
- Deletion

- ***NUMERICAL***
- loss or gain of whole chromosome
- loss of gain of whole chromosome set

Genes & cancer

- Four classes of normal regulatory genes are the principle target of genetic damage.

-The growth promoting **Proto-oncogenes**

-The growth inhibiting **tumor suppressor genes**

-Genes that regulate programmed cell death(Apoptosis)

- **DNA repair genes**

Proto-oncogene

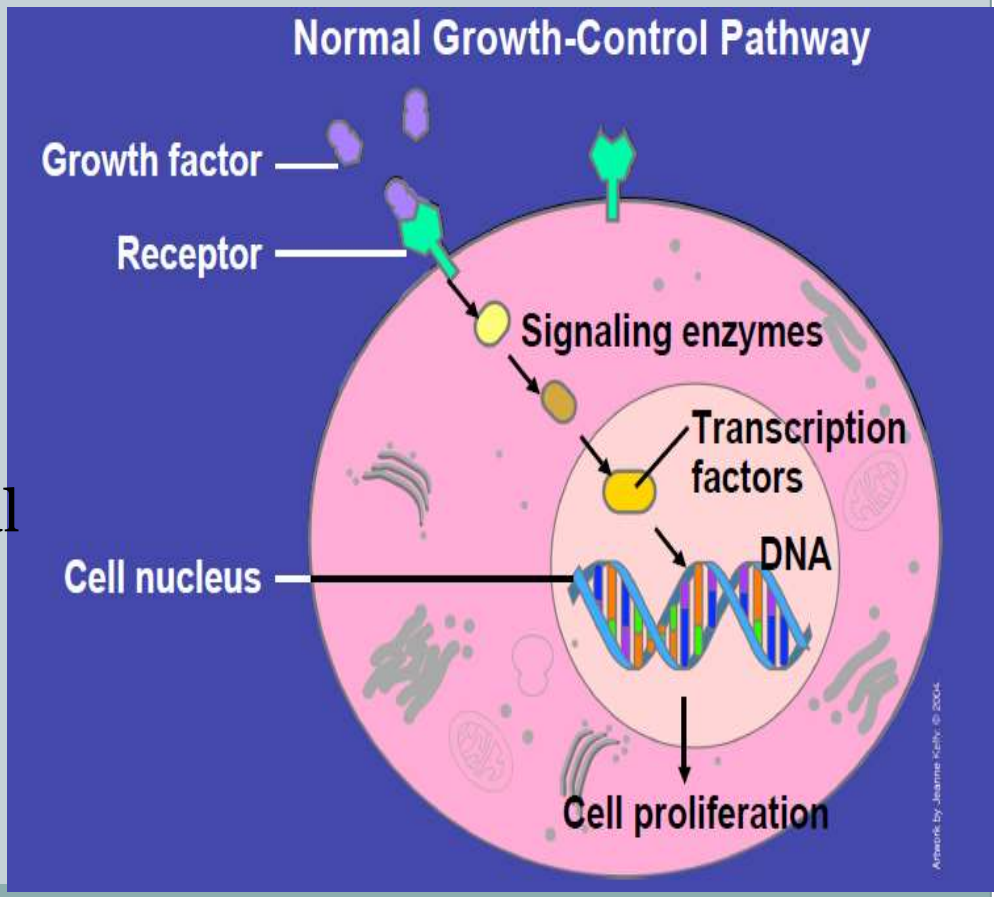
- Have multiple roles, participating in cellular functions related to growth & proliferation.
- Proteins encoded may function as growth factors or their receptors, signal transducers, transcription factors or cell cycle components.
- Mutations convert proto-oncogene into constitutively active cellular **oncogene** that are involved in tumor development.
- **Types of Proto-oncogenes:**

1)**Cellular oncogenes(c- oncogenes):** proto-oncogene which have been to mutate in any individual.

2)**Normal oncogene(n-oncogene):** proto-oncogenes that have not been found to mutate.

Proto-Oncogenes and Normal Cell Growth

Oncogenes are related to normal genes called proto-oncogenes that encode components of the cell's normal growth-control pathway. Some of these components are growth factors, receptors, signaling enzymes, and transcription factors. Growth factors bind to receptors on the cell surface,which activate signaling Enzymes inside the Cell that, in turn, activate special proteins called transcription factors inside the cell's nucleus. The activated transcription factors "turn on" the genes required for cell growth and proliferation.

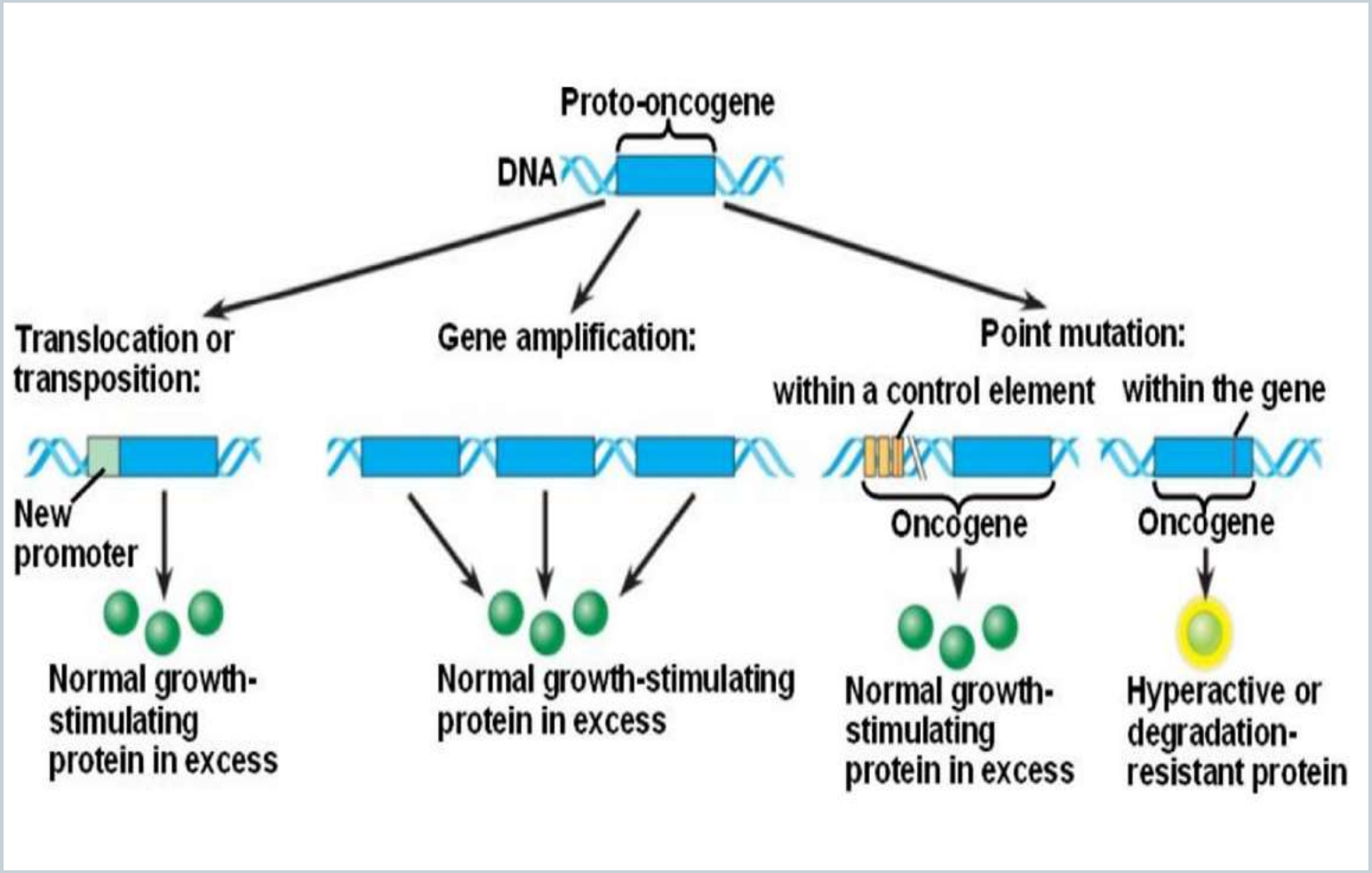


Oncogene

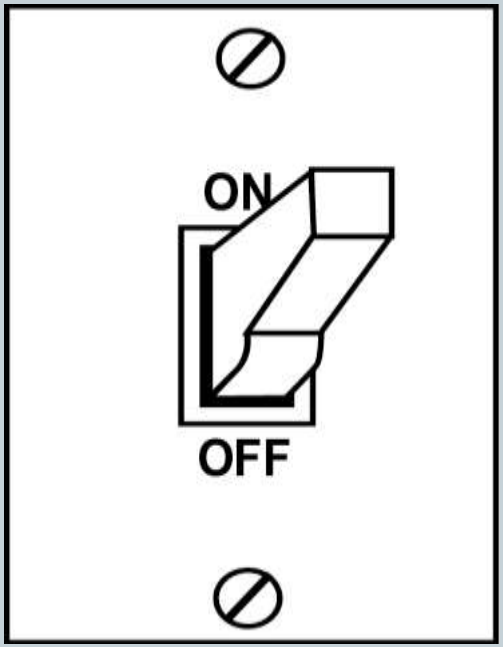
- Act by gain of function. a "gain of function" mutation because the cells with the mutant form of the protein have gained a new function not present in cells with the normal gene.
- Dominant(activation of one allele is sufficient).
- Activated by

- mutation
- chromosome translocation
- gene amplification
-retroviral insertion

Activation of proto-oncogene



When a proto-oncogene becomes activated it is called an oncogene.

Proto-oncogene>>>>> 

>>>>>Oncogene

When an oncogene becomes activated it might cause cancer.

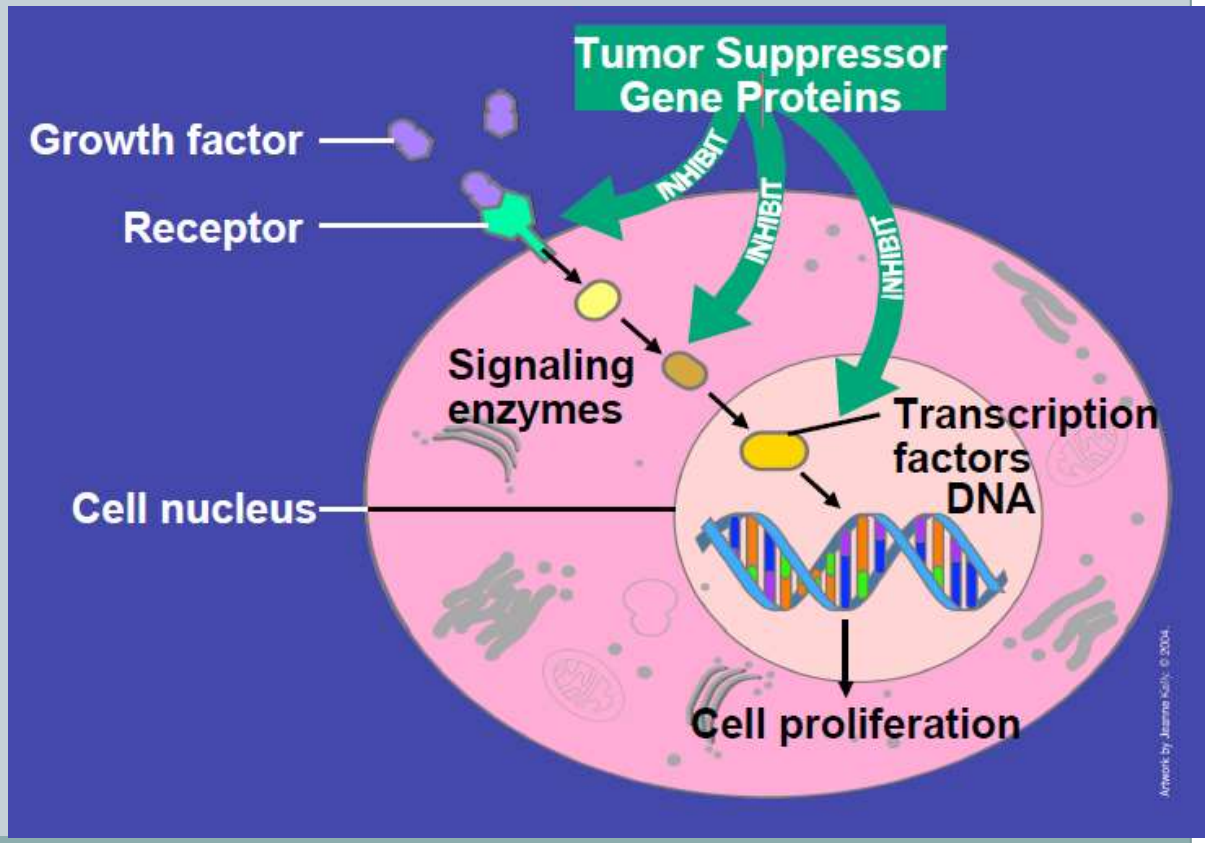
Proto-oncogene -> oncogene -> other steps -> cancer

Tumor suppressor gene

- Normal genes implicated in the control of cell cycle, repair DNA mistakes, and tell cells when to die (apoptosis or programmed cell death). The product of tumor suppressor genes normally block abnormal growth and malignant transformation and lead to malignancy when the function of both alleles is lost.
- When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer.
- In contrast to mutations in proto-oncogene, which are **dominant** in their action, most mutation in tumor suppressor genes are **recessive.**

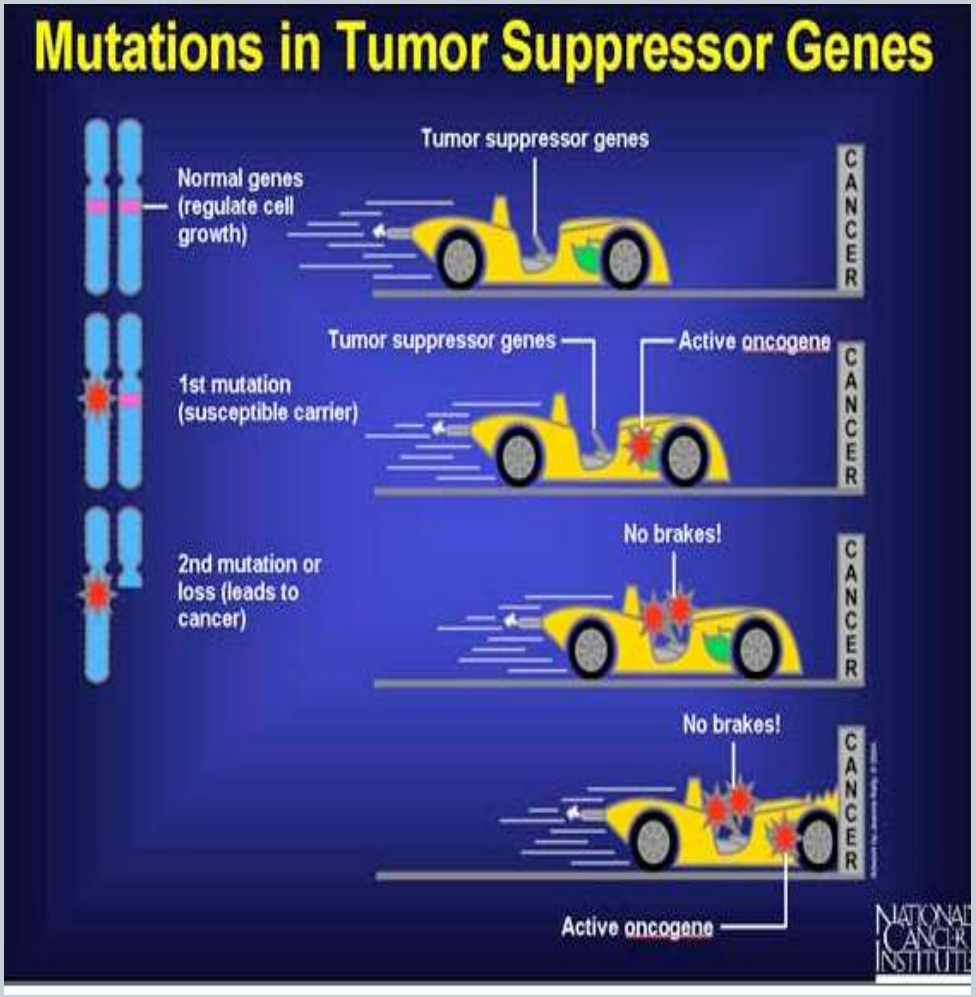
Tumor Suppressor Genes Act Like a Brake Pedal

- Tumor suppressor genes are a family of normal genes that instruct cells to produce proteins that restrain cell growth and division. Since tumor suppressor genes code for proteins that slow down cell growth and division, the loss of such proteins allows a cell to grow and divide in an uncontrolled fashion.



Tumor Suppressor Genes Act Like a Brake Pedal

Tumor suppressor genes are like the brake pedal of an automobile. The loss of a tumor suppressor gene function is like having a brake pedal that does not function properly, thereby allowing the cell to grow and divide continually.



- **Genes that control cell division:** Some tumor suppressor genes help control cell growth and reproduction. e.g. retinoblastoma gene (RB1). Abnormalities of the RB1 gene can lead to a type of eye cancer (retinoblastoma) in infants, as well as to other cancers.
- **DNA repair genes:**These are genes that fix any mistakes made when DNA is replicated(copied). Mistakes that aren't fixed become mutations, which may eventually lead cancer. e.g. Genes responsible for HNPCC (hereditary nonpolyposiscolon cancer). When these genes do not repair the errors in DNA, HNPCC can result.
- **Cell "suicide" genes** e.g. p53.

Tumor suppressor genes involved in human neoplasm

Subcellular Locations	Gene	Function	Tumors Associated with Somatic Mutations	Tumors Assocated with Inherited Mutations
Cell surface	TGF-β receptor	Growth inhibition	Carcinomas of colon	Unknown
	E-cadherin	Cell adhesion	Carcinoma of stomach	Familial gastric cancer
Inner aspect of plasma membrane	*NF1*	Inhibition of RAS signal transduction and of p21 cell cycle inhibitor	Neuroblastomas	Neurofibromatosis type 1 and sarcomas
Cytoskeleton	*NF2*	Cytoskeletal stability	Schwannomas and meningiomas	Neurofibromastosis type 2, acoustic schwannomas, and meningiomas
Cytosol	*APC*/β-catenin	Inhibition of signal transduction	Carcinomas of stomach, colon, pancreas; melanoma	Familial adenomatous polyposis coli/colon cancer
	PTEN	PI3 kinase signal transduction	Endometrial and prostate cancers	Cowden syndrome
	SMAD2 and *SMAD4*	TGF-β signal transduction	Colon, pancreas tumors	Unknown
Nucleus	*RB1*	Regulation of cell cycle	Retinoblastoma; osteosarcoma carcinomas of breast, colon, lung	Retinoblastomas, osteosarcoma
	p53	Cell cycle arrest and apoptosis in response to DNA damage	Most human cancers	Li-Fraumeni syndrome; multiple carcinomas and sarcomas
	WT1	Nuclear transcription	Wilms' tumor	Wilms' tumor
	P16/INK4a	Regulation of cell cycle by inhibition of cyclindependent kinases	Pancreatic, breast, and esophageal cancers	Malignant melanoma
	BRCA1 and *BRCA2*	DNA repair	Unknown	Carcinomas of female breast and ovary; carcinomas of male breast

DNA repair genes

- Each cell loses more than 10000 bases per day from spontaneous breakdown of DNA at body temperature.
- Fortunately, the DNA repair genes code for enzymes that fix crack in DNA.
- Genetics disorders in which DNA repair process is defective exhibit risk for certain type of cancers-

- Xeroderma pigmentosa
- Ataxia telangiectasia.
- Bloom syndrome.
- Fanconi's anaemia

P53 gene(TP53) : Guardian of genome

- Located in 17p13,1 & most common target for genetic alteration in human cancer. A little over 50% of human tumors contain mutations in this gene.
- Homozygous loss(deletion or mutation) of p53 occurs virtually every type of cancer, including carcinoma of lung, colon and breast.
- Assist in DNA repair by inducing DNA repair genes & direct the cells to undergo apoptosis.If damaged, DNA cannot be repaired. so p53 is called **guardian of genome.**
- The malignant tumors that retain normal p53 genes respond well to chemotherapy & radiotherapy.
- Inheritance of one mutant p53 allele predisposes malignancy. These individuals said to have Li-Fraumeni syndrome.

RB gene

- Located in 13q14 position.
- RB protein inactivates E2F(transcription factor) & thereby inhibit cell cycle at G1 phase.usually cyclin D rise in late G1 phase & later inactivates RB to maintain the usual process of cell kinetics.
- Certain tumor antigen(derived from viruses) may combine with RB protein& results in uncontrollable & continuous cell division leads to cancer.(Retinoblastoma)
- Associated neoplasm: osteosarcoma, carcinoma of breast colon & lung.

- **Inherited Abnormalities of Tumor Suppressor Genes** have been found in several cancers that tend to run in families.
- Mutations in p53, RB1, and the genes involved in HNPCC, .
- A defective APC gene causes familial polyposis, a condition in which people develop hundreds or thousands of colon polyps, some of which may eventually acquire several sporadic mutations and turn into colon cancer.
- Abnormalities of the BRCA genes account for 5% to 10% of breast cancers.
- **Non-inherited mutations of tumor suppressor genes :**
- Acquired mutations of the p53 gene appear to be involved in a wide range of cancers, including lung, colorectal, and breast cancer, as well as many others.
- Acquired changes in many other tumor suppressor genes also contribute to the development of sporadic (not inherited) cancers

Feature Suggestive of an Inherited Cancer Susceptibility Syndrome in Families

- Several close (first or second degree) relatives with a common cancer.
- Several close relatives with related cancers. e.g. breast and ovary or bowel and endometrial cancer.
- Two family members with the same rare cancer
- An unusually early age of onset
- Bilateral tumors in paired organs
- Synchronous or successive tumors
- Tumors in two different organ systems in one individual

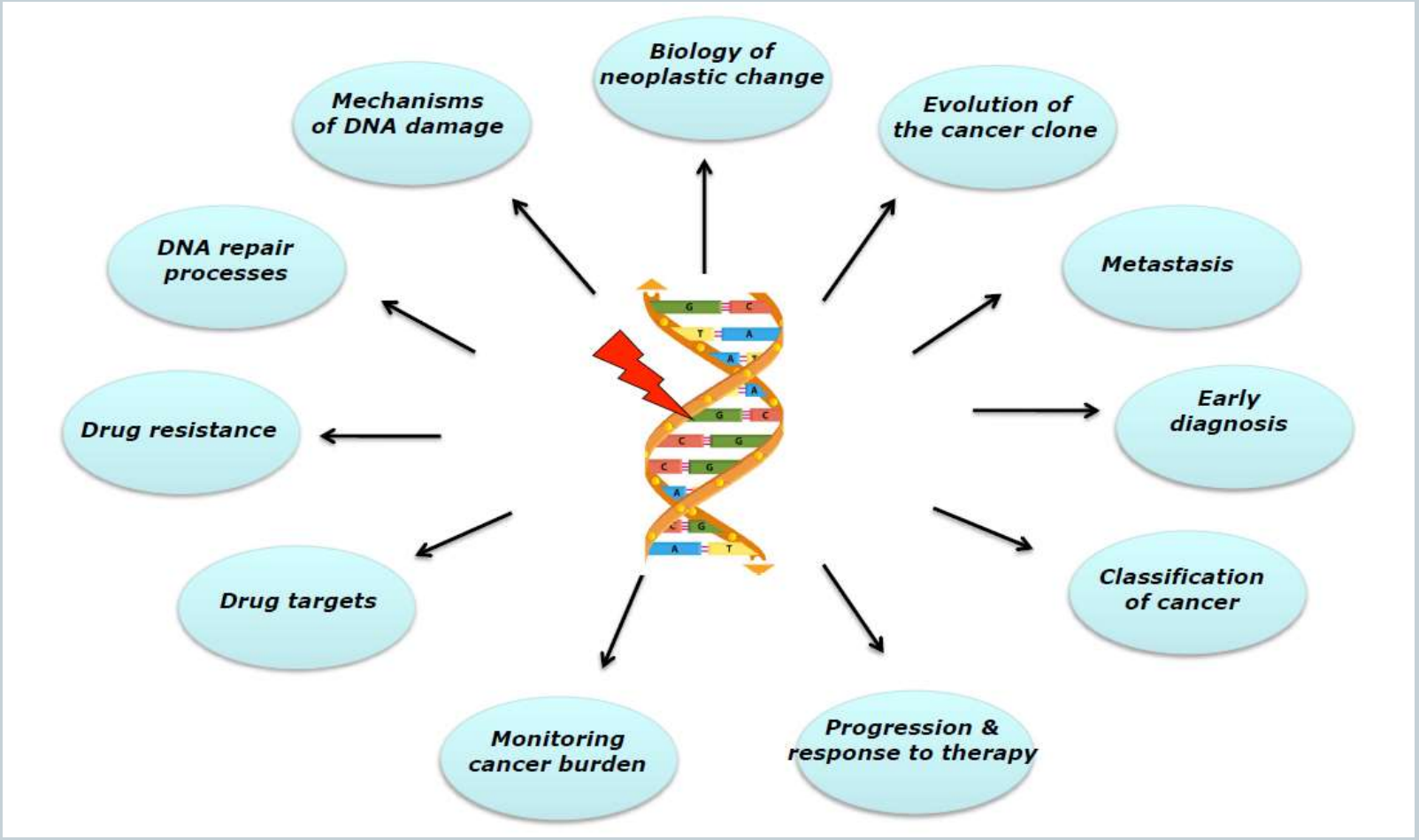
Inherited Susceptibility for the Common Cancers

- The heritability of cancers are usually affected by complex interactions between carcinogens and the host's genome.
- The level of risk for persons with a family history of one of the common cancers such as bowel or breast cancer depends on a number of factors. These include the number of person at risk to the affected individuals and the age at which the affected family members develop cancers,...
- The presence of an oncogene in a germ line cell (egg or sperm) results in an inherited predisposition for tumors in the offspring. However, a single oncogene is not usually sufficient to cause cancer, so inheritance of an oncogene does not necessarily result in cancer.
- Persons at risk of an inherited cancer susceptibility can be screened for associated features of a familial cancer predisposing syndrome or for particular cancer

Telomerase & cancer cells

- Replication of DNA at the telomeres is regulated by the enzyme telomerase.
- In normal cells, telomeres being the mitotic clock shorten at each cell division, and when they reduce below a critical length, the cells die.
- In cancer cells, however shortening of telomeres is prevented by telomerase.
- Telomerase inhibitors may have anti-cancer activity.

Uses of genetics in cancer diagnosis and treatment



Genetic testing

- Inherited cancer genes can significantly increase the lifetime risk of developing cancer . Therefore, the identification of well-characterized germline cancer genes can be used to predict both the type and extent of cancer susceptibility.
- Testing is done on a small sample of body fluid or tissue—usually blood, but sometimes saliva, cells from inside the cheek, skin cells, or amniotic fluid.
- A "**positive test result**" means that the laboratory found a specific genetic alteration (or mutation) that is associated with a hereditary cancer syndrome.
- A "**negative test result**" means that the laboratory did not find the specific alteration that the test was designed to detect. This result is most useful when working with a family in which the specific, disease-causing genetic alteration is already known to be present.

- When a person has a strong family history of cancer but the family has not been found to have a known mutation associated with a hereditary cancer syndrome, a negative test result is classified as an "**uninformative negative**".
- If genetic testing shows a change that has not been previously associated with cancer in other people, the person's test result may report "**variant of unknown significance**," or VUS.
- If the test reveals a genetic change that is common in the general population among people without cancer, the change is called a **polymorphism**.

Diagnosis and prognosis.

- Many cancers have a course that is highly variable and therefore difficult to predict. Because cancer genes dictate the aberrant phenotype of cancer cells, genotypic analysis can provide information on the capacity of a given tumor to grow and spread.
- This information can potentially be used to categorize tumors and to predict their course and responses to therapy.
- **Early detection.** The most treatable cancers are those that are diagnosed at an early stage.

Genetic counselling

- Genetic counselling is a communication process to inform the consultands about the recurrence risk of predisposing familial cancer which might affect the offsprings of future generations.
- Three important steps in genetic sounselling are –
- The establishment of diagnosis.
- Estimation of recurrence risk.
- Communication of relavant information to the consultands in a sympathetic manner so that latter can exercise their own choices or options available for dealing with the risk.

- As part of the process of genetic education and counseling, genetic testing may be considered when the following factors are present:
- An individual's personal history (including ethnicity)and/or family history is suspicious for a genetic predisposition to cancer.
- The genetic test has sufficient sensitivity and specificity to be interpreted.
- The test will impact the individual's diagnosis, cancer management or cancer risk management, and/or help clarify risk in family members

Gene therapy

- Gene therapy envisages the replacement of a deficient gene in the form of a protein or an enzyme or correction of abnormal gene.
- three different gene therapy treatment approaches:

1) **Immunotherapy** uses genetically modified cells and viral particles to stimulate the immune system to destroy cancer cells.
2) **Oncolytic virotherapy**, which uses viral particles that replicate within the cancer cell to cause cell death, is an emerging treatment modality that shows great promise, particularly with metastatic cancers.

3) **Gene transfer** is a new treatment modality that introduces new genes into a cancerous cell or the surrounding tissue to cause cell death or slow the growth of the cancer.

- No genetic disorders have been conclusively cured by gene therapy, but some promising results are obtained from ongoing clinical trials.