Cancer Genetics

Semester 4

Paper ANTH CE B3

BY

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What is Cancer?

- Cancer is a condition of unregulated cell division.

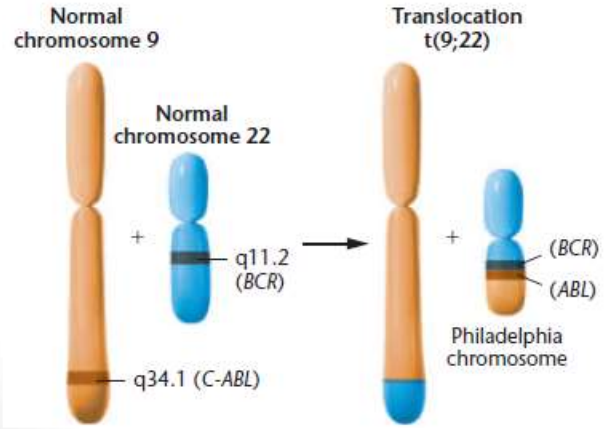
What causes cancer: Both Genetics and Environmental factors causes it but

- At molecular level : Mutation(point mutation, transversion , translocation, insertion , deletion or duplication) is reponsible for cancer

Characteristics of cancer cell

1. Abnormal cell growth and division (**proliferation**),
2. Defects in the normal restraints that keep cells from spreading and colonizing other parts of the body (**metastasis**). (Note: Not all cancer cell metastasis)
3. **Cancer cells contain higher than normal numbers of mutations and chromosomal abnormalities. high level of genomic instability seen in cancer cells is known as the mutator phenotype.**

- For example, leukemic white blood cells from patients with **chronic myelogenous leukemia (CML)** bear a specific translocation, in which the *C-ABL* gene on chromosome 9 is translocated into the *BCR* gene on chromosome 22. This translocation creates a structure known as the **Philadelphia chromosome** The *BCR-ABL* fusion gene codes for a chimeric BCR-ABL protein. The normal ABL protein is a **protein kinase** that acts within signal transduction pathways, transferring growth factor signals from the external environment to the nucleus. The BCR-ABL protein is an abnormal signal transduction molecule in CML cells, which stimulates these cells to proliferate even in the absence of external growth signals



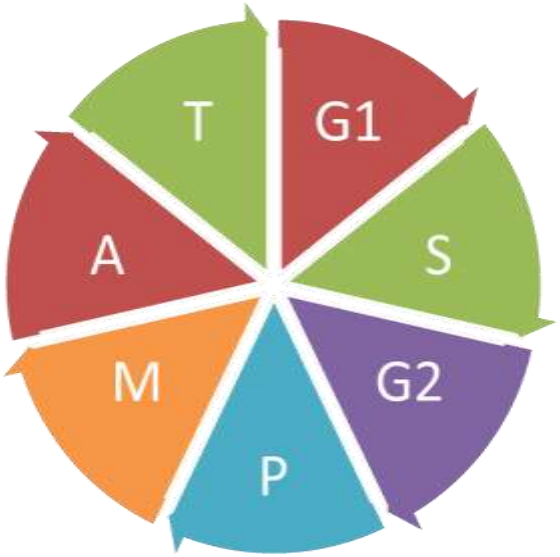
4. These mutation or chromosomal abnormalities can defects genes that control cell division and DNA repair, or has epigenetic mechanism.

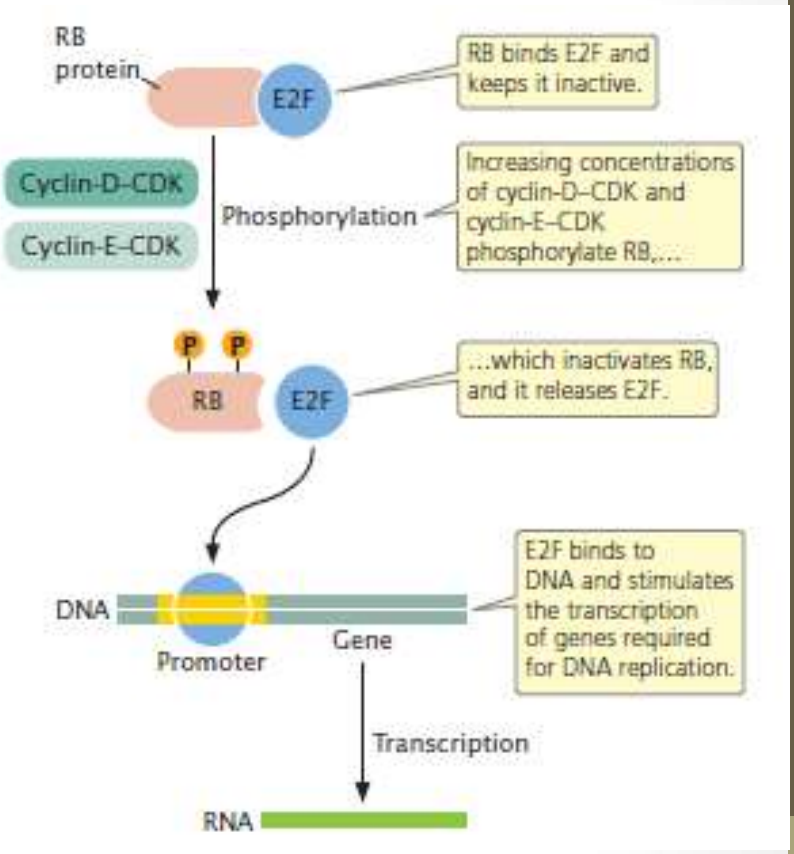
- DNA REPAIR For example, xeroderma pigmentosum (XP) is a rare hereditary disorder that is characterized by extreme sensitivity to ultraviolet light and other carcinogens. Patients with XP often develop skin cancer. XP cells are impaired in their ability to repair DNA lesions such as thymine dimers induced by UV light. Cells from patients with XP are defective in nucleotide excision repair, with mutations appearing in any one of seven genes whose products are necessary to carry out DNA repair.
- Epigenetics mechanisim: factors that affect gene expression but that do not alter the nucleotide sequence of DNA are also linked with cancer in some cases.
- Epigenetic: For ex. Cancer cells have been known to contain altered DNA methylation patterns. Overall, there is much less DNA methylation in cancer cells than in normal cells. At the same time, the promoters of some genes are hypermethylated in cancer cells. Histone modifications are also disrupted in cancer cells. Genes that encode histone acetylases, deacetylases,methyltransferases, and demethylases are often mutated or aberrantly expressed in cancer cells

- A cancer cell is **dedifferentiated**, which means that it is less specialized than the normal cell types near it that it might have descended from. A skin cancer cell, for example, is rounder and softer than the flattened, scaly, healthy skin cells above it in the epidermis, and is more like a stem cell in both appearance and division rate.
- When a cancer cell divides, both daughter cells are cancerous, because they inherit the altered cell cycle control. Therefore, cancer is said to be **heritable** because it is passed from parent cell to daughter cell
- The changes that craft a cancer cell from a healthy cell, and the proliferation of cancer cells and eventual invasion and metastasis, **take time.** Pancreatic cancer, for example, begins 10 to 15 years before the first abdominal pain, then progresses rapidly if not treated. Once a tumor has grown to the size of a pinhead, interior
- cancer cells respond to the oxygen-poor environment by secreting a protein called vascular endothelial growth factor (VEGF). It stimulates nearby capillaries (the tiniest blood vessels) to sprout new branches that extend toward the tumor, bringing in oxygen and nutrients and removing wastes. This growth of new capillary extensions to bring in a blood supply is called **angiogenesis**, and it is critical to a cancer's growth and spread. Capillaries may snake into and out of the tumor.
- Cancer cell also lack the ability to undergo apoptosis (cell death) in response to DNA damage . This condition is linked with mutation in p53 genes in cancerous cells . P53 mutation is linked to inability to arrest at cell-cycle checkpoints or to enter apoptosis in response to DNA damage.

- **Cancer Cells Contain Genetic Defects Affecting Cell-Cycle Regulation**:
- Key events of the cell cycle are controlled by **cyclin-dependent kinases** (**CDKs**), which are enzymes that phosphorylate (add phosphate groups to) other proteins. In some cases, phosphorylation activates the other protein, and in others, it inactivates the other protein.
- As their name implies, CDKs are functional only when associated with another type of protein, called a **cyclin**. The levels of cyclins oscillate over the course of the cell cycle; when bound to a CDK, a cyclin specifies which proteins the CDK will phosphorylate. Each cyclin appears at a specific point in the cell cycle, usually because its synthesis and destruction are regulated by another cyclin.
- Cell cycle has check points , which ensure that all cellular components are present and in good working order before the cell proceeds to the next phase. The G1/S checkpoint is at the end of G1,just before the cell enters the S phase and replicates its DNA. The cell is prevented from passing through the G1/S checkpoint by a molecule called the retinoblastoma (RB) protein which binds to another molecule called E2F and keeps it inactive.
- During G1, cyclin D and cyclin E continuously increase in concentration and combine with their associated CDKs. Cyclin-D–CDK and cyclin-E–CDK both phosphorylate molecules of RB. By late in G1, phosphorylation of RB is completed, which inactivates RB. Without the inhibitory effects of RB, E2F is released. The E2F protein stimulates the transcription of genes that produce enzymes necessary for replication of the DNA, and the cell moves into the S phase of the cell cycle. (Remember in Retinoblastoma : cancer of eyes due to mutation in RB gene, hence RB is inactivated all the time and hence cell division continues in unregulated way. SEE in Tumor supressor gene)
- Another important checkpoint controls the G2-to-M transition. This checkpoint is also regulated by CDKs and cyclins. Other checkpoints control the assembly of the mitotic spindle apparatus and the cell's exit from mitosis.
- Mutation in the genes controlling the these checkpoints leads to cancer. (example mutation in RB gene which normally holds the cell in G1 until the DNA is ready to be replicated—are associated with many cancers, including retinoblastoma. Similarly Overexpression of the gene that encodes cyclin D (which stimulates the passage of cells through the G1/S checkpoint) takes place in about 50% of all breast cancers as well as in some cases of esophageal and skin cancer. Likewise, the tumorsuppressor gene *p53*, which is mutated in about 75% of all colon cancers, regulates a potent inhibitor of CDK activity.

- Cell Cycle (Normal)





General cell properties of cancer cell

Oilier, less adherent

Loss of cell cycle control

Heritable

Transplantable

Dedifferentiated

Lack contact inhibition

Induce local blood vessel formation (angiogenesis)

Invasive

Increased mutation rate

Can spread (metastasize)

- Types of cancer: Familial or Genetic and Sporadic

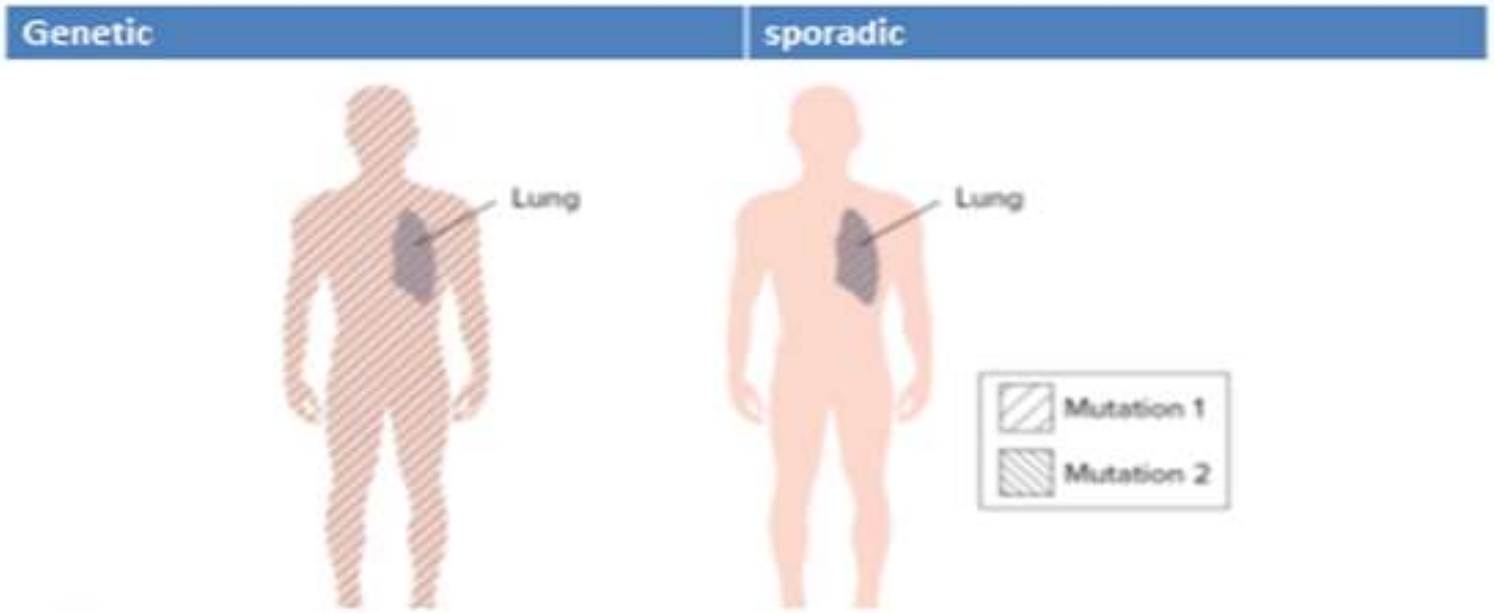


Figure 18.5 **Germline versus sporadic cancer.** **(a)** In germline cancer, every cell has one gene variant that increases cancer susceptibility and a somatic mutation occurs in cells of the affected tissue. This type of predisposition to cancer is inherited as a single-gene trait and is due to an initial germline mutation. **(b)** A sporadic cancer forms when a dominant mutation occurs in a somatic cell or two recessive mutations occur in the same gene on homologous chromosomes in a somatic cell. An environmental factor can cause the somatic mutations of cancer.

Types of cancer

Benign	Malignant
localized	Metastasis
Chromosomal makeup normal	Abnormal cell structure and chromosomal makeup
No Angiogenesis	Angiogenesis

Genetics of cancer :Properties of mutation in Cancer Cells

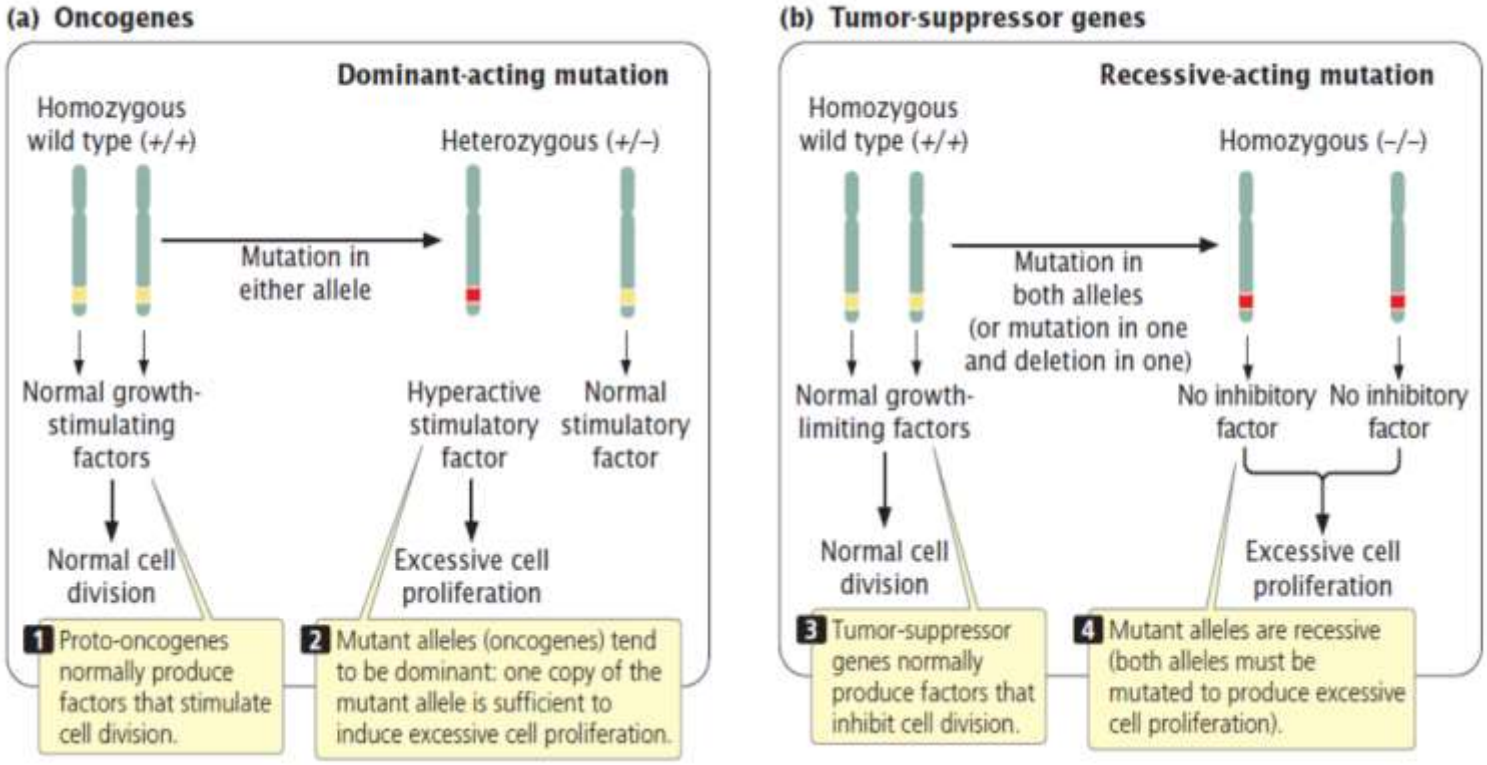
- In cancer genetics, some **mutations can** provides the selective growth advantage to a cell that defines the cancerous state(means they induce cancer). whereas some **mutation** occurs in a cancer cell, but does not cause or propel the cancer's growth or spread.
- The former can be think of as driver mutations while later as passenger
- 99%of the mutations in cancer cells are passengers, just along for the ride. About 1 %of all of our genes which are involved in the cell cycle or DNA repair and can be implicated in some way in cancer are due to driver mutations.

- These mutation can starts cells on an abnormally high rate of cell division.
- A mutation in one (or more) rapidly dividing cells may confers the ability to invade surrounding tissue.
- Additional mutations may accumulate to confer more invasive properties or the ability to metastasize.
- The chromosomes in cancer cells may be abnormal in number and/or structure. They may bear translocations,inversions, or have extra(duplication) or missing pieces(deletion).

Genes Controlling Cell cycle that leads to cancer

- Proto-oncogenes and Tumour-suppressor genes

P-Onco	T-Sup
Stimulates cell division	Stops cell division
Pushes through G1/S and G2/M check points	Inhibits
Accelerator	Breaks
When mutated Cell division permanently on	When mutated it cannot inhibit cell division and cell division become permanently on
Mutations are Dominant	Recessive
Gain in function	Loss of function


(a) Oncogenes
Dominant-acting mutation
Homozygous wild type (+/+)
Heterozygous (+/–)
Mutation in either allele
Normal growth-stimulating factors
Hyperactive stimulatory factor
Normal stimulatory factor
Normal cell division
Excessive cell proliferation
1 Proto-oncogenes normally produce factors that stimulate cell division.
2 Mutant alleles (oncogenes) tend to be dominant: one copy of the mutant allele is sufficient to induce excessive cell proliferation.
(b) Tumor-suppressor genes
Recessive-acting mutation
Homozygous wild type (+/+)
Homozygous (–/–)
Mutation in both alleles (or mutation in one and deletion in one)
Normal growth-limiting factors
No inhibitory factor
No inhibitory factor
Normal cell division
Excessive cell proliferation
3 Tumor-suppressor genes normally produce factors that inhibit cell division.
4 Mutant alleles are recessive (both alleles must be mutated to produce excessive cell proliferation).

oncogenes

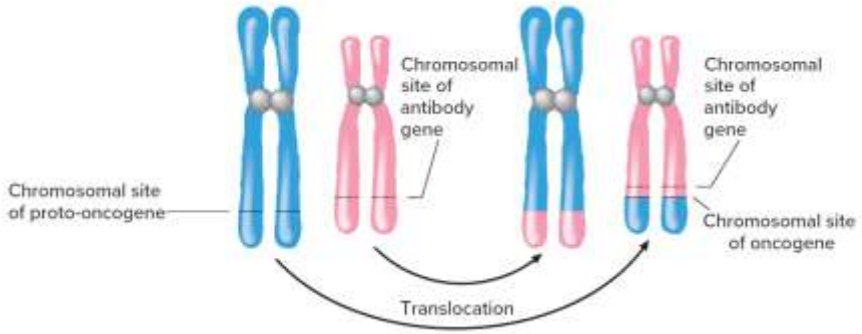
- Genes that normally trigger cell division are called **proto-oncogenes**. They are active where and when high rates of cell division are necessary. When proto-oncogenes are transcribed and translated too rapidly or frequently, or at the wrong time in development or place in the body, they function as oncogenes. (to remember cell division always ON in oncogenes)

- Three examples of genes that can activate proto-oncogenes and make them oncogenes are a viral gene, a gene encoding a hormone, and parts of antibody genes.
- A virus infecting a cell may insert DNA next to a protooncogene. When the viral DNA is rapidly transcribed, the adjacent proto-oncogene (now an oncogene) is also rapidly transcribed. increased production of the oncogene's encoded protein then switches on genes that promote mitosis, triggering the cascade of changes that leads to cancer. Example cervical cancer, T cell leukemia

- A proto-oncogene may be activated when it is moved next to a gene by chromosomal translocation or inversion that places the gene next to another that is more highly expressed example inversion on chromosome 11 places a protooncogene next to a DNA sequence that controls transcription of the parathyroid hormone gene. When the gland synthesizes the hormone, the oncogene is expressed, too. Cells in the gland divide, forming a tumor.

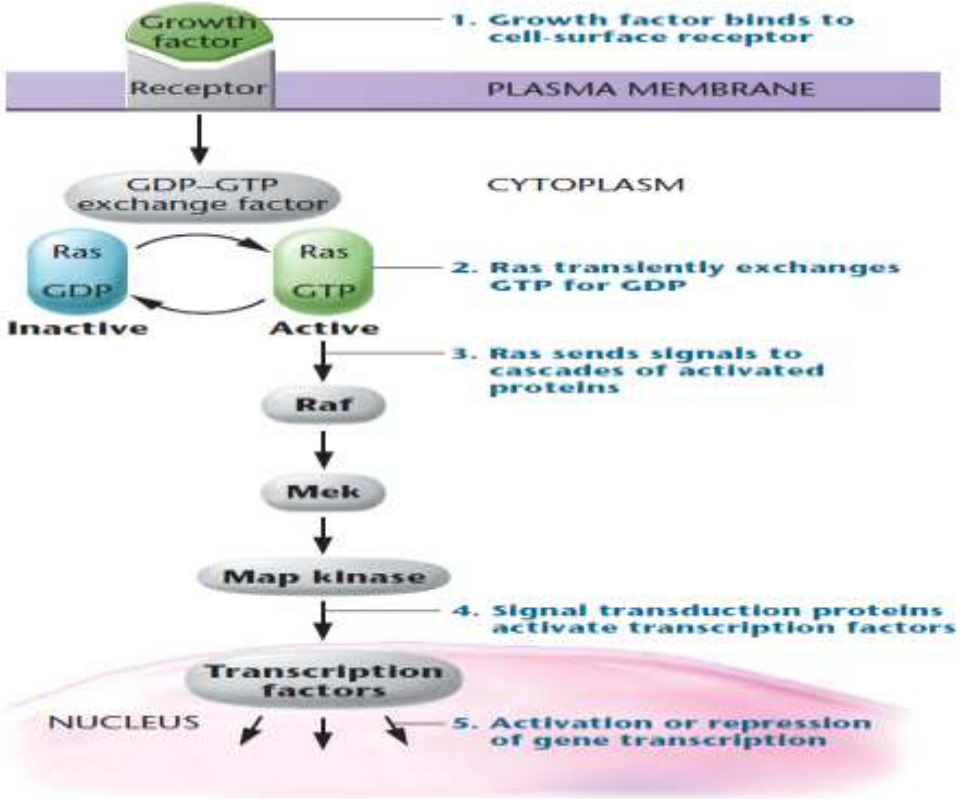
- Similarly Antibody genes are among the most highly transcribed,so it isn't surprising that a translocation or inversion that places a proto-oncogene next to an antibody gene causes cancer. Example Burkitt lymphoma, a cancer common in Africa, a large tumor develops from lymph glands near the jaw.

- Epstein-Barr virus stimulates specific chromosome movements in maturing B cells to assemble antibodies against the virus, and a translocation places a proto-oncogene on chromosome 8 next to an antibody gene on chromosome 14. The oncogene is overexpressed, and the cell division rate increases and Tumor is formed.



- **The ras Proto-oncogenes** Some of the most frequently mutated genes in human tumors are those in the ras gene family. These genes are mutated in more than 30 percent of human tumors. The ras gene family encodes signal transduction molecules that are associated with the cell membrane and regulate cell growth and division. Ras proteins normally transmit signals from the cell membrane to the nucleus, stimulating the cell to divide in response to external growth factors. (Ras proteins alternate between an inactive (switched off) and an active (switched on) state by binding
- either guanosine diphosphate (GDP) or guanosine triphosphate (GTP). When a cell encounters a growth factor,growth factor receptors on the cell membrane bind to the growth factor,. This causes recruitment of proteins known as nucleotide exchange factors to the plasma membrane. These nucleotide exchange factors cause Ras to release GDP and bind GTP, thereby activating Ras. The active, GTP-bound form of Ras then sends its signals through cascades of protein phosphorylations in the cytoplasm.The end-point of these cascades is activation of nuclear transcription factors that stimulate expression of genes which leads to cell division.
- Mutations that convert the ras proto-oncogene to an oncogene prevent the Ras protein from hydrolyzing GTP to GDP and hence freeze the Ras protein into its “on” conformation, constantly stimulating the cell to divide.

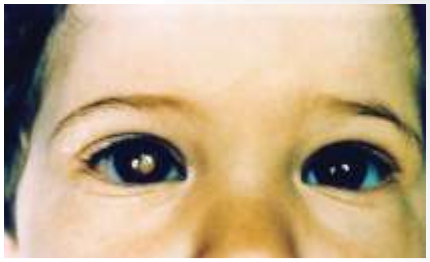
The ras Proto-oncogenes mechanism



Tumor suppressor gene

- A tumor suppressor normally inhibits expression of genes (stops cell cycle). Some cancers result from loss or silencing of TSG(MEANS NO BREAKS ON CELL CYCLE). Cancer can result when a tumor suppressor gene is deleted or if the promoter region binds too many methyl (CH3) groups, which blocks transcription(PROCEDURE FOR SILENCING TSG).
- Example are Retinoblastoma, breast cancer and P53 gene.

Retinoblastoma



- The first gene recognized as a tumor suppressor is associated with cancer of the eye, called retinoblastoma.. In 1971, geneticist Alfred Knudson suggested that one mutated allele of the gene was being passed from parent to child and that a mutation event in the child was required for the cancer to occur.
- This shows that Retinoblastoma often runs in families and shows up in very young children and inherited retinoblastoma requires two point mutations (deletions), one germline and one somatic. Or In some sporadic (noninherited) cases, two somatic mutations occur in the *RB1* gene, one on each copy of chromosome 13. the RB1 gene mutation is also linked in other forms of cancer such as breast, prostate, and bone

- Either way, the cancer usually starts in a cone cell of the retina, which provides color vision. And proves “two-hit” hypothesis of cancer causation—that two mutations (germline and somatic or two somatic) are required to cause a cancer related to tumor suppressor deletion or malfunction. (Note : A second form of retinoblastoma is caused by mutation in an oncogene, *MYCN.*)
- The RB1 protein normally binds transcription factors so that they cannot activate genes that carry out mitosis. It normally halts the cell cycle at G1. When the *RB1* gene is mutant or missing, the hold on the transcription factor is released, and cell division go out of control.

- Researchers have identified two breast cancer genes: *BRCA1* and *BRCA2* (for
- BReast CAncer genes 1 and 2). Breast cancers associated with mutations of *BRCA1* and/or *BRCA2* seem to be inherited as *autosomal dominant disorders* (genetic disorders resulting from one bad copy of a gene
- Other cancers are also associated with mutations in *BRCA1* and *BRCA2,* including ovarian, prostate, and male breast cancer.
- Both *BRCA* genes are tumor-suppressor genes. *BRCA1* has a role in regulating when cells pass through the critical G1-S checkpoint, but exactly how *BRCA1* does its job isn't clear. *BRCA1* encodes a protein that interacts with many other proteins that counter DNA damage in several ways. One important form of protection is the mending of areas of the genome where both DNA strands are broken at the same site. These double-stranded breaks are particularly dangerous because they
- cut the chromosomes all the way through, making rearrangements such as deletions and translocations possible. The most common *BRCA1* mutation deletes two adjacent DNA bases, altering the reading frame and shortening the protein. As for *BRCA2,* it apparently has some cell cycle duties and also plays a role in DNA repair, especially of double-strand breaks.

Environmental Agents Contribute to Human Cancers

- Any substance or event that damages DNA has the potential to be carcinogenic. Unrepaired or inaccurately repaired DNA introduces mutations, which, if they occur in protooncogenes or tumor-suppressor genes, can lead to abnormal regulation of the cell cycle or disruption of controls over apoptosis or metastasis.
- These include chemicals, radiation, some viruses, and chronic infections.
- Other environmental factors that induce cancer are certain types of chemicals, such as benzene (used as an industrial solvent), benzo[a]pyrene (found in cigarette smoke), and polychlorinated biphenyls (PCBs; used in industrial transformers and capacitors). Perhaps the most significant carcinogen in our environment is tobacco smoke, which contains at least 60 chemicals that interact with DNA and cause mutations.
- Diet is often implicated in the development of cancer. Consumption of red meat and animal fat is associated with some cancers, such as colon, prostate, and breast cancer. These substances may contribute to carcinogenesis may involve stimulation of cell division through hormones or creation of carcinogenic chemicals during cooking. Alcohol may cause inflammation of the liver and contribute to liver cancer

- natural substances realsed by natural processes can also be carcinogenic. For example, aflatoxin, a component of a mold that grows on peanuts and corn, is one of the most carcinogenic chemicals known. Most chemical carcinogens, such as nitrosamines, are components of synthetic substances and are found in some preserved meats; however, many are naturally occurring. Natural pesticides and antibiotics found in plants may be carcinogenic, and the human body itself
- creates alkylating agents in the acidic environment of the gut. In
- addition, normal metabolism creates oxidative end products
- that can damage DNA, proteins, and lipids however, some damage may lead to permanent mutations.(note some vegetables release chemicals that activate enzymes heterocyclic aromatic amines which detoxify and digest the natural carcinogens)
- that detoxify carcinogenic products of cooked meat, called
- Chronic inflammation due to infection also stimulates tissue repair and cell division, resulting in DNA lesions accumulating during replication. These mutations may persist, particularly if cell-cycle checkpoints are compromised due to mutations or inactivation of tumor-suppressor genes such as *p53* or *RB1.*

- Books : Concepts of genetics by Klug, William S.Cummings, Michael R.Spencer, Charlotte A.Michael A. Palladino.
- Genetics Essentials Concepts and Connections by Benjamin A. Pierce.
- Human Genetics Concepts and Applications by Ricki Lewis.
- Genetics for dummies.