

## **ONCOGENES AND TUMOR SUPPRESSOR GENES**

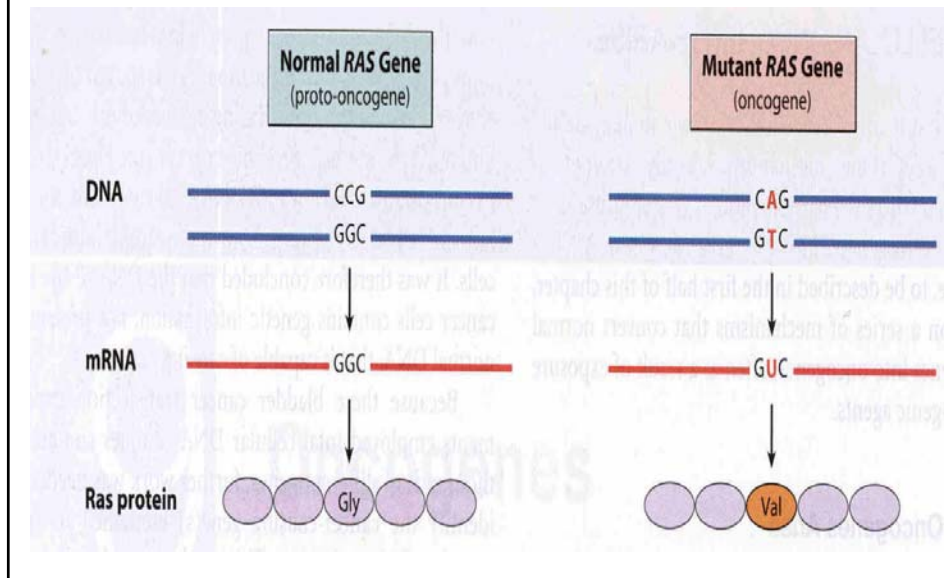
- **Proto-oncogenes are converted to c-oncogenes by gain-of-function mutations.**
- **Tumor suppressor genes function by loss-of-function mutations.**
- **Proto-oncogenes are normal genes contributing to cell proliferation and survival.**
- **C-oncogenes arise either by viral infections or by exposure to carcinogenic agents.**
- **Presence of oncogenes or absence / inactivation of tumor suppressor genes can lead to cancer.**

## **Oncogenes and Mutated/Deleted Tumor Suppressor Genes Disrupt Signal Transduction Pathways to Induce Cancer**

**In spite of diversity and complexity of signaling pathways, they have some common features:**

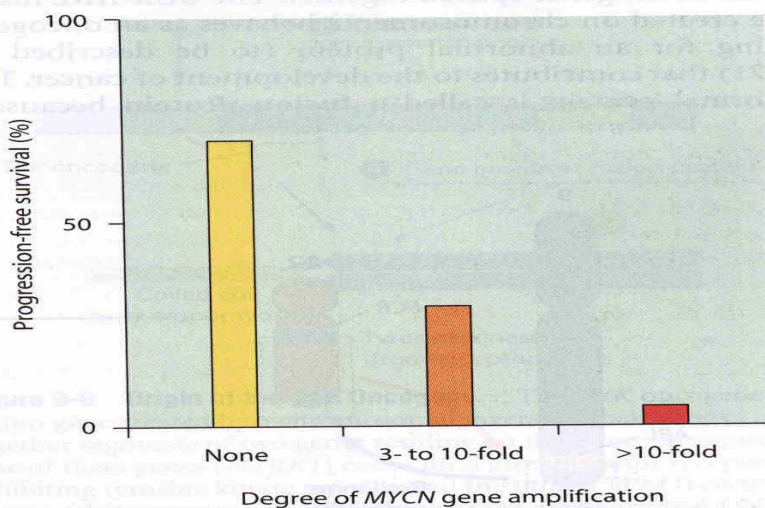
- 1. Growth factors bind to receptors and activate them.**
- 2. Activated receptors trigger a series of protein phosphorylations and other complex chains of events.**
- 3. Protein phosphorylations trigger changes in transcription factors that alter the expressions of specific genes.**
- 4. Activated or inhibited genes produce proteins that influence cell proliferation and cell death**

## Point Mutation in a RAS Oncogene



## MYCN Gene Amplification and Neuroblastoma Survival Rates

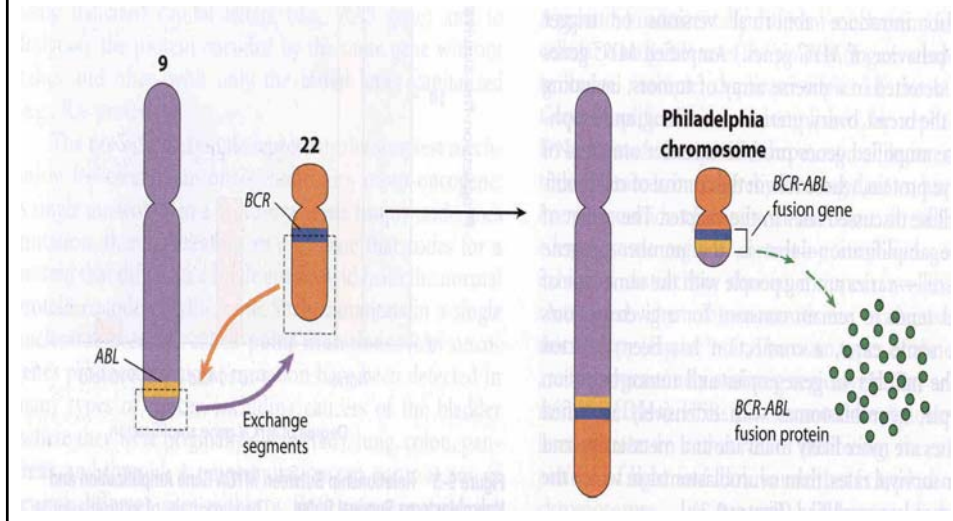
(Percent of patients who survive 18 months after diagnosis without disease progression)



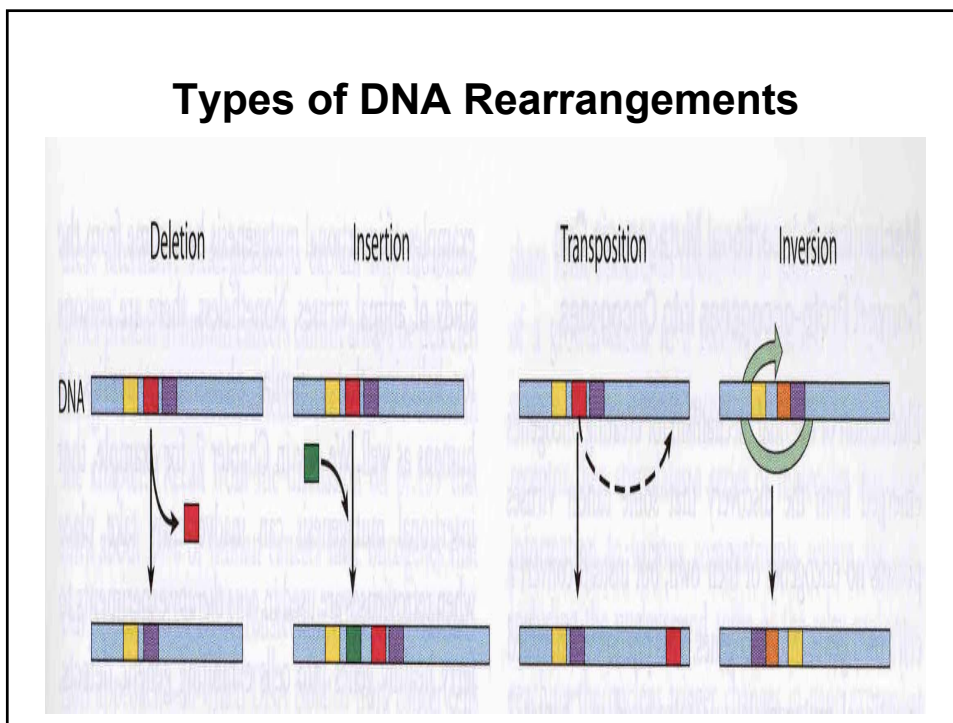
## Chromosomal Translocation that creates Philadelphia Chromosome

BCR-ABL Oncogene: Breaks in ABL Gene of Chromosome 9 and BCR Gene of Chromosome 22

Fusion Protein causes Chronic Myelogenous Leukemia

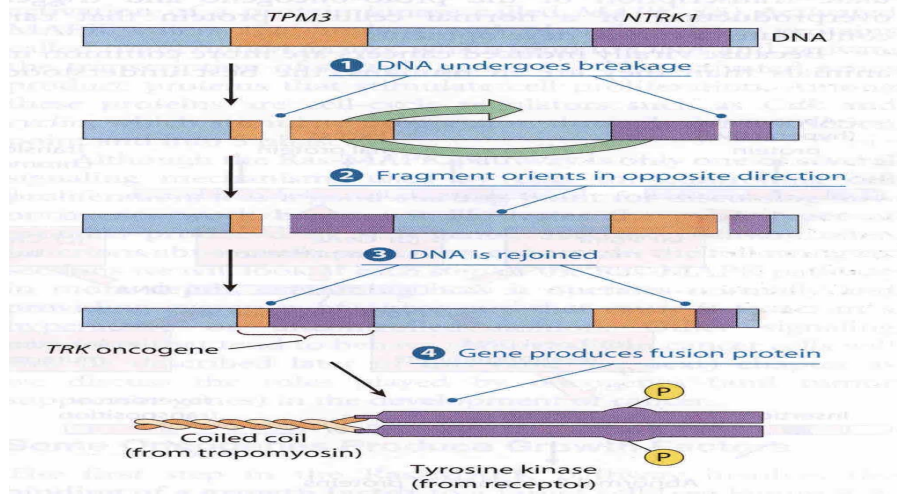


## Types of DNA Rearrangements

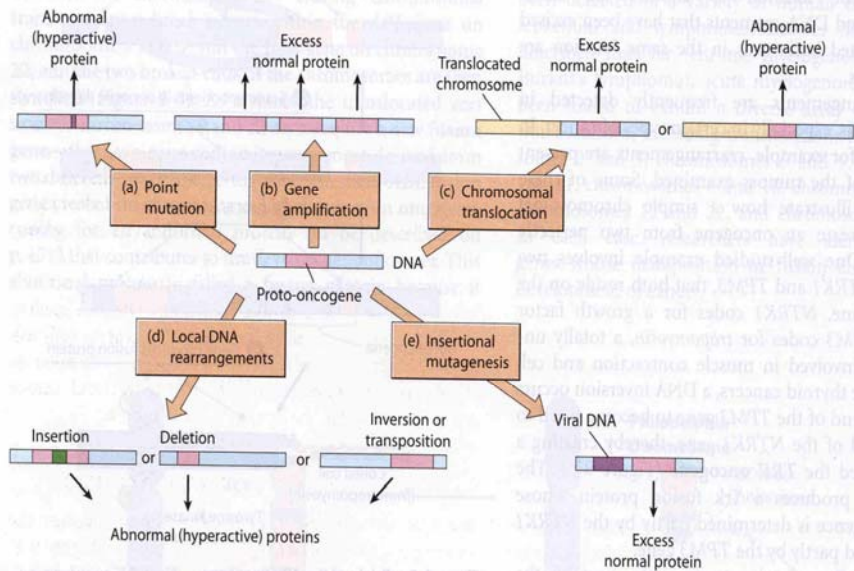


## Origin of TRK Oncogene by Chromosomal Inversion

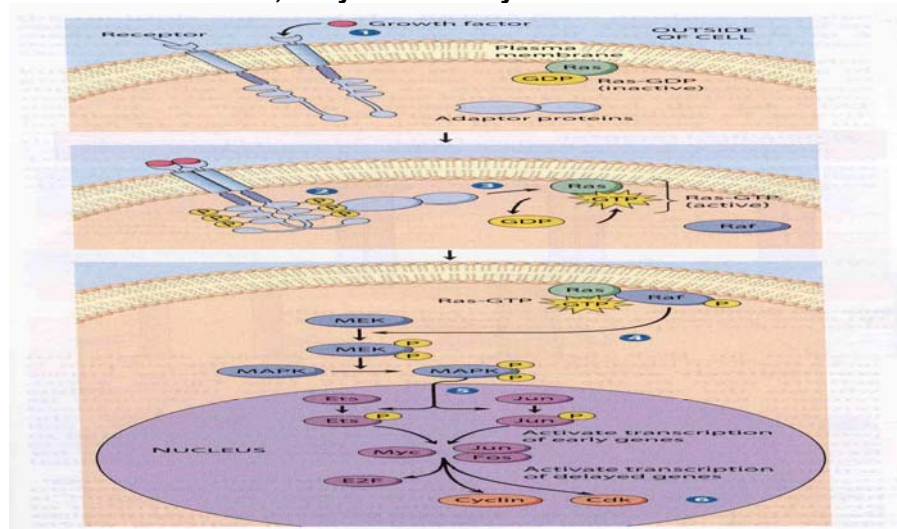
NTRK1 codes for a receptor with tyr. kinase activity. TPM3 codes for a tropomyosin which causes the receptor region to form a dimer. TRK oncogene codes for a fusion protein with receptor dimer formation with permanently activated tyr. kinase



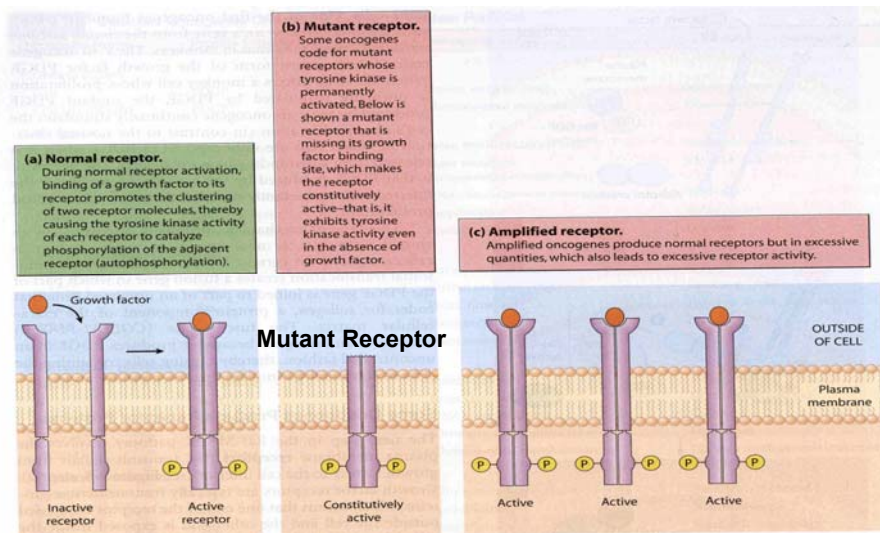
## Five Mechanisms for converting Proto-oncogenes into Oncogenes



**The Ras MAPK ( Mitogen Activated Prot. Kinase) Pathway**  
 Chain of events in 6 steps: 1. GF binds to receptor; 2. Clustering and autophosphorylation of receptor; 3. Activation of Ras; 4. Activation of cascade of protein kinases; 5. Activation of nuclear Trn. Factors; 6. Synthesis of cyclin and Cdk molecules

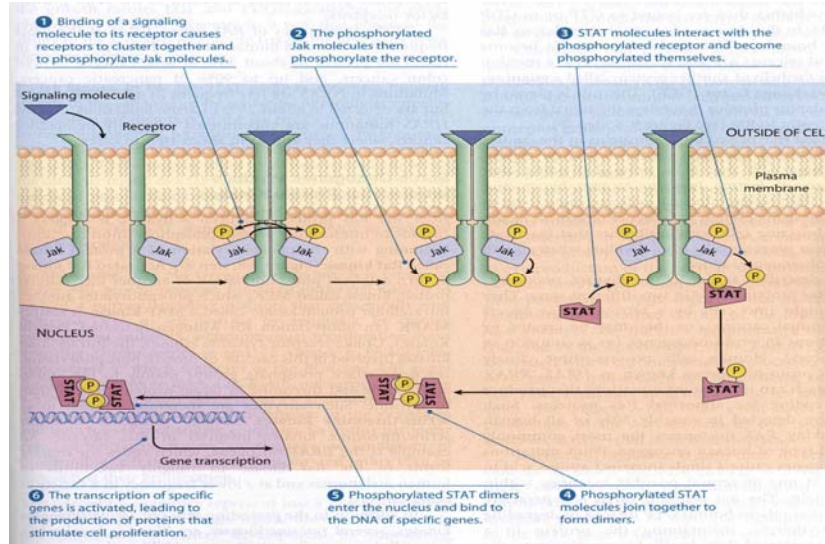


**Receptor Tyrosine Kinases under Normal and Abnormal Conditions.**  
 A: Normal Rs show Tyr. Kinase activity when GF is bound. B: Some oncogenes code for Rs with permanent Tyr. Kinase activity. C: Some oncogenes code for normal Rs but in excess leading to Amplified RS.



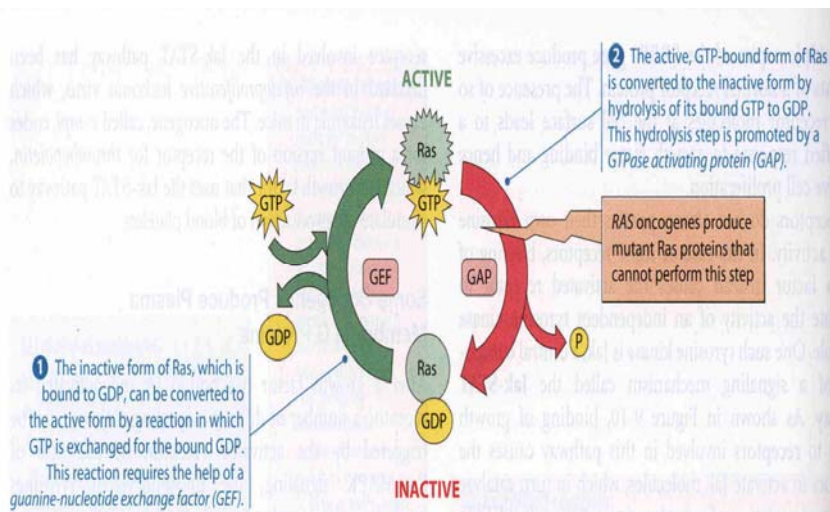
## The JAK-STAT Signaling Pathway

Signaling molecules trigger a chain of 6 steps for production of proteins that stimulate proliferation

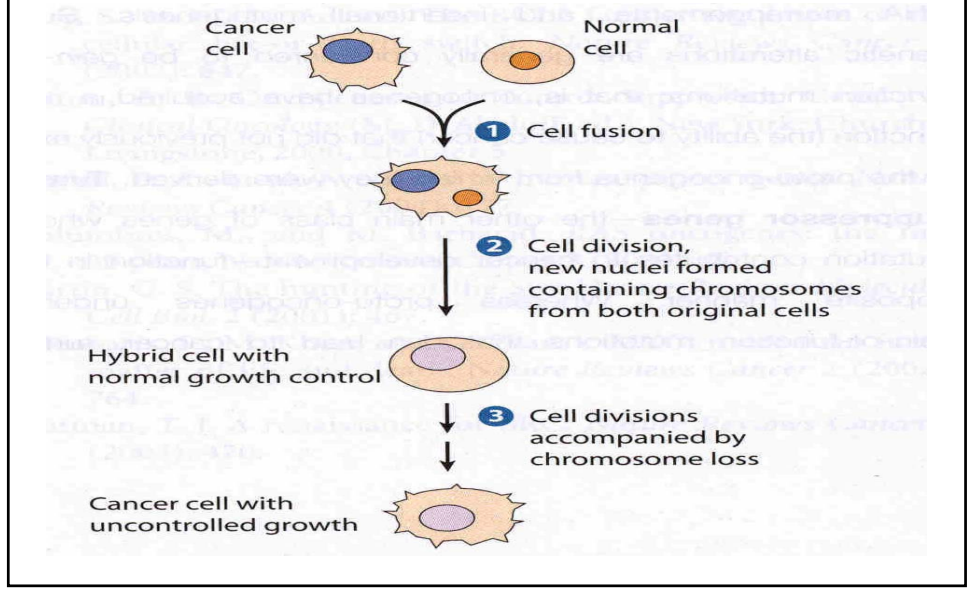


## Control of the Ras Protein

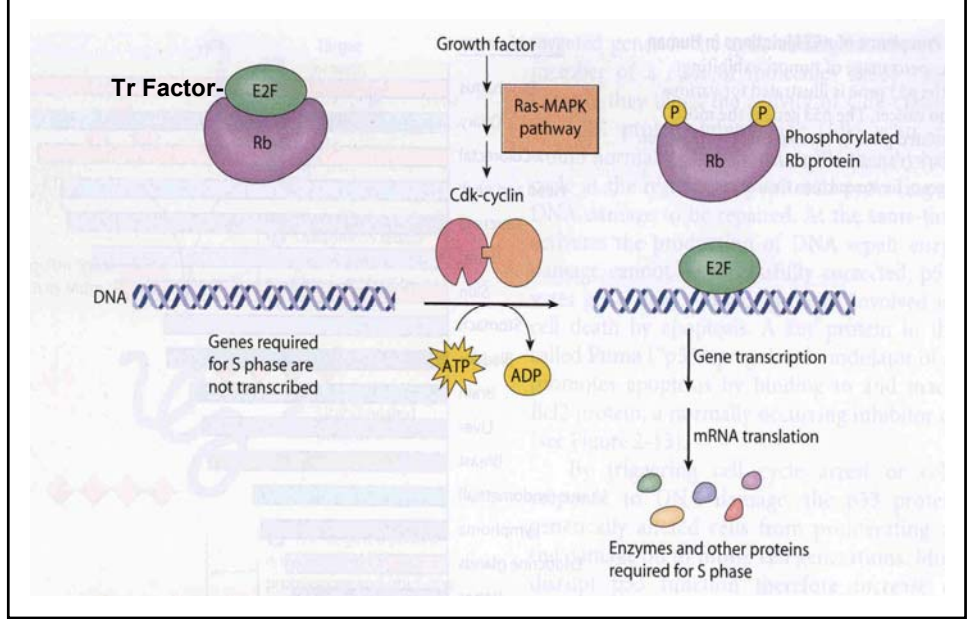
Activity of Ras determined whether it is bound to GDP or GTP. Some Ras proteins do not hydrolyze GTP maintaining Ras in a permanently activated form



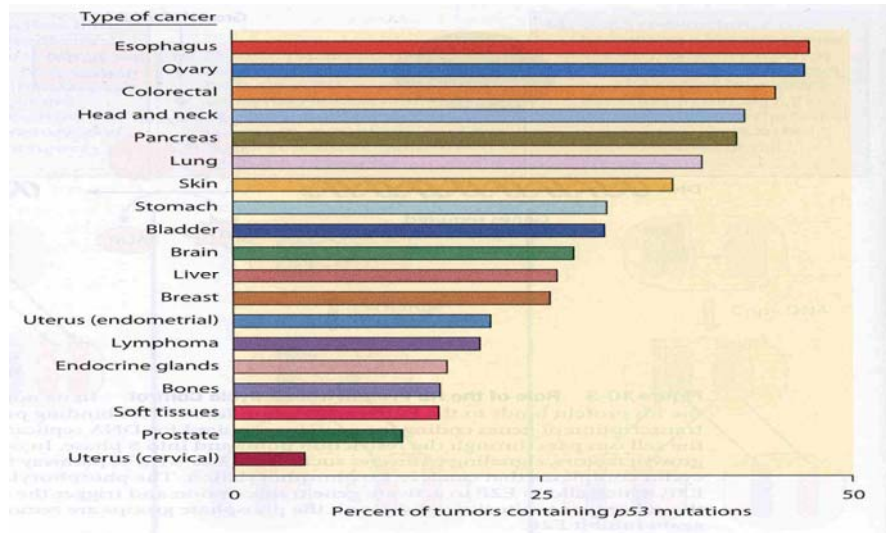
**Evidence showing that normal cells contain genes that suppress tumor growth. Loss of these genes can revive tumor growth**



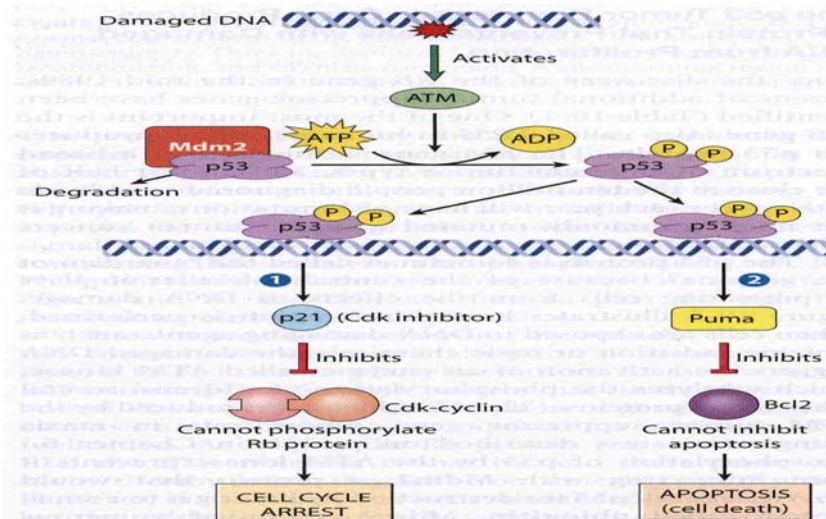
**How Rb protein controls cell cycle?**



## Percentage of Tumors exhibiting Mutations in the most Mutated Gene, p53 in Human Cancers

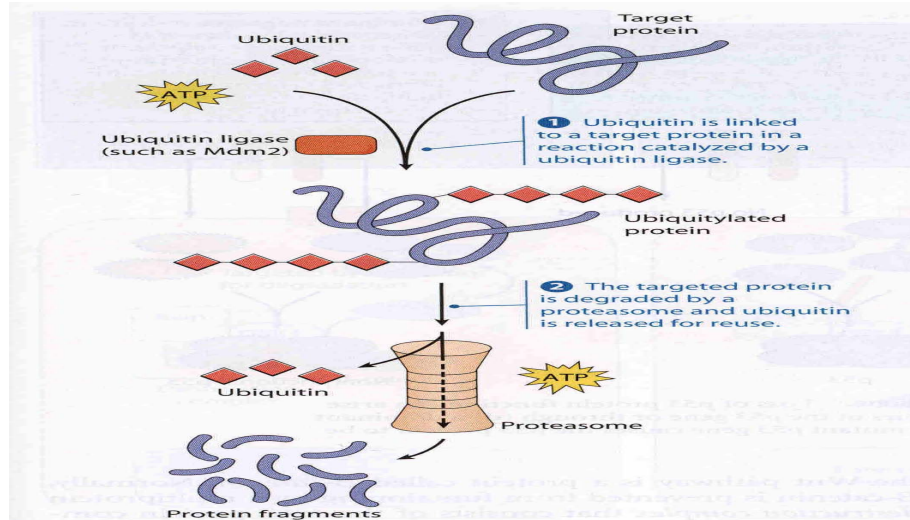


**How p53 protein responds to DNA damage?**  
 p53 protein is either degraded or converted to p53-P which triggers: 1) cell cycle arrest for DNA repair or; 2) If DNA is not repaired then promotes apoptosis



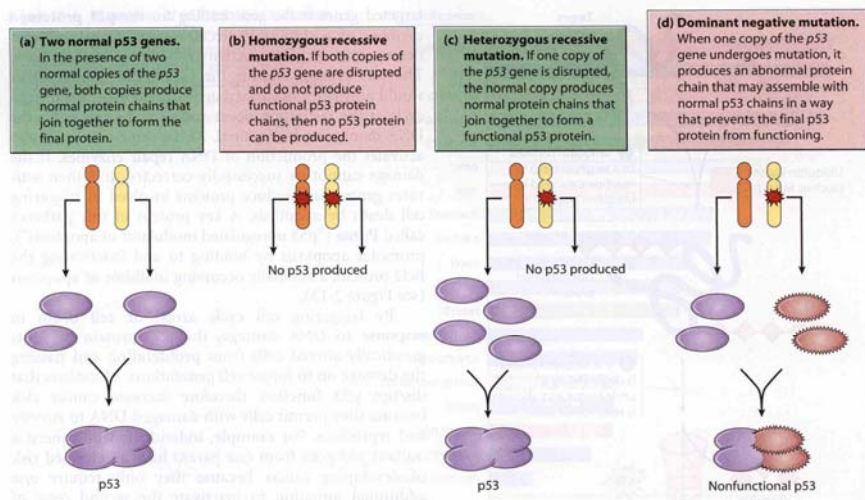
## Role of Ubiquitin in Targeting Proteins for Degradation

1. Ligases (like Mdm2) tag proteins to ubiquitin
2. Proteins are degraded by proteasomes using ATP



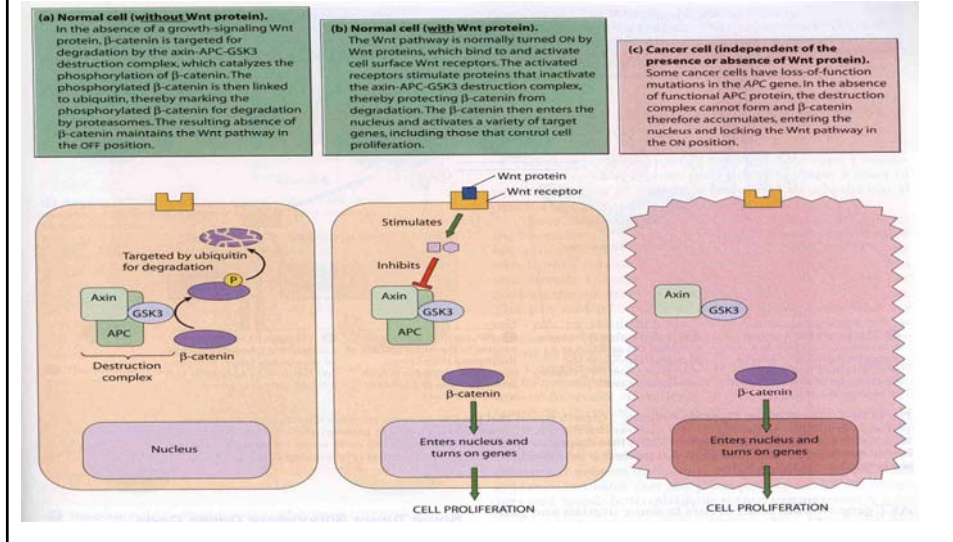
## Recessive and Dominant Negative p53 Mutations

p53 protein function can be lost by: (1) homozygous recessive mutations disrupting both copies of the gene; (2) a dominant -ve mutation in which abnormal protein chain coded by one copy of the gene inactivates normal p53 protein



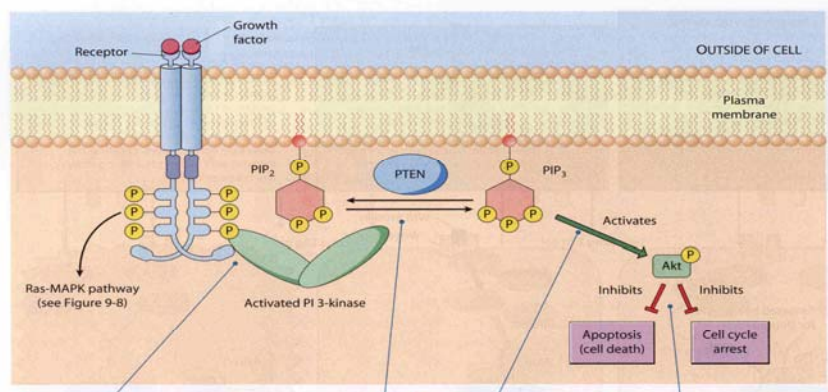
## The Wnt Signaling Pathway

Wnt external protein required in normal cells (Figs. a and b)  
Wnt not required for cancer cells (Fig. c)



## PI3K-AKT Signaling Pathway

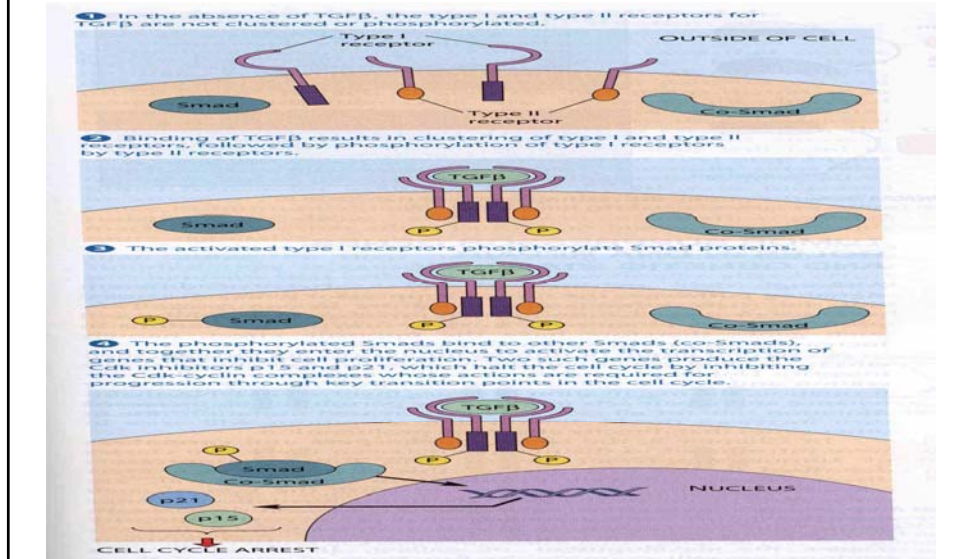
1. Activation of Akt, a protein kinase that suppresses apoptosis and inhibits cell cycle arrest by phosphorylating several target proteins. The enzyme PTEN reverses step 2 by breaking PIP<sub>3</sub> and PIP<sub>2</sub>



- 1 The enzyme PI 3-kinase is activated by interacting with phosphate groups that have been attached to a growth factor receptor in response to growth factor binding.
- 2 The activated PI 3-kinase catalyzes the addition of a phosphate group to the membrane lipid PIP<sub>2</sub>, thereby converting it to PIP<sub>3</sub>.
- 3 PIP<sub>3</sub> recruits protein kinases to the inner surface of the plasma membrane, leading to phosphorylation and activation of a protein kinase called Akt.
- 4 Through its ability to catalyze the phosphorylation of several key target proteins, Akt suppresses apoptosis and inhibits cell cycle arrest.

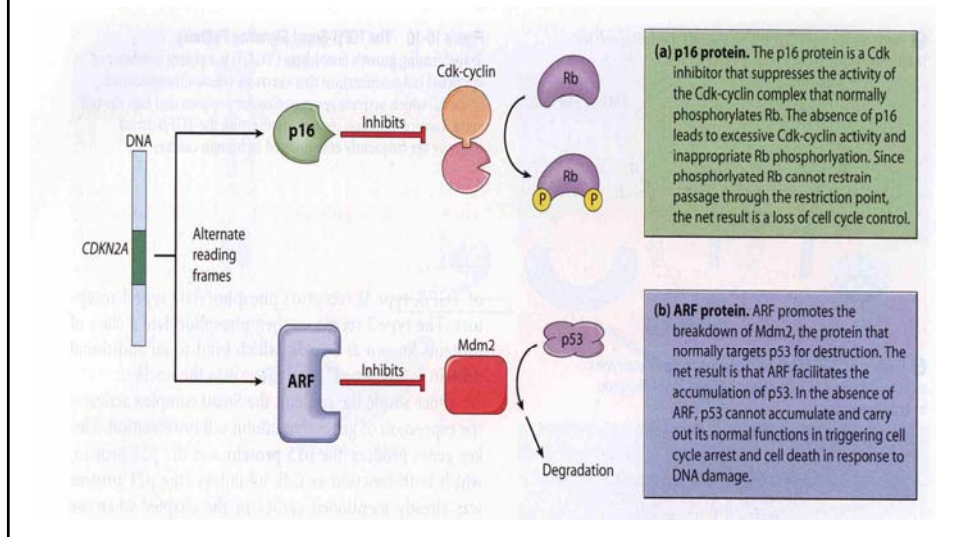
## The TGFβ-Smad Signaling Pathway.

TGFβ inhibits epithelial cell proliferation through Smad proteins. Smads activate genes for coding proteins to halt cell cycle. Loss- of- function mutations affecting this pathway are found in several human cancers

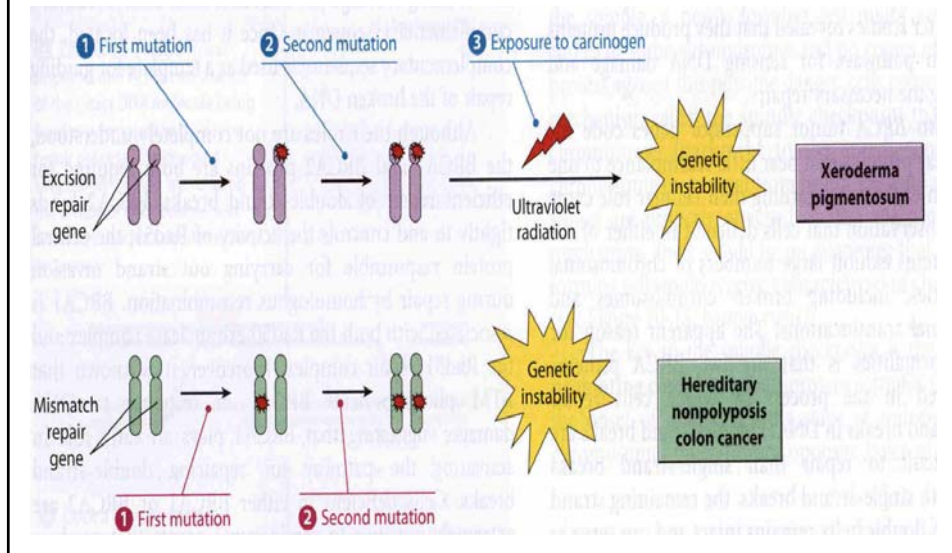


## Two Tumor Suppressor Proteins produced by the CDKN2A Gene

Shifting the reading frame of this gene allows it to produce two different tumor suppressor proteins (p16 and ARF)

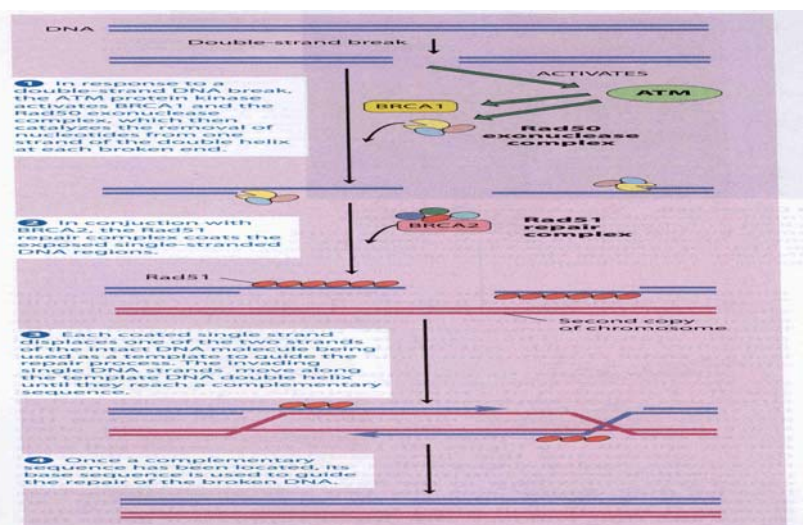


## Routes to Genetic Instability based on Defective DNA Repair



## Pathway for Repairing DS DNA Breaks by Homologous Recombination

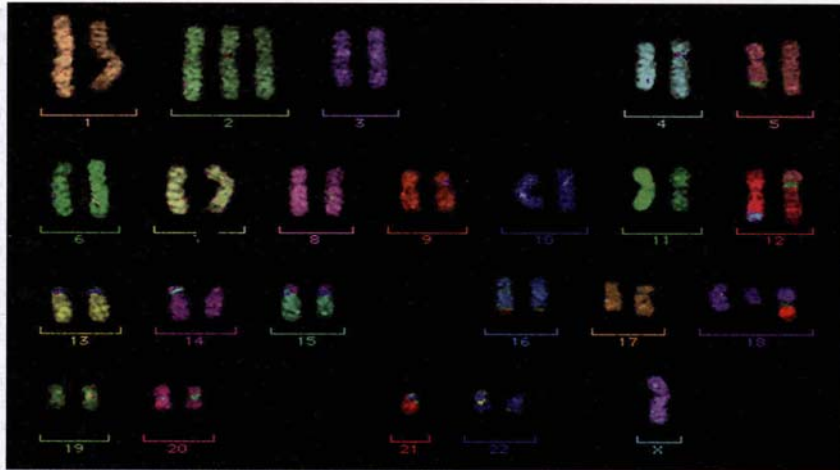
Rad50 exonuclease and Rad51 repair complexes use DNA in unbroken homologous chromosome to serve as template for the repair of DNA from broken chromosome



### Chromosomal Abnormalities in a Cancer Cell.

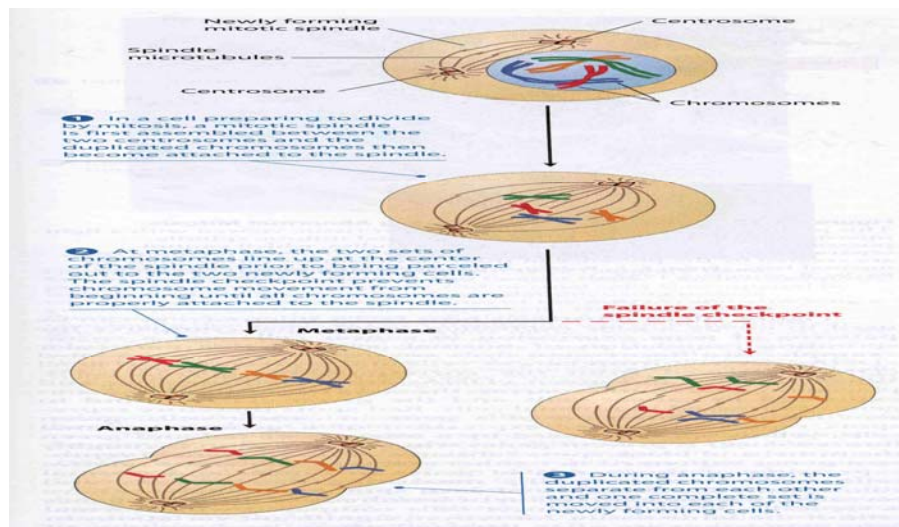
Chromosomes from a patient of acute lymphocytic leukemia were stained with different dyes to impart different colors to each type of chromosome.

Being an aneuploid, this cell has extra copies of chromosomes 2 and 16 with one X chromosome loss. Chr. 21 has been passed on to a part of 18, mutations in Chromosomes 4, 5, 12, 16 and 21 are also seen

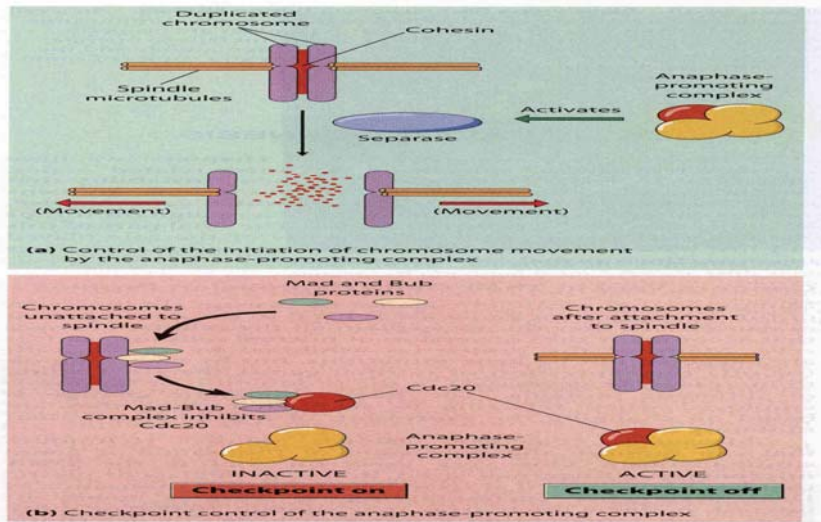


### Distribution of Chromosomes During Mitosis

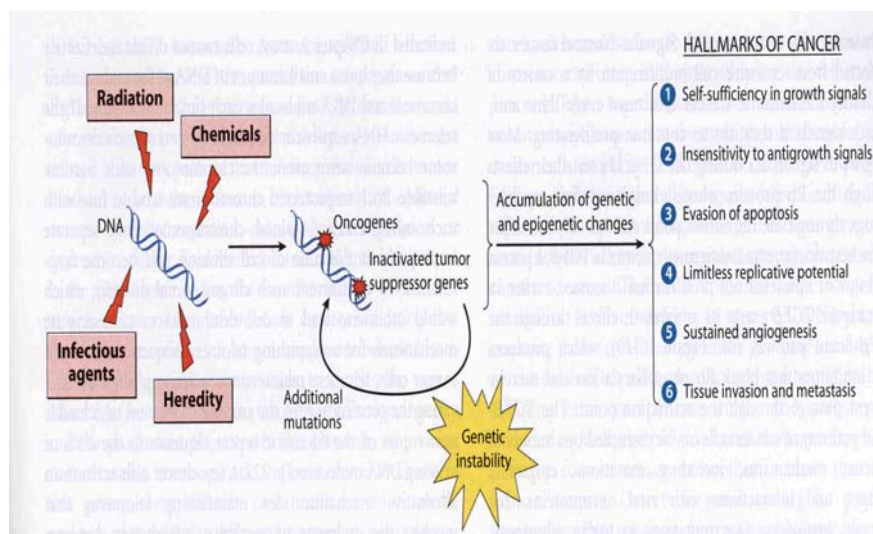
Spindle checkpoint restrains movements of chromosomes till they are attached to microtubules to protect the cells from aneuploidy



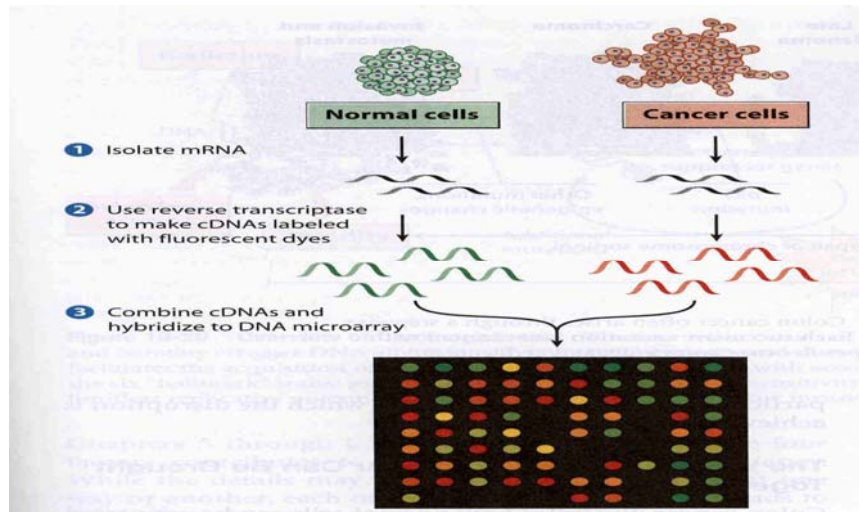
## The Anaphase-Promoting Complex and the Spindle Checkpoint



## Overview of Carcinogenesis



## DNA microarray to compare gene expression profiles in normal and cancer cells



**Stepwise model for the development of colon cancer which often arises by a series of stepwise mutations involving APC, KRAS, Smad 4 and p53 genes. Each mutation is associated with increasingly abnormal cell behavior**

