Lecture 12:
Cancer: a cellular perspective

Dr. Diala Abu-Hassan, DDS, PhD

School of Medicine

Dr.abuhassand@gmail.com

Principles of Genetics and Molecular Biology

What is cancer?

- A tumor is any abnormal proliferation of cells.
  - A benign tumor is confined to its original location.
  - A malignant tumor (cancer) is capable of both invading surrounding normal tissue and spreading throughout the body via the circulatory or lymphatic systems (metastasis).

How does cancer develop?

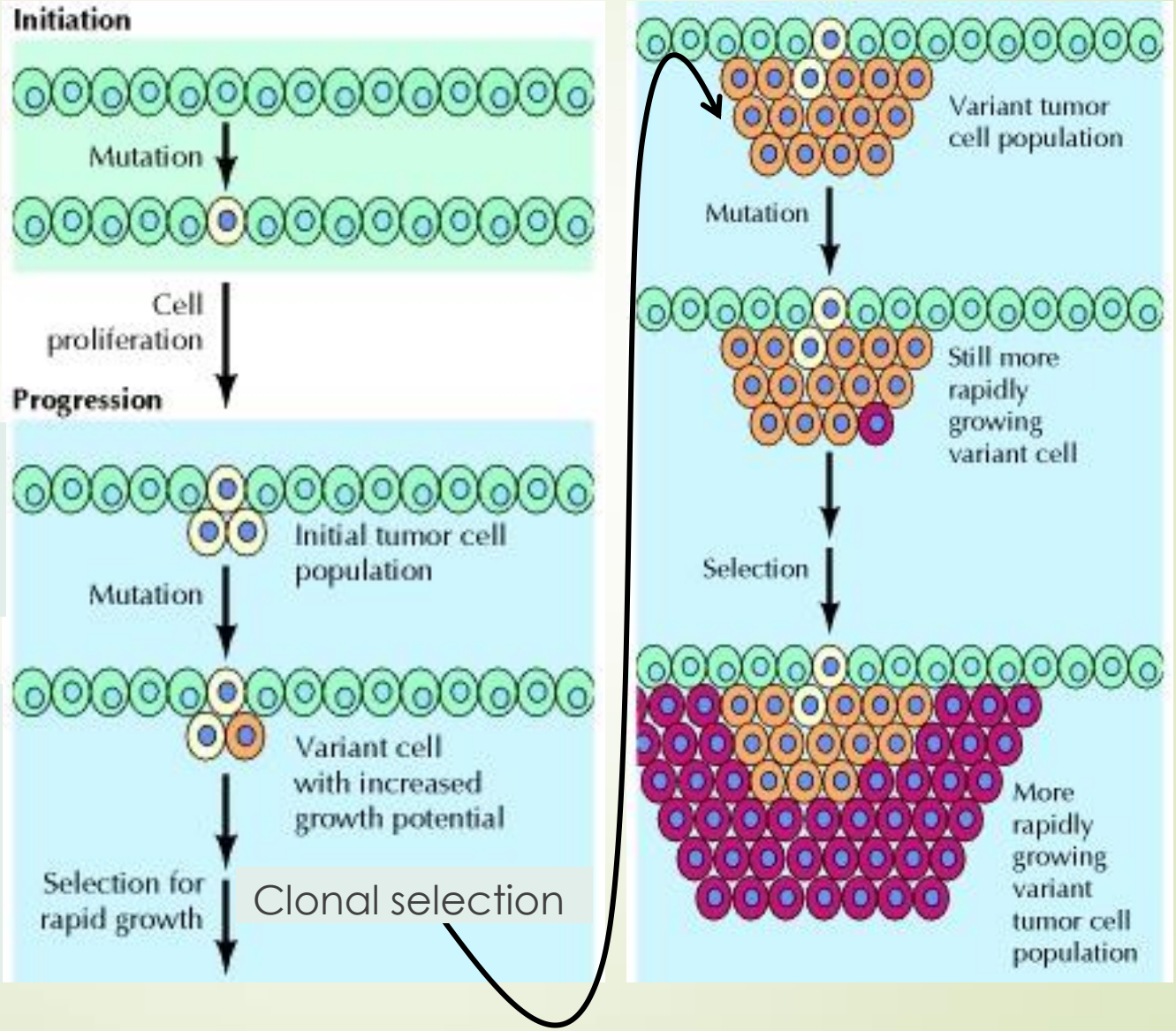
- It develops from a multistep process involving mutation with progressively increasing capacity for proliferation, survival, invasion, and metastasis.

Tumorigenesis is a multistep process

A genetic alteration leading to abnormal proliferation of a single cell.

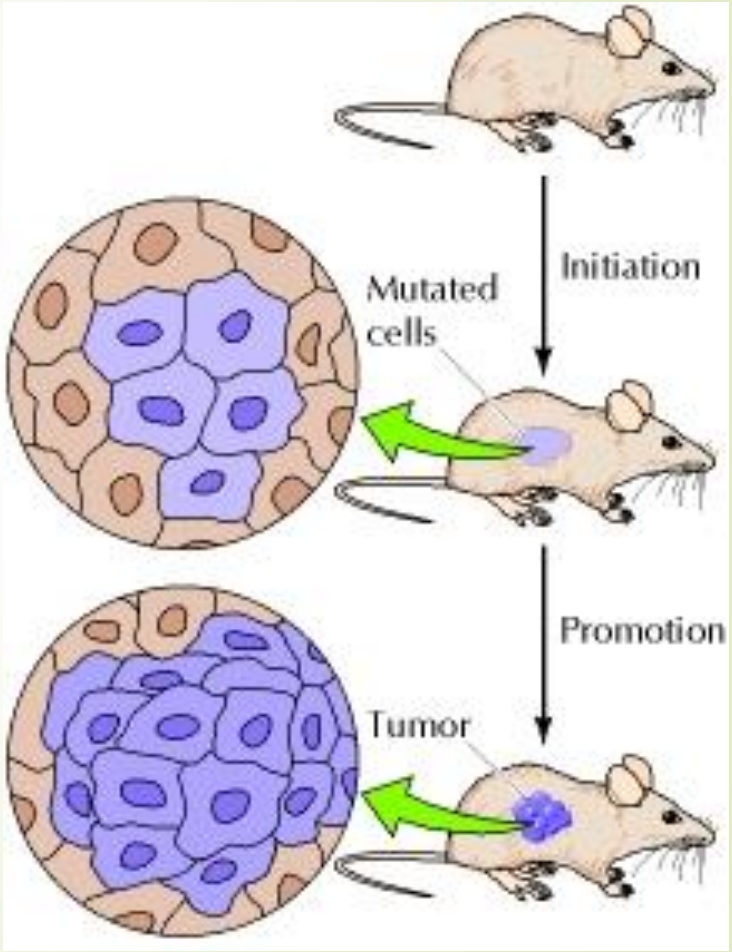
Accumulation of mutations within cells of the tumor population.

Some of these mutations confer a selective advantage to the cell, such as more rapid growth.



Environmental cause of cancer

- Carcinogens (substances that cause cancer) are of two types:
- Initiators: induce genetic mutations
  - Radiation, viral, and chemical carcinogens (chemicals in tobacco smoke and aflatoxin)
- Promoters: stimulate cell proliferation
  - The phorbol esters stimulate cell proliferation by activating protein kinase C.
  - Hormones (estrogens) increase risk of female cancers.
  - Pathogens such as, viruses, bacteria (*Helicobacter pylori*)



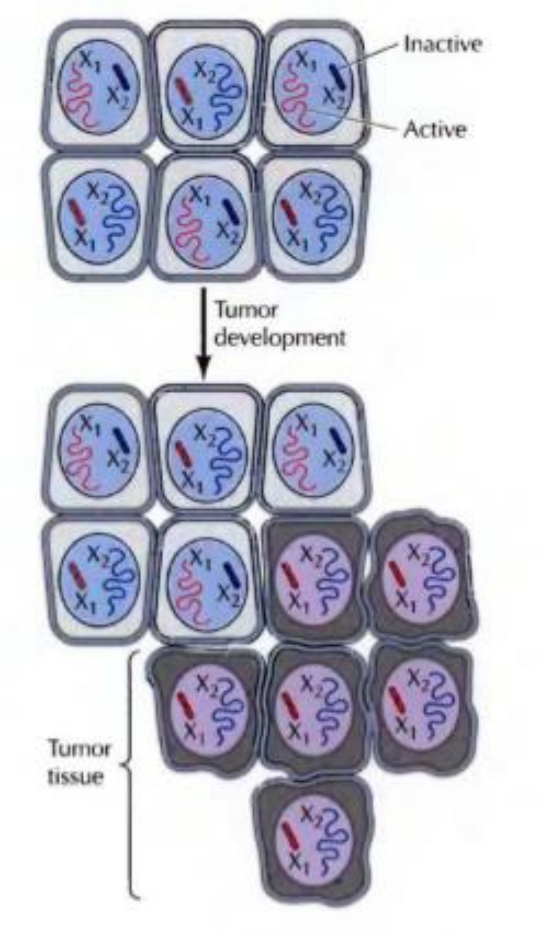
Tumor viruses

TABLE 18.2 Tumor Viruses

Virus family	Human tumors	Genome size (kb)
DNA Genomes		
Hepatitis B viruses	Liver cancer	3
SV40 and polyomavirus	None	5
Papillomaviruses	Cervical carcinoma	8
Adenoviruses	None	35
Herpesviruses	Burkitt's lymphoma, nasopharyngeal carcinoma, Kaposi's sarcoma	100–200
RNA Genomes		
Hepatitis C virus	Liver cancer	10
Retroviruses	Adult T-cell leukemia	9–10

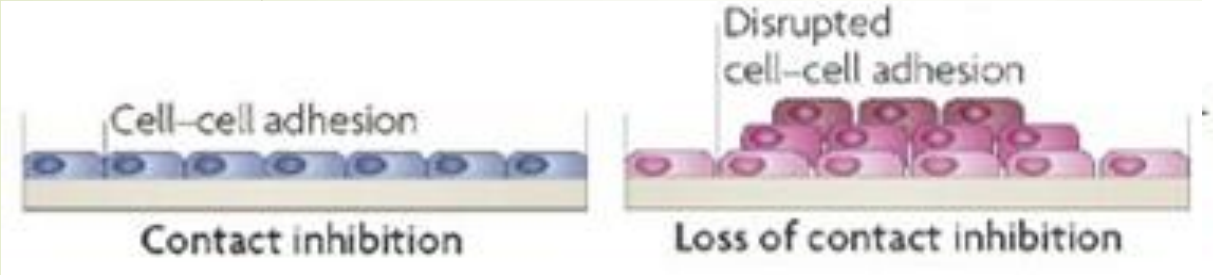
Features of cancer (1)

- Clonality is the development of tumors from single cells that begin to proliferate abnormally.
- Accumulation of genetic mutations
- Uncontrolled proliferation (telomerase)
- Reduced cell-cell contact and cell-matrix adhesion (metastasis)
- Autocrine growth stimulation

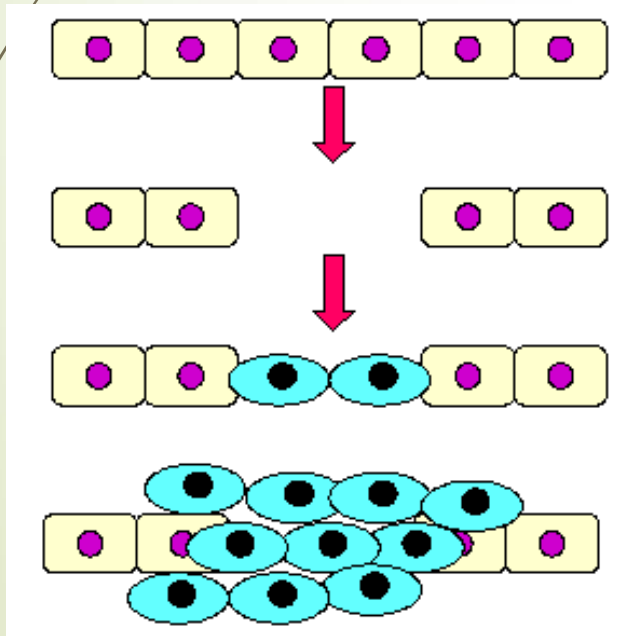


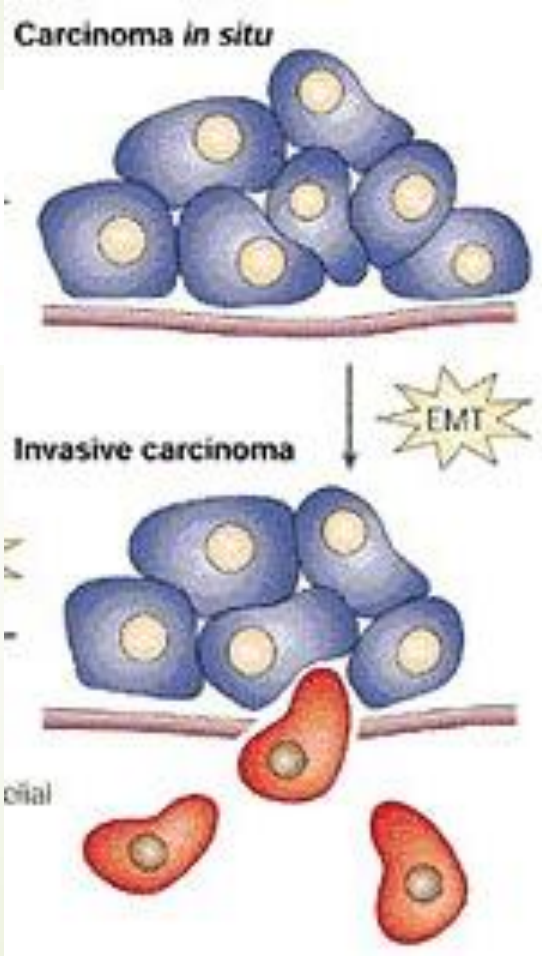
Features of cancer (2)

- Contact inhibition



- Density-dependent inhibition

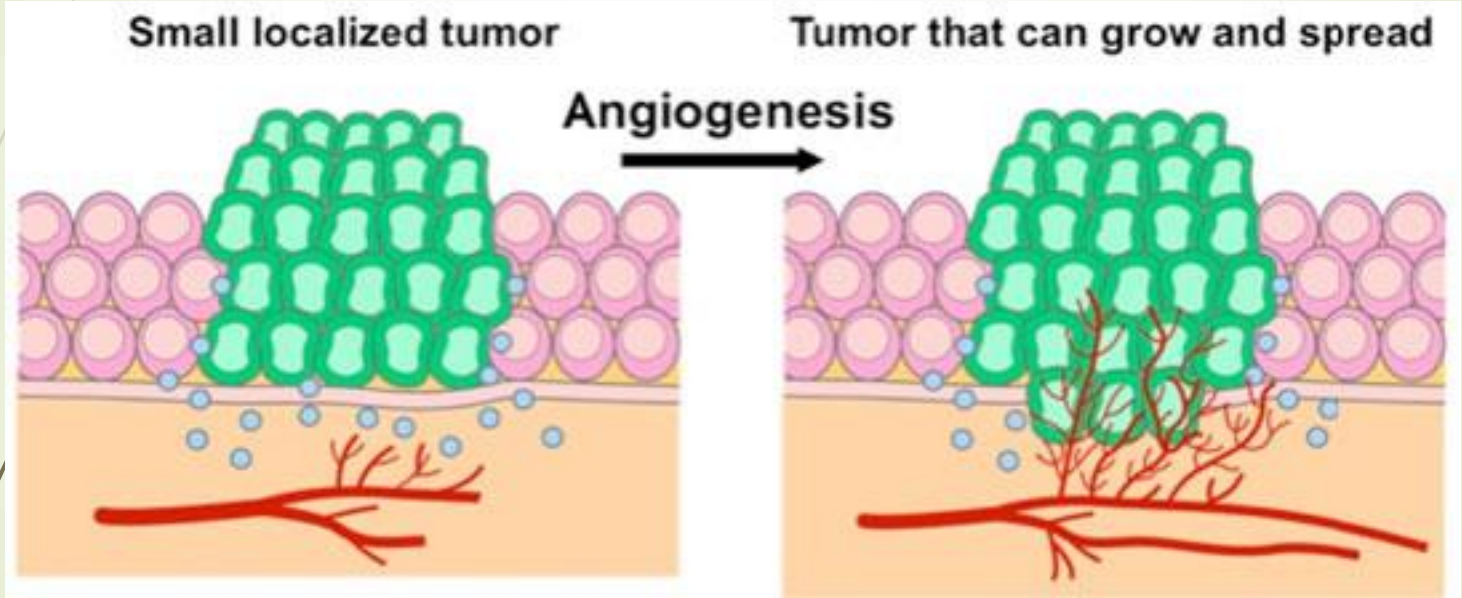




Invasiveness and extracellular proteolysis

Features of cancer (3)

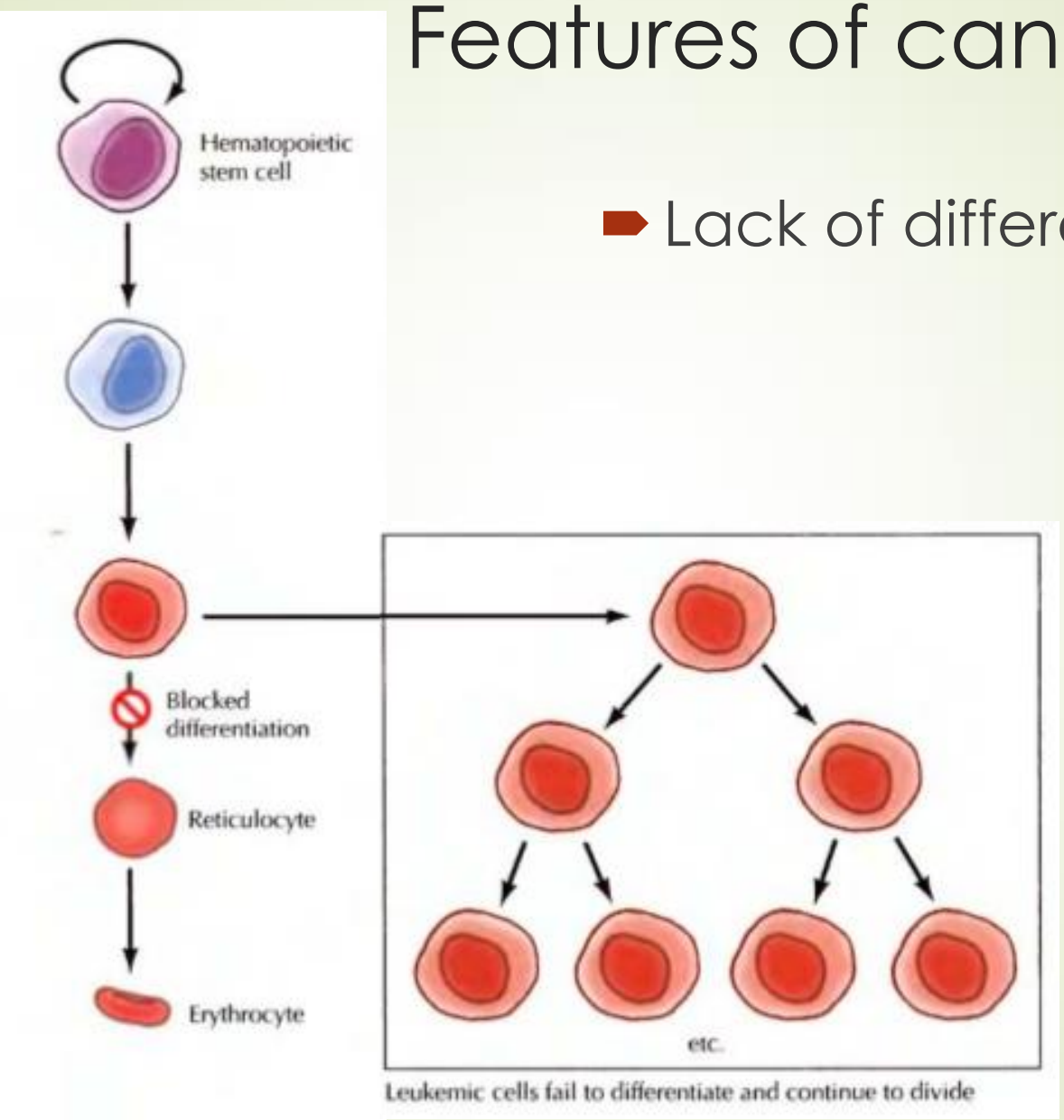
- Angiogenesis (tumor growth and metastasis)



- Loss of apoptotic capability (resistance to therapy)
- Cessation of senescence

Features of cancer (4)

- Lack of differentiation



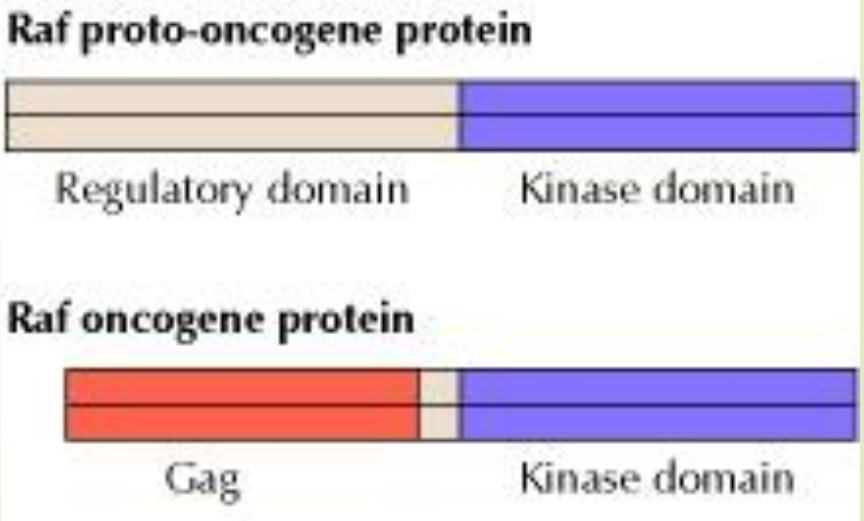
Oncogenes and tumor suppressor genes

Oncogene

- A gene capable of inducing one or more characteristics of cancer cells when activated.
- *A proto-oncogene: a normal cell gene that can be converted into an oncogene.*

Tumor suppressor gene

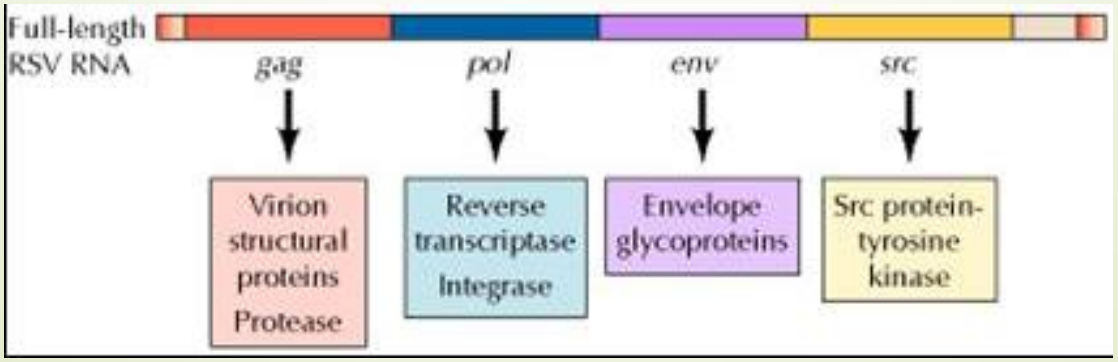
- A gene whose inactivation leads to tumor development.



Viral oncogenes

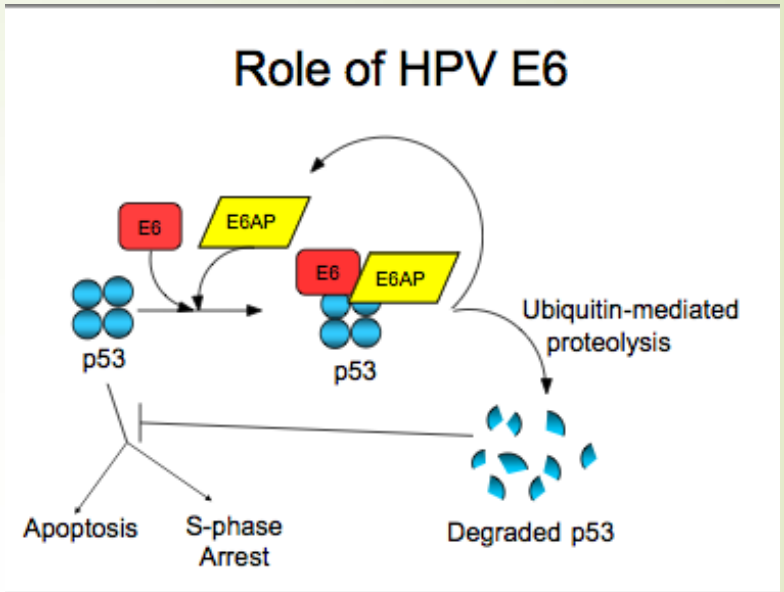
Oncogene	Virus
abl	Abelson leukemia
akt	AKT8 virus
erbA	Avian erythroblastosis-ES4
erbB	Avian erythroblastosis-ES4
raf	3611 murine sarcoma
rasH	Harvey sarcoma
rasK	Kirsten sarcoma
src	Rous sarcoma

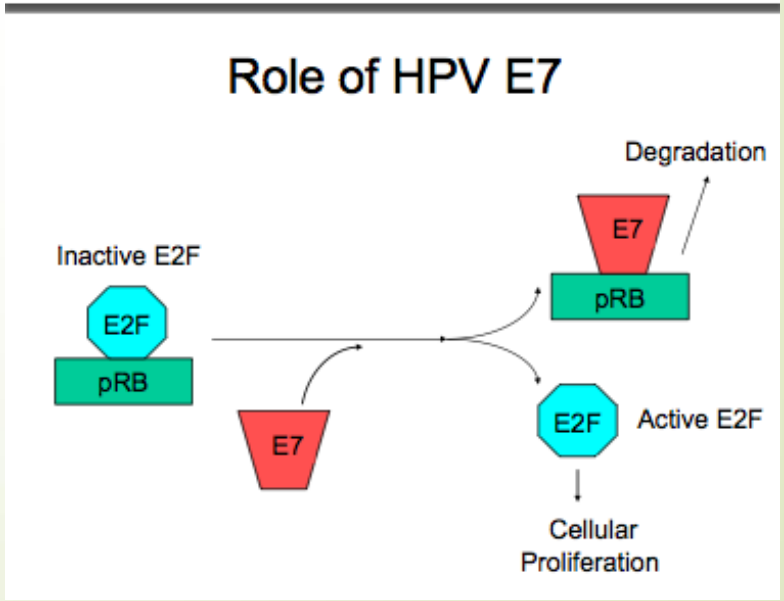
Rous sarcoma virus



A mechanism of viral carcinogenesis

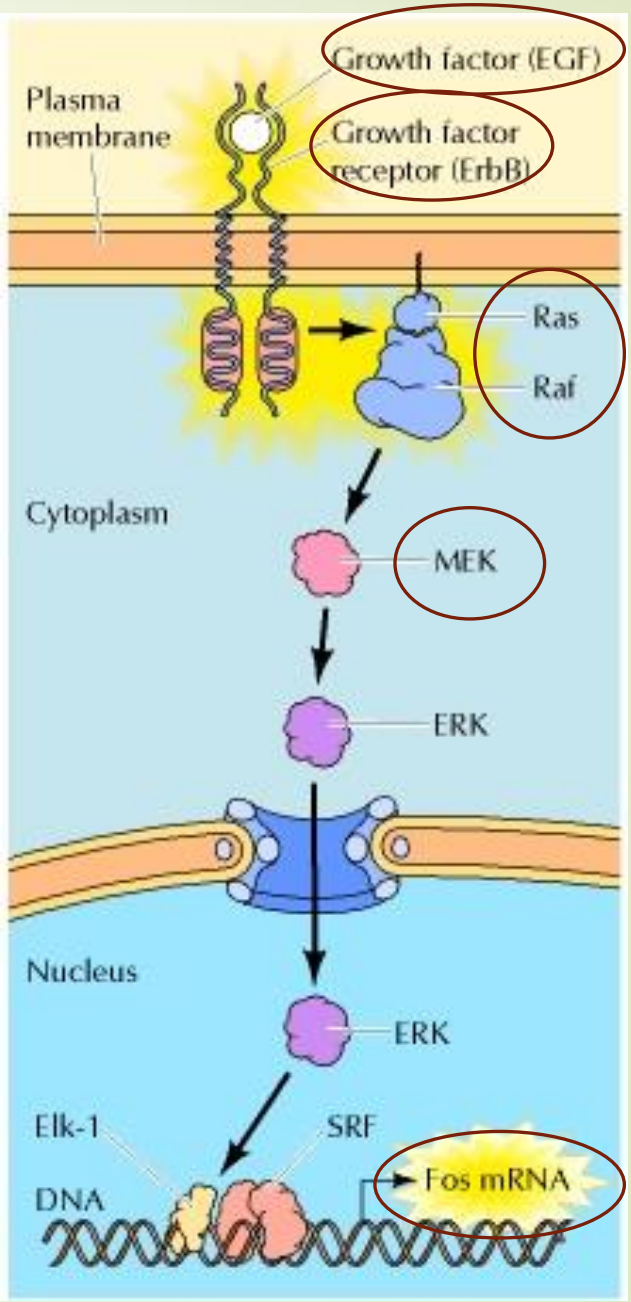
- The E6 and E7 proteins of the human papillomavirus (HPV) block the function of the cellular Rb and p53 proteins.
- In particular, E7 binds to Rb, and E6 stimulates the degradation of p53 by proteolysis.



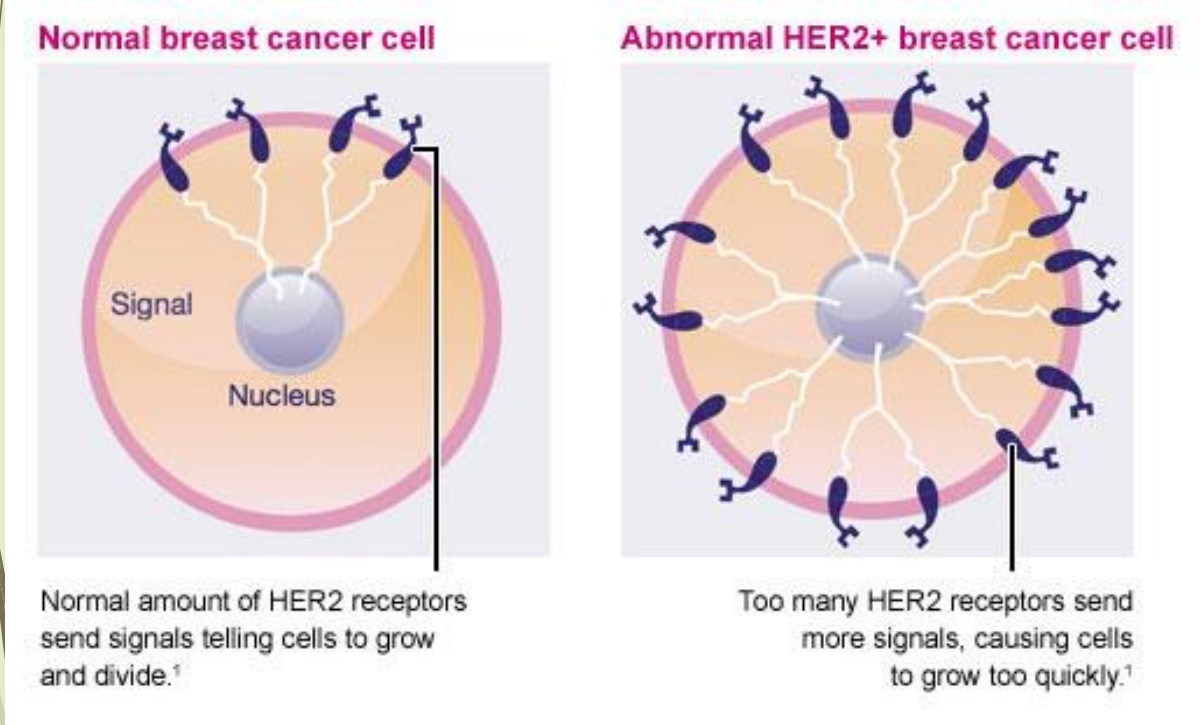


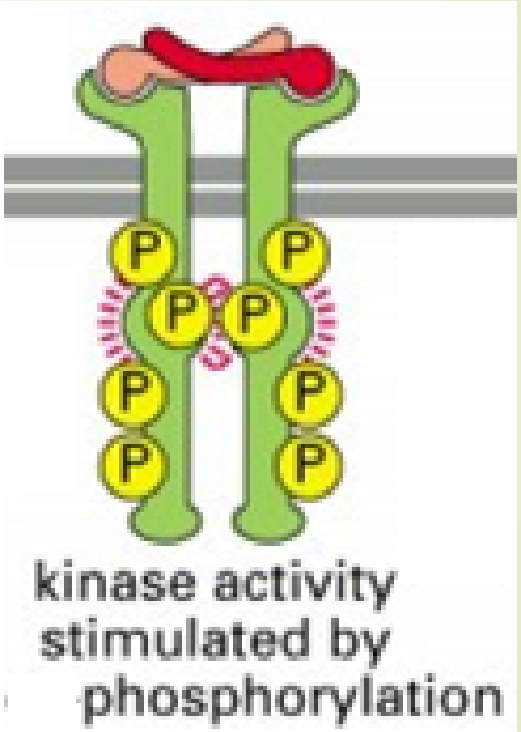
Oncogenes and signal transduction

- Oncogene proteins act as:
  - Growth factors (e.g., EGF)
  - Growth factor receptors (e.g., ErbB)
  - Intracellular signaling molecules (Ras and Raf)
  - Transcription factors (e.g., *fos*)



Oncogenes and receptors

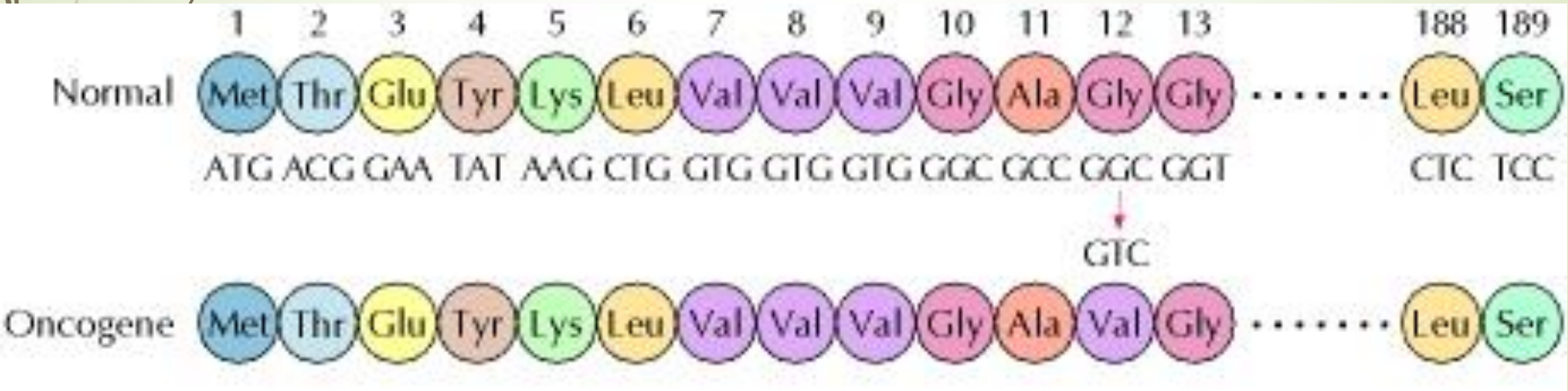




- PDGFR fusion to Tel transcription factor result in constitutively active kinase domain.

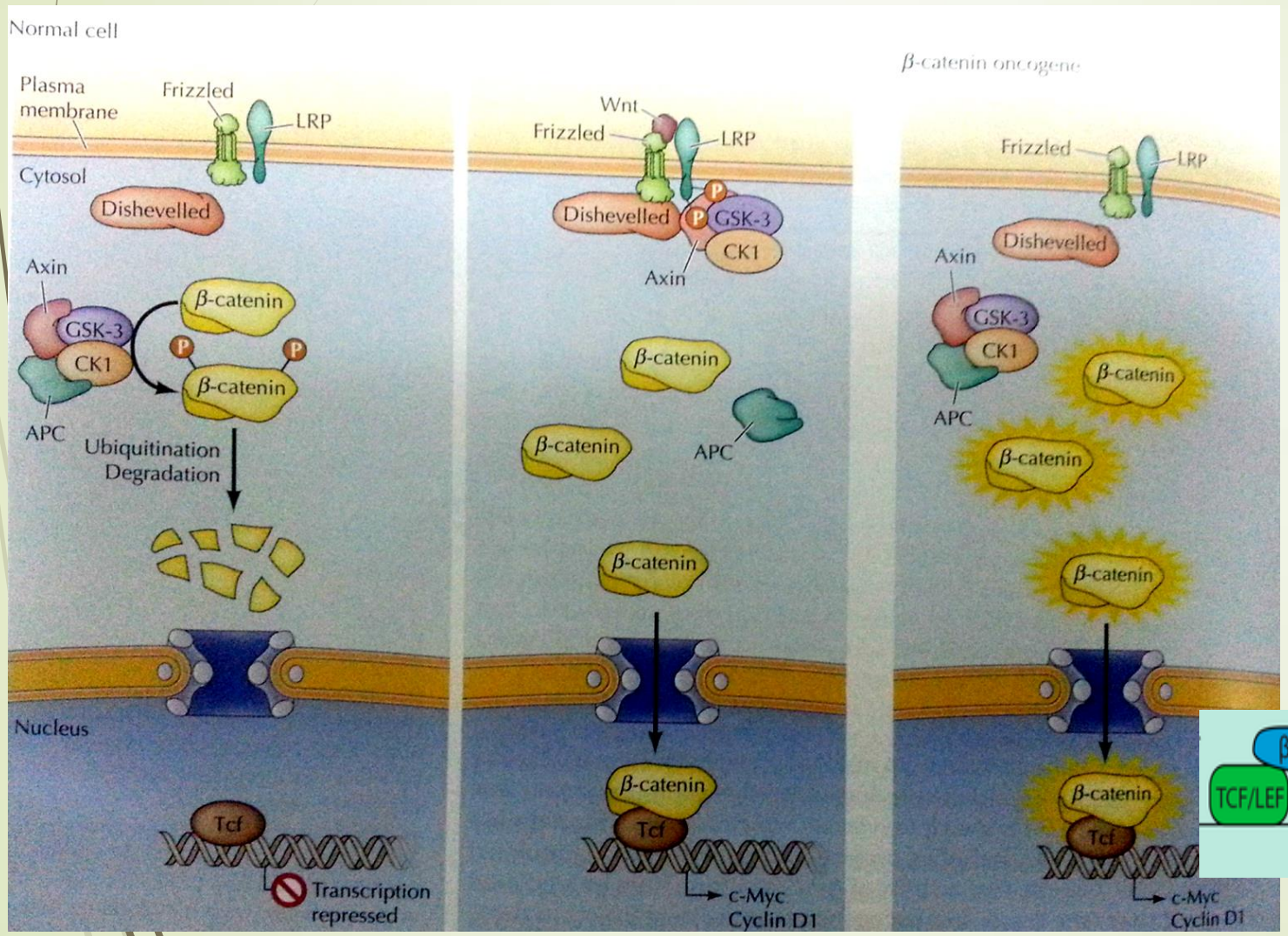
Oncogenes and transducers

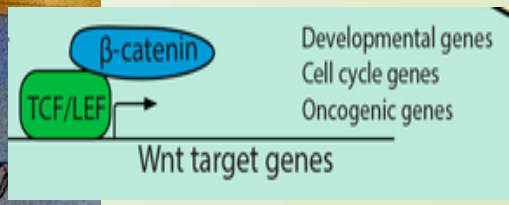
- A single nucleotide change, which alters codon 12 from GGC (Gly) to GTC (Val), is responsible for the tumorigenic activity of the *ras*H oncogene.
- The mutation maintains the Ras proteins constitutively in the active GTP-bound conformation.



Oncogenes and transcription factors

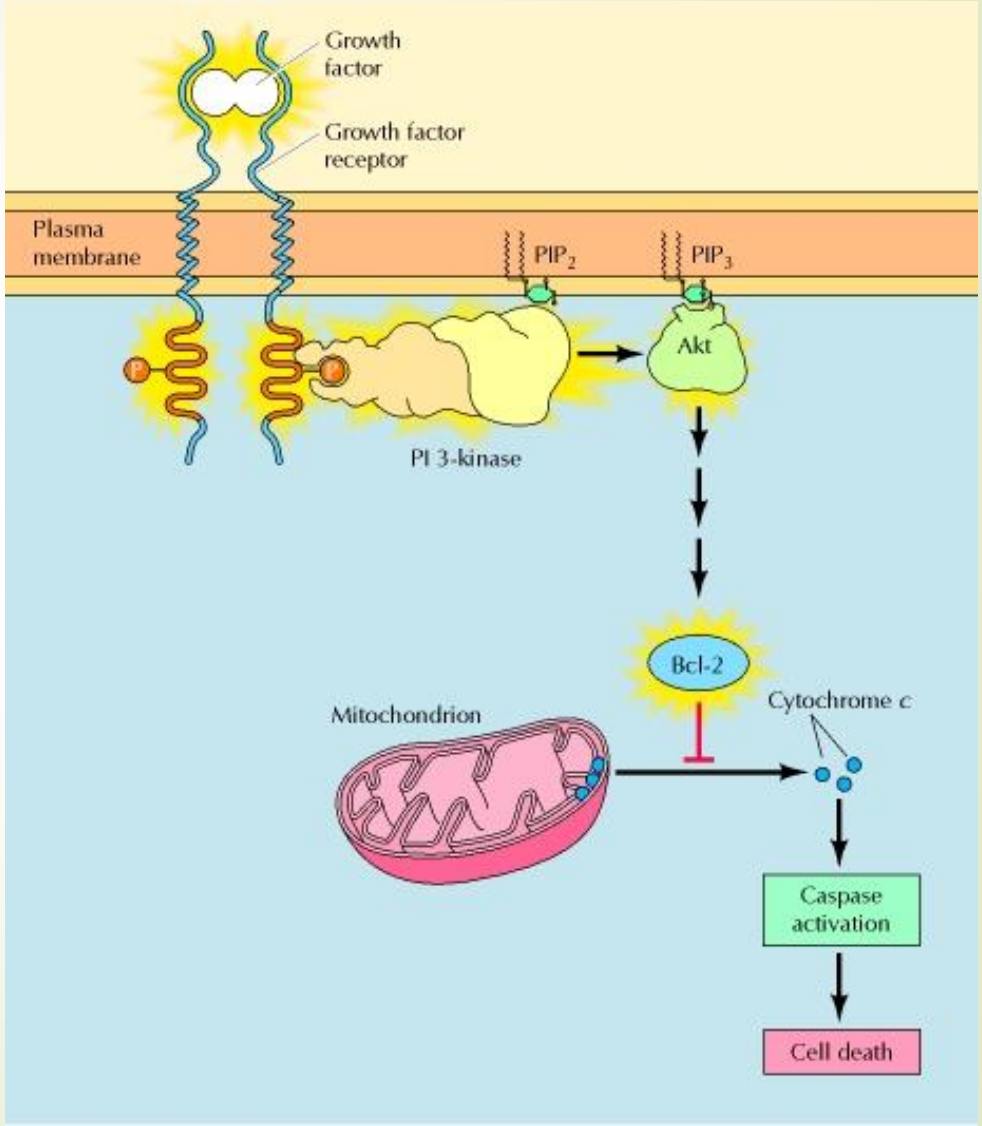
Normal cell **Tumor cell**



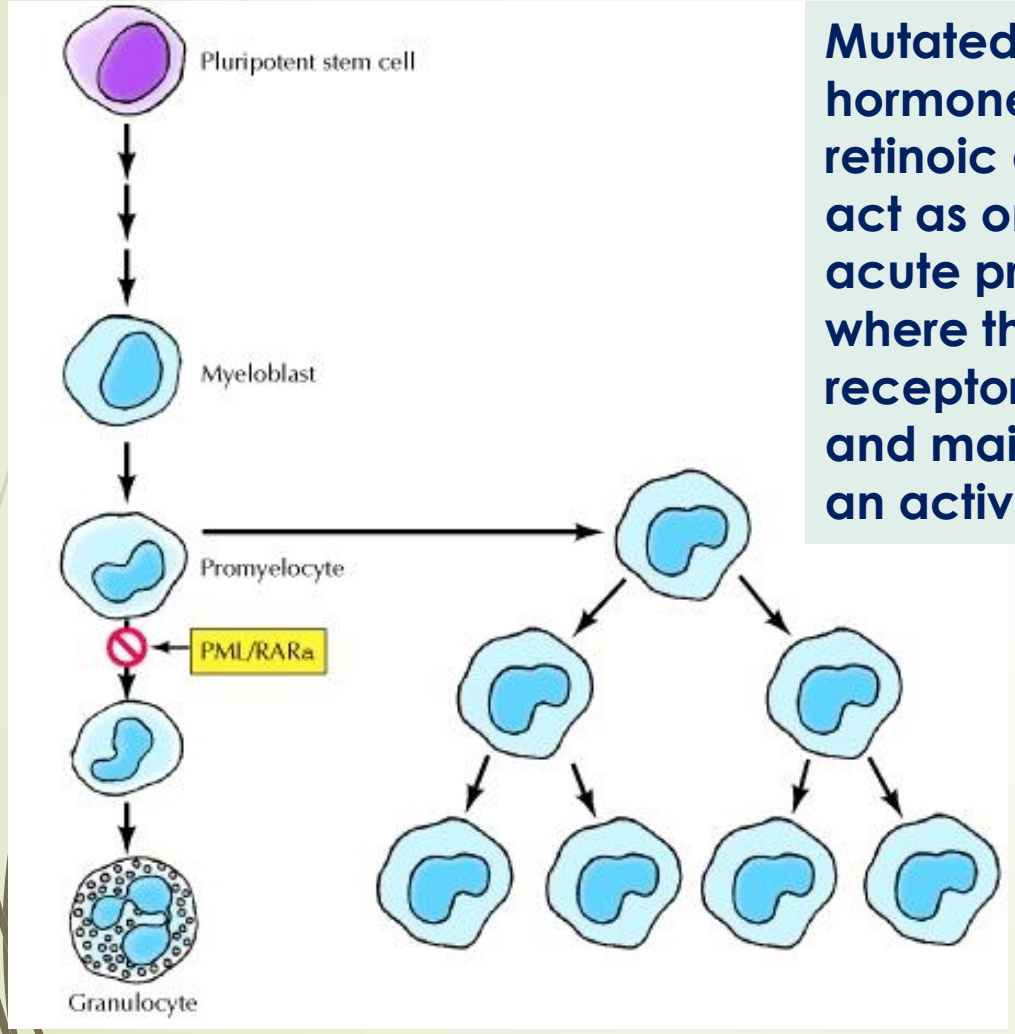


Oncogenes and cell survival

- The Akt pathway involving proto-oncogenes (ligands, receptors, PI-3 kinase, and AKT) promotes cell survival by inhibiting pro-apoptotic proteins and inducing anti-apoptotic proteins.



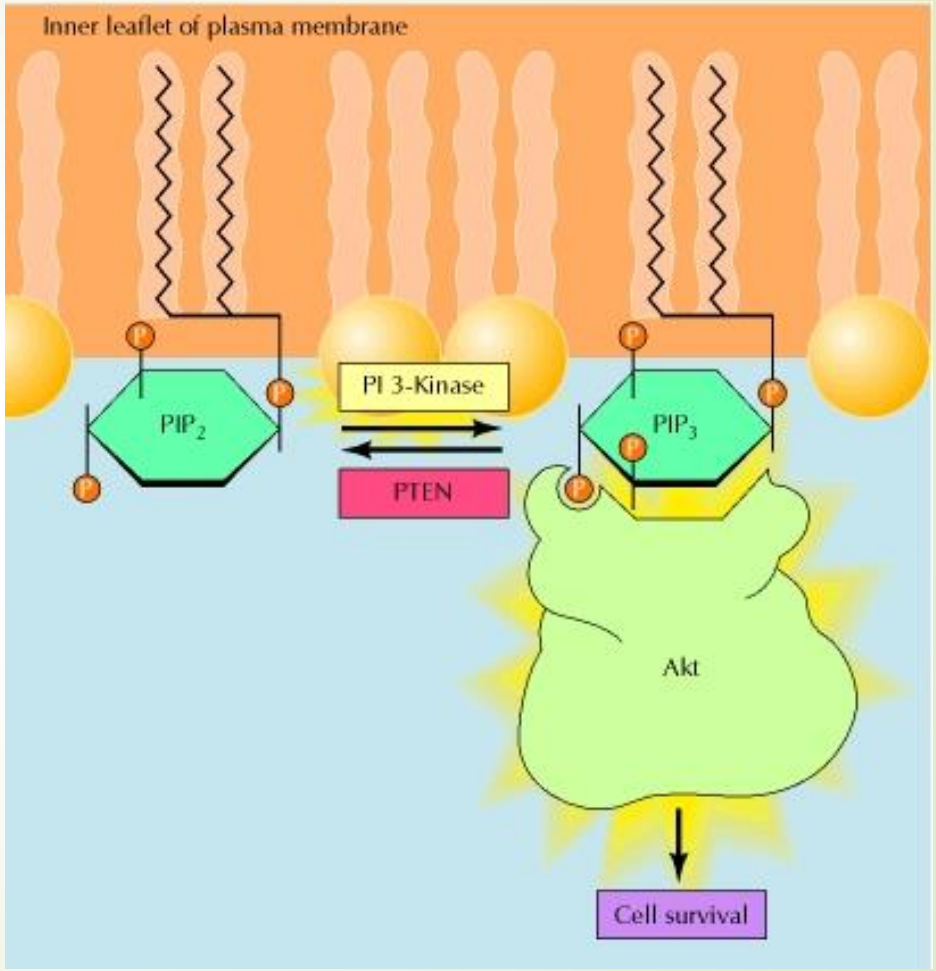
Oncogenes and cell differentiation



Mutated forms of both the thyroid hormone receptor (ErbA) and the retinoic acid receptor (PML/RARa) act as oncogene proteins in human acute promyelocytic leukemia where the mutated oncogene receptors block cell differentiation and maintain the leukemic cells in an actively proliferating state.

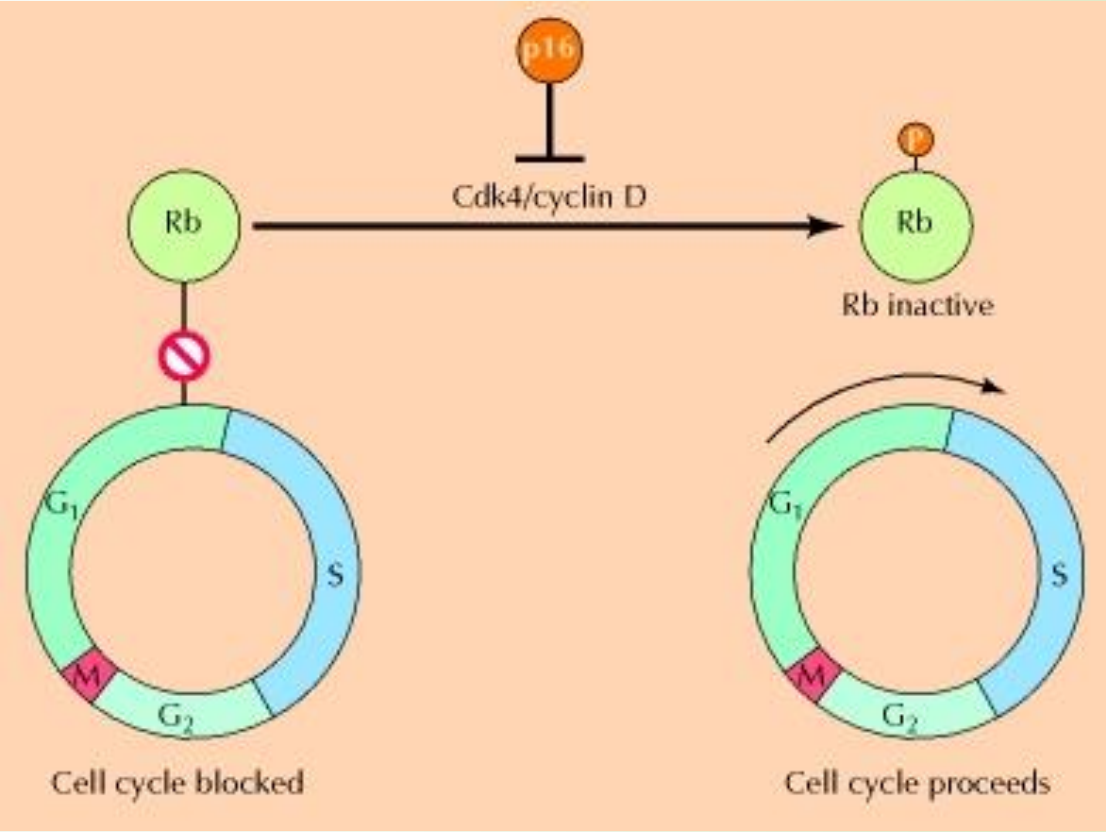
TSG and proliferation and survival

- The tumor suppressor protein PTEN is a lipid phosphatase that dephosphorylates PIP_3 into PIP_2.
- It counters the action of the oncogenes PI 3-kinase and Akt, which promote cell survival.



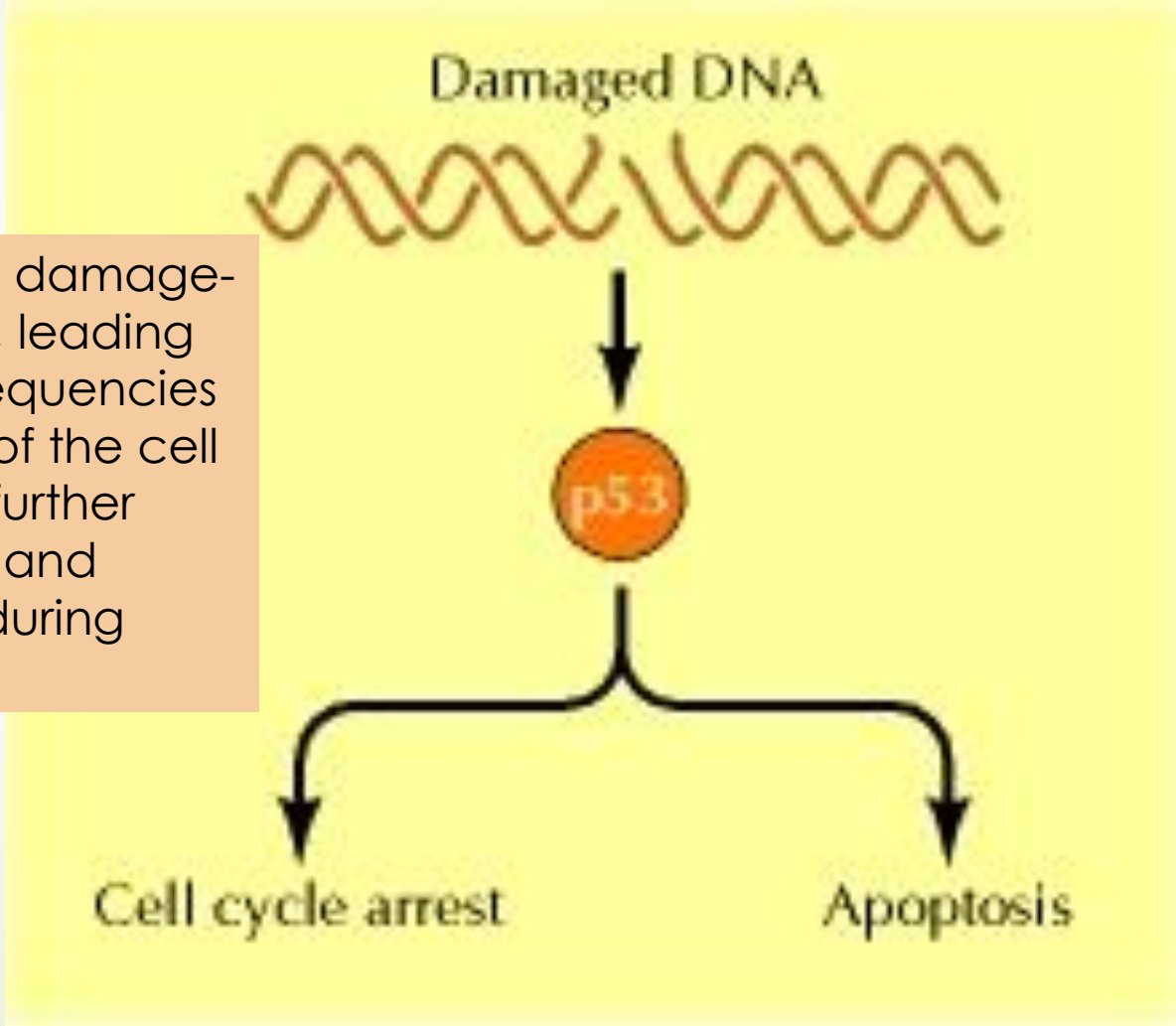
TSG and cell cycle

- Rb inhibits progression past the restriction point in G_1.
- Cdk4/cyclin D complexes promote passage through the restriction point by phosphorylating and inactivating Rb.
- Inactivation of Rb results in increased cell cycle progression and tumor formation.



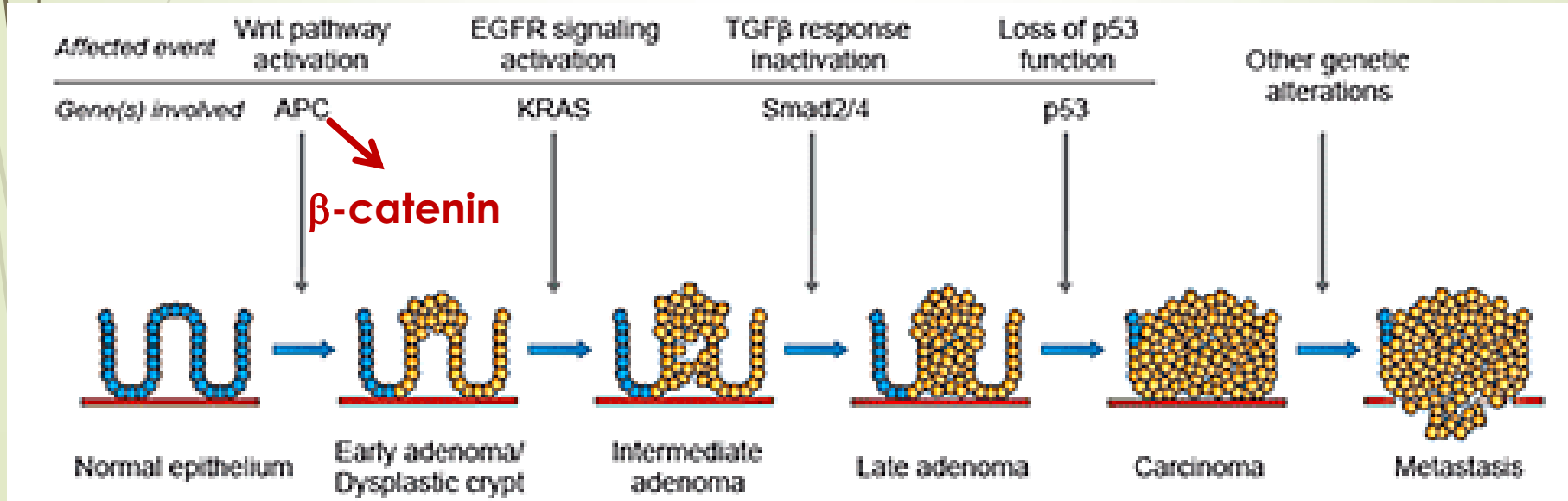
Role of p53

Loss of p53 prevents DNA damage-induced cell cycle arrest, leading to increased mutation frequencies and a general instability of the cell genome contributing to further alterations in oncogenes and tumor suppressor genes during tumor progression.



The multistep genetic model for the formation of colorectal cancer

- Inactivation of TSGs and the activation of oncogenes leading to dyfunctional pathways.
- Accumulation of mutations in a sequential manner, with mutations of some genes preceding that of others.



Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990.