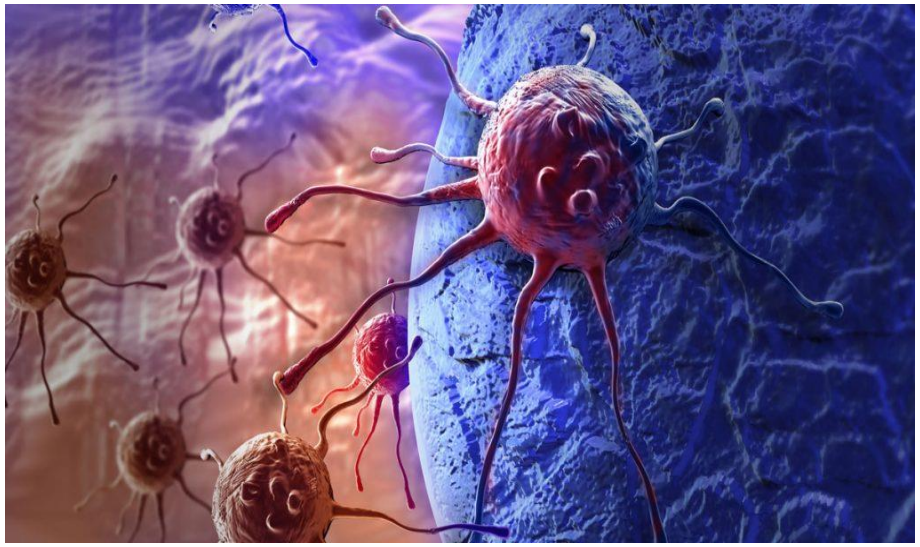
Molecular Basis of Cancer

Oncogenetics:

(Oncogenes, Tumour Suppressor Genes)



By : Dr/ Aya El-Hanafy

Associate Professor of biochemistry & Molecular Biology

Learning Outcomes

1. Discuss carcinogenesis mechanism & related genes.
2. Recognize different oncogenes types with examples.
3. Recognize different tumor suppressor genes with examples.
4. Discuss importance of tumor suppressor genes.
5. Correlate different tumors with abnormalities in different oncogenes & tumor suppressor genes.

Case Scenario II

A 58-year-old male presents to the dental clinic with:

A **non-healing ulcer** on the lateral border of the tongue for 1 month, mild pain and occasional bleeding,Difficulty in chewing

History:

Heavy smoker (30 years)

Occasional alcohol use

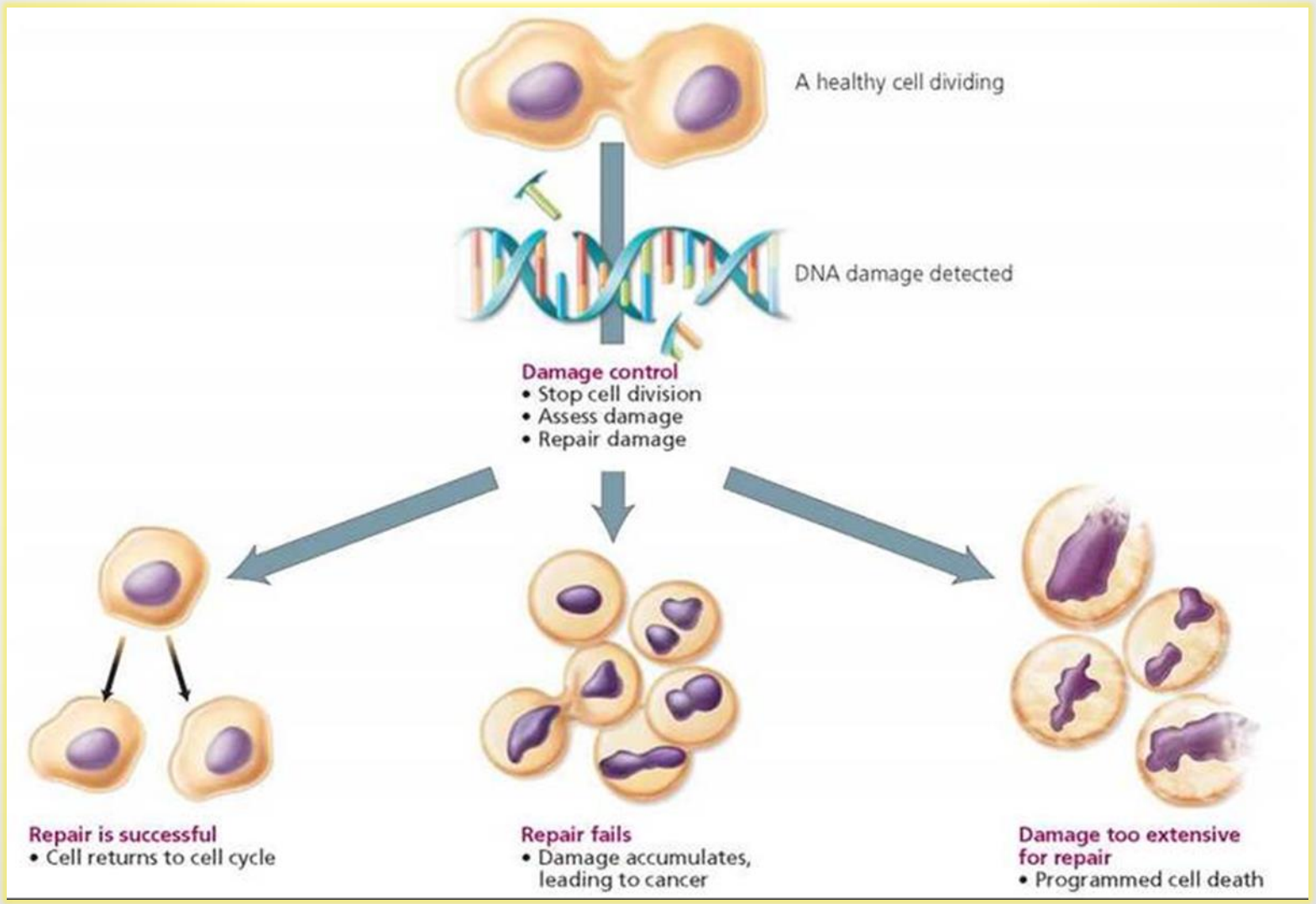
Clinical Examination:

Indurated ulcer with raised margins with obvious lymph node enlargement

- **What is the most likely diagnosis?**
- **Mention two genetic changes commonly associated with OSCC**
- **What is the role of TP53 in normal cells? What happens when TP53 is mutated?**
- **What is the dentist's role in managing such cases?**

Carcinogenesis mechanism & related genes.

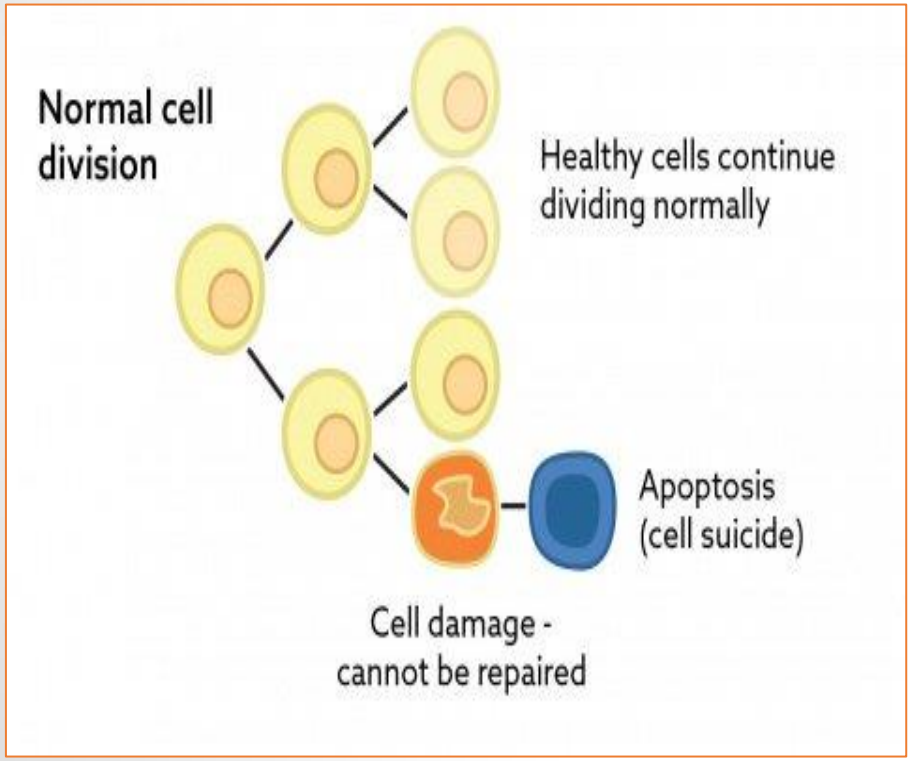
Introduction: Normal cell division

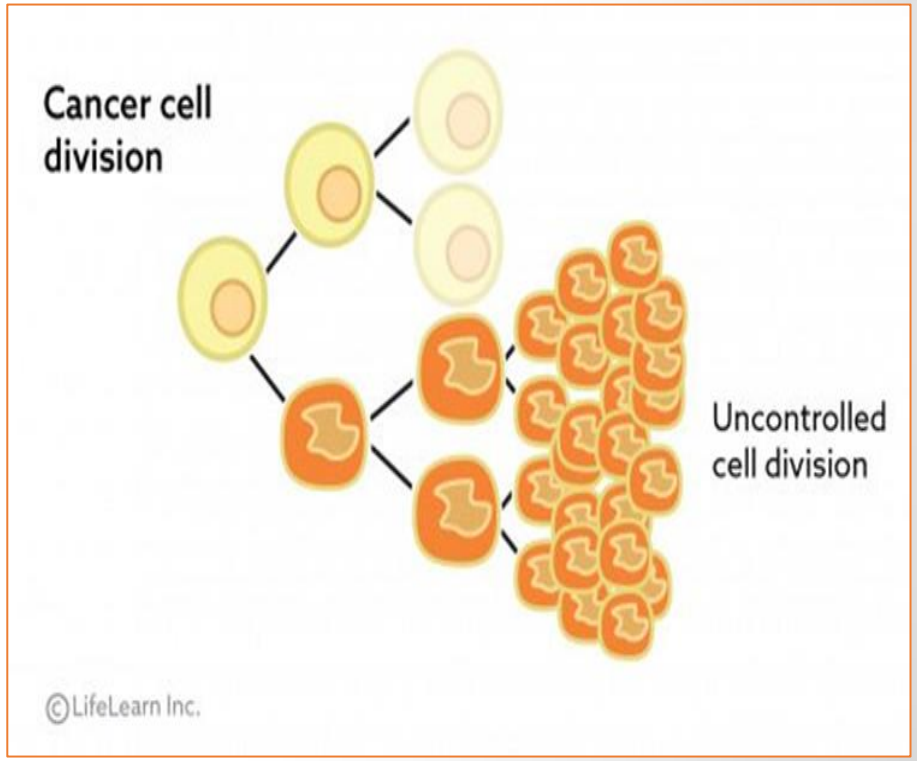


Steps in controlling DNA damage during the cell cycle

Definition of cancer

- **Abnormal and Uncontrolled** cell growth and proliferation.
- Cancer cell can invade the surrounding & metastasize to distant tissues.



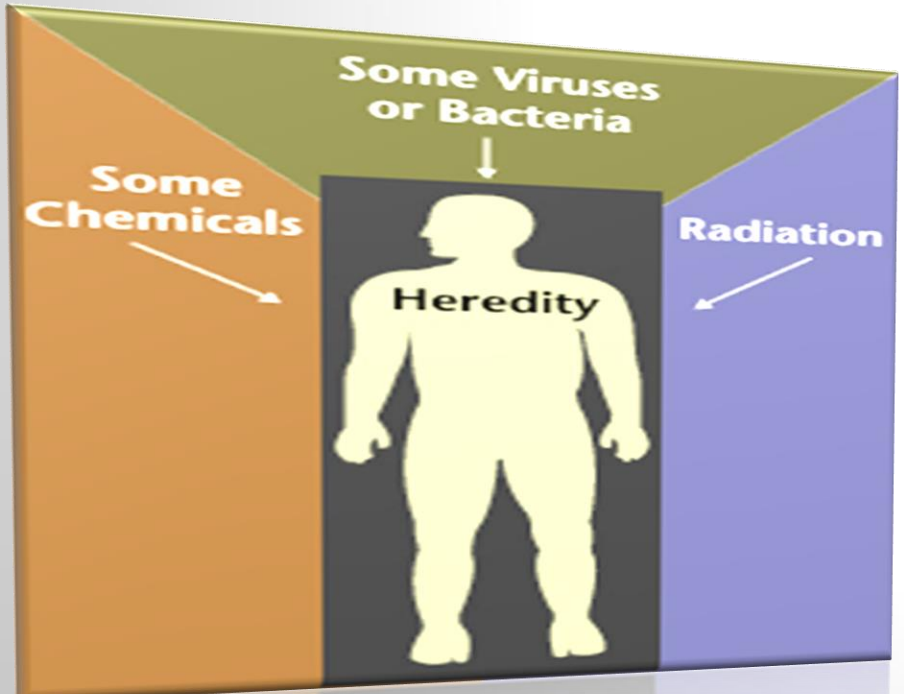


While normal cells will stop dividing if there is a mutation in the DNA, cancer cells will continue to divide with mutation.

Etiology of cancer

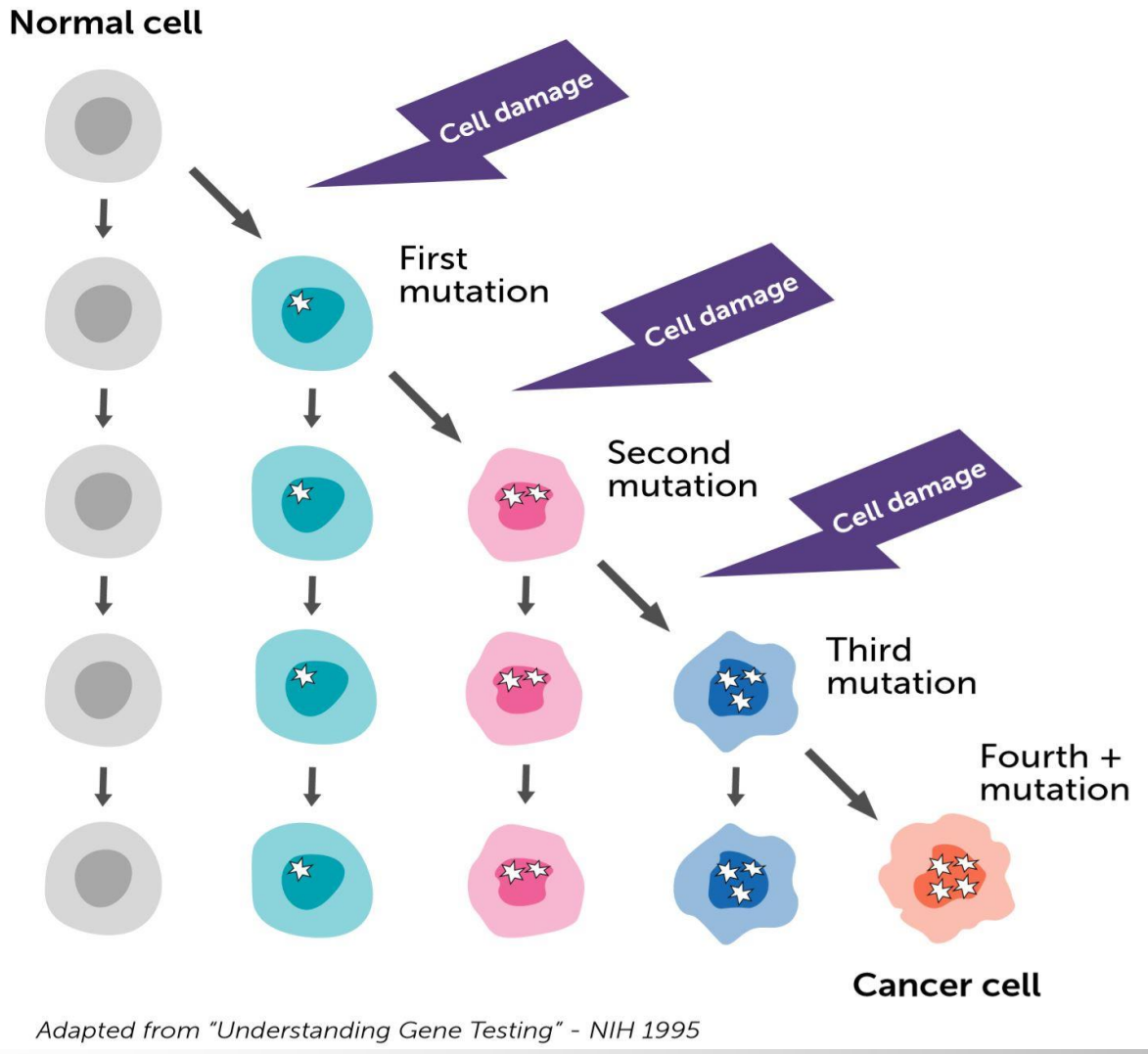
- **Genetic damage (mutation)/(changes in DNA structure)** is the initiating event in carcinogenesis.
- This genetic damage may be: -Inherited (familial)

  -Acquired (environmental factors“chemical, physical, and biological”).



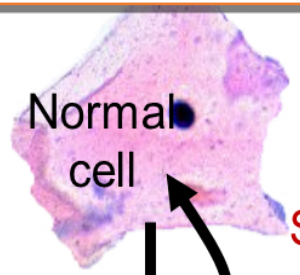
Why cancer is more common in old age?

- Typically, the body corrects most mutations.
- A single mutation will likely not cause cancer.
- Usually, cancer occurs from **multiple mutations over a lifetime**.
  That is why cancer occurs more often in older people (they have had more opportunities for mutations to build up).



Mechanism of carcinogenesis

Environmental agents that damage DNA
- •Chemicals
- •Radiation
- •Viruses



Successful repair

DNA damage

?

Inherited mutations

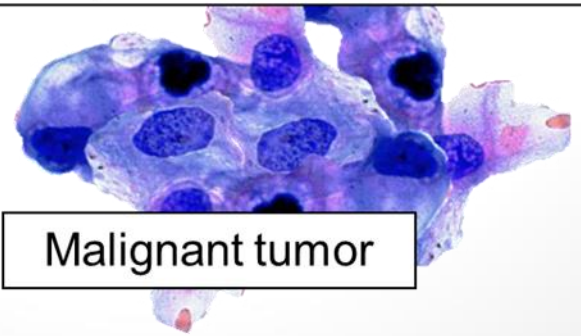
Genes ?

Failed repair

Mutations in somatic cells

Genes ?

Altered gene products (proteins); abnormal structural & regulatory proteins

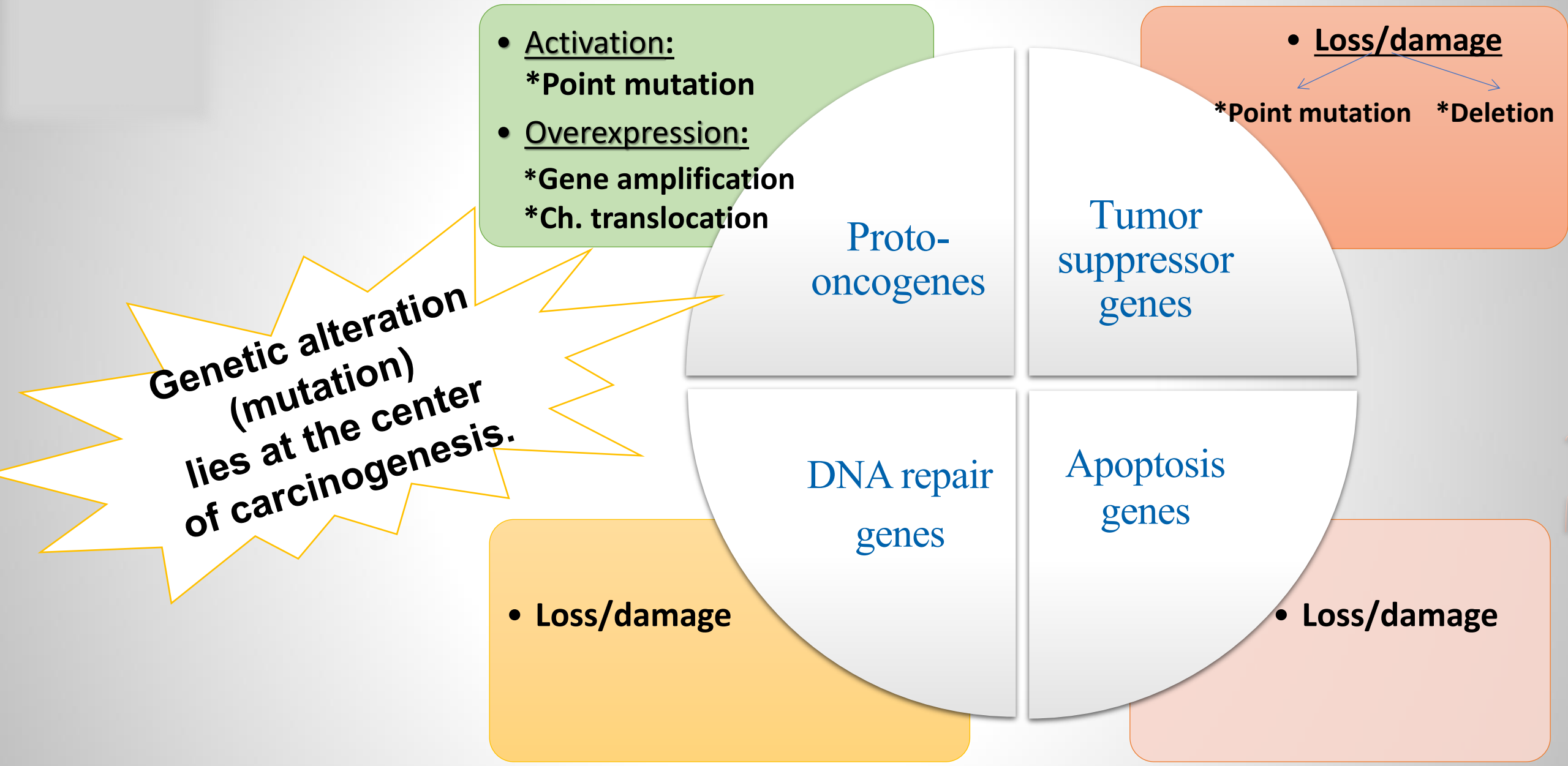


Malignant tumor

What are the genes targeted for genetic damage (carcinogenesis)?

-There are 4 classes of normal regulatory genes (when affected by such genetic damage /mutation, can result in tumor development**):**

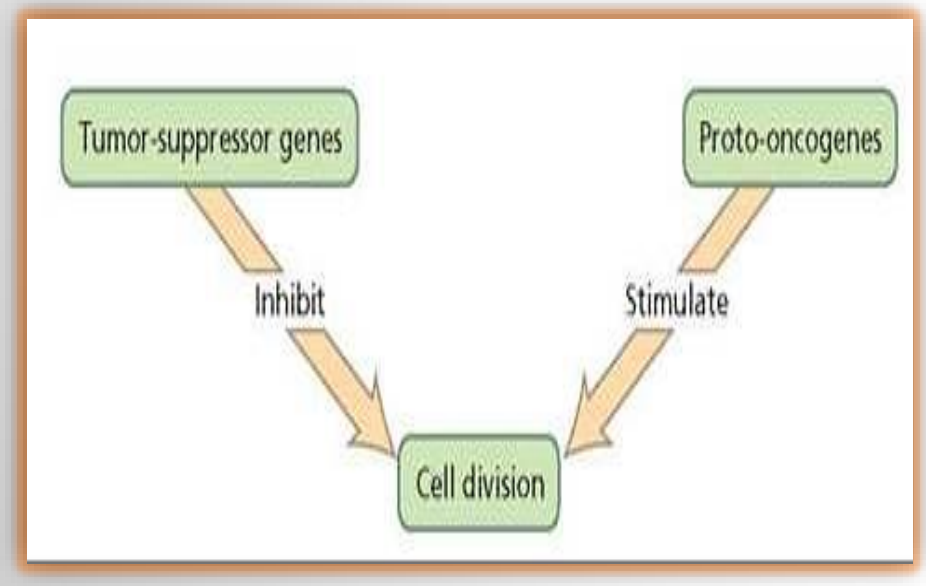
- The growth promoting **"Protoncogenes"**
- The growth inhibitory **"Tumor suppressor genes"**
- **Genes regulating DNA repair**
- **Genes controlling apoptosis**: (Programmed cell death).


• Activation:
*Point mutation
• Overexpression:
*Gene amplification
*Ch. translocation
• Loss/damage
*Point mutation
*Deletion
Genetic alteration (mutation) lies at the center of carcinogenesis.
Proto-oncogenes
Tumor suppressor genes
DNA repair genes
Apoptosis genes
• Loss/damage
• Loss/damage

Genes controlling cell growth/division (proto-oncogenes / Tumor suppressor genes)

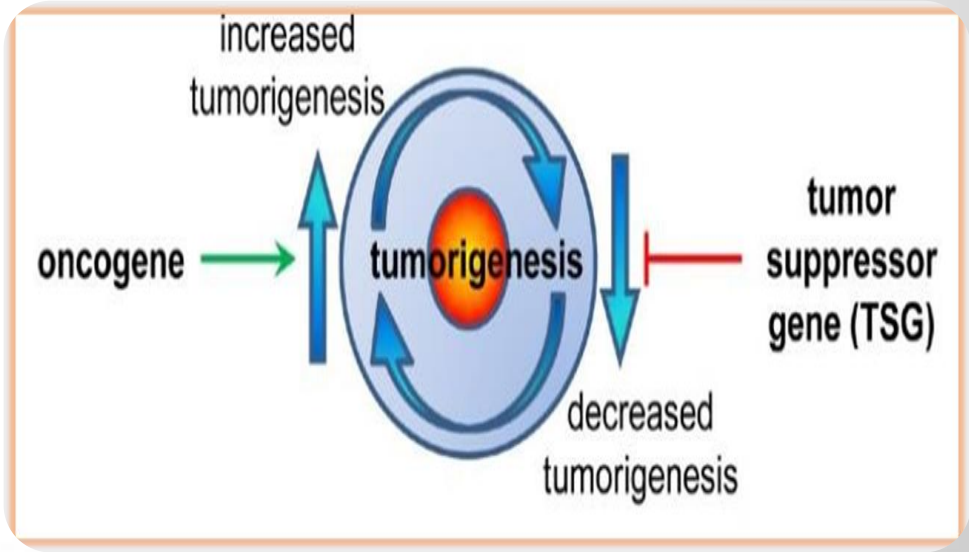
Normal

- Tumor-suppressor genes and proto-oncogenes normally control cell division so that it occurs only when needed



Cancer

- Mutations in these genes (“activated” oncogenes & “inactivated” Tumor suppressor genes) lead to loss of control over cell division and cancer.



Recognize different oncogenes types

Correlate different tumors with abnormalities in different oncogenes.

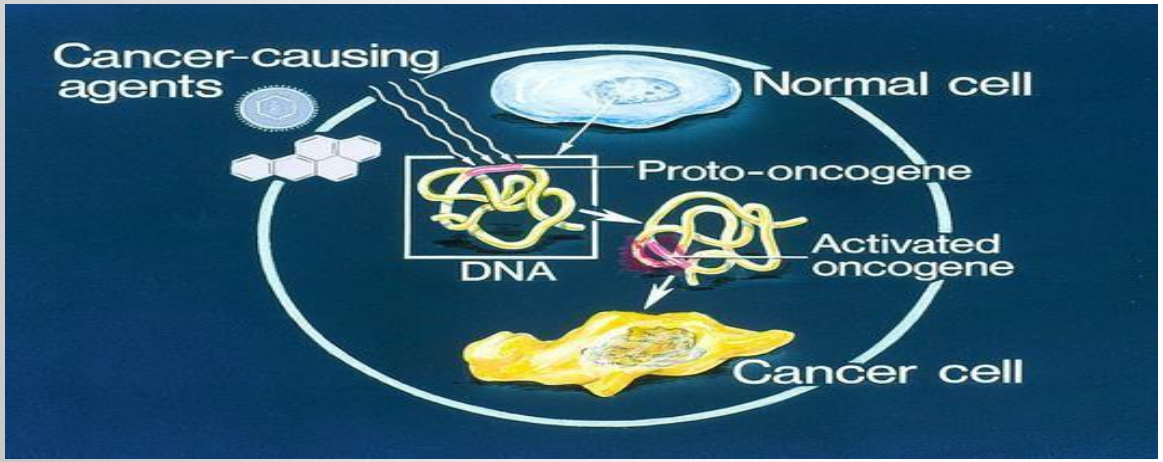
Oncogenes

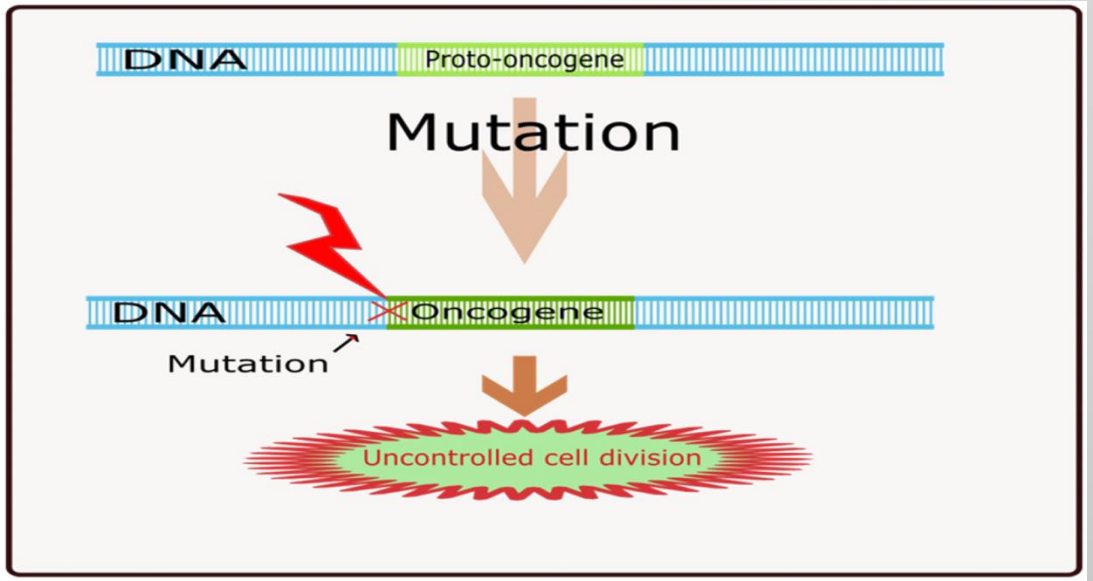
- **Definition:** -These are genes capable of causing cancer.

  -Oncogenes results from mutation of proto-oncogenes.

- **Proto-oncogenes:** are normal cellular genes which encode for proteins responsible for normal cell growth and proliferation.

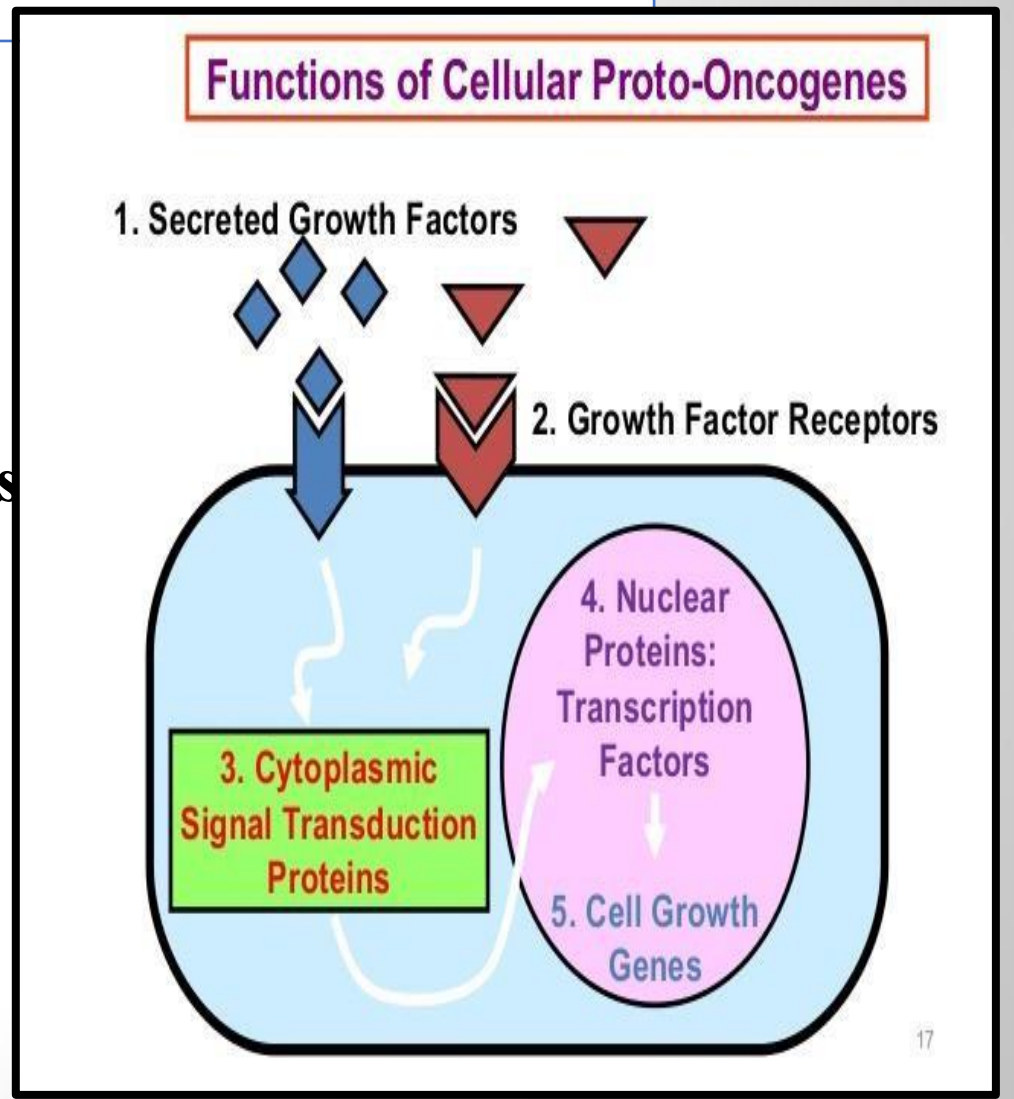
- If mutated or mis-expressed, the **proto-oncogenes** ⇒ **oncogenes** ⇒ **abnormal cell growth**





Five types of proteins encoded by proto-oncogenes participate in control of cell growth:

- **Class I:** Growth Factors
- **Class II:** Receptors for Growth Factors
- **Class III:** Intracellular Signal Transducing proteins
- **Class IV:** Nuclear Transcription Factors
- **Class V:** Cell-Cycle Control Proteins



Methods of Activation of Oncogenes
(proto-oncogene --> oncogene)

1. **Point mutations:** Ra*s* proteins

2. **Chromosomal rearrangements (translocation)** : Philadelphia chromosome.

3. **Gene Amplification:** duplication, multiplication of DNA sequences in the genome.

Methods of Activation of Oncogenes (proto-oncogene --> oncogene)

1. Point mutations

- Ras gene

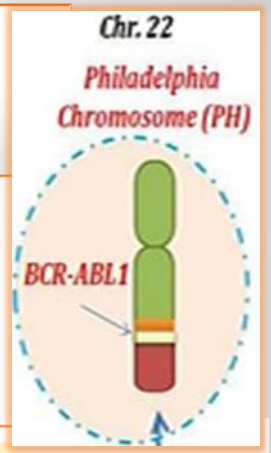
2. Gene Amplification

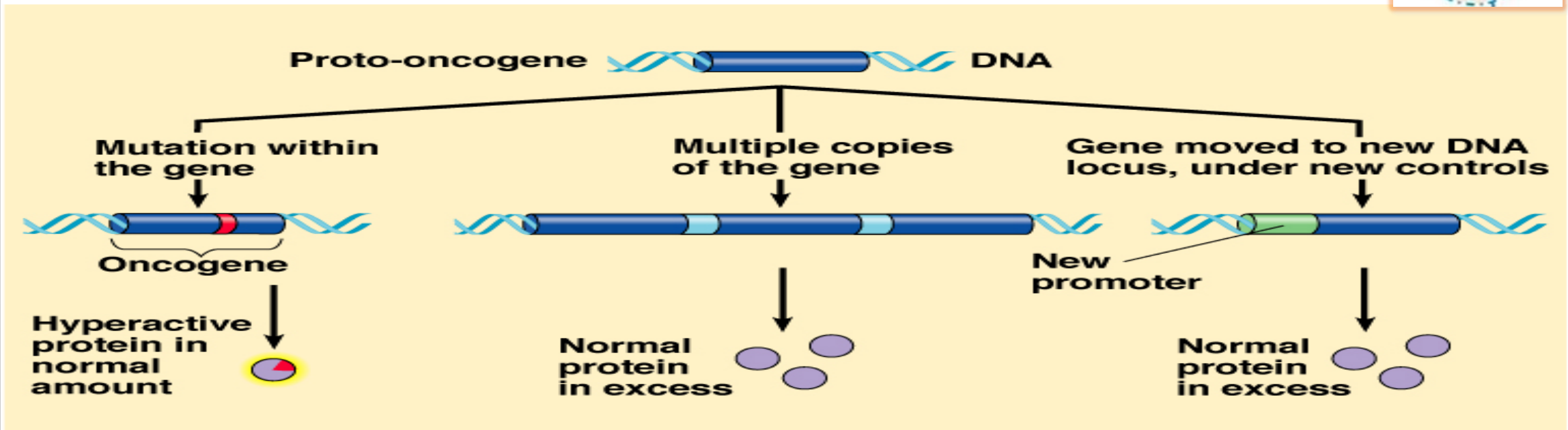
(duplication, multiplication)

- Myc gene

3. Chromosomal Translocation

- Philadelphia chromosome (translocation between chromosomes 9 and 22





Examples of human tumors associated with Activated oncogenes

- **Growth factors**
  - –PDGF(Platelet derived growth factor): in Glioblastoma (brain tumor)
- **Growth factor receptors**
  - –EGFR (epidermal growth factor receptor): -ERBB1 in lung cancer,
    -ERBB2 in breast & ovarian cancer
- **Signal transducing proteins**
  - –RAS: Colon cancer, lung cancer, pancreatic cancer
  - –ABL: (BCR-ABL) in Chronic myelogenous leukemia (CML)
- **Transcription factors:** –MYC: in Burkitt lymphoma, neuroblastoma.
- **Cyclins and CDK:** –Cyclin D: in breast cancer, liver cancer, lymphoma

Recognize different tumor suppressor genes.

Discuss importance of tumor suppressor genes.

Correlate different tumors with abnormalities in different tumor suppressor genes.

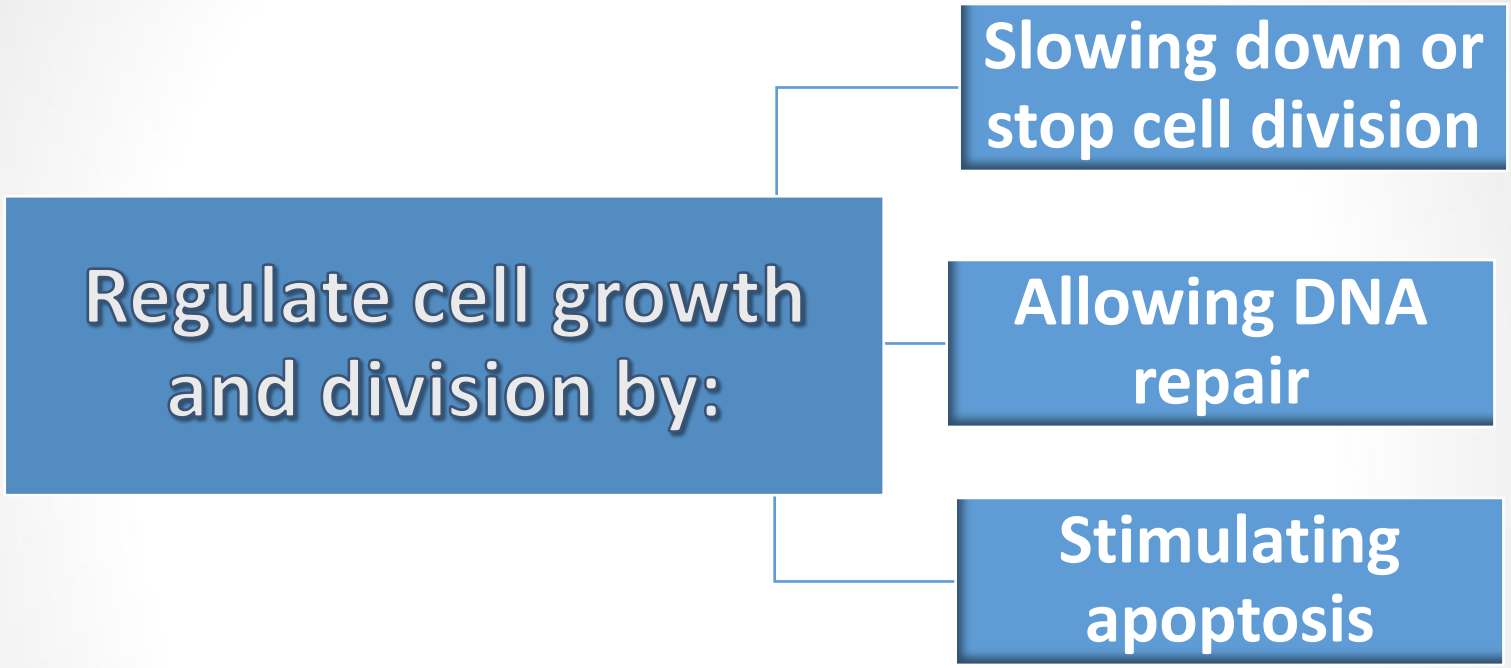
Tumor suppressor genes

- **Defintion:** **These are genes which code for proteins that normally suppress cell growth/proliferation.**
- **Common examples:** **-p53**

  -Rb

  -BRCA1 and BRCA2

Importance of Tumor suppressor genes



Inactivation of TSG :

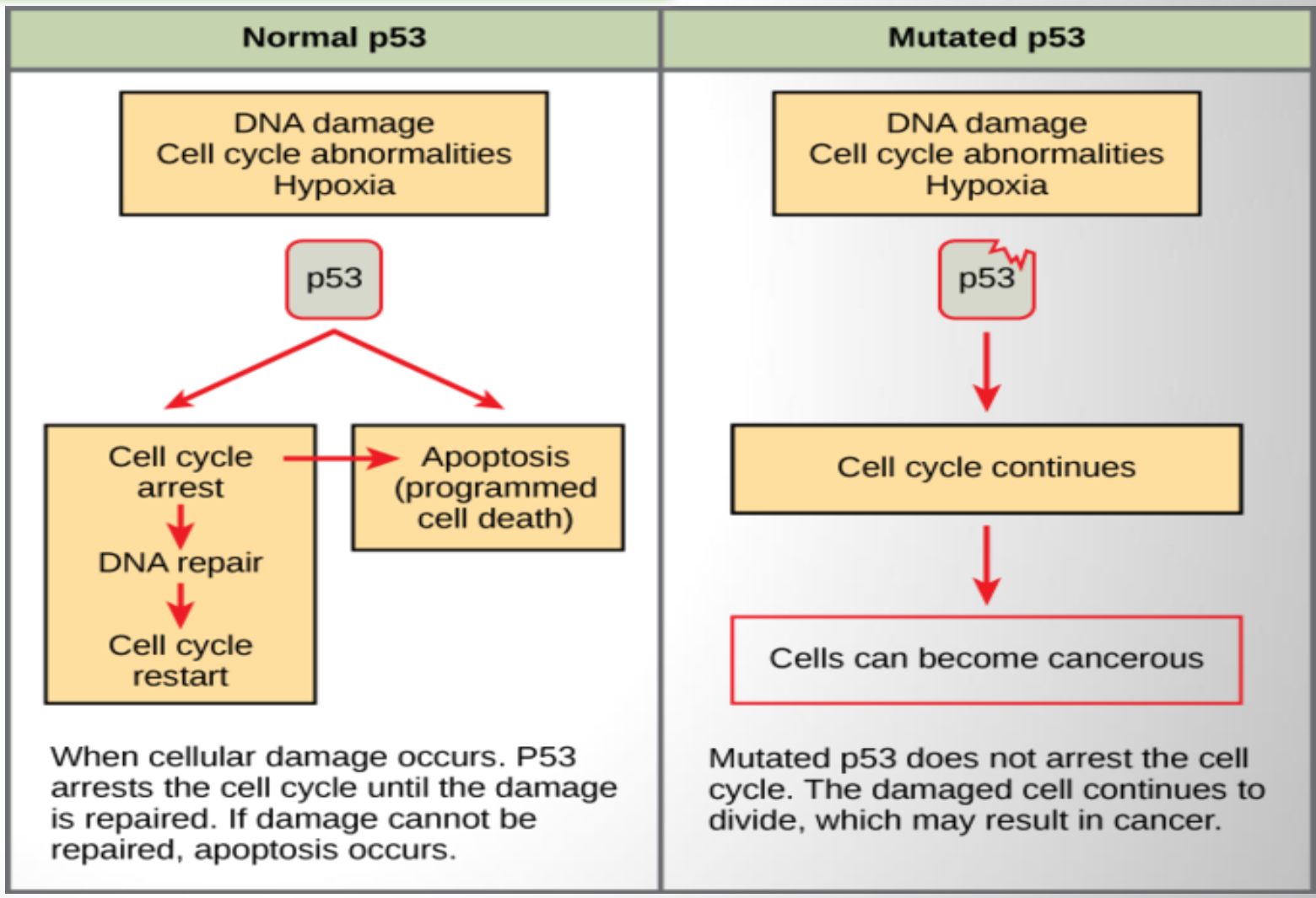
Cells grow out of control, which can lead to cancer.

-Tumor suppressor gene.

- p53 detect DNA damage resulting in:

1. **Arresting the cell cycle.**
2. **Enhance repair** of the damaged DNA before further progression into the cycle.
3. **Induction of apoptosis** (Stimulate **cell death)**

–Mutations of P53 are common in 50% of human cancer, eg: carcinomas of the breast, colon, and lung.



Ex: Tumor suppressor genes implicated in human cancers

	p53	Rb	BRCA1/BRCA2
Protein function:	-Arrest the cell cycle. -DNA repair -Induction of apoptosis	A key inhibitor of the cell cycle	Initiate DNA repair
Effect of Mutation:	Failure to arrest cell division, accumulation of mutations	Cell division continues without control	Damaged DNA is not repaired. Mutations then accumulate
Related tumors:	**Inherited mutation:** Li-Fraumeni Syndrome **Somatic mutation:** breast, colon, and lung cancers	Many cancer including Retinoblastoma (a rare form of childhood eye cancer)	-Breast cancer -Ovarian cancer

Case Scenario

A 32-year-old female with strong family history of breast ,colon and ovarian cancers presented with right breast lump. Patient underwent an examination which revealed a fixed, non tender breast mass on right side measuring 3 cm with mild right axillary lymphadenopathy. A biopsy was performed and revealed breast carcinoma.

- **What is the most likely cancer predisposing gene?**

Answer: BRCA 1/ 2 genes

- **What is the likely mechanism?**

Answer: Inactivation of Tumor suppressor genes

Case Scenario II

A 58-year-old male presents to the dental clinic with:

A **non-healing ulcer** on the lateral border of the tongue **for 1 month,** mild pain and occasional bleeding,Difficulty in chewing

History:

Heavy smoker (30 years)

Occasional alcohol use

Clinical Examination:

Indurated ulcer with raised margins with obvious lymph node enlargement

- **What is the most likely diagnosis?**
- **Mention two genetic changes commonly associated with OSCC**
- **What is the role of TP53 in normal cells? What happens when TP53 is mutated?**
- **What is the dentist's role in managing such cases?**


THANK
YOU!