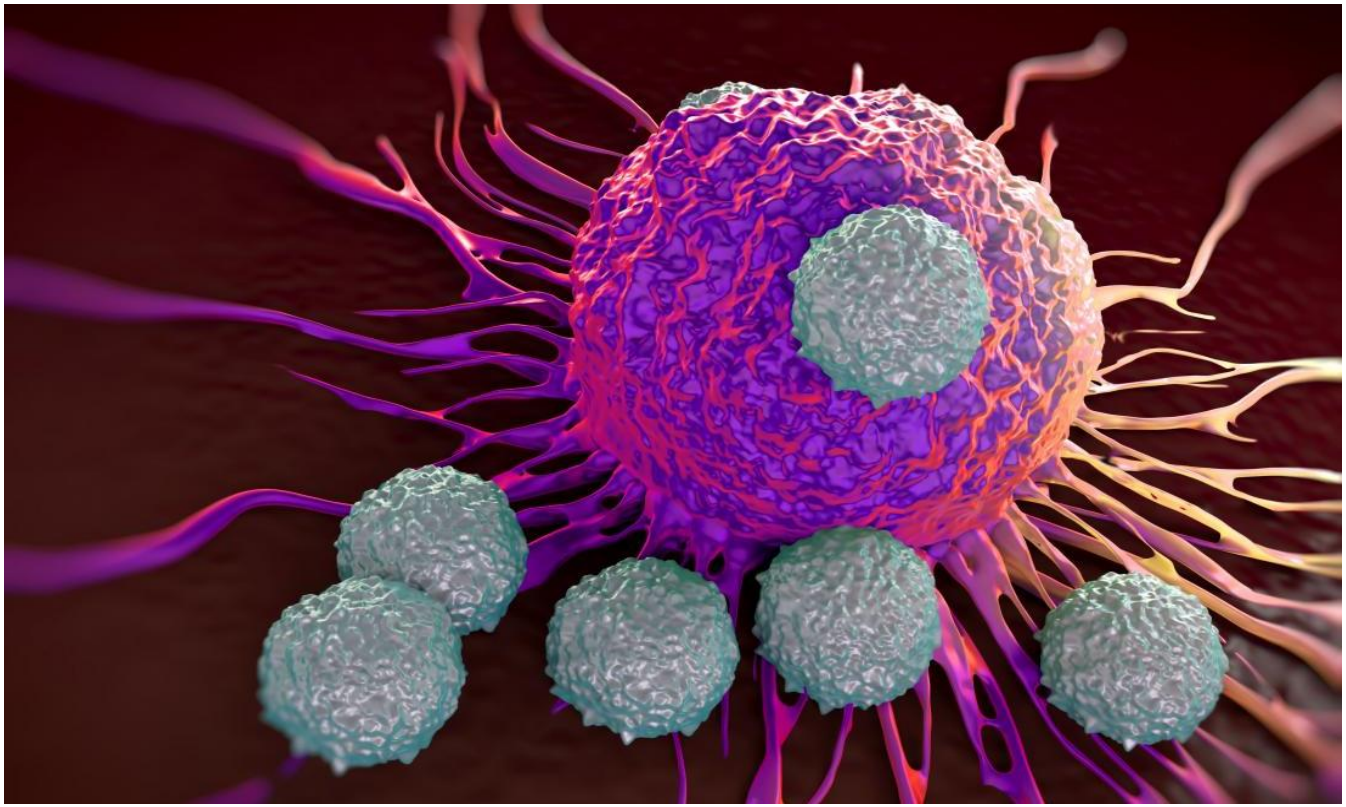
BS20001: Science of Living Systems: Spring2022

Cell Cycle Regulation & Cancer



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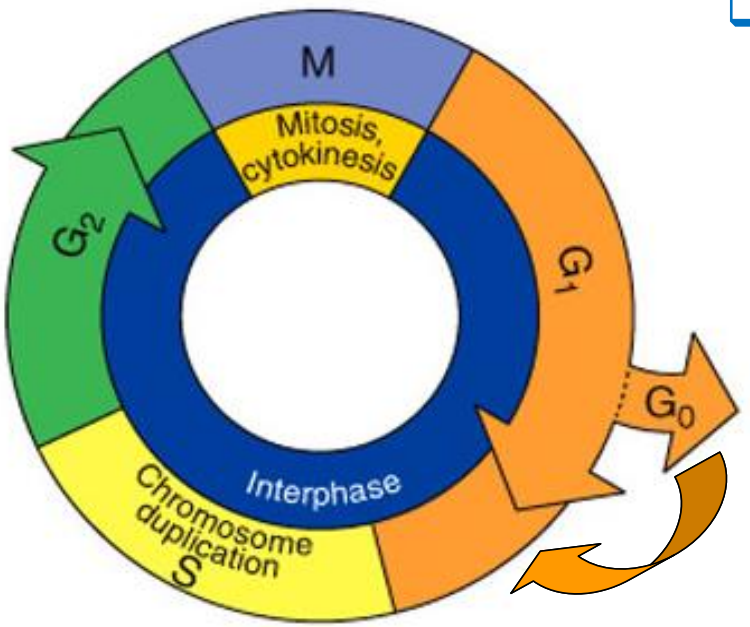
Important Features of Eukaryotic Cell Division Cycle

- There is a delicate balance between cell growth and division
- Cell division is tightly controlled
- Partial or complete **loss of normal control** on cell division cycle leads to **cancer**
- The **duration of the cell division cycle vary** between cell types:
- During early development i.e. embryonic stage, cells divide rapidly
- The epithelial cells in the lining of our intestine divide once in **1 day**
- Liver cells divide in **1 year**
- Most brain cells (neurons) don't divide

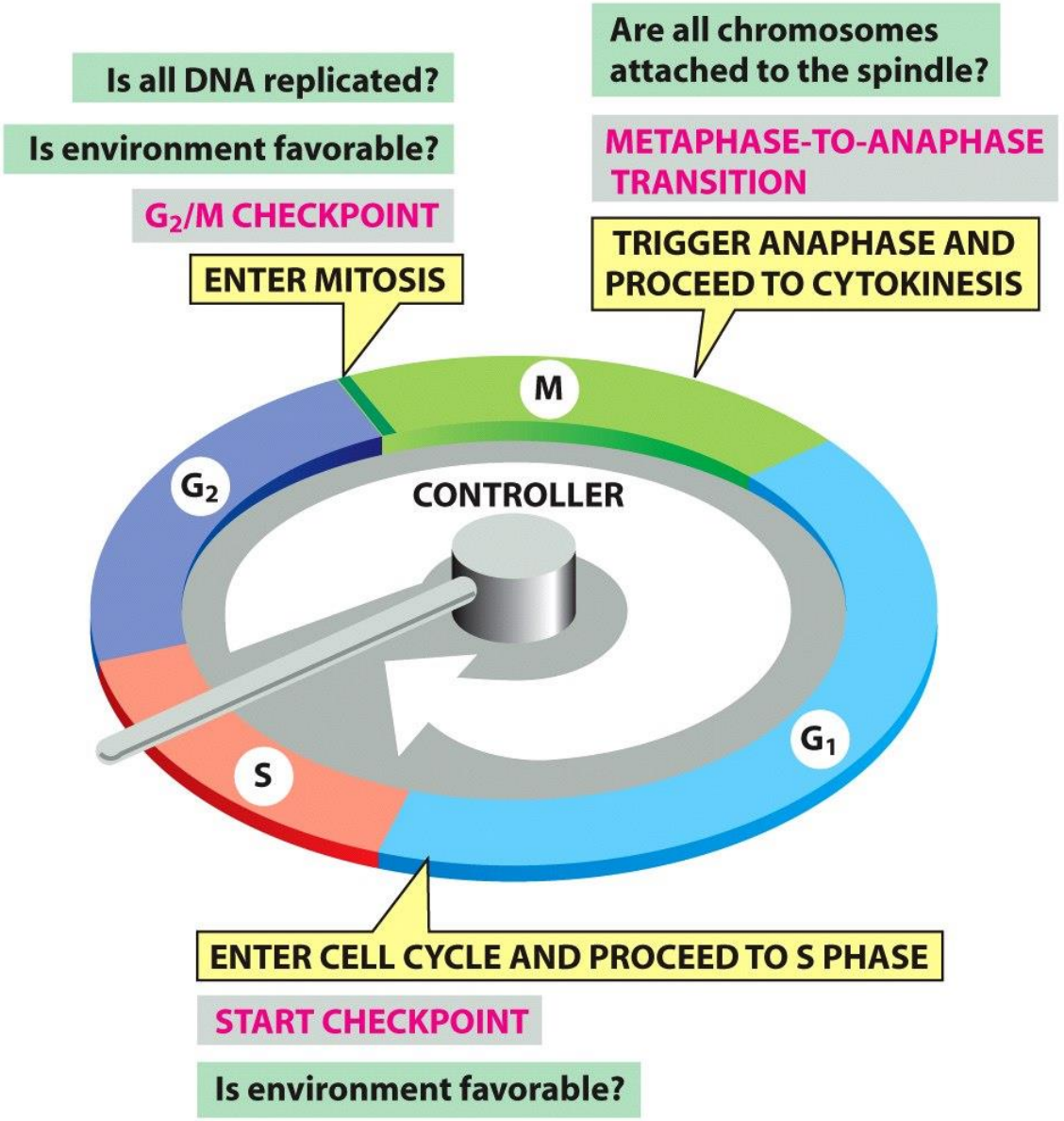
Cell Cycle Alternates Between Mitosis (M) and Interphase (G1, S, G2)



- **Interphase** – long period between two divisions during which cells grow, duplicate chromosomes and prepare for division
  - **G1 (Gap phase 1)** – birth of cell to the onset of chromosome duplication
  - **S (Synthesis phase)** – chromosome duplication (formation of sister chromatids) due to replication of DNA
  - **G2 (Gap phase 2)** – end of chromosome duplication to the onset of mitosis.

- **M: Mitosis phase** – **nuclear division** follows division of **cytoplasmic content** (cytokinesis) to separate sister chromatids into daughter cells
- **G0: resting phase** – cells exit from cell cycle and survive for days or years

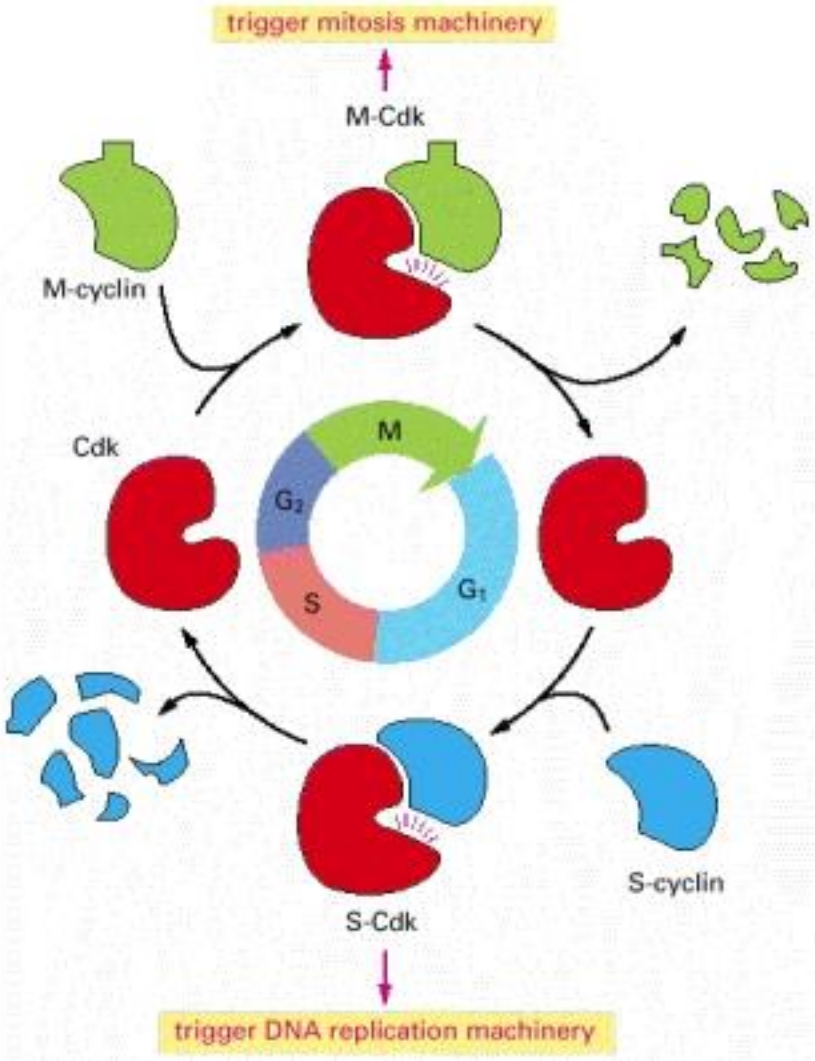
Cell cycle control system



The eukaryotic **cell cycle control system** has **three major checkpoints** as surveillance mechanism for cell cycle progression or transitions :

1. Start or restriction point (between G1 and S)
2. G2/M checkpoint
3. Metaphase/anaphase transition

Cyclins & cyclin-dependent kinases (Cdks): central components of the cell cycle control system

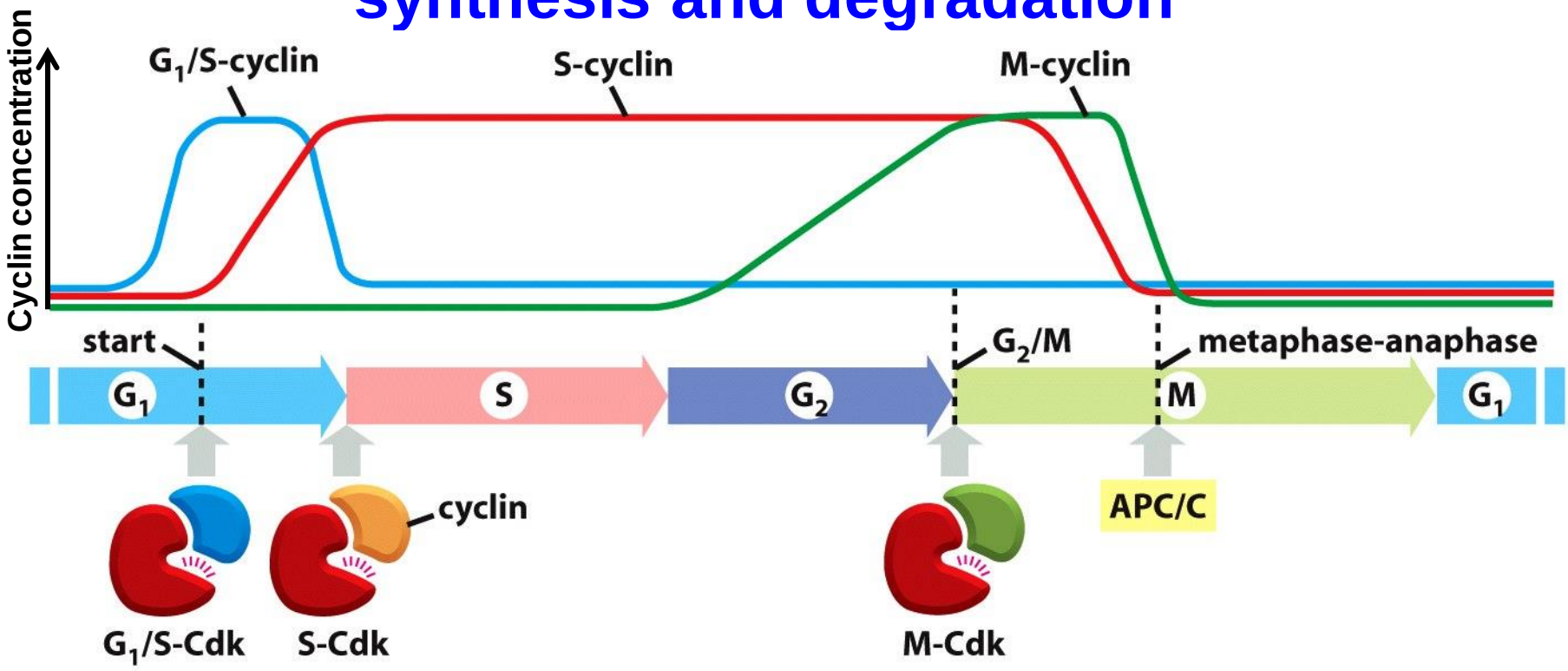


Central component of cell cycle control system are **cyclin-dependent kinases (Cdks)**. Their activities rise and fall as the cell progresses through its cycle. This leads to cyclical changes in the phosphorylation of proteins that initiate or regulate major cell cycle events.

Cdk activity is primarily controlled by **Cyclin** proteins. Cdks are active only when they tightly bind cyclin.

The levels of cyclin proteins periodically rise and fall which result in periodic activation and deactivation of the Cdks.

Different classes of cyclins undergo cyclical synthesis and degradation



Three classes of cyclins are required in all Eukaryotic cells:

1. **G1/S-cyclins** bind Cdks at the end of G1 and commit the cell to DNA replication.
2. **S-cyclins** bind Cdks during S phase and are required for the initiation of DNA replication.
3. **M-cyclins** promote the events of mitosis.

In most cells, a fourth class of cyclins, the G1-cyclins, helps promote passage through Start or the restriction point in late G1.

What happens when cell cycle regulation goes wrong?

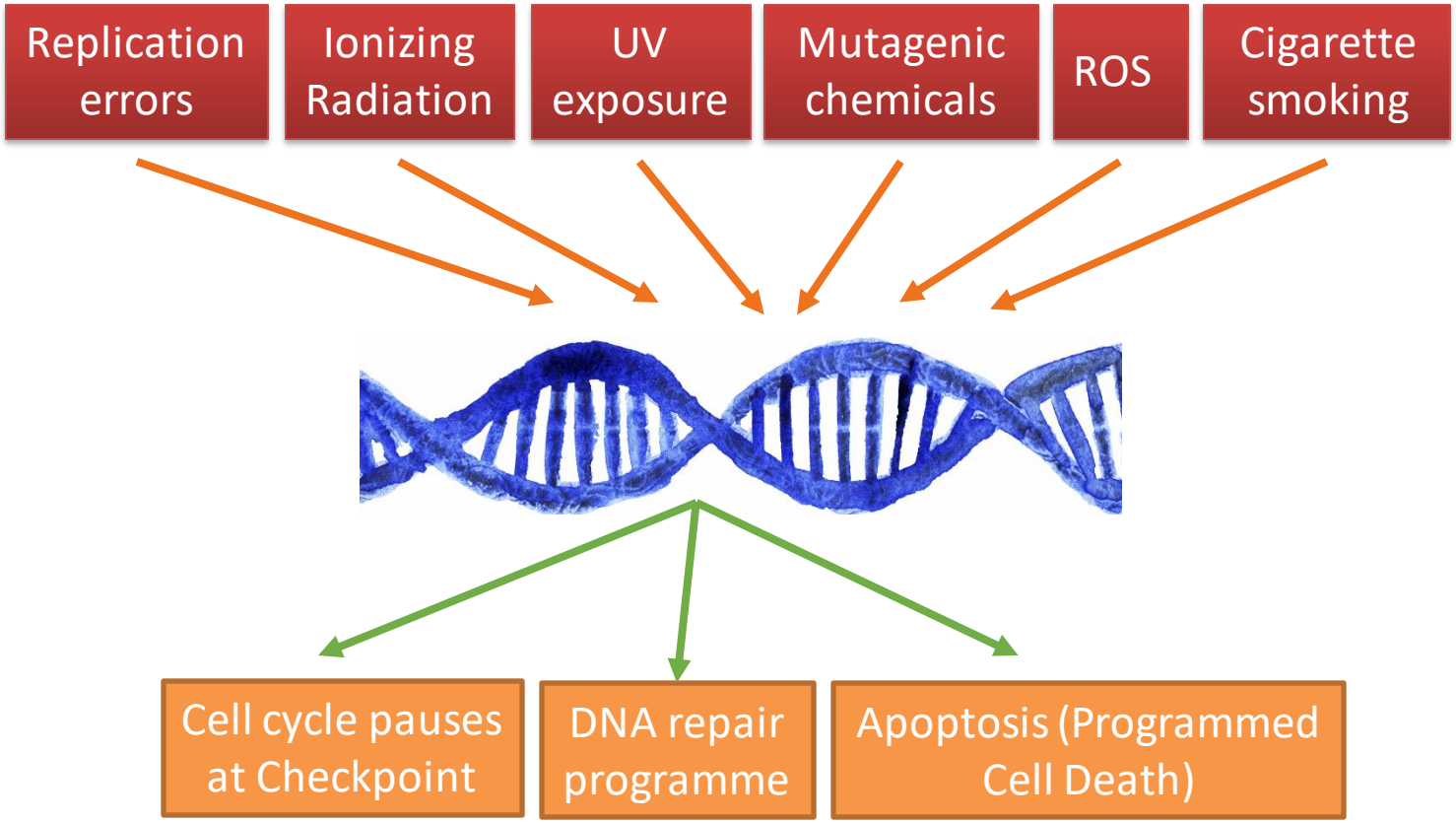
- Uncontrolled proliferation- **TUMOUR/Cancer**
- Cell division without checking for DNA damage/sequence change
  - ➢ DNA **replication errors** are not corrected
  - ➢ DNA damage due to external ***mutagens*** are not corrected
    - ➢ ACCUMULATION OF **MUTATIONS** IN GENOME

- ❑ Error rate of DNA Polymerase= 1 in 10^5 nucleotides
- ➢ A human cell has 6 billion base pairs
- ➢ So 1 round of replication of the human genome will make 120,000 errors!!!

- ❑ How are those errors repaired?
- ➢ During replication: DNA Polymerase has proofreading activity
- ➢ After replication: A well designed DNA repair machinery repairs the damage

- ❑ If the DNA damage is beyond repair:
- ➢ The cell dies by initiating Apoptosis

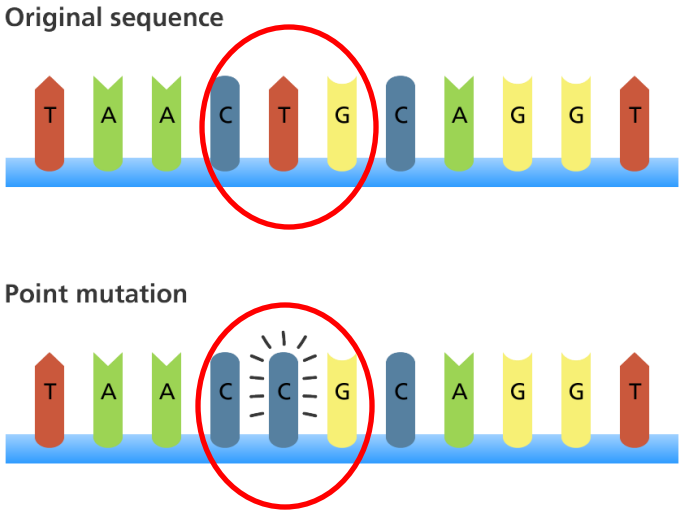
What happens when DNA is damaged/mutated?



What is a mutation?

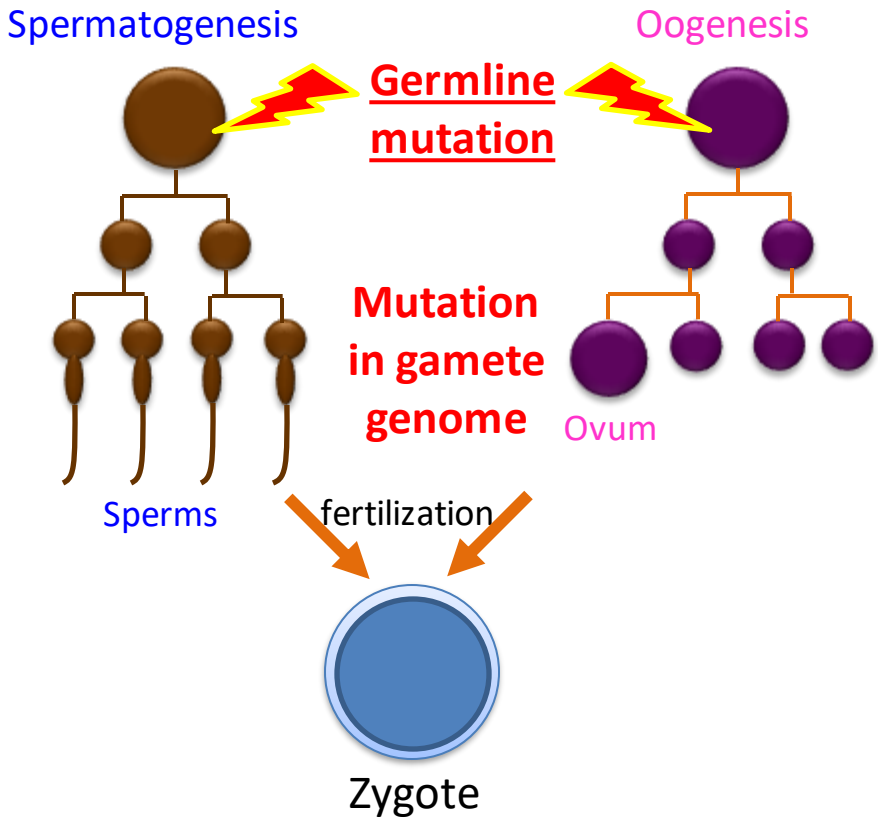
A **mutation** is an alteration in the nucleotide sequence of the genome of an organism

- Mutation in a gene results in alteration in the protein product
- **Spontaneous mutations:** due to replication error
- **Induced mutations:** caused by mutagens

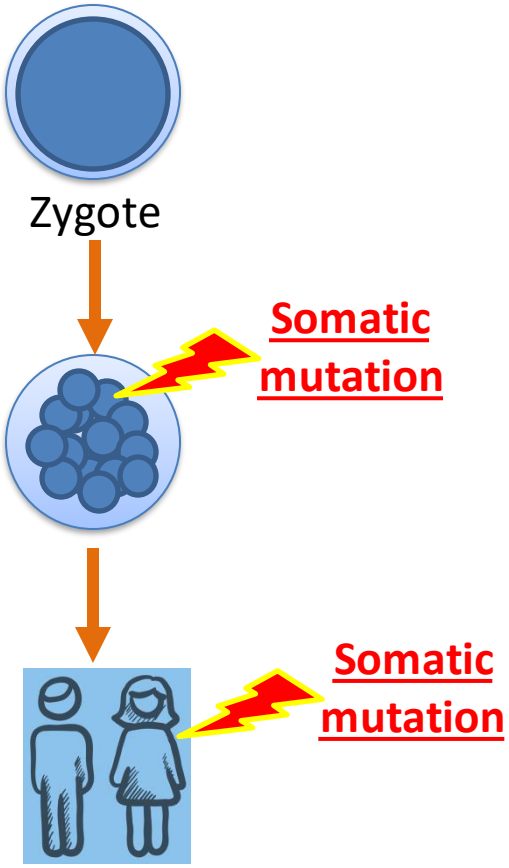


- **Mutagen:** a physical or chemical agent that changes the DNA sequence
  - Examples: radiation (UV, X ray etc.), tobacco, chemical agents
- **Carcinogen:** a substance or agent that promotes carcinogenesis or cancer formation
  - Examples: Asbestos, tobacco smoke, aflatoxin, arsenic, radiation, food colors, certain viruses etc.

Germline mutations vs Somatic Mutations



Mutation transmitted to progeny



Mutation may lead to Cancer

Which Gene Mutations may lead to Cancer?

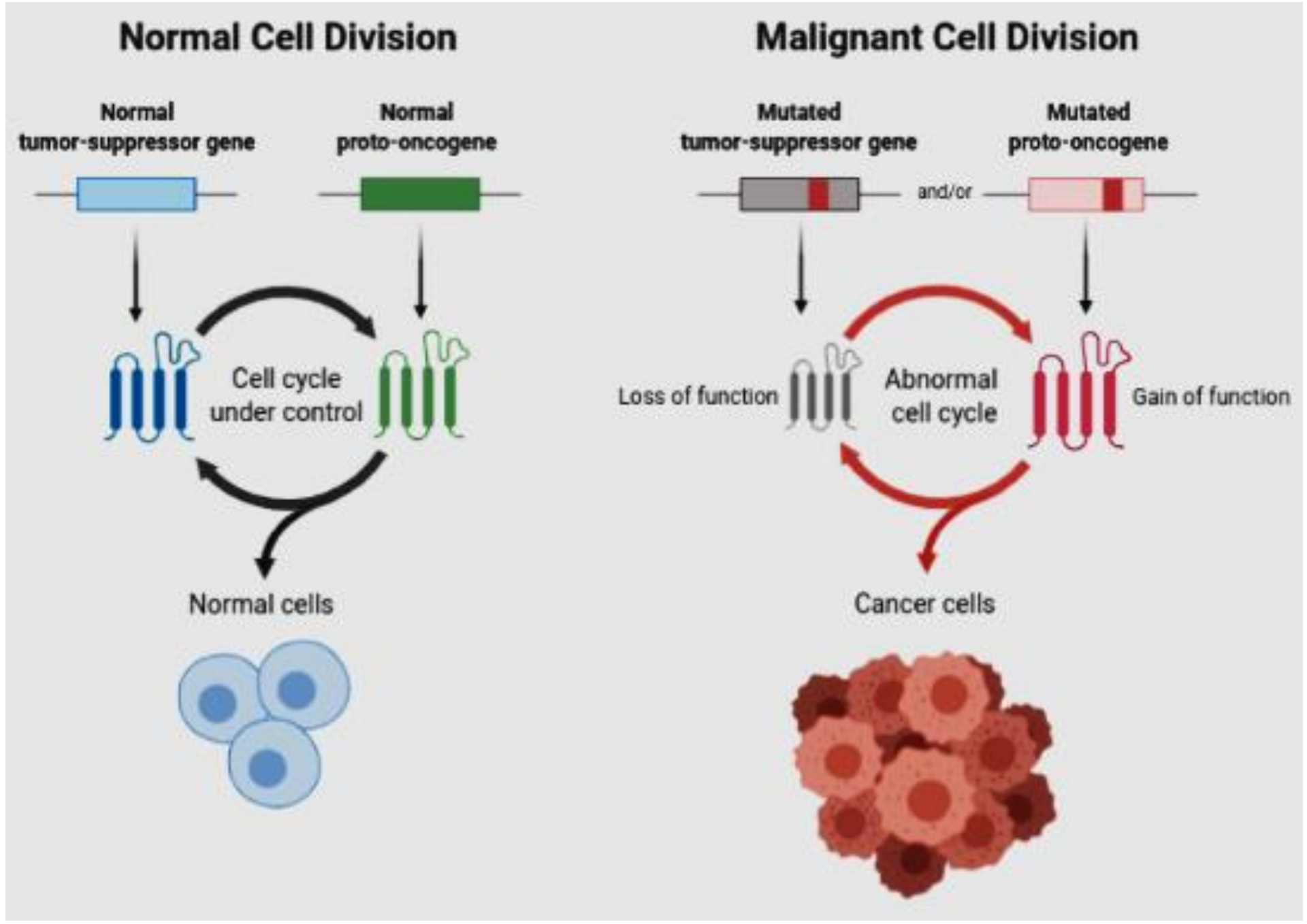
A. Tumor Suppressor Genes:

- Products are involved in
  - ➢ Cell cycle regulation
  - ➢ DNA repair
  - ➢ Cell death
- **Loss-of-function mutation** leads to uncontrolled cell division

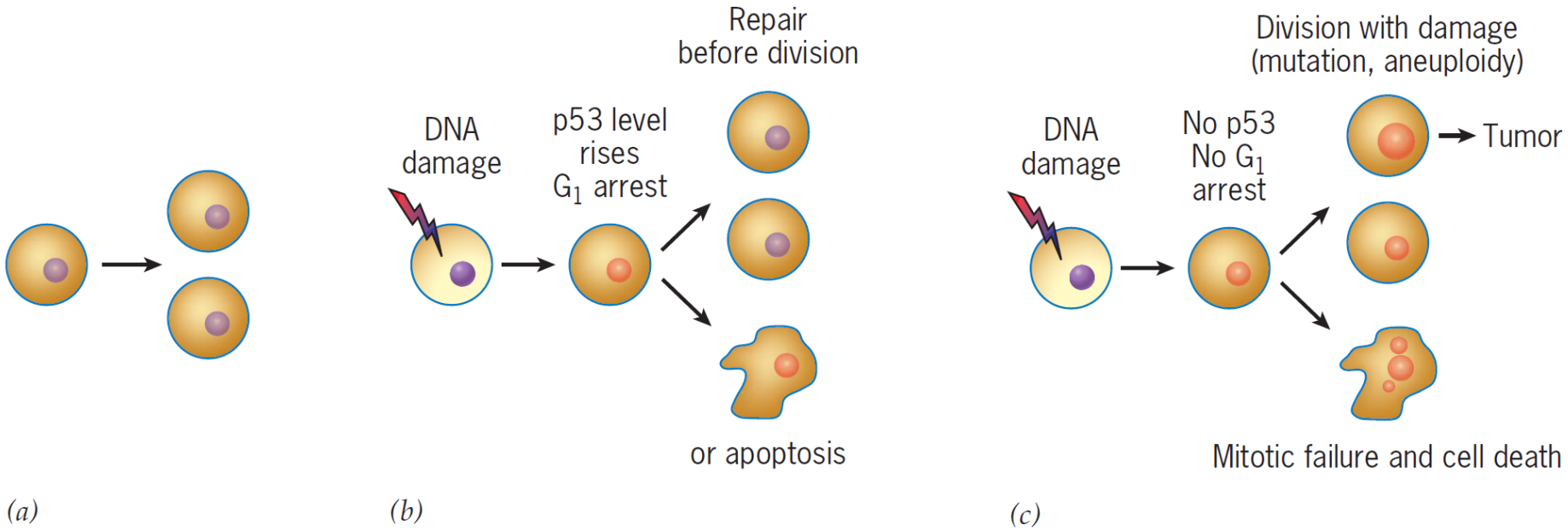
B. Proto-oncogenes:

- Products are involved in
  - ➢ Growth regulation
  - ➢ Regulation of cell division
  - ➢ Cellular communication
  - ➢ Cell death
- **Gain-of-function mutation** converts them to **Oncogenes**, which leads to uncontrolled cell division

❑ About One Percent of the Genes in the Human Genome Are Cancer-Critical


Normal Cell Division
Normal
tumor-suppressor gene
Normal
proto-oncogene
Cell cycle
under control
Normal cells
Malignant Cell Division
Mutated
tumor-suppressor gene
and/or
Mutated
proto-oncogene
Loss of function
Abnormal
cell cycle
Gain of function
Cancer cells

Role of tumour suppressor gene *p53*



Normal cell division does not depend on p53 protein

DNA damage – rise in P53 level:

(i) cell cycle arrest for DNA repair

or

(ii) Induction of cell death

DNA damage and p53 absent-

(i) no cell cycle arrest

and

(ii) no apoptosis

the cell continues to divide with DNA damage/genetic abnormality

Cancer is a <u>multistep</u> process:

in each step accumulating mutations and altering cells properties

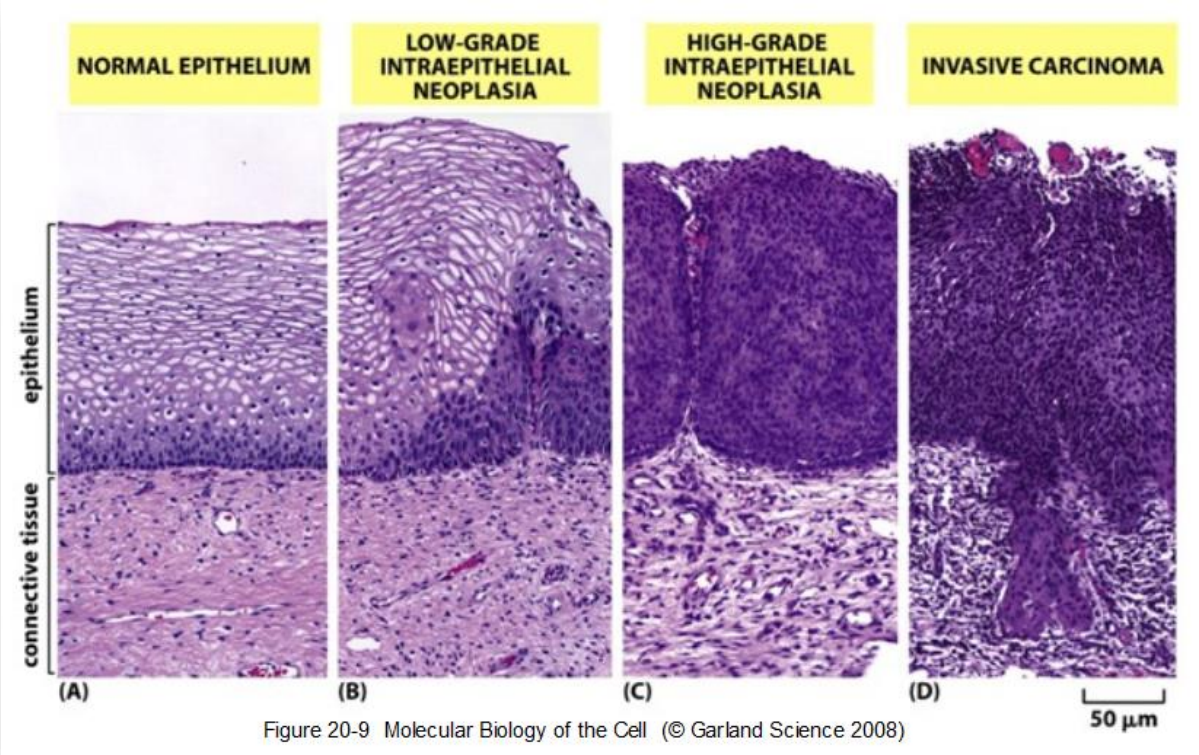
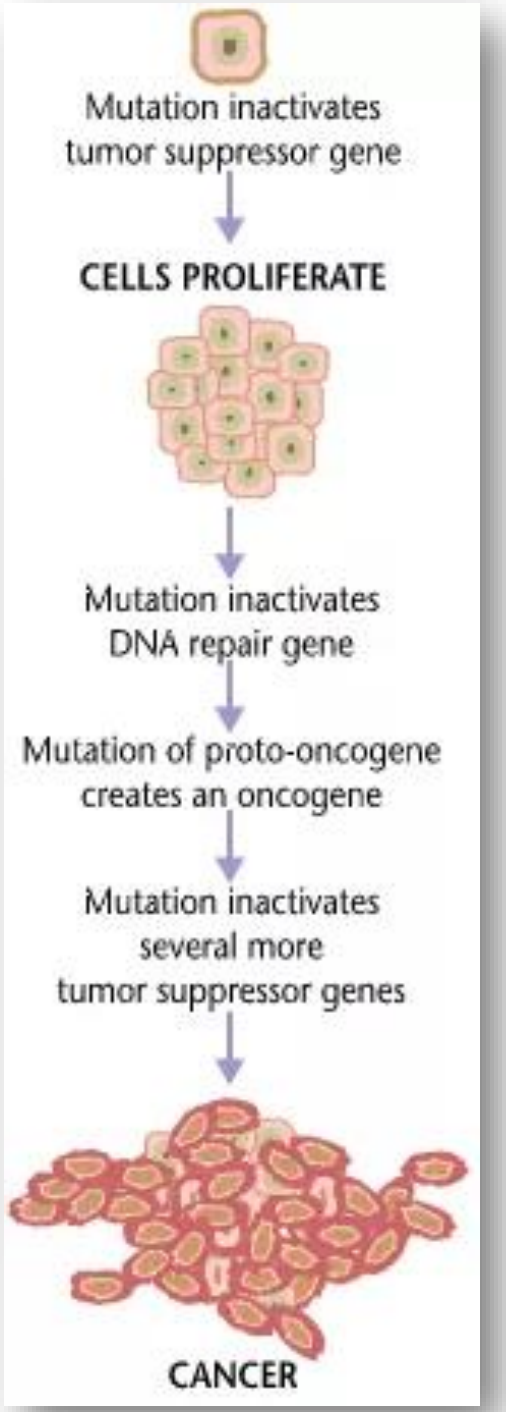


Figure 20-9 Molecular Biology of the Cell (© Garland Science 2008)

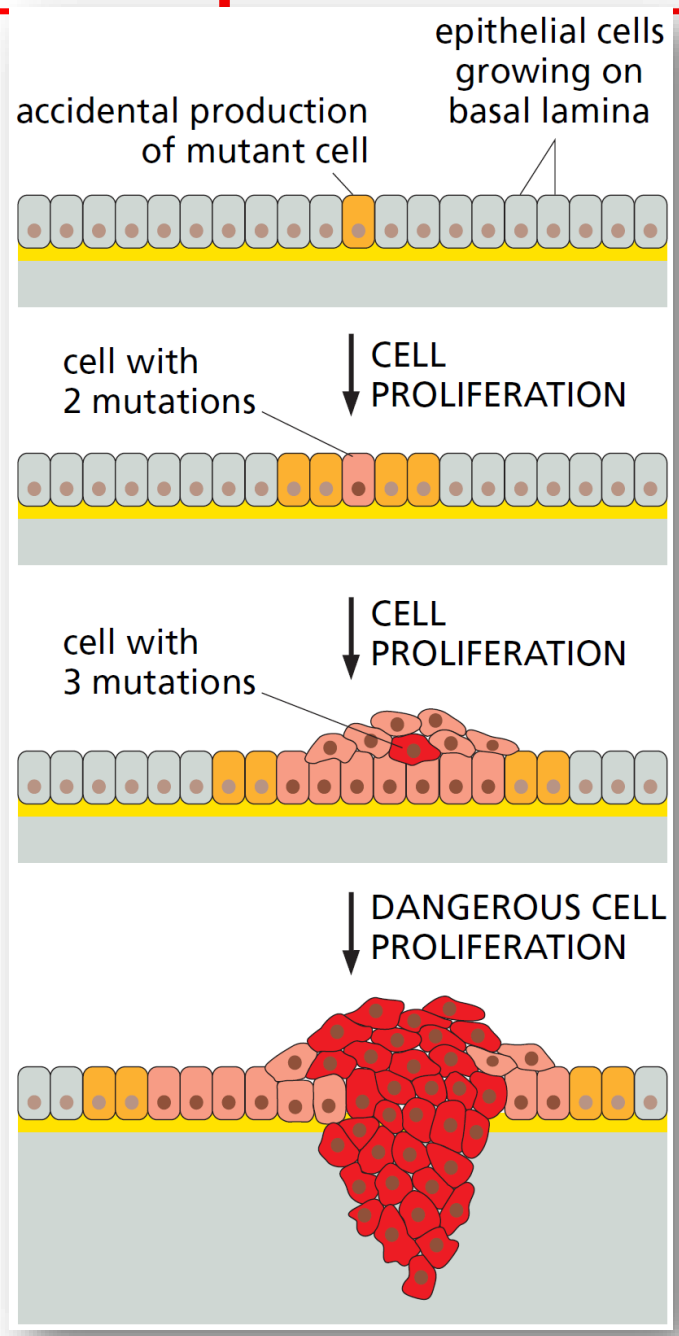


Hallmarks of Cancer Cells

- ❑ Uncontrolled mitotic division- **TUMORIGENESIS**
- ❑ Evasion of cell death signals- **IMMORTALIZATION**
- ❑ Induce formation of blood vessels- **ANGIOGENESIS**
- ❑ Invade healthy tissue- **METASTASIS**

Hallmarks of Cancer

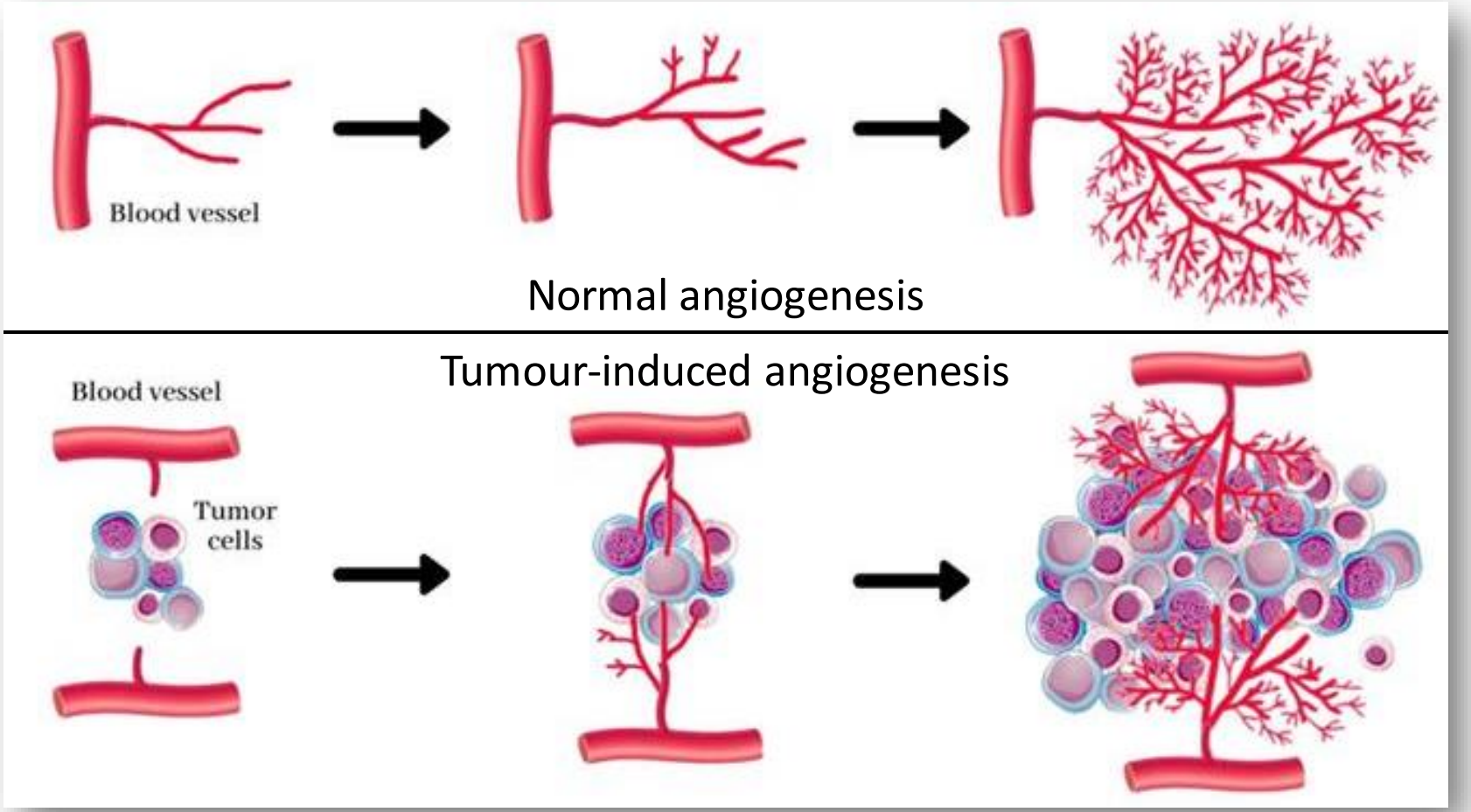
1. Development of Tumor



Hallmarks of Cancer

2. Angiogenesis:

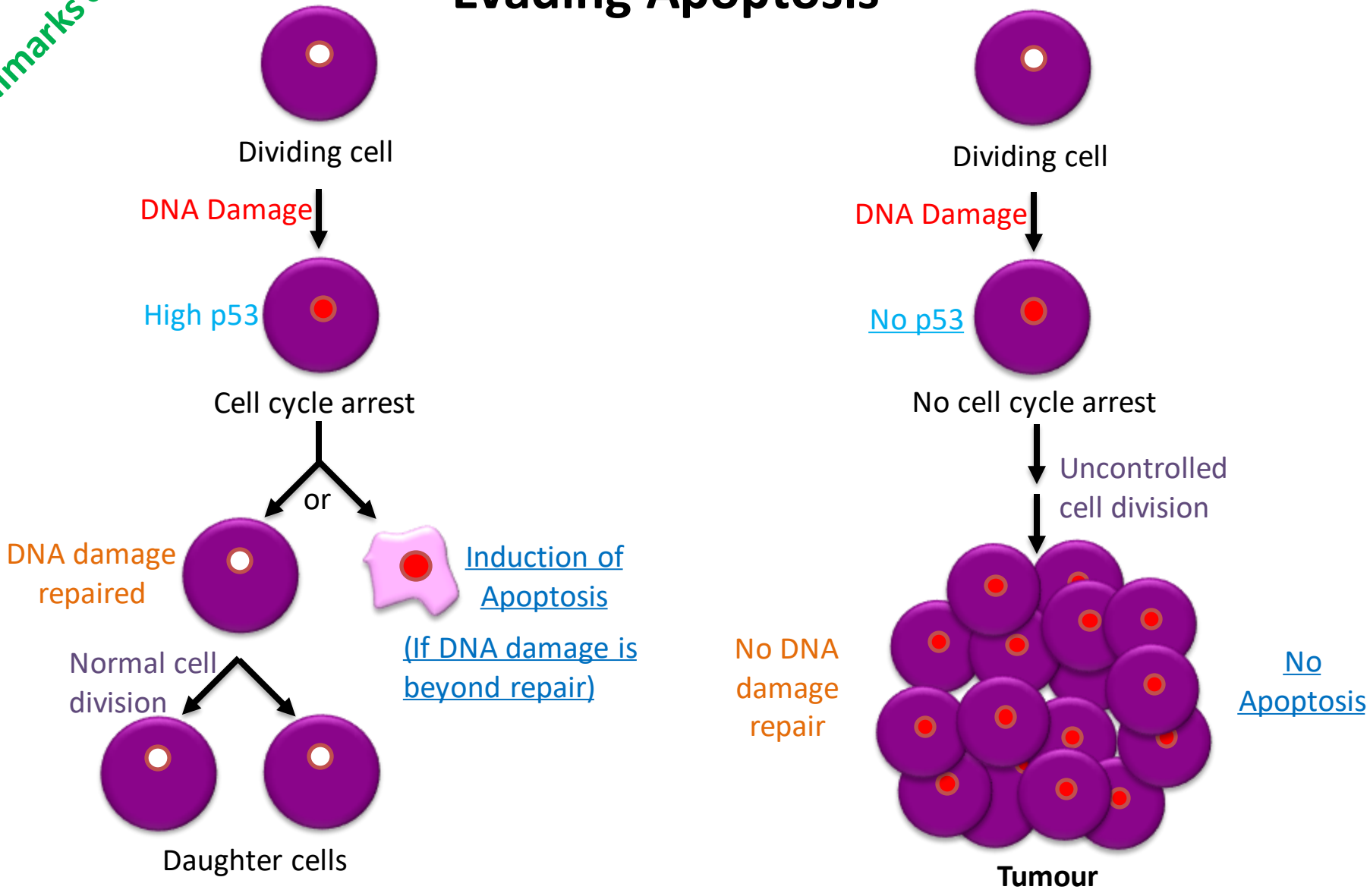
Formation of blood vessels in tumour



Hallmarks of Cancer

3. Immortalization:

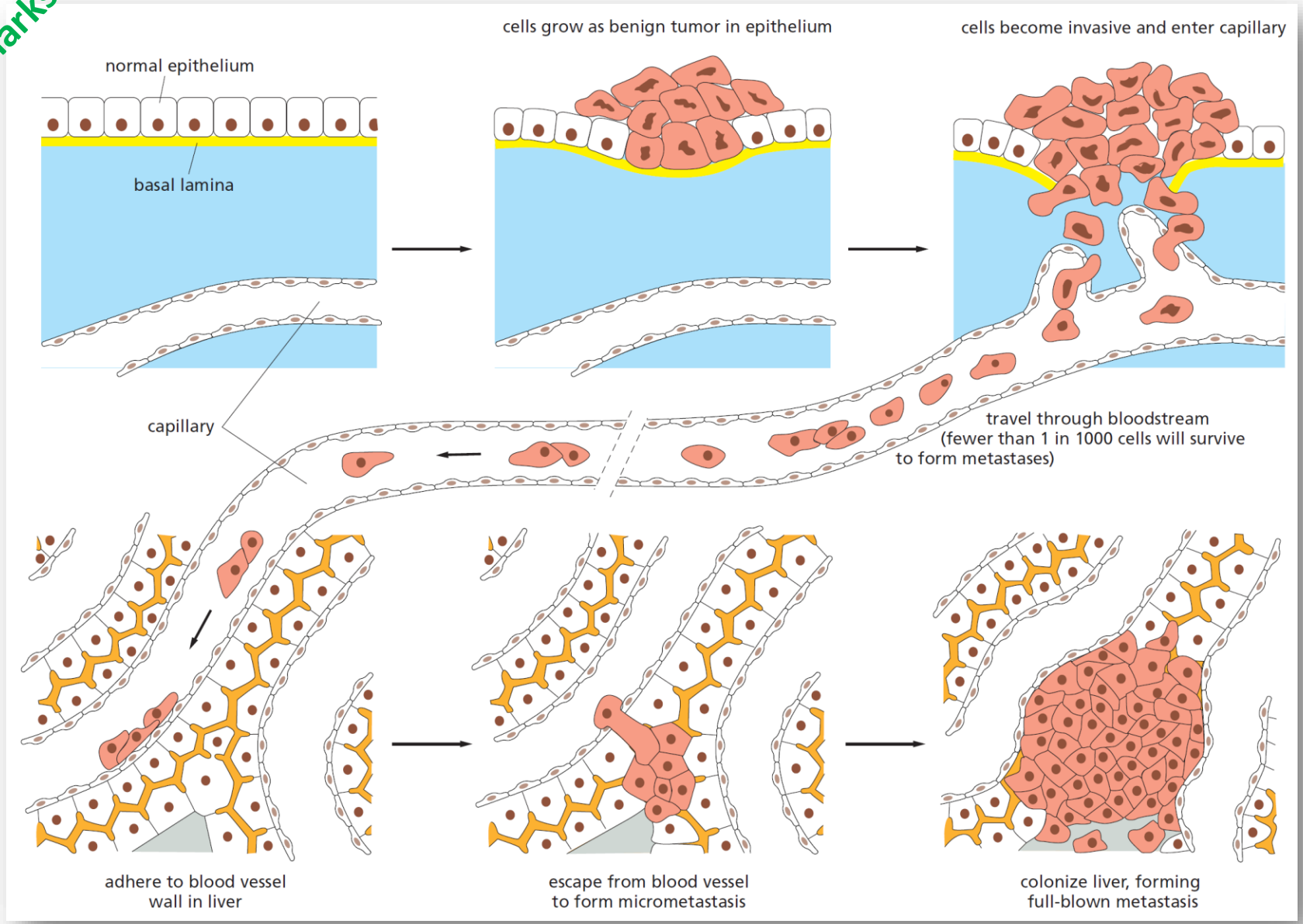
Evading Apoptosis



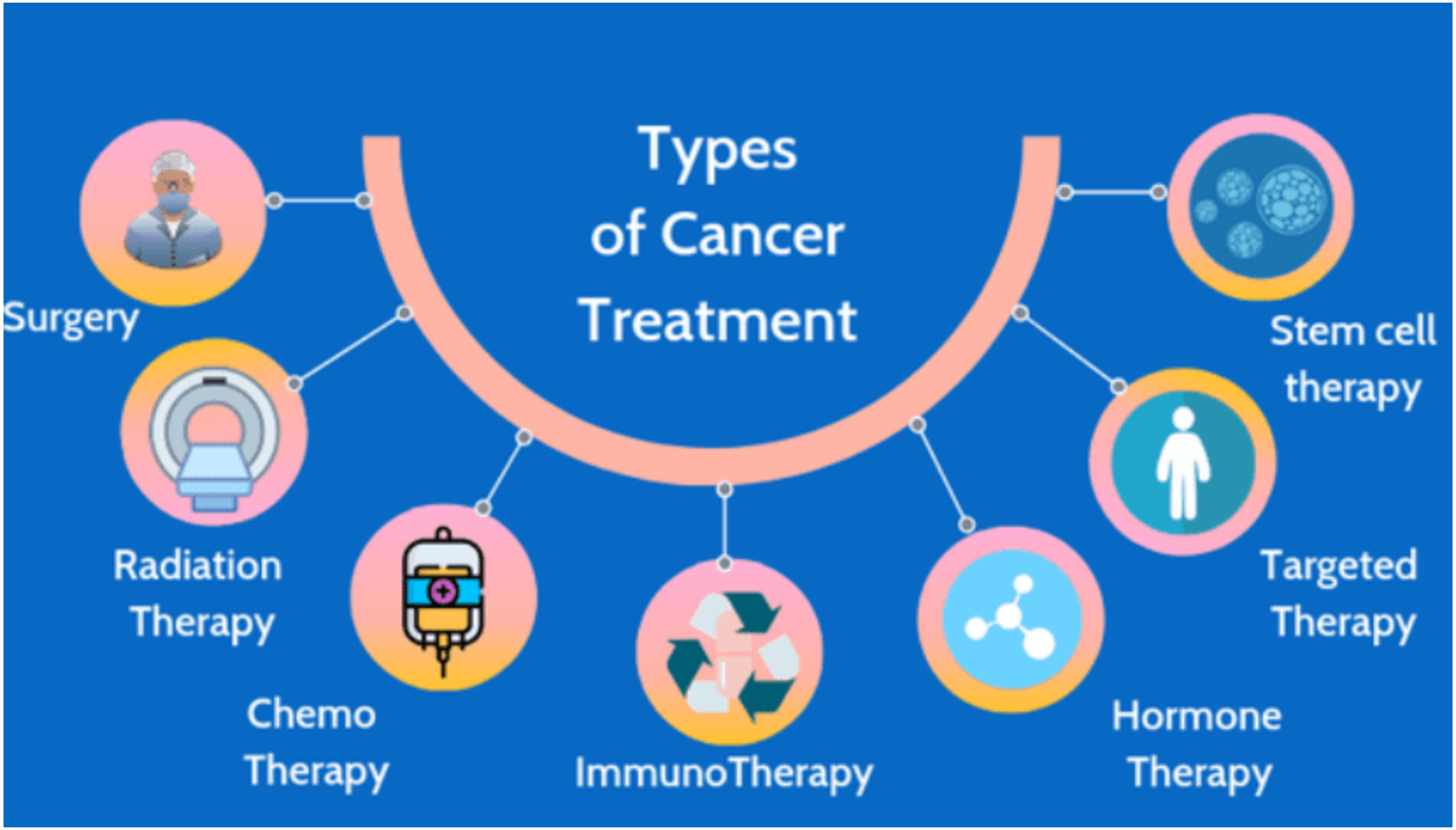
Hallmarks of Cancer

4. Metastasis:

Invasion and tumor formation at a new site



Various modalities of cancer treatment



Apoptosis / Programmed Cell Death (PCD)

Evolutionarily conserved

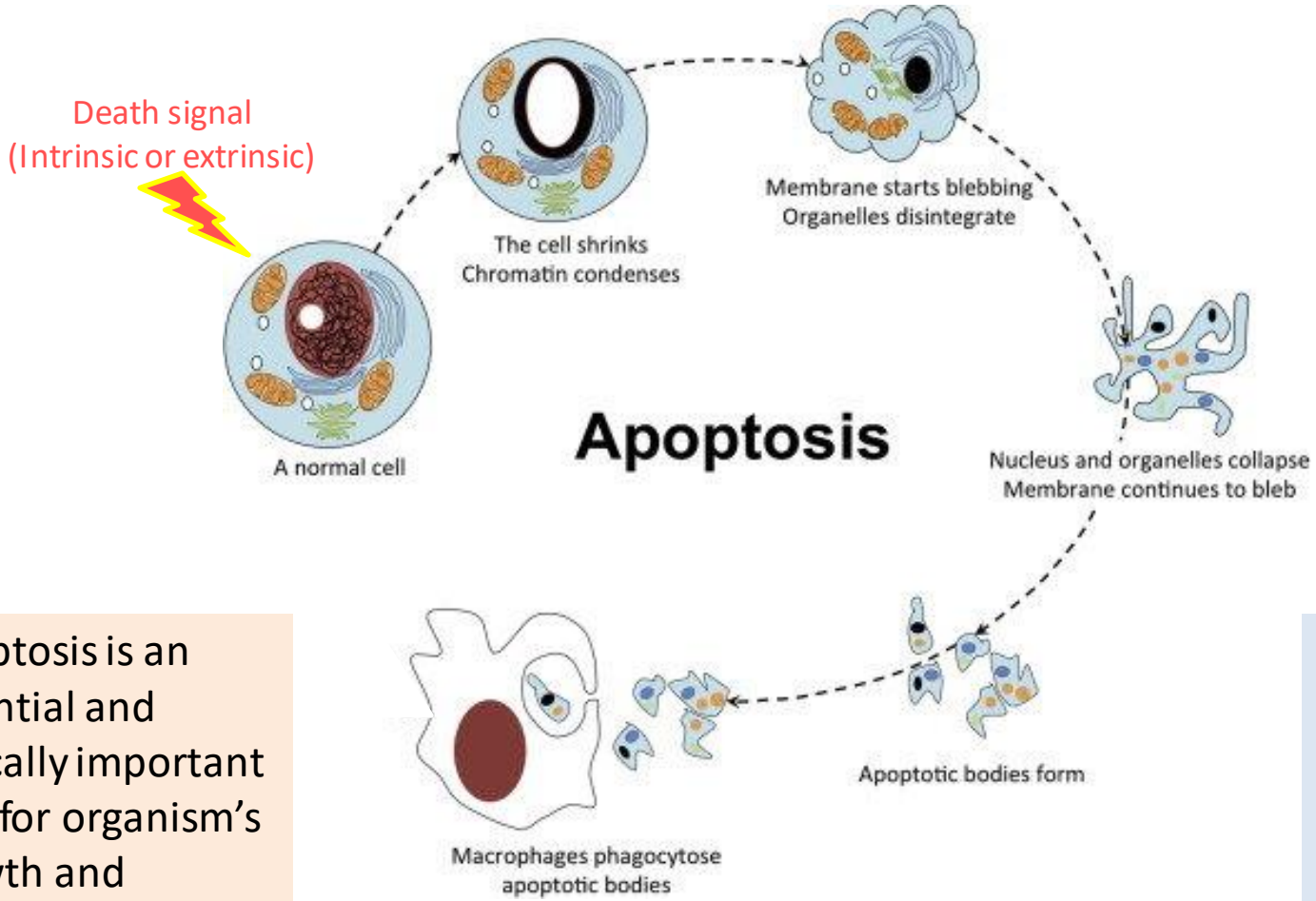
Occurs in all multicellular animals studied (plants too)

Stages and genes conserved from nematodes (worms) and flies to mice and humans

- In contrast to apoptosis, the animal cells that die accidentally in response to an acute **injury** (e.g. trauma or lack of blood supply) or pathogen **infection** by a process called cell **necrosis**.

Apoptosis / Programmed Cell Death (PCD)

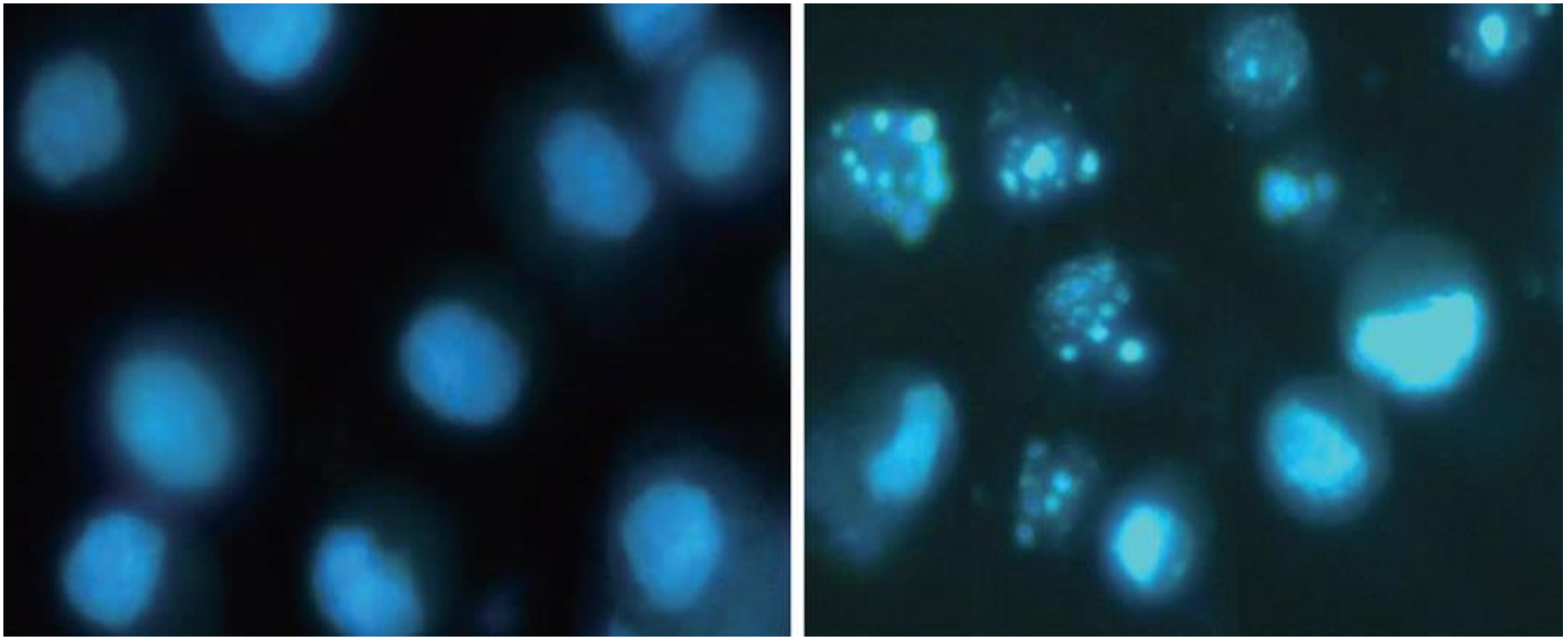
- Apoptosis is an orderly cellular self destruction pathway
- When DNA damage is not immediately repaired, the cells kill themselves by apoptosis
- In absence of apoptosis the cell can accumulate cancer-promoting mutation



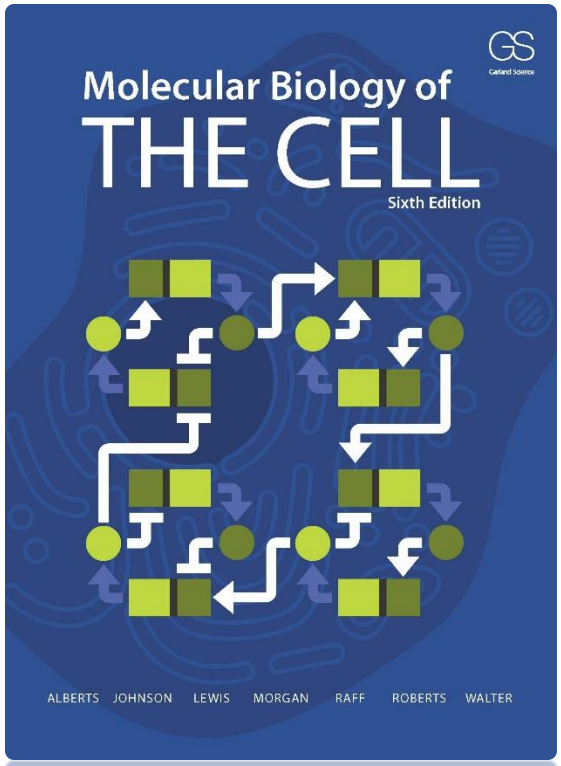
Apoptosis is an essential and critically important part for organism's growth and development

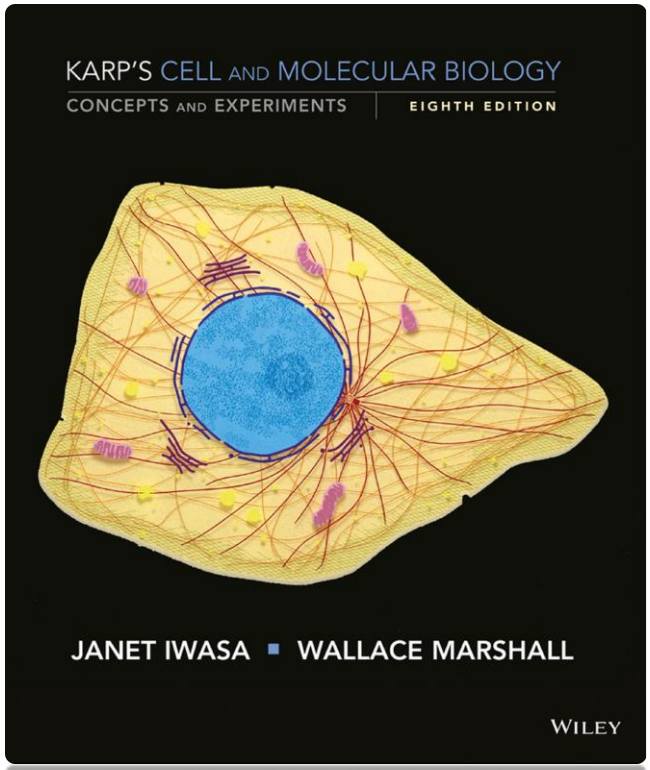
Apoptosis eliminates unwanted cells during organ formation / early development

Visualization of apoptosis



Reading and references





Websites:

- https://www.microscopyu.com/microscopy-basics/resolution
- www.zeiss-campus.magnet.fsu.edu/articles/basics/resolution.html
- https://svi.nl/AiryDisk

Caspase: mediator of apoptosis

- These are **c**ysteine-**asp**artic prote**ases.**
- Cysteine in the enzyme active site nucleophilically attacks and cleaves a target protein only after an aspartic acid residue.
- Caspases are synthesized as inactive pro-caspases and activated following an appropriate stimulus.
- **Initiator caspases** activated auto-proteolytically.
- **Executive caspases** are activated by initiator caspases.
- There are 12 caspases reported in human.