The Cell Cycle & Cancer

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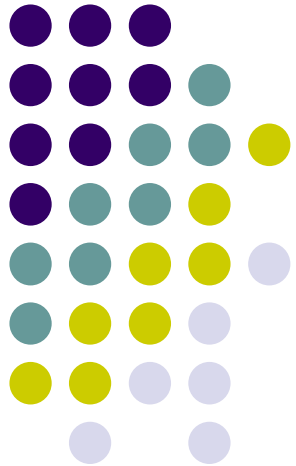
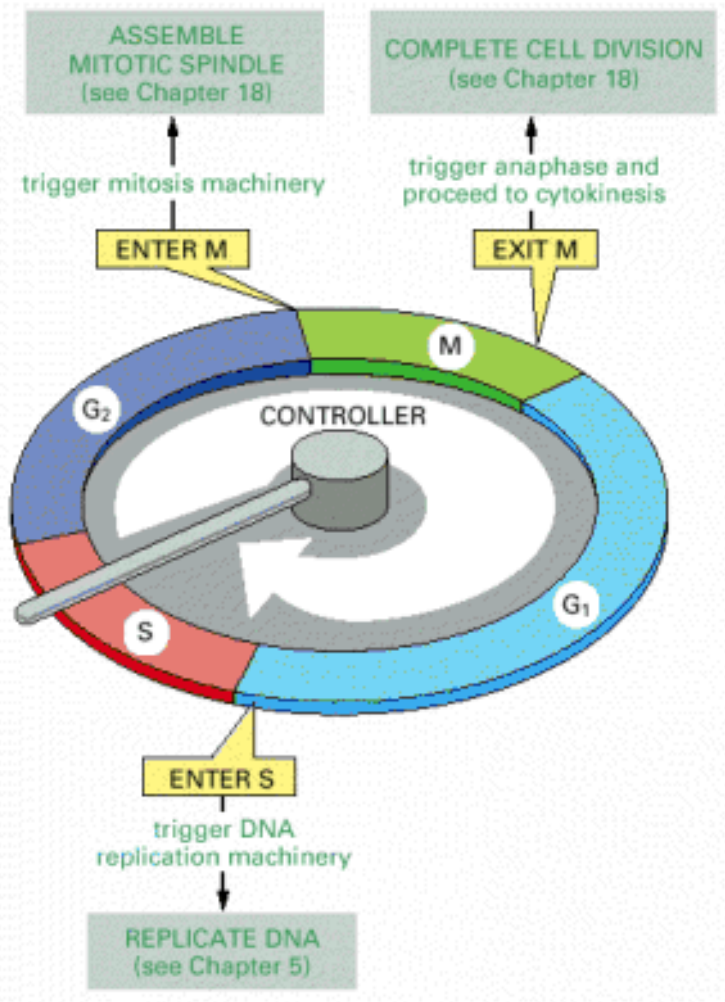
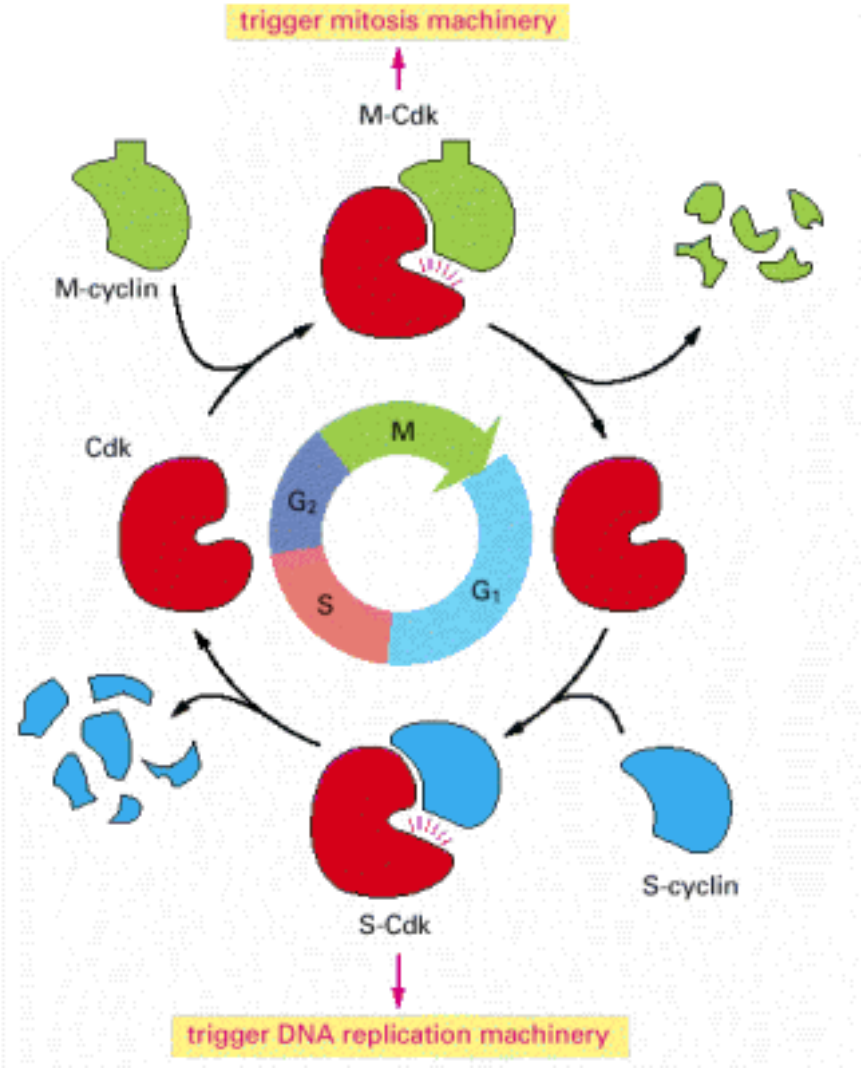


The cell cycle is an ordered process

- The cell cycle is controlled by a cyclically operating set of reaction sequences that both trigger and coordinate key events in the cell cycle
- The cell-cycle control system is driven by a built-in clock that can be adjusted by external stimuli (chemical messages)



The Cyclins Control Progress through the Cell Cycle



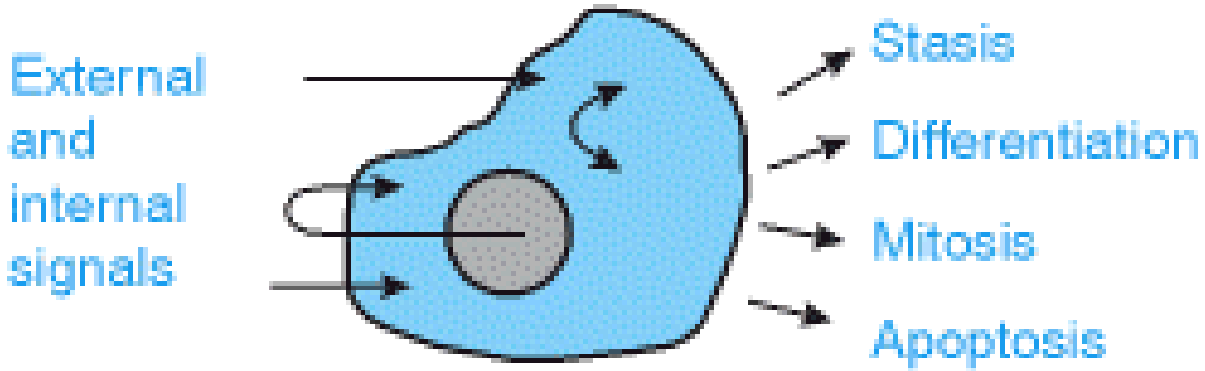
The Cell Cycle is Monitored at Check Points

- **Checkpoint** - a critical control point in the cell cycle where stop and go-ahead signals can regulate the cell cycle
  - Animal cells have built-in stop signals that halt the cell cycles at checkpoints until overridden by go-ahead signals.
  - Three Major checkpoints are found in the G1, G2, and M phases of the cell cycle

The G1 Checkpoint

- The G1 checkpoint - the Restriction Point
  - The G1 checkpoint ensures that the cell is large enough to divide, and that enough nutrients are available to support the resulting daughter cells.
  - If a cell receives a go-ahead signal at the G1 checkpoint, it will usually continue with the cell cycle
  - If the cell does not receive the go-ahead signal, it will exit the cell cycle and switch to a non-dividing state called G0
- Actually, most cells in the human body are in the G0 phase

Life Decisions a Cell Must Make



External Influences

- **1.** *Mitogens,* which stimulate cell division, primarily by relieving intracellular negative controls that otherwise block progress through the cell cycle.

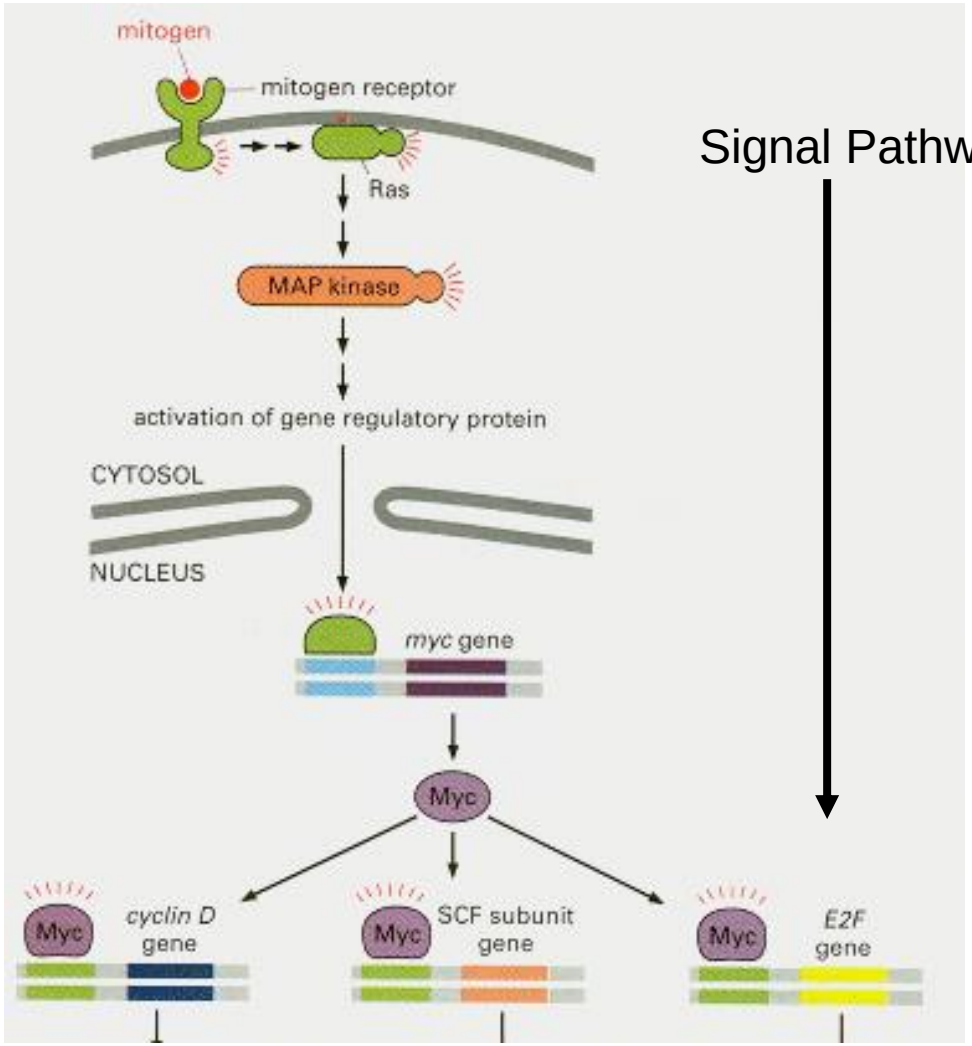
  2. *Growth factors,* which stimulate cell growth (an increase in cell mass) by promoting the synthesis of proteins and other macromolecules and by inhibiting their degradation.

  3. *Survival factors,* which promote cell survival by suppressing apoptosis.

Other Factors Influencing Growth & Division

- **Density Dependent Inhibition**
  - Cells grown in culture will rapidly divide until a single layer of cells is spread over the area of the petri dish, after which they will stop dividing
  - If cells are removed, those bordering the open space will begin dividing again and continue to do so until the gap is filled - this is known as **contact inhibition**
  - Apparently, when a cell population reaches a certain density, the amount of required growth factors and nutrients available to each cell becomes insufficient to allow continued cell growth
- **Anchorage Dependence**
  - For most animal cells to divide, they must be attached to a substratum, such as the extracellular matrix of a tissue or the inside of the culture dish
- **Cells Which No Longer Respond to Cell-Cycle Controls**
  - **They divide excessively and invade other tissues**
  - **If left unchecked, they can kill the organism**

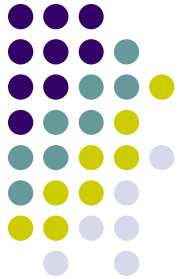
Mitogens Push Cells Past the Restriction point



Signal Pathway

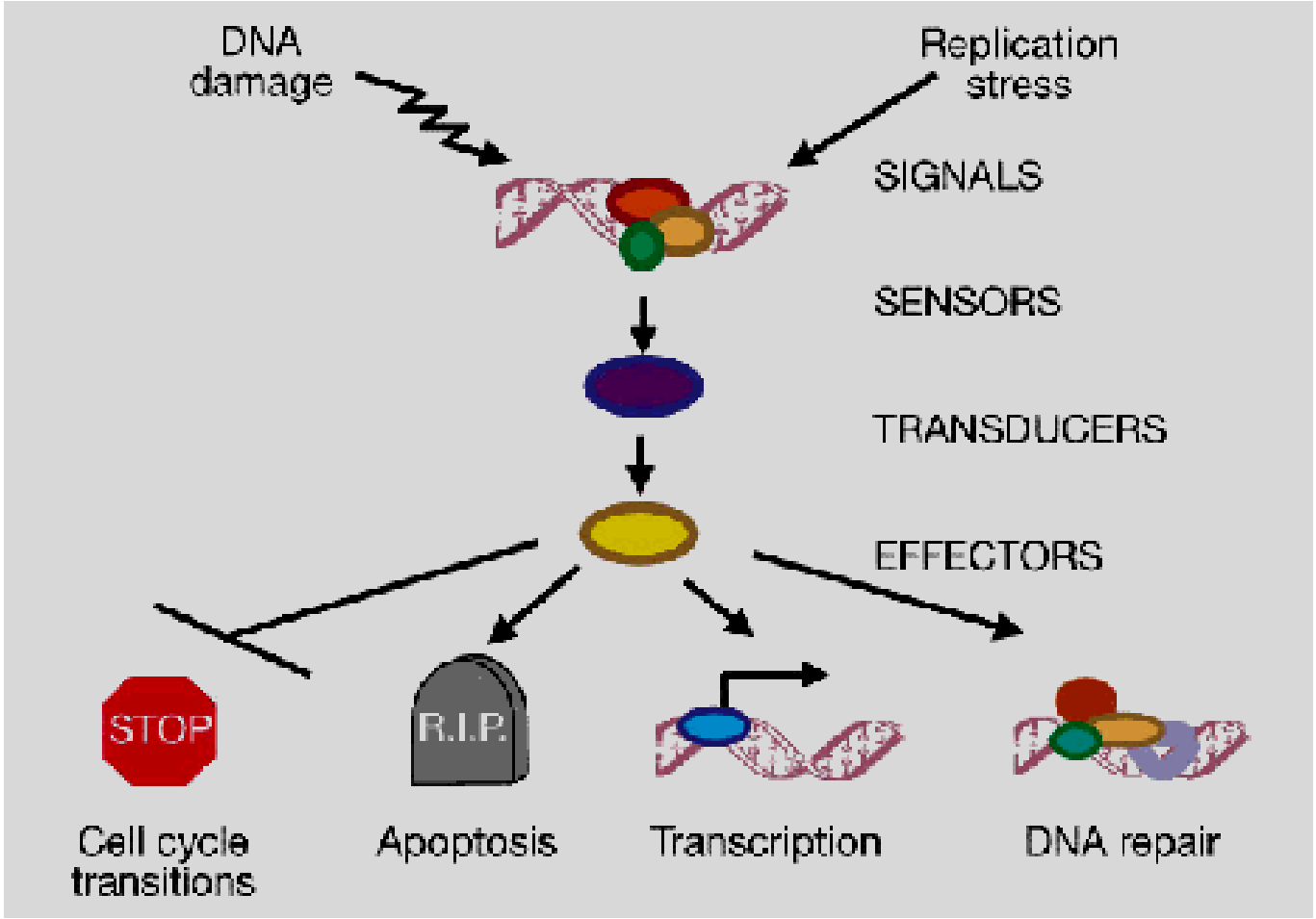
The Proteins From These Genes Stimulate Entry Into S phase

G2 & M Checkpoints

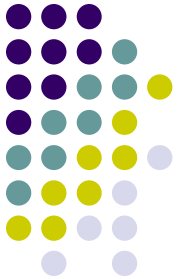


- The G2 checkpoint ensures that DNA replication in S phase has been completed successfully.
- The metaphase checkpoint ensures that all of the chromosomes are attached to the mitotic spindle by a kinetochore.

The G2 Checkpoint Prevents the Production of Cells with Damaged DNA



Normal growth is closely regulated



- Summary
  - In multicellular animals, cell size, cell division, and cell death are carefully controlled to ensure that the organism and its organs achieve and maintain an appropriate size. Three classes of extracellular signal proteins contribute to this control, although many of them affect two or more of these processes. Mitogens stimulate the rate of cell division by removing intracellular molecular brakes that restrain cell-cycle progression in G1. Growth factors promote an increase in cell mass by stimulating the synthesis and inhibiting the degradation of macromolecules. Survival factors increase cell numbers by inhibiting apoptosis. Extracellular signals that inhibit cell division or cell growth, or induce cells to undergo apoptosis, also contribute to size control.

Table 24.1

Table 24.1 Cancer Cells versus Normal Cells

Characteristics	Cancer Cells	Normal Cells
Differentiation	Do not become differentiated	Do become differentiated
Appearance of nucleus	Abnormal nucleus	Normal nucleus
Replicated potential	Unlimited replicated potential	Limited replicated potential
Form tumors	Do form tumors	Do not form tumors
Need for growth factors	Growth factors not needed	Growth factors are needed
Angiogenesis	Induce and sustain angiogenesis	Do not encourage angiogenesis
Metastasis	Metastasize	Do not metastasize

Proto-oncogenes→Oncogenes

- Proto-oncogenes are genes that control normal cell growth- code for:
  - Growth factor receptors
  - Mitogen receptors
  - Growth/Division signal pathway components
  - Survival factors
- Mutation converts Proto-oncogenes to oncogenes

Tumor Suppressor Genes

- Tumor suppressor genes code for check point control proteins.
  - Prevent entry of cells into S
  - Prevent replication of DAMAGED DNA
  - Prevent abnormal cell division
- Tumor suppressor mutations are recessive
  - Both copies must be knocked out to cause abnormal cell division
  - Tumor suppressor mutations are heritable

Rb is a Critical Tumor Supressor

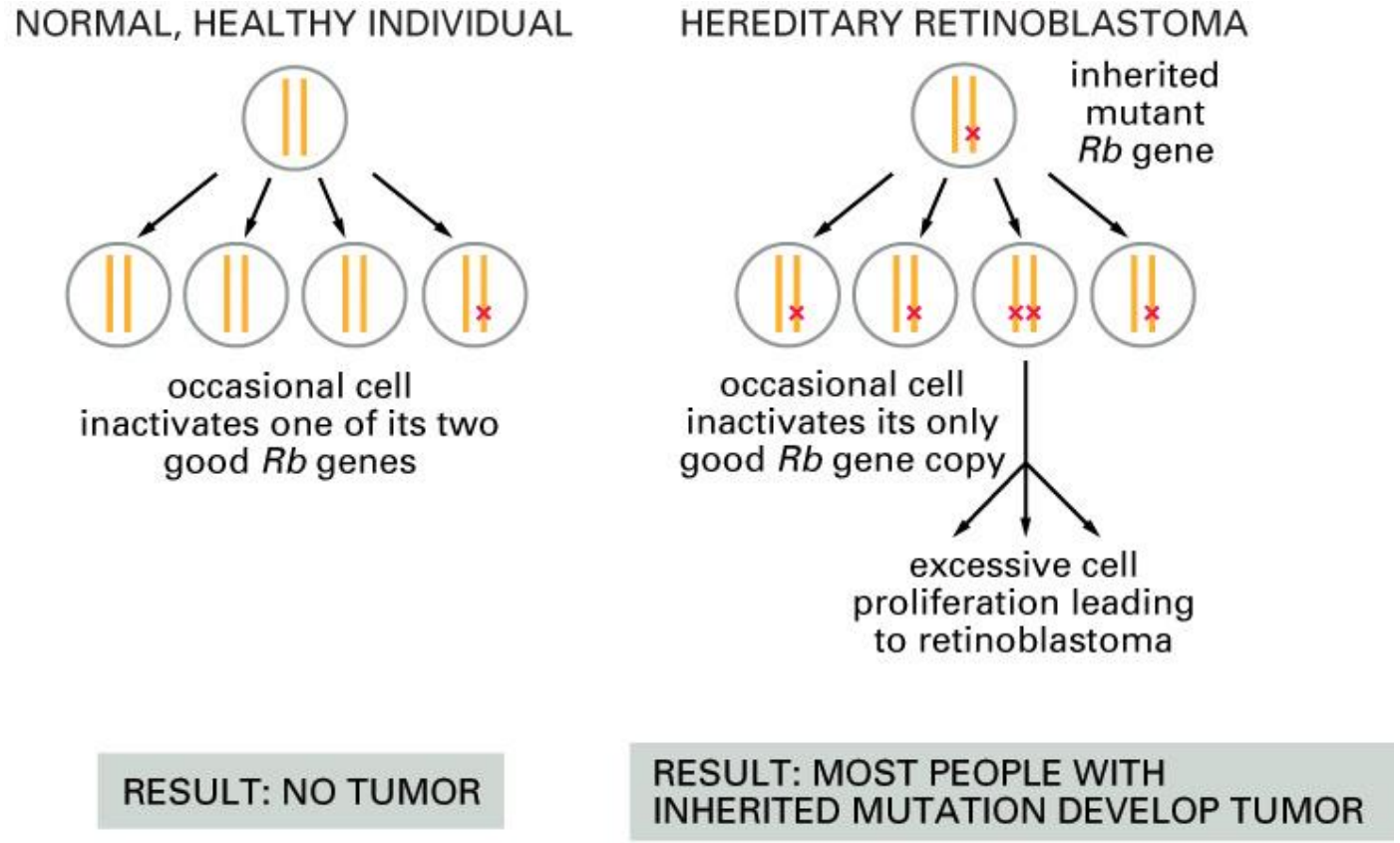
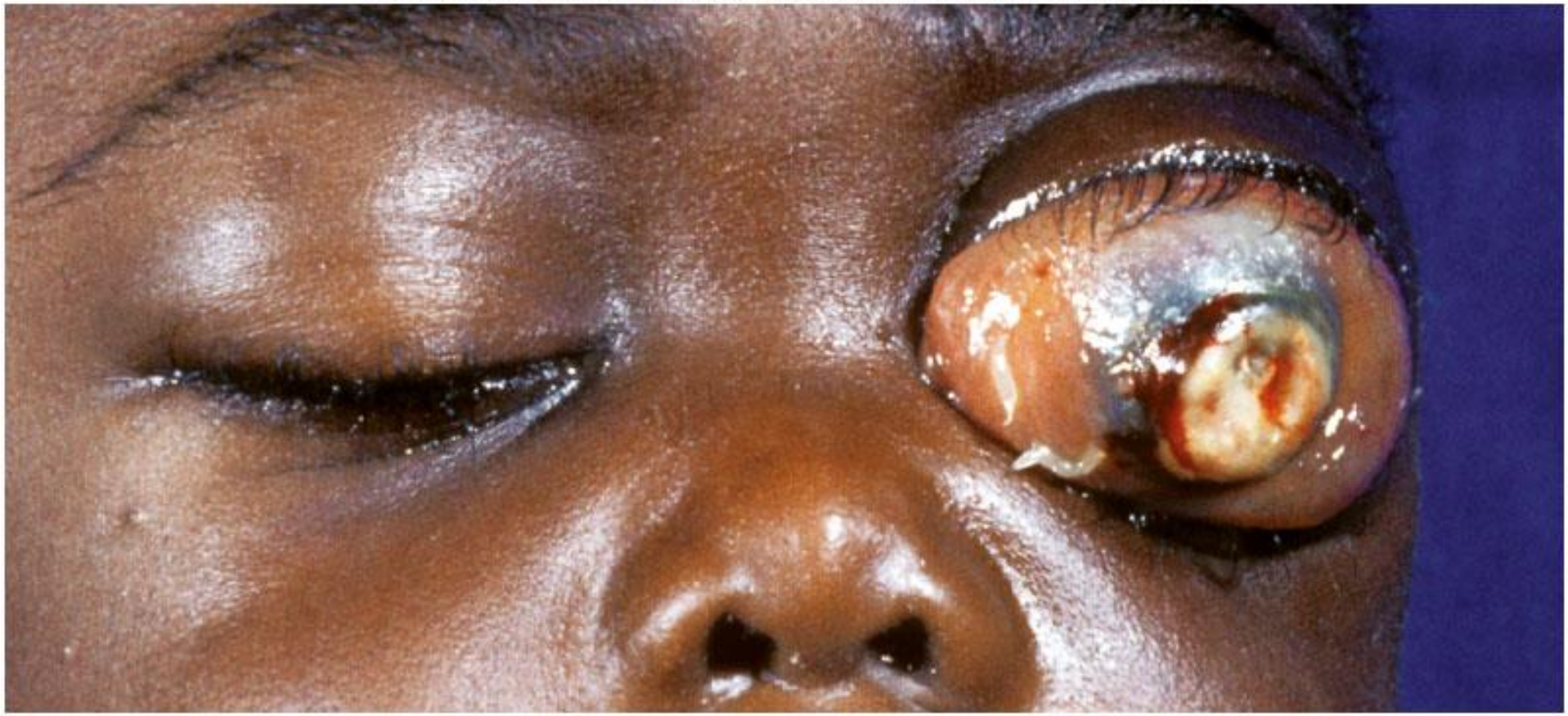
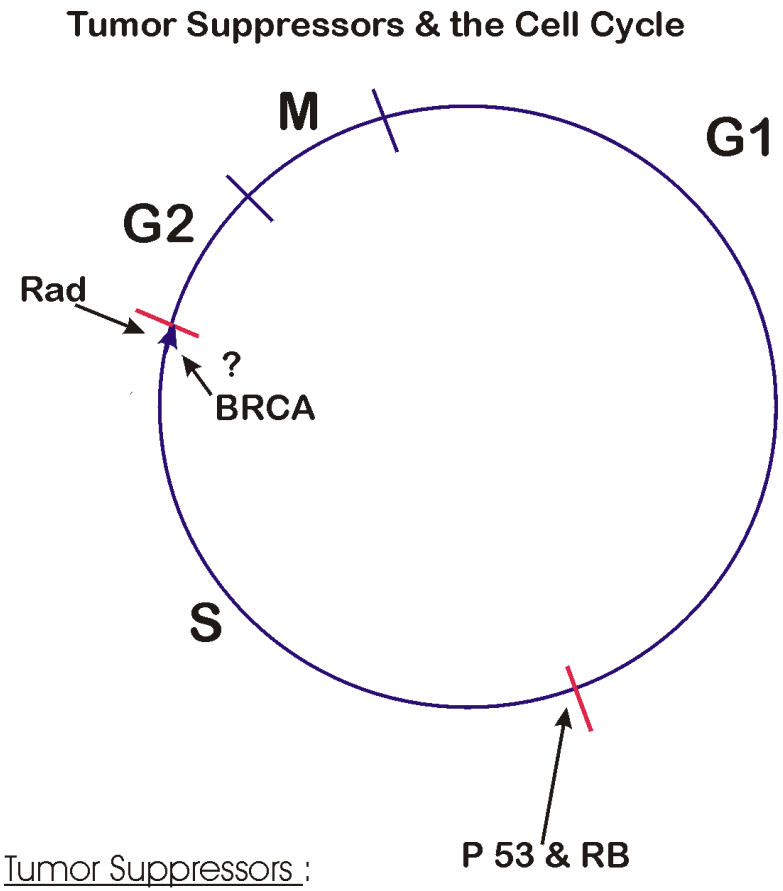


Figure 23–26 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Retinoblastoma is a heritable cancer



Tumor Suppressors Man the Checkpoints



Tumor Suppressors :

1. P 53 and RB control progress from G1 to "S" Both tend to reduce the rate of cell division.
2. Rad and BRCA both appear to detect damaged DNA at the end of "S". This prevents cells with DNA damage from reproducing.

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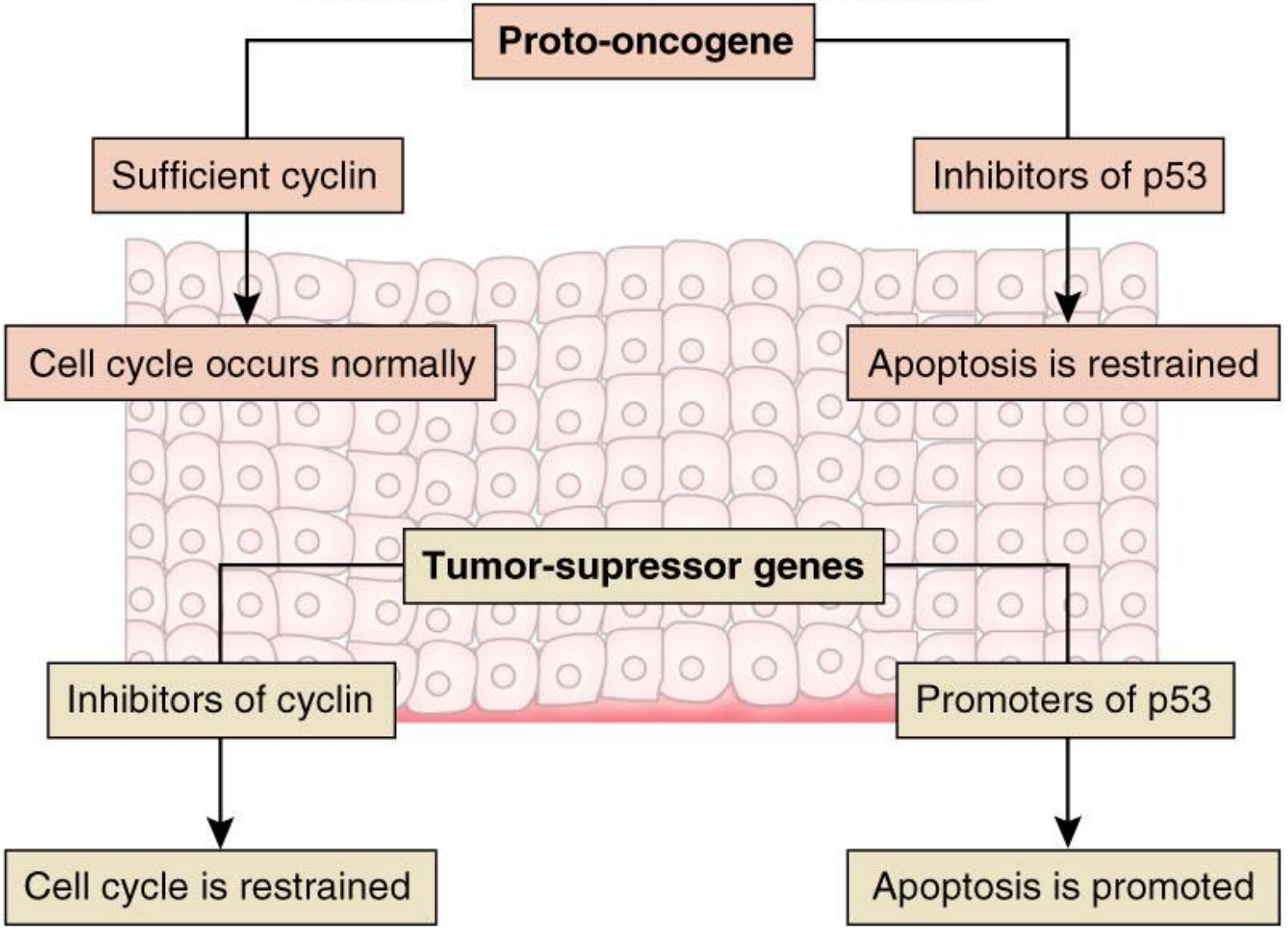
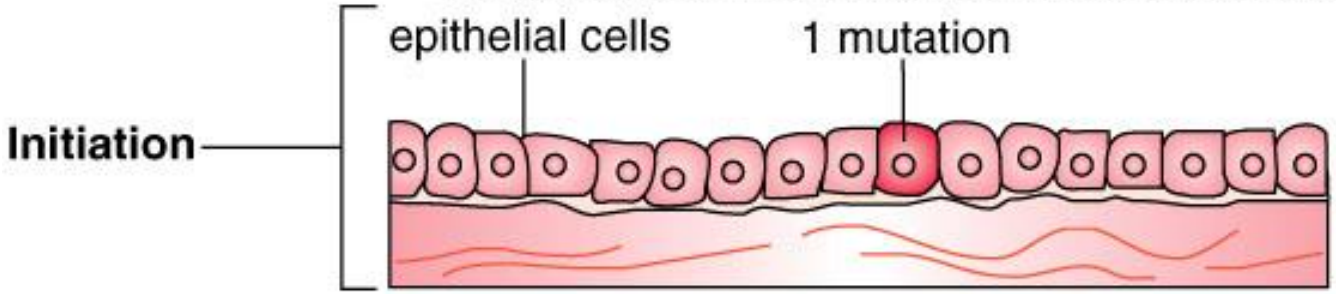
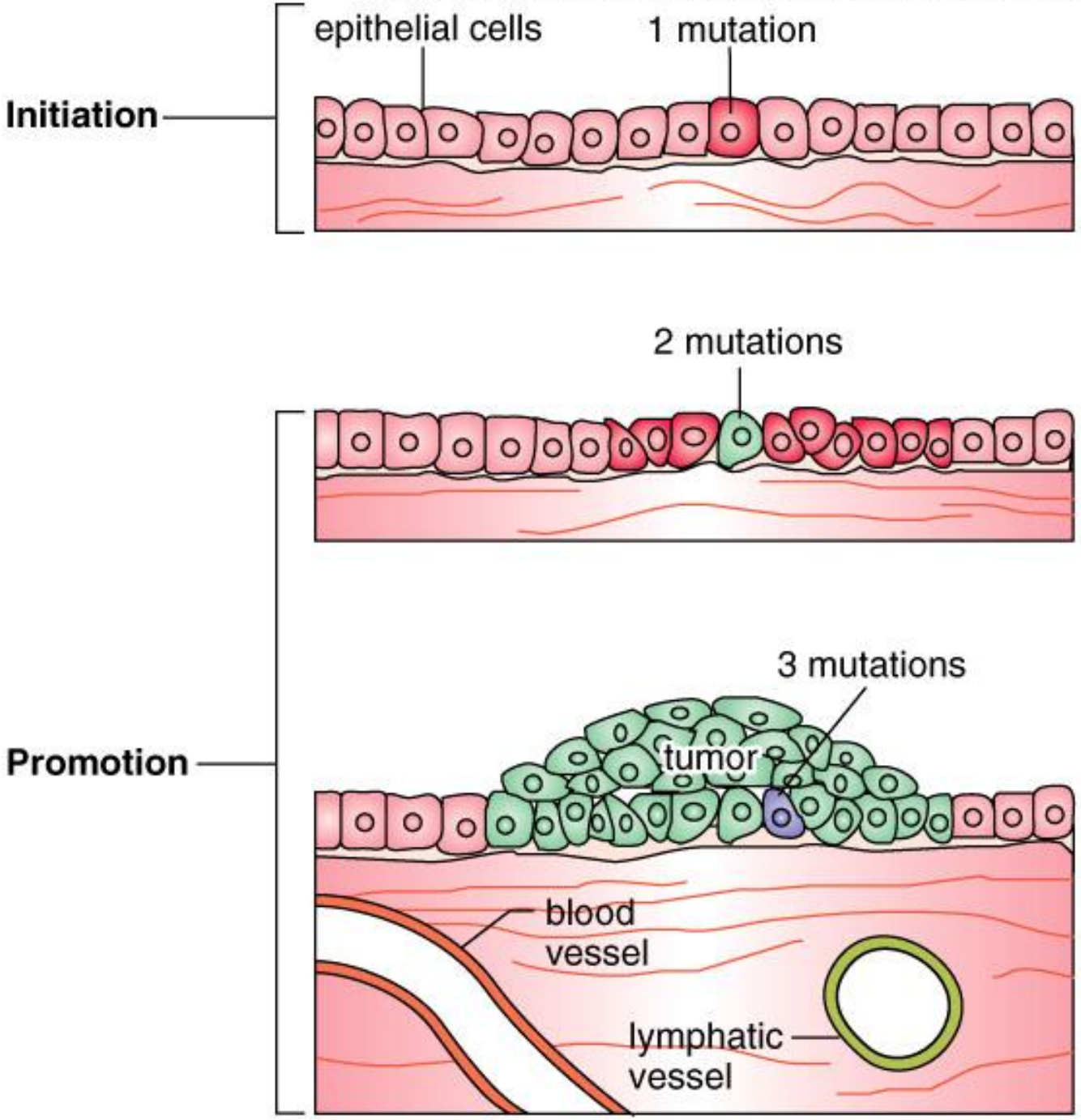
Proto-Oncogenes & Tumour Supressors- Normal Functions



Cancer starts from a single mutant cell



a. Cell (dark pink) acquires a mutation for repeated cell division.

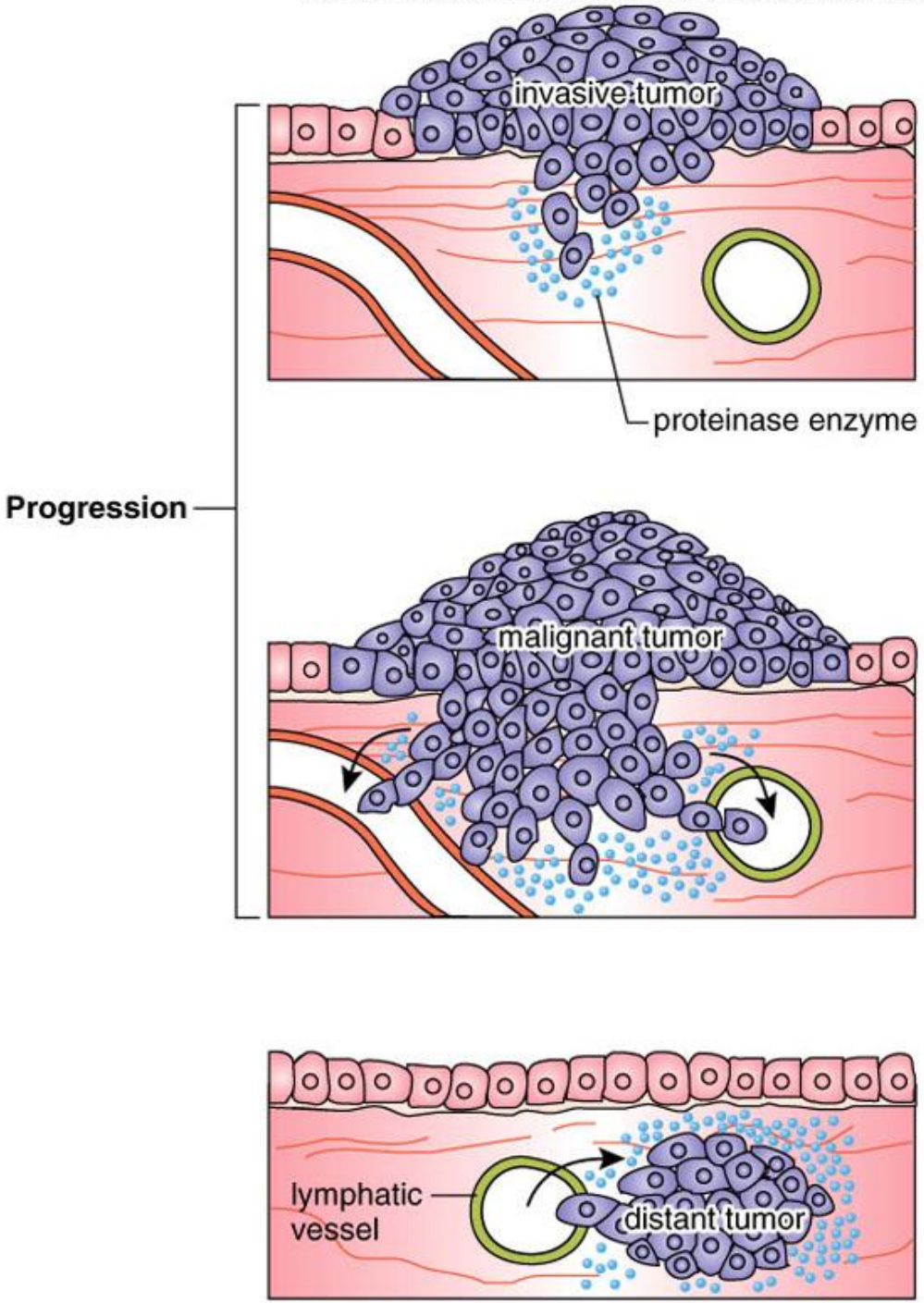


a. Cell (dark pink) acquires a mutation for repeated cell division.

b. New mutations arise, and one cell (green) has the ability to start a tumor.

c. Cancer in situ. The tumor is at its place of origin. One cell (purple) mutates further.

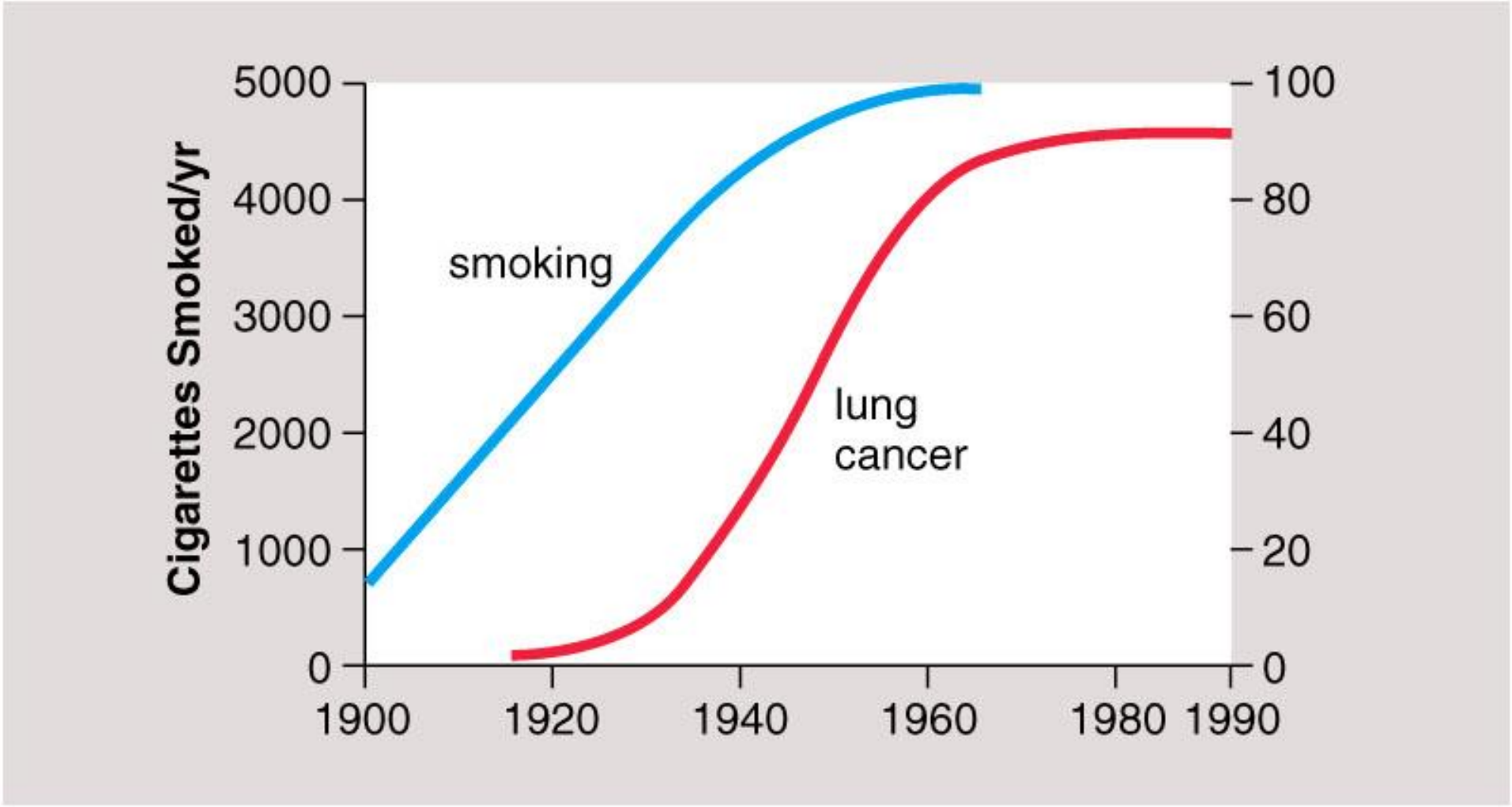
Fig



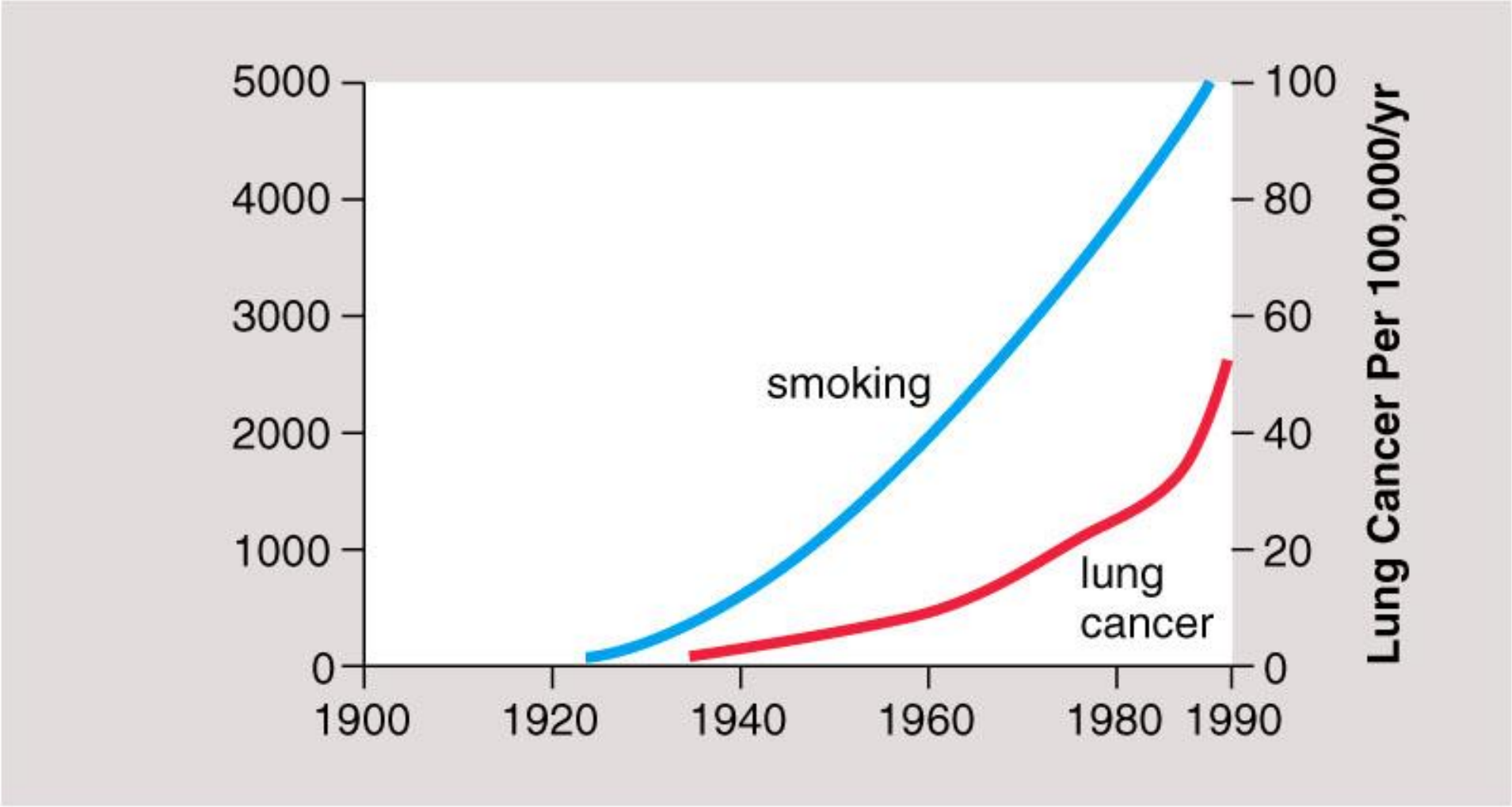
d. Cells have gained the ability to invade underlying tissues by producing a proteinase enzyme.

e. Cancer cells now have the ability to invade lymphatic and blood vessels.

f. New metastatic tumors are found some distance from the tumor.



a. Men in the United States



b. Women in the United States