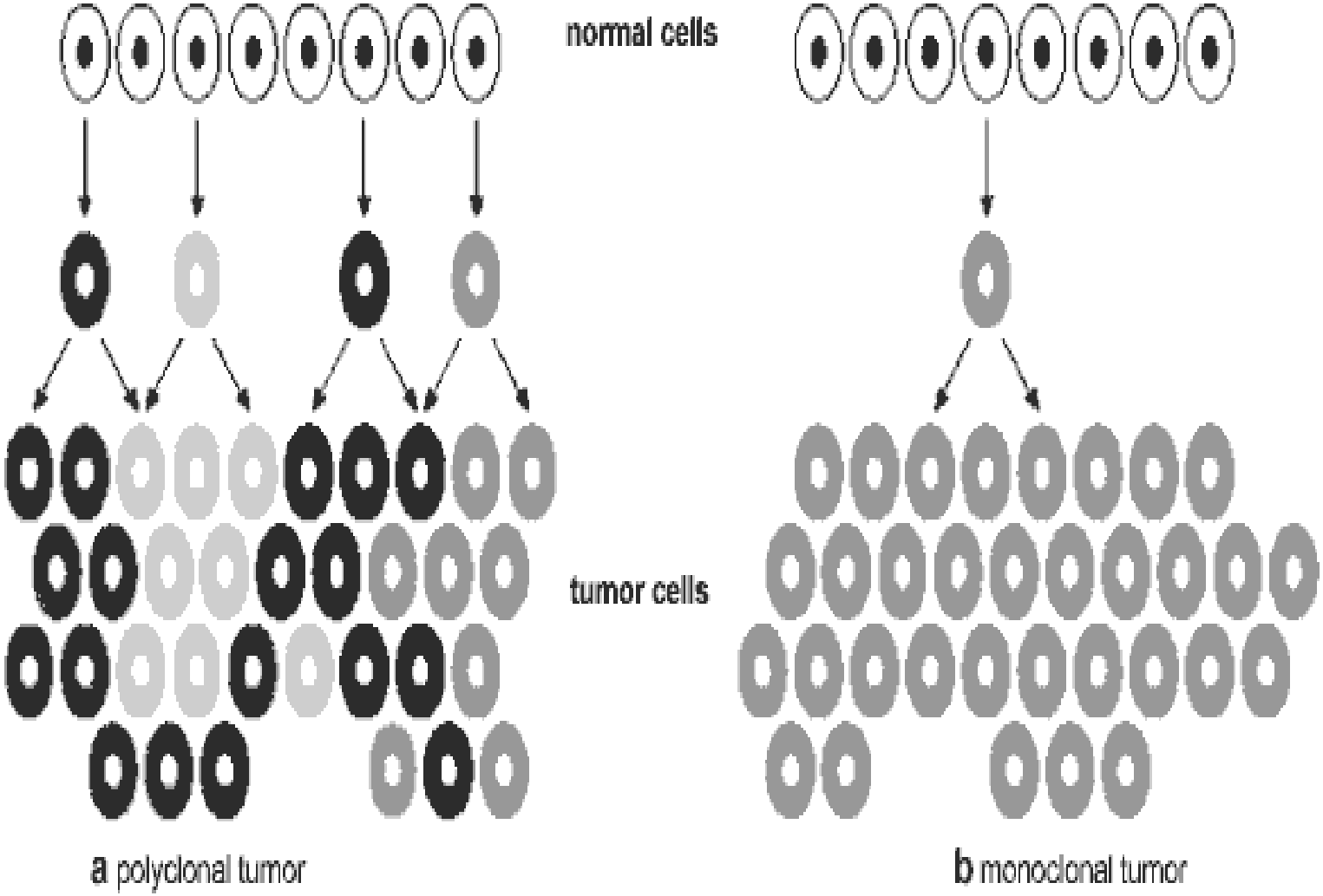
CARCINOGENESIS

MOLECULAR BASIS OF CANCER

- **Carcinogenesis** is a multistep process resulting from the accumulation of multiple genetic alterations that collectively give rise to cancer transformation.
- So that over a period of time, many tumors become more aggressive and acquire greater malignant potential. This phenomenon is referred to as **tumor progression.**
- Most malignant tumors are monoclonal in origin, by the time they become clinically evident their extremely heterogeneous. Thus, genetic evolution can explain two of the most properties of cancers:(1) the tendency for cancers to become more aggressive and (2) less responsive to therapy over time.

Molecular basis of cancer

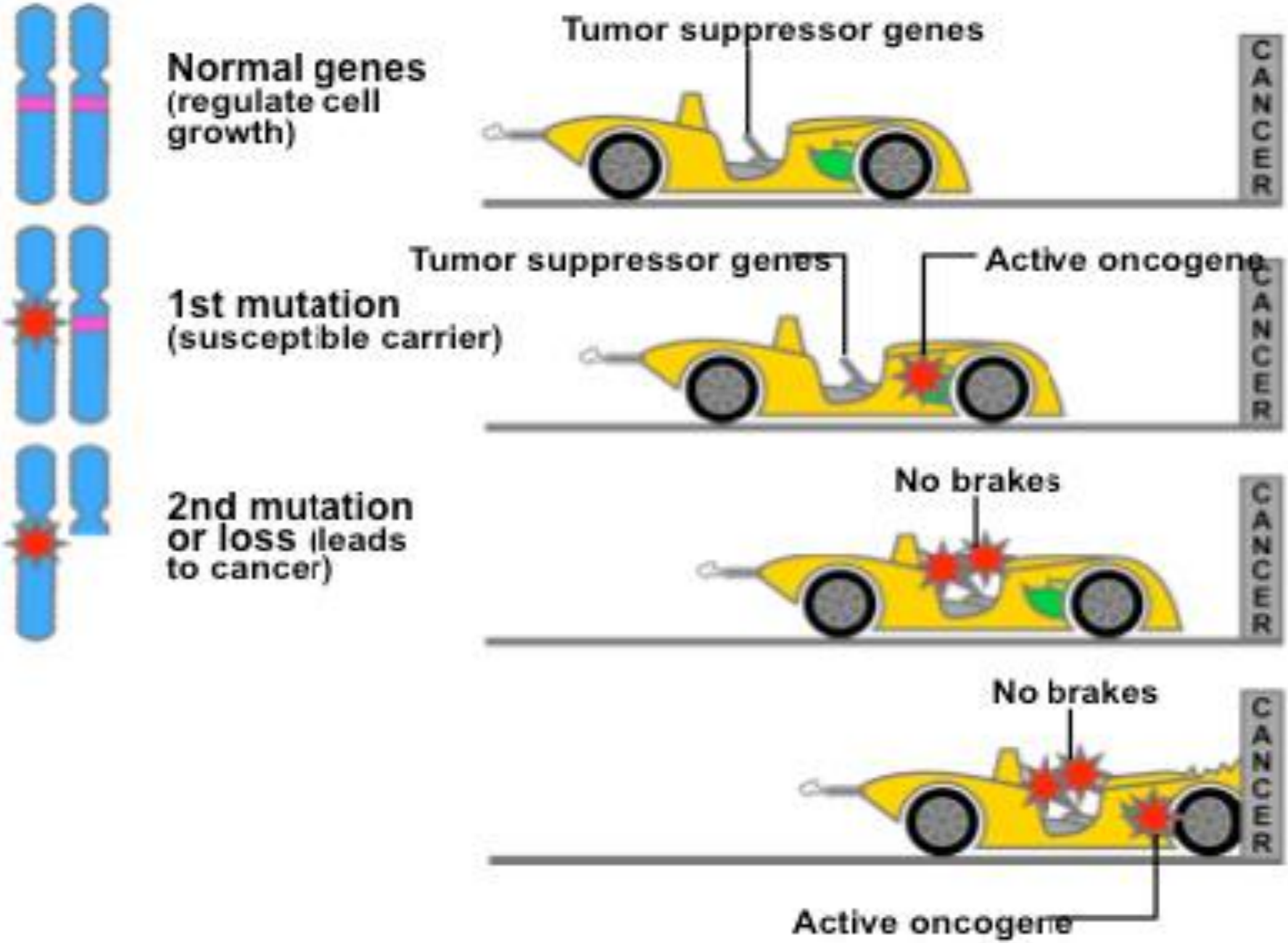
- Nonlethal genetic damage
- Tumors are monoclonal
- Four classes of normal regulatory genes are principal targets of genetic damage
  - growth-promoting proto-oncogenes
  - growth-inhibiting tumor suppressor genes
  - genes that regulate programmed cell death (apoptosis)
  - genes involved in DNA repair
- Carcinogenesis is a multistep process
  - accumulation of multiple mutations required
  - monoclonally initiated tumors evolve

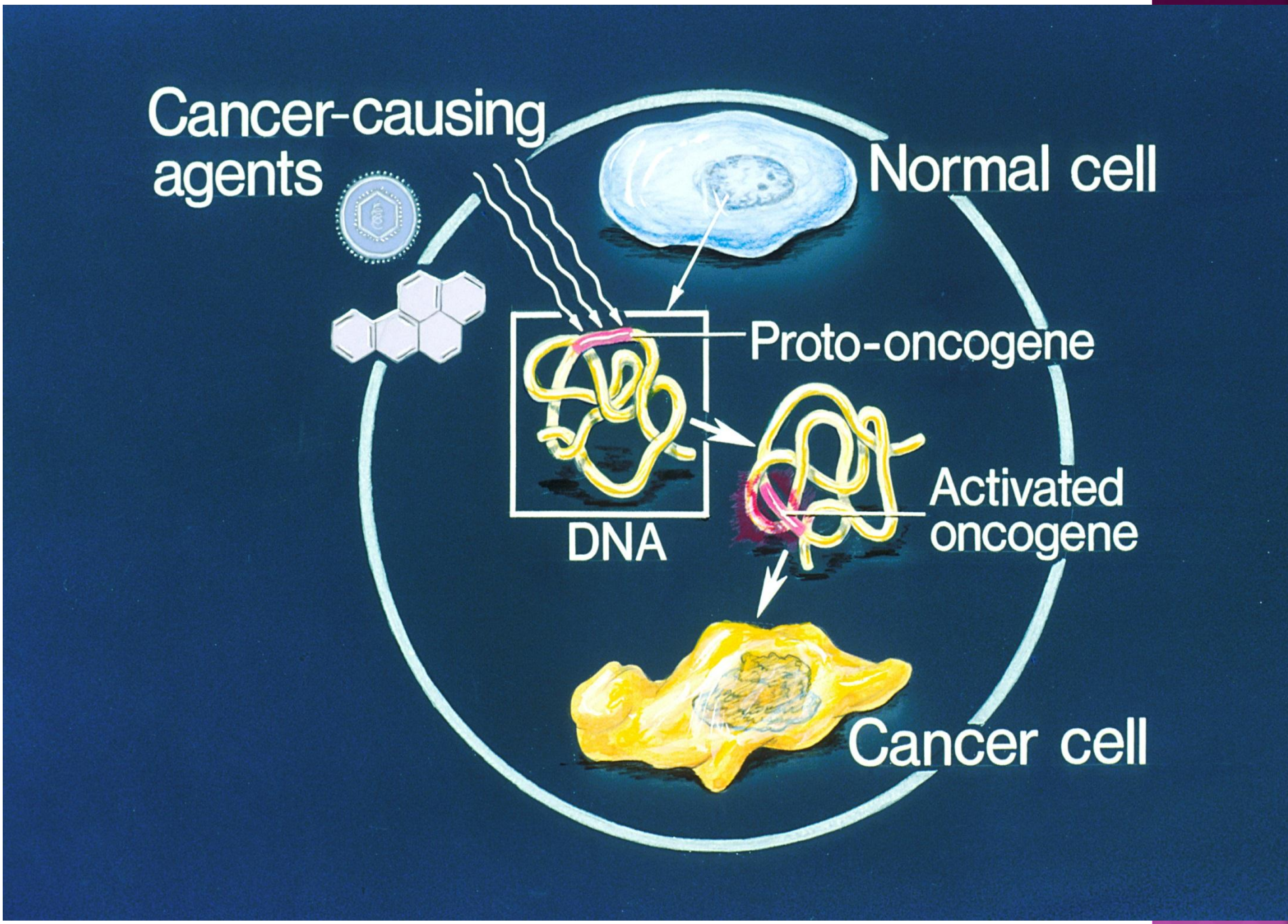

normal cells
tumor cells
a polyclonal tumor
b monoclonal tumor

* **Protooncogenes** are physiological regulators of the cell cycle—control cell proliferation and differentiation.
* **Oncogenes** –are characterized by ability to promote cell growth in the absence of normal mitogenic signals.
* **Oncoproteins** –are products of oncogenes: the production of which is independent of growth factors.

Tumor suppressor genes

- Normal function - inhibit cell proliferation
- Absence/inactivation of inhibitor --> cancer
- Both gene copies must be defective

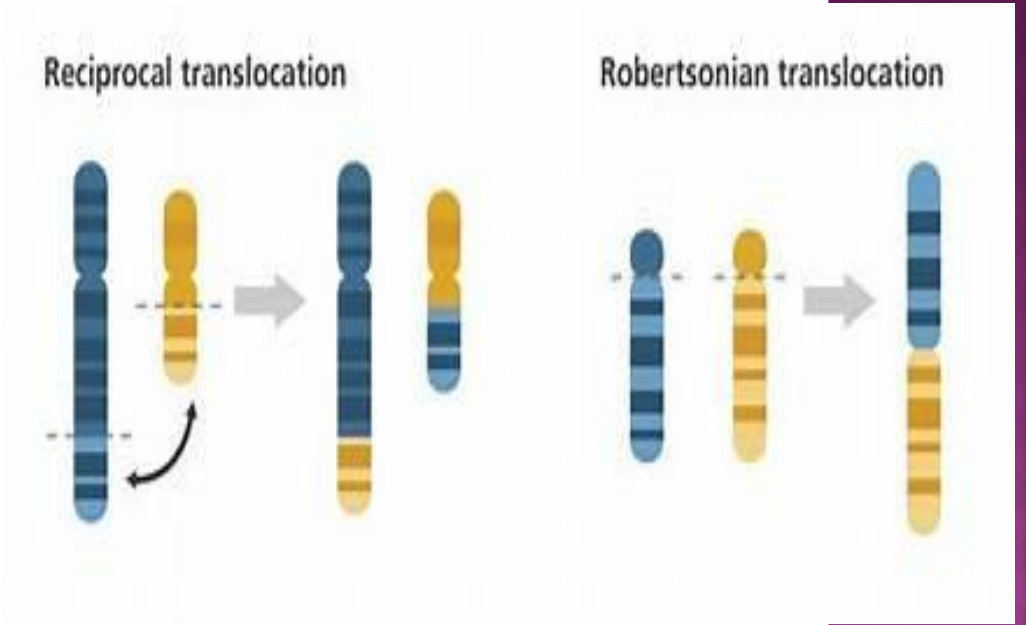

Normal genes
(regulate cell growth)
Tumor suppressor genes
CANCER
1st mutation
(susceptible carrier)
Tumor suppressor genes
Active oncogene
CANCER
2nd mutation
or loss (leads
to cancer)
No brakes
CANCER
No brakes
CANCER
Active oncogene


Cancer-causing agents
Normal cell
Proto-oncogene
DNA
Activated oncogene
Cancer cell

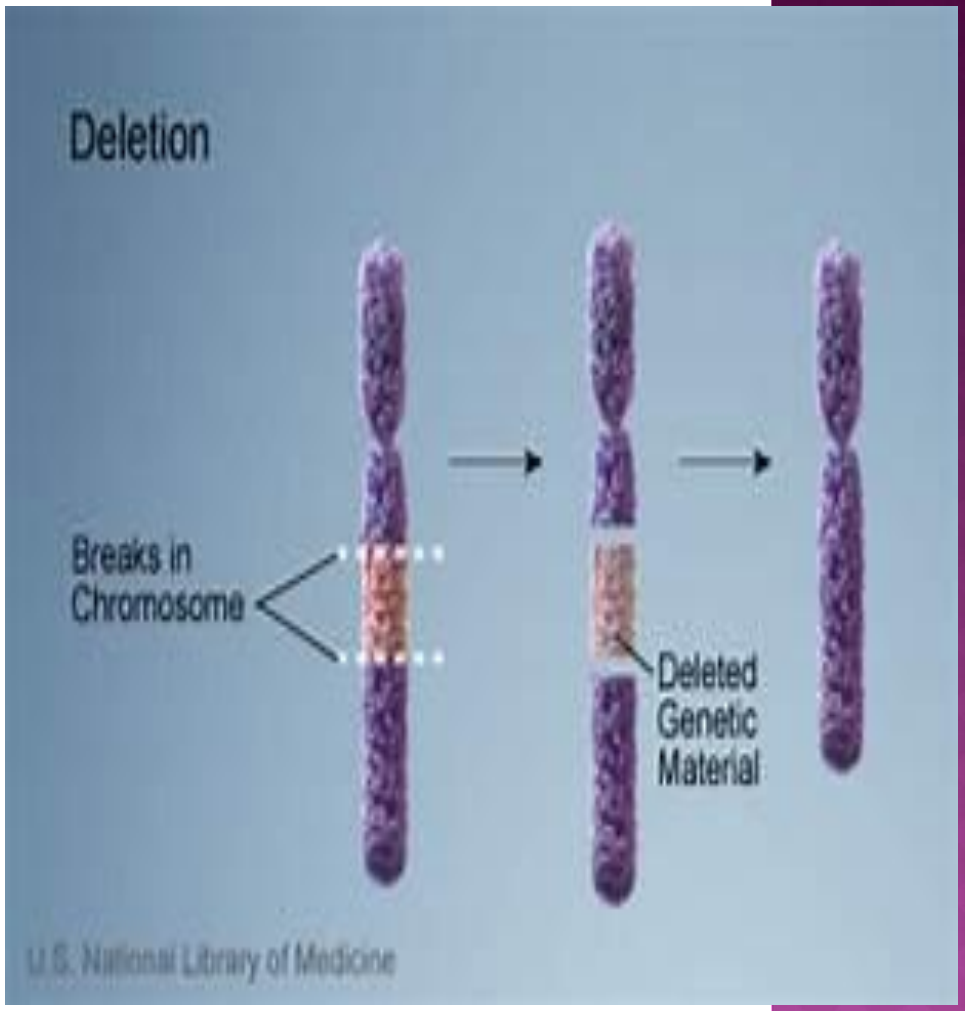
GENETIC CHANGES ASSOCIATED CARCINOGENESIS

- Tumor cells may acquire mutations through several means, including point mutations, and nonrandom chromosomal abnormalities that contribute to malignancy; these include balanced translocations, deletions, and gene amplification.

- Balanced translocations are overexpression of oncogenes or generation of proteins with altered signaling capacity.



- Deletions frequently affect tumor suppressor genes,
- whereas gene amplification increases the expression of oncogenes.
- amplification may produce several hundred copies of the proto-oncogene in the tumor cell.



Molecular Basis of multistep carcinogenesis

- Neoplastic transformation is a progressive process involving multiple "hits" or genetic changes.
- Accumulation of multiple mutations since we need six fundamental changes

Hallmarks of Cancer
Six fundamental changes

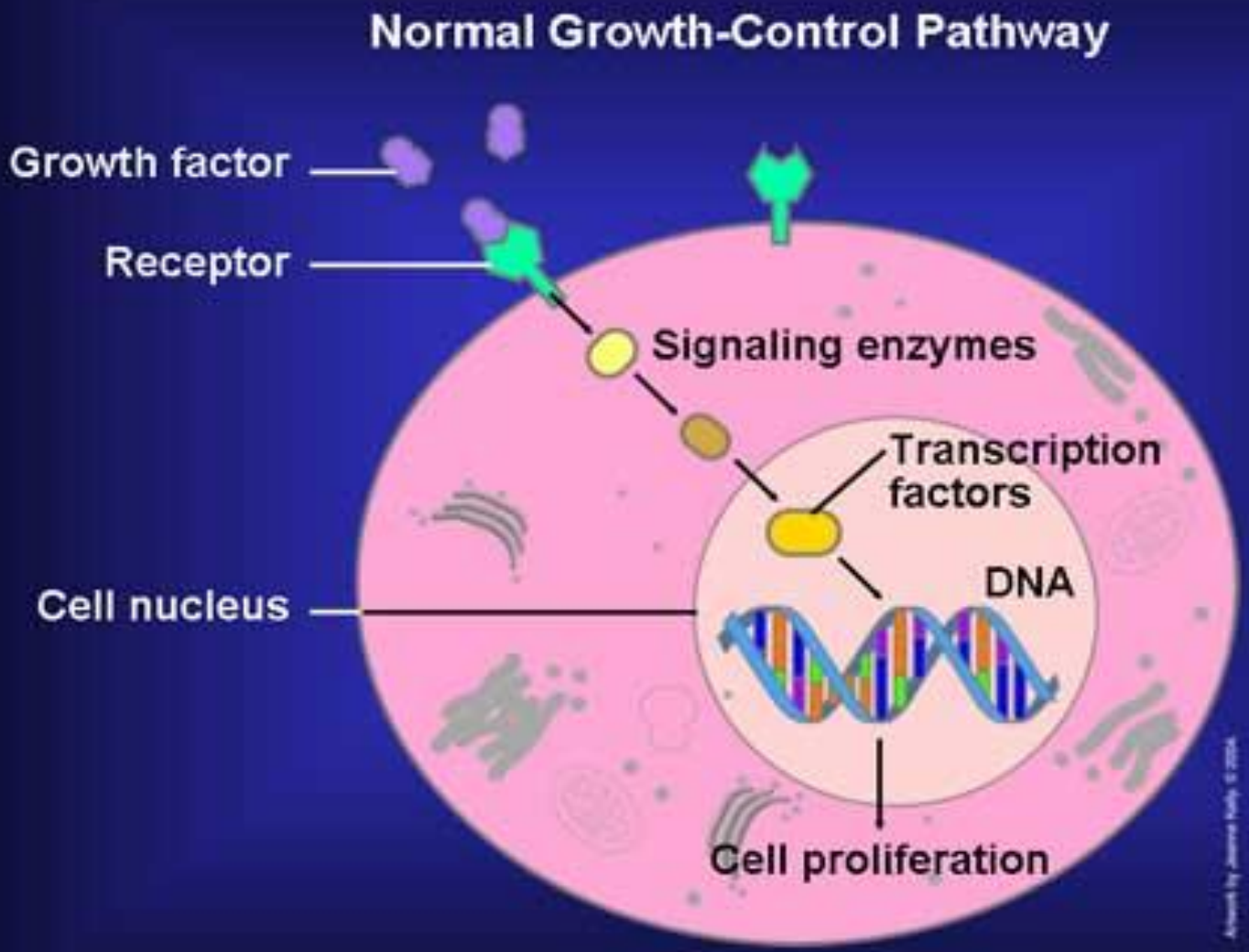
1. Self sufficiency in growth factors
2. Insensitivity to growth-inhibitory signals
3. Evasion of apoptosis
4. Limitless replicative potential
5. Sustained angiogenesis
6. Ability to invade and metastasize

SELF-SUFFICIENCY IN GROWTH SIGNALS

- Cancer cells use a number of strategies to drive their proliferation and become insensitive to normal growth regulators. All normal cells require stimulation by growth factors to undergo proliferation. Most soluble growth factors are made by one cell type and act on a neighboring cell to stimulate proliferation (paracrine action).

- Many cancer cells acquire growth self-sufficiency by acquiring the ability to synthesize the same growth factors to which they are responsive , in some cases, tumor cells send signals to activate normal cells in the supporting stroma, which in turn produce growth factors that promote tumor growth.

Proto-Oncogenes and Normal Cell Growth

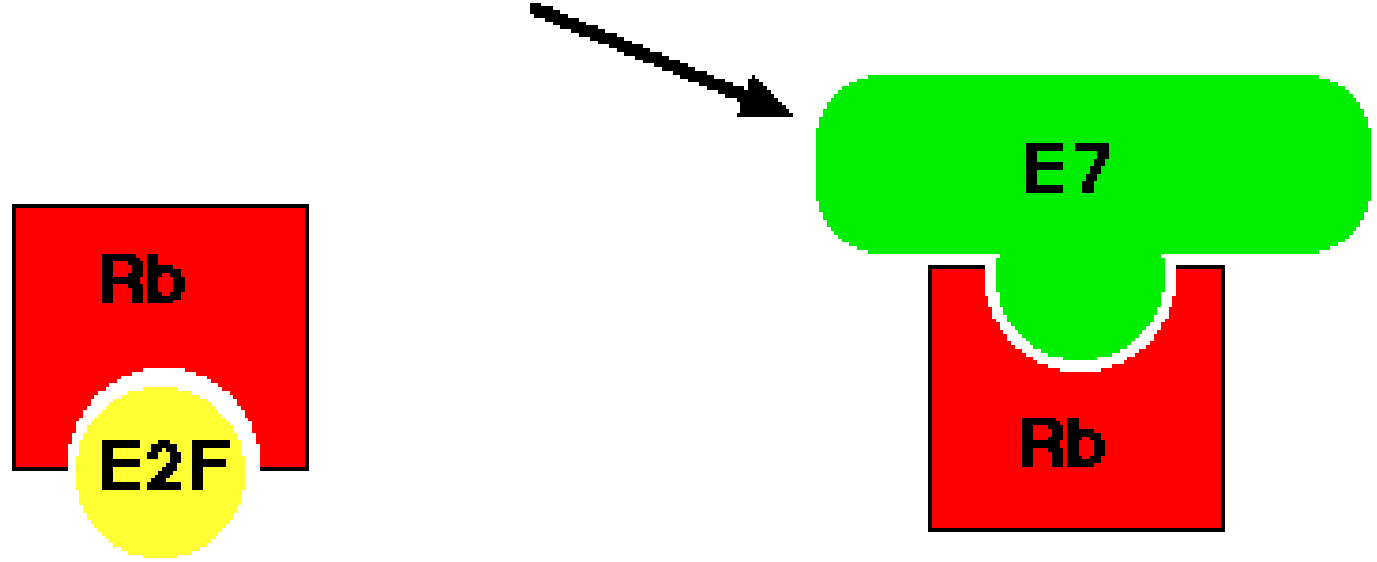


INSENSITIVITY TO GROWTH INHIBITORY SIGNALS

- The products of tumor suppressor genes apply brakes to cell proliferation.
- RB Gene: Governor of the Cell Cycle
  It is useful to begin with the retinoblastoma gene (*RB*),the first tumor suppressor gene to be discovered.
- Unlike oncogenes, both copies of the gene must be dysfunctional for tumor development to occur.

- Loss of cell cycle control is fundamental to malignant transformation.
- Almost all cancers have a disabled G1 checkpoint due to mutation of either *RB* or genes that affect Rb function, such as cyclin D, CDK4, and CDKIs.
- Many oncogenic DNA viruses, like HPV, encode proteins (e.g., E7) that bind to Rb and render it nonfunctional.

E7 - an oncogene product of one of the human papilloma viruses



Promoters

Promoters "off";
cell remains in G0

Promoters

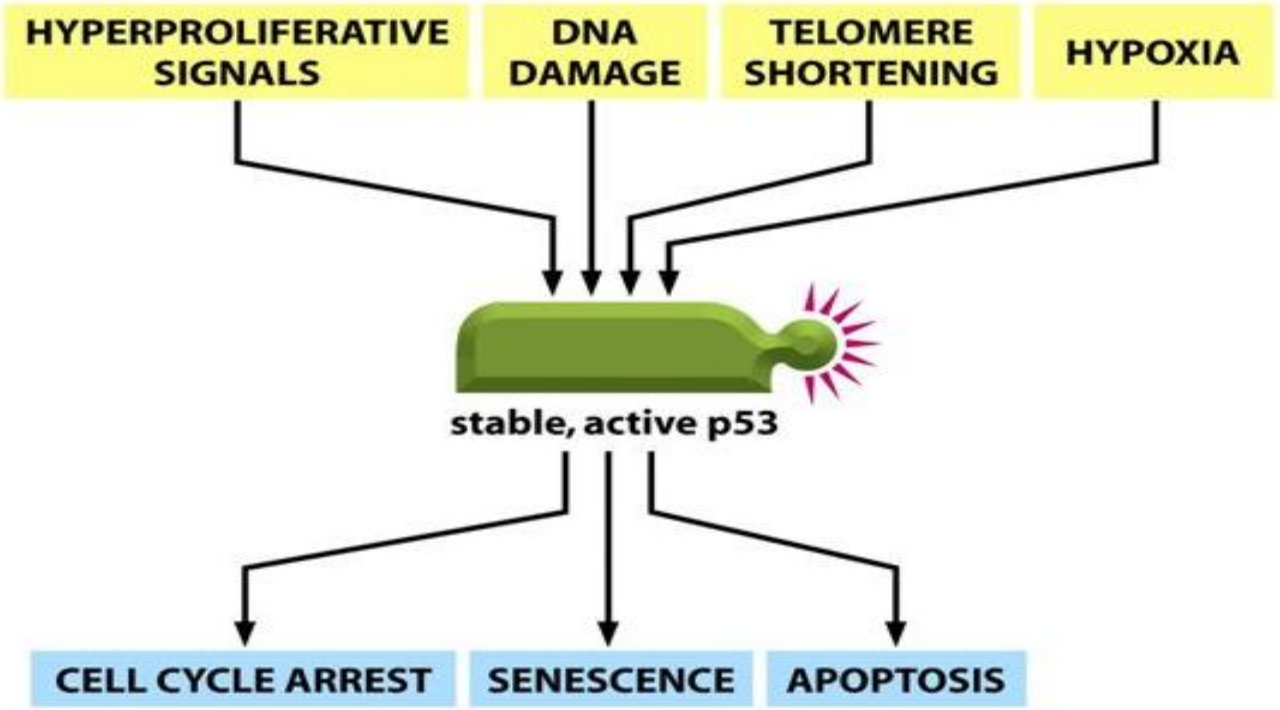
Promoters "on";
cell begins mitosis

P53 GENE: GUARDIAN OF THE GENOME

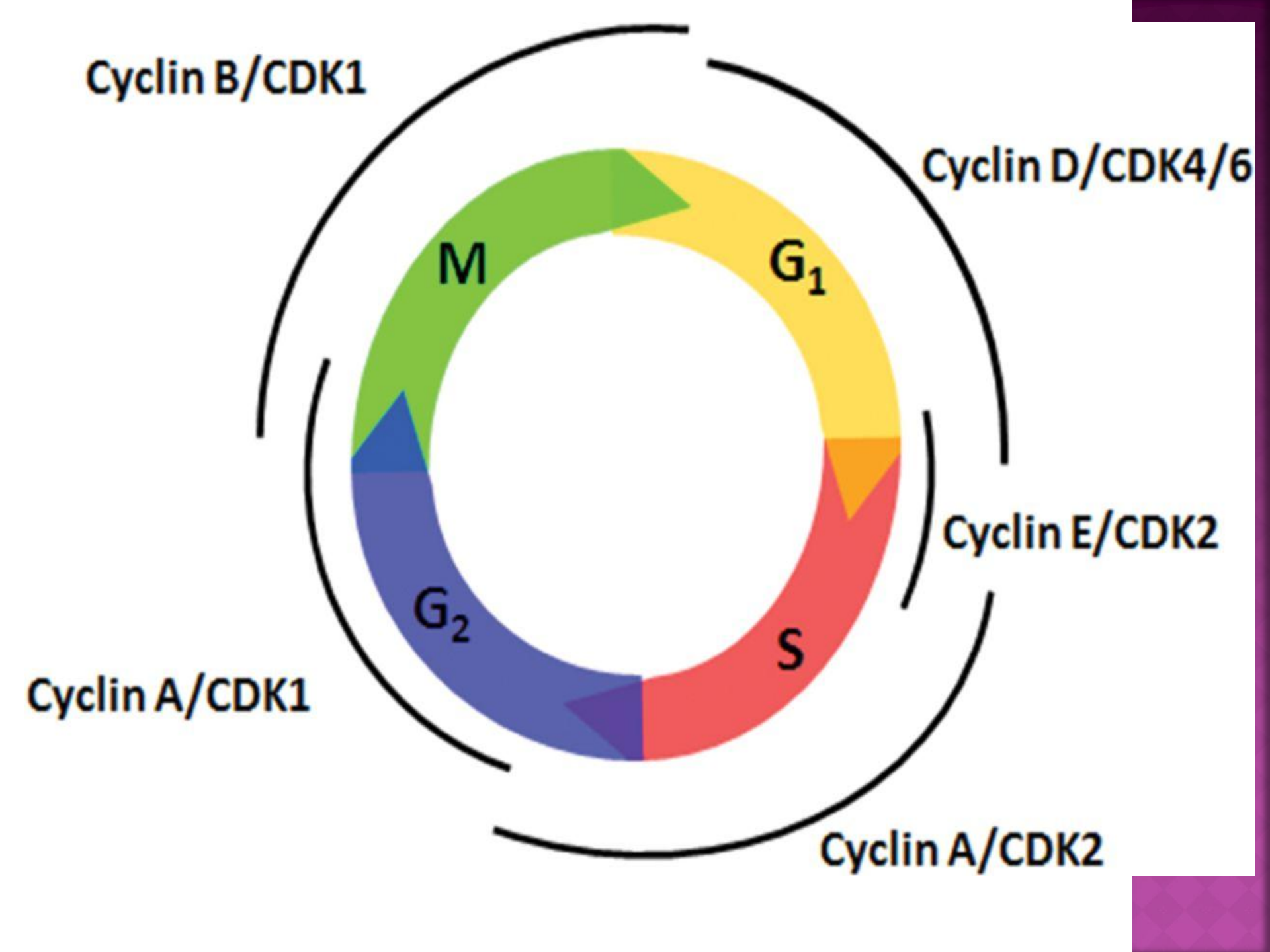
- The p53 is a tumor suppressor gene which is one of the most commonly mutated genes in human cancers.
- The P53 have a central monitor of internal stress, directing the stressed cells toward one of these three pathways.

- p53 protein prevents neoplastic transformation by three interlocking mechanisms:
- activation of temporary cell cycle arrest (termed quiescence)
- induction of permanent cell cycle arrest (termed senescence),
- or triggering of programmed cell death (termed apoptosis).

p53 Tumor Suppressor Gene



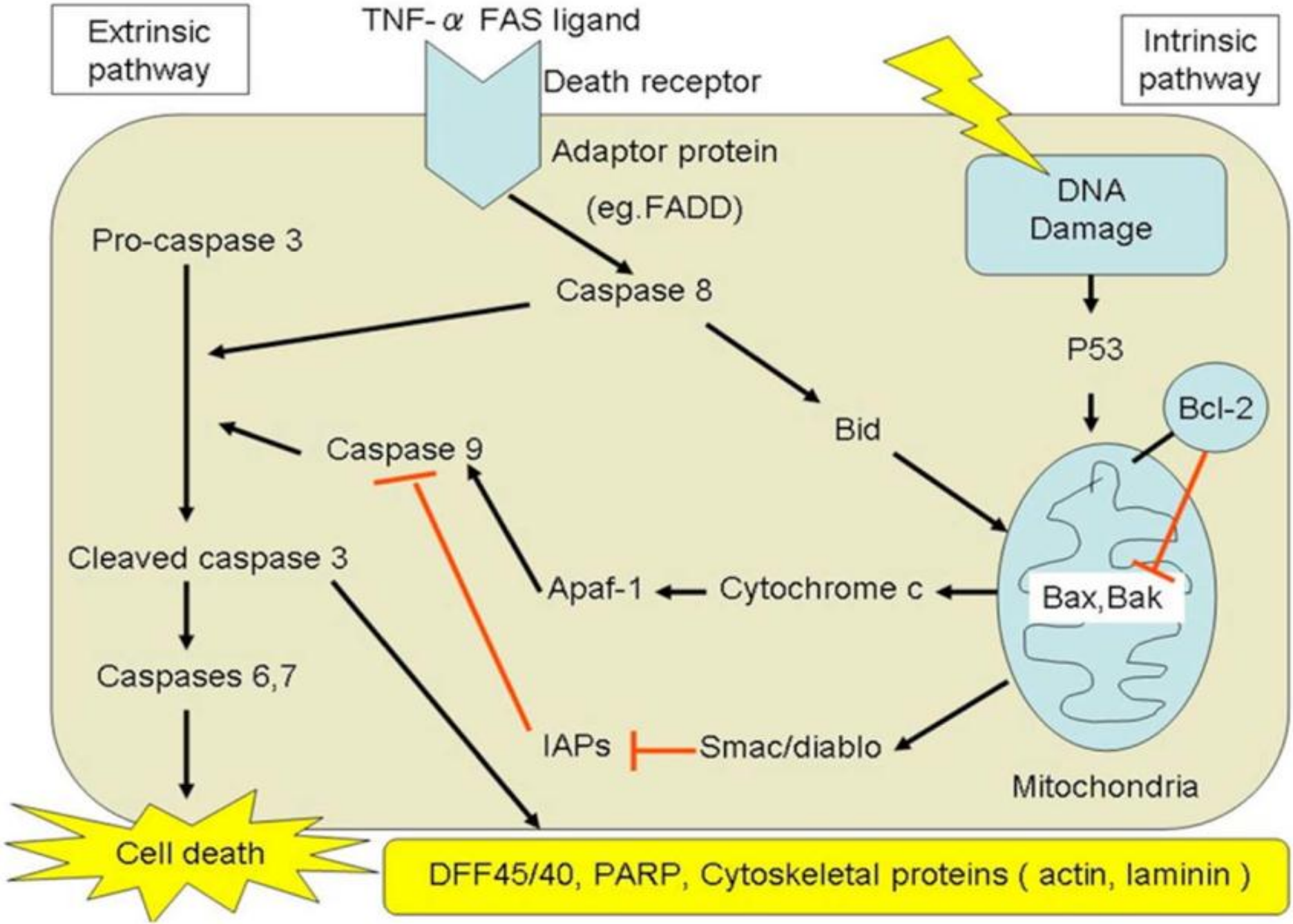
- Functions in checkpoint pathway for DNA damage or other cell stresses
- Can either induce apoptosis or block cell division
- Inactivation leads to further genetic alterations


Cyclin B/CDK1
Cyclin D/CDK4/6
M
G1
Cyclin E/CDK2
G2
S
Cyclin A/CDK1
Cyclin A/CDK2

EVATION OF CELL DEATH

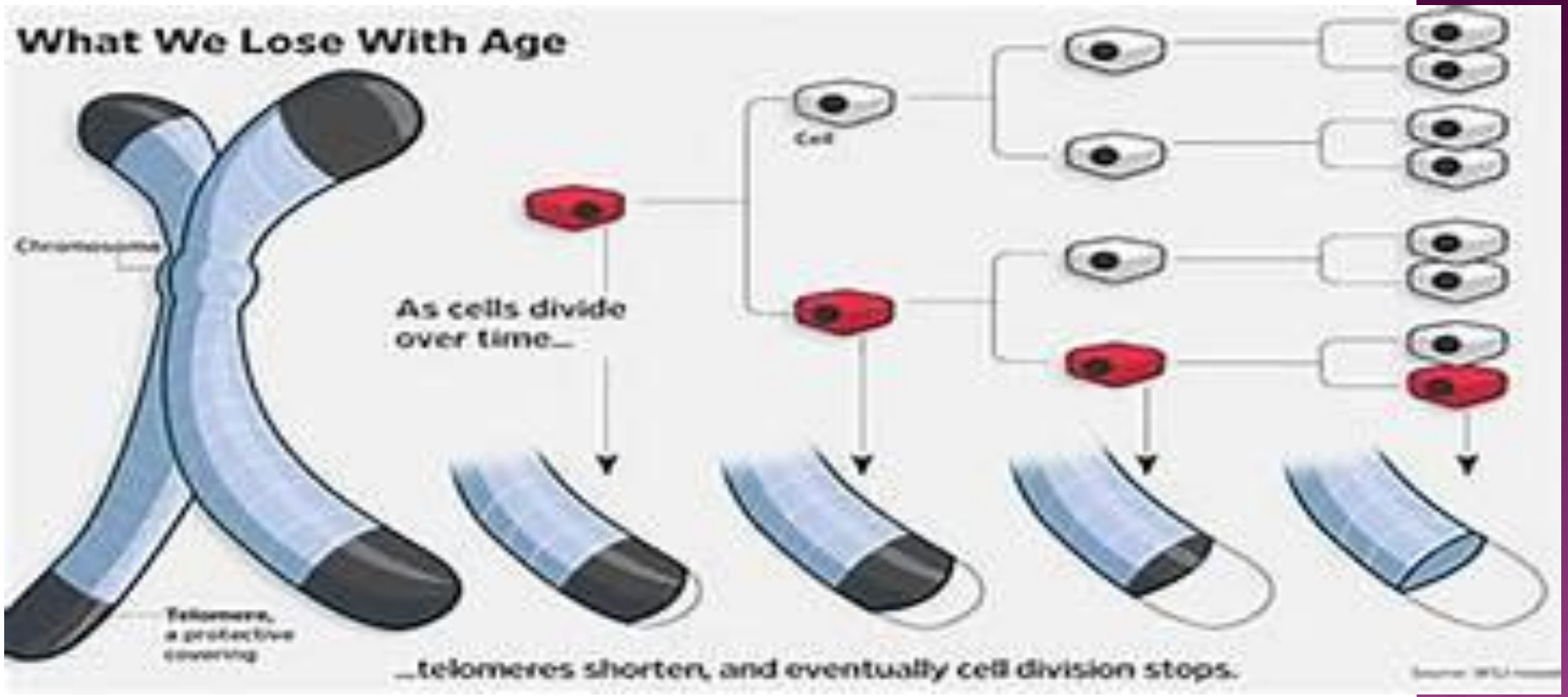
- Accumulation of neoplastic cells may result not only from activation of growth promoting oncogenes or inactivation of growth-suppressing tumor suppressor genes but also from mutations in the genes that regulate apoptosis.

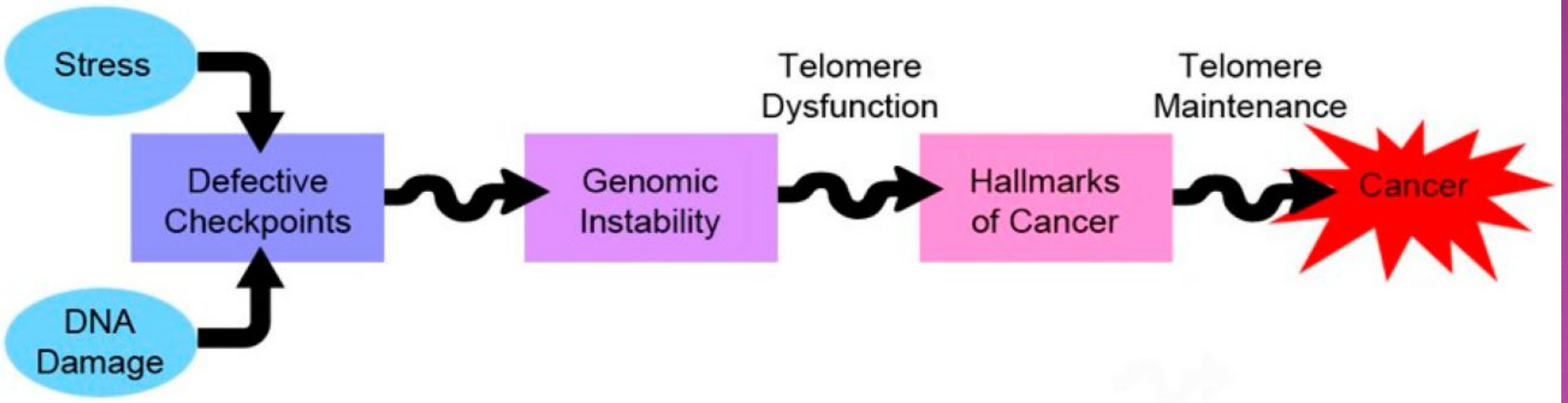
- Apoptosis can be initiated through extrinsic or intrinsic pathways. Both pathways result in the activation of a proteolytic cascade of caspases that destroys the cell. Mitochondrial outer membrane permeabilization is regulated by the balance between pro-apoptotic (e.g., BAX) and anti-apoptotic molecules (BCL2).
- In 85% of follicular B cell lymphomas, the anti-apoptotic gene *BCL2* is activated by the translocation.


Extrinsic pathway
TNF-α FAS ligand
Death receptor
Intrinsic pathway
Adaptor protein
(eg.FADD)
DNA Damage
Pro-caspase 3
Caspase 8
P53
Bcl-2
Bid
Caspase 9
Cleaved caspase 3
Apaf-1
Cytochrome c
Bax,Bak
Caspases 6,7
IAPs
Smac/diablo
Mitochondria
Cell death
DFF45/40, PARP, Cytoskeletal proteins (actin, laminin)

LIMITLESS REPLICATIVE POTENTIAL

- **Most normal human cells have a capacity of 60 to 70 doublings. Thereafter, the cells lose the capacity to divide and enter senescence. This phenomenon take place as a result of progressive shortening of *telomeres* , *cancer cell gain telomerase dysfunction* at the ends of chromosomes to achieving immortality.**

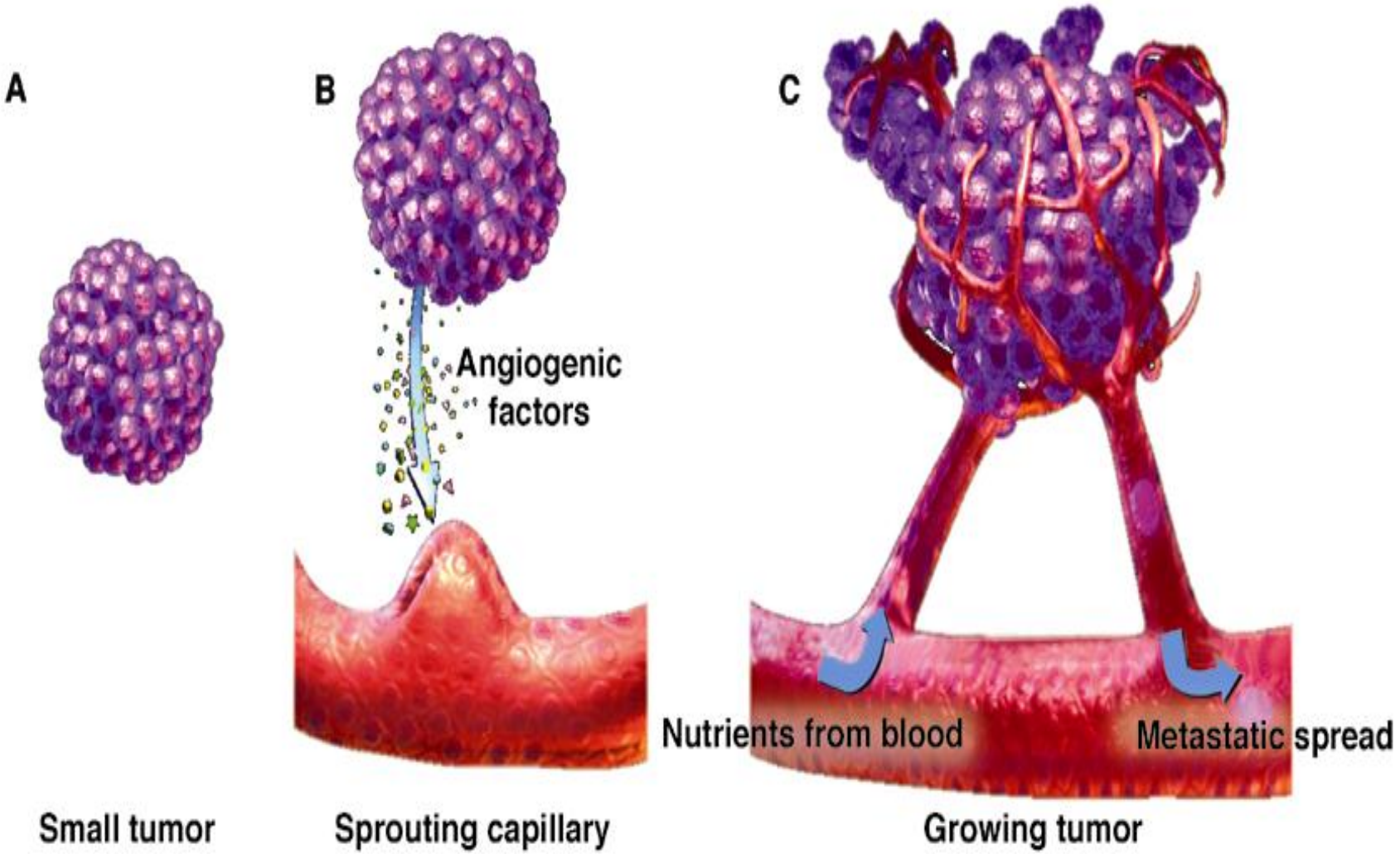

What We Lose With Age
As cells divide over time...
...telomeres shorten, and eventually cell division stops.

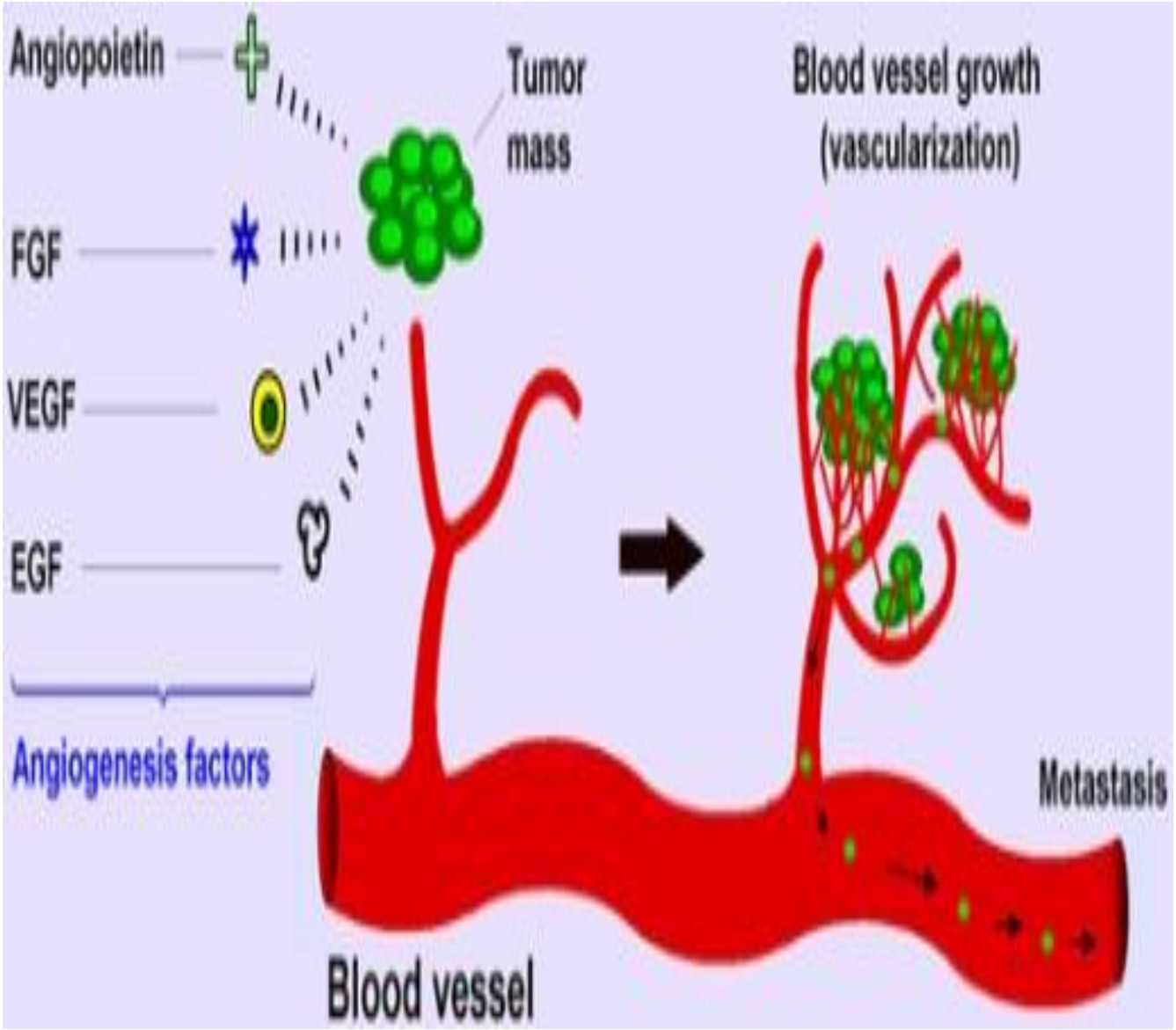

Stress
DNA Damage
Defective Checkpoints
Genomic Instability
Telomere Dysfunction
Hallmarks of Cancer
Telomere Maintenance
Cancer

DEVELOPMENT OF SUSTAINED ANGIOGENESIS

- Like normal tissues,tumors require delivery of oxygen and nutrients and removal of waste products;
- 1- to 2-mm zone represents the maximal distance across which oxygen, nutrients, and waste can diffuse from blood vessels

- . Cancer Angiogenesis is required not only for continued tumor growth but also for access to the vasculature and hence for metastasis.
- Angiogenesis is thus a necessary biologic correlate of neoplasia, both benign and malignant.
- Vascularization of tumors is essential for cancer growth and is controlled by Hypoxia triggers angiogenesis through the actions of HIF-1α and VEGF.


A
B
C
Angiogenic factors
Nutrients from blood
Metastatic spread
Small tumor
Sprouting capillary
Growing tumor

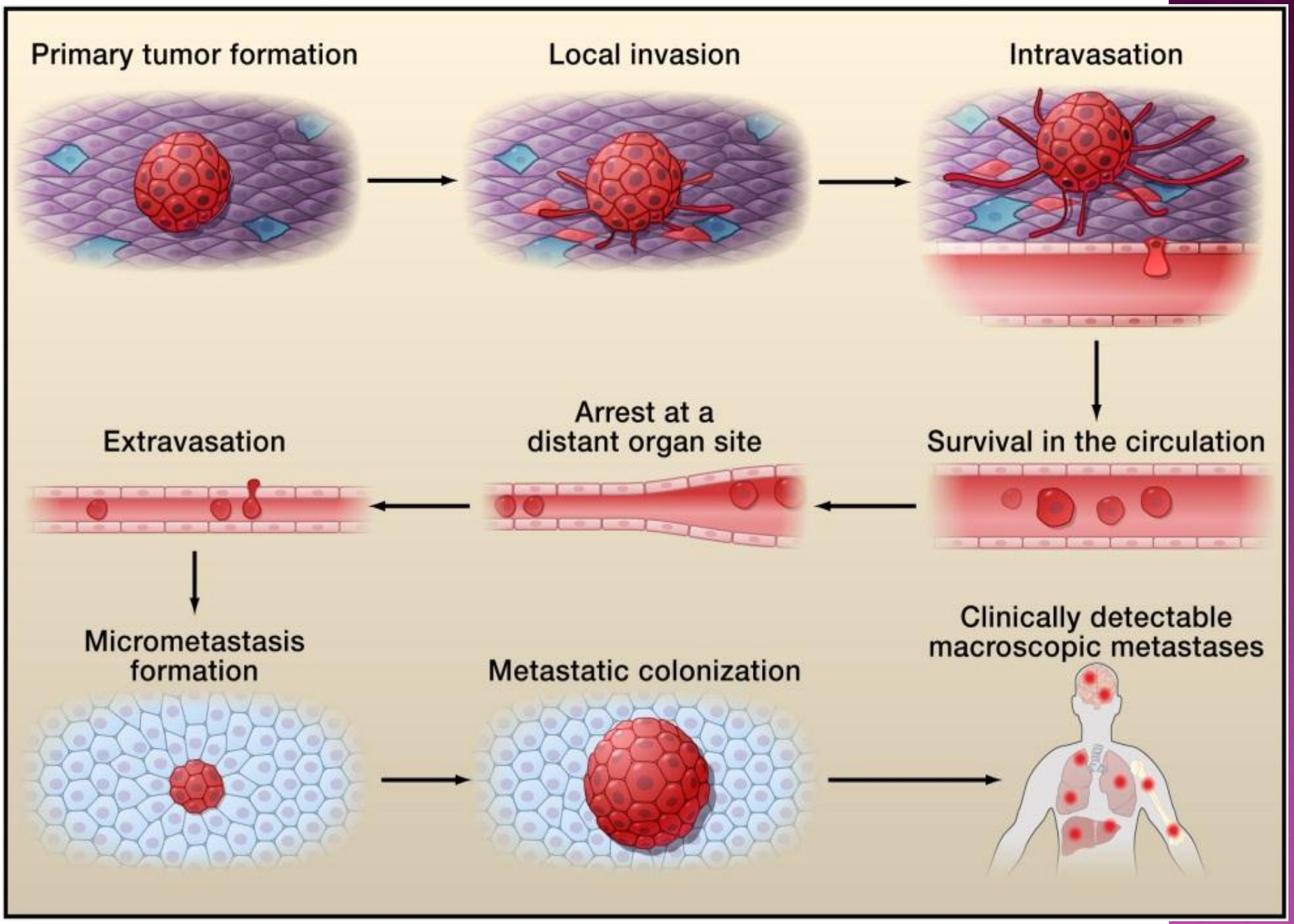

Angiopoietin
FGF
VEGF
EGF
Angiogenesis factors
Tumor mass
Blood vessel growth (vascularization)
Metastasis
Blood vessel

ABILITY TO INVADE AND METASTASIZE

- **The first step in the metastatic cascade is a *loosening* of tumor cells. E-cadherins act as intercellular glues, and their cytoplasmic portions bind to ß-catenin. Adjacent E-cadherin molecules keep the cells together; in addition, E-cadherin can transmit antigrowth signals by sequestering ß-catenin.**

- **The second step in invasion is local *degradation of the basement membrane and interstitial connective tissue by the action of* MMPs that regulate tumor invasion by remodeling insoluble components of the basement membrane and interstitial matrix.**

- The metastatic site of many tumors can be predicted by the location of the primary tumor. Many tumors arrest in the first capillary bed they encounter (lung and liver). Some tumors show organ tropism, probably due to activation of adhesion or chemokine receptors whose ligands are expressed by endothelial cells at the metastatic site.


Primary tumor formation
Local invasion
Intravasation
Survival in the circulation
Arrest at a
distant organ site
Extravasation
Micrometastasis
formation
Metastatic colonization
Clinically detectable
macroscopic metastases

Suggestive Reading

Vinay Kumer, Apul L. Abbass, Jon C. Aster. Rubbin Basic pathology, Elsevier, 9th edition, 2013

THANK YOU