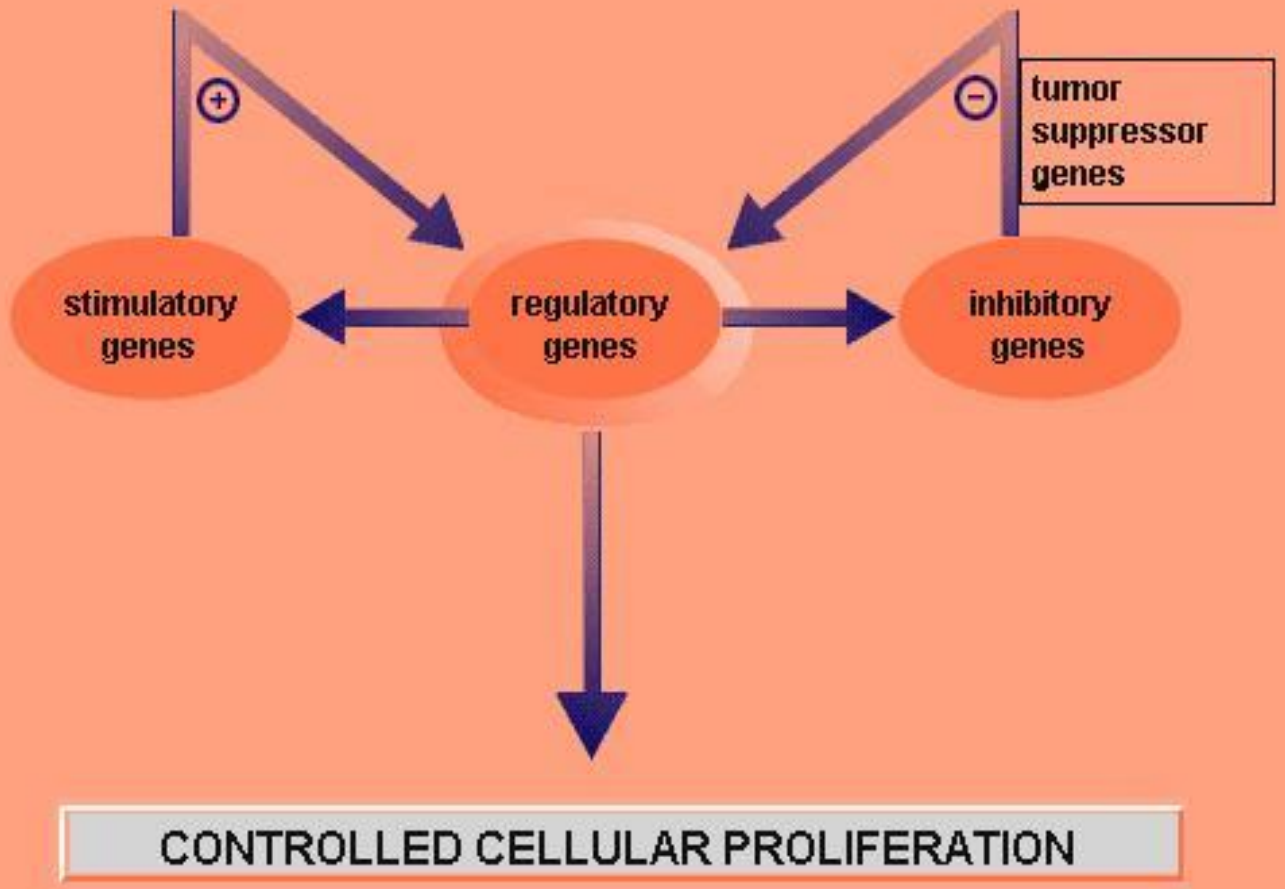
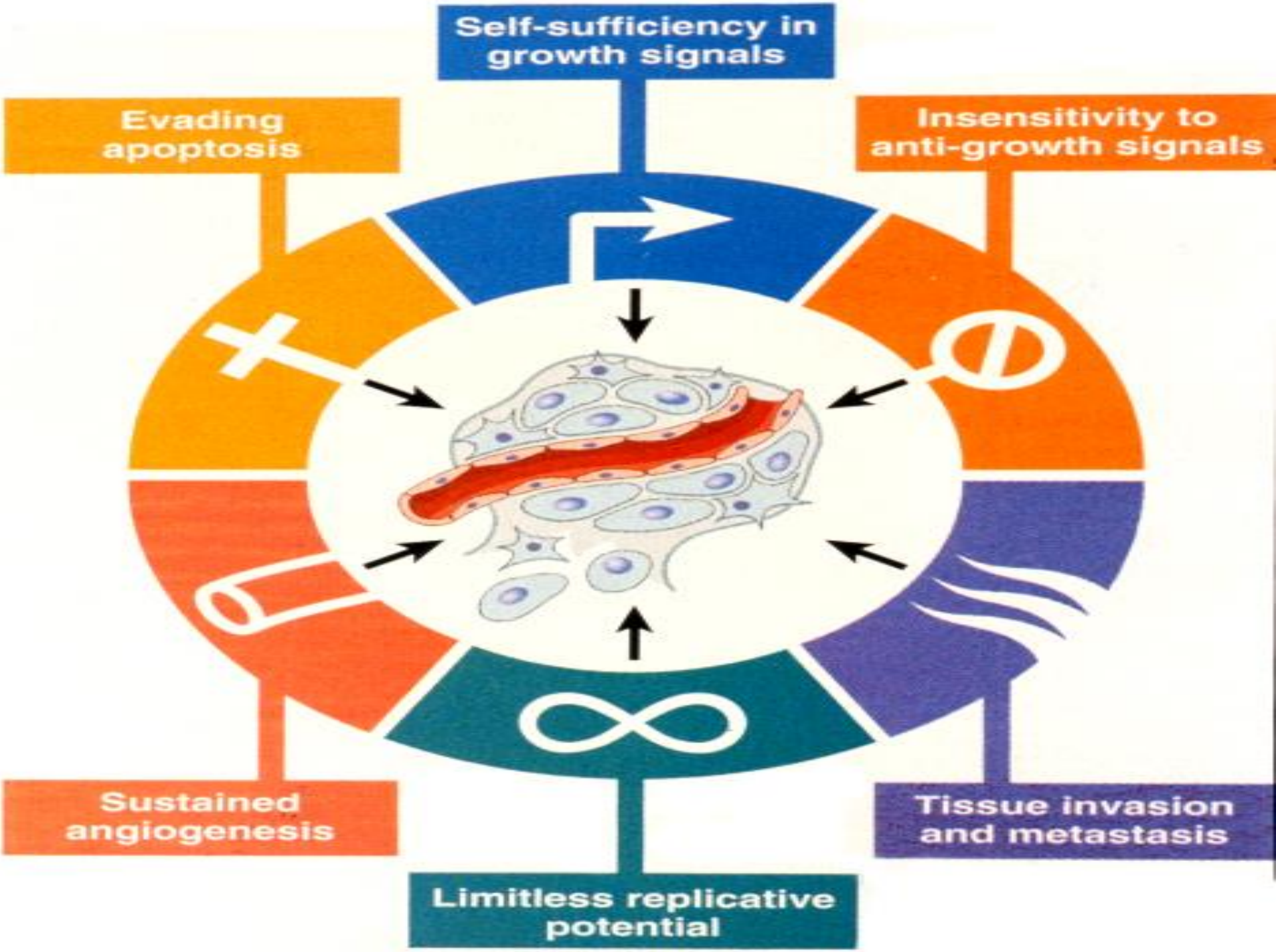
Principles of Carcinogenesis

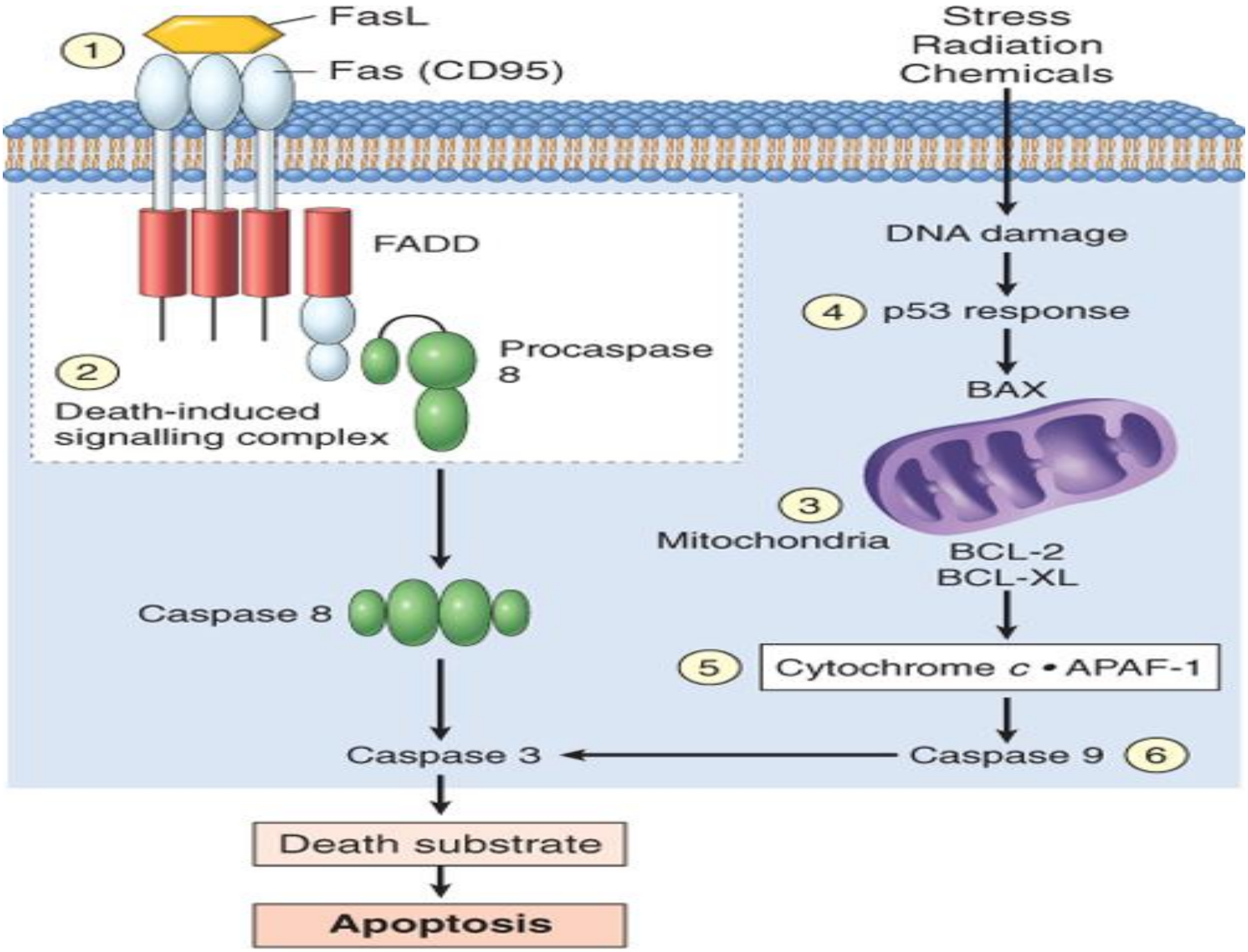
- Neoplastic transformation is a progressive process involving multiple "hits" or genetic changes.
- Alterations in DNA cause changes in one or more of the following types of genes:
  - Proto- oncogenes
  - Tumor suppressor genes
  - Genes regulate apoptosis
  - DNA repair genes


tumor
suppressor
genes
stimulatory
genes
regulatory
genes
inhibitory
genes
CONTROLLED CELLULAR PROLIFERATION

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
Evading apoptosis
Insensitivity to anti-growth signals
Sustained angiogenesis
Tissue invasion and metastasis
Limitless replicative potential

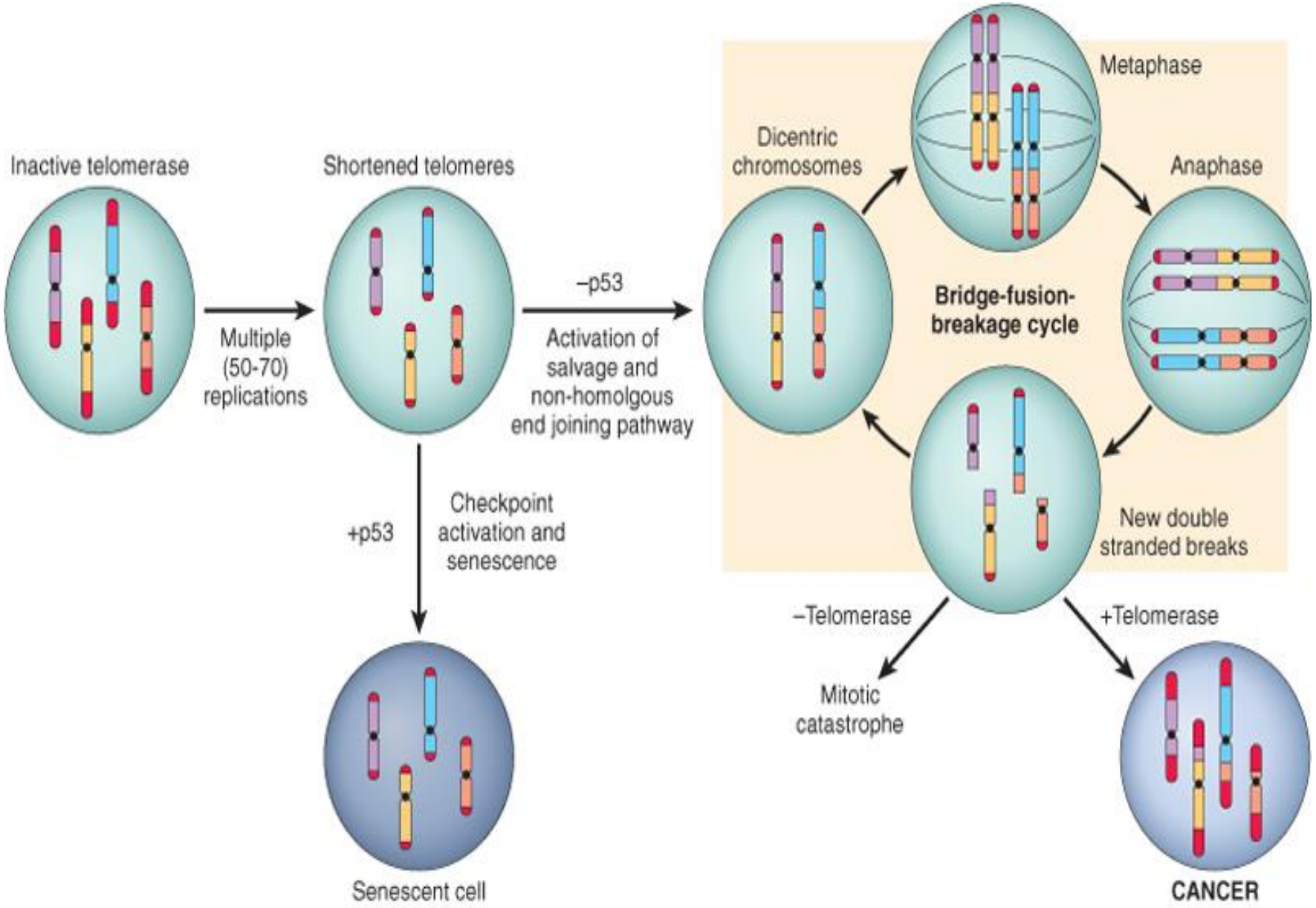


Evasion of Apoptosis

- CD95 is reduced in HCC
- Some tumors have high level of protein that bind to death inducing signals complex &that prevent the activation of caspase 8
- BCL2 activation in Burkitt lymphoma in the translocation of chromosome t(14:18) helps in protecting lymphocytes from apoptosis

Limitless Replicative Potential

- Most normal human cells have a capacity of 60-70 doubling, after the cell will enter non replicative senescence & result in shortening of telomeres at the end of chromosome & loss of telomeres beyond a certain point will lead to massive chrosomal abnormalities & death
- In order to develop tumor, need to maintain cells i.e. avoid cell senescence
- This is done by enzyme TOLEMERASE which maintain chromosome length
- 85-95% of cancer have up regulation of enzyme telomerase



Development of Sustained Angiogenesis

- Tumors cannot enlarge beyond **1-2** mm thickness unless they are vascularized, hypoxia will induce apoptosis by activation of ***TP53*** .
- Angiogenesis is required for tumor growth & metastasis.
- Tumor-associated angiogenic factors may be produced by the tumor or by inflammatory cells
- ***TP53*** inhibit angiogenesis by stimulation of
- anti-angiogenesis molecules
- VEGF is under the control of ***RAS*** oncogene .
- Proteases are involved in regulating angiogenic & antiangiogenic factors .

Ability to Invade & Metastasize

1) Invasion of extracellular matrix

2) Vascular dissemination & homing of tumor cells

2)Vascular dissemination & homing of tumor cells

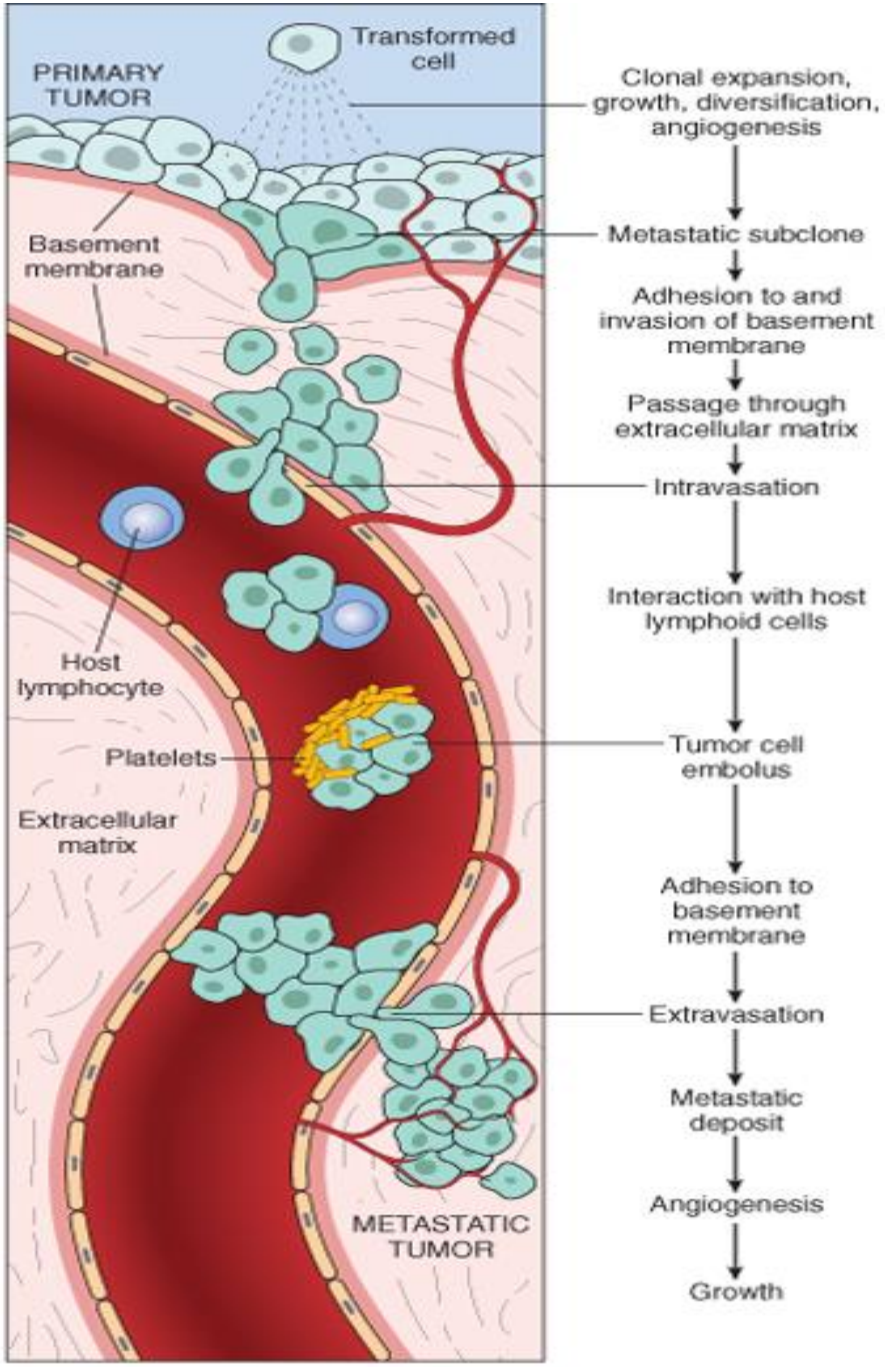
- Tumor cells binds to leukocytes, this protect them from host defense mechanisms
- Tumor cells adhere to vascular endothelium & pass through BM
- Site of extravasations & Meyts depends on:

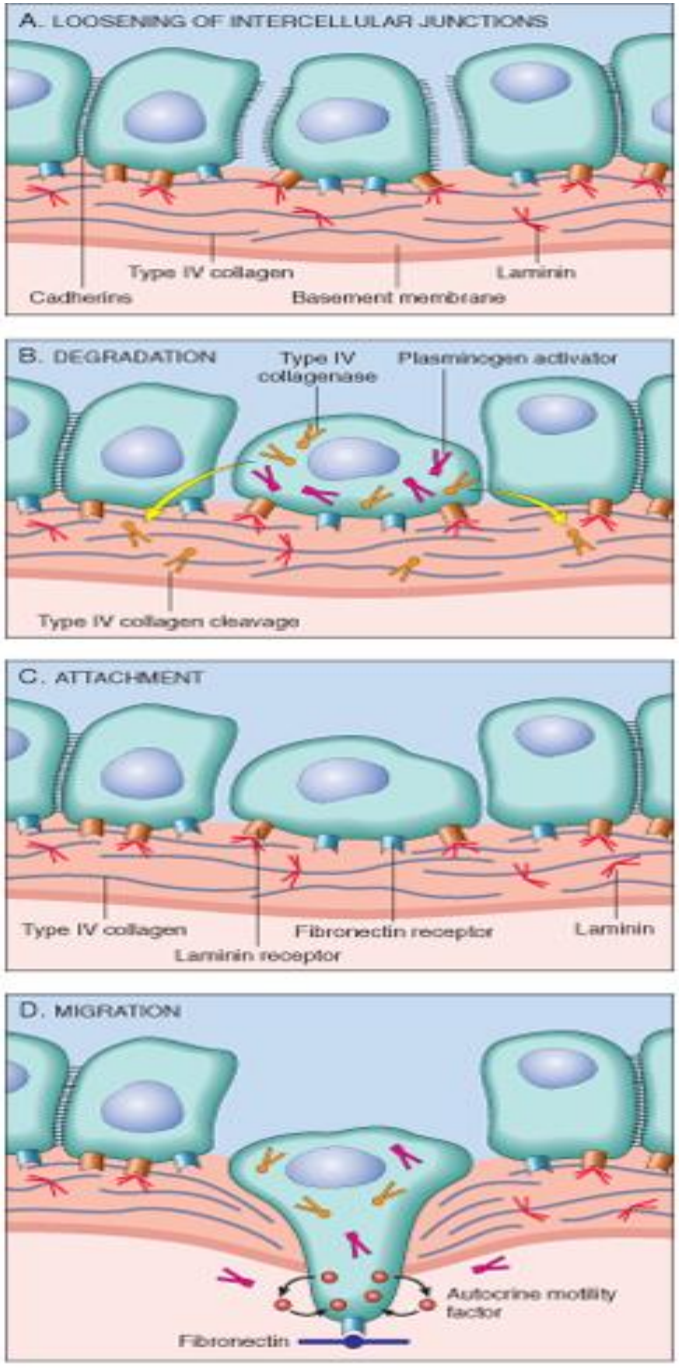
  -Blood & Lymphatic supply

  -Organ tropism/adhesion molecules

  -Some tumors have increase CXcr4 and its legends is only seen in sites of breast Mets

NOT ALL SITES CAN BE PREDICTED





Genomic Instability-Enabler Of Malignancy

- BRCA1&BRCA2 mutation in 80% of familial breast ca,
- BRCA1&BRCA2 mutation in **males & females** increase risk of **breast , prostate,ovaries,pancrease,bile duct, & melanocytes**
- **Females with BRCA1** mutation are at higher risk of developing ovarian ca & males are at higher risk of prostate ca

Molecular Basis of multistep carcinogenesis

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
- Evidence is both

  Epidemiologic: cancer increase with age

  Molecular : cancers analyzed show multiple genetic mutations

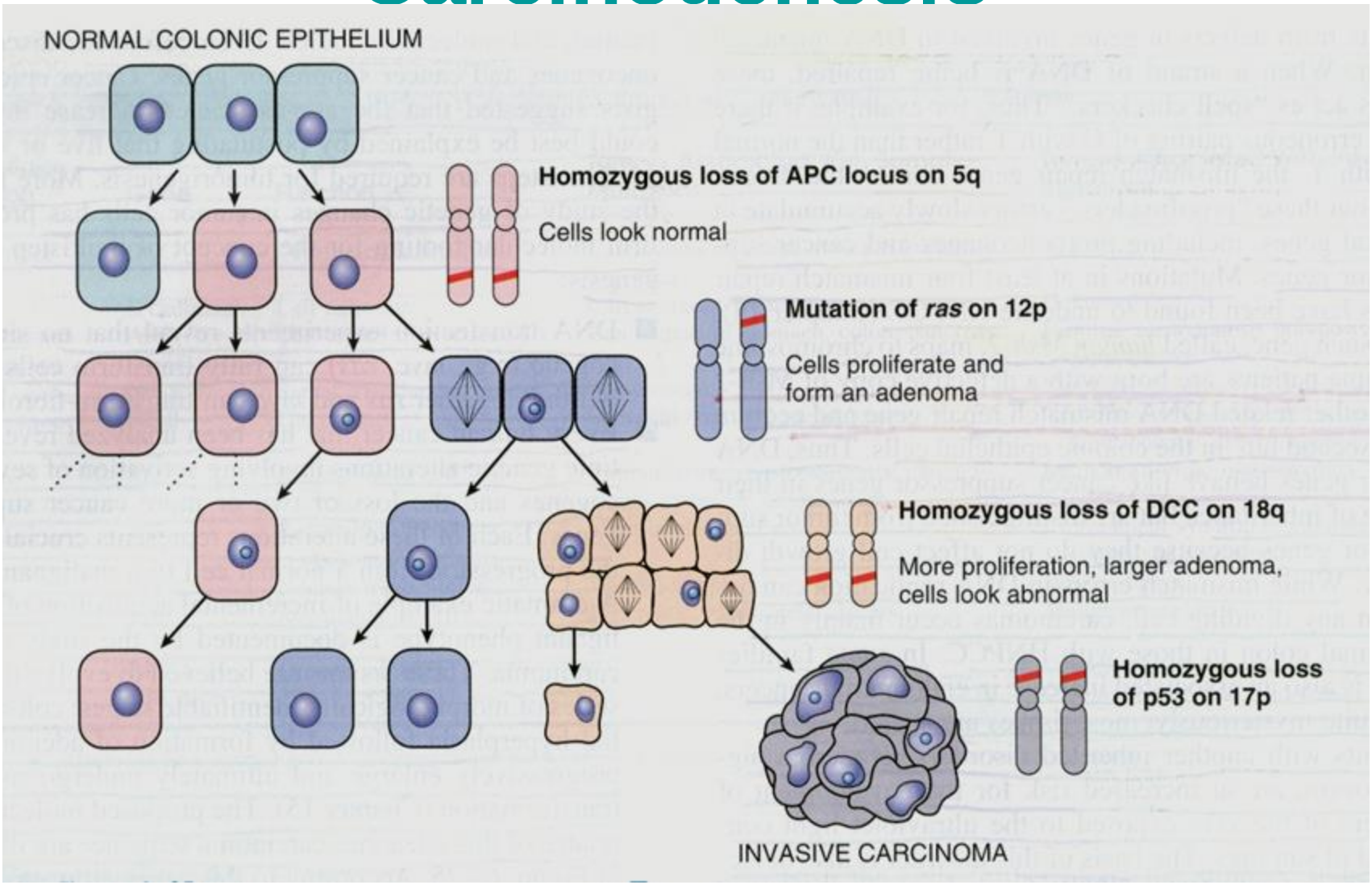
Molecular Basis of multistep carcinogenesis

- Alterations in DNA cause changes in one or both of the following types of genes:
  - Proto-oncogenes
  - Tumor suppressor genes

  Best example is colonic cancer

  APC→RAS→18q→p53

Molecular Basis of Multistep Carcinogenesis

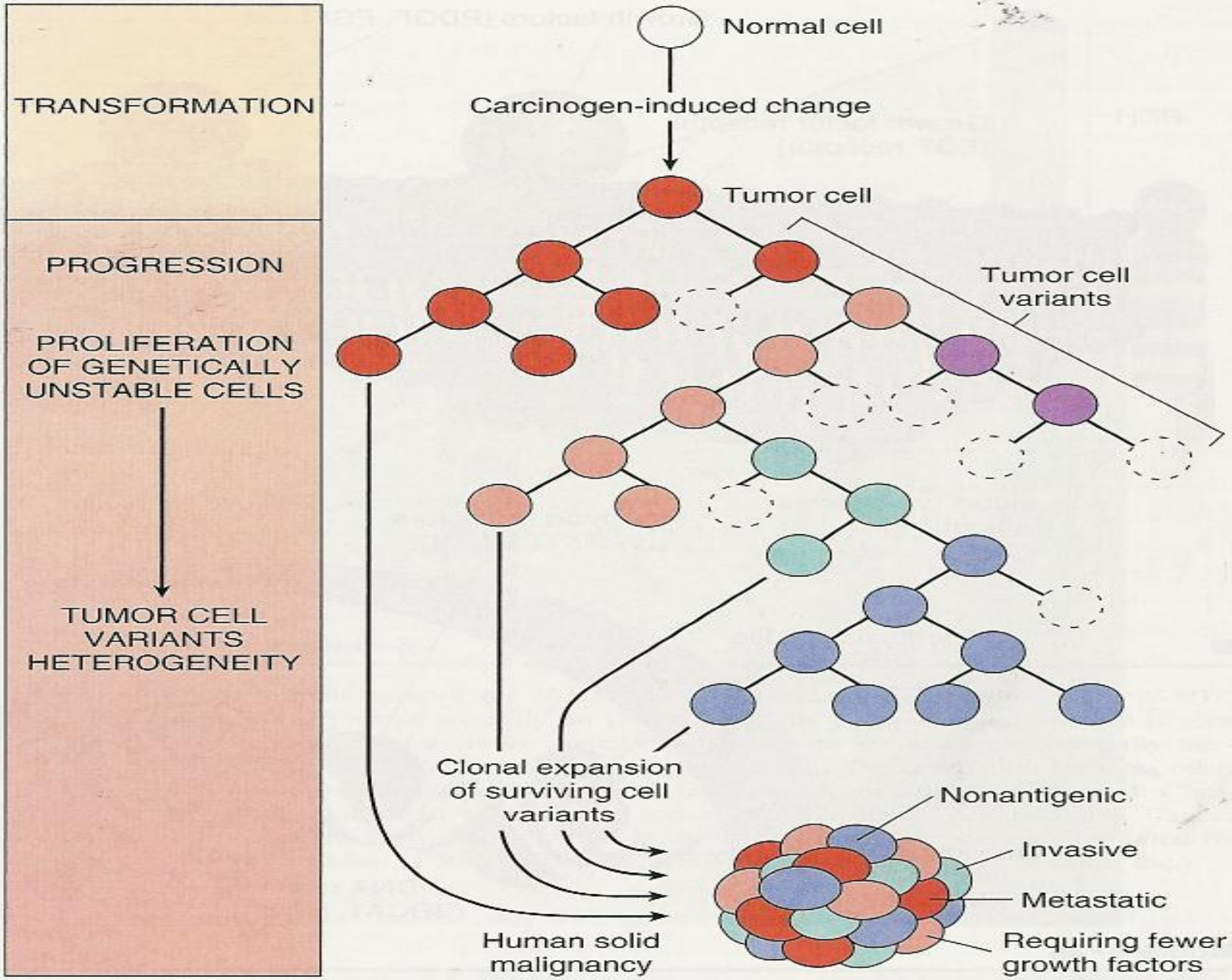


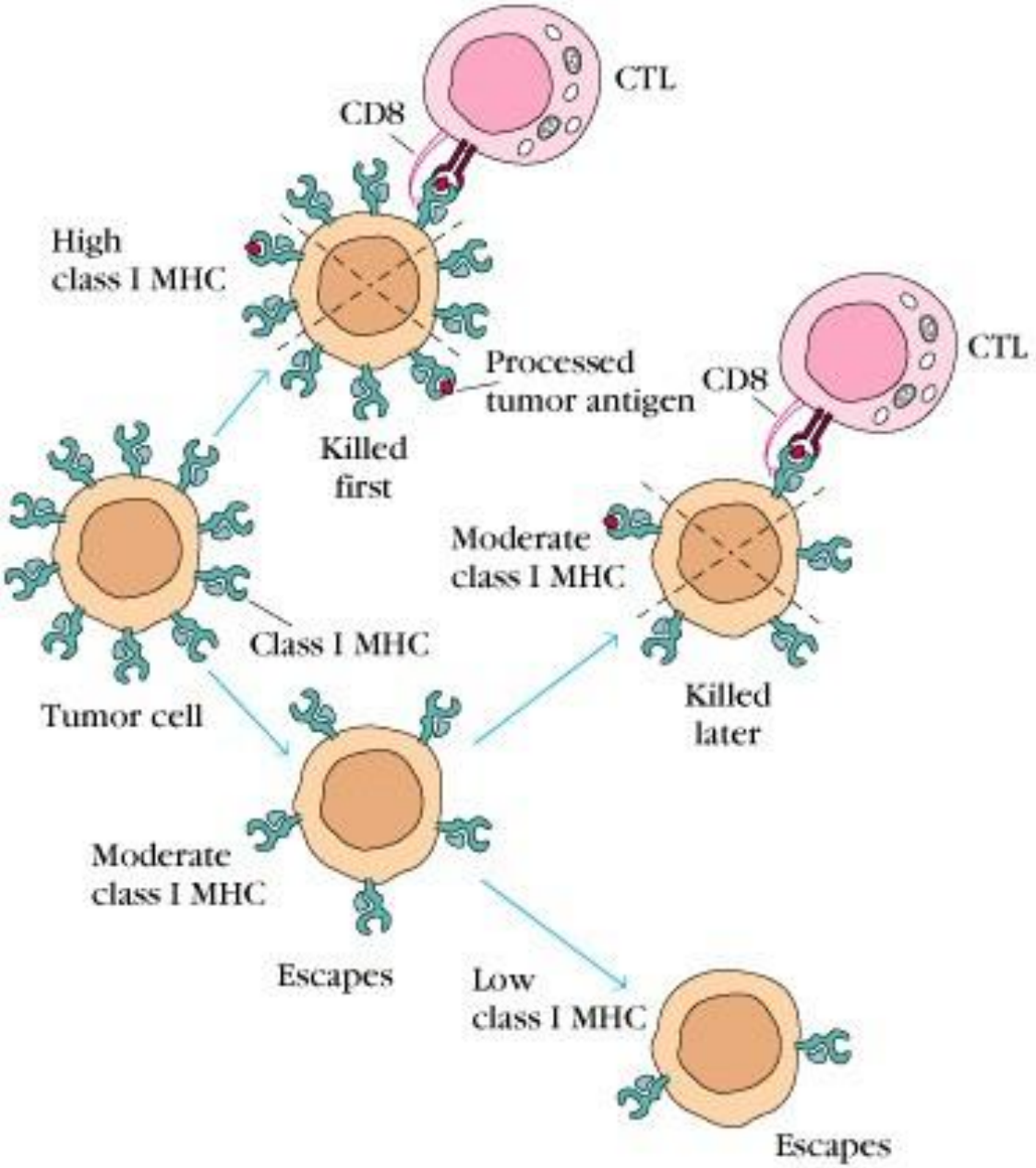
Tumor Progression & Heterogeneity

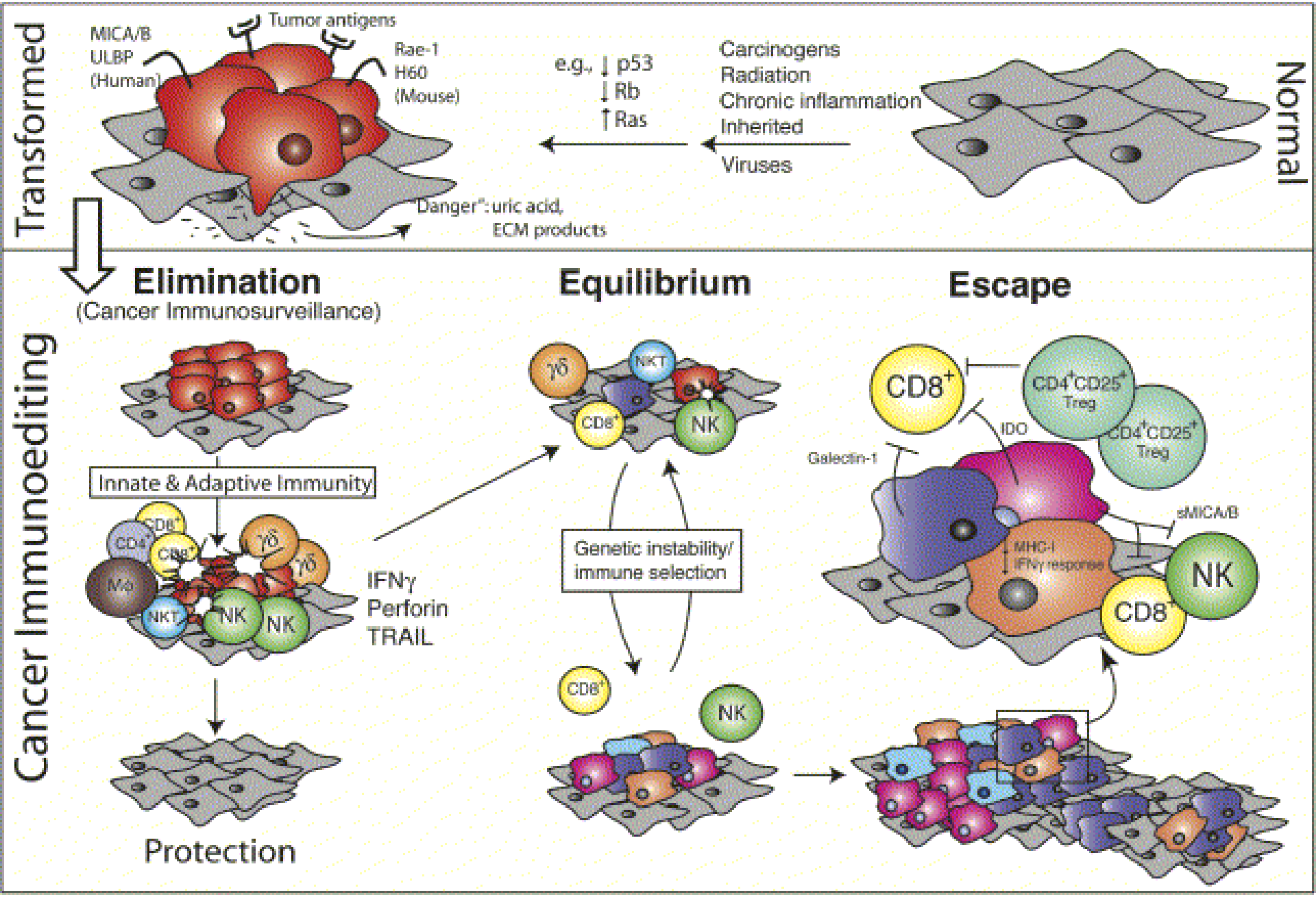
- Tumor progression: means increase aggressiveness & and is acquired occurring in an increasing fashion

- Development of new subset of cells that are different in aspects such as invasivness,ability to Mets, hormonal response-→Heterogeneous group

- Results from multiple mutations occurring independently in different cells→subclone of cells that is different


TRANSFORMATION
PROGRESSION
PROLIFERATION OF GENETICALLY UNSTABLE CELLS
TUMOR CELL VARIANTS HETEROGENEITY
Normal cell
Carcinogen-induced change
Tumor cell
Tumor cell variants
Clonal expansion of surviving cell variants
Human solid malignancy
Nonantigenic
Invasive
Metastatic
Requiring fewer growth factors


CTL
CD8
High
class I MHC
Processed
tumor antigen
Killed
first
CTL
CD8
Moderate
class I MHC
Killed
later
Class I MHC
Tumor cell
Moderate
class I MHC
Escapes
Low
class I MHC
Escapes


Transformed
MICA/B
ULBP
(Human)
Tumor antigens
Rae-1
H60
(Mouse)
e.g., ↓ p53
↓ Rb
↑ Ras
Carcinogens
Radiation
Chronic inflammation
Inherited
Viruses
Normal
Danger*: uric acid,
ECM products
Cancer Immunoediting
Elimination
(Cancer Immunosurveillance)
Innate & Adaptive Immunity
IFNγ
Perforin
TRAIL
Protection
Equilibrium
Genetic instability/
immune selection
Escape
CD8+
CD4+CD25+
Treg
IDO
Galectin-1
sMICA/B
MHC-I
IFNγ response
NK
CD8+