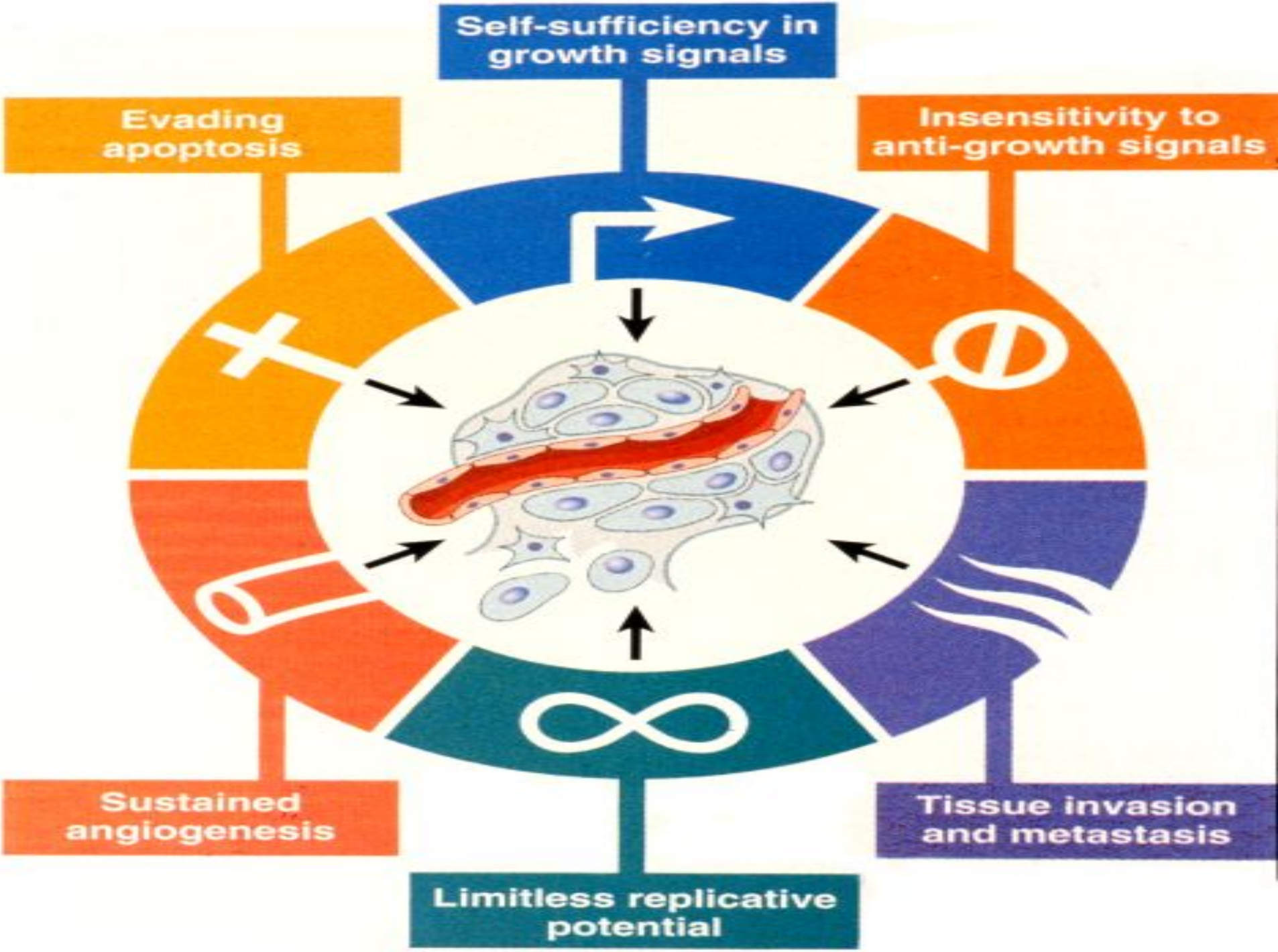
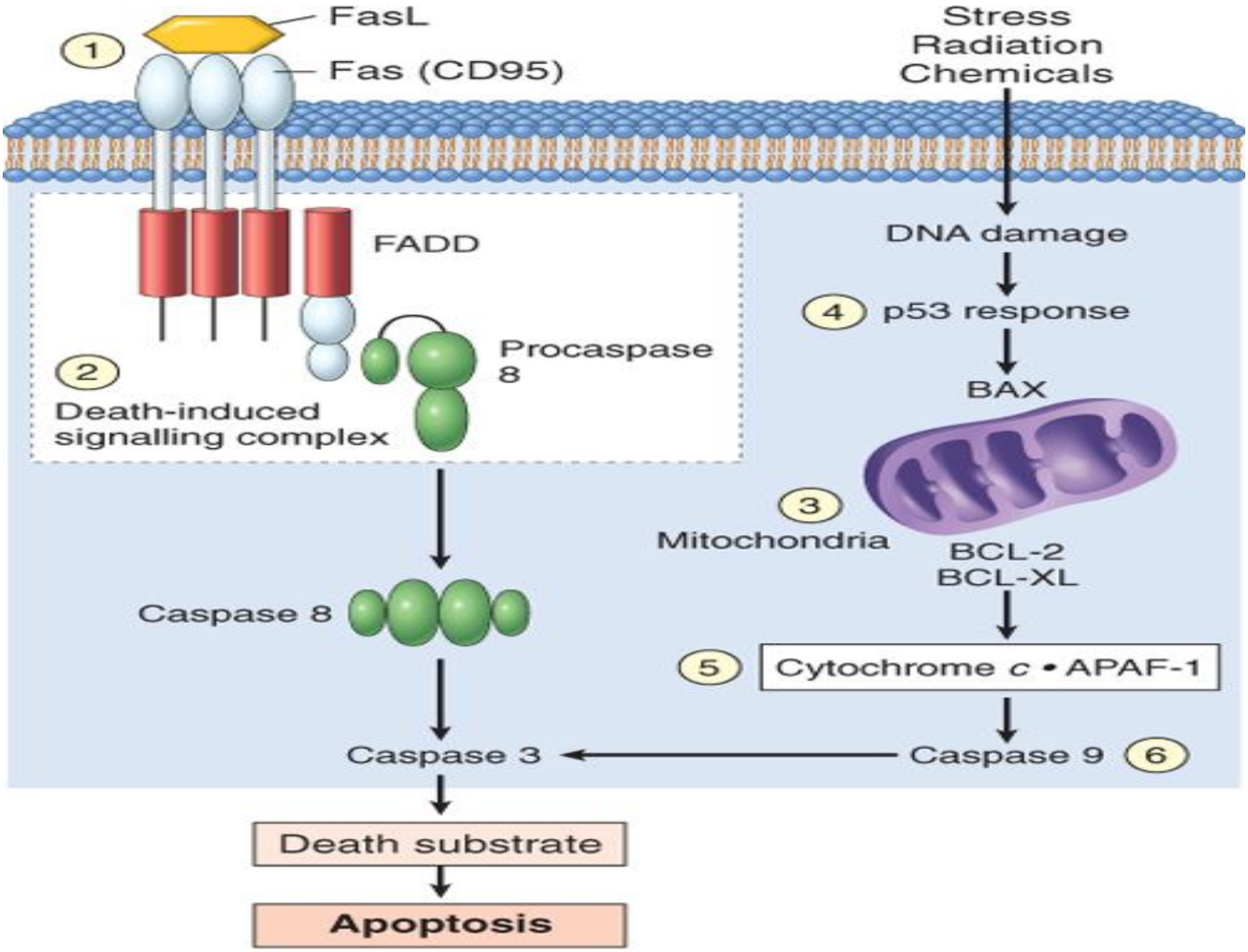
Hallmarks of Cancer
Six fundamental changes

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

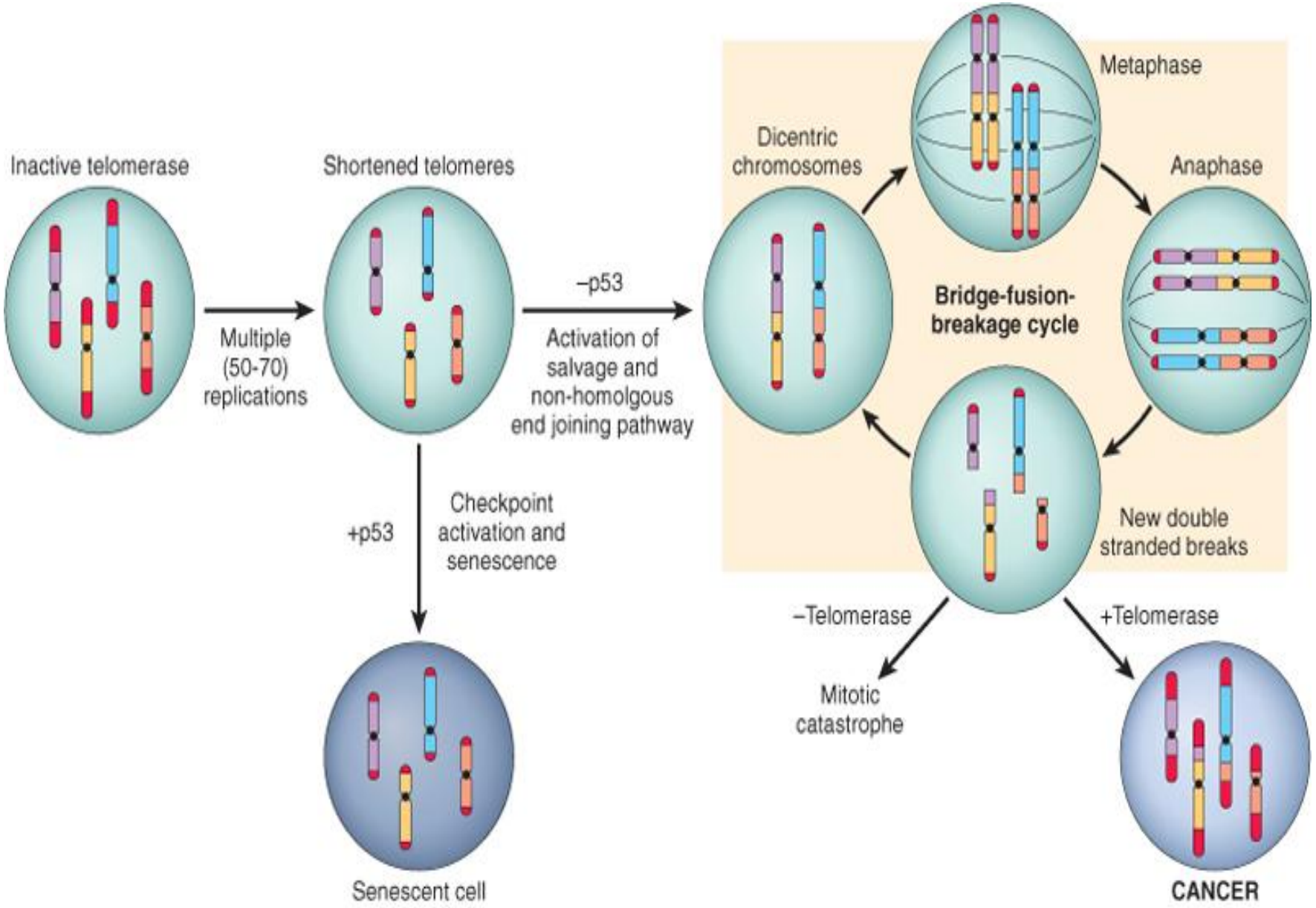


Evasion of Apoptosis

- 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

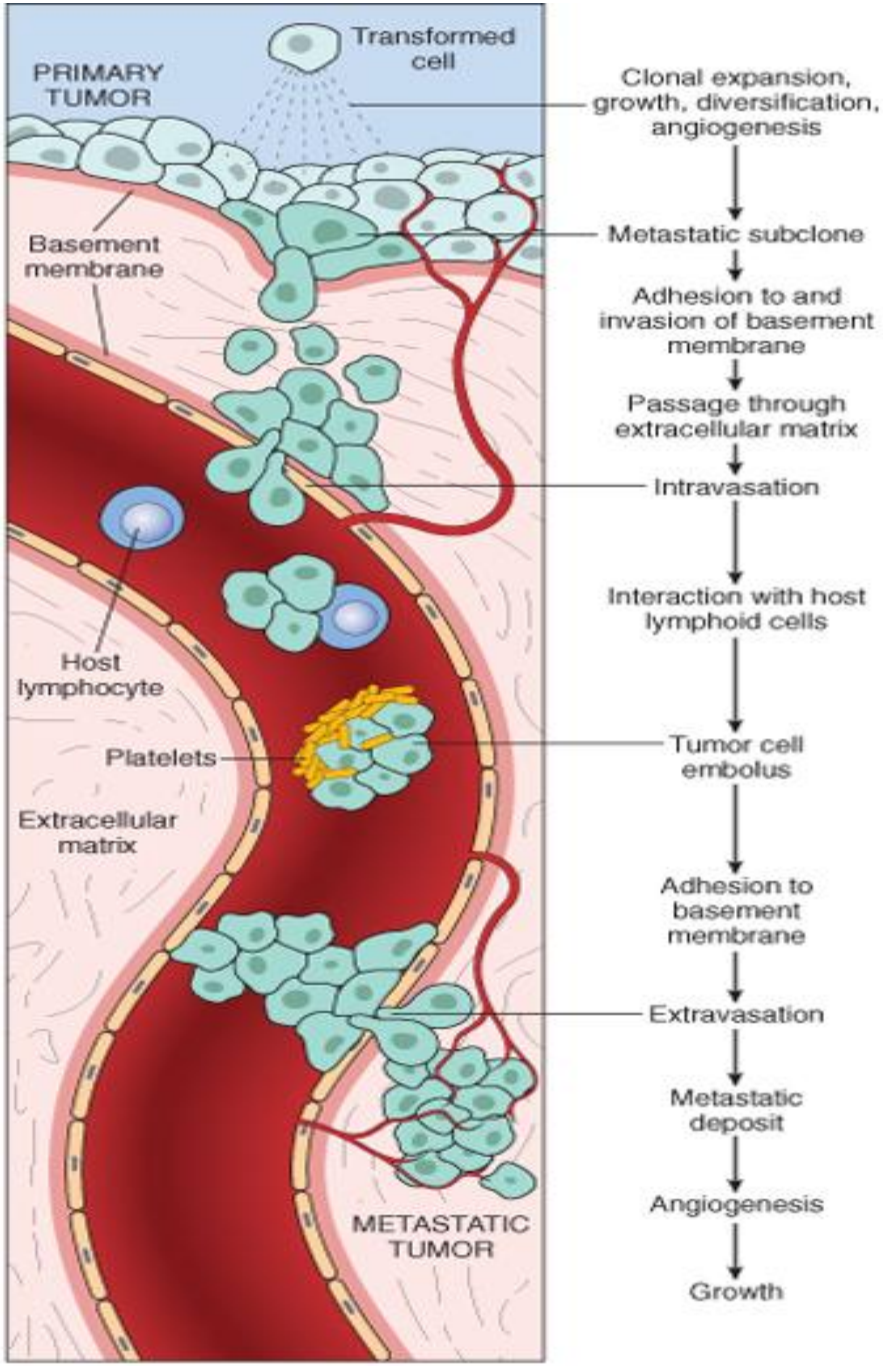
- Tumor cells binds to leukocytes, this protect them from host defense mechanisms
- Tumor cells adhere to vascular endothelium & pass through BM
- Site of extravasations & Meyts depends on:

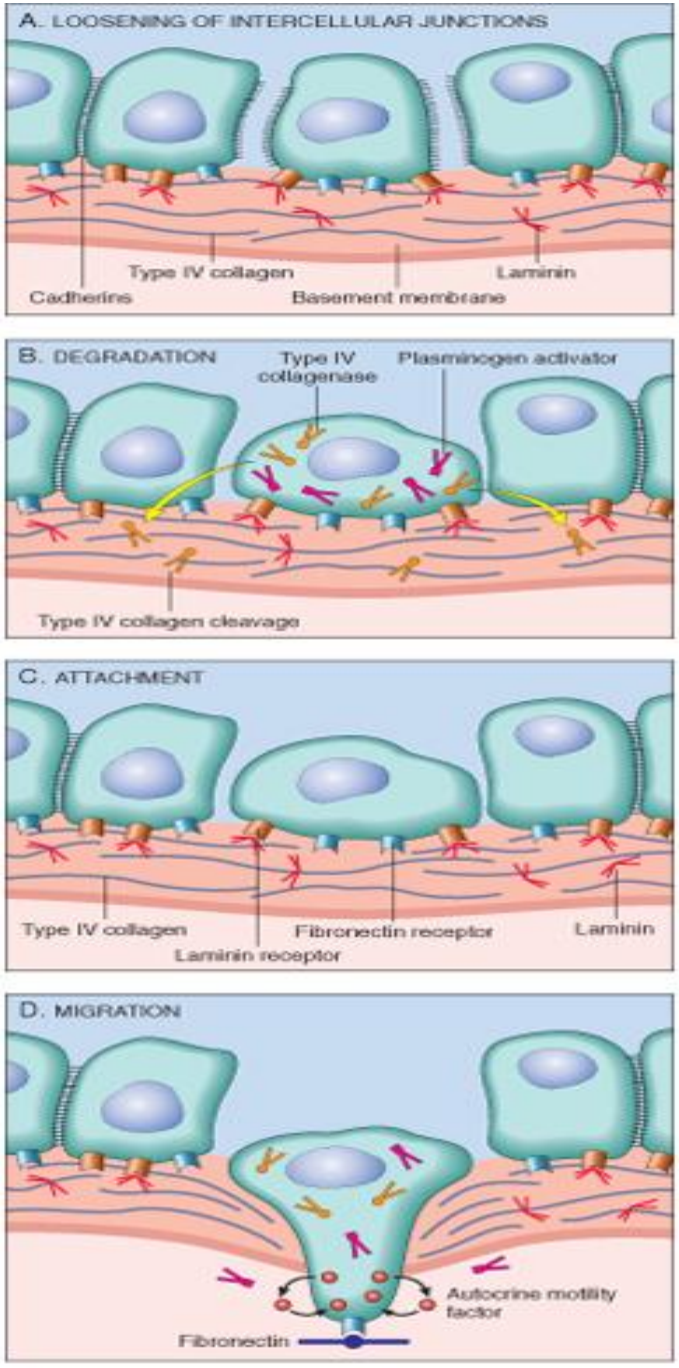
  -Blood & Lymphatic supply

  -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

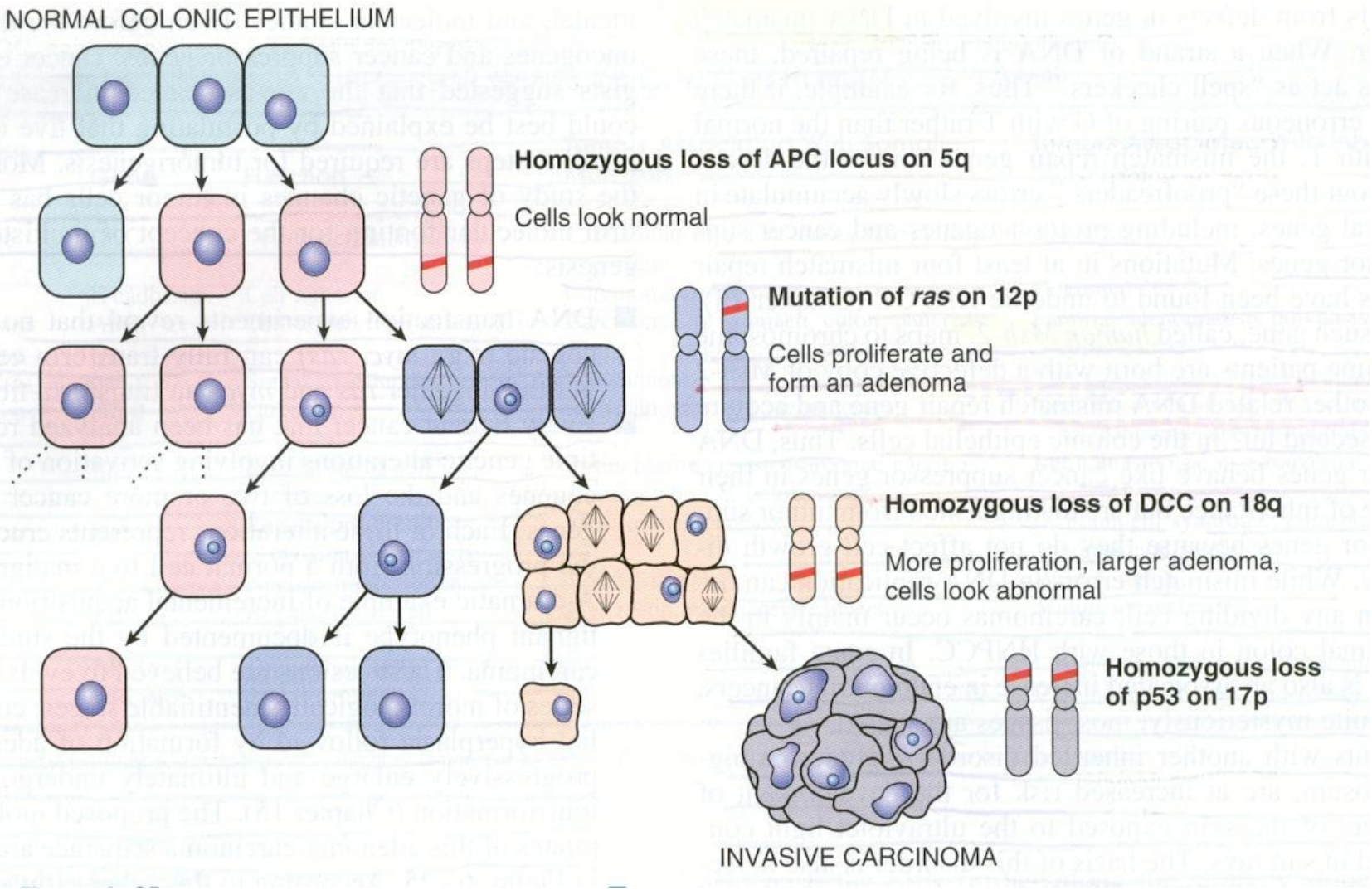
Molecular Basis of multistep carcinogenesis

- 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

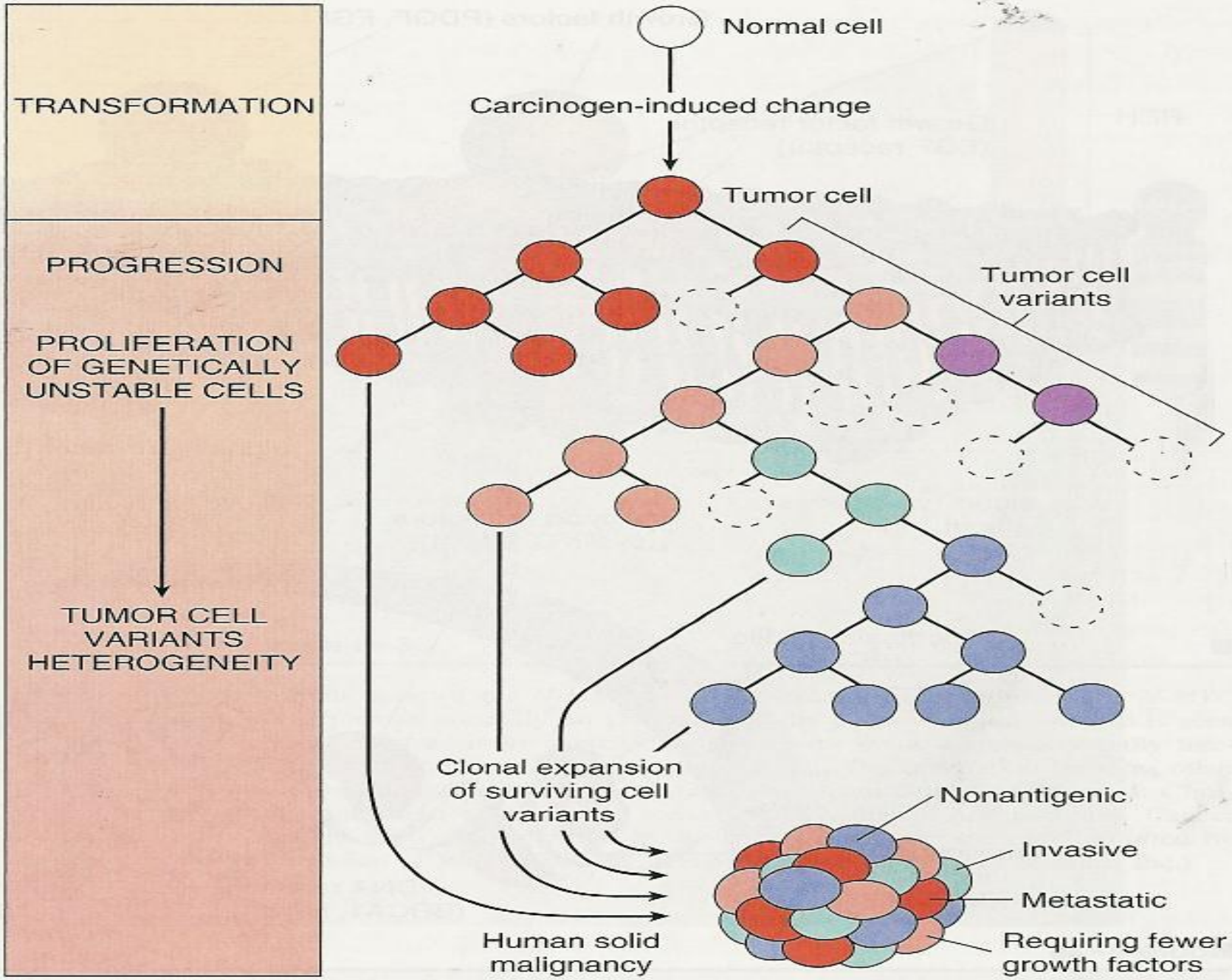


Tumor Progression & Heterogeneity

- 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

Karyotypic changes in tumor

- The genetic damage range from point mutations to chromosomal changes
- Translocation:t(22:9) in CML
  t(8:14) in Burkitt's
  t(14:18) F. Lymphoma
- Deletions: 13q14 retinoblastoma
  17p,5q colon ca
- Gene amplification N-myc neuroblastoma
  Her-2 Breast ca