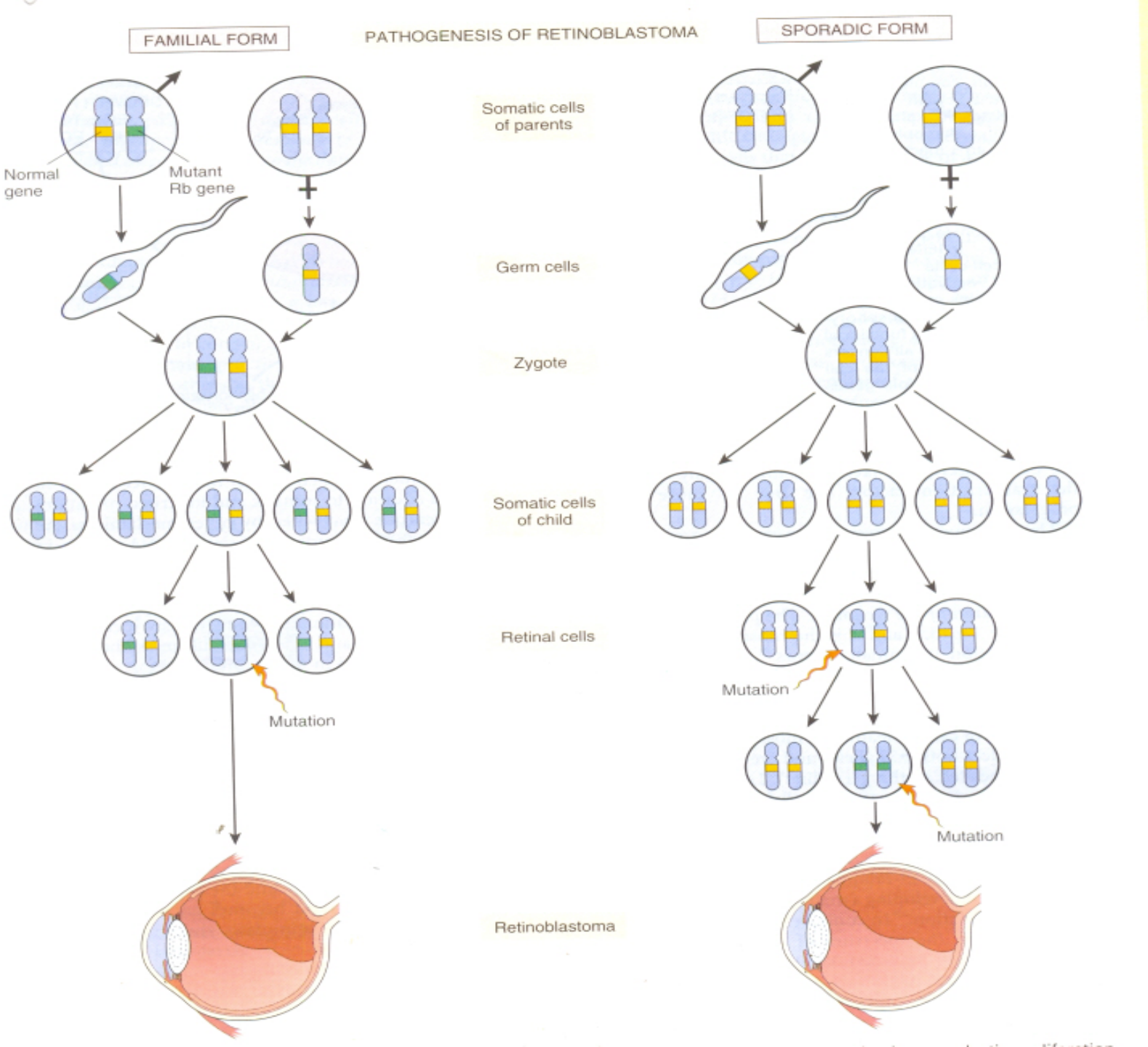
Growth Factors

- All normal cells require stimulation by growth factors to undergo proliferation
- Most GF are made by one cell type, act on neighbouring cell
- Normally cells that produce GF,do not express cognate receptors-this prevents formation of +ve feedback loops within the same cell

GF Receptors and Non-Receptor Tyrosine Kinases

II. INSENSITIVITY TO GROWTH INHIBITORY SIGNALS

- RB Gene: Governor of cell cycle,13q14
- RB-1st tumor suppressor gene, a prototypical representative
- Involved in Retinoblastoma:Familial & sporadic
- **Two Hit Hypothesis:**Both normal alleles of RB locus must be inactivated
- **Familial cases:**Children inherit 1 defective copy of RB gene,other copy is normal which is lost as a result of somatic mutation, so AD
- **Somatic cases:**Both normal RB alleles are lost by somatic mutation


FAMILIAL FORM
PATHOGENESIS OF RETINOBLASTOMA
SPORADIC FORM
Normal gene
Mutant Rb gene
Somatic cells of parents
Germ cells
Zygote
Somatic cells of child
Retinal cells
Mutation
Mutation
Mutation
Retinoblastoma

P53 Gene: Guardian of Genome

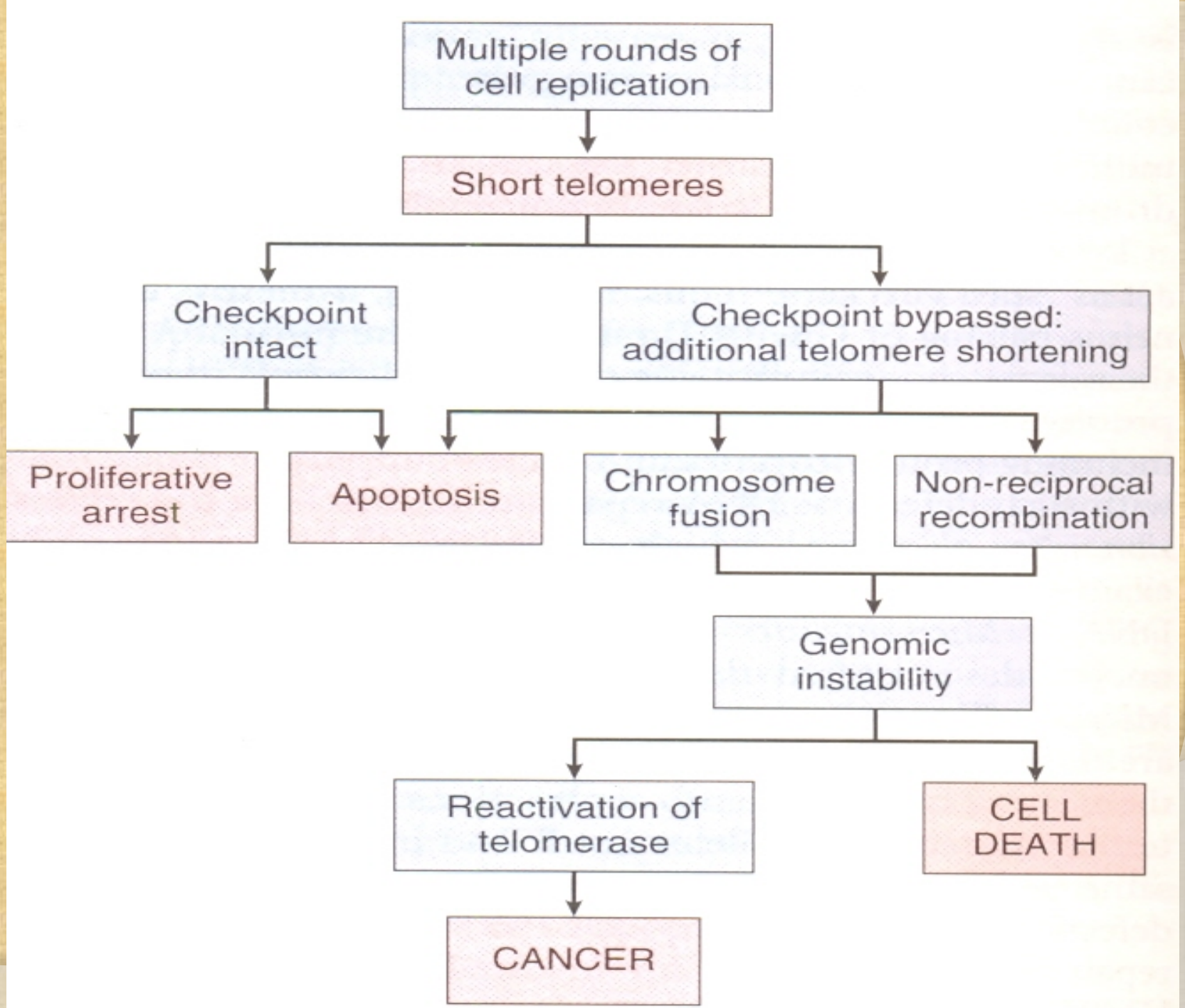
- One of the most commonly mutated gene
- It does neoplastic transformation by 3 mechanisms:
  I. Activation of temporary cell cycle arrest (**Quiescence**)
  II. Induction of permanent cell cycle arrest (**Senescence**)
  III. Triggering of progammed cell death (**Apoptosis**)

III. EVASION OF APOPTOSIS

- Apoptotic pathway,divided into upstream regulators and downstream effectors
- Regulatosrs divided into two
  - i. One interpreting E/C signals
  - Ii. Other interpreting I/C signals
- Stimulation of either results in activation of normally inactive proteases: Caspase 8 & 9
- So cell is disassembled-phagocytosis

IV. LIMITLESS REPLICATIVE POTENTIAL

- Each normal divided normal cell can count their cell division.
- After each cell division there is shortening of some specialized structure, called telomere.
- Once the telomeres are shortened beyond cretin point it leads to activation of p53 dependent cell cycle check points, causing proliferative arrest or apoptosis.
- Telomerase activity and maintenance of telomere are essential for maintenance of replicative potential in cancer cell.


Multiple rounds of cell replication
Short telomeres
Checkpoint intact
Checkpoint bypassed: additional telomere shortening
Proliferative arrest
Apoptosis
Chromosome fusion
Non-reciprocal recombination
Genomic instability
Reactivation of telomerase
CELL DEATH
CANCER

EXTRINSIC (DEATH RECEPTOR) PATHWAY

- Initiated when a TNF receptor such as CD95(Fas) is bound to CD95L
- Trimerization of receptor & its cytoplasmic death domains which attract I/C adaptor protein FADD
- This recruits Caspase 8
- activation of downstream Caspases such as Caspase 3
- this cleaves DNA & other substances
- Cell Death

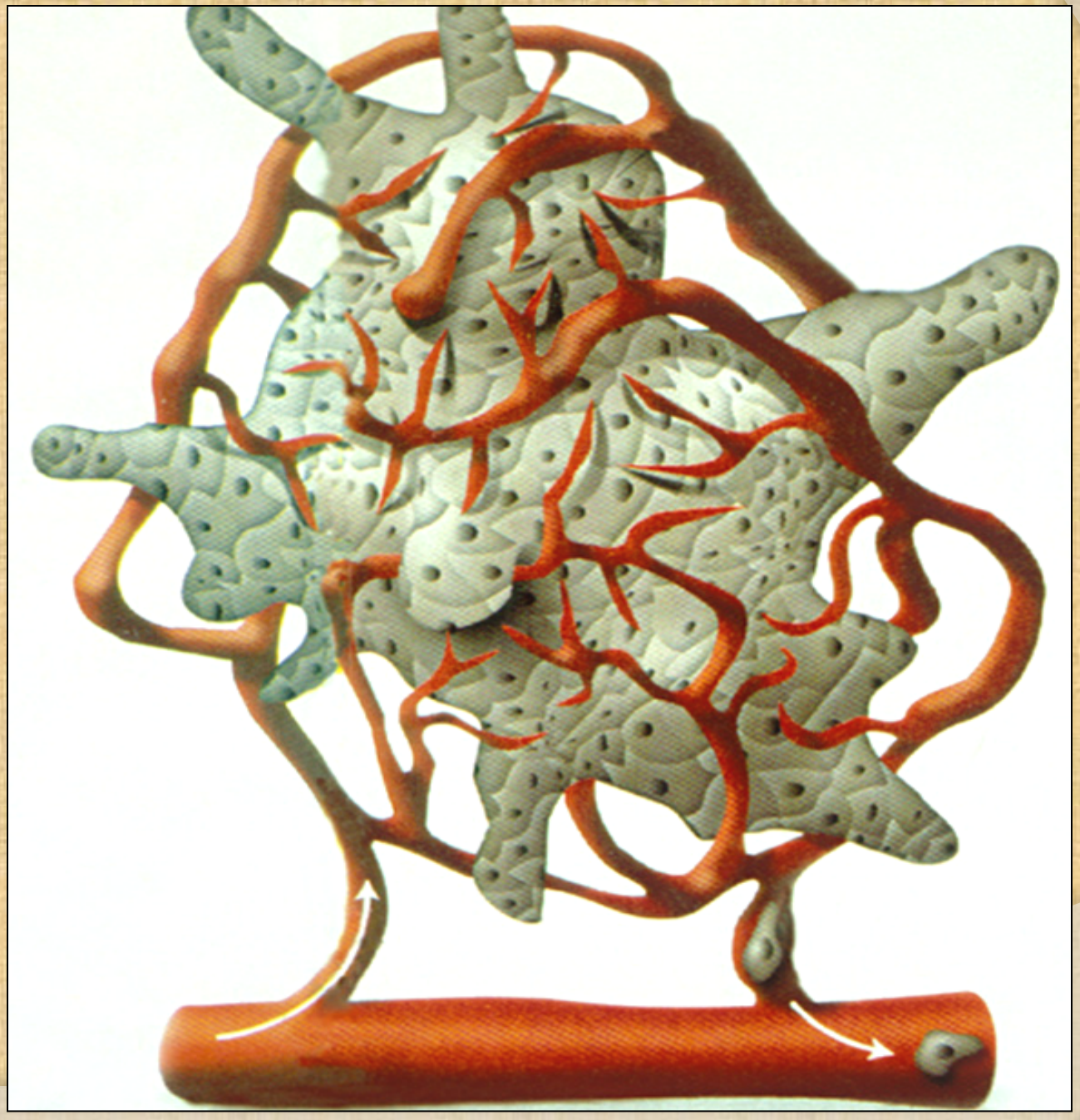
INTRINSIC (MITOCHONDRIAL) PATHWAY

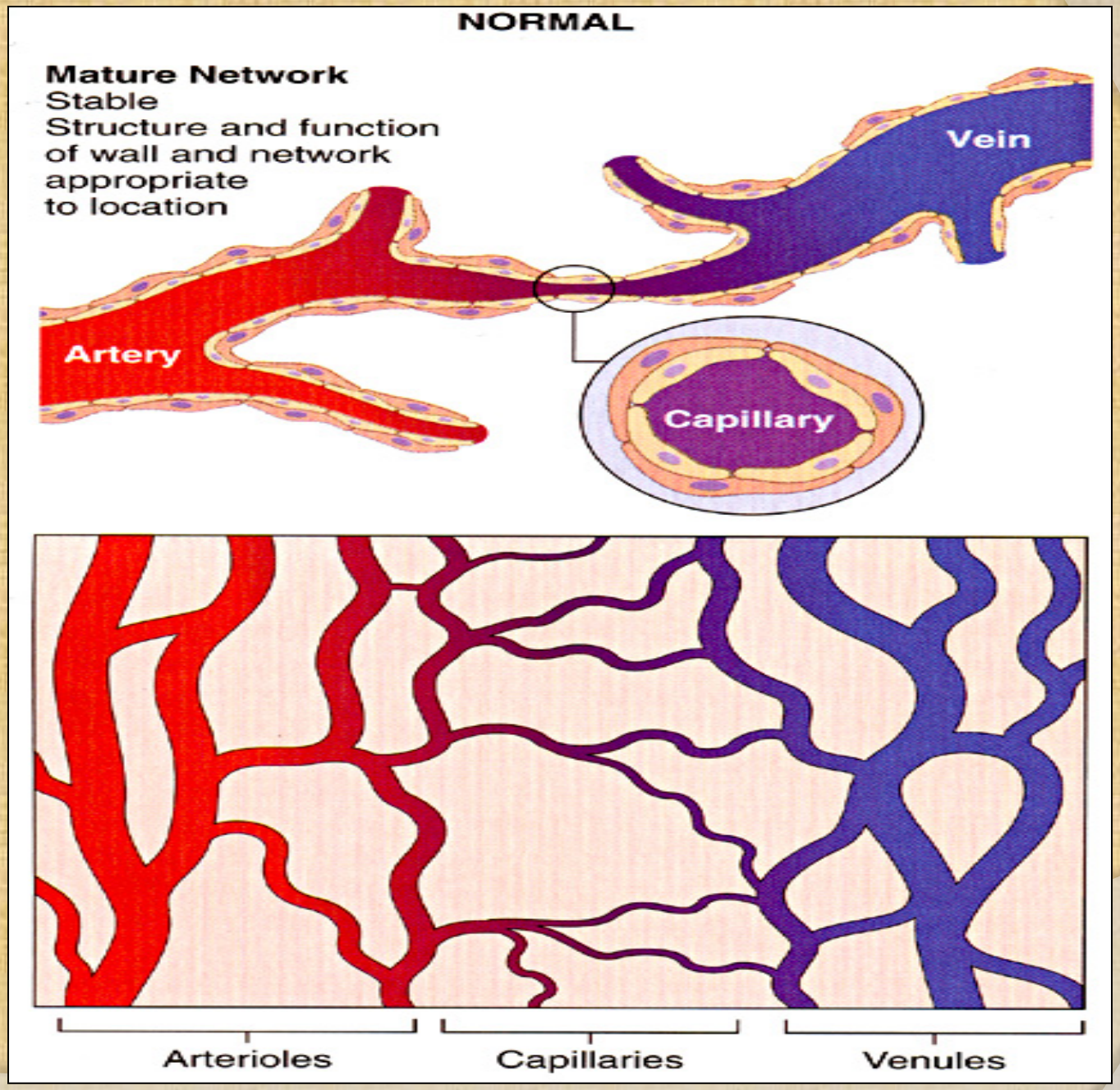
- Initiated by stress, injury
- Its activation leads to permeabilization of mitochondrial outer memb Release of cytochrome c this initiates apoptosis
- Integriyt of mitochondrial memb is regulated by pro-apoptotic(BAX & BAK) and anti-apoptotic(BCL2 & BCL-XL) proteins
- A 3rd set called **BH3-only** proteins include BAD, BID & PUMA regulate balance b/w pro & anti-apoptotic members

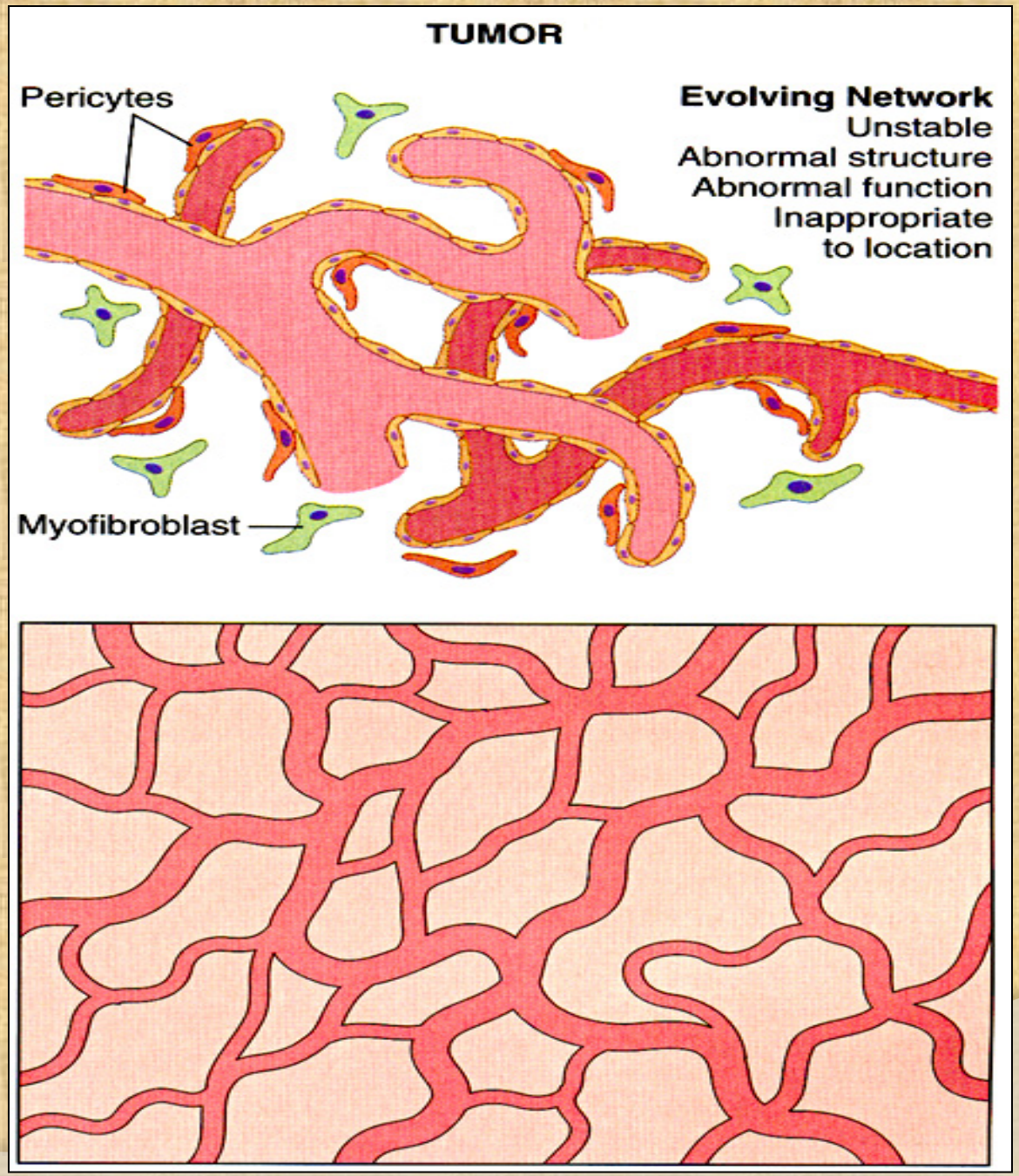
- Cancer cells exhibit evasion of apoptosis
- Best established is the role of BCL2 in protecting tumor cells from apoptosis
- BCL2 is over-expressed in Lymphomas (Follicular), Protects lymphocytes from apoptosis

V. SUSTAINED ANGIOGENESIS

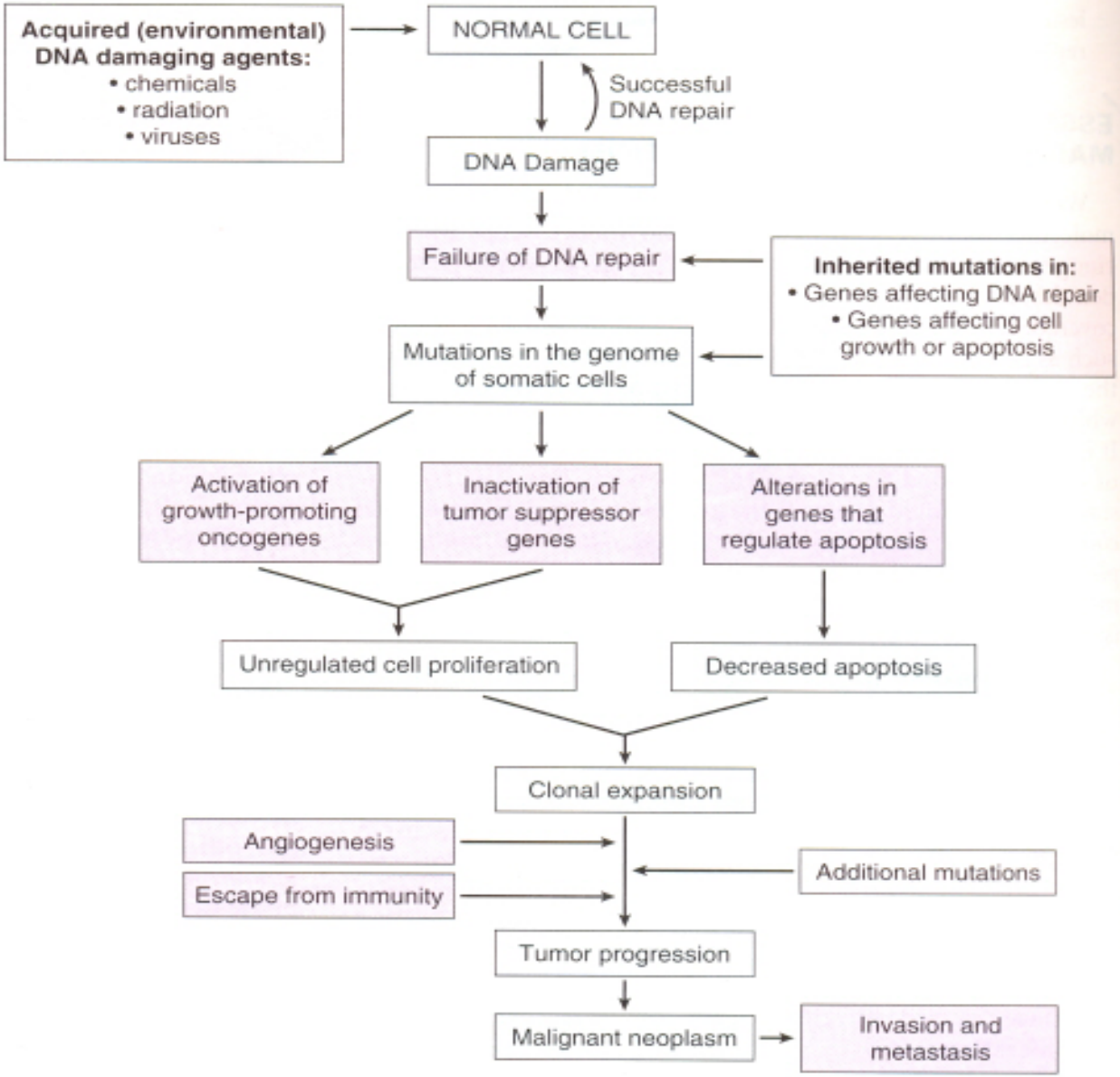
- Solid tumors can not enlarge beyond 1-2mm in diameter unless they are vascularized

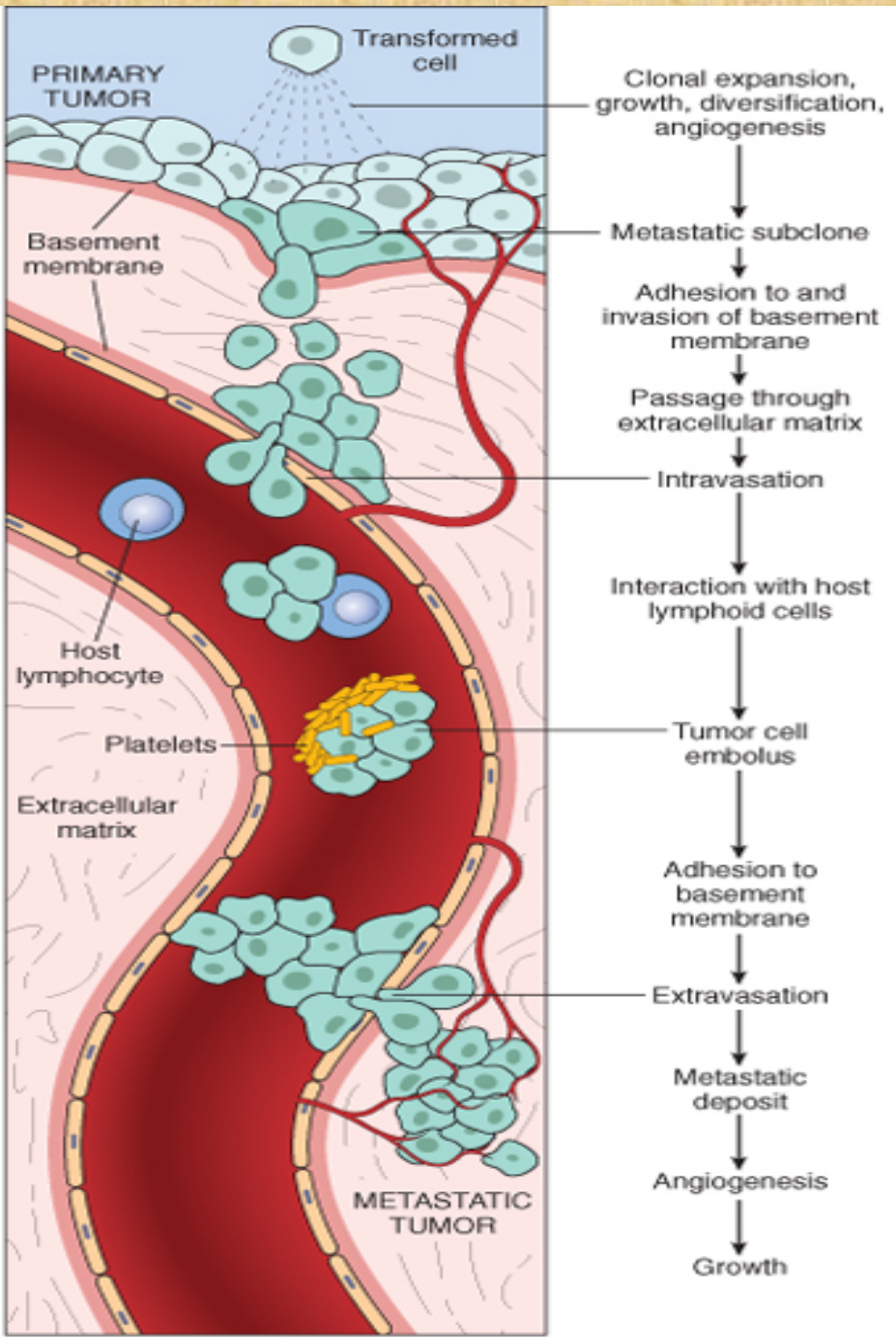



NORMAL
Mature Network
Stable
Structure and function
of wall and network
appropriate
to location
Vein
Artery
Capillary
Arterioles
Capillaries
Venules


TUMOR
Pericytes
Evolving Network
Unstable
Abnormal structure
Abnormal function
Inappropriate
to location
Myofibroblast

VI. INVASION AND METASTASIS


Acquired (environmental) DNA damaging agents:
• chemicals
• radiation
• viruses
NORMAL CELL
Successful DNA repair
DNA Damage
Failure of DNA repair
Inherited mutations in:
• Genes affecting DNA repair
• Genes affecting cell growth or apoptosis
Mutations in the genome of somatic cells
Activation of growth-promoting oncogenes
Inactivation of tumor suppressor genes
Alterations in genes that regulate apoptosis
Unregulated cell proliferation
Decreased apoptosis
Clonal expansion
Angiogenesis
Escape from immunity
Additional mutations
Tumor progression
Malignant neoplasm
Invasion and metastasis



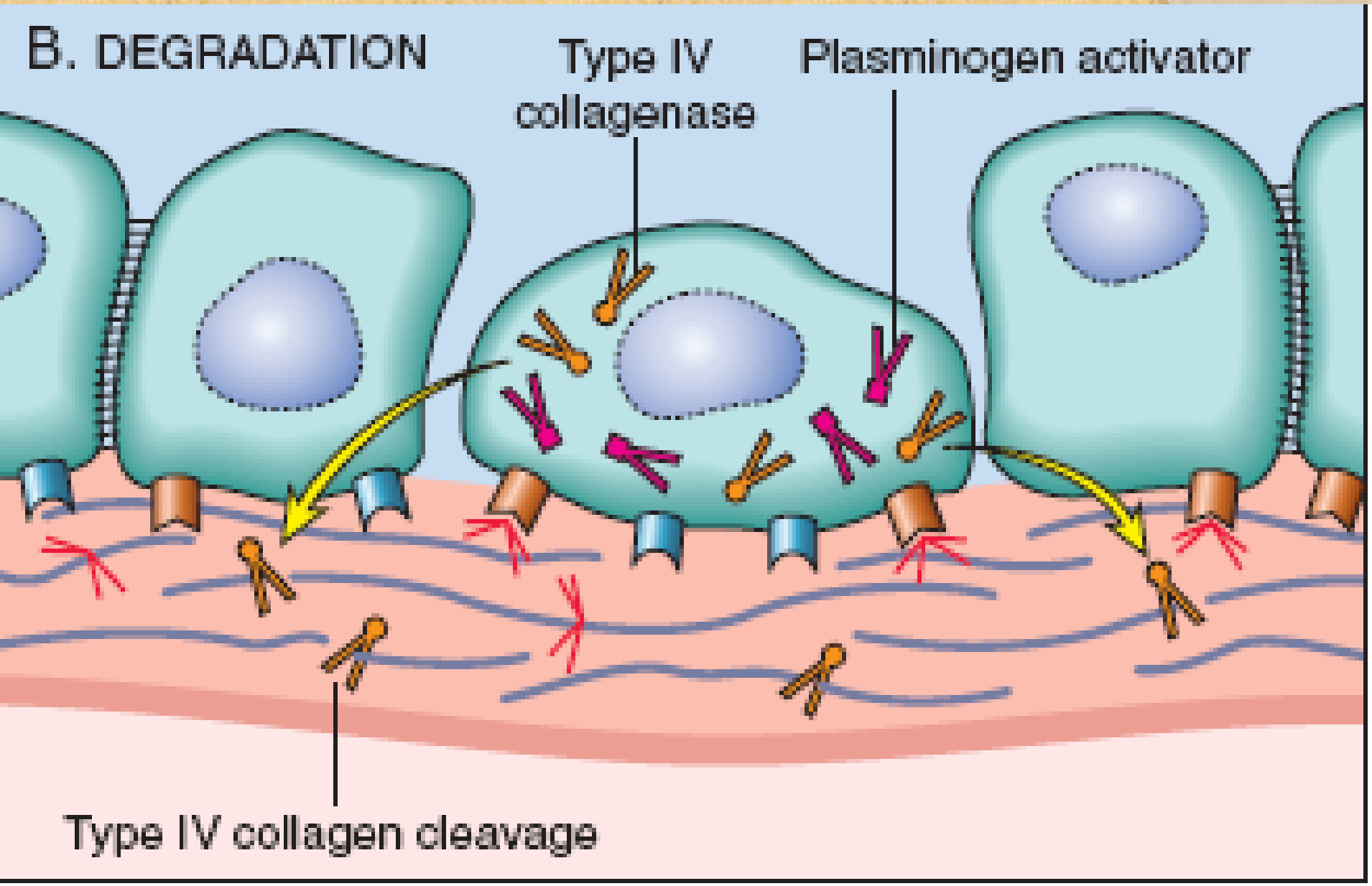
clonal growth

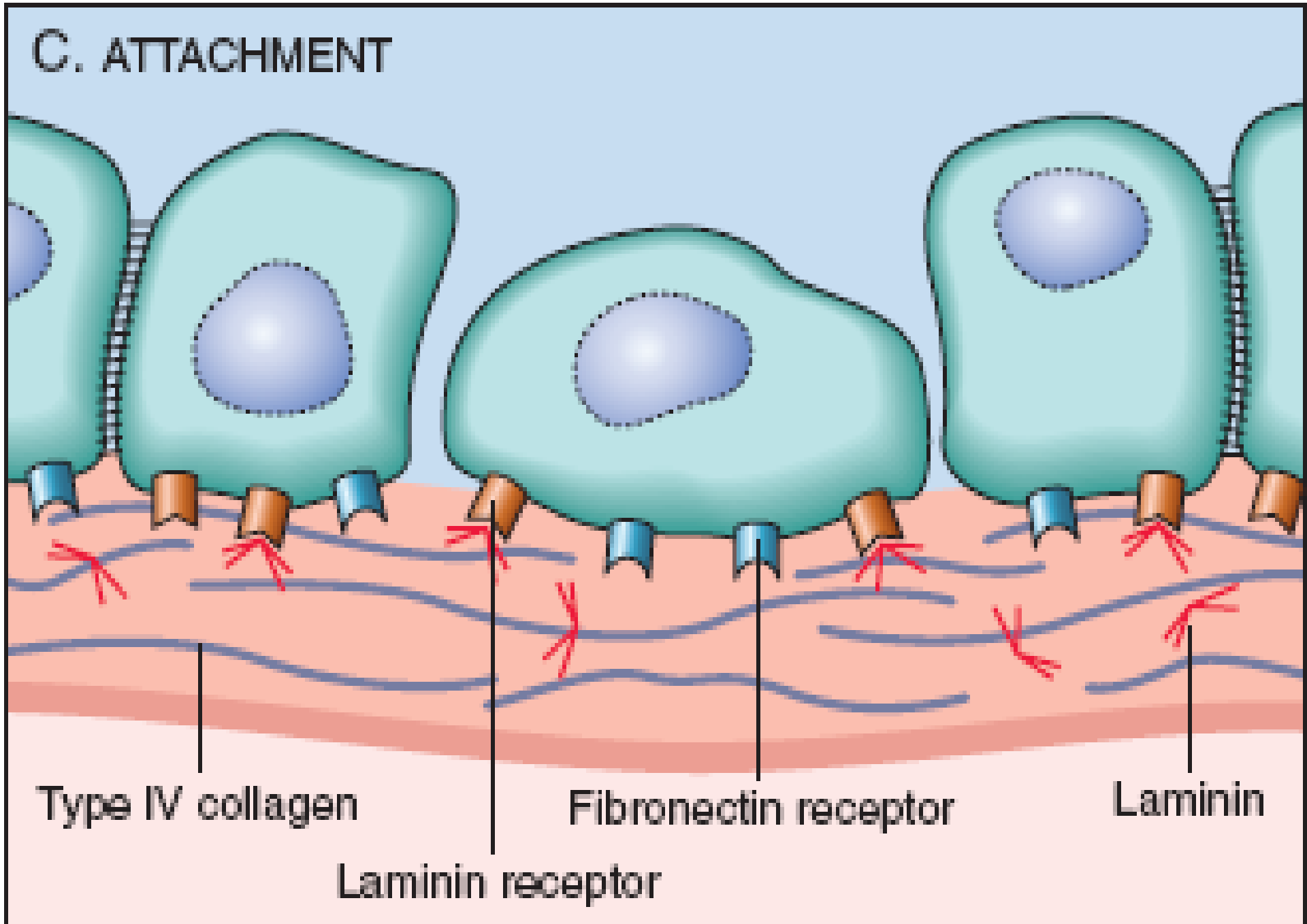
metastatic subclone

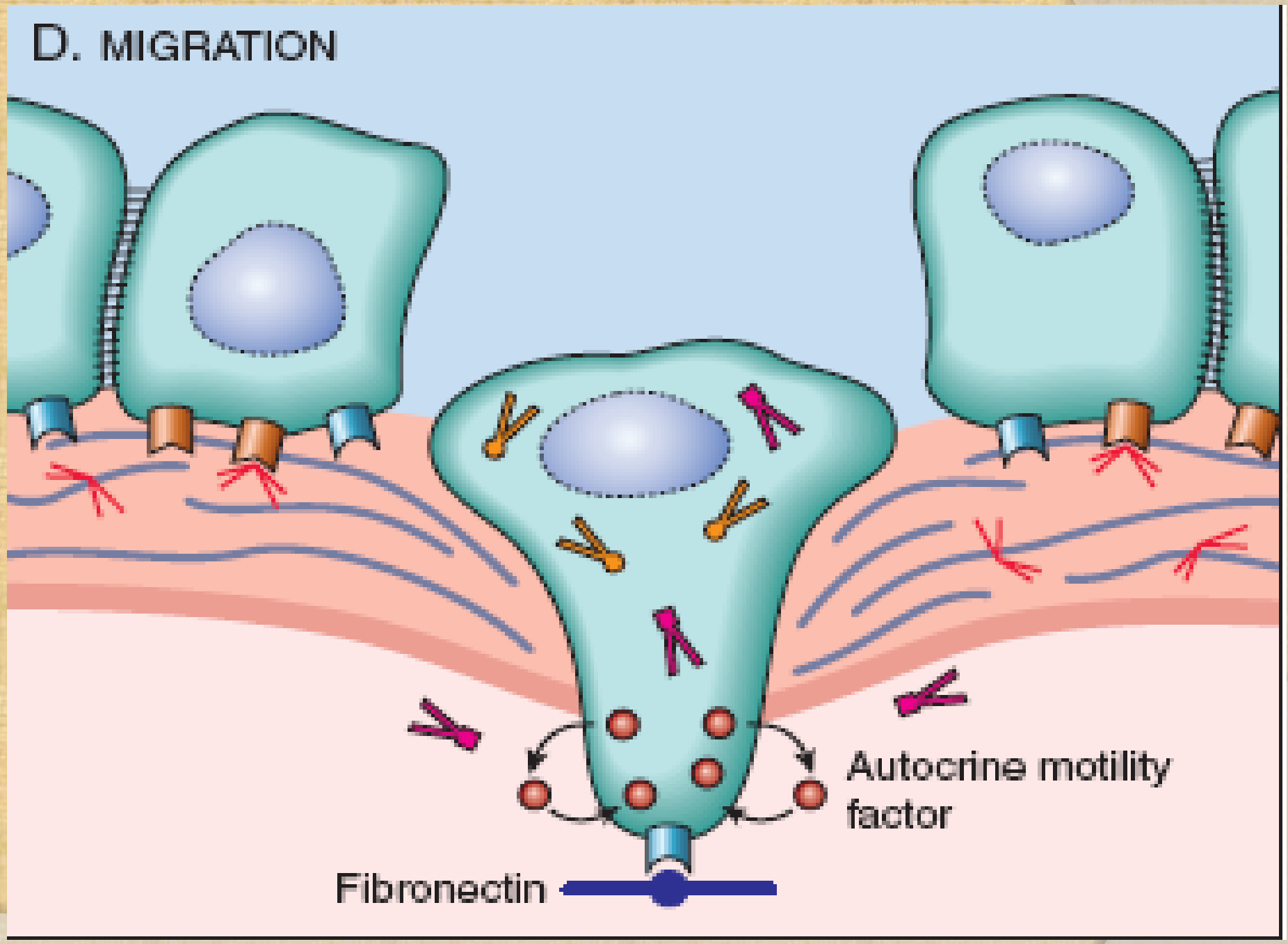
intravasation

tumor cell embolus

extravasation


B. DEGRADATION
Type IV collagenase
Plasminogen activator
Type IV collagen cleavage


C. ATTACHMENT
Type IV collagen
Laminin receptor
Fibronectin receptor
Laminin


D. MIGRATION
Autocrine motility factor
Fibronectin

THANK YOU