NEOPLASIA 3

Fe A. Bartolome, MD, FPASMAP
Department of Pathology
Our Lady of Fatima University

MOLECULAR BASIS

Fundamental Changes in Cell Physiology That Determine Malignant Phenotype

1. Self-sufficiency in growth signals
2. Insensitivity to growth-inhibiting signals
3. Evasion of apoptosis
4. Limitless replicative potential
5. Sustained angiogenesis
6. Ability to invade and metastasize
7. Defects in DNA repair

Evasion of apoptosis

Review of Apoptosis

- **Programmed cell death**
- **Triggers: range from DNA damage to loss of adhesion to the basement membrane (“anoikis”)**
- **Two pathways: extrinsic (via death receptor CD95/Fas) and intrinsic (mitochondrial)**

Evasion of apoptosis

Extrinsic Pathway

1. **Binding of CD95/Fas to CD95L/FasL**
2. **Trimerization of receptor and its cytoplasmic *death domain* → attract FADD**
3. **Recruitment of procaspase 8 by FADD → formation of *death-inducing signalling complex***
4. **Generation of caspase 8**
5. **Activation of caspase 3 (executioner caspase) → cell death**

Evasion of apoptosis

Intrinsic Pathway

1. **Cleavage and activation of BH3-only protein BID by caspase 8**
2. **Permeabilization of mitochondrial membrane**
3. **Release of cytochrome c**
4. **Binding of cytochrome c to APAF-1 → activation of caspase 9 → cleavage and activation of executioner caspases**

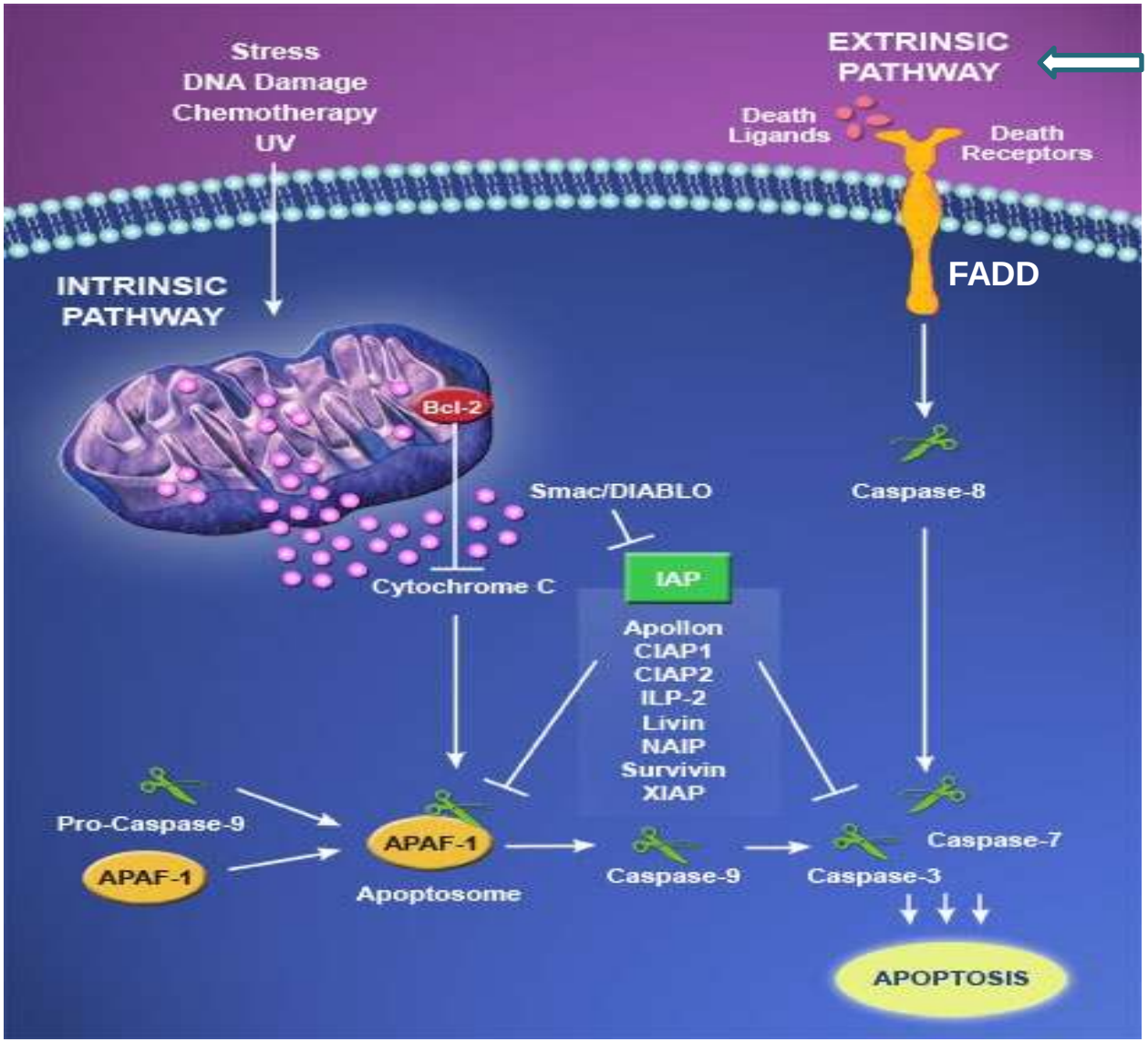
MOLECULAR BASIS

Evasion of apoptosis

- **Integrity of mitochondrial outer membrane regulated by anti-apoptotic proteins BCL2 & BCL-XL**
- **Pro-apoptotic proteins: BAX & BAK**
- **BH3-only proteins (BAD, BID, PUMA) → regulate the balance between pro- and anti-apoptotic proteins**

MOLECULAR BASIS

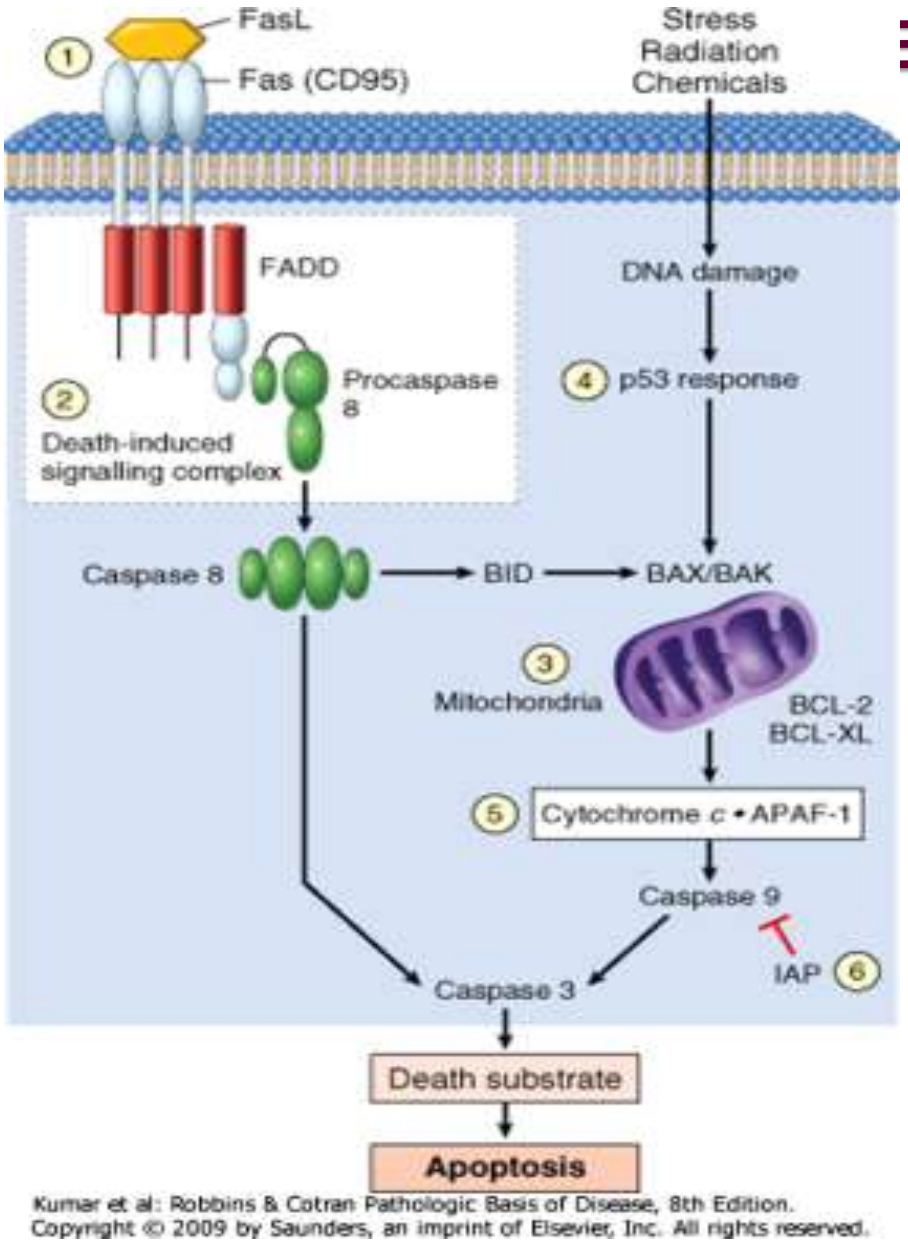
Evasion of apoptosis



CD95/Fas

MOLECULAR BASIS

Evasion of apoptosis



CD95 receptor-induced and DNA damage-triggered pathways of apoptosis and mechanisms used by tumor cells to evade cell death.

(1) Reduced CD95 level. (2) Inactivation of death-induced signaling complex by FLICE protein (caspase 8; apoptosis-related cysteine peptidase). (3) Reduced egress of cytochrome *c* from mitochondrion as a result of up-regulation of BCL2. (4) Reduced levels of pro-apoptotic BAX resulting from loss of p53. (5) Loss of apoptotic peptidase activating factor 1 (APAF1). (6) Up-regulation of inhibitors of apoptosis (IAP). FADD, Fas-associated via death domain

MOLECULAR BASIS

Evasion of apoptosis

1. **Reduced levels of CD95/Fas → decreased susceptibility of tumor cells to apoptosis**

2. **Some tumors with high FLIP levels → prevent activation of caspase 8**

3. **Overexpression of *BCL2* → inhibit apoptosis**

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7. Defects in DNA repair

MOLECULAR BASIS

Limitless replicative potential

- **Most normal human cells with capacity of 60 – 70 doublings → after doublings, cell lose ability to divide → become senescent → due to shortening of telomeres at ends of chromosomes**

- **Short telomeres → recognized by DNA-repair machinery → cell cycle arrest mediated by p53 and RB**

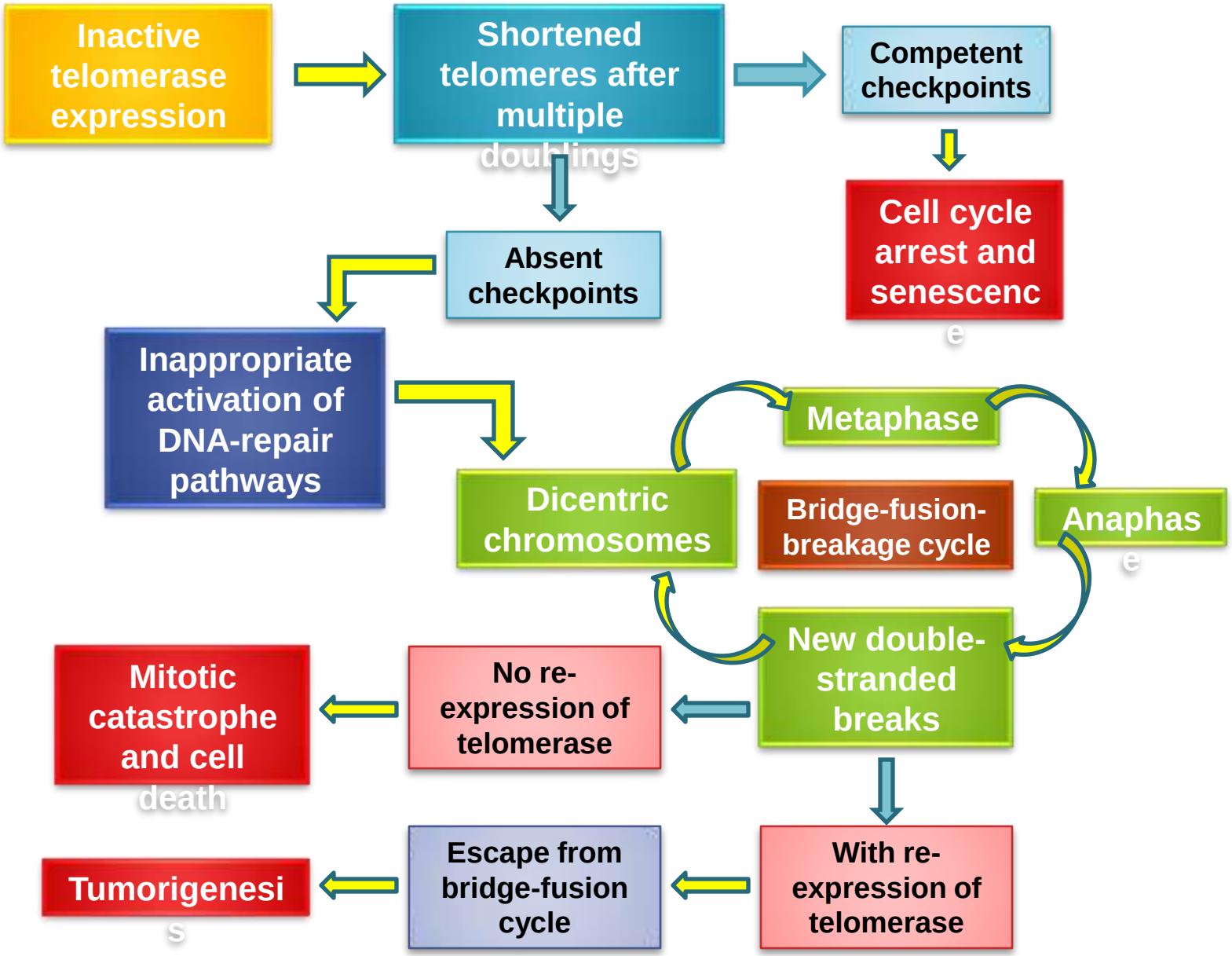
MOLECULAR BASIS

Limitless replicative potential

1. **Cells with disabled checkpoints → nonhomologous end-joining pathway activated → fusion of shortened ends of two chromosomes → dicentric chromosomes → (+) genomic instability**

2. **Reactivation of telomerase → bridge-fusion-breakage cycle cease → cell survives despite genomic instability → accumulation of numerous mutations → malignancy**

MOLECULAR BASIS



MOLECULAR BASIS

Limitless replicative potential

- **Telomerase active in normal stem cells but normally absent, or expressed at very low levels in most somatic cells**
- **85% - 95% of cancers with up-regulation of enzyme telomerase → lengthening of telomeres → no cell cycle arrest or senescence**

MOLECULAR BASIS

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Sustained angiogenesis

- Solid tumors cannot enlarge beyond 1 to 2 mm in diameter unless they are vascularized

- Cancer cells can stimulate:
  1. Neoangiogenesis – new vessels from previously existing capillaries
  2. Vasculogenesis – endothelial cells recruited from bone marrow

MOLECULAR BASIS

Sustained angiogenesis

- **Tumor vasculature abnormal**
  - ✓ Leaky and dilated
  - ✓ Haphazard pattern of connection

- **Effects of neovascularization on tumor growth:**
  1. Supply of nutrients and oxygen
  2. (+) secretion of growth factors (e.g. IGFs, PDGF, granulocyte-macrophage colony stimulating factor) → stimulation of growth of adjacent tumor cells

MOLECULAR BASIS

Sustained angiogenesis

- ***Angiogenesis is required for:***
  1. ***Continued tumor growth***
  2. ***Access to the vasculature → metastasis***

- ***Angiogenesis is a necessary biologic correlate of malignancy***

Sustained angiogenesis

Anti-angiogenesis factors

1. **Thrombospondin**
   - Platelet factor 4; regulated by p53
2. **Angiostatin**
   - Cleavage product of plasminogen
3. **Endostatin**
   - Cleavage product of collagen type XVIII
4. **Vasostatin**
   - Cleavage product of transthyretin

MOLECULAR BASIS

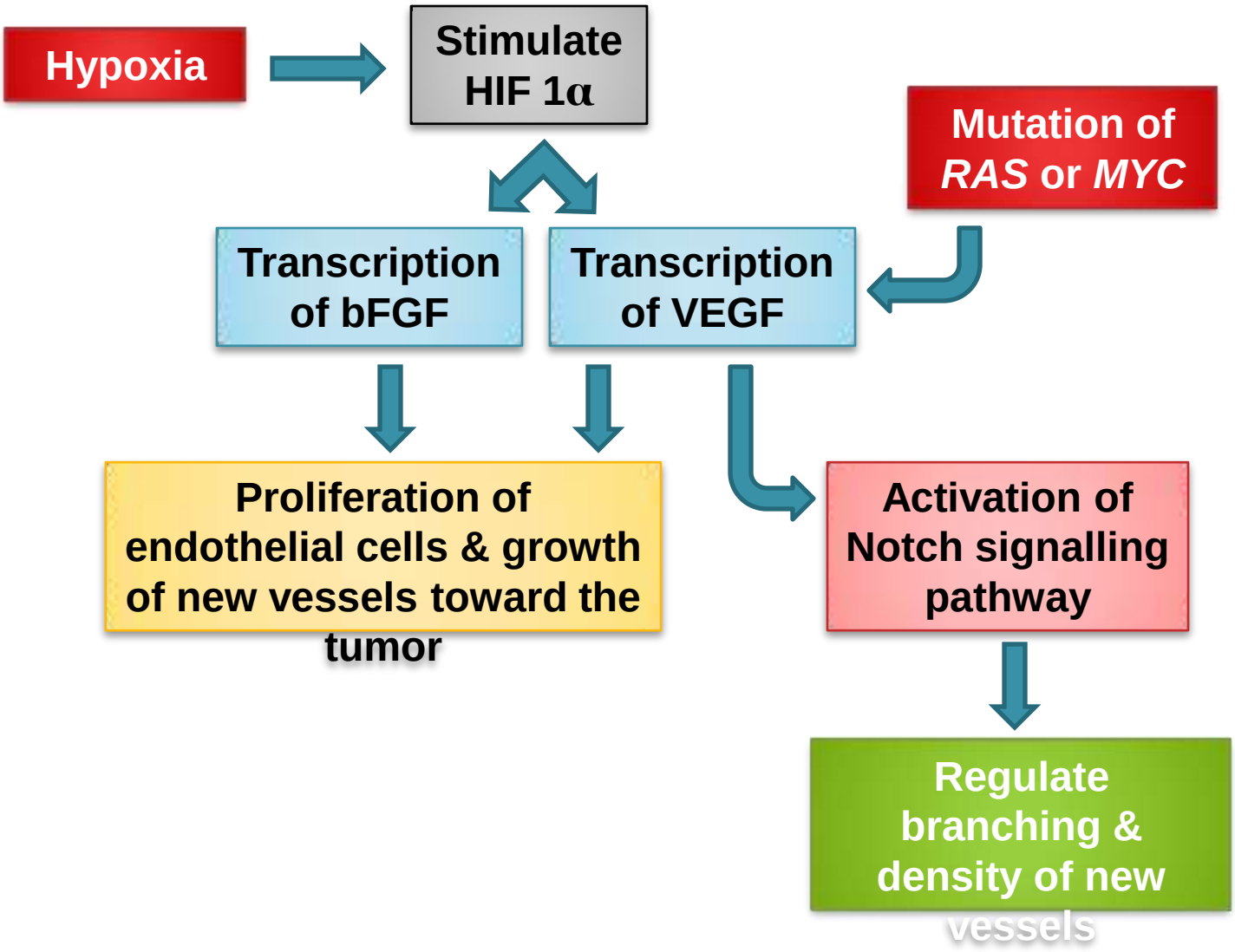
Sustained angiogenesis

- ***Tumor angiogenesis is controlled by a balance between angiogenesis promoters and inhibitors → involves proteases secreted by tumor cells or inflammatory cells***
  - ✓ ***Increased production of angiogenic factors and/or loss of angiogenic inhibitors***

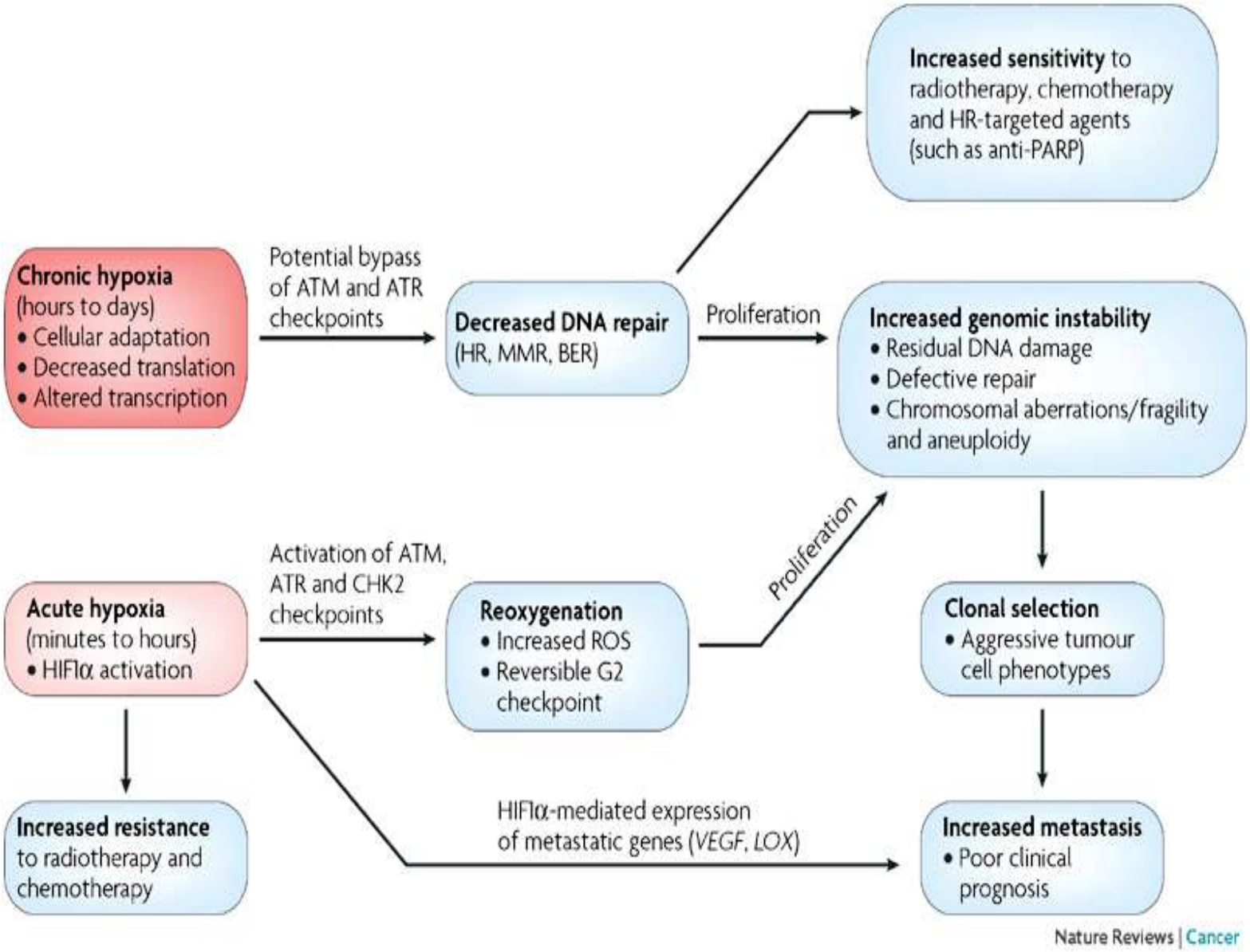
- ***Angiogenic switch controlled by physiologic stimuli such as hypoxia***

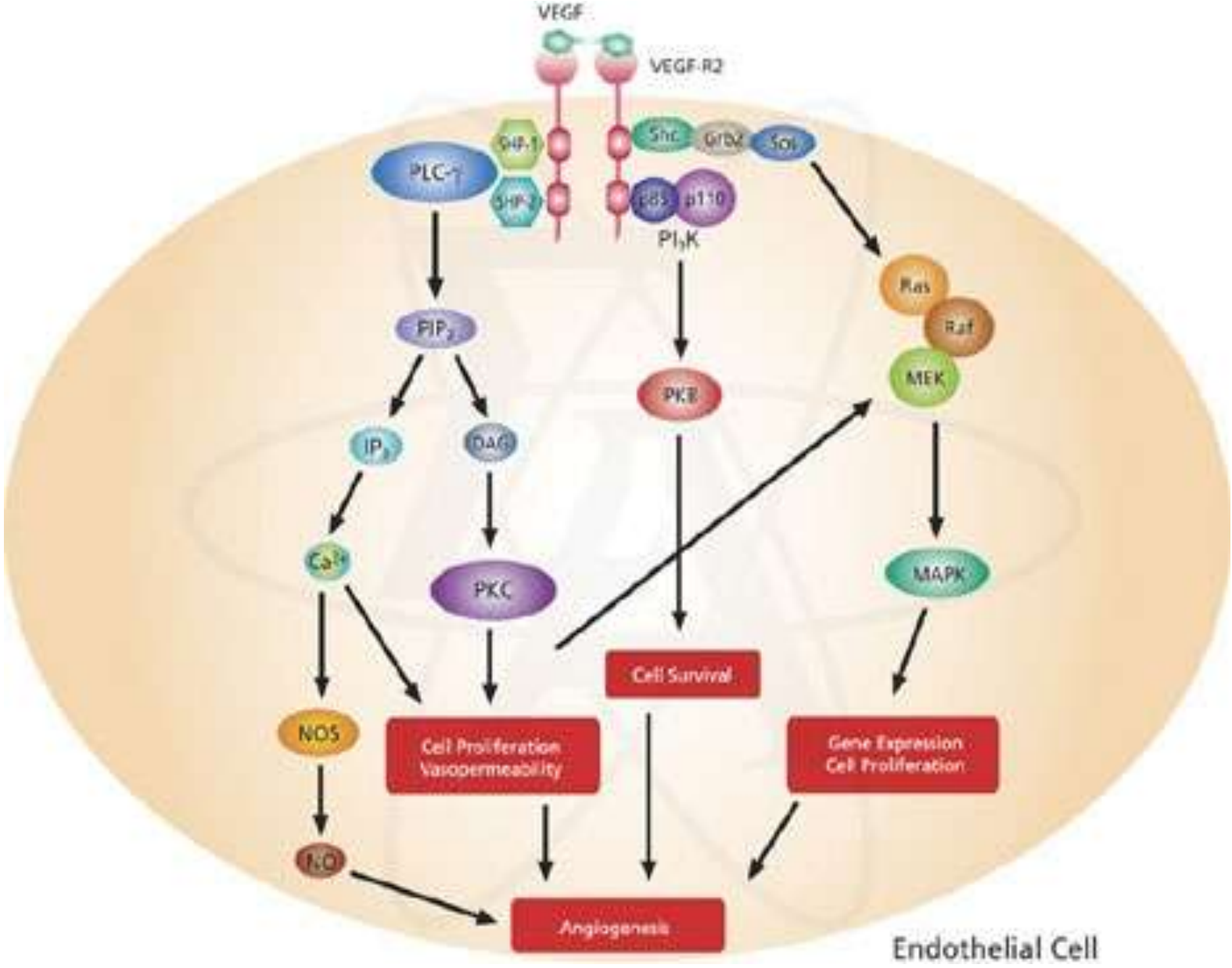
MOLECULAR BASIS

Sustained angiogenesis



MOLECULAR BASIS




VEGF
VEGF-R2
SHP-1
SHP-2
Shc
GrB2
Sos
PLC-γ
p85
p110
PI3K
Ras
Raf
MEK
PIP2
PKB
IP3
DAG
Ca2+
PKC
MAPK
Cell Survival
NOS
Cell Proliferation
Vasopermeability
Gene Expression
Cell Proliferation
NO
Angiogenesis
Endothelial Cell

Sustained angiogenesis

- **Angiogenesis factors produced by tumor cells include:**

1. **Vascular endothelial growth factor (VEGF)**
2. **Basic fibroblast growth factor (bFGF)**
3. **Angiopoietin (Ang)**

MOLECULAR BASIS

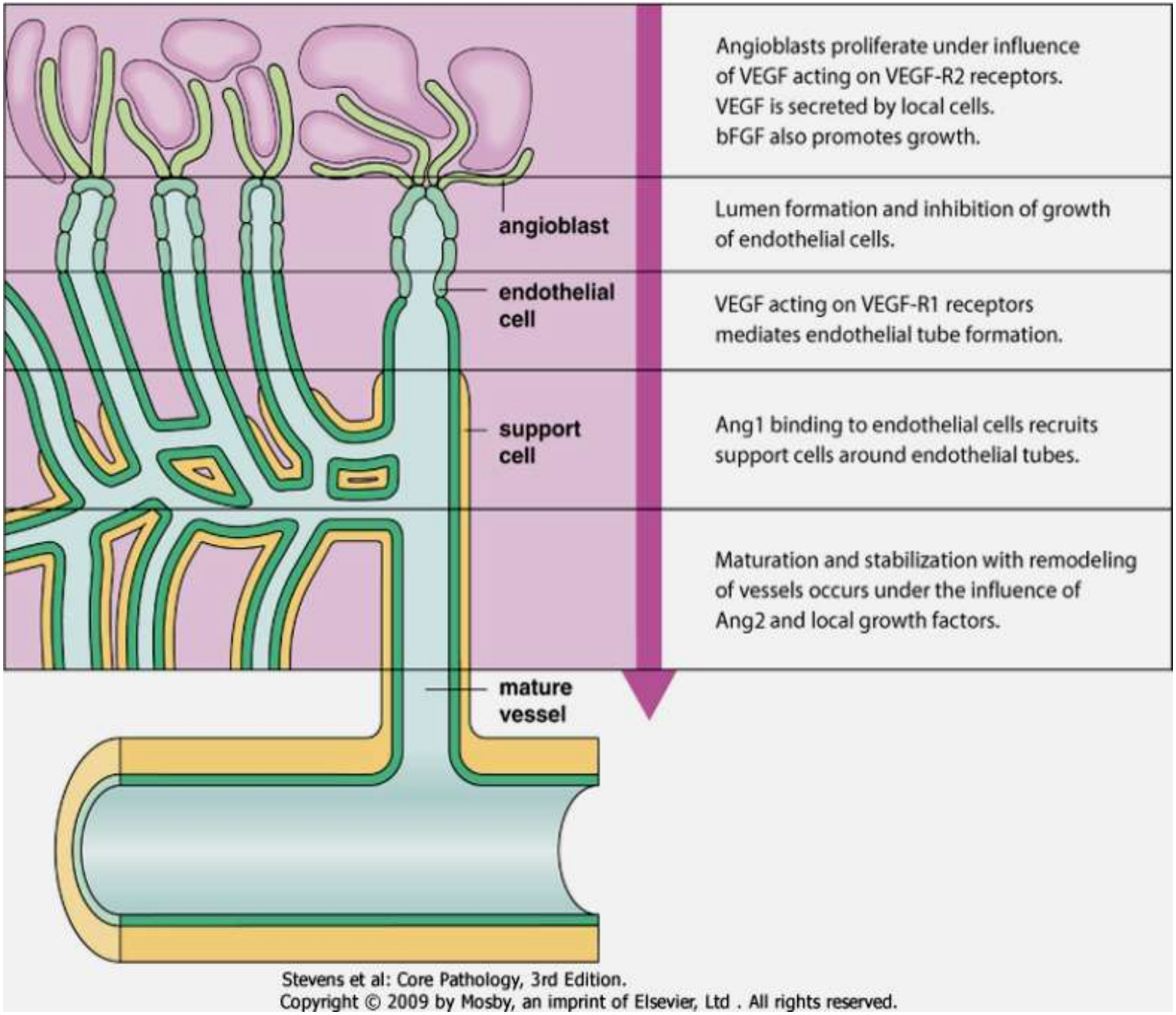
Sustained angiogenesis

Angiopoietins (Ang)

a) **Ang 1**
   - Promotes stabilization and growth of vessels from capillary types to larger types by recruiting peri-endothelial cells

b) **Ang 2**
   - Promotes remodelling and maturation of developing vascular networks

MOLECULAR BASIS



Stevens et al: Core Pathology, 3rd Edition.

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MOLECULAR BASIS

Ability to invade and metastasize

- **Biologic hallmarks of malignant tumors**
- **Metastatic cascade divided into two phases:**

1. ***Invasion of extracellular matrix (basement membrane & interstitial connective tissue)***
2. ***Vascular dissemination, homing of tumor cells, and colonization***

Local Invasion

Invasion of Extracellular Matrix: Steps

1. Dissociation of cells from one another

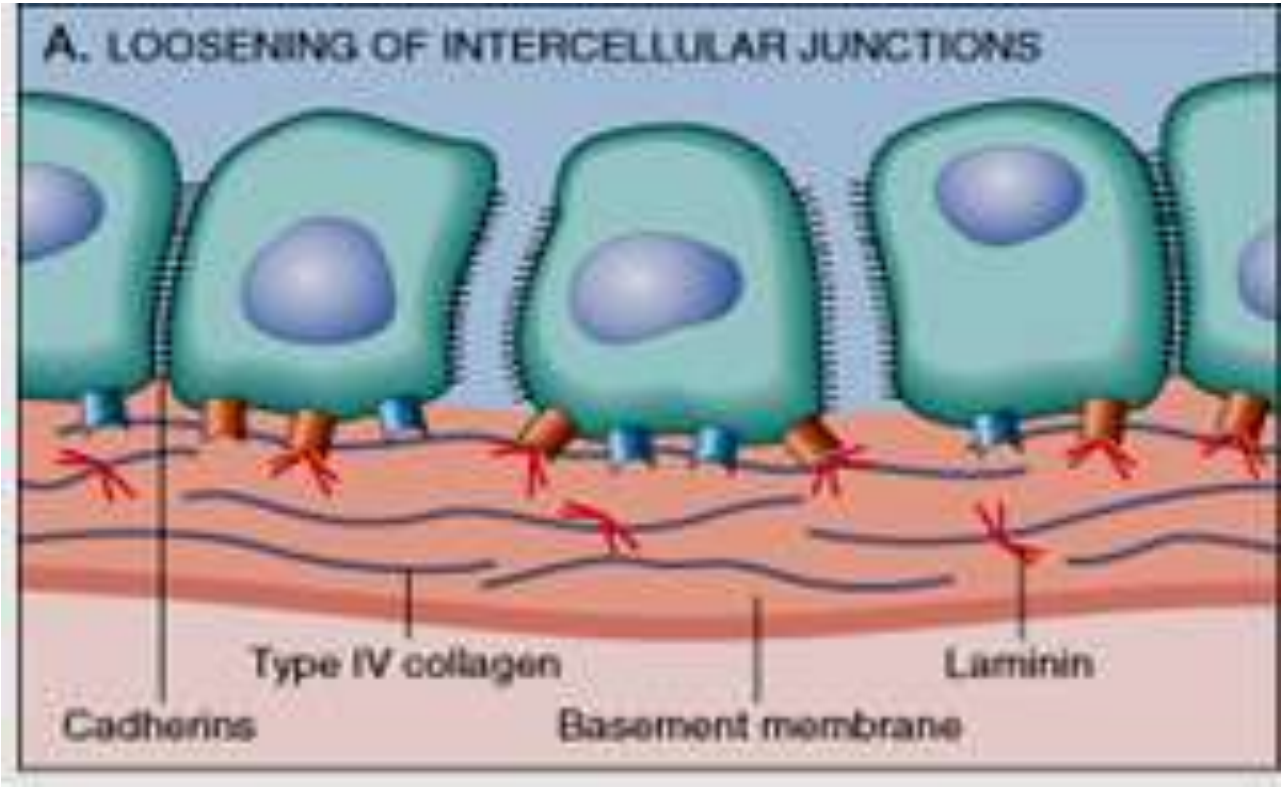
- **Down regulation of E-cadherin due to mutation in the gene for E-cadherin or gene for catenins → reduced ability of cells to adhere to each other → facilitate detachment from primary tumor**

MOLECULAR BASIS

Local Invasion

Invasion of Extracellular Matrix: Steps

1. Dissociation of cells from one another



Local Invasion

2. Local degradation of the basement membrane and interstitial connective tissue

- **Tumor cells:**
  - **a) Secrete proteolytic enzymes**
    - ✓ **Matrix metalloproteinases (MMPs) → remodel insoluble components of basement membrane & release ECM-sequestered growth factors**
    - ✓ **cathepsin D, urokinase plasminogen activator**
    - ✓ **MMP9 → cleave type IV collagen of epithelial and vascular basement membrane & stimulate release of VEGF**

MOLECULAR BASIS

Local Invasion

2. Local degradation of the basement membrane and interstitial connective tissue

- **Tumor cells:**
  a) **Secrete proteolytic enzymes**
  b) **Induce stromal cells (e.g. Fibroblasts, inflammatory cells) to elaborate proteases**

Local Invasion

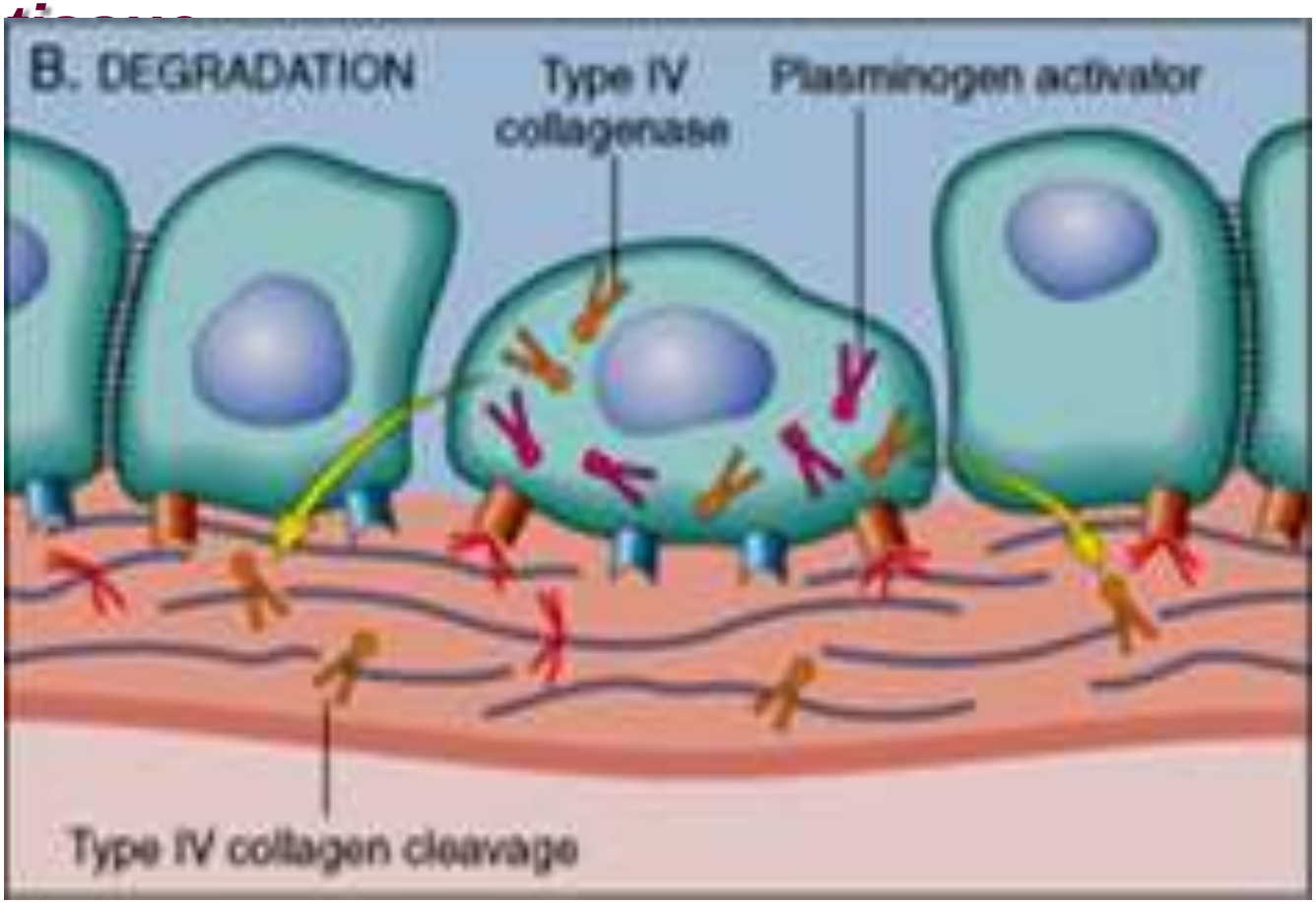
2. Local degradation of basement membrane and interstitial connective tissue

- **Tumor cells can adopt a second mode of invasion called amoeboid migration**
  - ✓ **Tumor cells squeeze through spaces in the matrix → utilize collagen fibers as high-speed "railways"**
  - ✓ **Quicker**

MOLECULAR BASIS

Local Invasion

2. Local degradation of basement membrane and interstitial connective tissue



Local Invasion

3. Changes in attachment of tumor cells to ECM proteins

- **Normal epithelial cells with receptors such as integrins for basement membrane laminin and collagen → help maintain cells in a resting, differentiated state**

- **Loss of adhesion in normal cells → induction of apoptosis but tumor cells resistant**

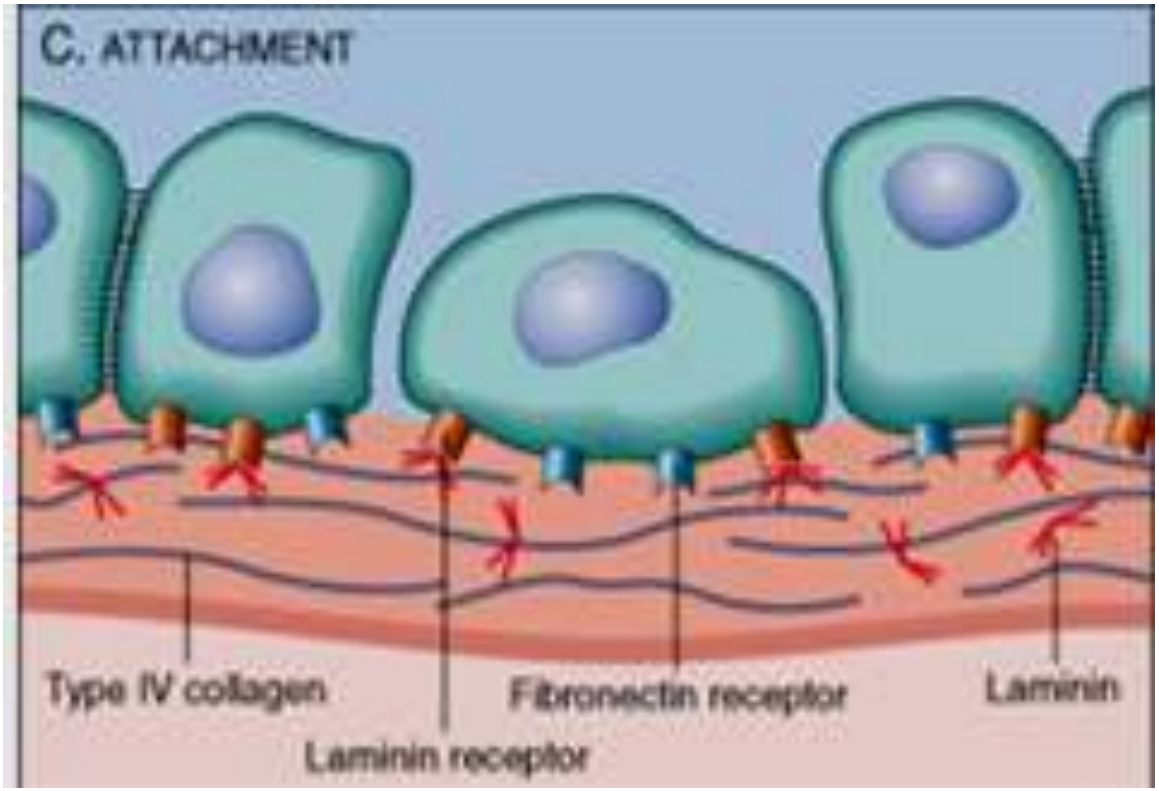
Local Invasion

3. Changes in attachment of tumor cells to ECM proteins

- **Cleavage of basement membrane proteins collagen IV and laminin by MMP2 or MMP9 → generate novel sites → bind to receptors on tumor cells → stimulate migration**

Local Invasion

3. Changes in attachment of tumor cells to ECM proteins



Local Invasion

4. Locomotion

- Final step in invasion
- Tumor cells attach to the matrix at the leading edge → detach from matrix at trailing edge → contract the actin cytoskeleton to ratchet forward
- Movement potentiated and directed by tumor-derived cytokines
  - ✓ Autocrine motility factors

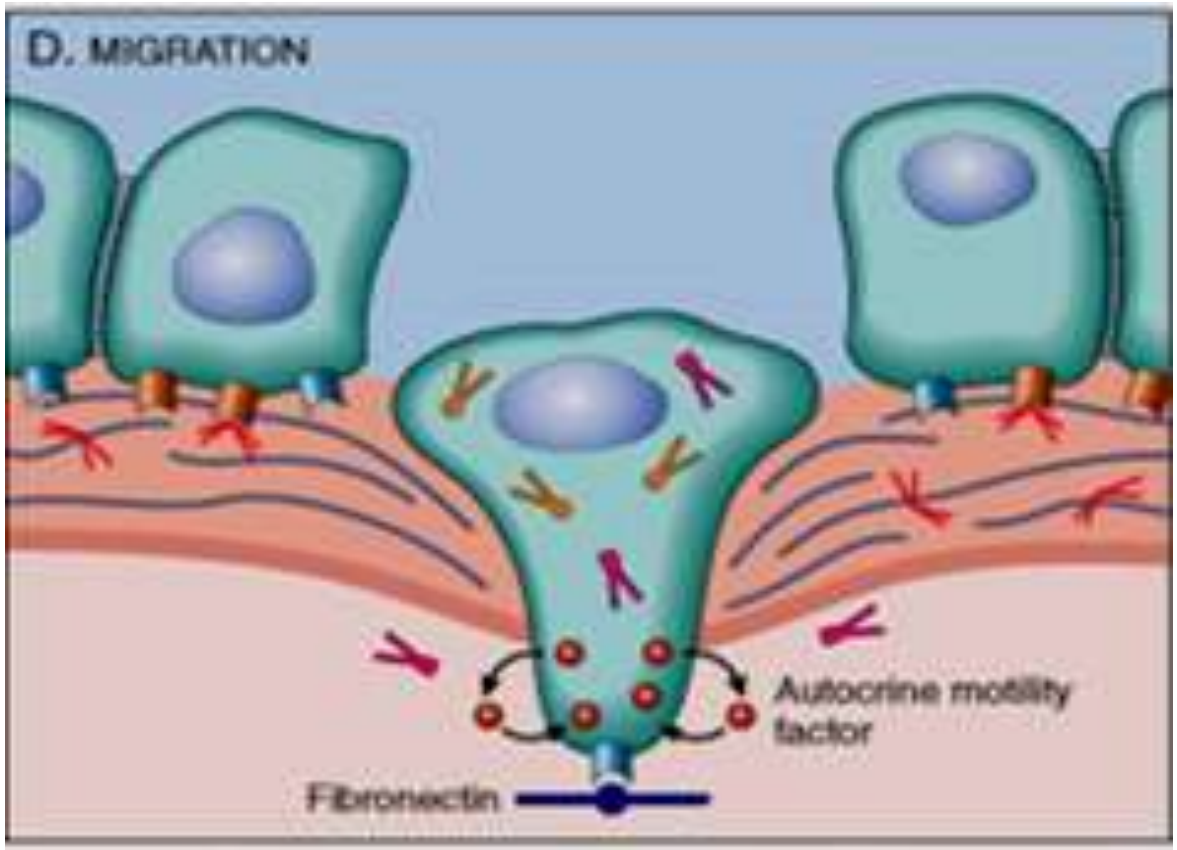
Local Invasion

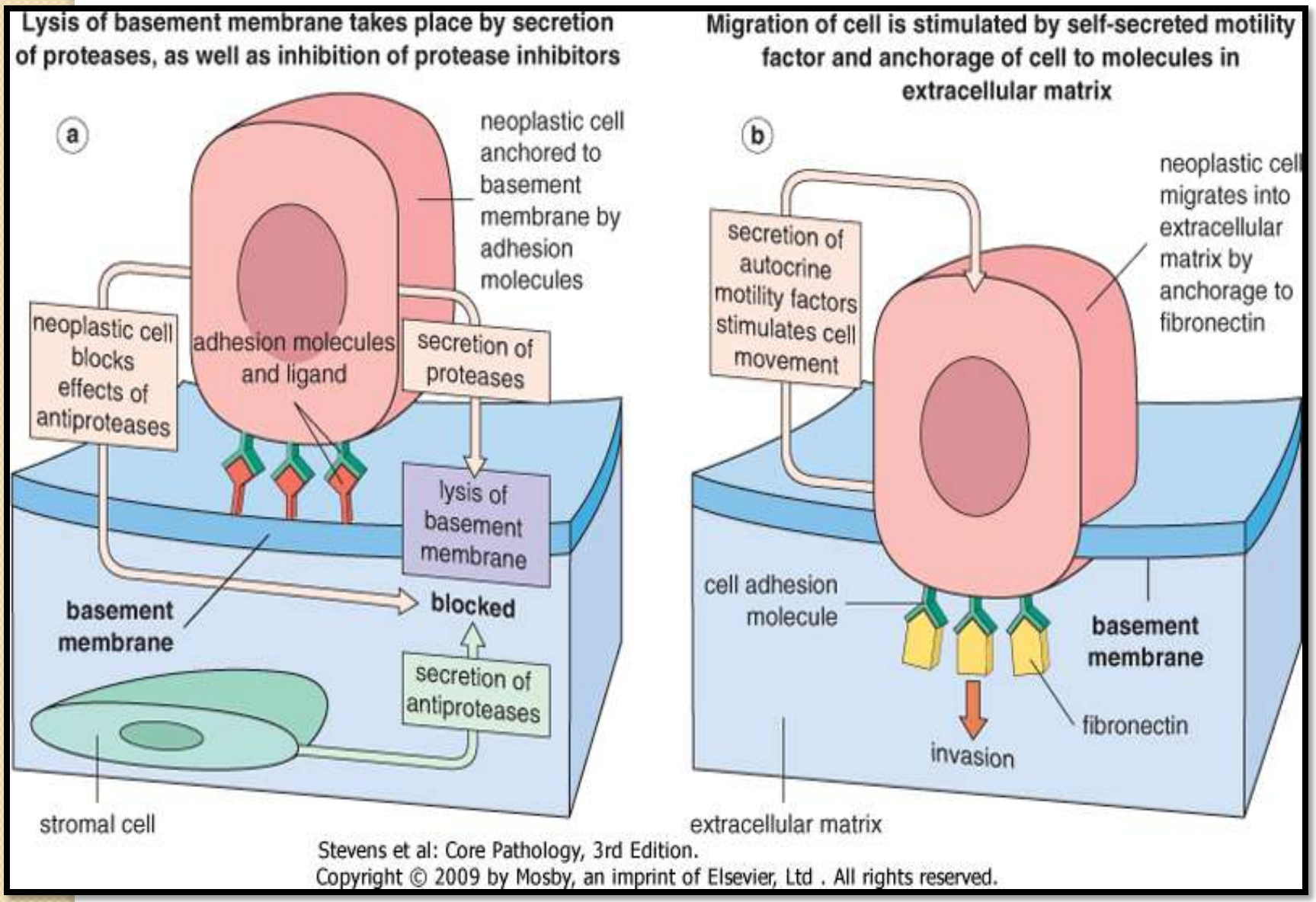
4. Locomotion

- Cleavage products of matrix components (collagen, laminin) and some growth factors (IGFs I and II) → with chemotactic activity for tumor cells
- Stromal cells → produce paracrine effectors of cell motility (e.g. Hepatocyte growth factor-scatter factor) → bind to receptors on tumor cells

Local Invasion

4. Locomotion





Local Invasion

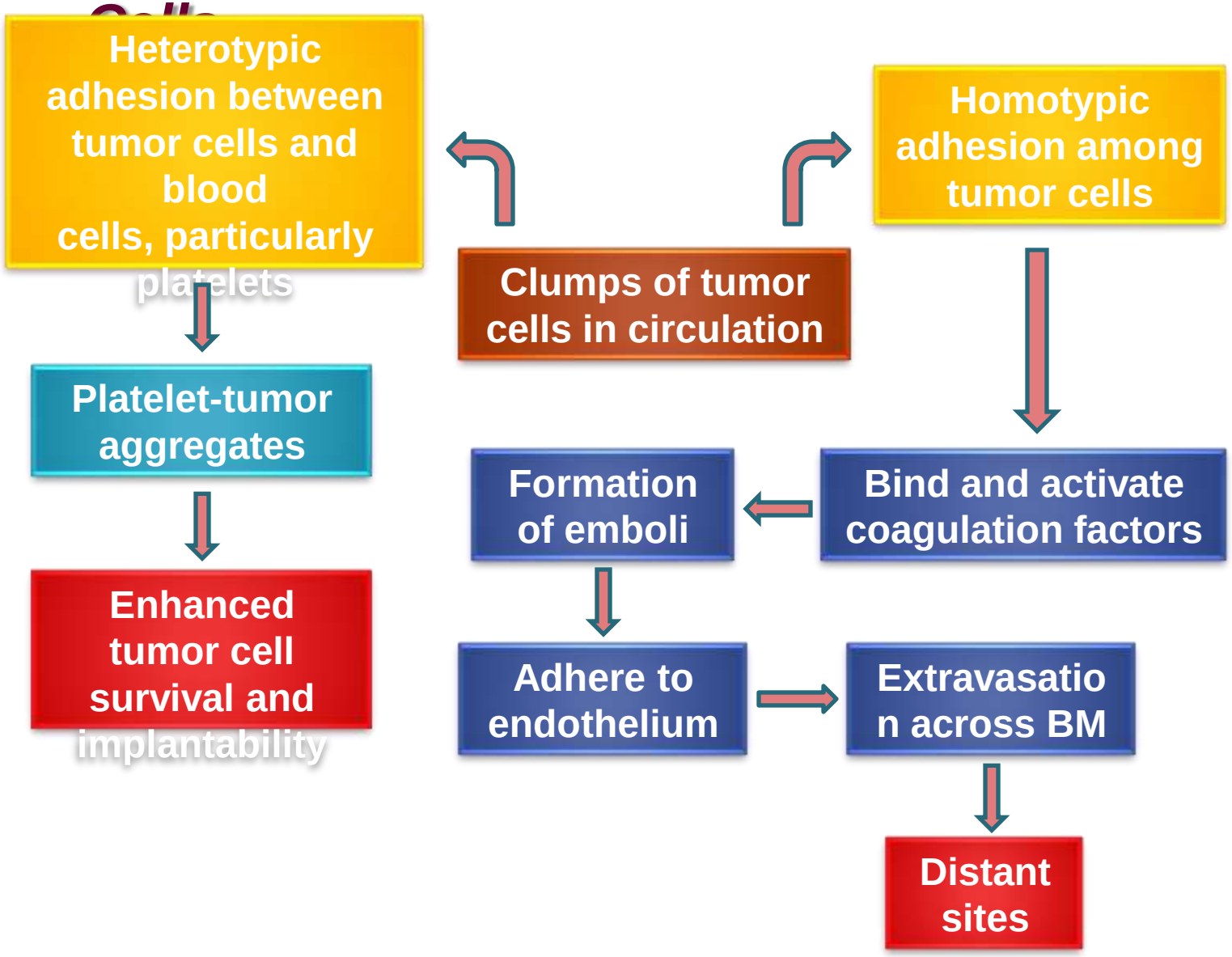
Vascular Dissemination & Homing of Tumor Cells

- In the circulation, tumor cells are vulnerable to destruction by the following mechanisms:
  1. *Mechanical shear stress*
  2. *Apoptosis stimulated by loss of adhesion*
  3. *Innate and adaptive immune defenses*

- Within the circulation, tumor cells tend to aggregate in clumps

MOLECULAR BASIS

Vascular Dissemination & Homing of Tumor Cells



MOLECULAR BASIS

Vascular Dissemination & Homing of Tumor Cells

- **Involvement of adhesion molecules (integrins, laminin receptors) & proteolytic enzymes**
  - ✓ **CD44 adhesion molecule**
    - **Expressed on normal T cells**
    - **Bind to hyaluronate on high endothelial venules**
    - **Overexpression → favor metastatic spread**
- **Most metastases occur in the first capillary bed available to the tumor**

MOLECULAR BASIS

Vascular Dissemination & Homing of Tumor Cells

- **Certain tumors with organ tropism for spread not explained by natural pathways of drainage, which may be related to the following mechanisms:**

1. ***Preferential expression of ligands for tumor cell-adhesion molecules on the endothelial cells of the target organ.***

Vascular Dissemination & Homing of Tumor Cells

2. ***Chemokines have an important role in determining the target tissues for metastasis.***
   - ***Breast cancer cells express the chemokine receptors CXCR4 and CCR7 → chemokines highly expressed in tissues to which breast cancers commonly metastasize***
   - ***Some target organs liberate chemo- attractants that recruit tumor cells to the site (e.g. IGFs I***

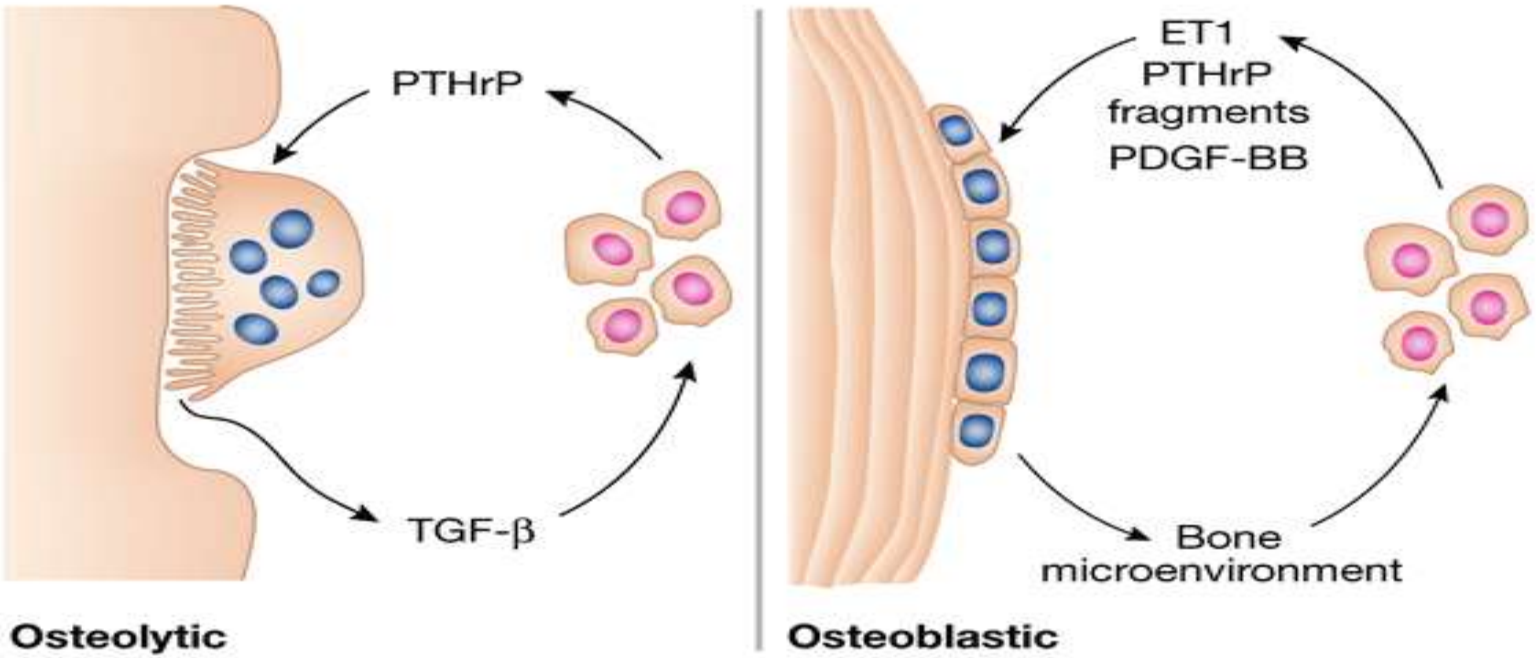
Vascular Dissemination & Homing of Tumor Cells

3. ***In some cases, the target tissue may be a non-permissive environment for the growth of tumor seedlings***

   - ***Skeletal muscles are rarely the site of metastases***

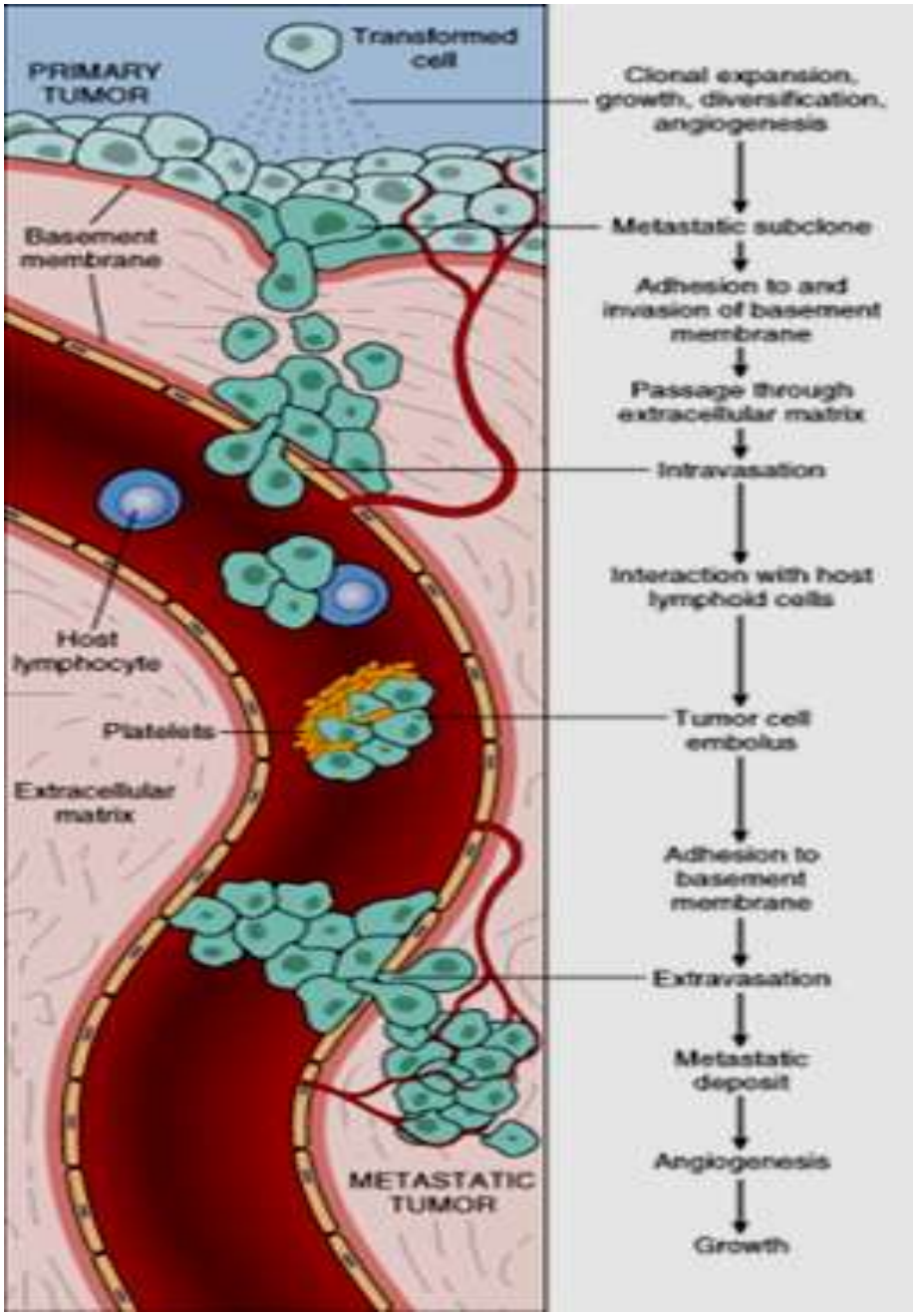
Vascular Dissemination & Homing of Tumor Cells

- ***Tumor cells secrete cytokines, growth factors, and ECM molecules that act on resident stromal cells → make the metastatic site habitable for the cancer cells***
  - ✓ ***Breast cancer cells secrete para-thyroid hormone-related protein (PTHRP) → stimulate osteoblasts to make RANK ligand → activate osteoclasts → breast cancer metastases to bone osteolytic***



Tumour–bone paracrine interactions. Left-hand side, an osteolytic interaction in which parathyroid-hormone-related protein (PTHrP), which is produced by tumour cells, stimulates the activity of bone-eating osteoclasts (multinucleate cell). Osteoclasts in turn produce transforming growth factor- (TGF-), which stimulates the tumour cells. Right-hand side, osteoblastic interactions. Tumour cells produce many factors, including endothelin 1 (ET1), PTHrP and platelet-derived growth factor (PDGF)-BB, which stimulate the activity of bone-producing osteoblasts (blue nuclei). Osteoblasts in turn produce factors that stimulate the growth of the tumour cells.

MOLECULAR BASIS

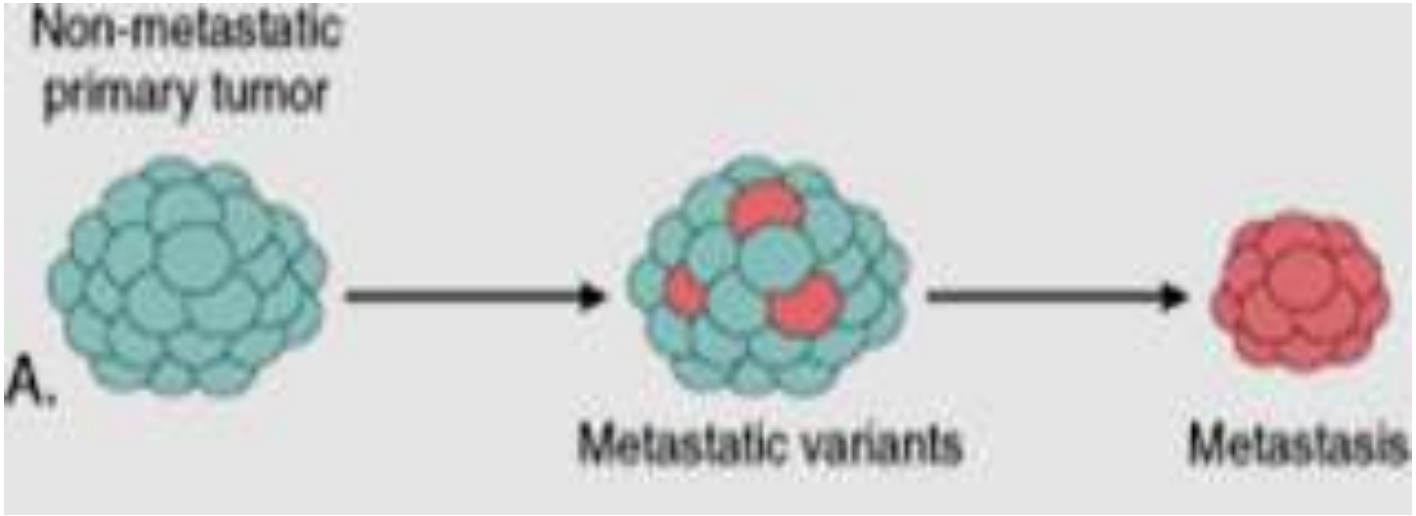


The metastatic cascade. Sequential steps involved in the hematogenous spread of a tumor.

Mechanisms of metastasis development within a primary tumor:

1. Clonal evolution model

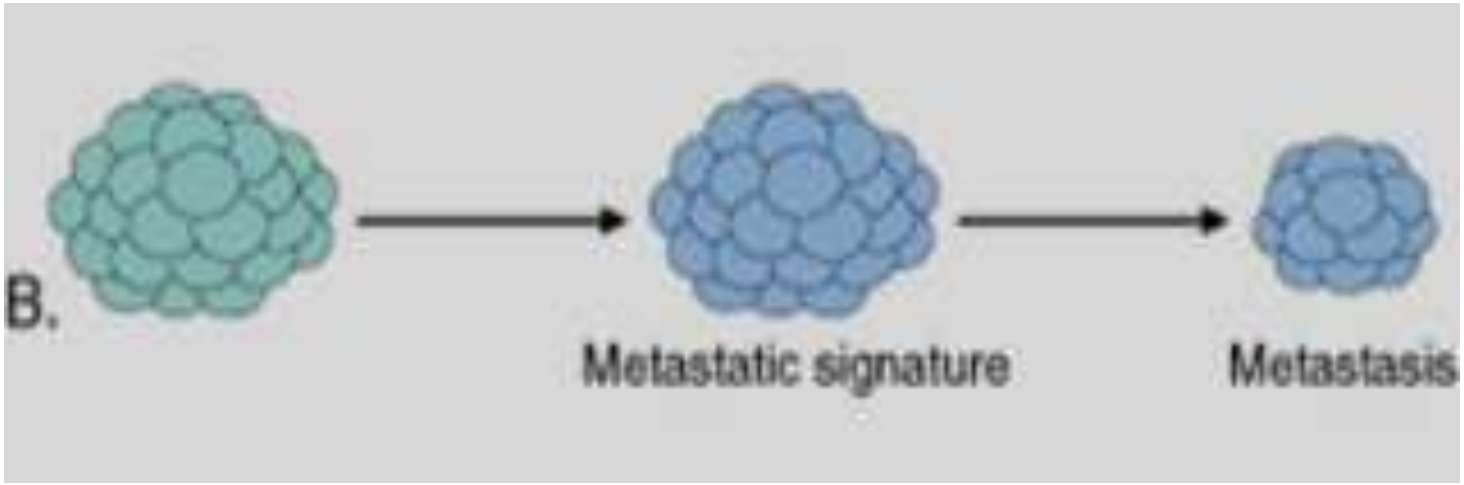
- **Metastasis is caused by rare variant clones that develop in the primary tumor.**



Mechanisms of metastasis development within a primary tumor:

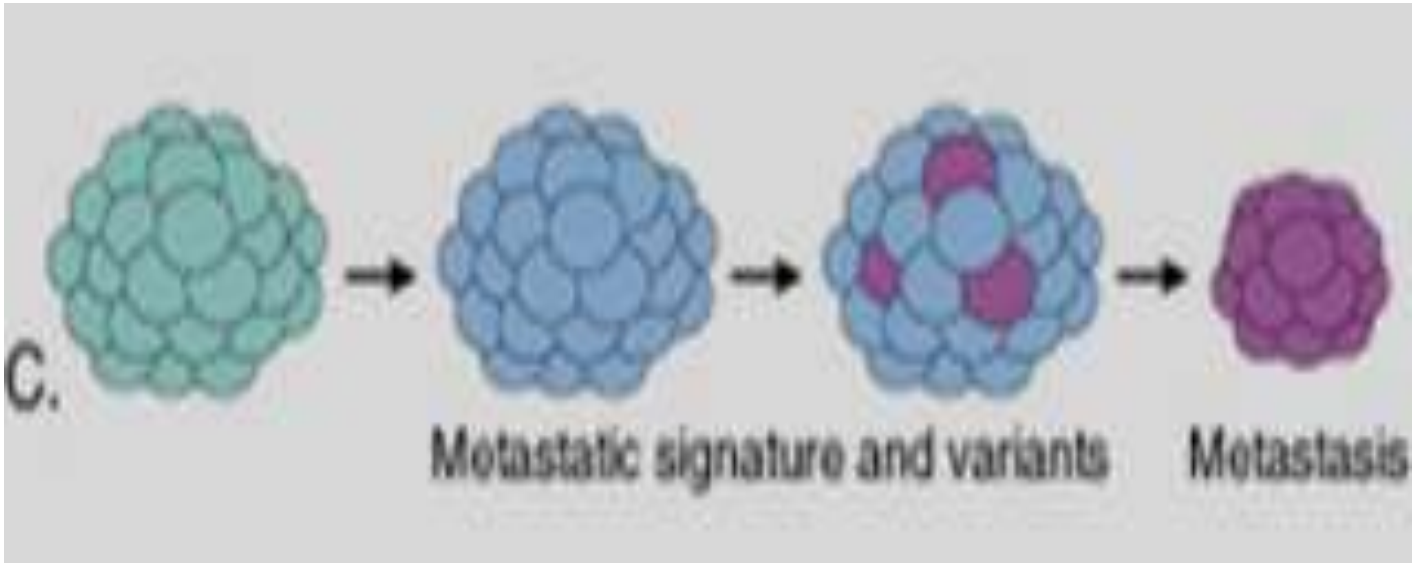
2. Expression of metastasis signature

- **Metastasis is caused by multiple abnormalities that occur in most cells of the primary tumor early in the development of the tumor**



Mechanisms of metastasis development within a primary tumor:

3. Appearance of metastatic variants in a tumor with a metastatic gene signature



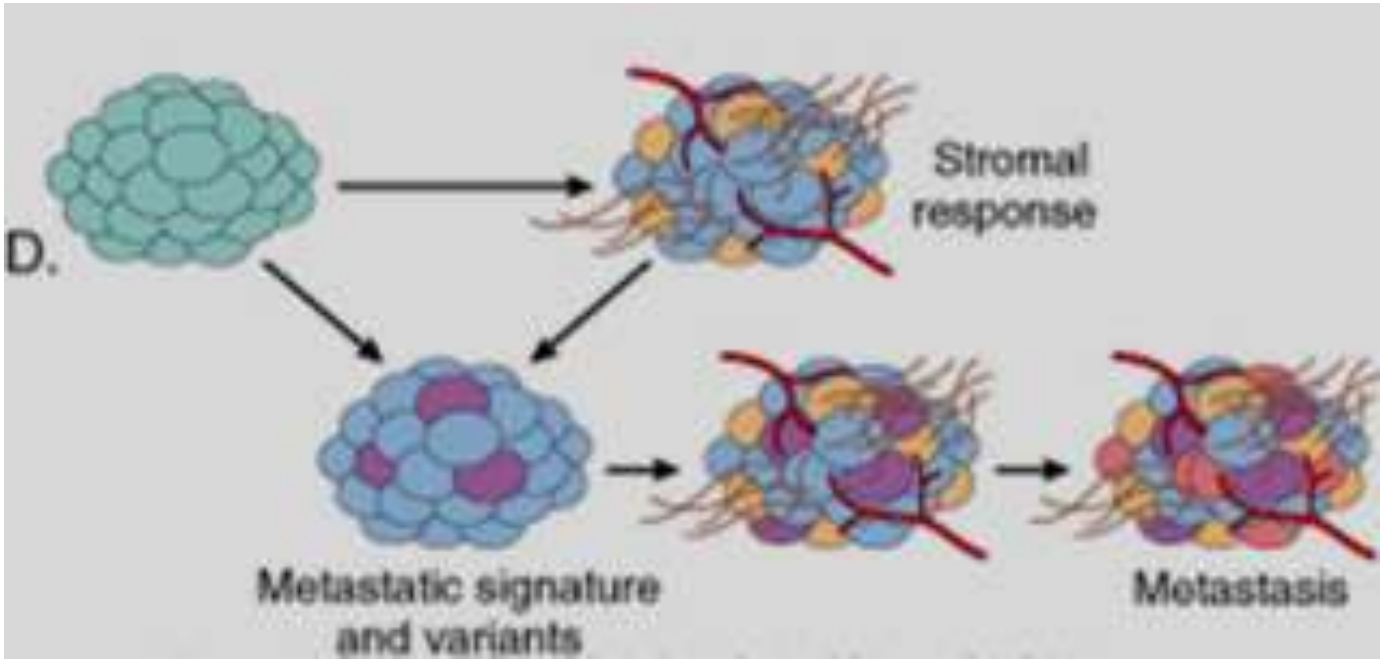
Mechanisms of metastasis development within a primary tumor:

4. Corollary of tumor stem cell hypothesis

- **Metastasis development is greatly influenced by the tumor stroma, which may regulate angiogenesis, local invasiveness, and resistant to immune elimination → allow cells of the primary tumor to become metastatic**

Mechanisms of metastasis development within a primary tumor:

4. Corollary of tumor stem cell hypothesis



MOLECULAR BASIS

Genes implicated in control of metastasis

Metastatic suppressor gene

- **A gene whose loss promotes the development of metastasis without an effect on the primary tumor**
- **Examples: mir335 and mir126 → suppress metastasis in breast cancer**

MOLECULAR BASIS

Genes implicated in control of metastasis

Metastatic oncogene

- **A gene that favors the development of metastasis without effect upon the primary tumor**
- **Examples:**
  - ✓ **Mir10b**
  - ✓ **SNAIL & TWIST → promote epithelial-to-mesenchymal transistion (EMT) → down-regulate E-cadherin expression in breast carcinoma**

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7. ***Defects in DNA repair***

MOLECULAR BASIS

Defects in DNA repair

- ***Individuals born with inherited defects in DNA-repair proteins are at a higher risk of developing cancer.***
- ***Defects in repair mechanisms are present in sporadic human cancers.***
- ***DNA-repair genes are not oncogenic → abnormalities allow mutations in other genes during the process of normal cell division.***

Defects in DNA repair

- Three types of DNA-repair systems:
  1. Mismatch repair
  2. Nucleotide excision repair
  3. Recombination repair

- Genomic instability occurs when both copies of the DNA-repair genes are lost.

Defects in DNA repair

Defects in genes involved in mismatch repair

Hereditary Nonpolyposis Colon Cancer Synd.

- Familial carcinomas of the colon affecting predominantly the cecum and proximal colon
- Result of error in "proofreading"
- Hallmark is microsatellite instability
  - ✓ Microsatellites – tandem repeats of one to six nucleotides; length constant in normal people
  - ✓ In HNPCC, length varies in tumor cells

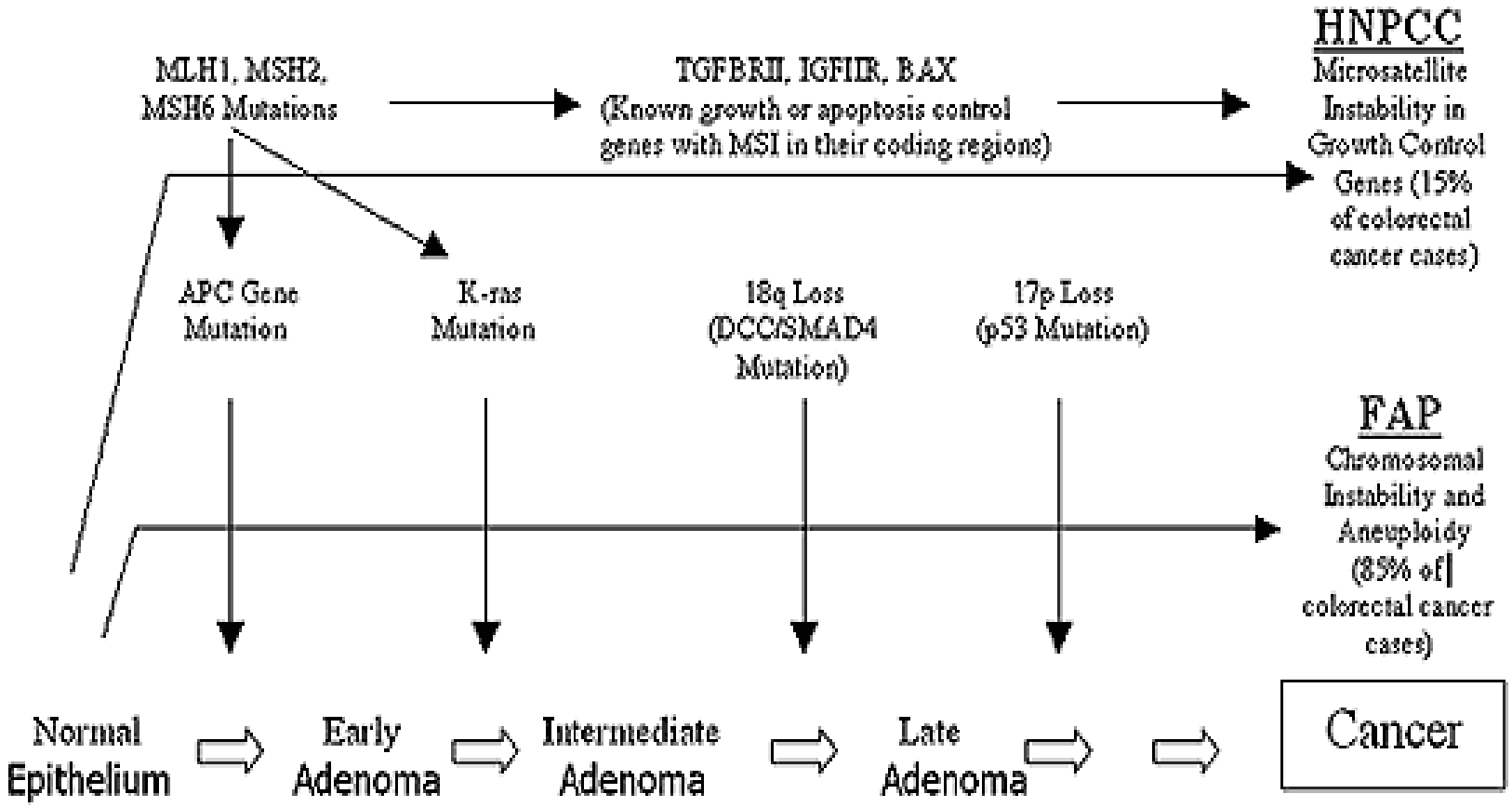
MOLECULAR BASIS

Defects in DNA repair

Defects in genes involved in mismatch repair

Hereditary Nonpolyposis Colon Cancer Synd.

- **Affected individuals inherit one defective copy of a DNA mismatch-repair gene → "second hit" occurs in colonic epithelial cells**
- **Involves mutations in the growth regulating genes encoding *TGF-ß receptor II, TCF component of ß-catenin pathway, BAX***

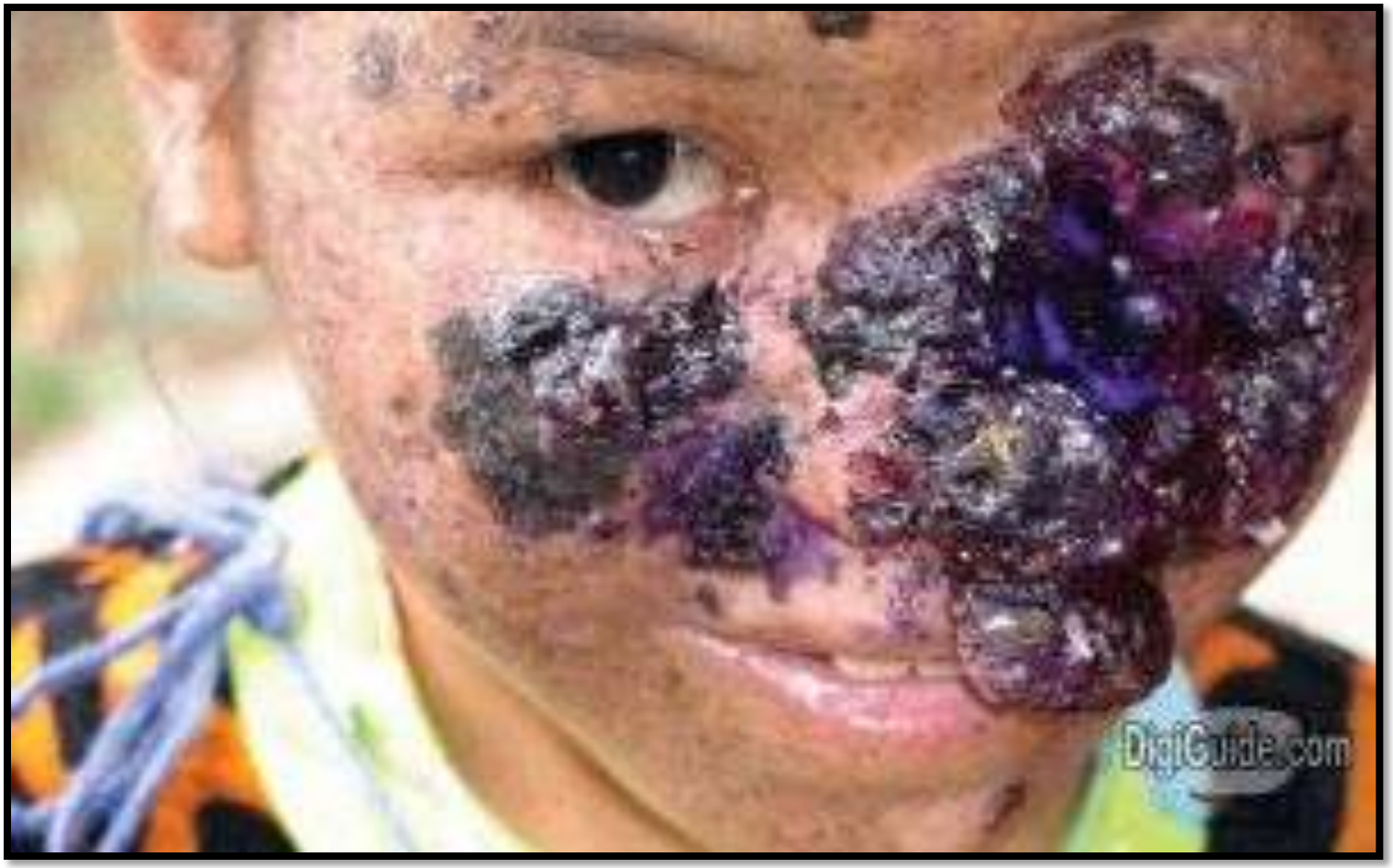

HNPCC
Microsatellite Instability in Growth Control Genes (15% of colorectal cancer cases)
MLH1, MSH2, MSH6 Mutations
TGFBRII, IGFIIR, BAX
(Known growth or apoptosis control genes with MSI in their coding regions)
APC Gene Mutation
K-ras Mutation
18q Loss (DCC/SMAD4 Mutation)
17p Loss (p53 Mutation)
FAP
Chromosomal Instability and Aneuploidy (85% of colorectal cancer cases)
Normal Epithelium
Early Adenoma
Intermediate Adenoma
Late Adenoma
Cancer

Defects in DNA repair

Defects in nucleotide excision repair

Xeroderma pigmentosum

- Increased risk for cancers of the skin, particularly after exposure to UV radiation from sunlight
- UV radiation → cross-linking of pyrimidine residues → inhibit DNA replication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Defects in DNA repair

Defects in recombination repair

Bloom syndrome, Ataxia telangiectasia, Fanconi anemia

- **Characterized by hypersensitivity to other DNA-damaging agents such as:**
  - ✓ **Ionizing radiation (Bloom synd. and ataxia telangiectasia)**
  - ✓ **DNA cross-linking chemo-therapeutic agens (Fanconi anemia)**

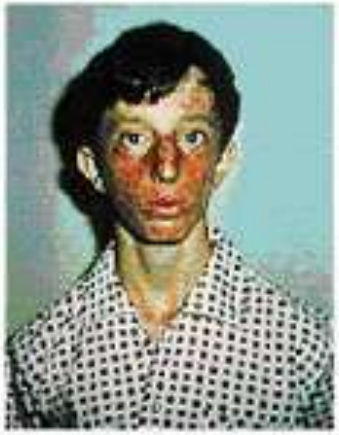
Defects in DNA repair

Defects in recombination repair

Bloom syndrome

- **Defective gene on chromosome 15**
- **Predisposition to cancer + develop-mental defects**

Bloom Syndrome (BS)



- sun-sensitive skin
- dwarfism
- immune deficiencies
- male infertility
- female subfertile
- cancer as primary cause of death before age of 30

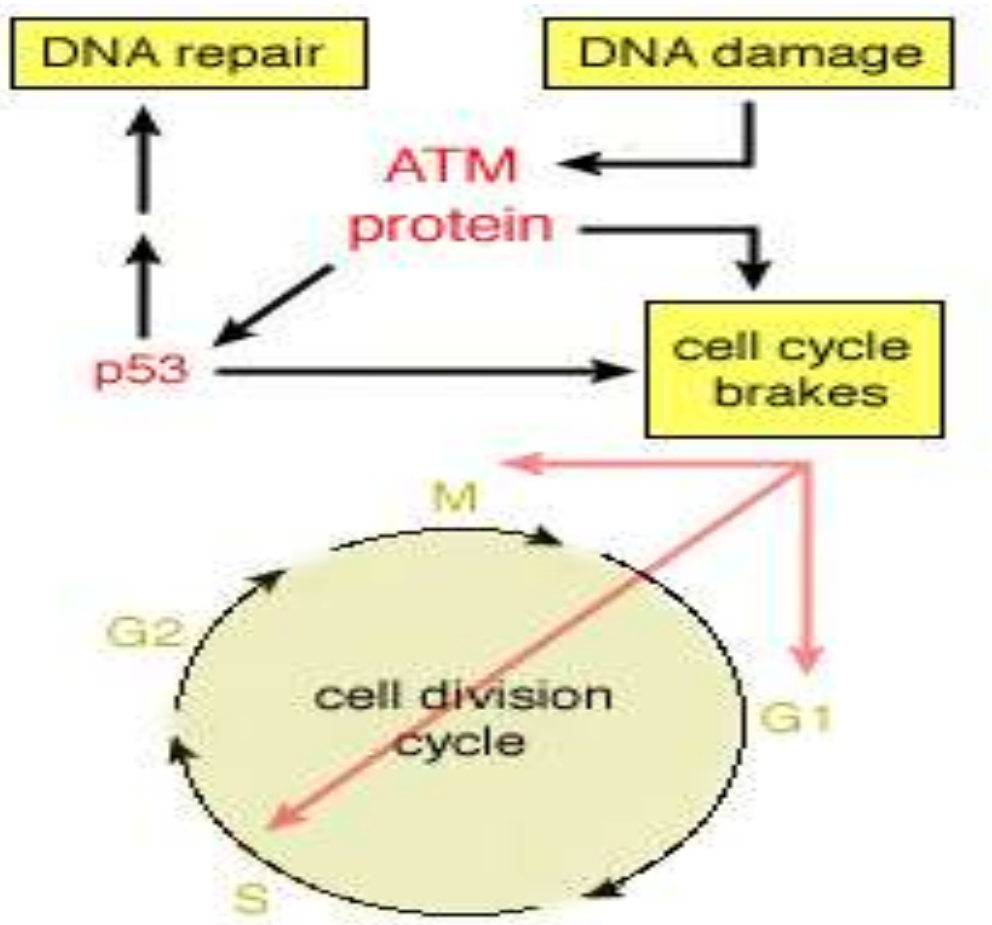
Defects in DNA repair

Defects in recombination repair

Ataxia telangiectasia

- **Predisposition to cancer + neural symptoms**
- **Mutation of *ATM* gene → gene product important in recognizing and responding to DNA damage caused by ionizing radiation**

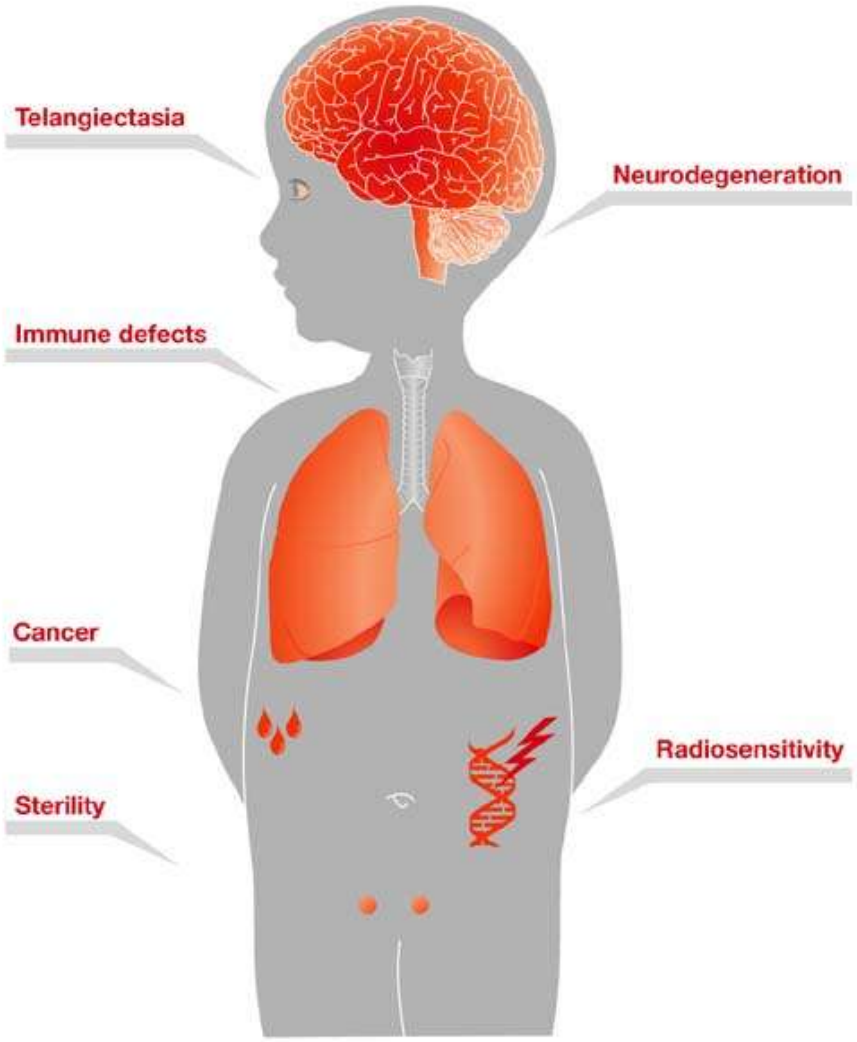
Defects in DNA repair



The ATM protein mediates responses to DNA damage, in particular those that control progression through the cell cycle.

MOLECULAR BASIS

Defects in DNA repair



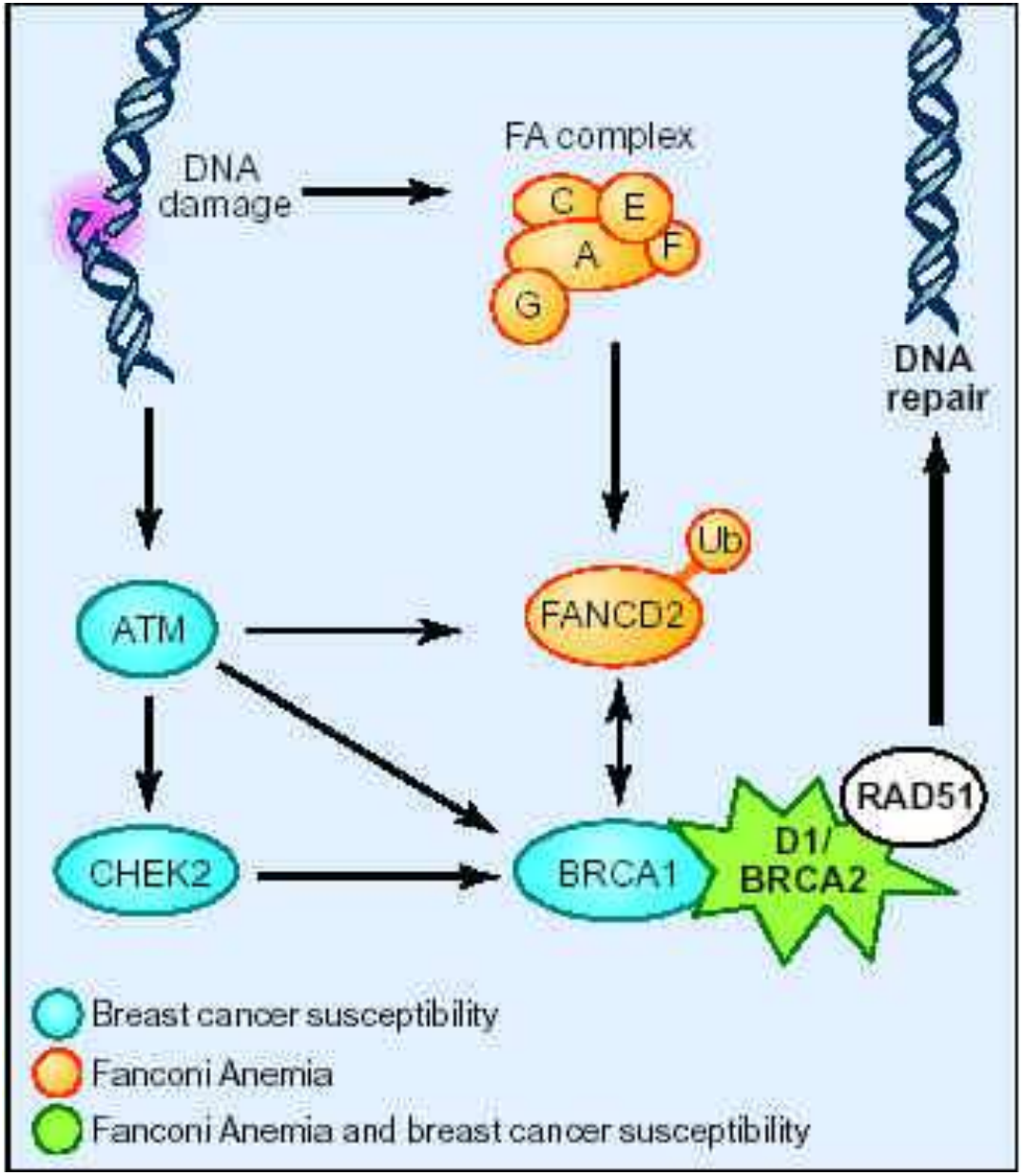
Ataxia telangiectasia. **The hallmark of clinical presentation is a debilitating progressive neurodegeneration. Other characteristics are extreme radiosensitivity, immun odeficiency, a predisposition to cancer (haematopoietic malignancy) and sterility due to defective meiotic recombination. Ocular and facial telangiectasia are also associated with AT.**

Defects in DNA repair

Defects in recombination repair

Fanconi anemia

- Predisposition to cancer + bone marrow aplasia
- Fanconi anemia proteins and the BRCA proteins form a DNA-damage response network → resolve and repair intrastrand and interstrand cross-links induced by chemical agents


DNA damage
FA complex
C
E
A
F
G
DNA repair
Ub
FANCD2
ATM
RAD51
D1/ BRCA2
CHEK2
BRCA1
Breast cancer susceptibility
Fanconi Anemia
Fanconi Anemia and breast cancer susceptibility

Metabolic alterations in tumors

Warburg effect (aerobic glycolysis)

- **Glycolysis that occurs in the face of adequate oxygen for oxidative phosphorylation**
- **Eighth hallmark of cancer**

MOLECULAR BASIS

Metabolic alterations in tumors

Warburg effect: Hypotheses

1. ***Altered metabolism confers a growth advantage in the hypoxic tumor micro-environment.***
   - **Hypoxia → HIF 1α → stimulate angiogenesis and up-regulate expression of enzymes for glycolysis**
2. ***Continuous rounds of hypoxia followed by normoxia select for tumor cells that constitutively upregulate glycolysis.***

Metabolic alterations in tumors

Warburg effect: Hypotheses

3. *Mutations in oncogenes and tumor suppressors that favor growth (e.g. RAS, p53, and PTEN) also stimulate metabolic changes in the cell.*
   - **Alterations in signalling pathways in cancer can also stimulate the uptake of glucose and other nutrients → favor glycolysis**

Metabolic alterations in tumors

Warburg effect: Hypotheses

4. *Tumor cells are able to grow under marginal environmental conditions without triggering autophagy*
   - **Mutation or epigenetic silencing of genes involved in autophagy, most notably PTEN**

MOLECULAR BASIS

Dysregulation of cancer-associated genes

Chromosomal Changes

- **Change in chromosome number (aneuploidy) and chromosomal instability may be the initiating events in tumor growth**
- **Two types of chromosomal re-arrangements that can activate proto-oncogenes: translocations (more common) and inversions**

Dysregulation of cancer-associated genes

Chromosomal Changes

- **Mechanisms of activation by translocation:**

1. **Swapping of regulatory elements with those of another gene → over-expression of proto-oncogene (e.g. lymphoid tumors - Burkitt's lymphoma)**

Dysregulation of cancer-associated genes

Chromosomal Changes

- **Mechanisms of activation by translocation:**

  2. **Recombination of unrelated sequences from two different chromosomes → form hybrid fusion genes → e.g. Philadelphia chromosome of CML; hemato-poietic tumors, sarcomas**

Dysregulation of cancer-associated genes

Chromosomal Changes

- **Deletions**
  - ✓ **Second most common structural abnormality in tumor cells**
  - ✓ **More common in nonhemato-poietic solid tumors**
  - ✓ **Associated with loss of particular tumor suppressor genes**
  - ✓ **e.g. Retinoblastoma (deletion of chr. 13q14)**

MOLECULAR BASIS

Dysregulation of cancer-associated genes

Gene Amplification

- **Reduplication and amplification of DNA sequences of proto-oncogenes → over-expression of products**
- **Examples:**
  - ✓ **Amplification of N-*MYC* in neuroblastoma**
  - ✓ ***ERBB2* amplification in breast cancers**
  - ✓ ***C-MYC, L-MYC, N-MYC* amplification in small cell lung CA**

Dysregulation of cancer-associated genes

Epigenetic Changes

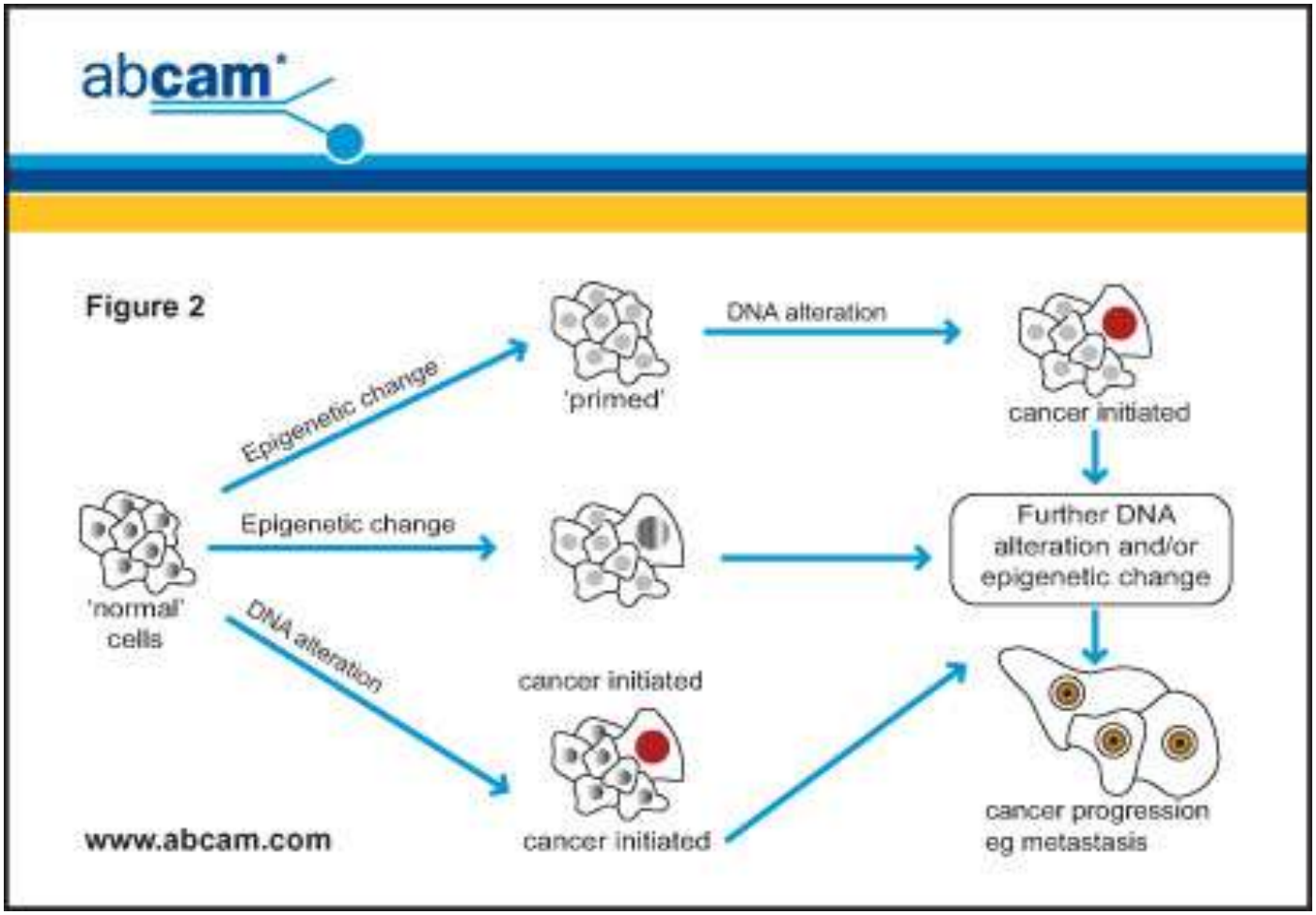
- **Reversible, heritable changes in gene expression that occur without mutation**
- **Involve post-translational modifications of histones and DNA methylation**

MOLECULAR BASIS

Dysregulation of cancer-associated genes

Epigenetic Changes

- **Normal cells:**
  - ✓ **Majority of genes not expressed → silenced by DNA methylation and histone modification → heterochromatin formation**
- **Cancer cells:**
  - ✓ **Characterized by global hypo-methylation and selective promoter-localized hyperme-thylation**

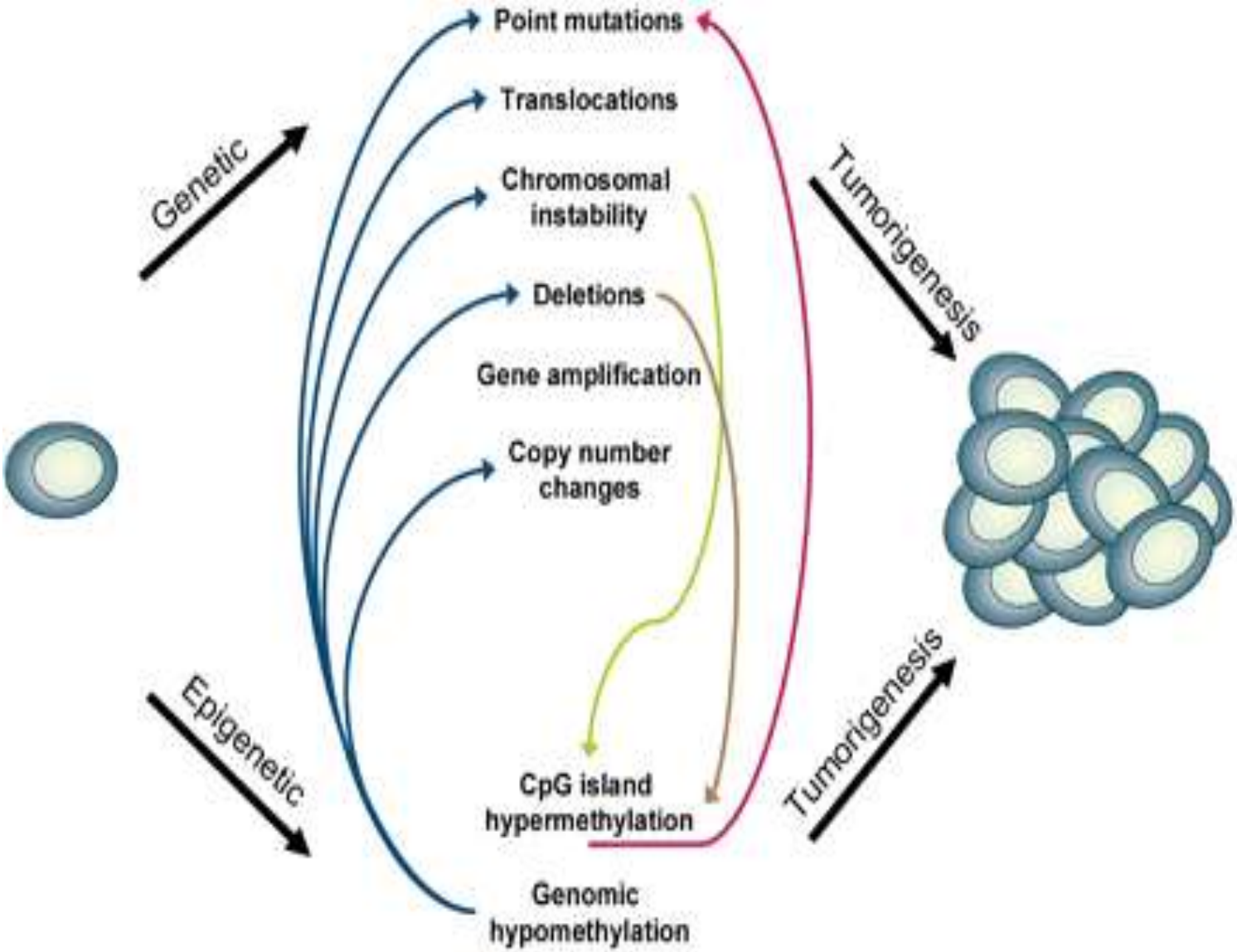


How genetic and epigenetic alterations may cooperate in the genesis of cancer. Potential pathways are shown indicating how genetic change may precede epigenetic change, and vice versa, as the cause of cancer.

Dysregulation of cancer-associated genes

Epigenetic Changes

- **Tumor suppressor genes are sometimes silenced by hyper-methylation of promoter sequences rather than mutation**
  - ✓ **Example: CDKN2A → codes for tumor suppressors p14/ARF and p16/INK4a → affect p53 and Rb → inhibit two checkpoints**
  - ✓ ***BRCA 1* (breast cancer) and *VHL* (renal cell CA)**


Point mutations
Translocations
Chromosomal instability
Deletions
Gene amplification
Copy number changes
CpG island hypermethylation
Genomic hypomethylation
Genetic
Epigenetic
Tumorigenesis
Tumorigenesis

miRNAs and Cancer

miRNAs

- **Small, non-coding, single-stranded RNAs (~22 nucleotides long) that are incorporated into the RNA-induced silencing complex**
- **Mediate sequence-specific recognition of mRNAs and mediate post-transcriptional gene silencing**
- **Control cell growth, differentiation, and cell survival**

miRNAs and Cancer

miRNAs

- **If a miRNA inhibits the translation of an oncogene → acts as a tumor suppressor**
- **If a miRNA inhibits a tumor suppressor gene → acts as an oncogene**

MOLECULAR BASIS

miRNAs and Cancer

miRNAs

- **Frequent amplifications and deletions of miRNA loci identified in many cancers**
- ***Reduced activity of a miRNA that inhibits translation of an oncogene → excess oncoprotein***
- ***Overactivity of miRNA that targets a tumor suppressor gene → decreased production of tumor suppressor protein***

miRNAs and Cancer

miRNAs

- ***Down-regulation or deletion of certain miRNAs in some leukemias and lymphomas → increased expression of BCL2 → decreased apoptosis***

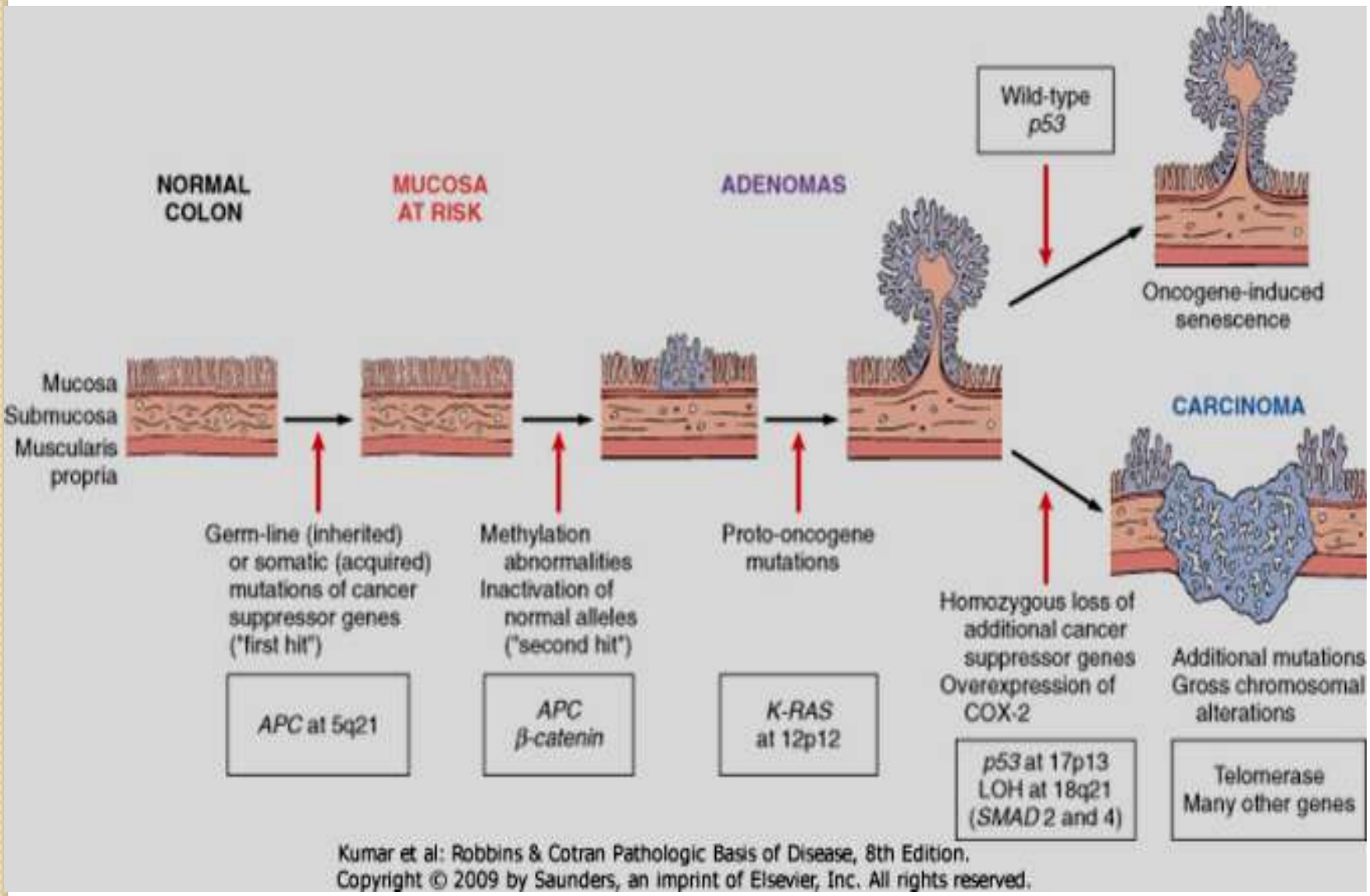
- ***miRNA-mediated up-regulation of RAS (lung tumors) and MYC (B-cell leukemias) oncogenes***

Multistep Carcinogenesis

- **Each cancer must result from the accumulation of multistep mutations**
  - ✓ **Individual tumors accumulate an average of 90 mutant genes**
- **No single oncogene can fully transform non-immortalized cells in vitro**
- **Cells can generally be transformed by combinations of oncogenes**

Multistep Carcinogenesis

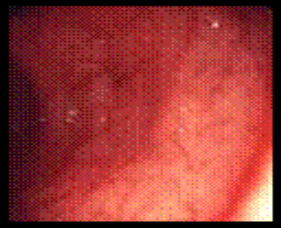
- **"intrinsic tumor-suppressive mechanisms" thwart the actions of growth-promoting mutations**
  - ✓ ***In cells with competent checkpoints, oncogenic signalling leads to senescence or apoptosis rather than transformation***
  - ✓ ***Emergence of malignant tumors requires mutational loss of many genes, including those that regulate apoptosis and senescence***



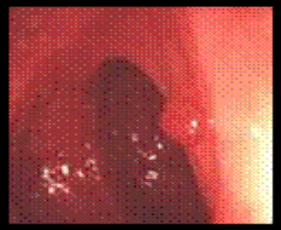
Normal

Loss or mutation of APC gene on chromosome 5q
Over-expression of cyclo-oxygenases (COX1 and 2)

Hyperproliferative Epithelium



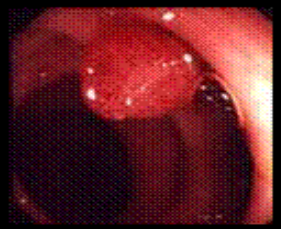
Early Adenoma



DNA hypomethylation

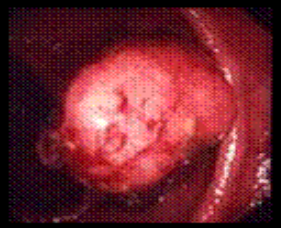
Mutation of K-ras gene on chromosome 12p

Intermediate Adenoma



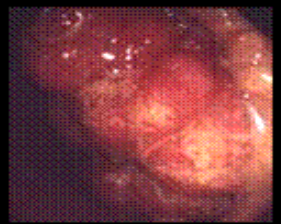
Loss or mutation of DCC gene on chromosome 18q

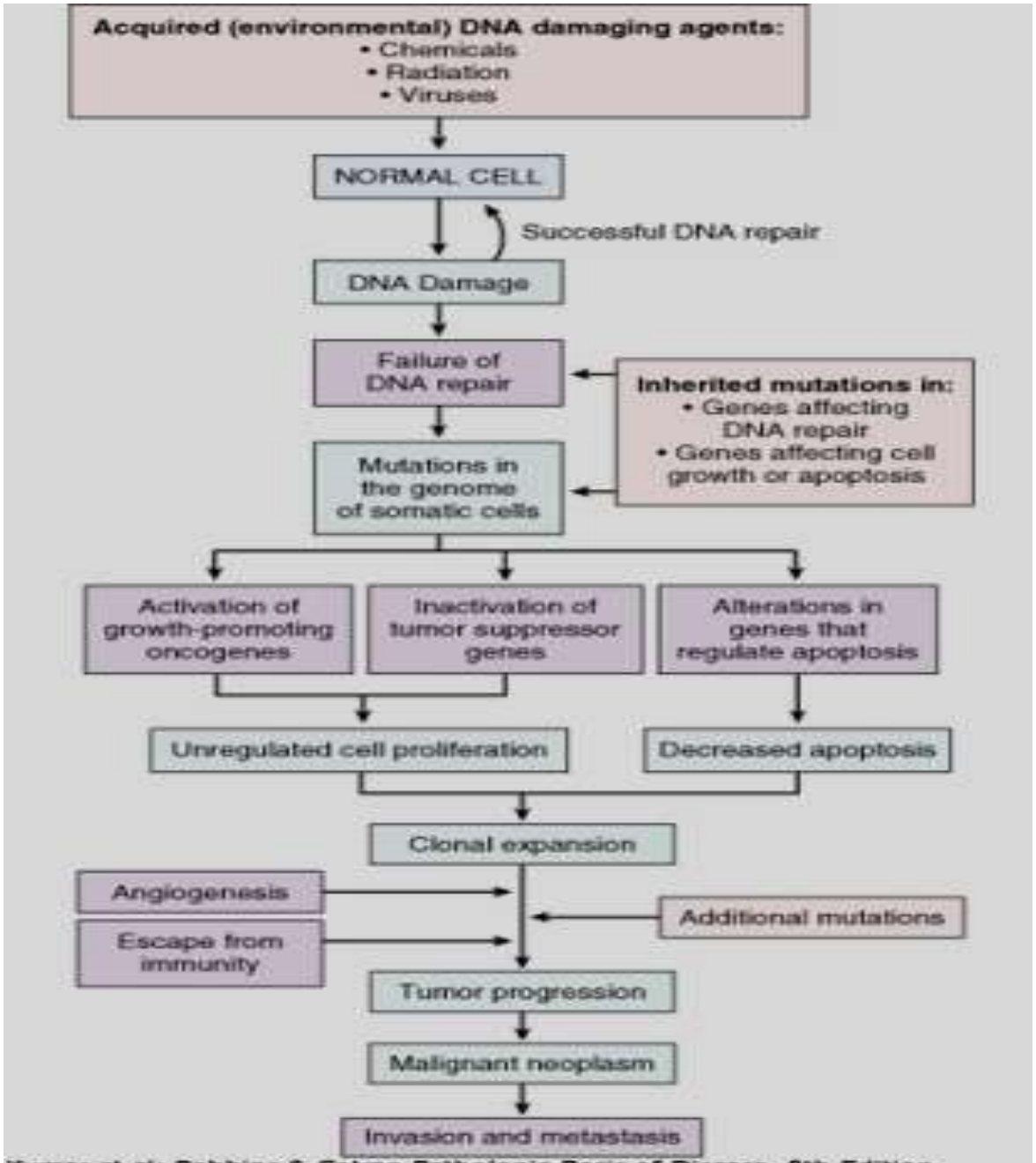
Late Adenoma



Loss or mutation of p53 gene on chromosome 17p

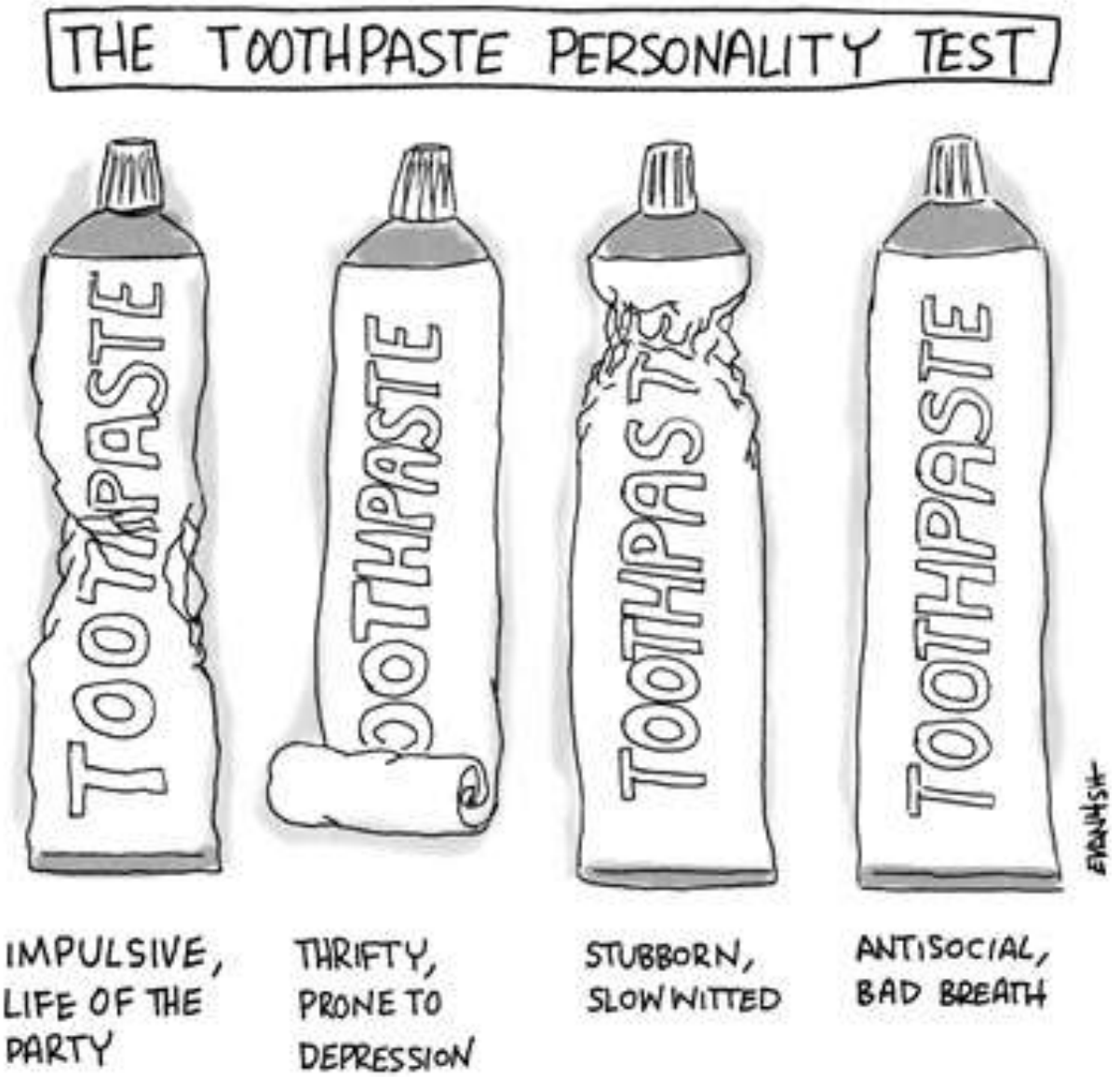
Carcinoma





Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition.

END of PART 3


THE TOOTHPASTE PERSONALITY TEST
TOOTHPASTE
TOOTHPASTE
TOOTHPASTE
TOOTHPASTE
IMPULSIVE, LIFE OF THE PARTY
THRIFTY, PRONE TO DEPRESSION
STUBBORN, SLOW WITTED
ANTISOCIAL, BAD BREATH