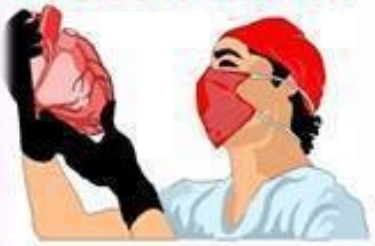
PATHOLOGY



Medical Committee
The University of Jordan

☐ SHEET

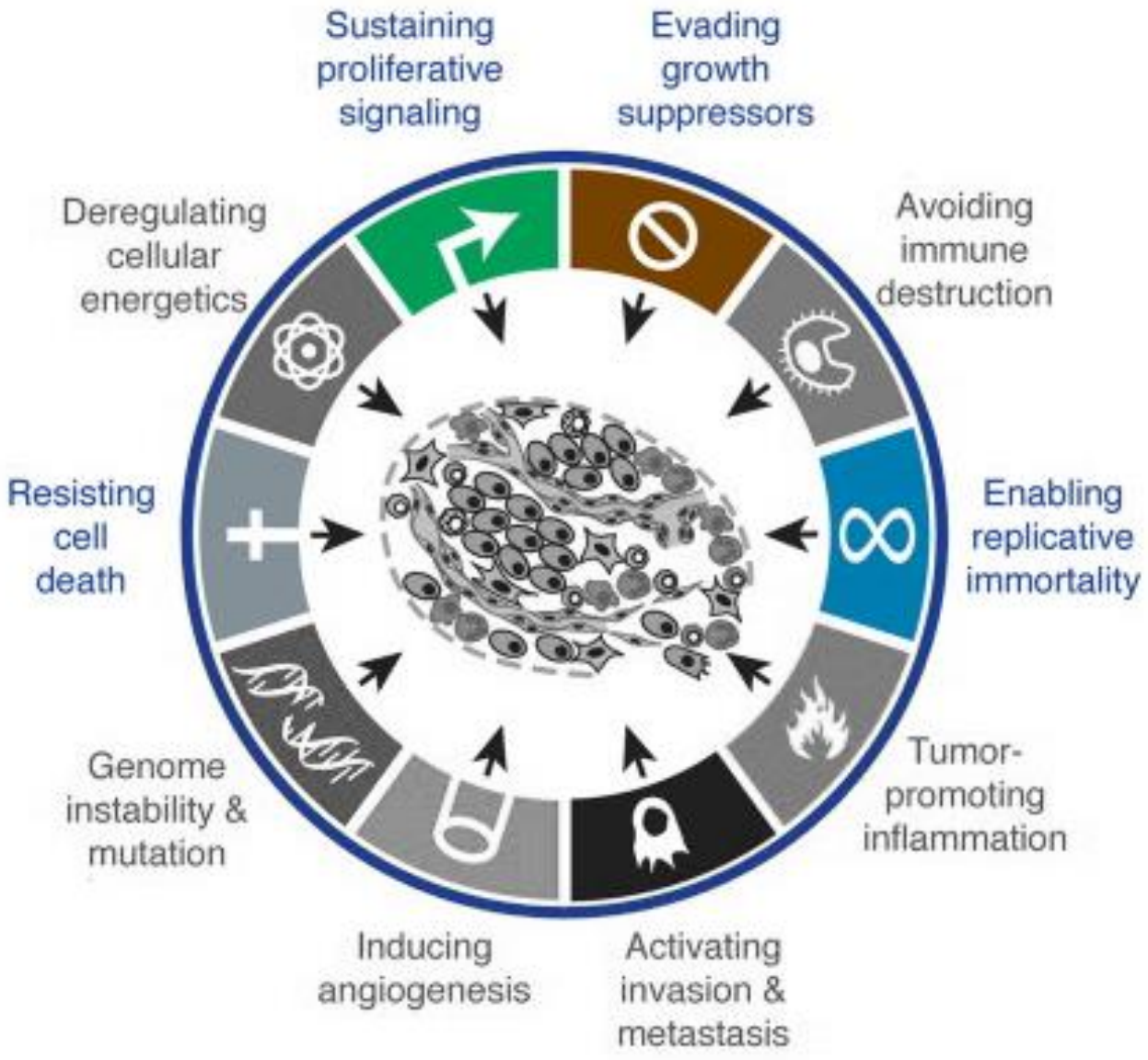
■ SIIDE

Slide : 18- Hallmarks

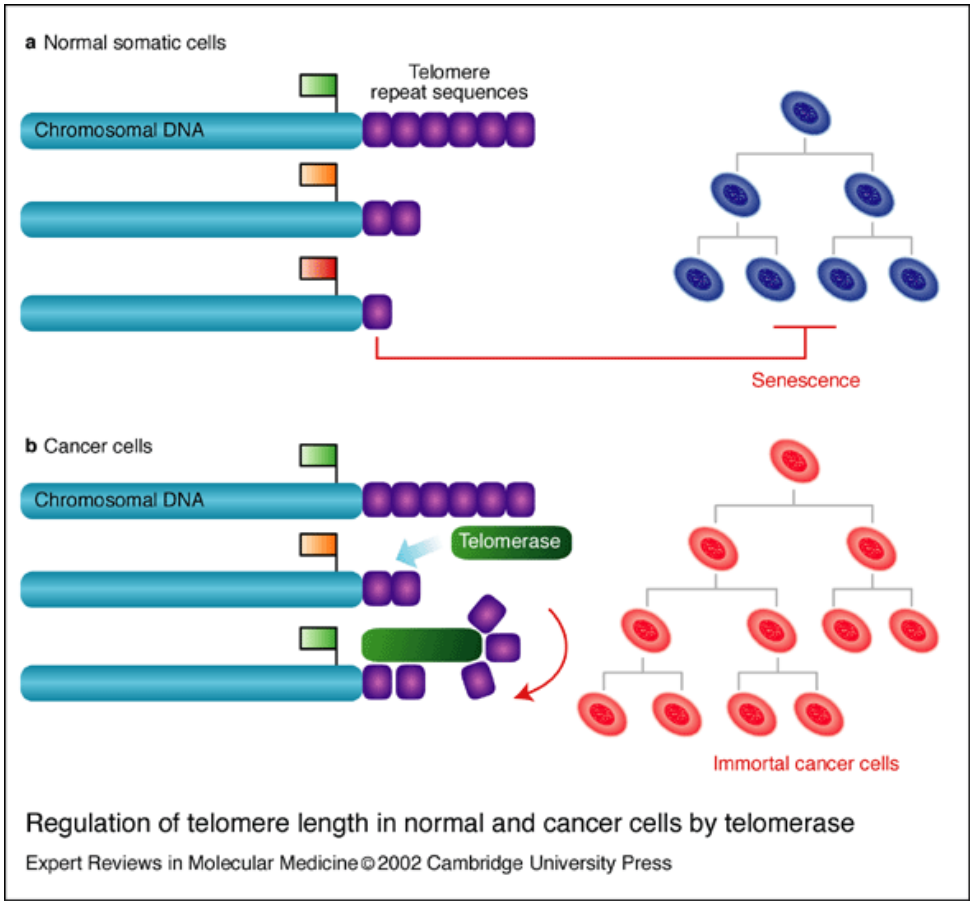
Doctor: Dr. Mazen

Designed by: Majida Al-Foqara'

Hallmarks of Cancer
Immortality

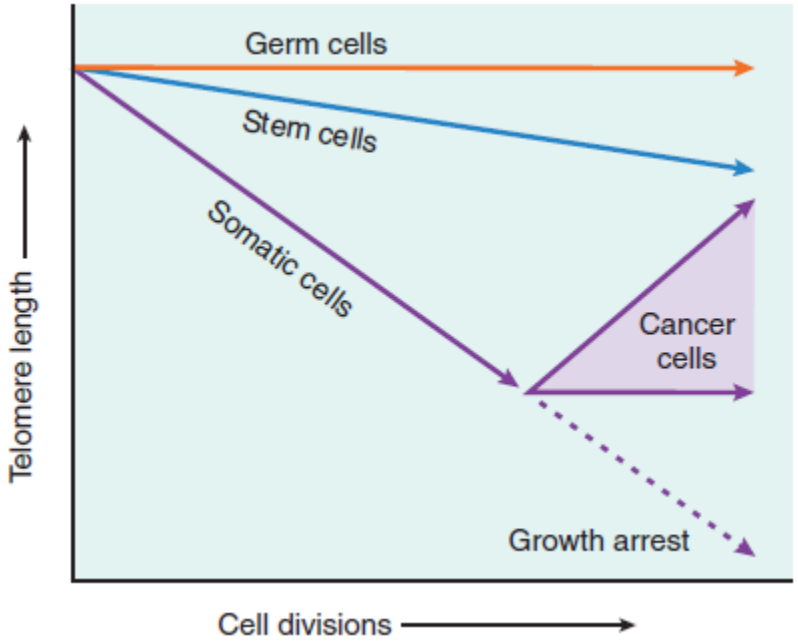

Sustaining proliferative signaling
Evading growth suppressors
Avoiding immune destruction
Enabling replicative immortality
Tumor-promoting inflammation
Activating invasion & metastasis
Inducing angiogenesis
Genome instability & mutation
Resisting cell death
Deregulating cellular energetics

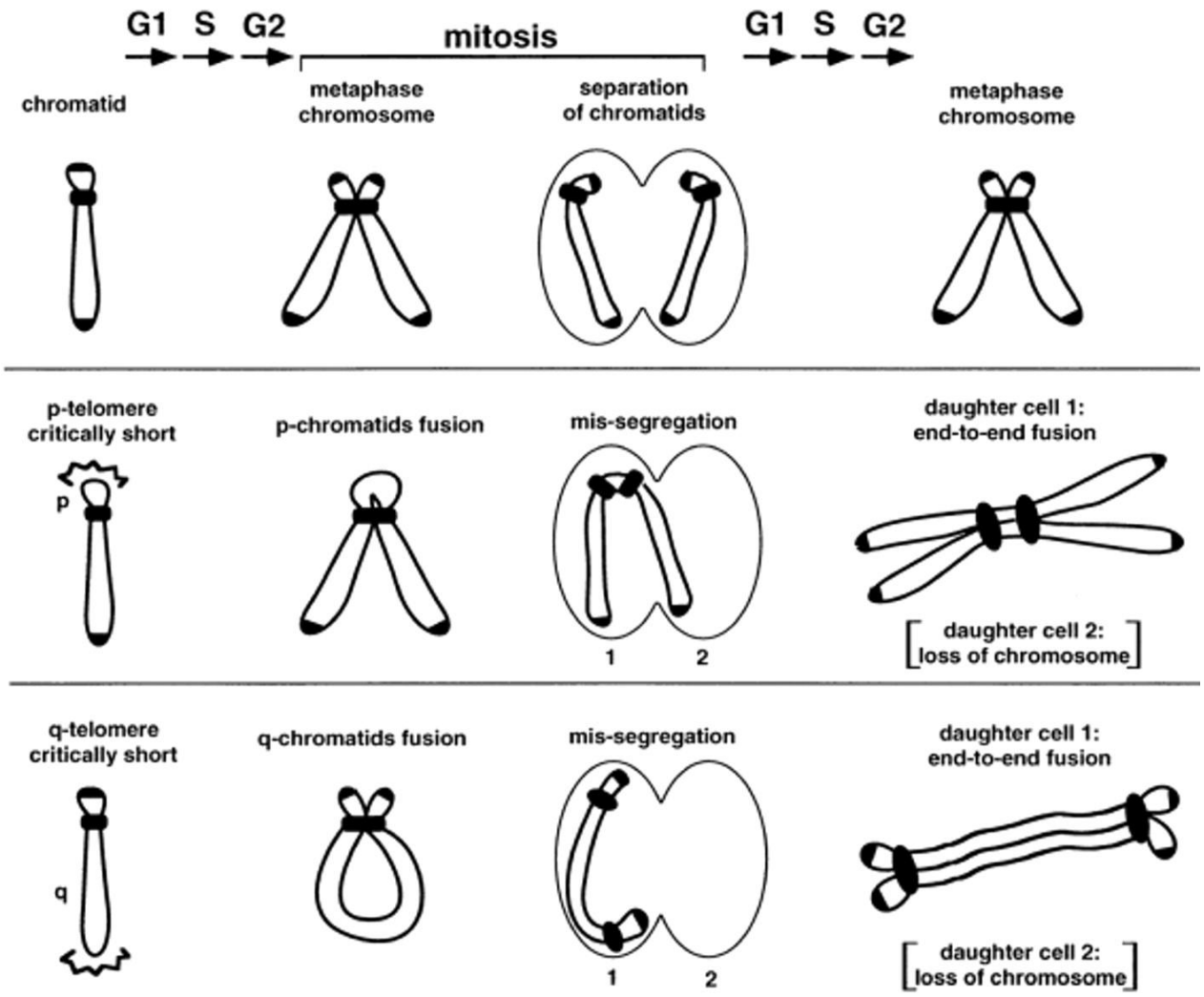
Cell Senescence & Telomeres



Regulation of telomere length in normal and cancer cells by telomerase

Expert Reviews in Molecular Medicine © 2002 Cambridge University Press





or at anaphase
Dicentric chromosome pulled apart
Double-stranded DNA breaks

BFB cycle

Short telomeres detected as double-stranded DNA breaks → cell cycle arrest & senescence (requires p53/RB)

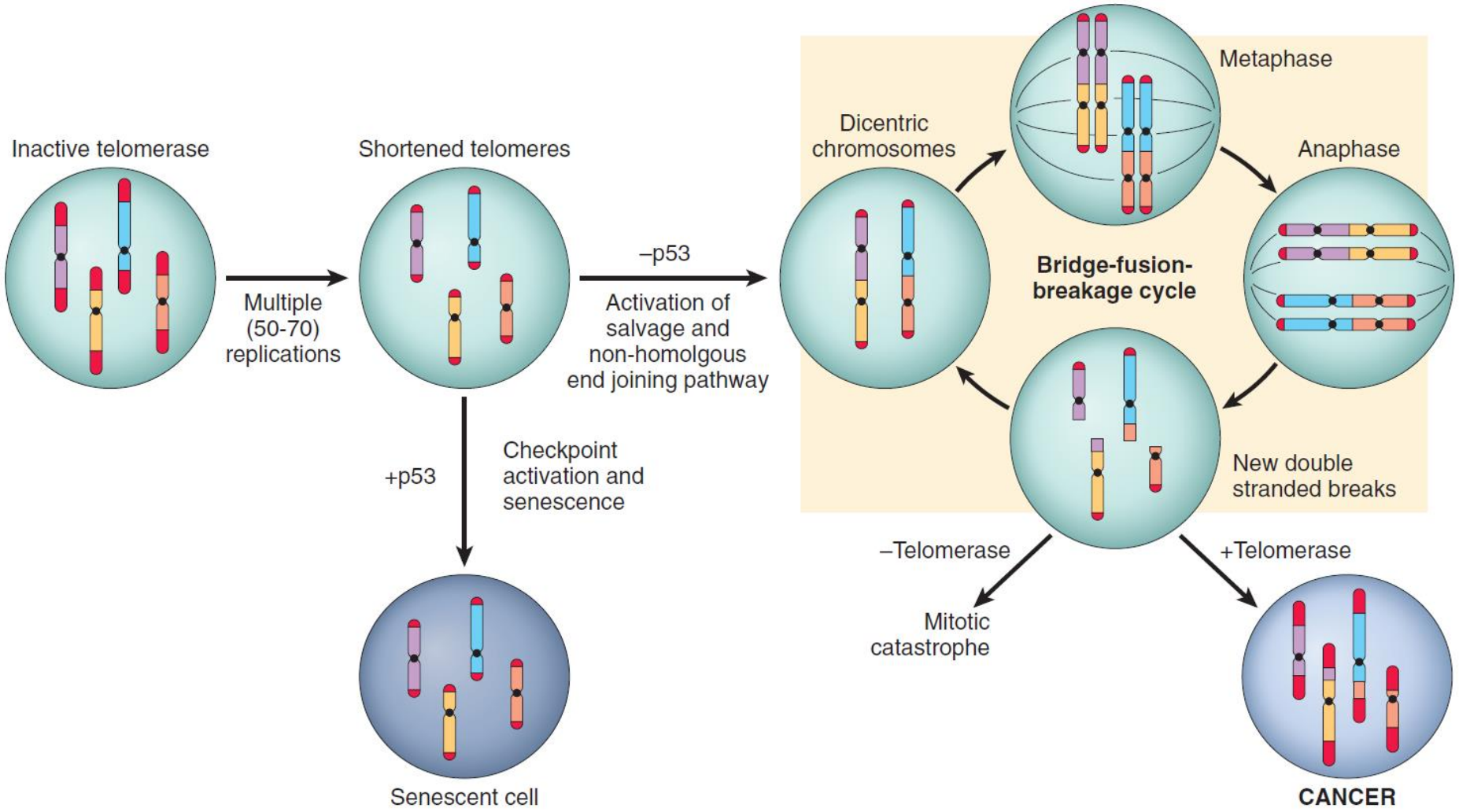
Mutant p53/RB → non-homologous end joining repair (inappropriate)

Anaphase: new real double-stranded breaks

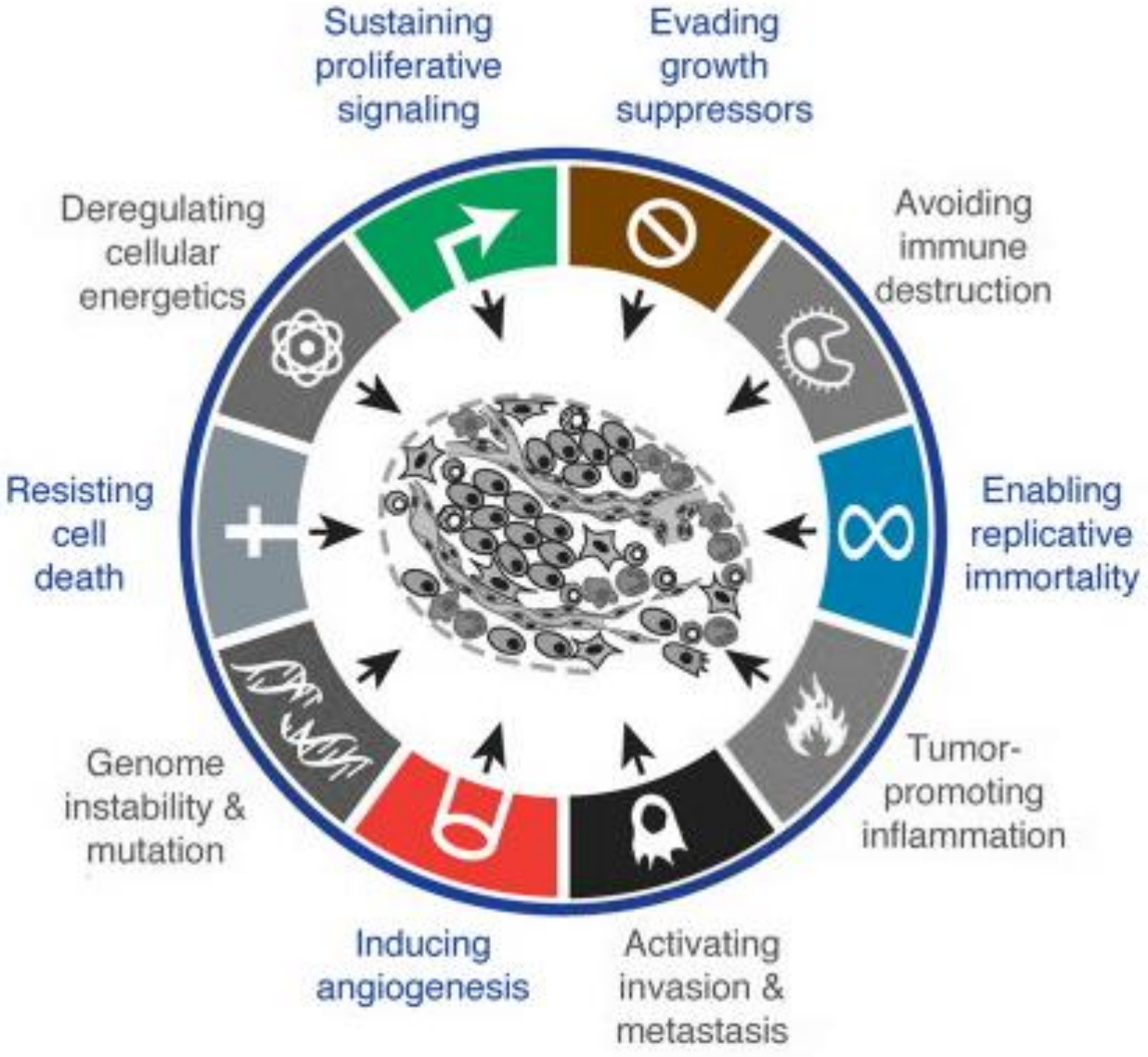
Repeat

Bridge-fusion-breakage cycles (genomic instability)

BFB cycles & Telomerase activation



Hallmarks of Cancer
Angiogenesis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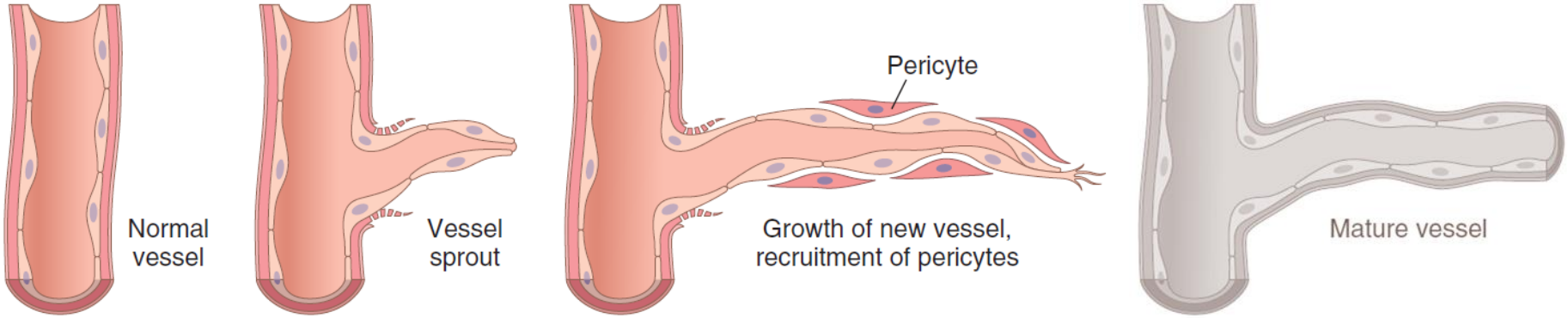
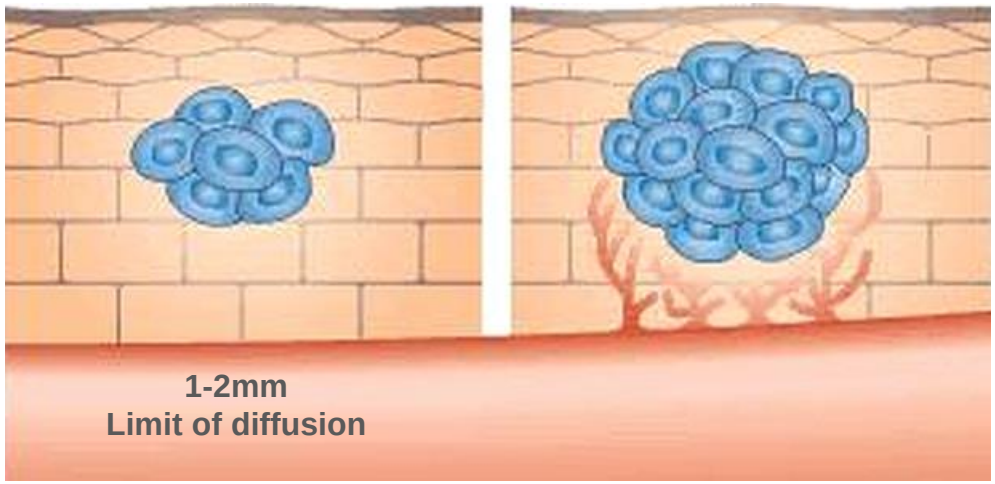
Angiogenesis





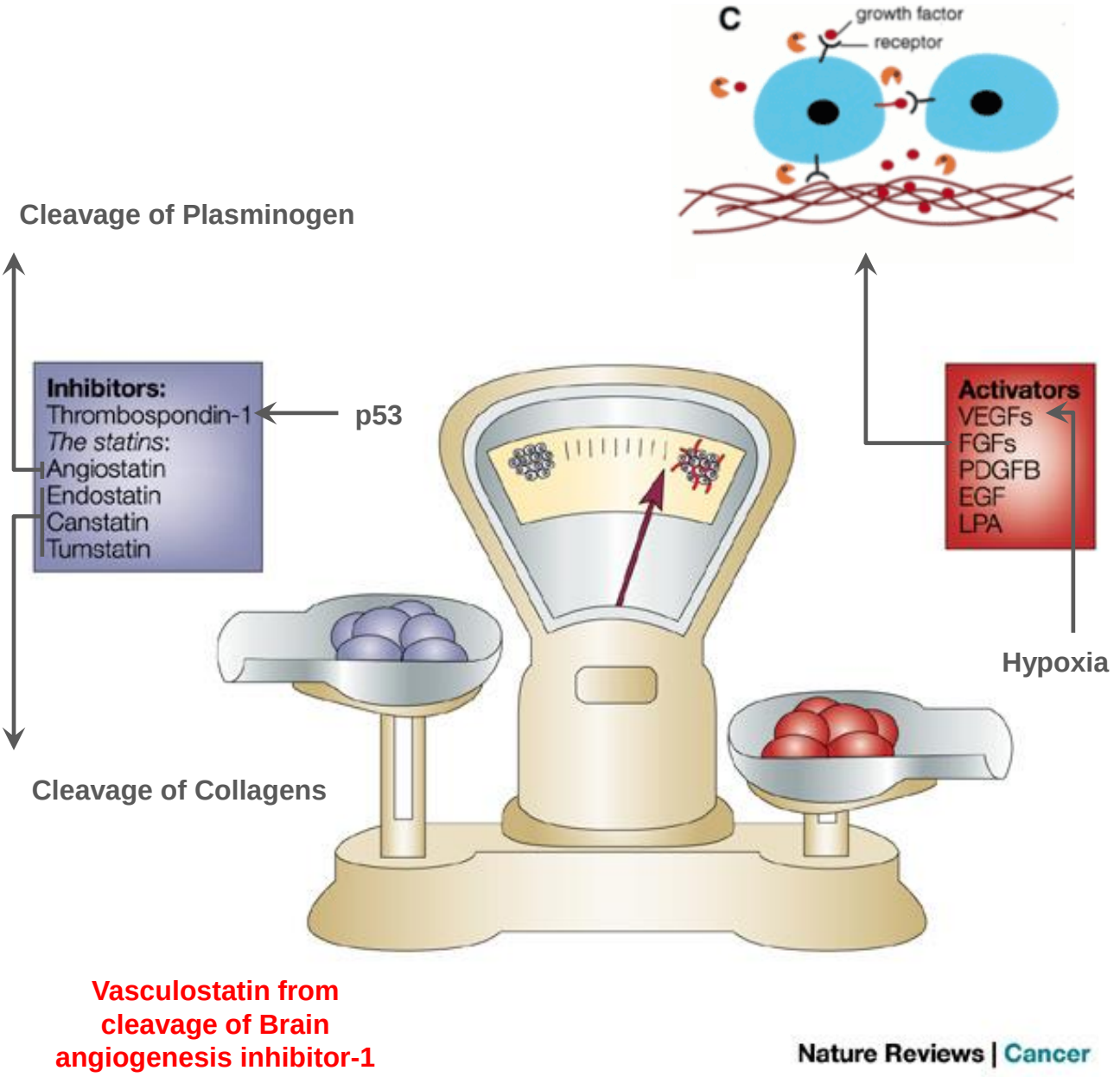
Abnormal vessels

- **Leaky**
- **Dilated**
- **Haphazard connections**

Functions

- **Nutrients, O_2**
- **Growth factors (ILGF, PDGF, GM-CSF)**
- **Metastasis**

Angiogenic balance & switch

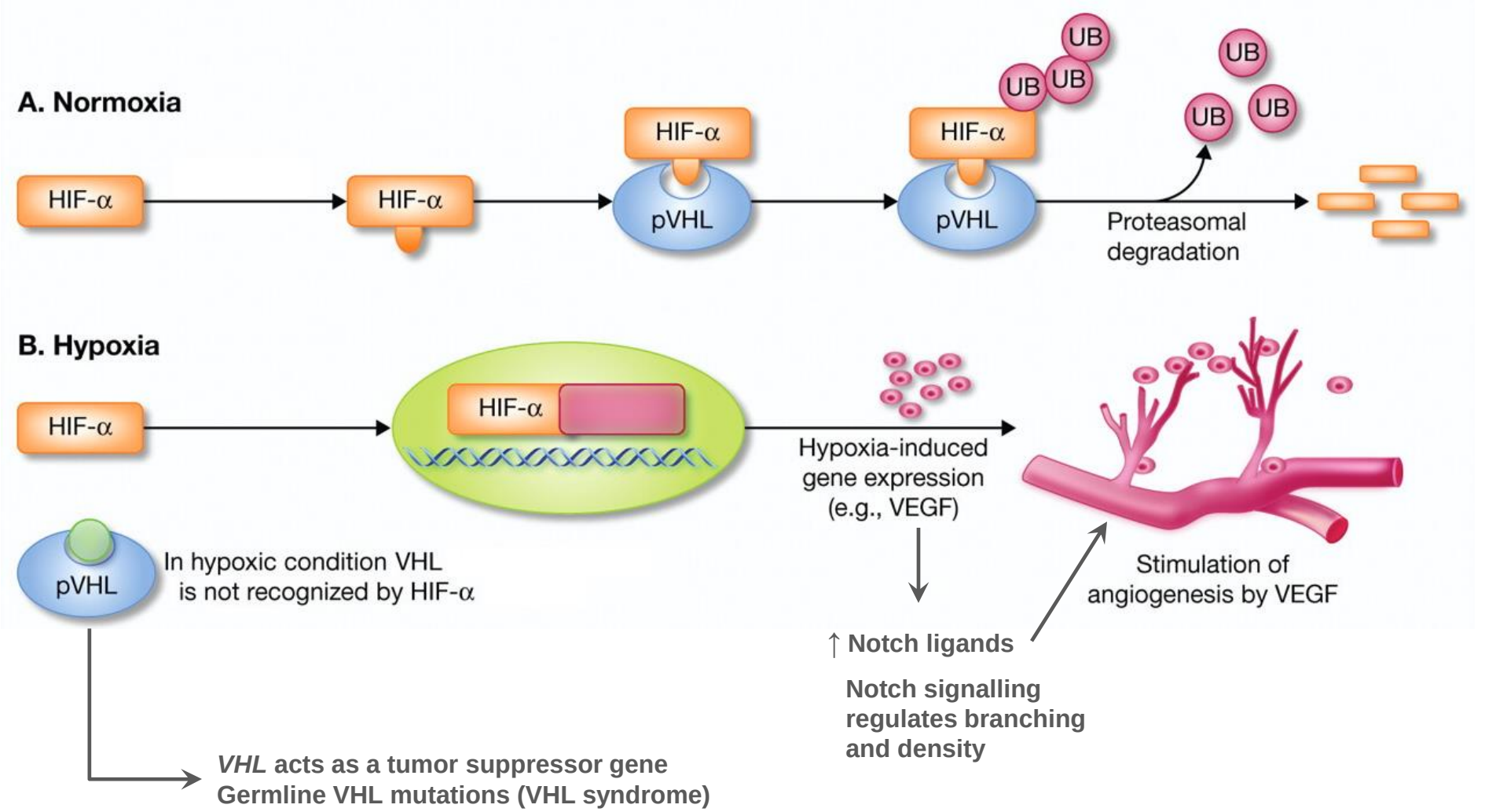


Vasculostatin from cleavage of Brain angiogenesis inhibitor-1

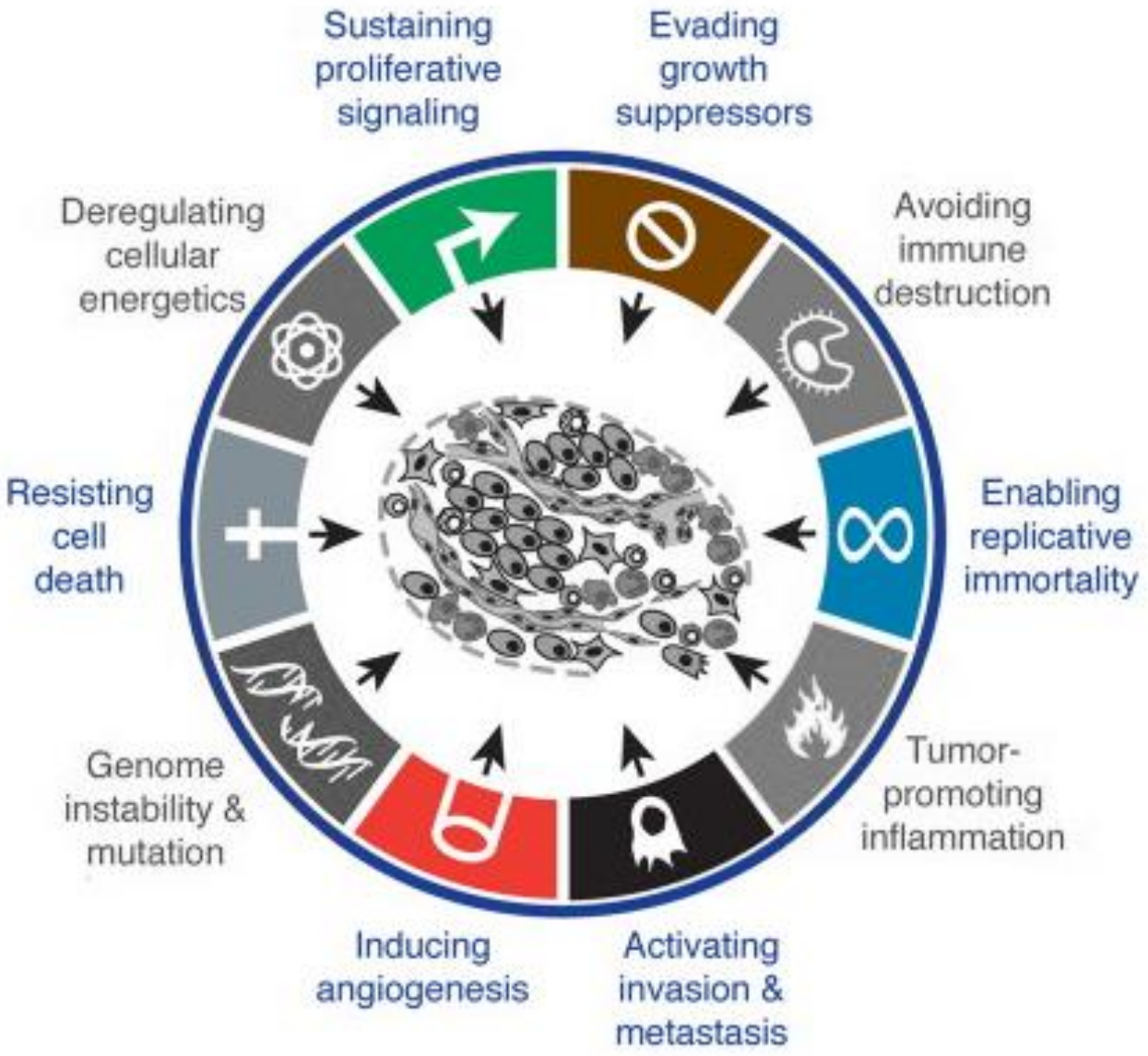
Increased production of angiogenic factors and/or loss of angiogenesis inhibitors

Factor production:
- Tumor cells
- Inflammatory cells (e.g., macrophages)
- Tumor associated stromal cells

Hypoxia, *HIF-1α*, *VHL*, & *VEGF*



Hallmarks of Cancer
Invasion & Metastasis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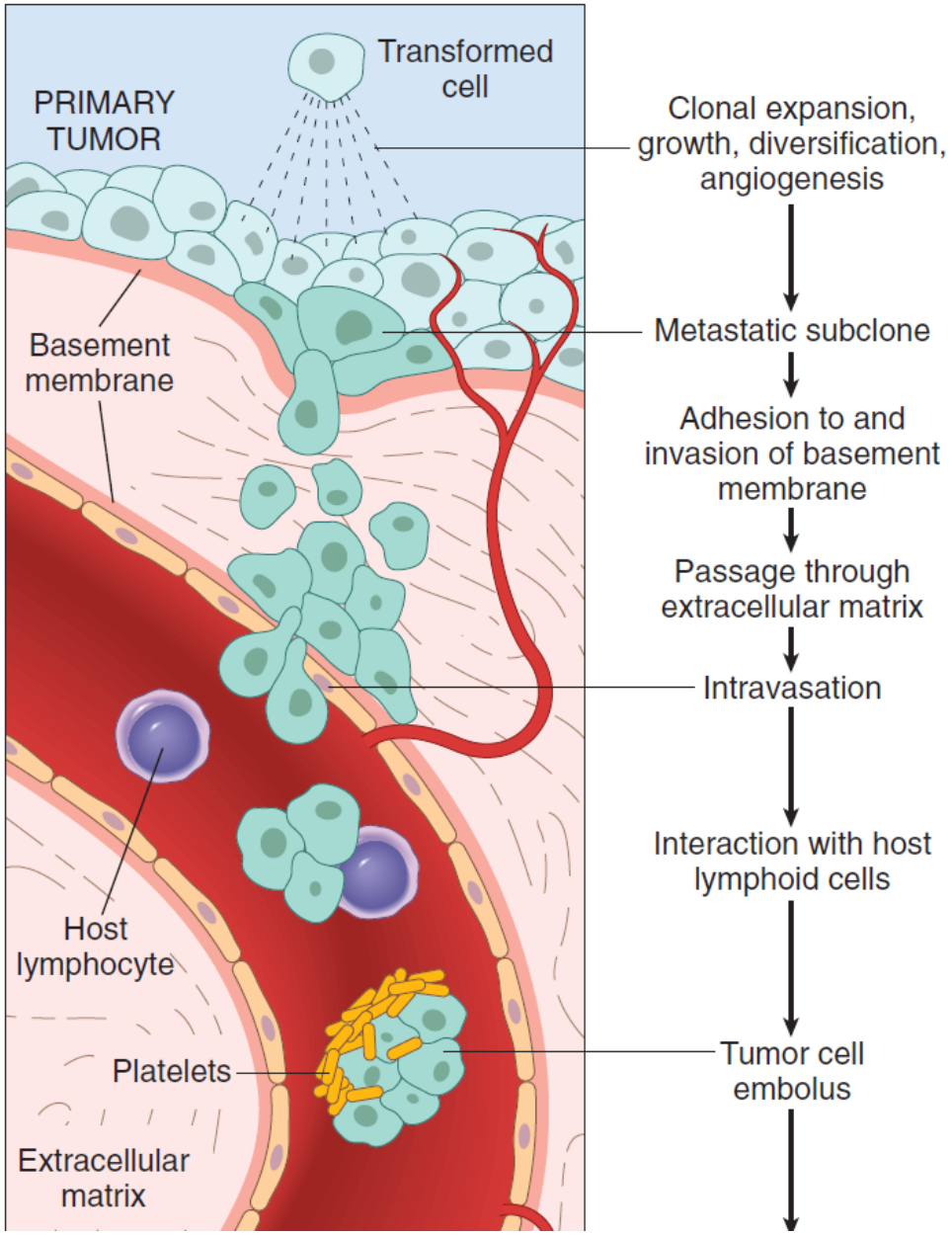


Invasion-metastasis cascade

Local invasion

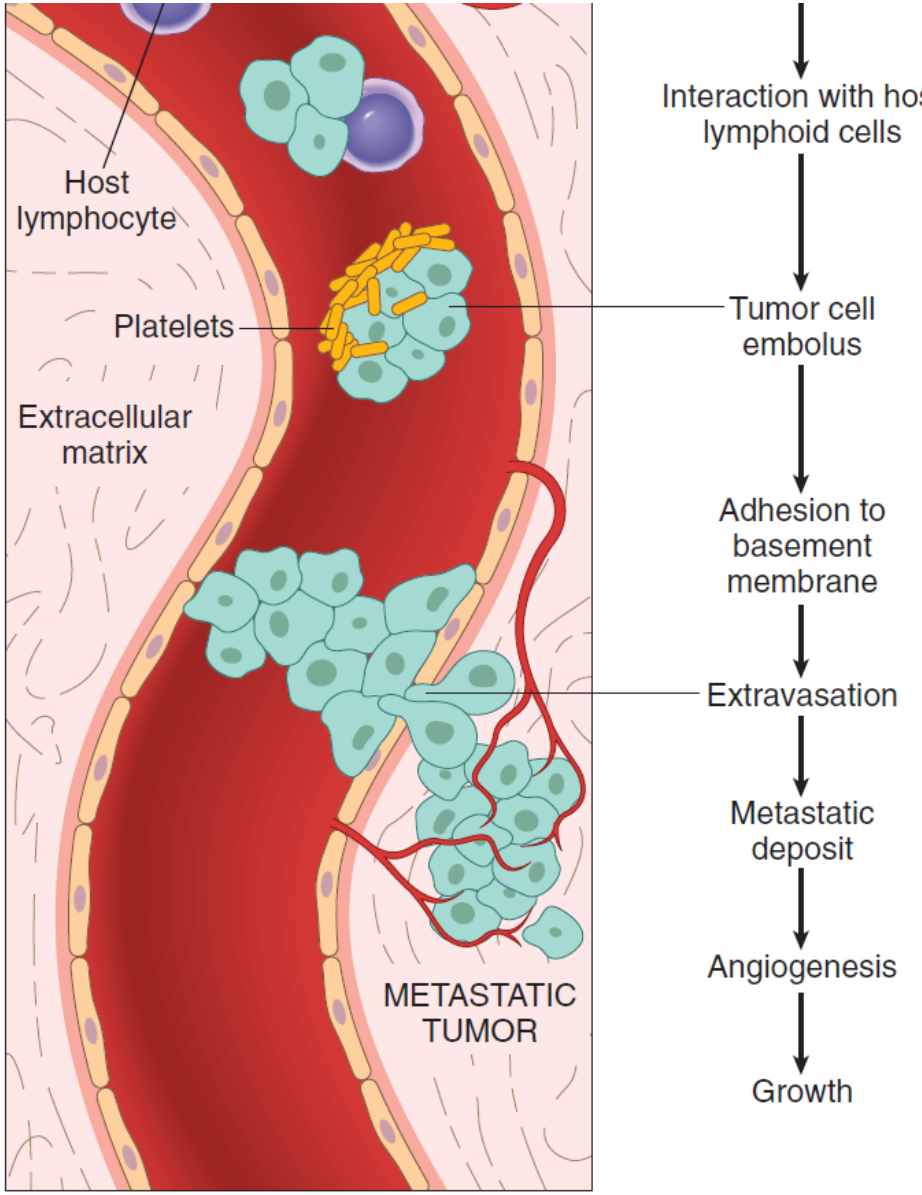
Intravasation (Blood/Lymph vessles)

Transit

Extravasation

Micrometastasis

Growth



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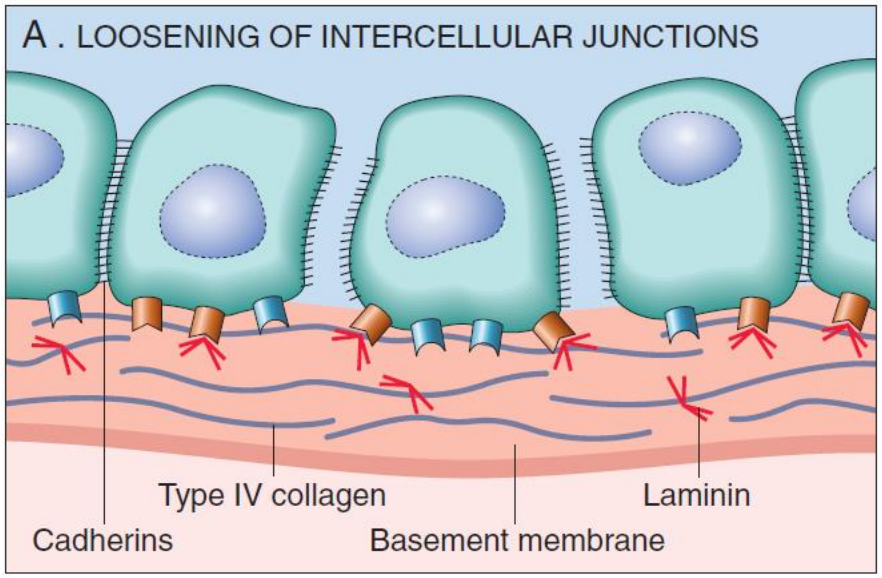
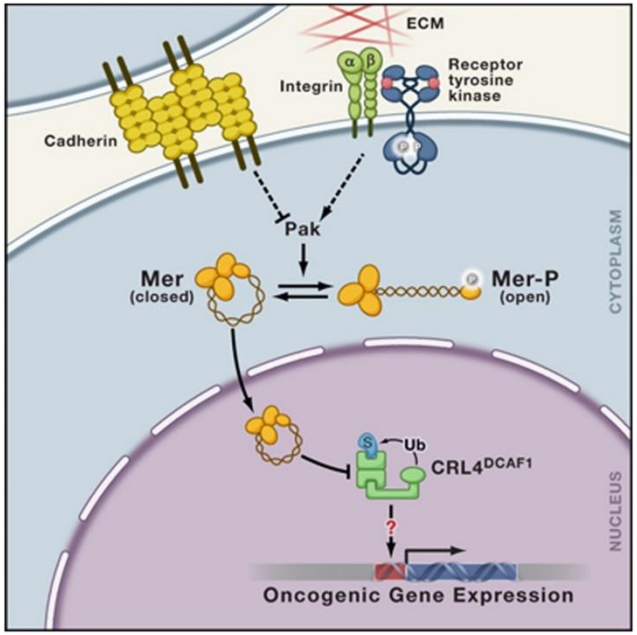
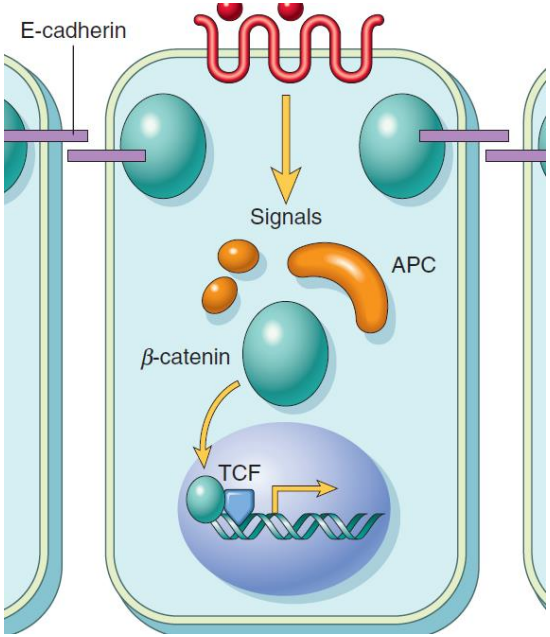


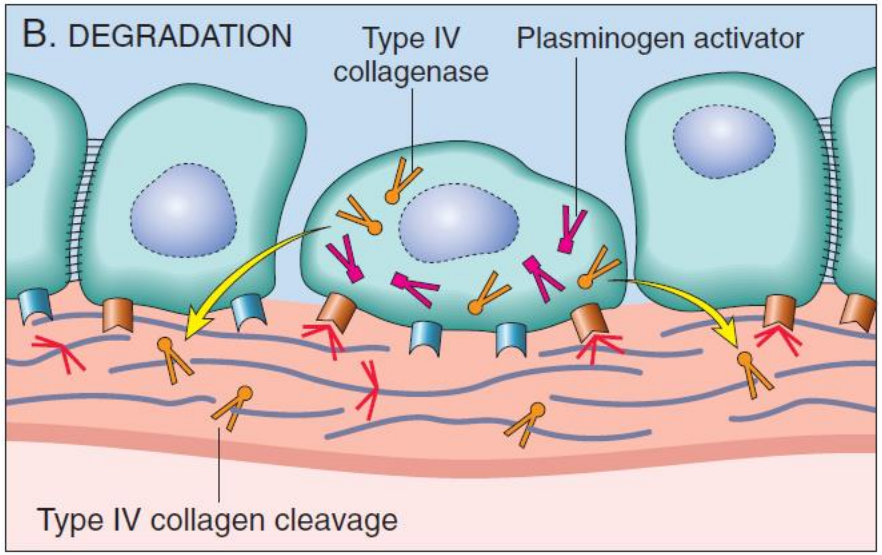


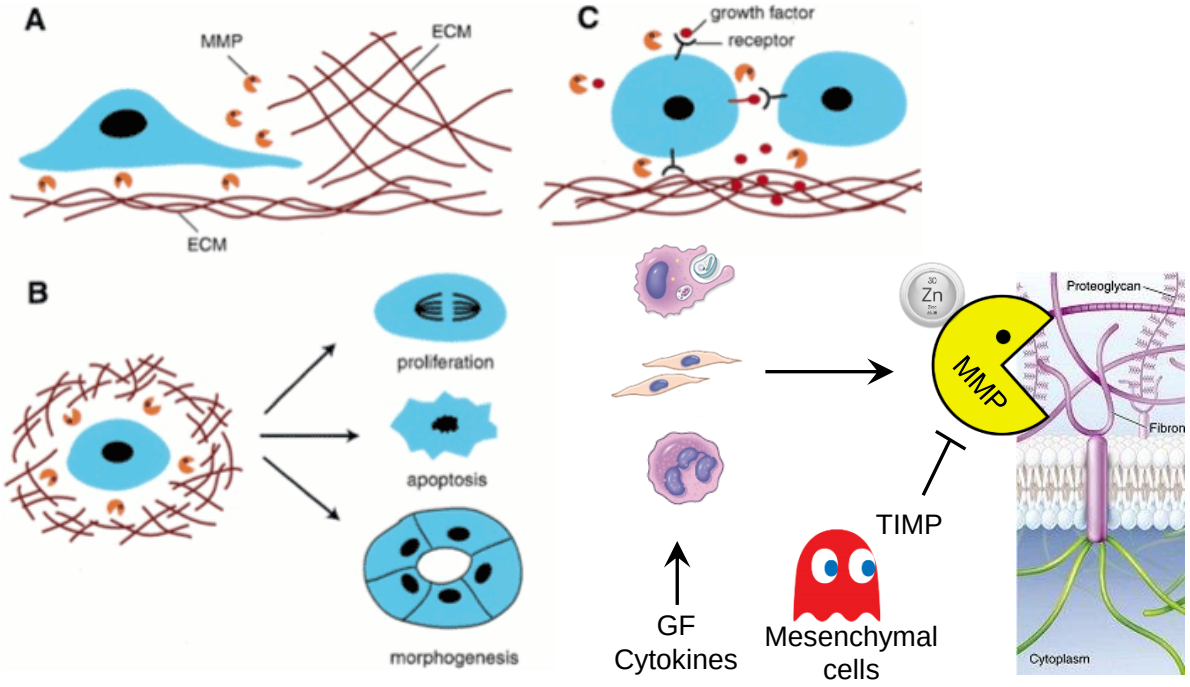


ECM Invasion

E-cadherin function is lost in almost all epithelial cancers:

- E-cadherin mutation
- Activation of β-catenin genes
  ↑ SNAIL/SLUG & TWIST
  ↓
↓ E-cadherin expression
→ ↓ Contact inhibition
Role in EMT





ECM Invasion

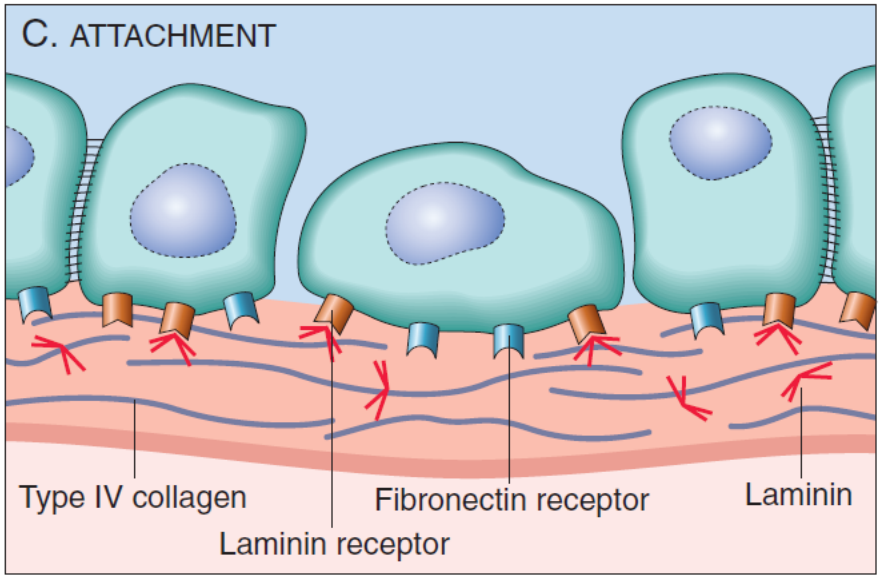
Degradation of the BM/IM:

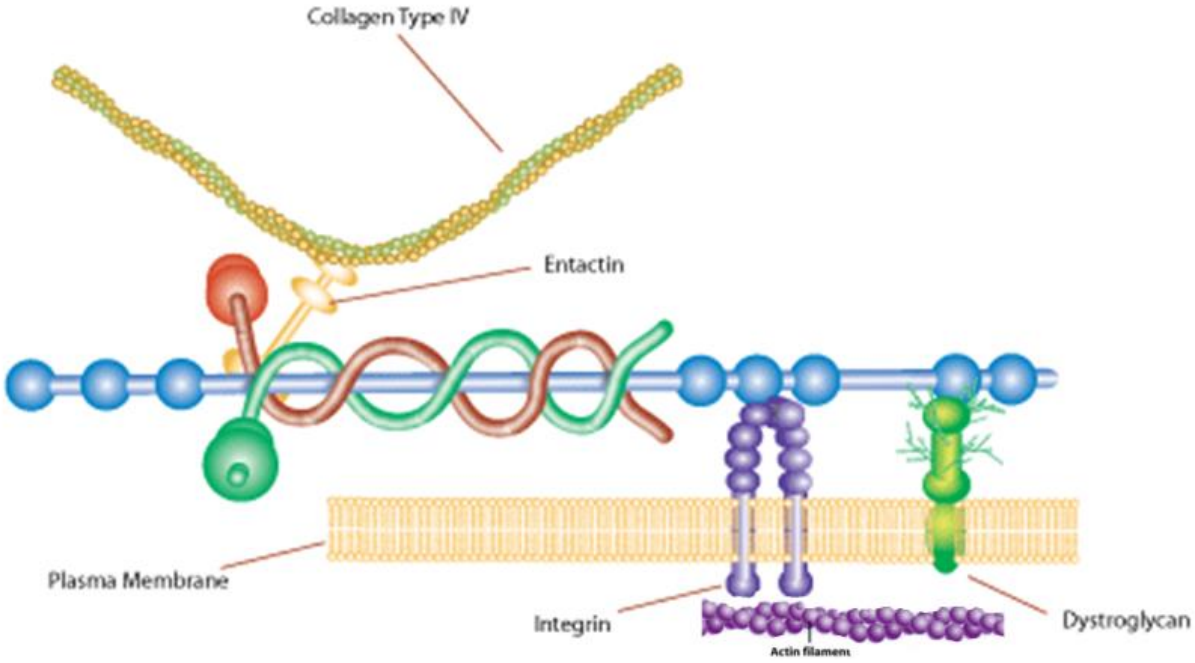
- Increased proteases (cancer/stroma)

  ↓

  Remodelling
  Release of GF
  ECM degradation:
  (Chemotactic,
  Angiogenic,
  ↑ Growth)

- Reduced TIMPs

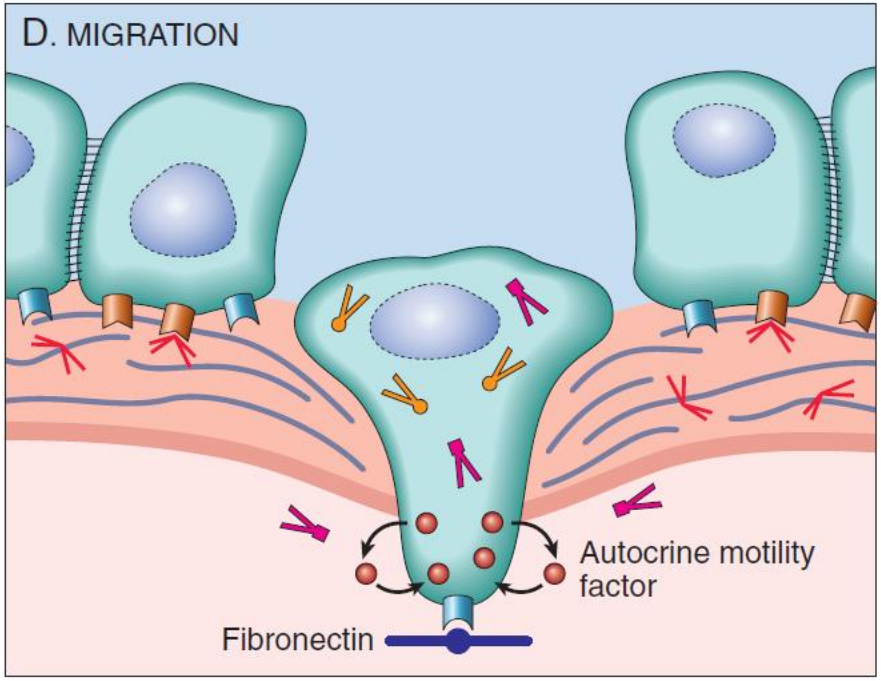


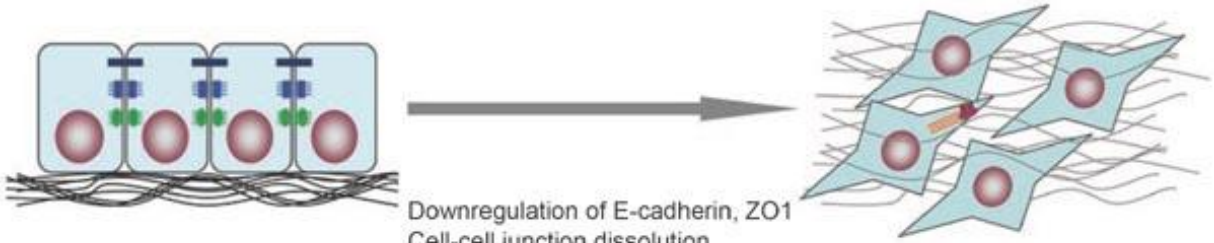


ECM Invasion

Changes in attachment of tumor cells to ECM proteins

- Integrin signalling change (resistance of apoptosis)
- New binding sites on degraded ECM stimulates migration





Downregulation of E-cadherin, ZO1
Cell-cell junction dissolution

Loss of apical-basolateral cell polarity

Actin reorganization

Upregulation of metalloproteases
Increased deposition of extracellular matrix proteins

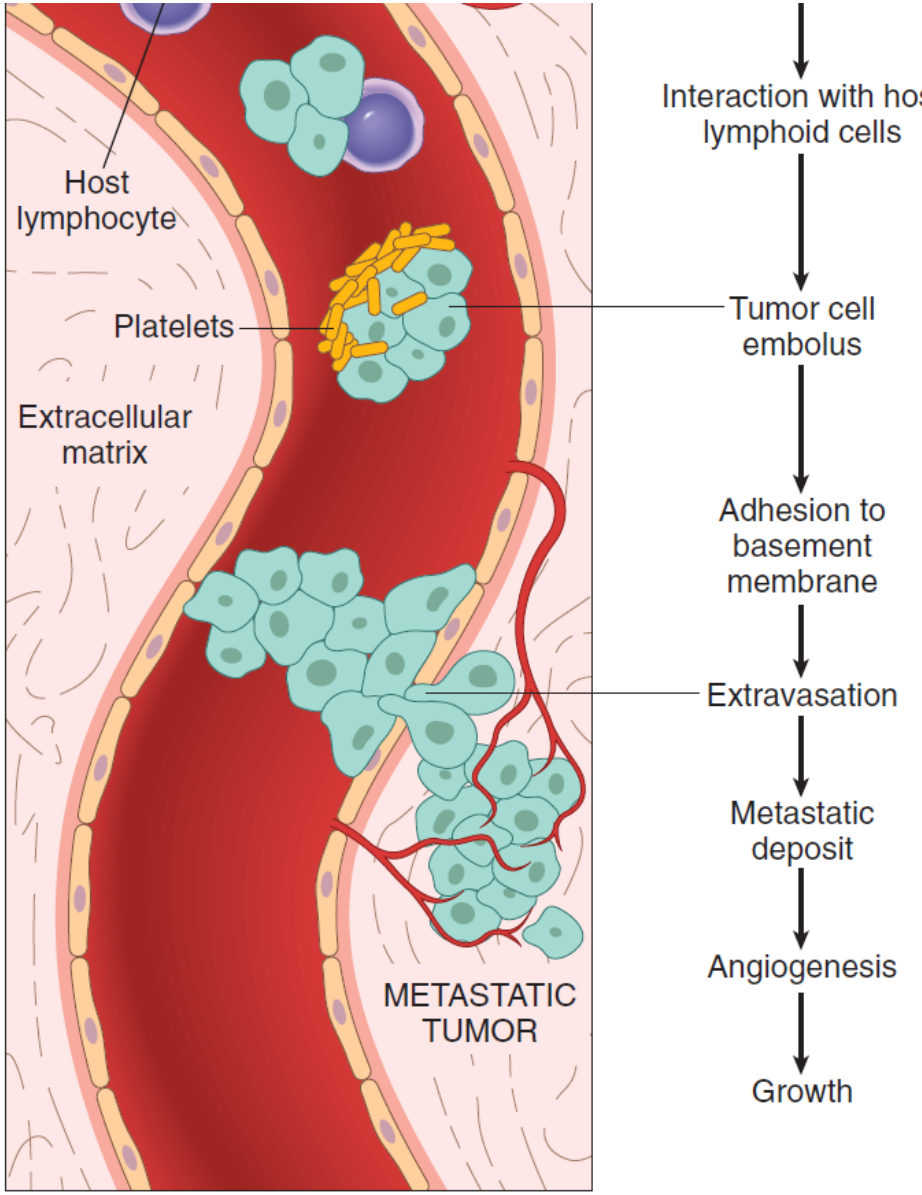
Migration and invasion

ECM Invasion

Migration

- Complex signalling
  Autocrine (cytokines)
  Paracrine (HGF/SCF)
  Chemotactic ECM
  Chemotactic GFs

- Actin reorganization



Vascular Dissemination & Homing

Single circulating cells vs emboli

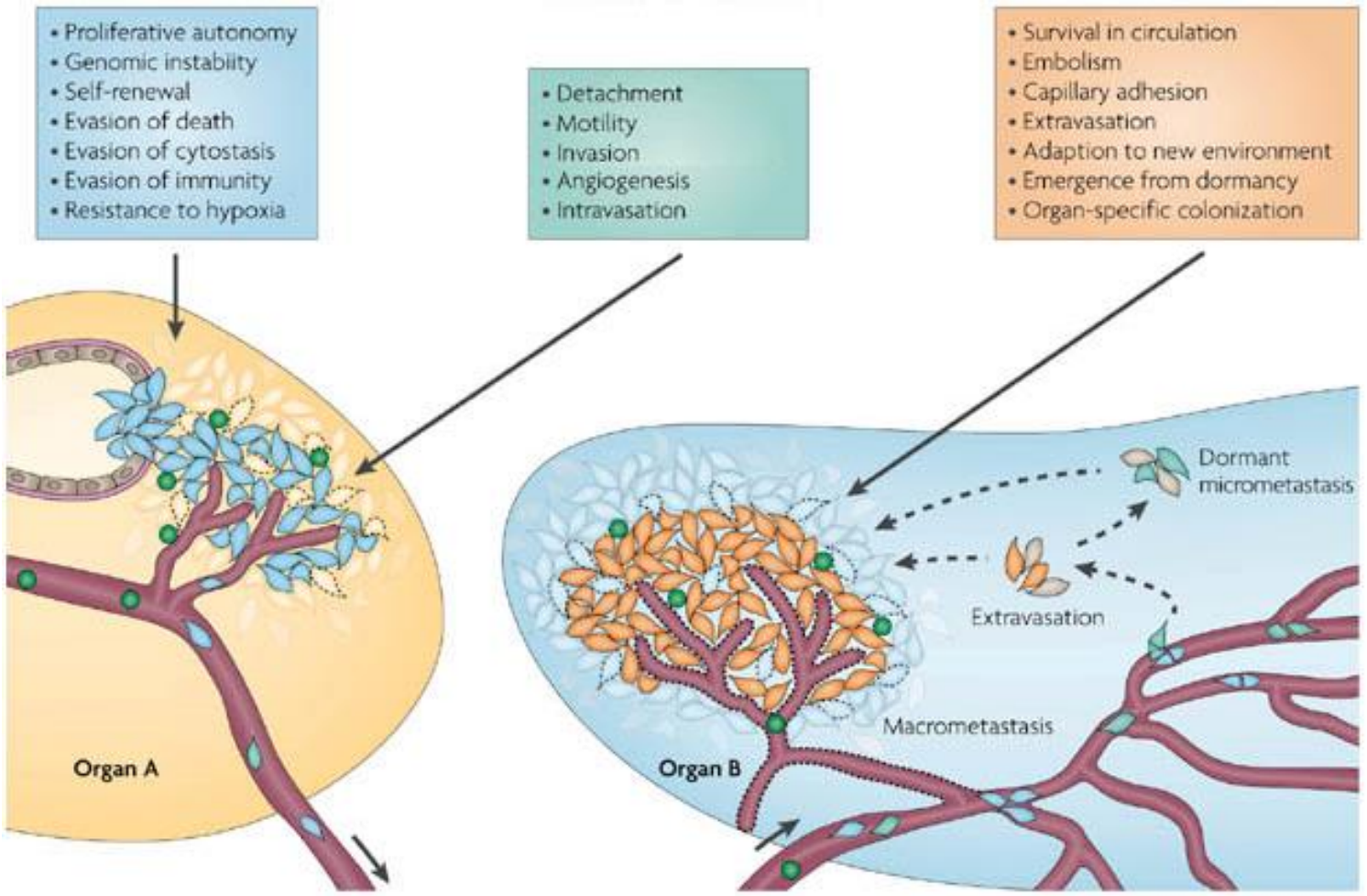
Avoidance of host immunity

Extravasation site:
- Vascular/lymphatic anatomy
- Tumor biology

1. Adhesion molecules
2. Chemokine homing
3. Permissive stroma

Cancer Dormancy

Genetic alterations required for metastasis early vs late?
(SMT vs contradicting experimental evidence)



Acquisition of a metastatic phenotype through interactions with the stroma (TOFT)

“Precise localization of metastases cannot be predicted with any form of cancer”