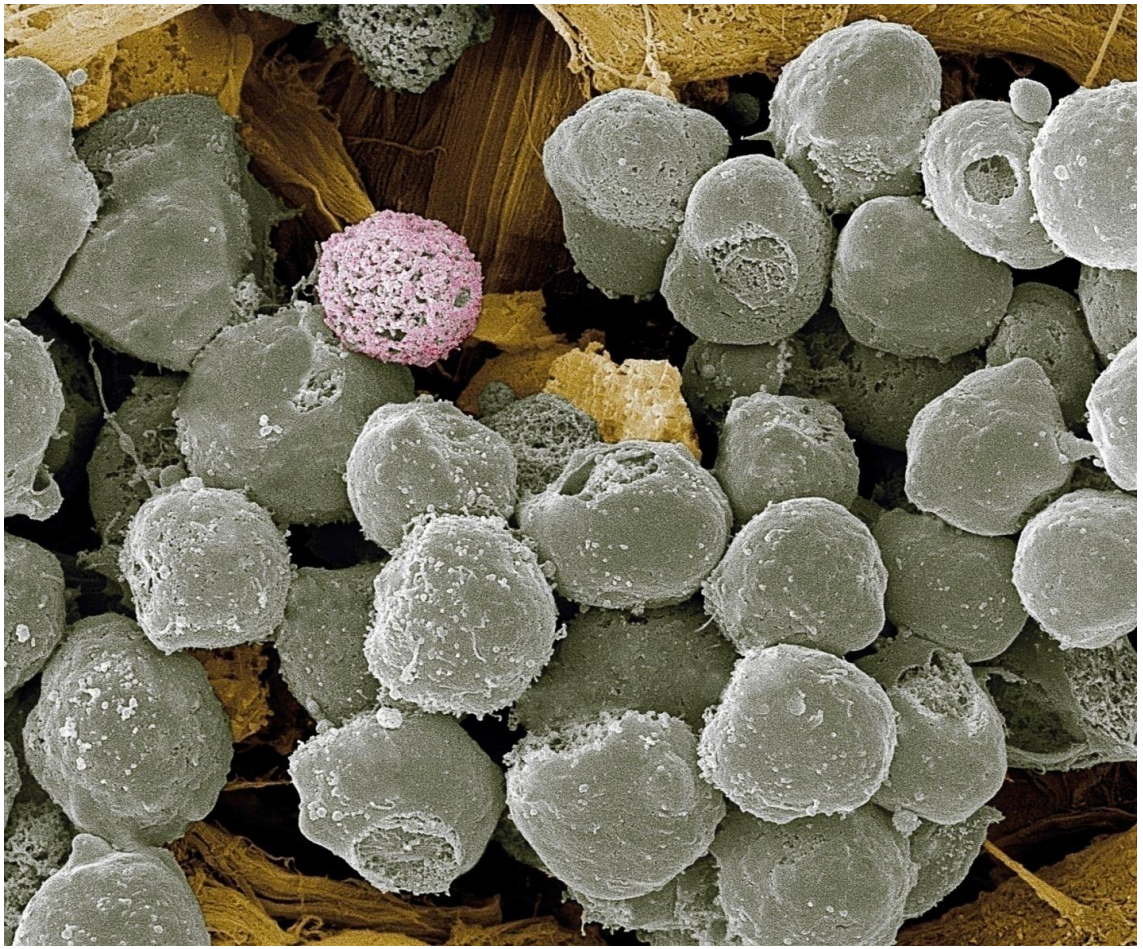
Pathophysiology of malignant transformation



Pavel Klener, MD, PhD

Institute of Pathological Physiology and Dept. of Hematology, Charles University General Hospital and First Faculty of Medicine

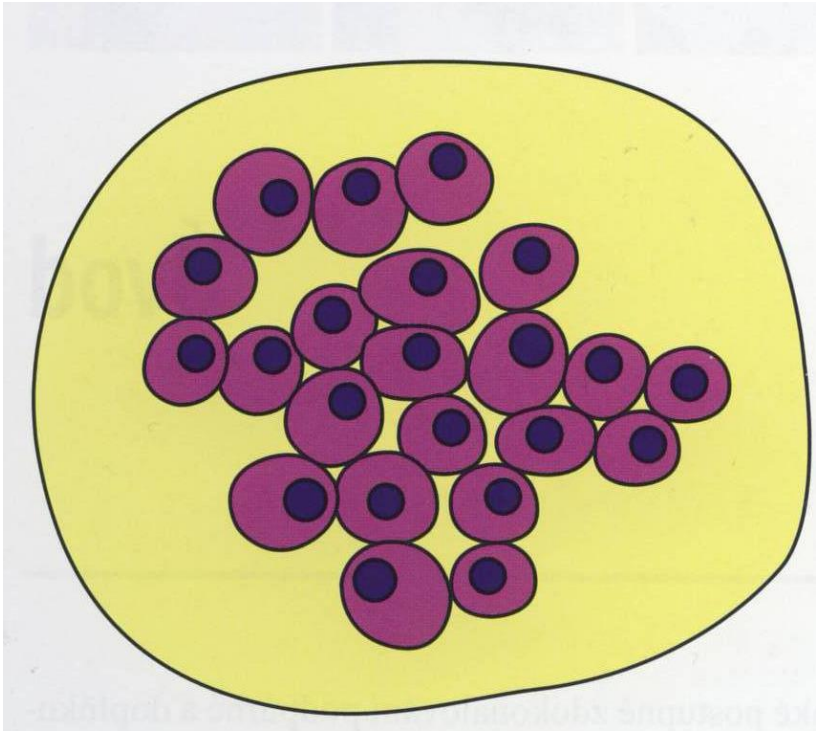
CANCER / TUMOR / MALIGNANCY / NEOPLASM

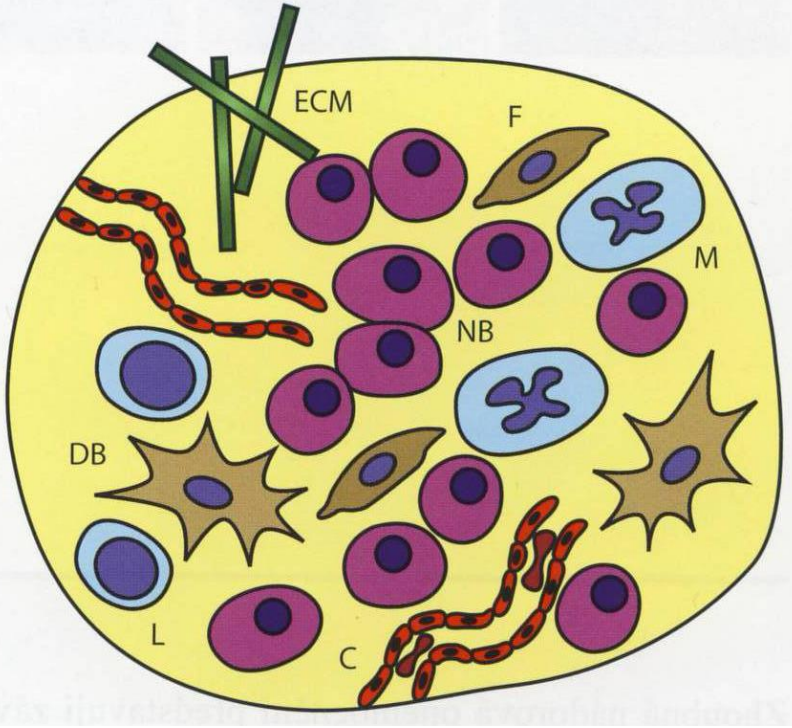
- Benign vs malignant
- Solid vs disseminated (hematologic)
- Carcinomas (epithelial) vs sarcomas (stromal)

The nomenclature of malignancies is largely historical:

-leukemia, lymphoma, myeloma, chloroma, hemoblastosis, hemoblastoma

TUMOR MICROENVIRONMENT





-tumor parenchyma

-tumor stroma

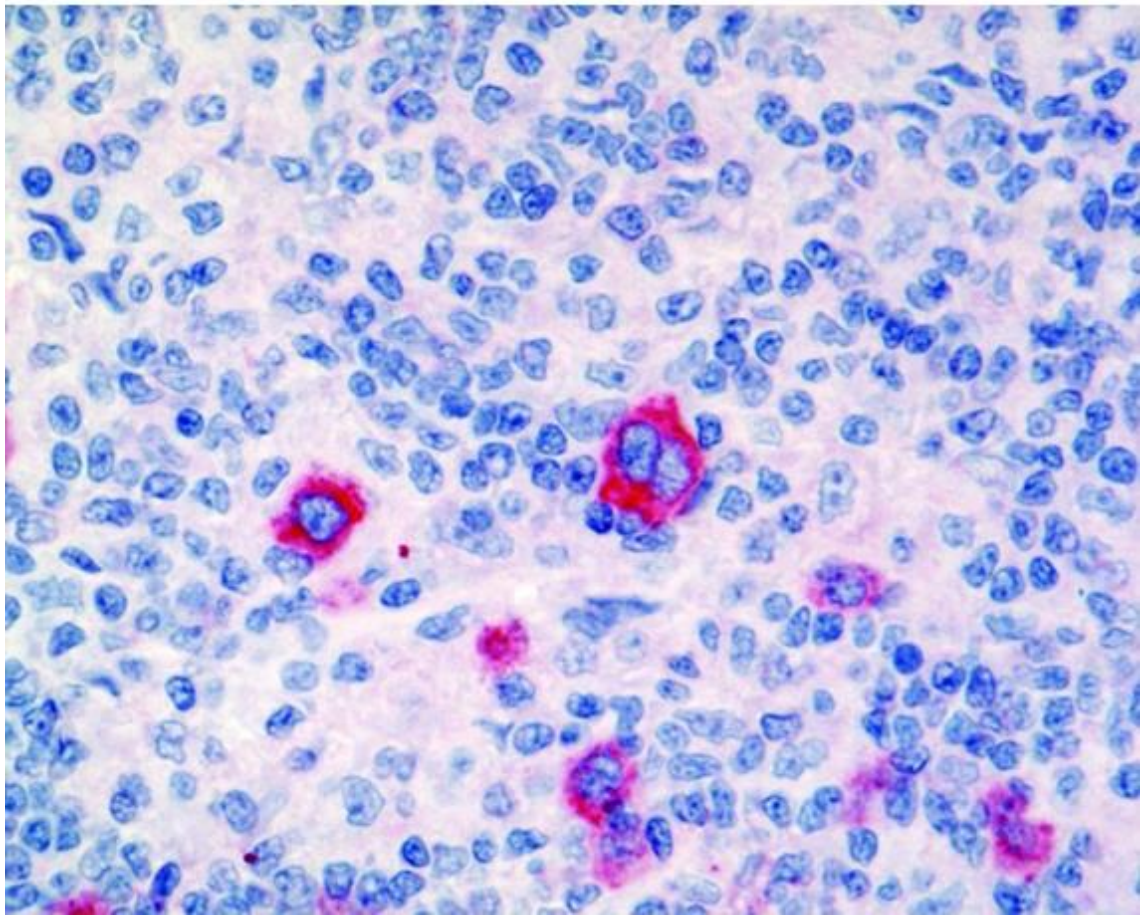
-“non-malignant“ component

HODGKIN LYMPHOMA

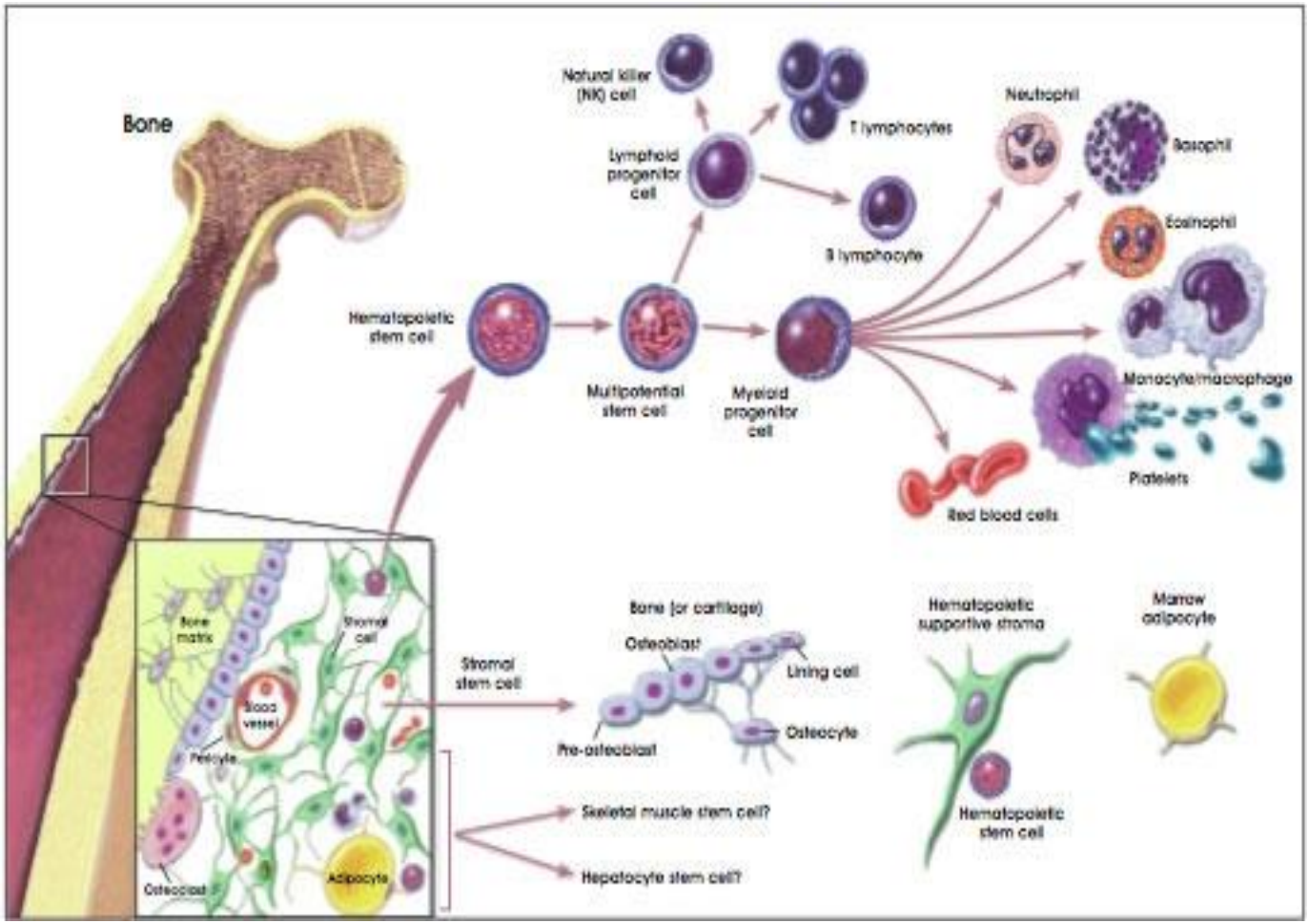
Hodgkin / Reed-Sternberg (HRS) cells ← malignant transformation of B-lymphocytes

HRS cells → loss of most of the B-cell markers

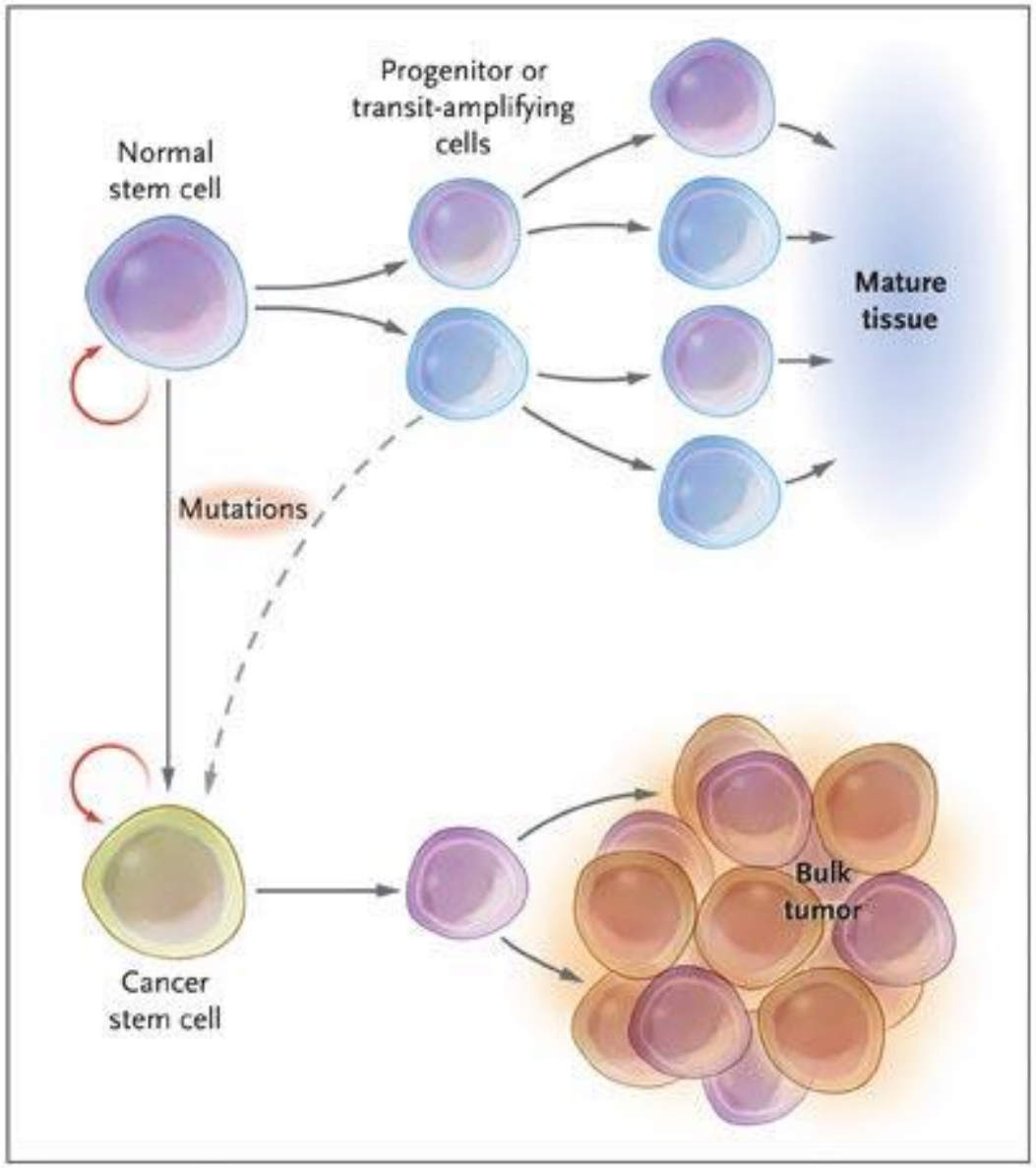
Figure 9
Child with lymphadenopathy of the neck (Dorothy Reed, ref.



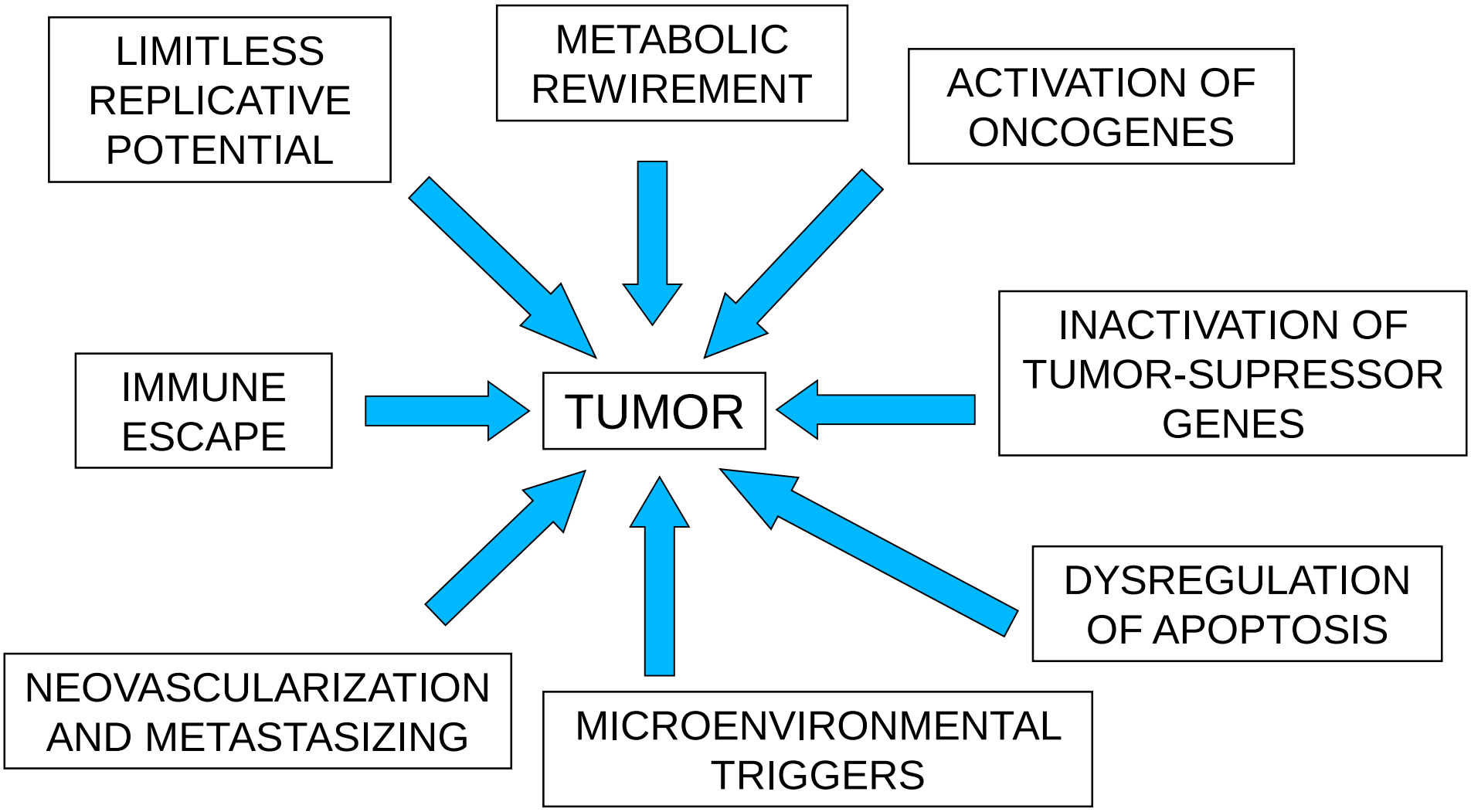
TUMOR MICROENVIRONMENT / ECOSYSTEM



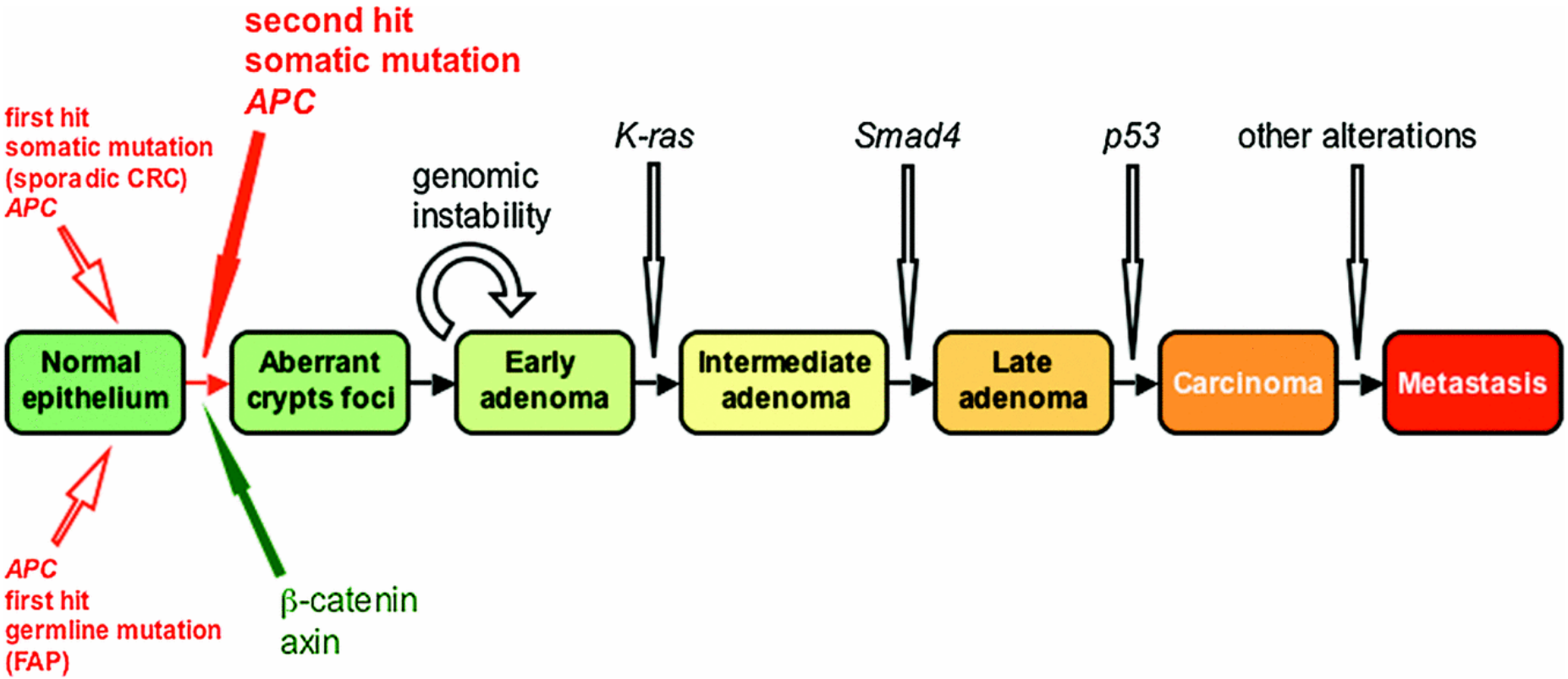
CANCER STEM CELL PARADIGM



MALIGNANT TRANSFORMATION = A PROCESS

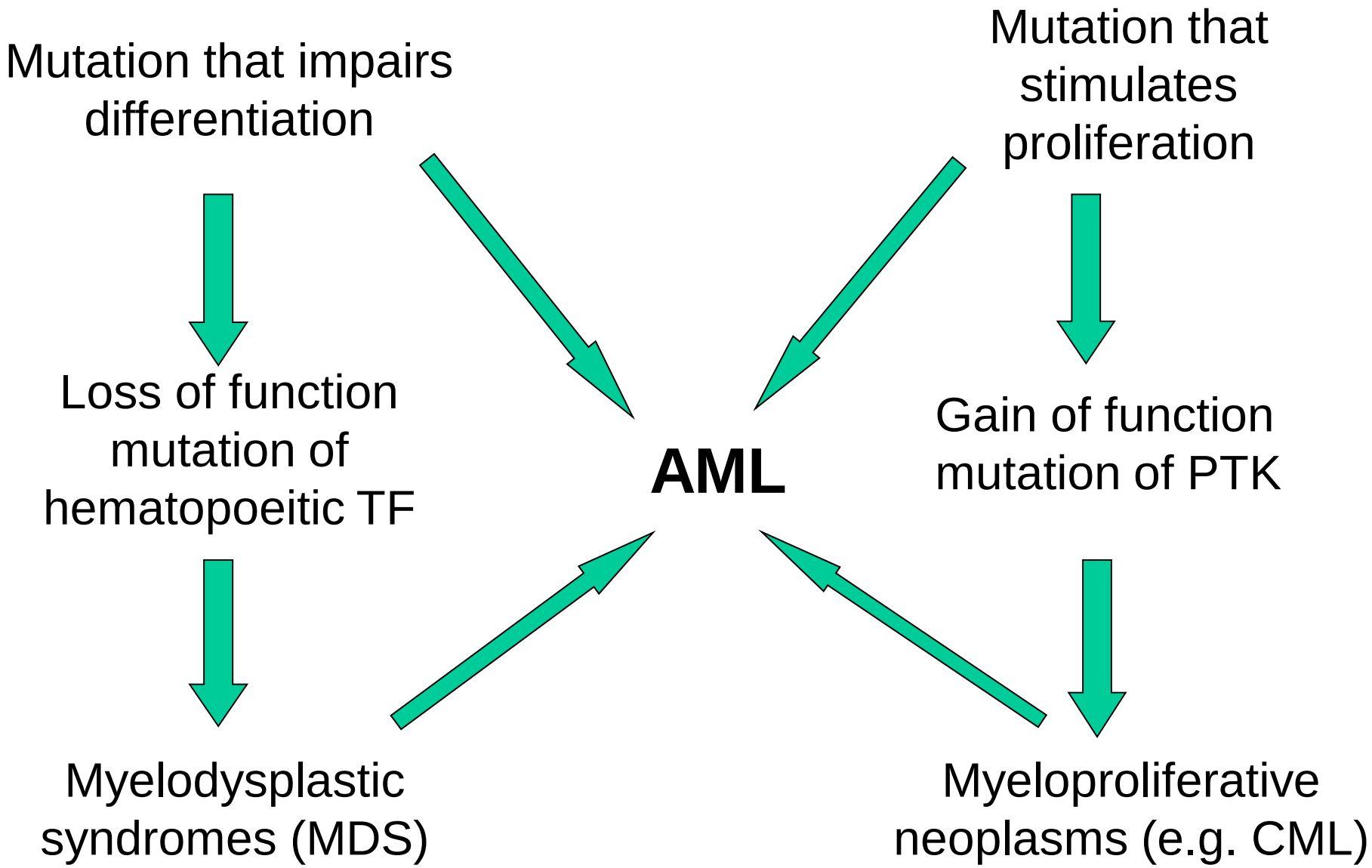


MODEL OF COLORECTAL CARCINOGENESIS



Biol. Cell (2006) 97, 185-196

TWO-HIT MODEL OF THE PATHOGENESIS OF MYELOPROLIFEATIVE DISORDERS



HALLMARKS OF CANCER

1.

LIMITLESS SELF-RENEWAL

CANCER STEM CELLS,

TELOMERES AND TELOMERASES

SELF-RENEWAL VS PROLIFERATION

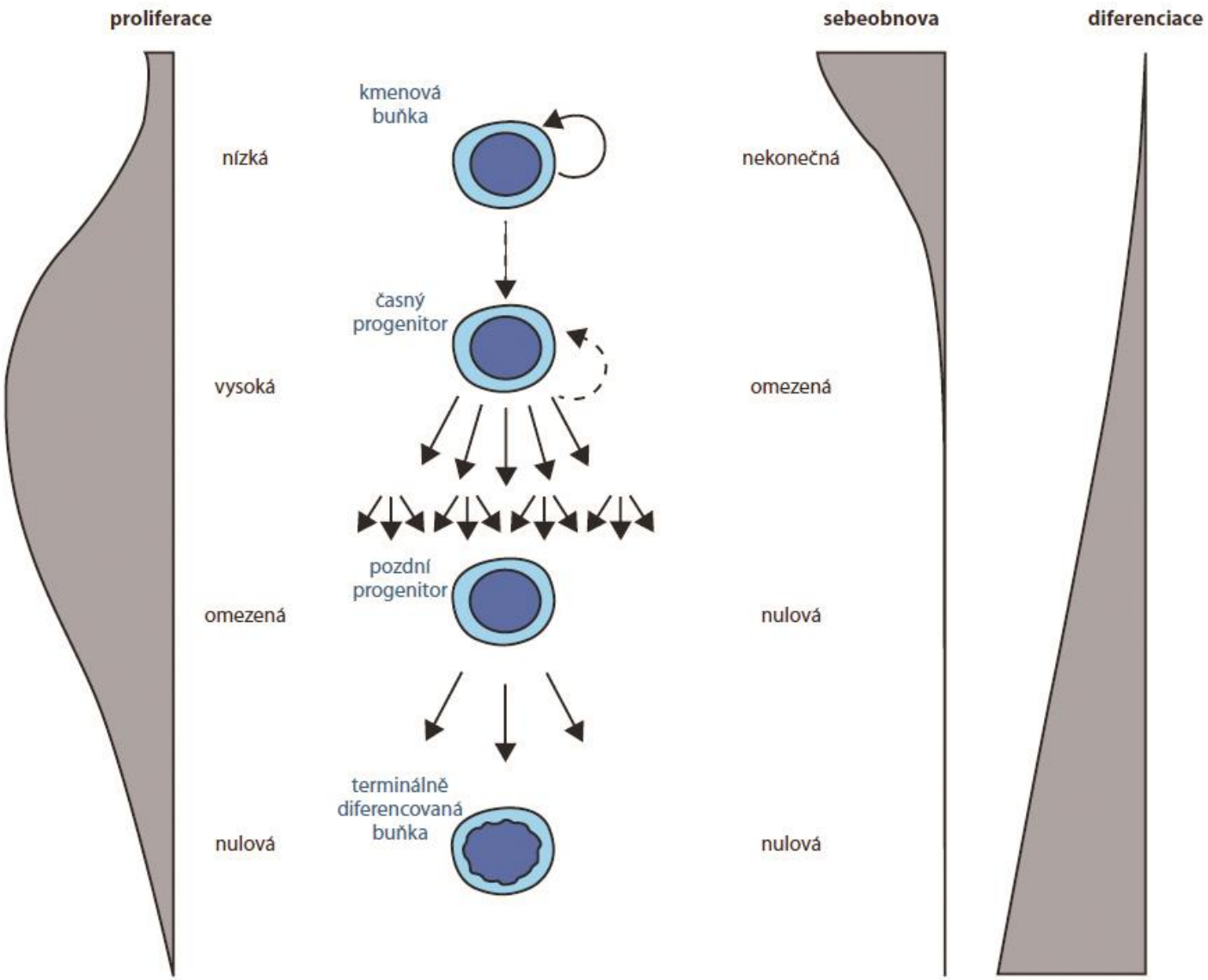
Self-renewal enables maintenance of low numbers of adult stem cells in undifferentiated state

Self-renewal is associated with low mitotic activity (as majority of stem cells are in G0 quiescent state).

Proliferation occurs during **differentiation** from the stem and progenitor cells toward mature, effector cells

Proliferation is associated with high mitotic activity, which is indispensable to provide large numbers of effector mature cells.

SELF-RENEWAL VS PROLIFERATION

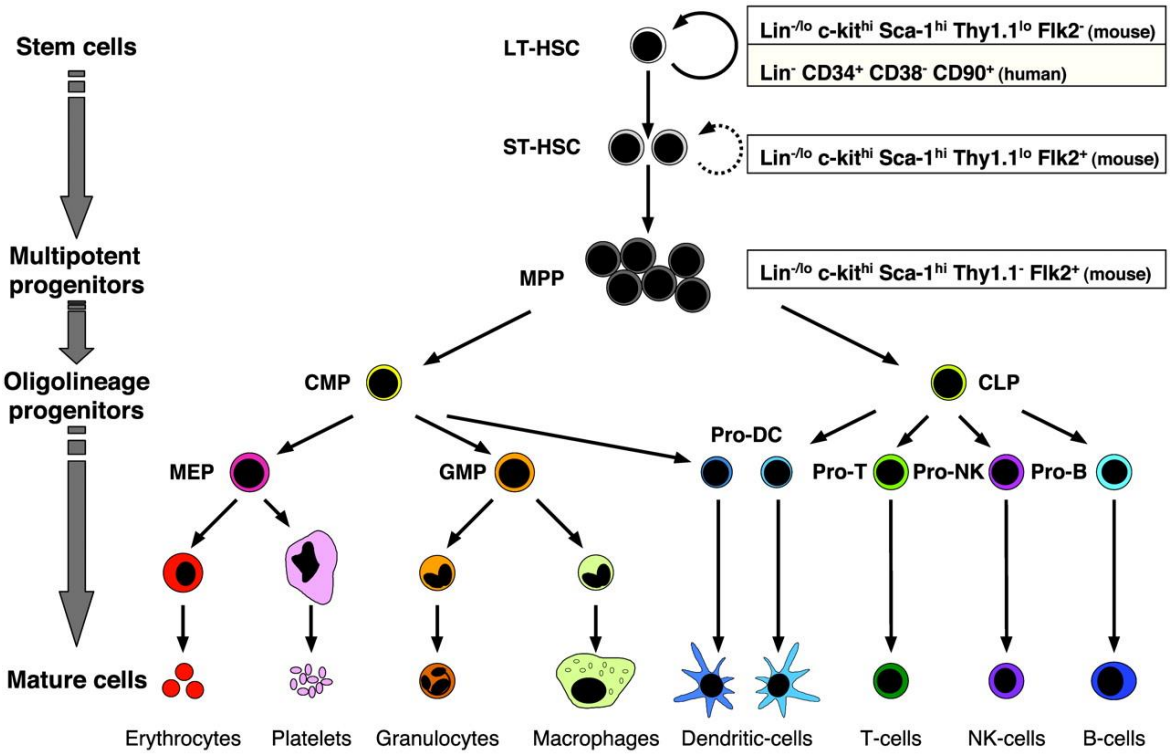


SELF-RENEWAL VS PROLIFERATION

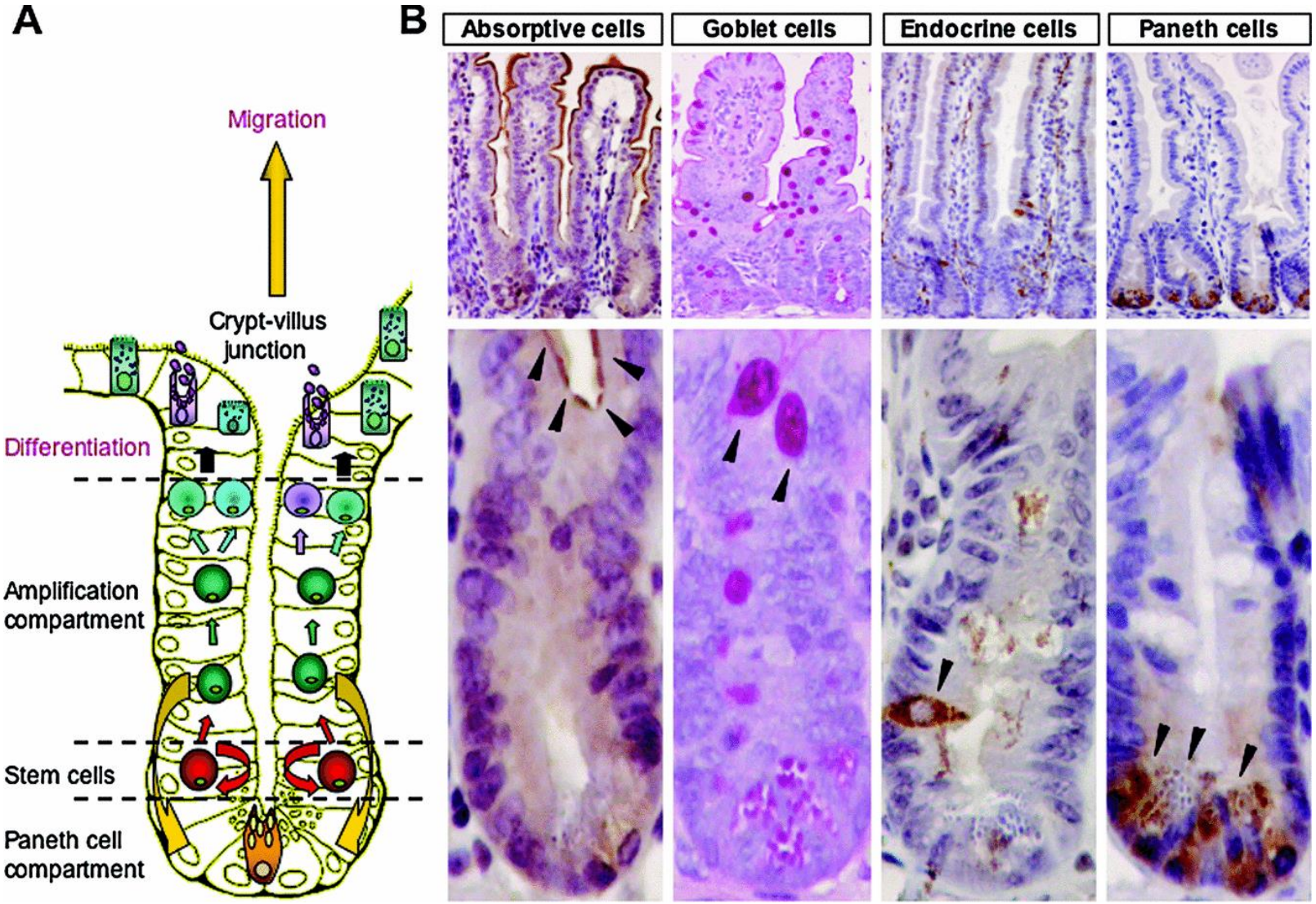
Self-renewal (low mitotic activity)

Proliferation (high mitotic activity)

Terminal Differentiation (no mitotic activity)



SELF-RENEWAL VS PROLIFERATION



Biology of the Cell www.biolcell.org Biol. Cell (2006) 97, 185-196

SELF-RENEWAL

Self-renewal **in normal cells** is always limited, with the exception of **stem cells**.

Malignant cells aberantly acquire ability for unlimited self-renewal, which constitutes (from the definition of malignancy) one of the hallmarks of cancer.

REPLICATIVE SENESCENCE

With the exception of stem cells, the mitotic activity of all other cells is always limited.

Progenitor cells proliferate during differentiation process to yield mature effector cells.

Proliferation of mature cells is always limited to certain number of mitoses, after which the cells can no more divide. This phenomenon is called **replicative senescence**.

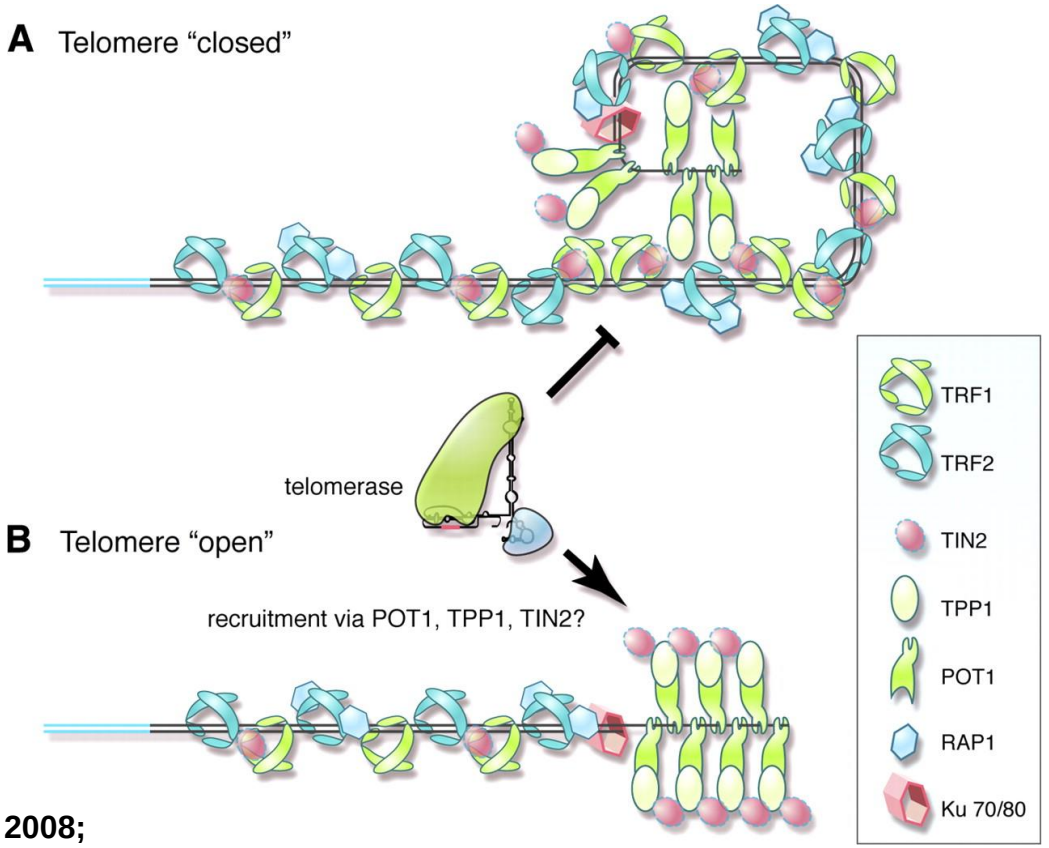
The non-dividing cells comprise two groups:

1. **Terminally-differentiated cells** (osteocyte, keratinocyte, enterocyte etc.).
2. **Quiescent cells** (in G0 phase). They can re-enter cell cycle under special circumstances (naïve B-cells, stem cells etc.).

REPLICATIVE SENESCENCE AND CRITICAL ROLE OF TELOMERES

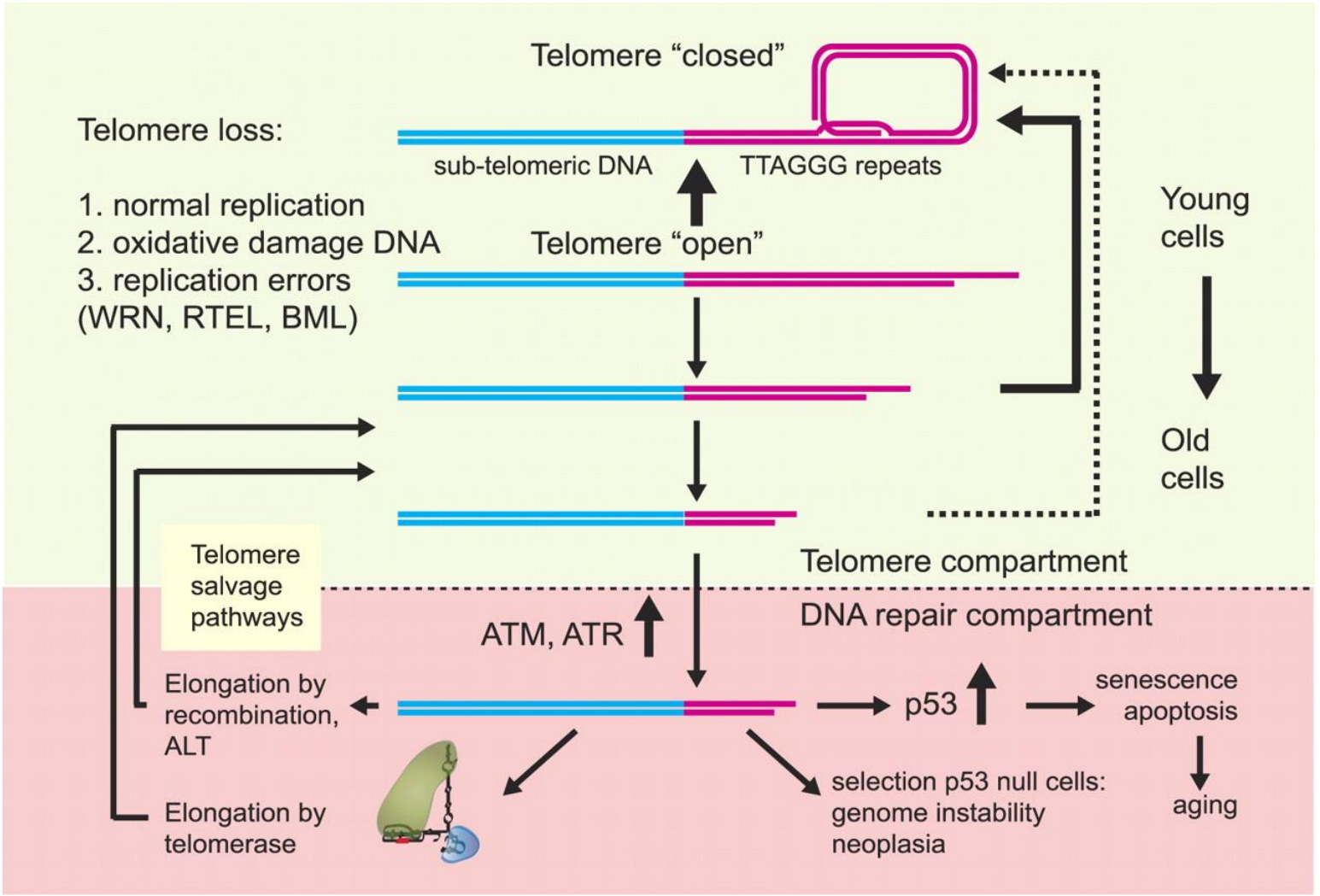
progressive shortening of telomeres

„closed“ telomeres“ → → → critically short „open“ telomeres → recognition of double-strand DNA breaks → senescence / apoptosis



Aubert, G. et al. Physiol. Rev. 88: 557-579 2008; doi:10.1152/physrev.00026.2007

TELOMERE LENGTH AND SENESCENCE / AGING



Aubert, G. et al. Physiol. Rev. 88: 557-579 2008; doi:10.1152/physrev.00026.2007

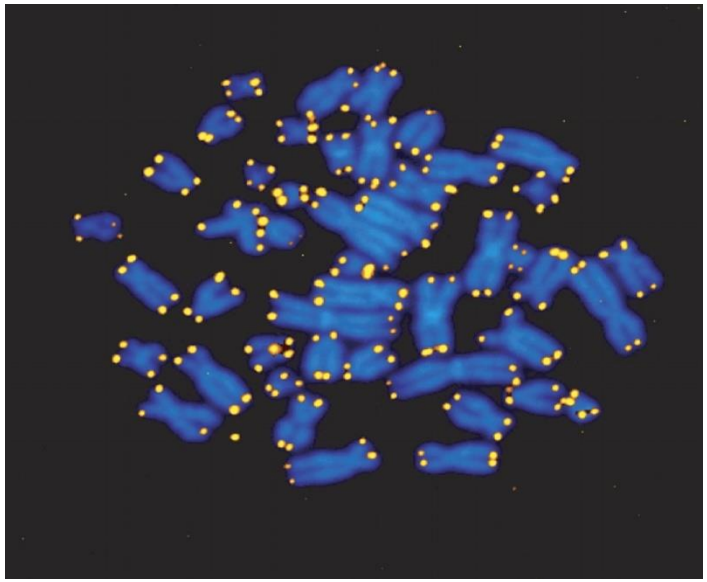
Physiological Reviews

TELOMERES, TELOMERASES AND CANCER

Telomerase is reverse transcriptase enzyme that elongates telomeres.

Telomerase carries its own RNA molecule, which is used as a template.

Malignant cells aberantly acquire ability for unlimited self-renewal, which constitutes (from the definition of malignancy) one of the hallmarks of cancer.



HALLMARKS OF CANCER

2.-3.

ENHANCED PROLIFERATION

AND

IMPAIRED DIFFERENTIATION

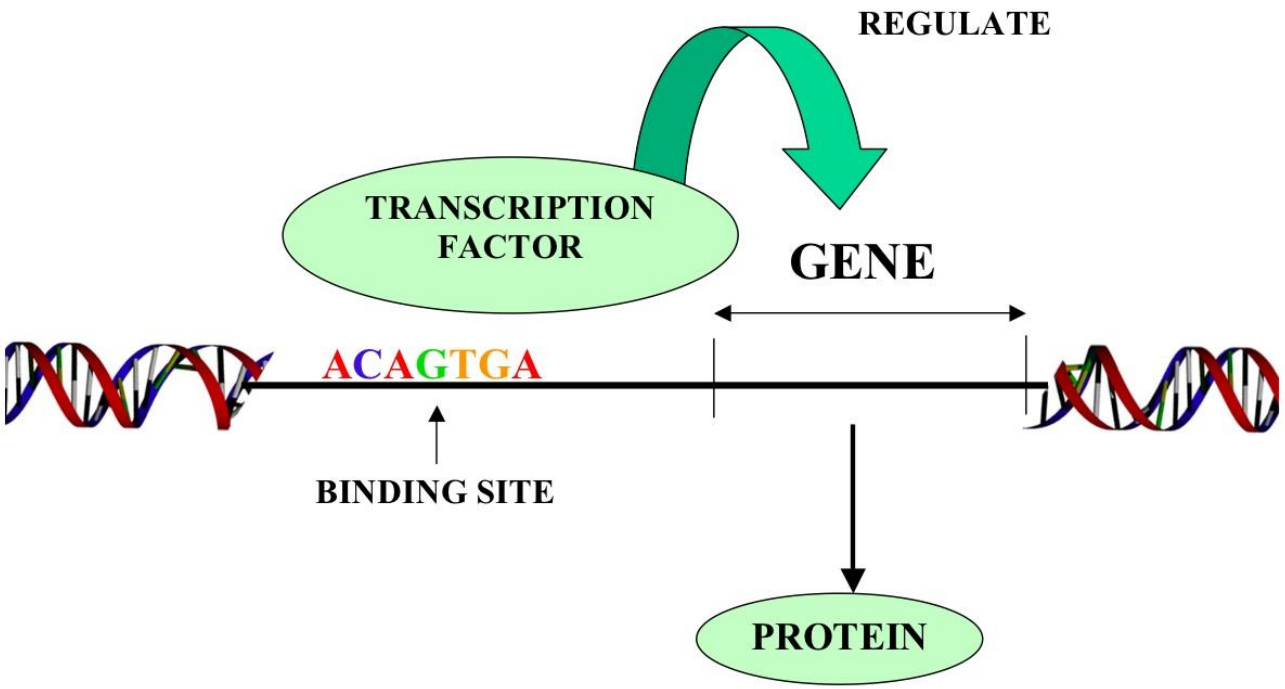
ONCOGENES

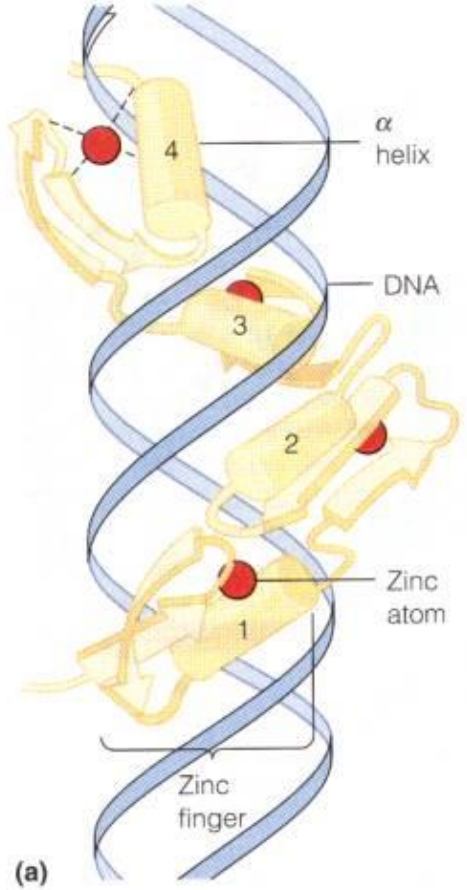
AND

TUMOR SUPPRESSORS

TRANSCRIPTION FACTORS

Legend: A transcription factor molecule binds to the DNA at its binding site, and thereby regulates the production of a protein from a gene.





DIFFERENTIATION AND TRANSCRIPTION FACTORS

Differentiation ← changes in gene-expression regulated by a variety of transcription factors (TFs).

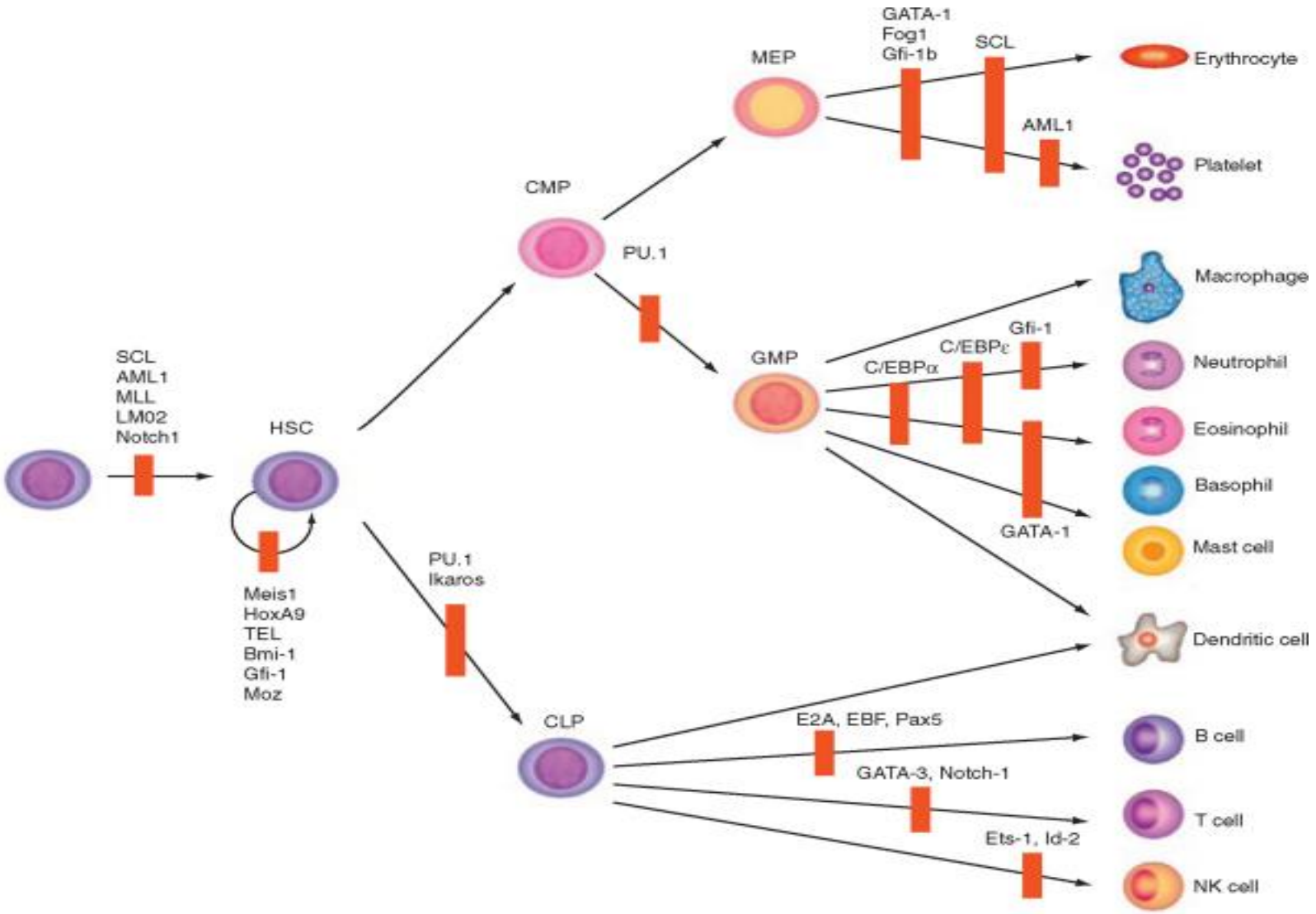
Different TFs are responsible for various stages of differentiation.

TFs are frequently deregulated and/or mutated in cancers.

Stem and progenitor cells that acquire **loss-of-function / inactivating mutations** of a particular TF cannot properly differentiate

→ **maturational arrest / block of differentiation**.

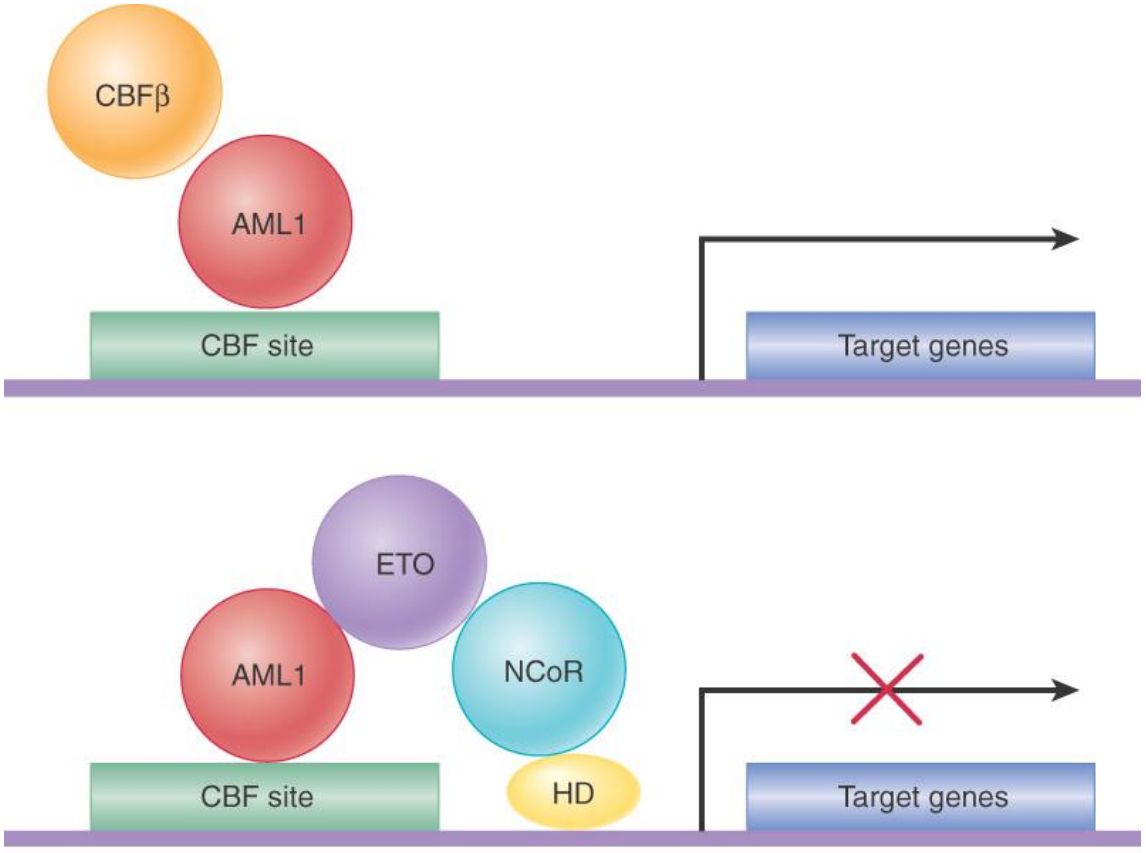
MUTATION OF TF → MATURATIONAL ARREST



ACUTE MYELOGENEOUS LEUKEMIA AND *AML1-ETO*

AML1 / RUNX1 / CBFα = normal hematopoietic TF

t(8;21) → AML1-ETO fusion protein = dominant negative competitive inhibitor of normal transcription factor *AML1*



ONCOGENES AND LIGAND-INDEPENDENT MITOGENIC STIMULATION

Mitogens (growth factors, cytokines, interleukines, hormones etc.) → increased mitotic activity to provide organism with sufficient numbers of mature, terminally differentiated, effector cells.

Rate of proliferation of malignant cells directly translates into the rapidity of growth of the tumor = biological aggressiveness

Proto-oncogenes = genes that encode mitogens (growth factors, cytokines etc.) or proteins involved in mitogen signaling (receptors, signal cascade mediators, transcription factors etc.)

Activation of (proto-)oncologenes by overexpression, mutation, chromosomal translocation etc → **ligand-independent signalling** mimicking the corresponding physiological mitogene-activated pathway(s).

LIGAND-INDEPENDENT (ONCOGENIC) SIGNALING

Mutations of RTK

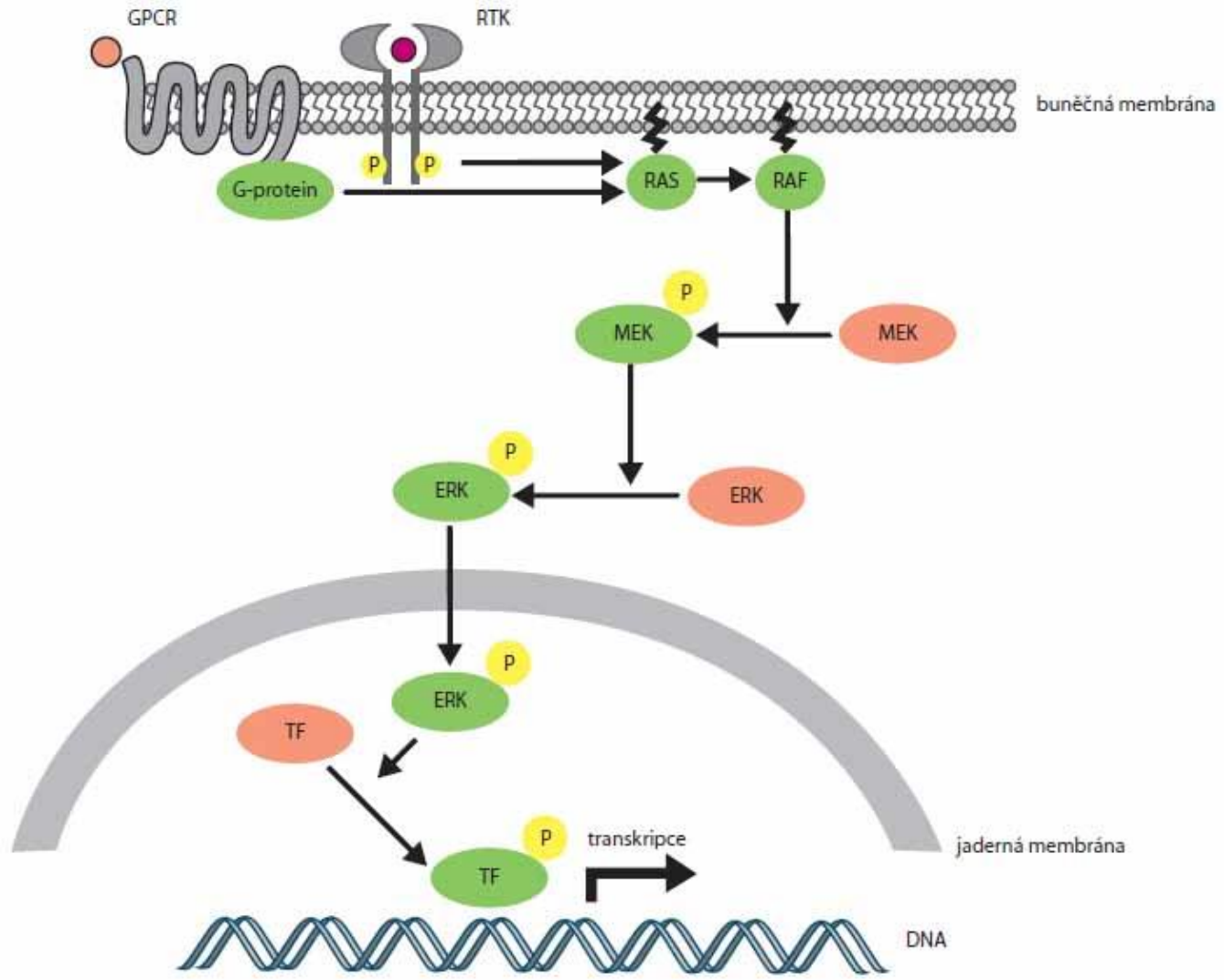
Mutations of Ras

Mutations of Raf

Mutations of MEK

Mutations of ERK

Mutations of TF



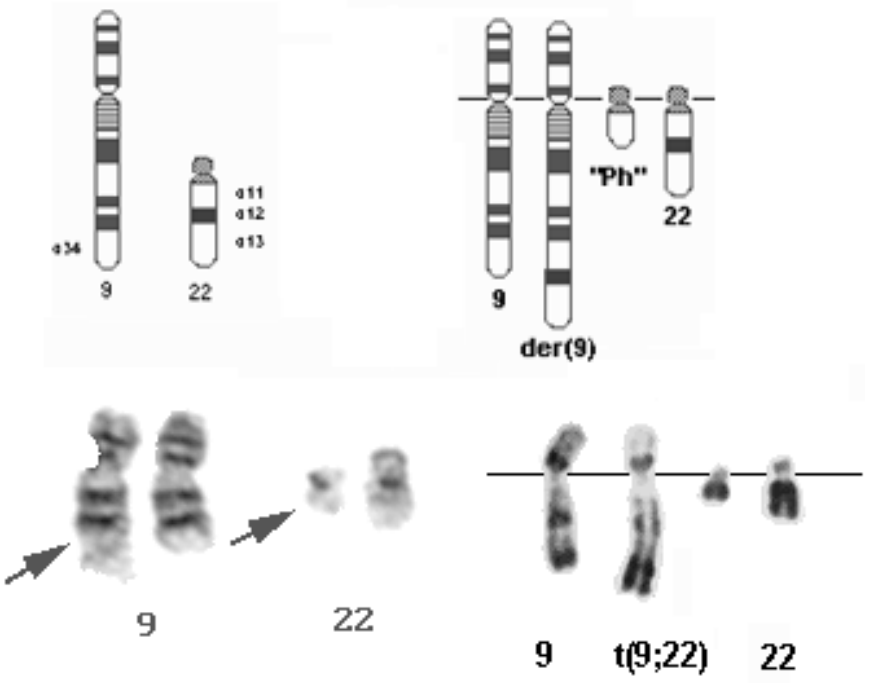
ONCOGENES AND PROTO-ONCOGENES

Cellular proto-oncogene	Function	Viral oncogene	Viral strain	Alteration of viral oncogene compared to proto-oncogene	Most common somatic mutation of proto-oncogene
c-Src	PTK	v-src	Rous Sarcoma Virus	Gene truncation	Point mutation
EGFR	RTK (ligand= EGF)	v-erbB	Avian Erythroblastosis Virus	Gene truncation	Point mutation
c-Myc	Transcription factor	v-myc	MC29 Avian Myelocytomatosis Virus	Fusion gene GAG-MYC	Point mutation, chromosomal translocation
K-Ras	GTPázový *switch* protein	v-kras	Kirsten Murine Sarcoma Virus	Overexpression from viral promotor	Point mutation
c-Mpl	Receptor (ligand= Tpo)	v-mpl	Myelo-Proliferative Leukemia Virus	Gene truncation	Point mutation
PDGF	Growth factor	v-sis	Simian Sarcoma Virus	Fusion gene ENV-SIS	Chromosomal translocation
Akt/PKB	Non-receptor tyrosin-kinase	v-akt	AKT8 Murine Leukemia Virus	Overexpression from viral promotor	Overexpression

CHRONIC MYELOGENOUS LEUKEMIA

- **t(9q34;22q11)** BCR-ABL

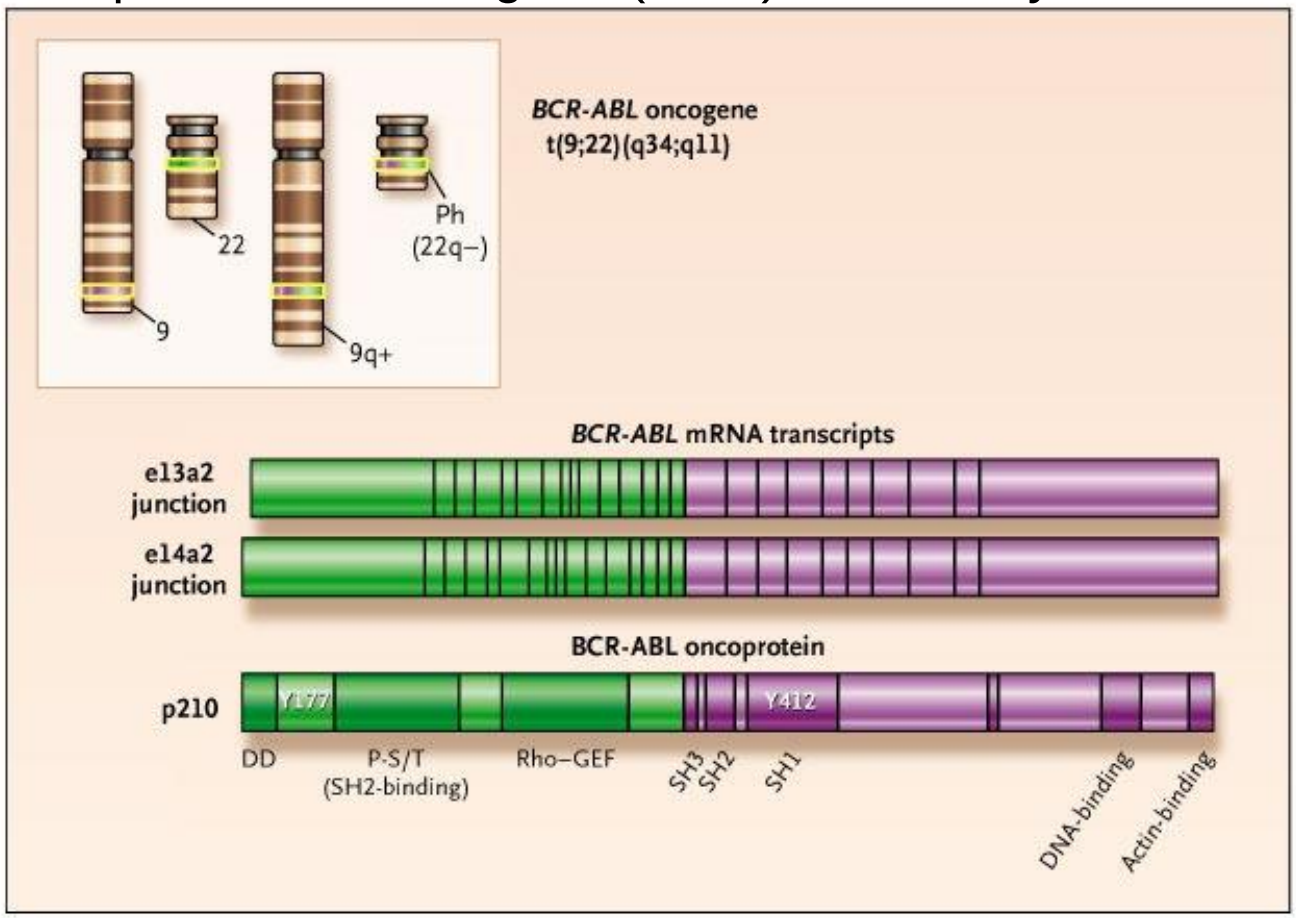
Breakpoint Cluster Region- ABeLson Tyrosine Kinase



BCR-ABL ONCOGENE IN CML CELLS

- **t(9q34;22q11)** BCR-ABL

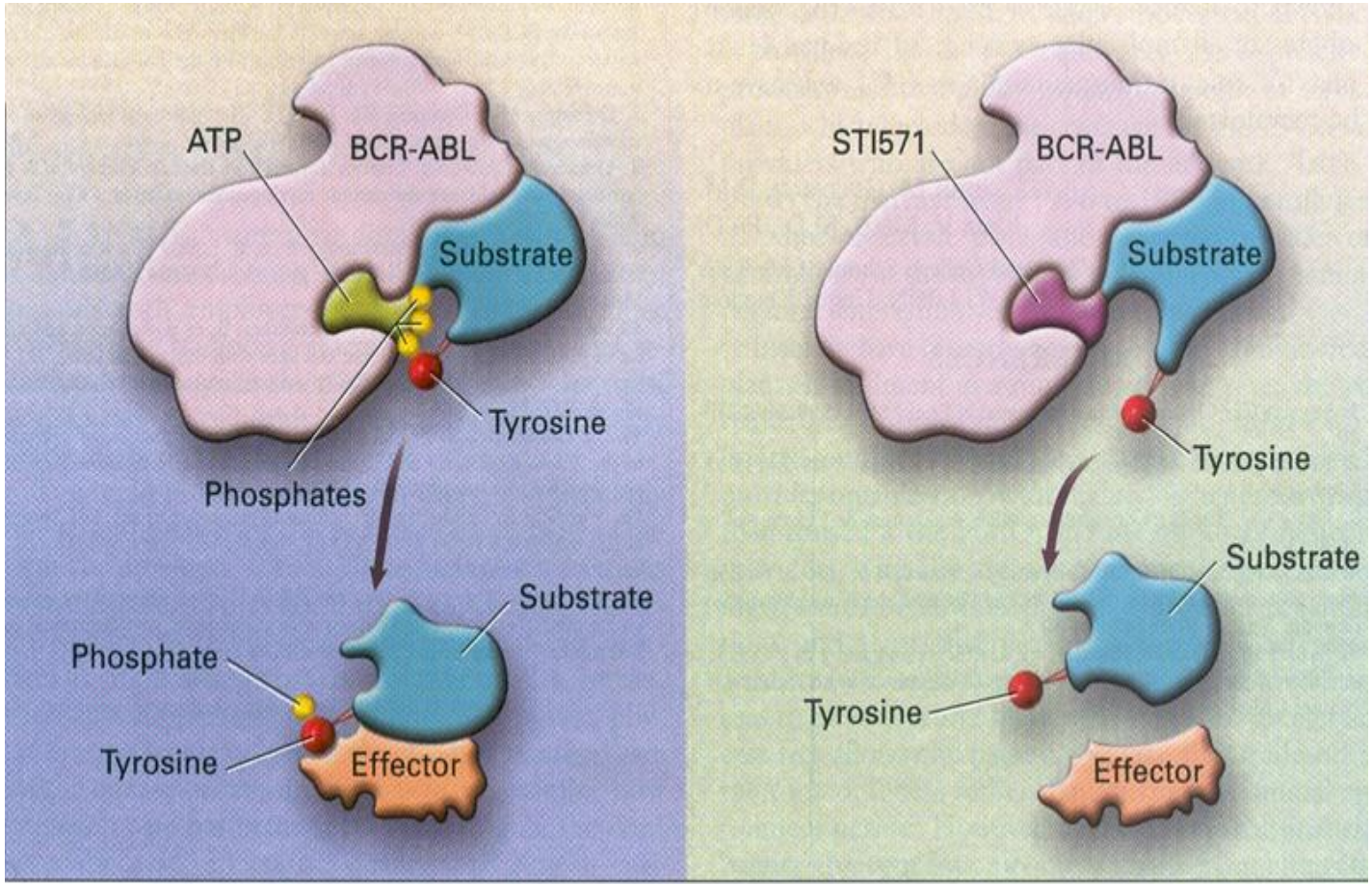
Breakpoint Cluster Region- (John) Abelson Tyrosine Kinase



Goldman, J. M. et al. N Engl J Med 2003;349:1451-1464

The NEW ENGLAND JOURNAL of MEDICINE

IMATINIB MESYLATE AND BEGINNING OF THE ERA OF TARGETED-THERAPY



TUMOR-SUPPRESSOR GENES AND GROWTH-INHIBITORY SIGNALS

Tumor-suppressor genes = anti-oncogenes: control cell cycle, proliferation, self-renewal

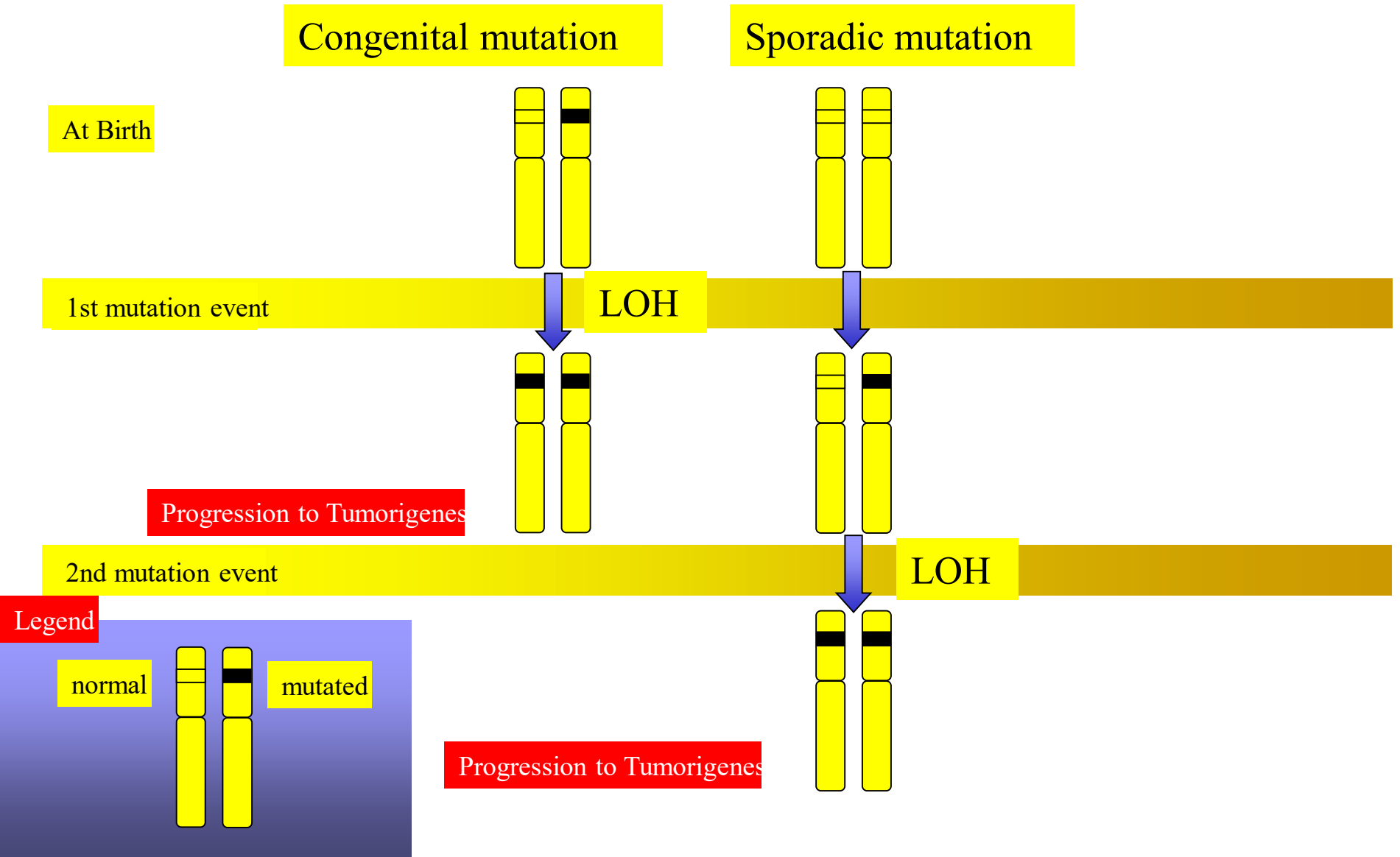
Loss-of-function mutation of anti-oncogenes → cancerogenesis

Inactivation of **both alleles** usually required.

Congenital mutation of one allele = **hereditary cancer syndromes**

→ postnatal loss-of-heterozygocyty (LOH) → cancer

HEREDITARY CANCER SYNDROMES



TP53 AND CANCER

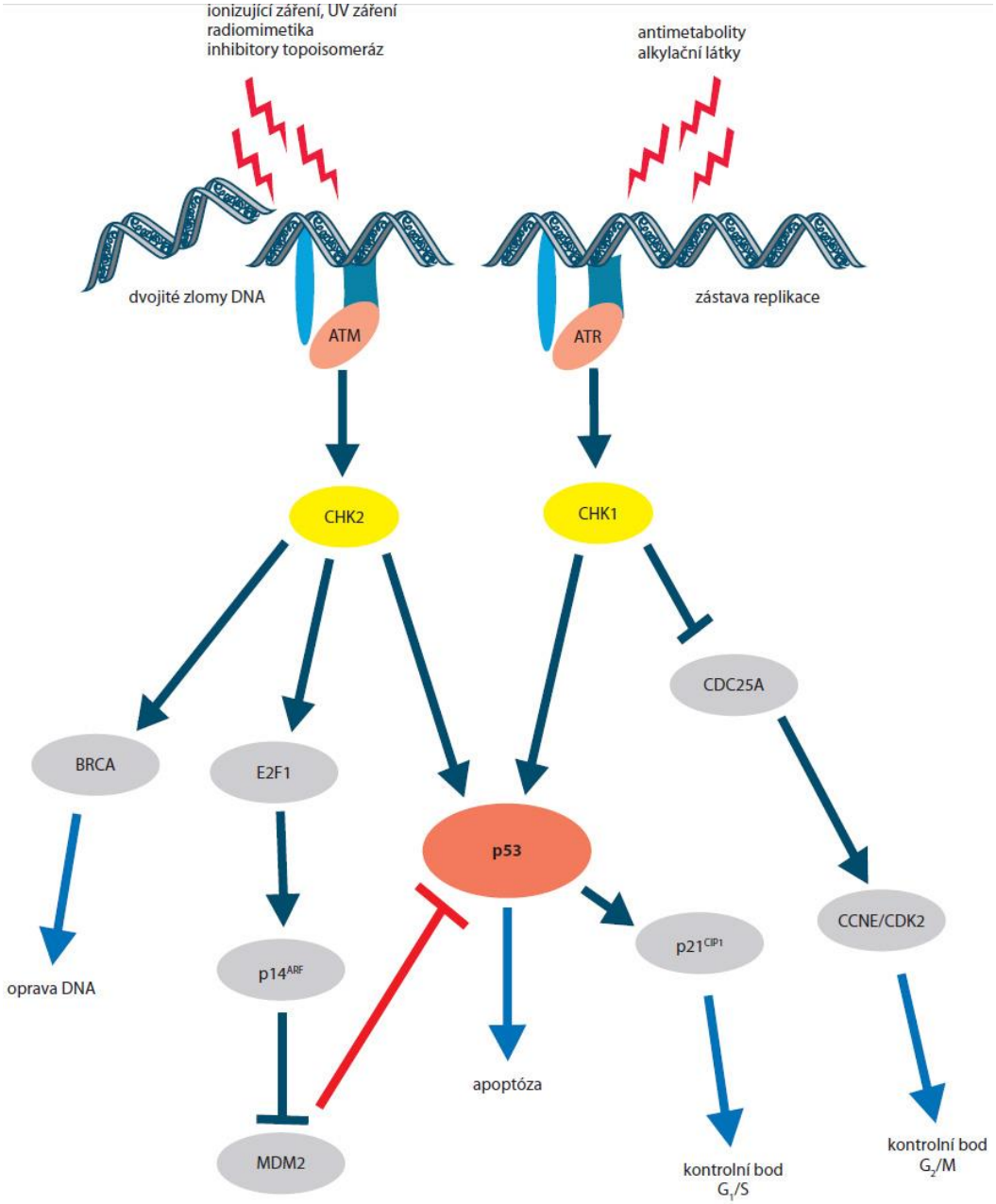
p53 is transcription factor coded on chromosome 17p.

p53 is upregulated and stabilized in response to DNA damage

Over 50% solid cancers have mutations of p53 (del 17p).

Hereditary Li-Fraumeni syndrome = germline mutations of the p53 tumor suppressor gene = high risk for a wide range of malignancies.

DNA DAMAGE AND p53



RETINOBLASTOMA (RB) PROTEIN, RB PATHWAY AND CELL CYCLE MACHINERY

Retinoblastoma (Rb) protein is key regulator of cell cycle progression, encoded on chromosome 13q.

Congenital mutation of RB gene is associated with early retinoblastoma development.

13q deletions is frequent finding in many tumors.

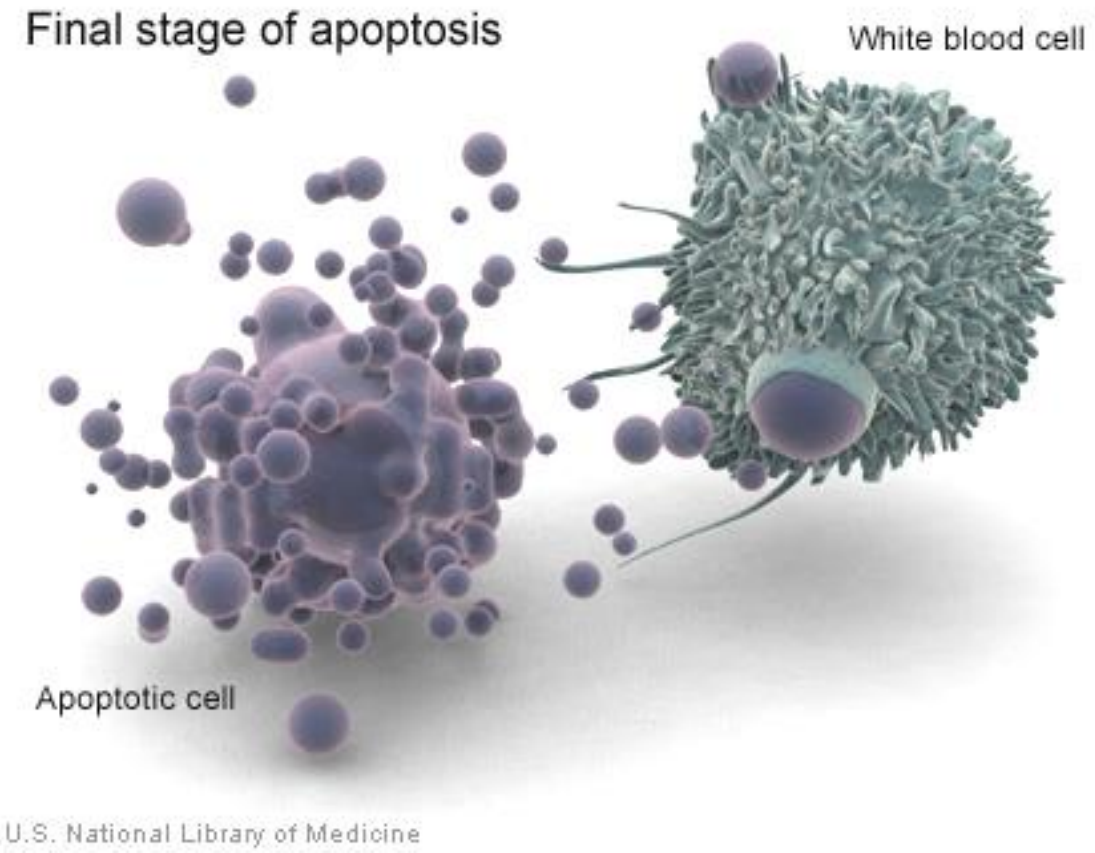
HALLMARKS OF CANCER

4.

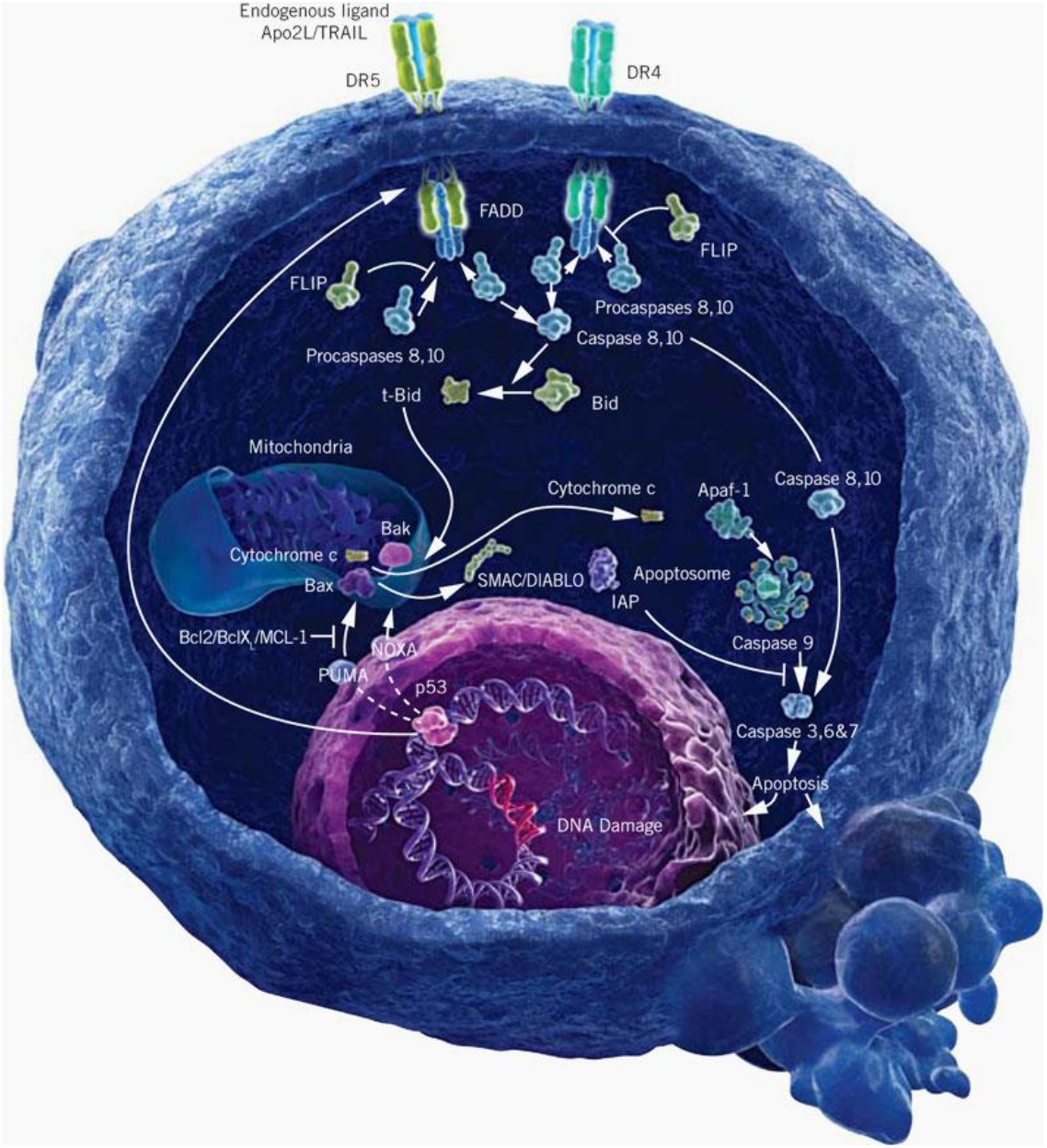
INCREASED SURVIVAL (IMPAIRED APOPTOSIS)

DEREGULATION OF ANTI- AND PRO-APOPTOTIC PLAYERS

APOPTOSIS

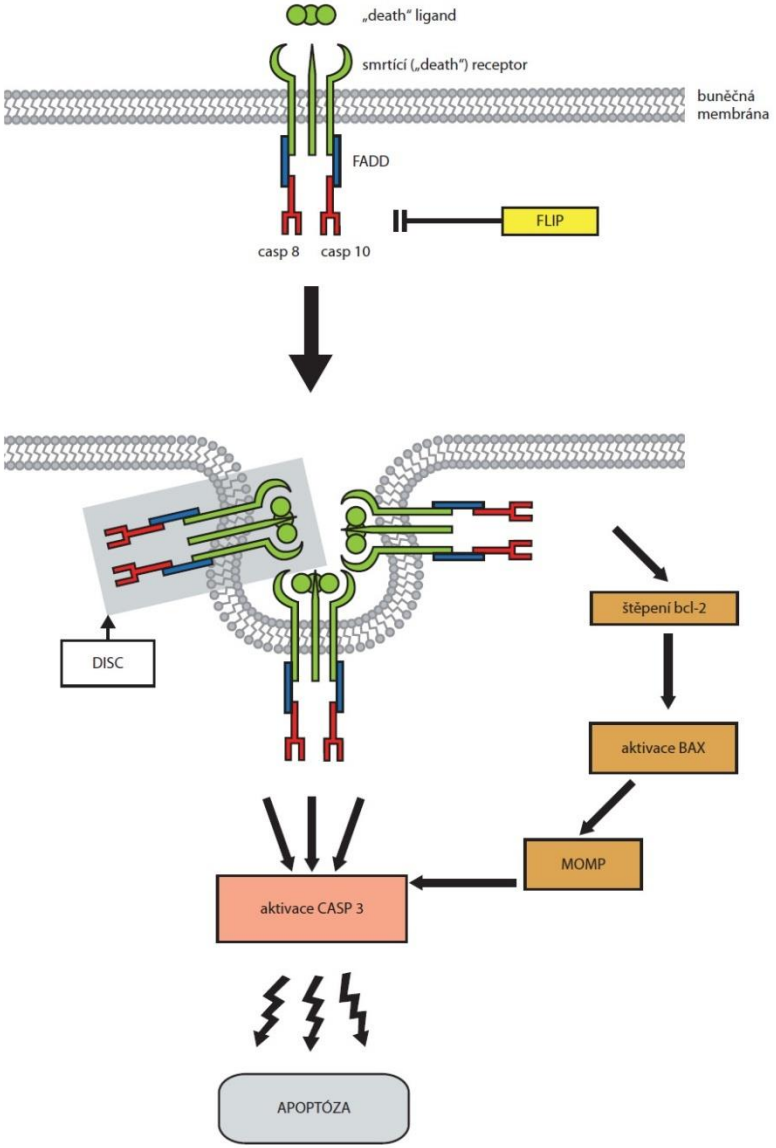

Final stage of apoptosis
White blood cell
Apoptotic cell
U.S. National Library of Medicine

APOPTOSIS

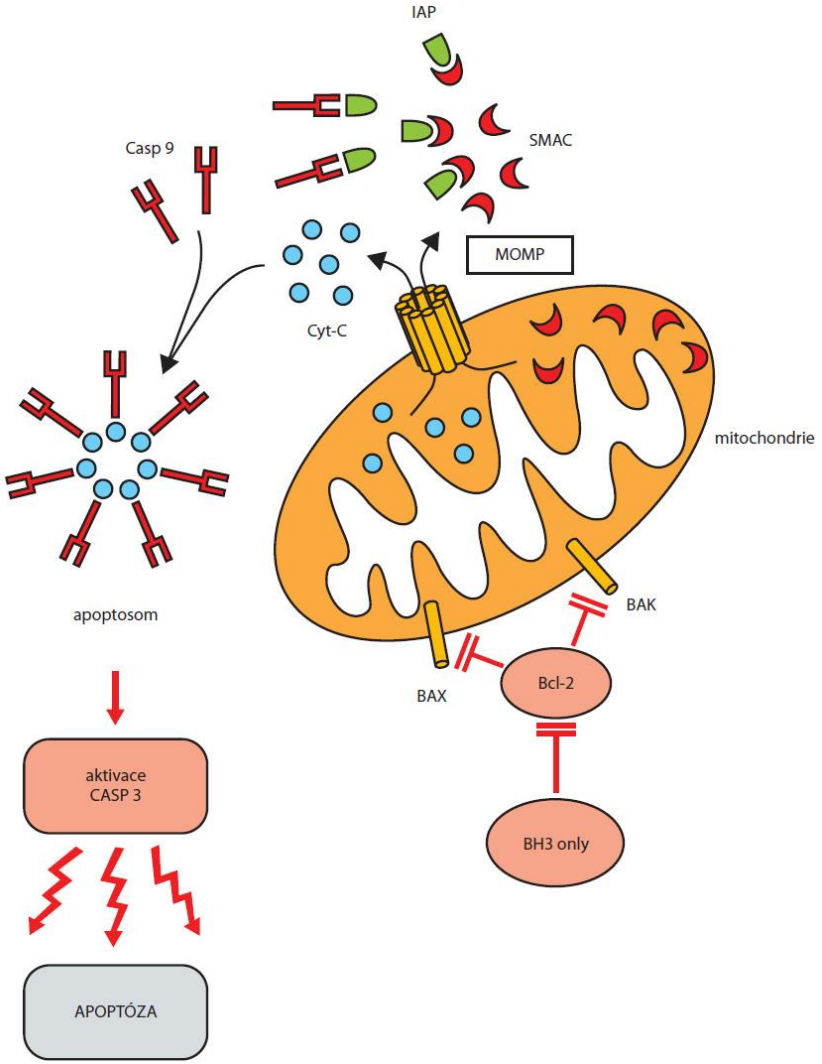

Endogenous ligand
Apo2L/TRAIL
DR5
DR4
FADD
FLIP
FLIP
Procaspases 8,10
Caspase 8,10
Procaspases 8,10
t-Bid
Bid
Mitochondria
Cytochrome c
Apaf-1
Caspase 8,10
Bak
Cytochrome c
Bax
SMAC/DIABLO
Apoptosome
IAP
Bcl2/BclX$_L$/MCL-1
NOXA
PUMA
p53
Caspase 9
Caspase 3,6&7
Apoptosis
DNA Damage

APOPTOTIC PATHWAYS

Death-receptor pathway



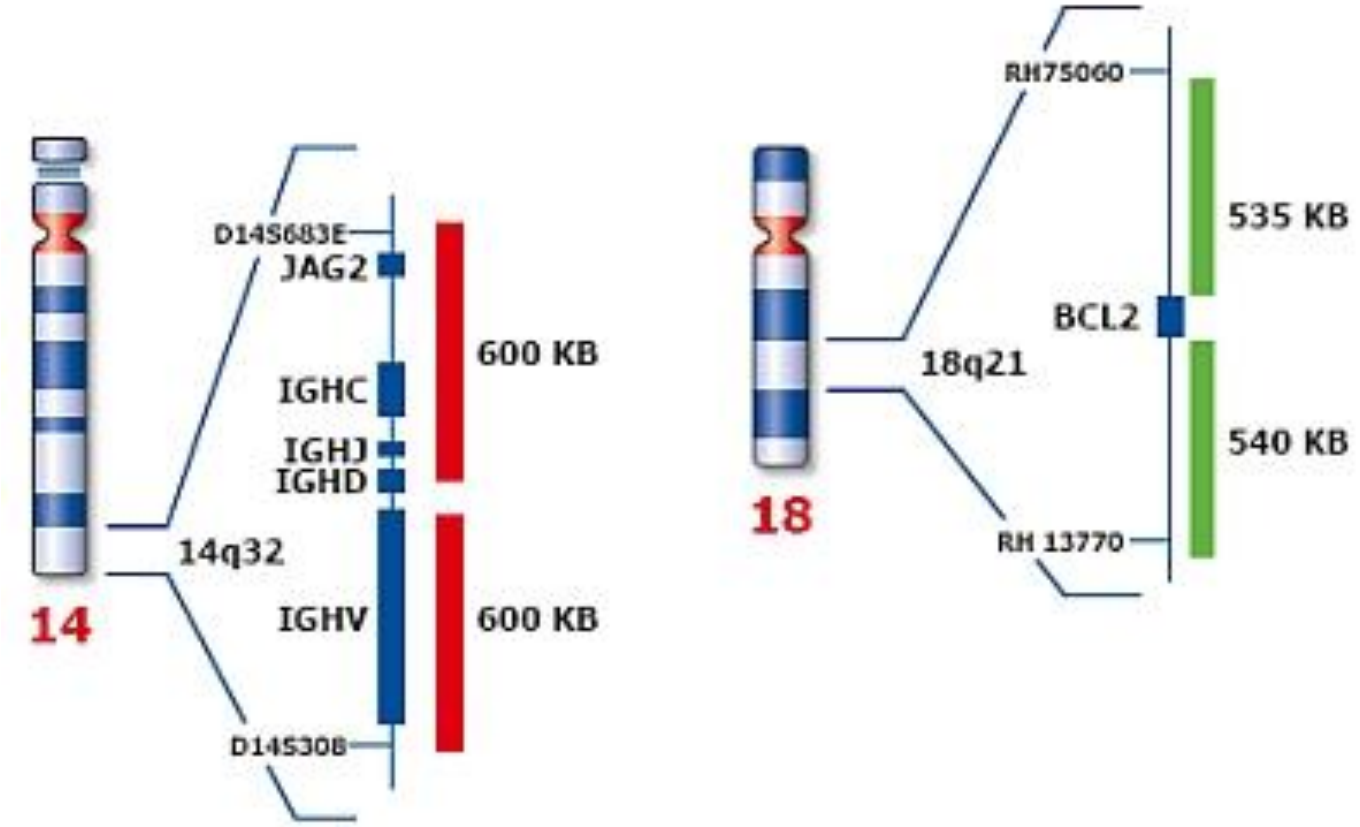
Mitochondrial pathway



FOLLICULAR LYMPHOMA

- t(14;18)= juxtaposition of BCL2 into the IgH heavy chain promotors

→ Blockage of apoptosis



HALLMARKS OF CANCER

5.

ANGIOGENESIS

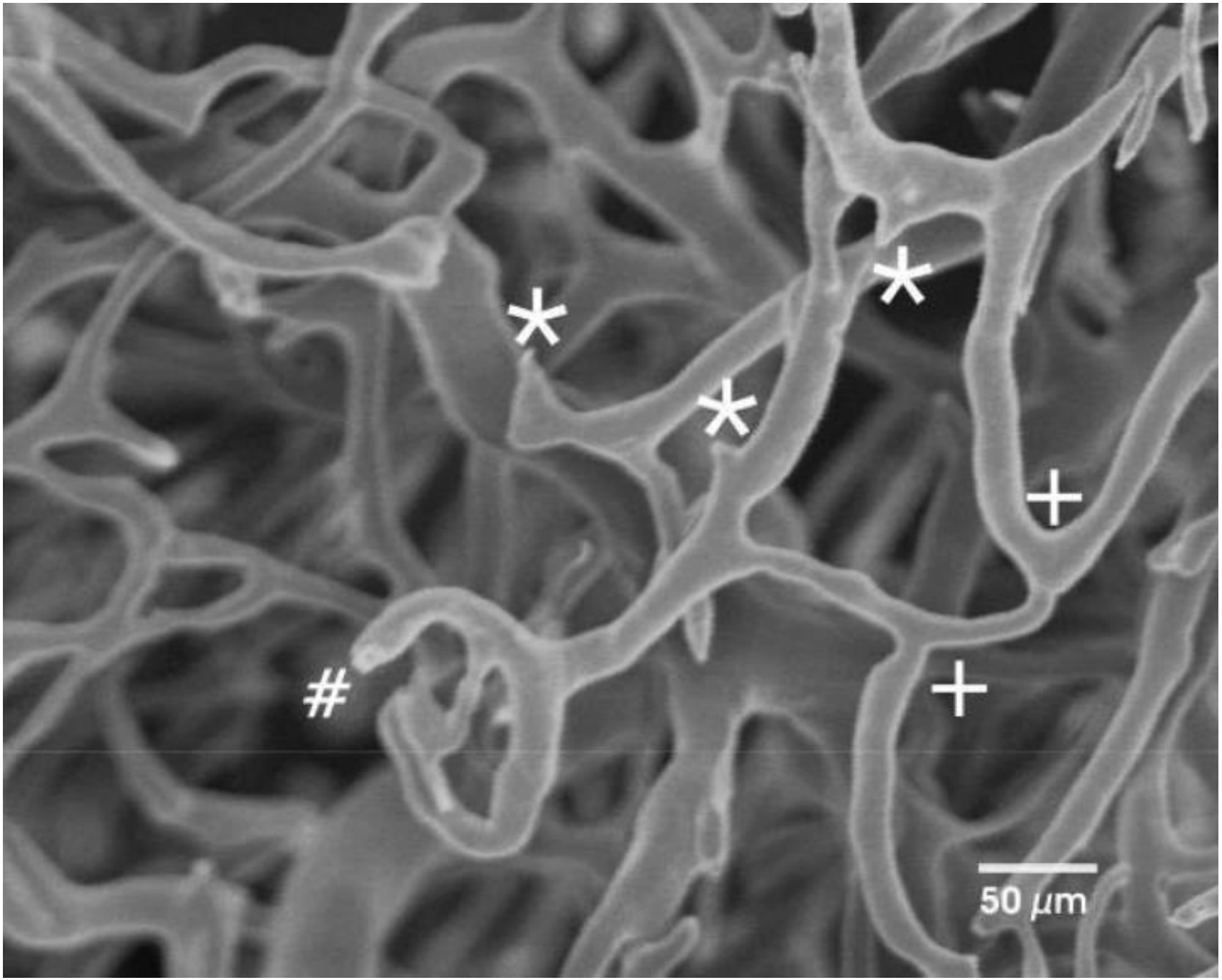
AND

NEOVASCULARISATION

ANGIOGENIC SWITCH

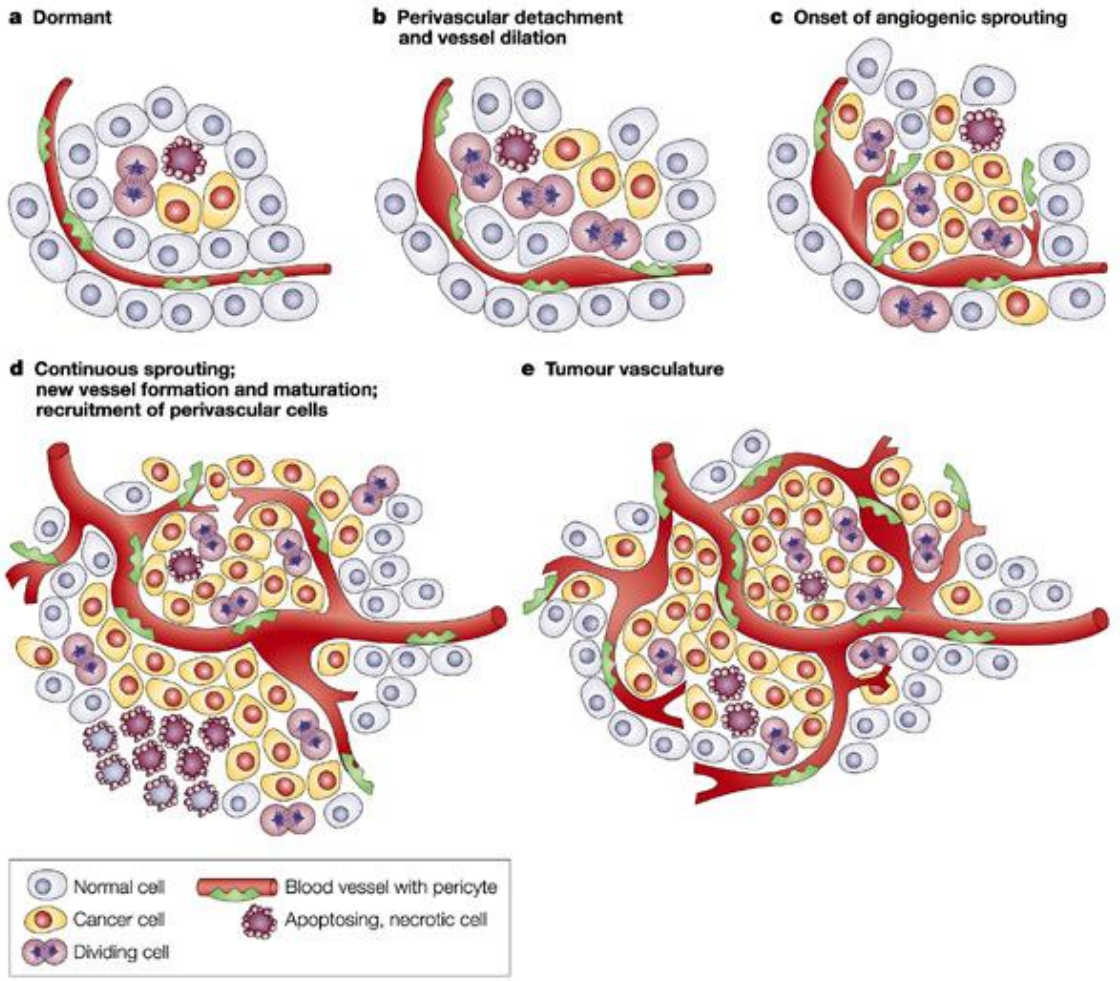
AND

ACQUIRED ABILITY TO GROW FURTHER


*
*
*
+
+
#
50 μm

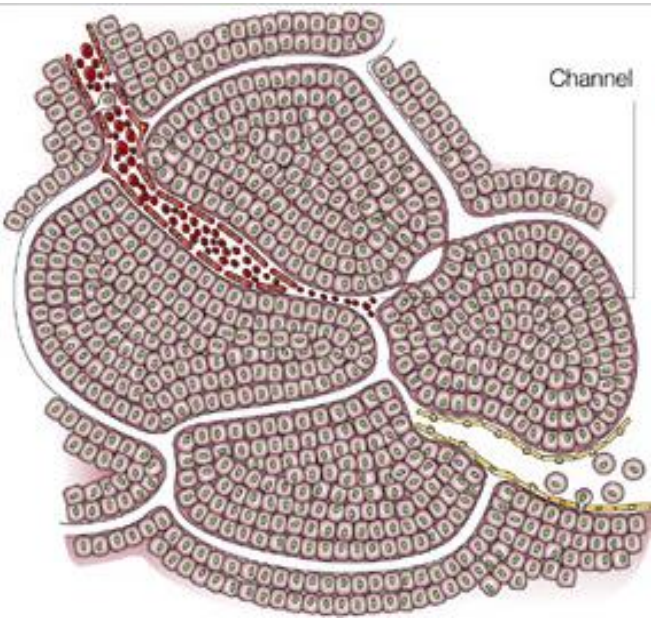
SPROUTING ANGIOGENESIS

Angiogenic switch = acquisition of angiogenic phenotype.

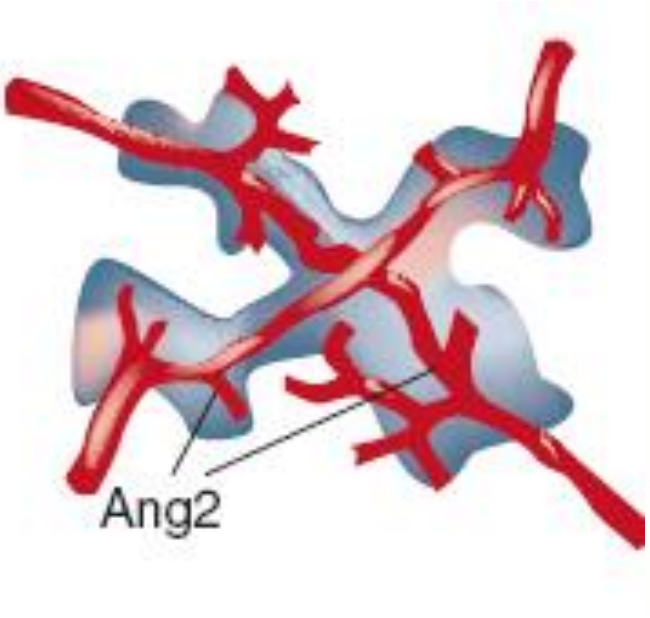


ALTERNATIVE MECHANISMS OF ANGIOGENESIS

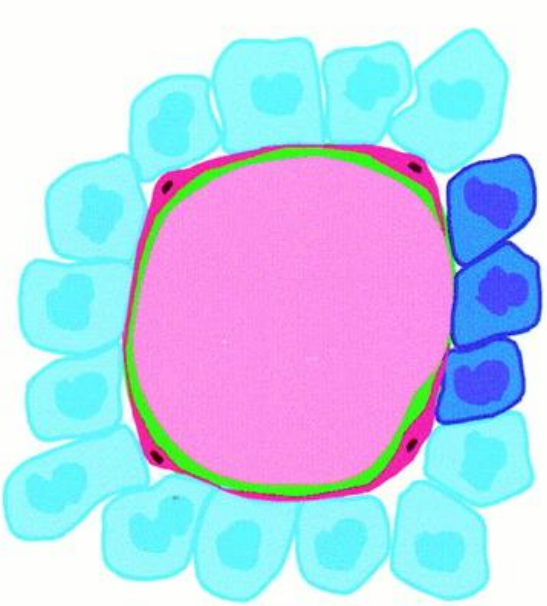
VASCULOGENIC MIMICRY



VESSEL CO-OPTION

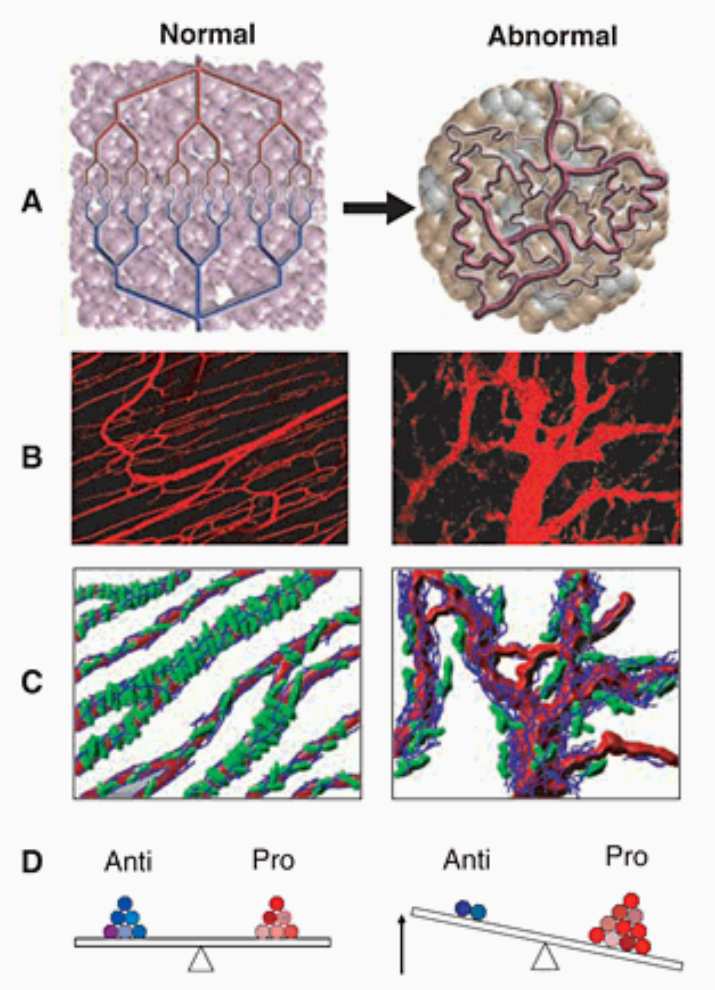


MOSAIC VESSELS



TUMOR VASCULATURE IS CHAOTIC

Tumor vasculature is chaotic, deregulated, desorganized, both structurally and functionally abnormal.



ANGIOGENIC FACTOR

Proangiogenic factors

VEGFs

Angiopoietins

Ephrins

FGFs

HGF

SDF-1

IL-8 atd.

Antiangiogenic factors

Thrombospondins

Angiostatin

Endostatin

BAI-1

Chondromodulin

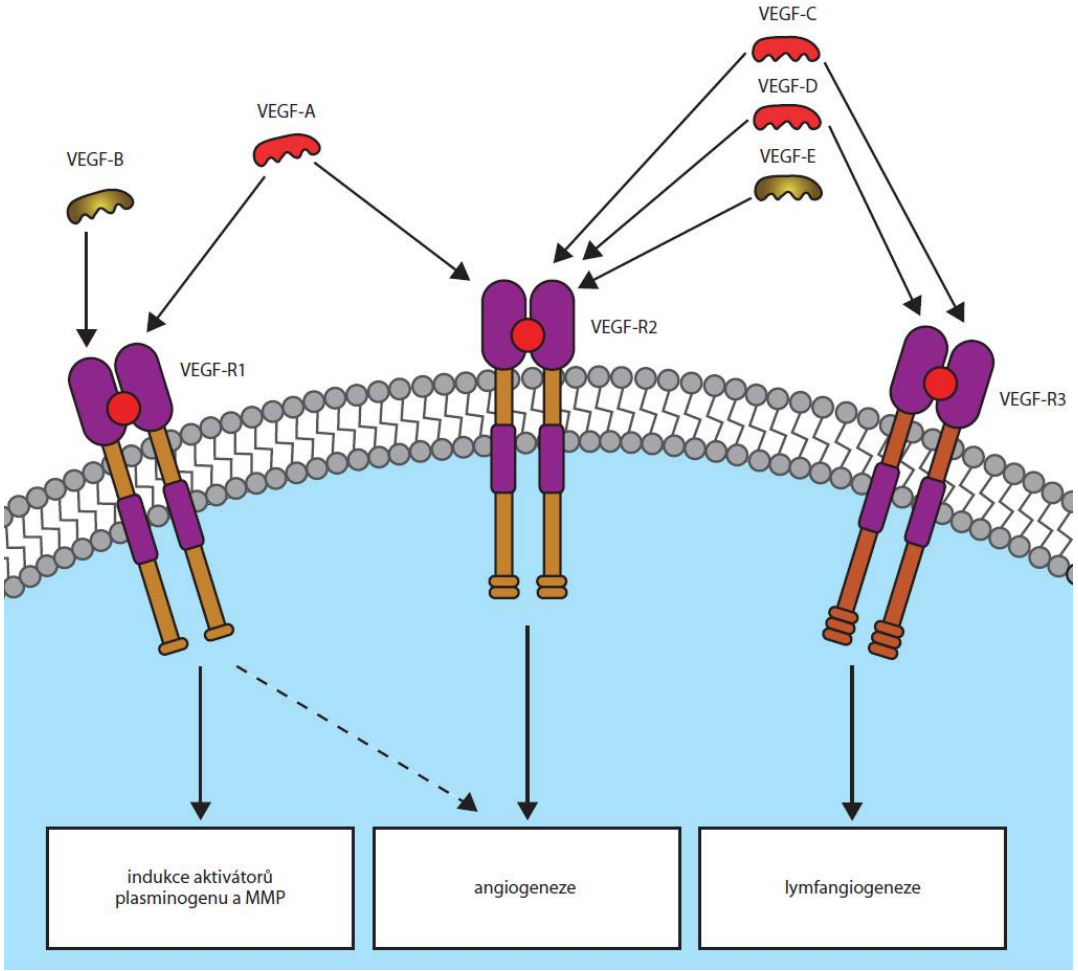
IP-10

PEDF atd.

VASCULAR ENDOTHELIAL GROWTH FACTORs

Hypoxia = the key factor that induces expression of VEGFs

Other factors that enhance expression of VEGFs = oncogenes



HALLMARKS OF CANCER

6.

ADHESION, INVASION

AND

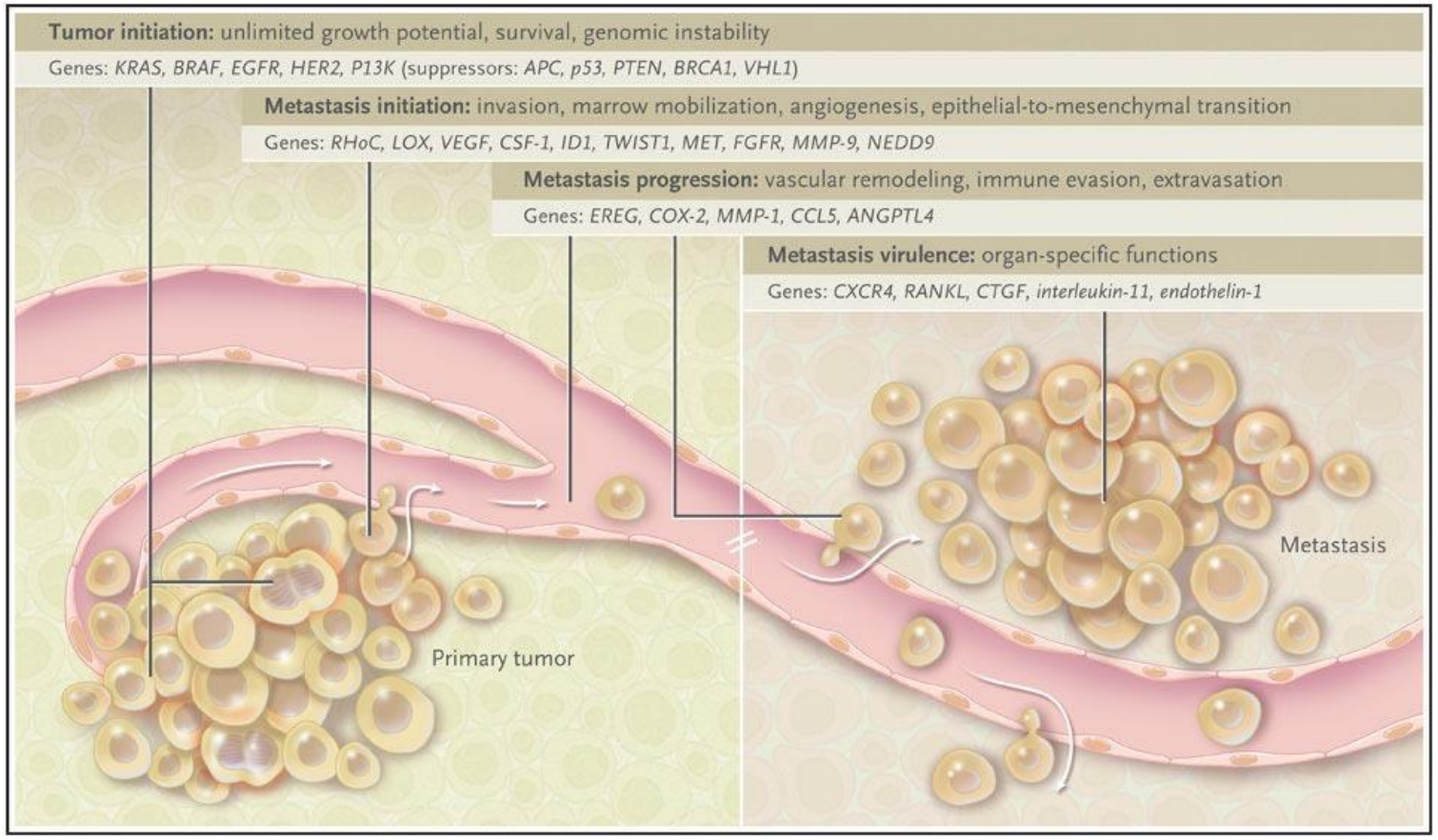
METASTASIS

METASTATIC SWITCH

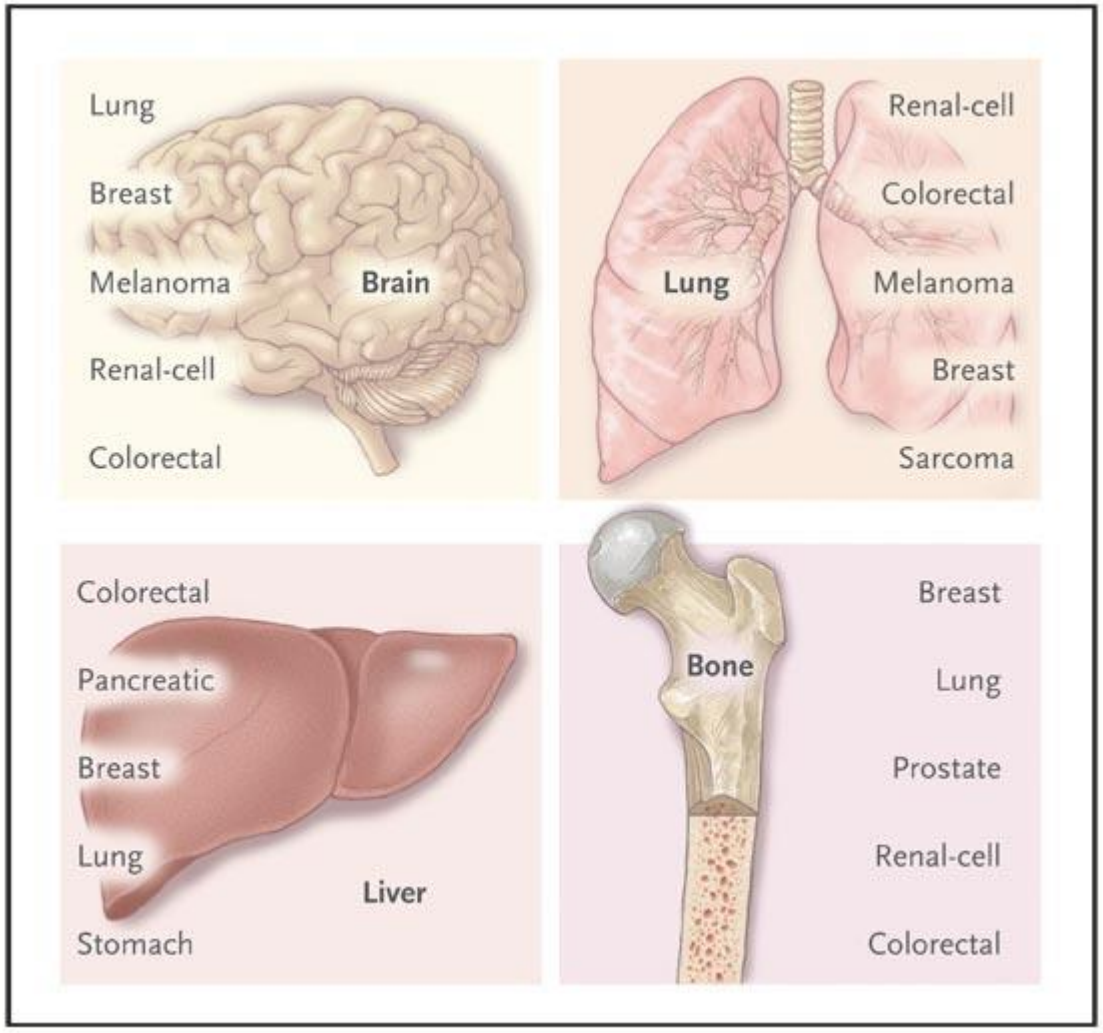
AND

ACQUIRED ABILITY TO SPREAD

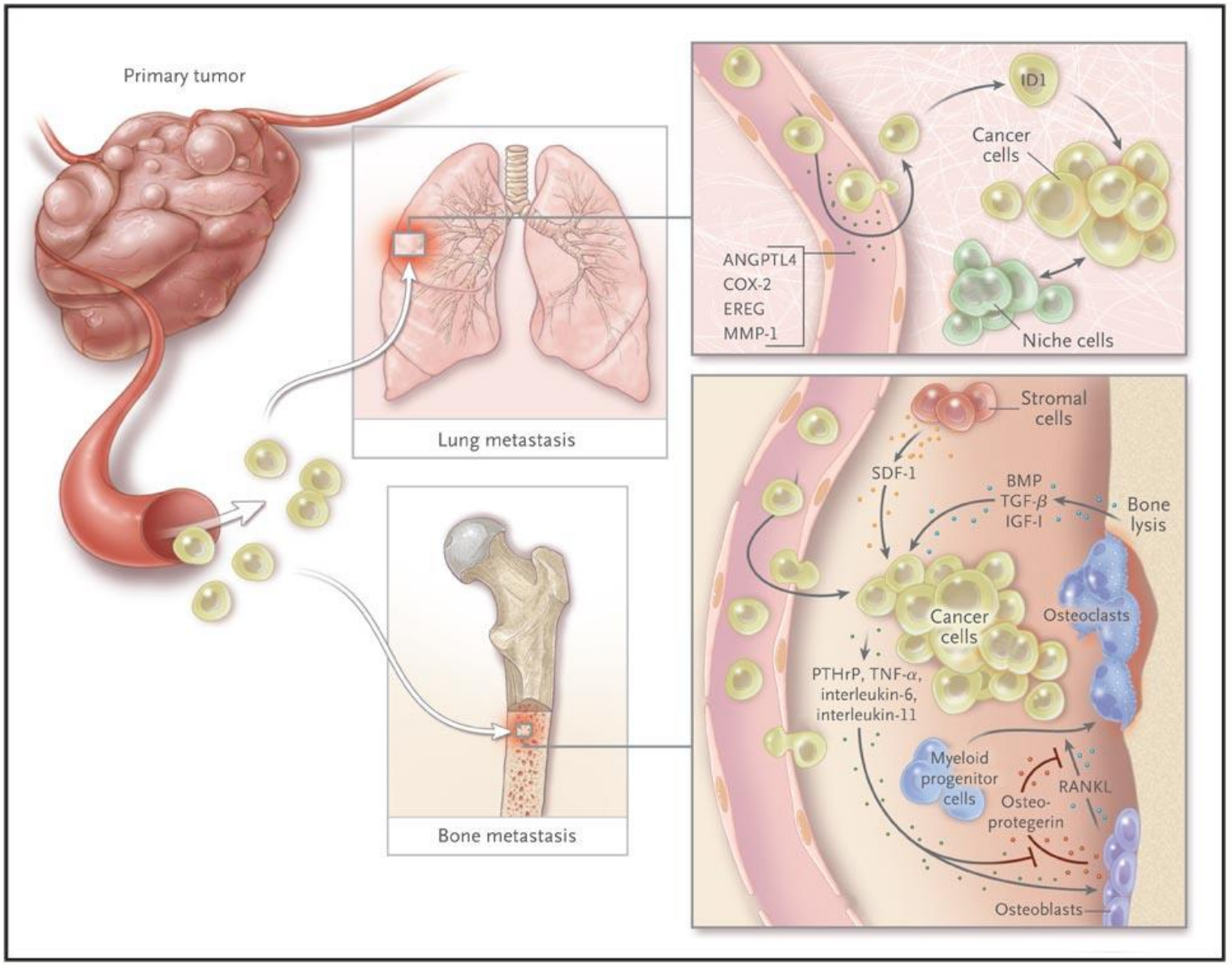
METASTATIC CASCADE



DIFFERENT TUMORS FORM METASTASES IN DIFFERENT ORGANS/TISSUES



A TUMOR FORMS METASTASES IN MULTIPLE ORGANS

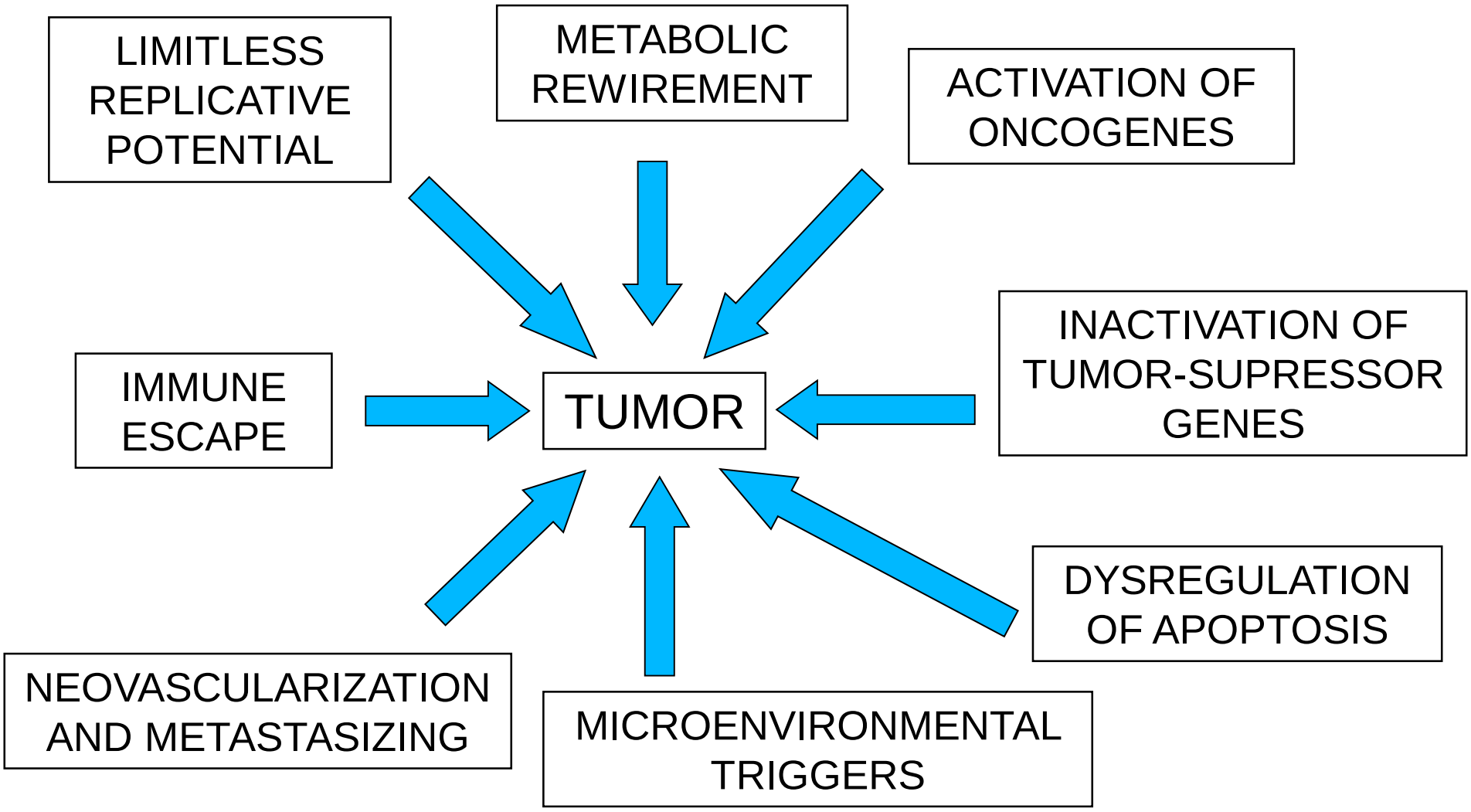


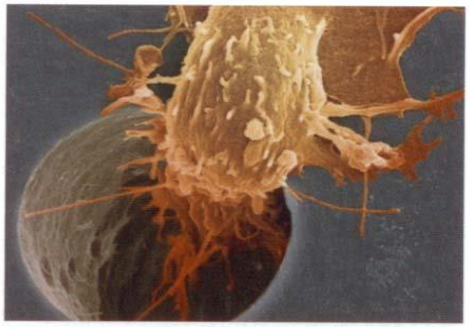
TUMORS FORM METASTASES IN MULTIPLE ORGANS

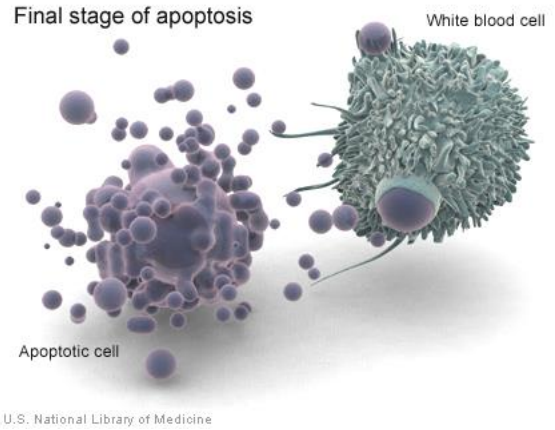
Specific sets of genes are responsible for metastasis initiation, others facilitate metastasis progression, while yet others are in charge of metastasis virulence.

Integrins, Matrix Metallo-Proteases (MMP), Transforming Growht Factor-beta (TGF-beta), Ephrin B, beta-Catenin

MALIGNANT TRANSFORMATION = A PROCESS







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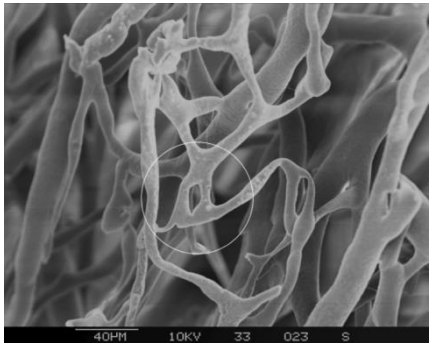

THANK YOU