Malignant transformation

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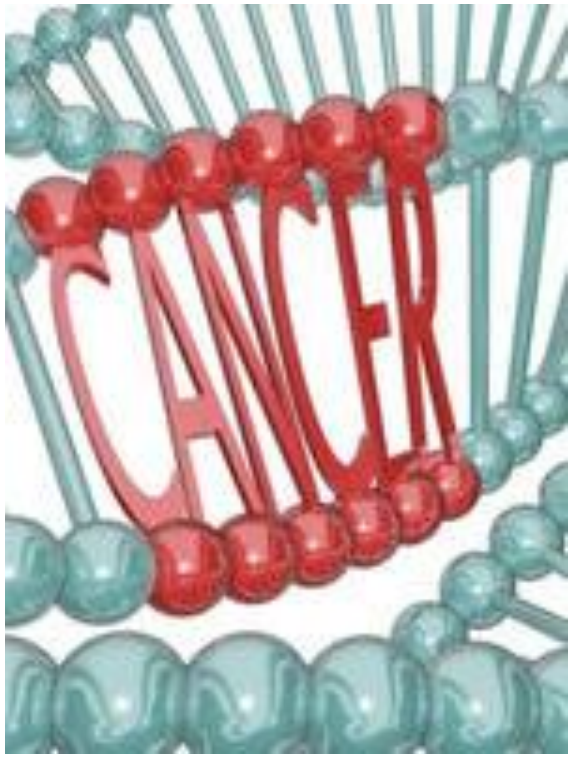
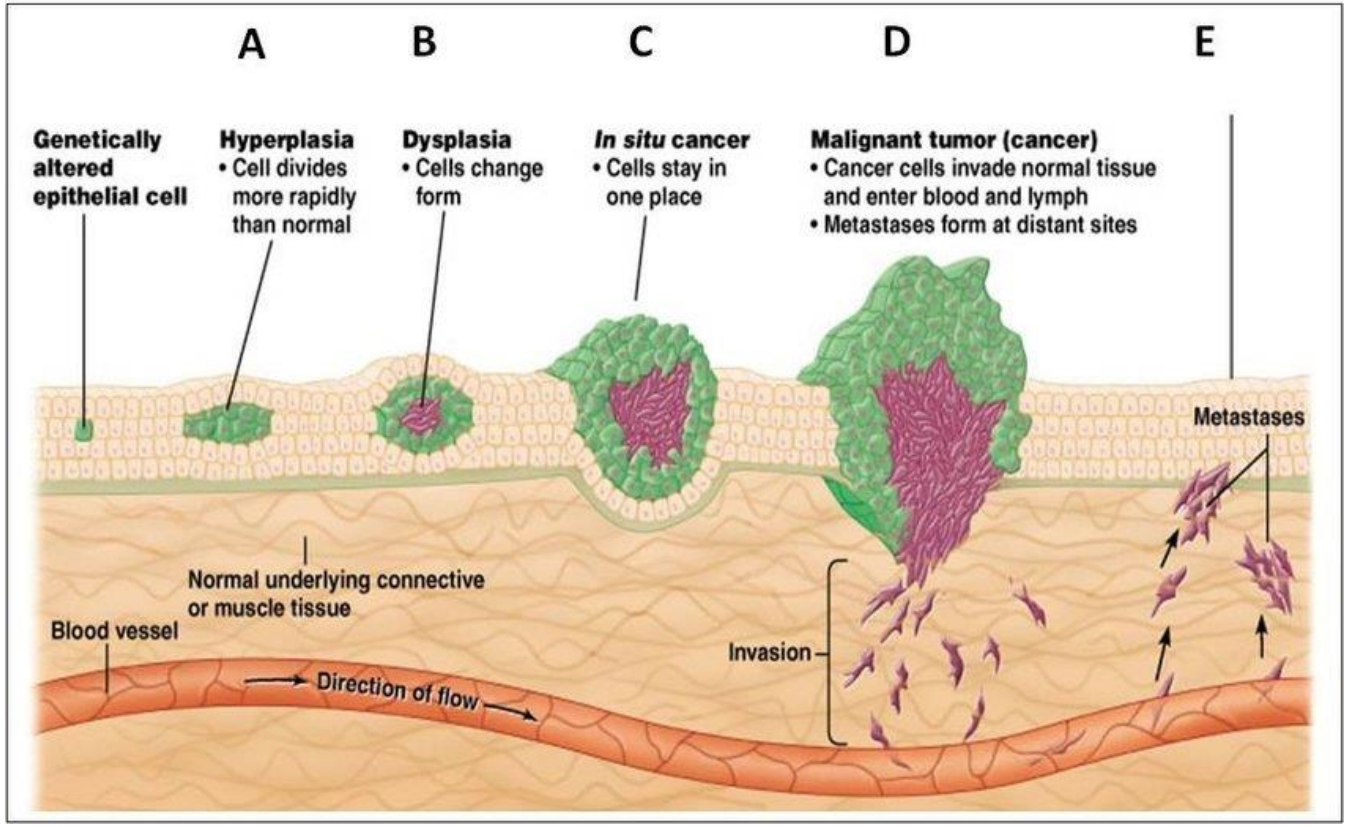
Topics

Stages of tumor development
Theories of cancerogenesis
Hallmarks of cancer
Oncogenes and tumor suppressors
Metastases
Interaction of tumor and organism
Cancer biomarkers



Tumor development

The process of tumor formation is a **complex** involving multiple alterations of cells/tissues and their physiologic control mechanisms.
The complexity of this process is reflected in the **long time periods** required for most human cancers to develop.
Multi-step tumor progression can be depicted as a form of **Darwinian evolution** occurring within tissues.



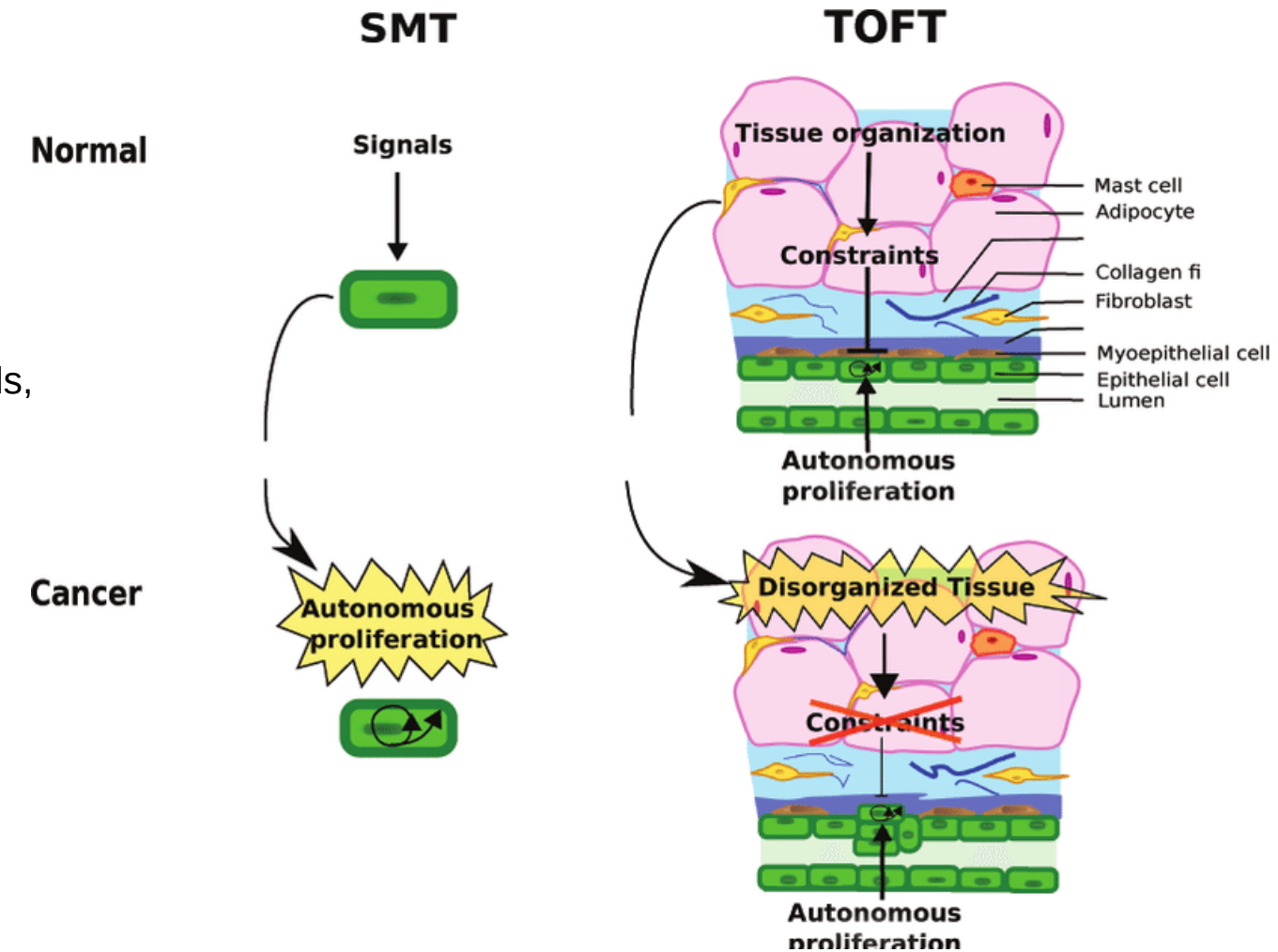
Theories of carcinogenesis

Somatic Mutation Theory (SMT)

- Changes in the DNA of the founder cell make this cell unable to control its proliferation.

Tissue Organization Field Theory (TOFT).

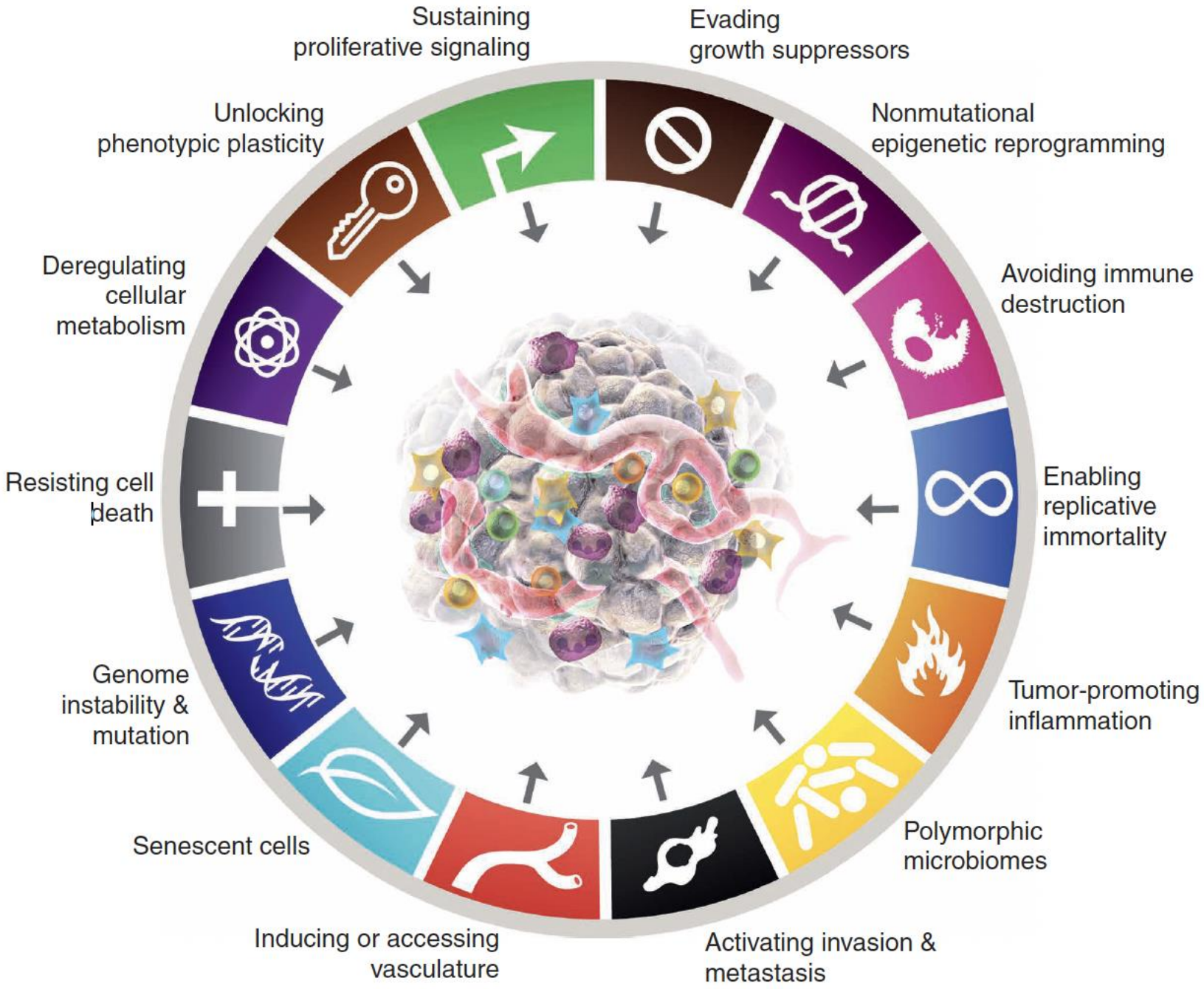
- Carcinogenesis is “development gone awry.”
- Normal tissue blocks the proliferation and motility of cells, leading to tissue homeostasis.
- Carcinogenesis is characterized by a disruption of the normal tissue organization that leads to the loss of constraints and subsequent cell proliferation and cell invasion.
- Abnormal tissue architecture.
- Significant role of the microenvironment.
- DNA mutations are less significant.



Enabling characteristics of cancer

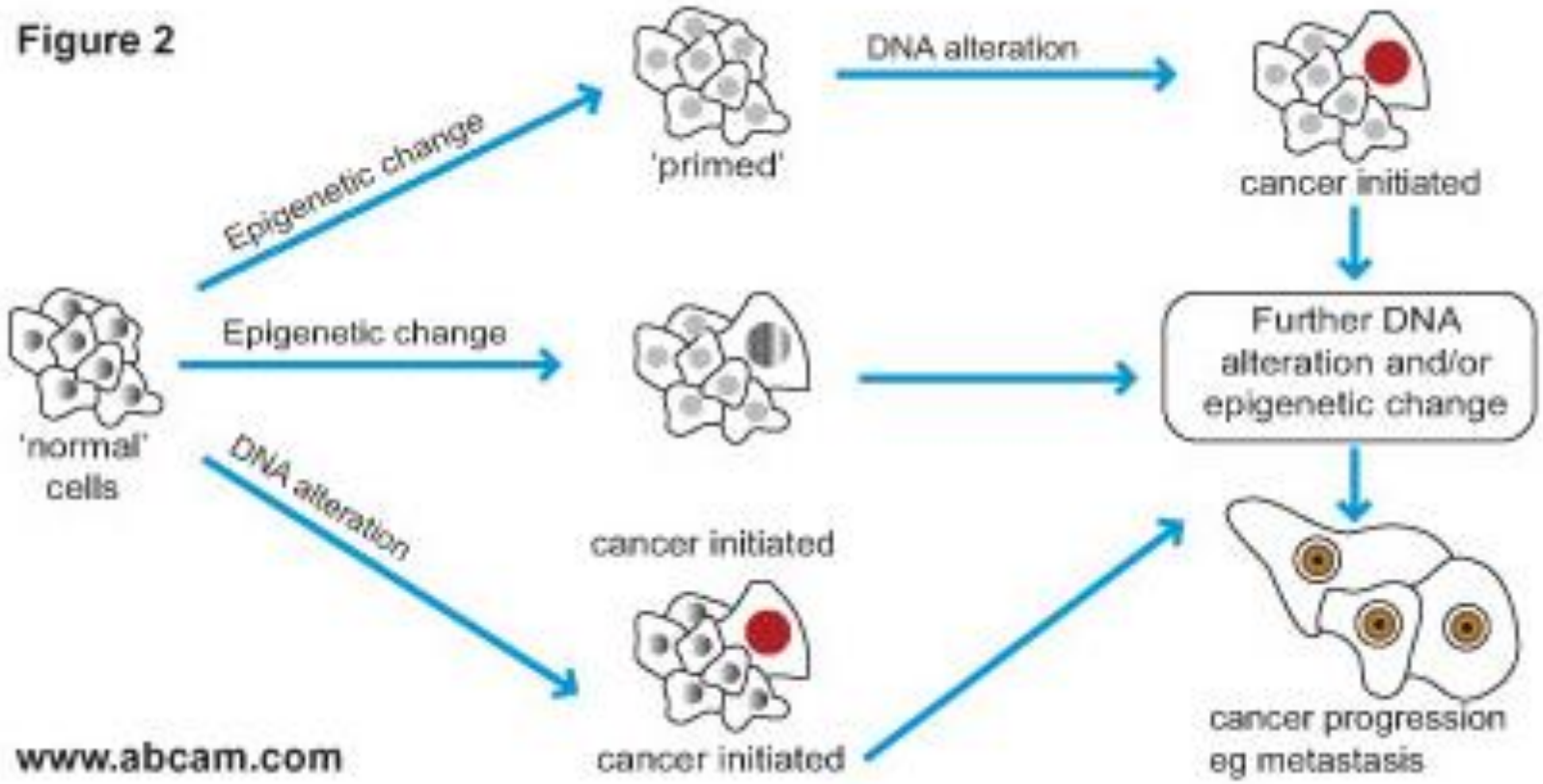
and cancer hallmarks

- Genomic instability
- nonmutational epigenetic reprogramming
- Tumor-promoting inflamation



Genomic instability and nonmutational epigenetic reprogramming

- **Genetic alterations** can appear due to internal errors during DNA replication and cell division or as a consequence of exposure to external factors (**carcinogens**)
- physical – e.g. UV and ionizing light
- chemical – organic substances, toxins, heavy metals
- biologic – some RNA and DNA viruses
- **Epigenetic alterations** can contribute to the acquisition of hallmark capabilities during tumor development and malignant progression.
- hypoxia-mediated epigenetic changes
- the acidic tumor microenvironment-mediated epigenetic changes
- extracellular matrix (ECM) motifs or ECM stiffness-induced signaling



Genomic instability–new oportunities for evolution

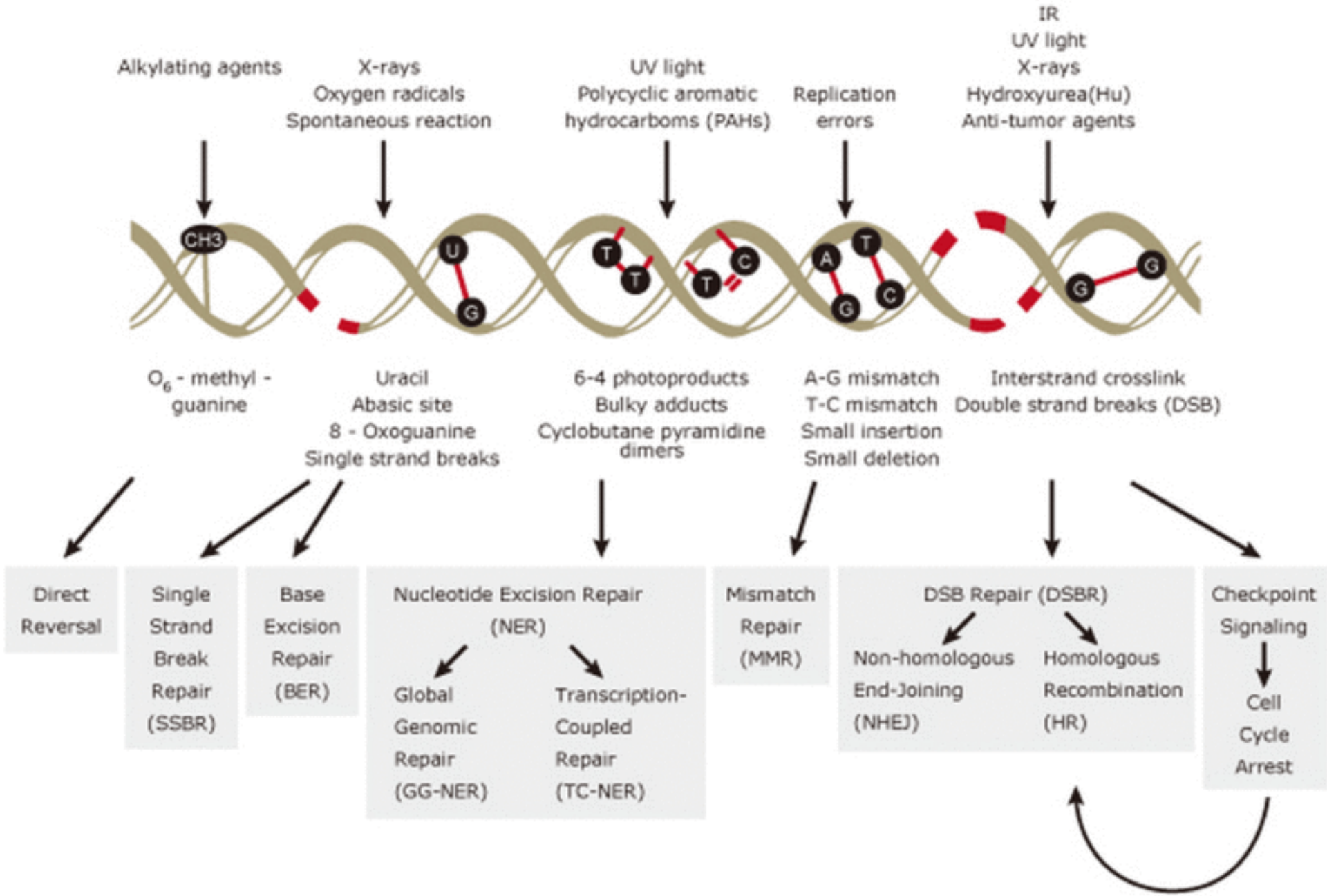
- **DNA damage** may predispose individuals to increased tumorigenesis.
- An **increase of copy number of chromosomes** or genes allows cells to overexpress certain genes or mutate the extra copies to acquire growth, survival, or invasion ability.
- Genomic instability is a characteristic of most cancer cells due to **over-replication**.
- Excessive DNA damage is associated with problems in DNA replication (broken chromosomes and aneuploidy).
- Genomic integrity is closely monitored by several surveillance mechanisms, DNA damage checkpoint, DNA repair machinery, and the mitotic checkpoint.
- DNA methylation status is also important for genomic integrity.

DNA repair genes/proteins

MMR genes/proteins (“Mismatch repair”)
defect in respective genes leads to the microsatellite instability (MSI). Variable length of microsatellites (e.g. (CA)n repetition) leads to the DNA replication errors. MSI is most prevalent in colon cancers.

Nucleotide excision repair genes/proteins (“single strand break repair”)
NER-defects cause xeroderma pigmentosum (XP). XP patients show severe sun sensitivity and develop skin cancers during childhood.

Genes/proteins of homologous recombination (“ double strand break repair ”)
BRCA1 and **BRCA2** "breast cancer susceptibility genes"
ATM and **ATR** (ATM-related) kinases ("mutated in ataxia-telangiectasia")


Alkylating agents
X-rays
Oxygen radicals
Spontaneous reaction
UV light
Polycyclic aromatic
hydrocarboms (PAHs)
Replication
errors
IR
UV light
X-rays
Hydroxyurea(Hu)
Anti-tumor agents
CH3
U
G
T
T
T
C
A
T
G
C
G
G
O6 - methyl -
guanine
Uracil
Abasic site
8 - Oxoguanine
Single strand breaks
6-4 photoproducts
Bulky adducts
Cyclobutane pyramidine
dimers
A-G mismatch
T-C mismatch
Small insertion
Small deletion
Interstrand crosslink
Double strand breaks (DSB)
Direct
Reversal
Single
Strand
Break
Repair
(SSBR)
Base
Excision
Repair
(BER)
Nucleotide Excision Repair
(NER)
Global
Genomic
Repair
(GG-NER)
Transcription-
Coupled
Repair
(TC-NER)
Mismatch
Repair
(MMR)
DSB Repair (DSBR)
Non-homologous
End-Joining
(NHEJ)
Homologous
Recombination
(HR)
Checkpoint
Signaling
Cell
Cycle
Arrest

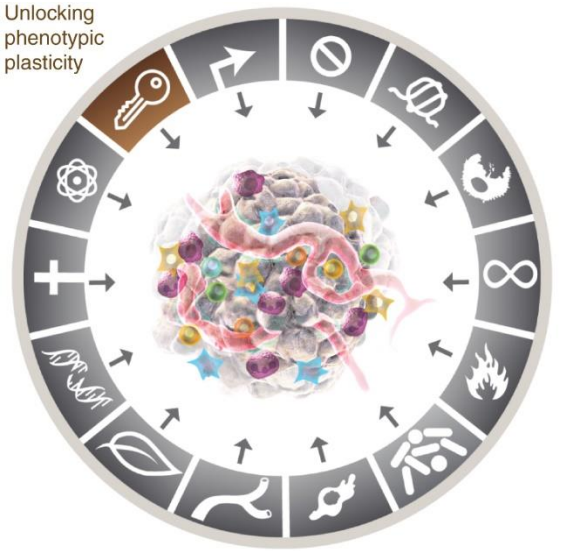
Unlocking phenotypic plasticity

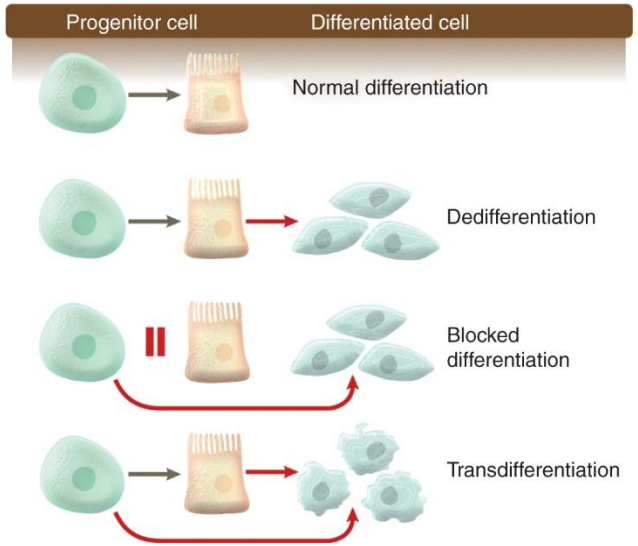
Disruptions of cellular differentiation

Dedifferentiation from mature to progenitor states.
Suppressed expression of the *MITF* master regulator of melanocyte differentiation is involved in the genesis of aggressive forms of malignant melanoma.

Blocked (terminal) differentiation from progenitor cell states
Acute promyelocytic leukemia can result from a chromosomal translocation that fuses the promyelocytic leukemia protein locus (PML) with the gene encoding the retinoic acid α nuclear receptor (RARα). Myeloid progenitor cells bearing such translocations are unable to differentiate into granulocytes, resulting in cells trapped in a proliferative, promyelocytic progenitor stage.

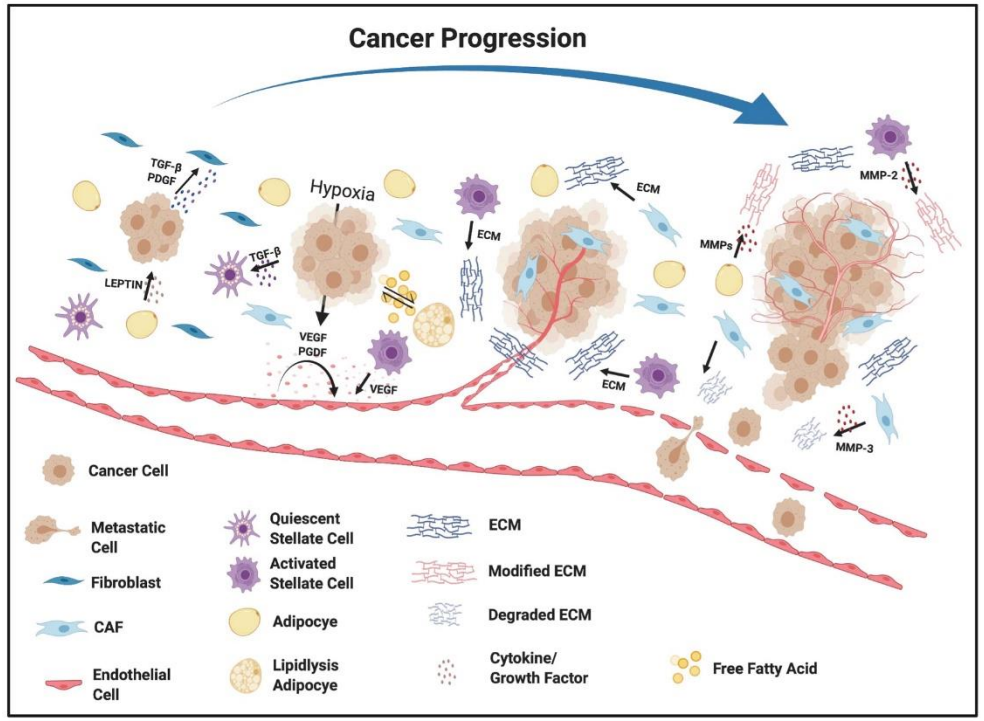
Transdifferentiation into different cell lineages.
The pancreatic acinar cells can become transdifferentiated into a ductal cell phenotype during the initiation of neoplastic development.

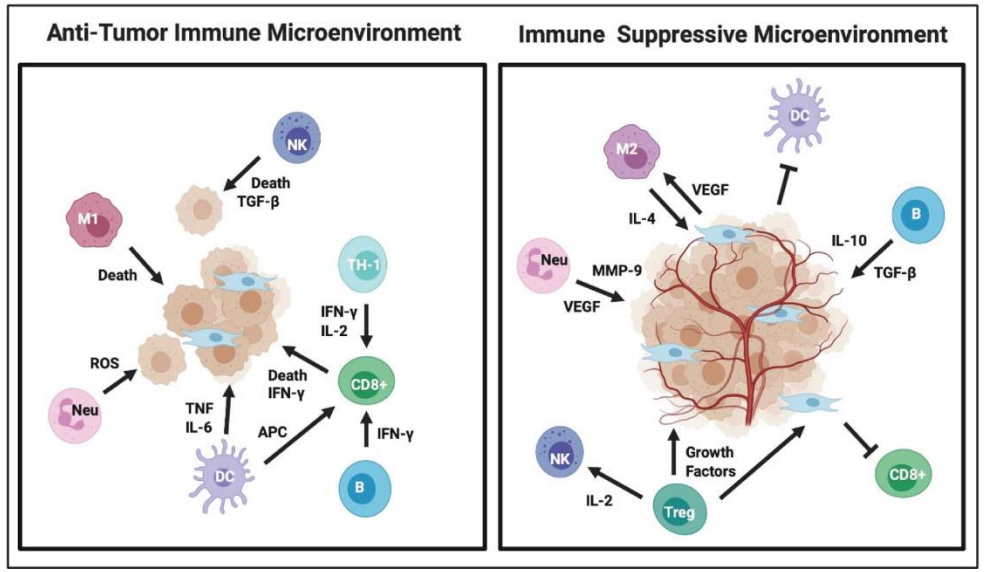




Tumor microenvironment

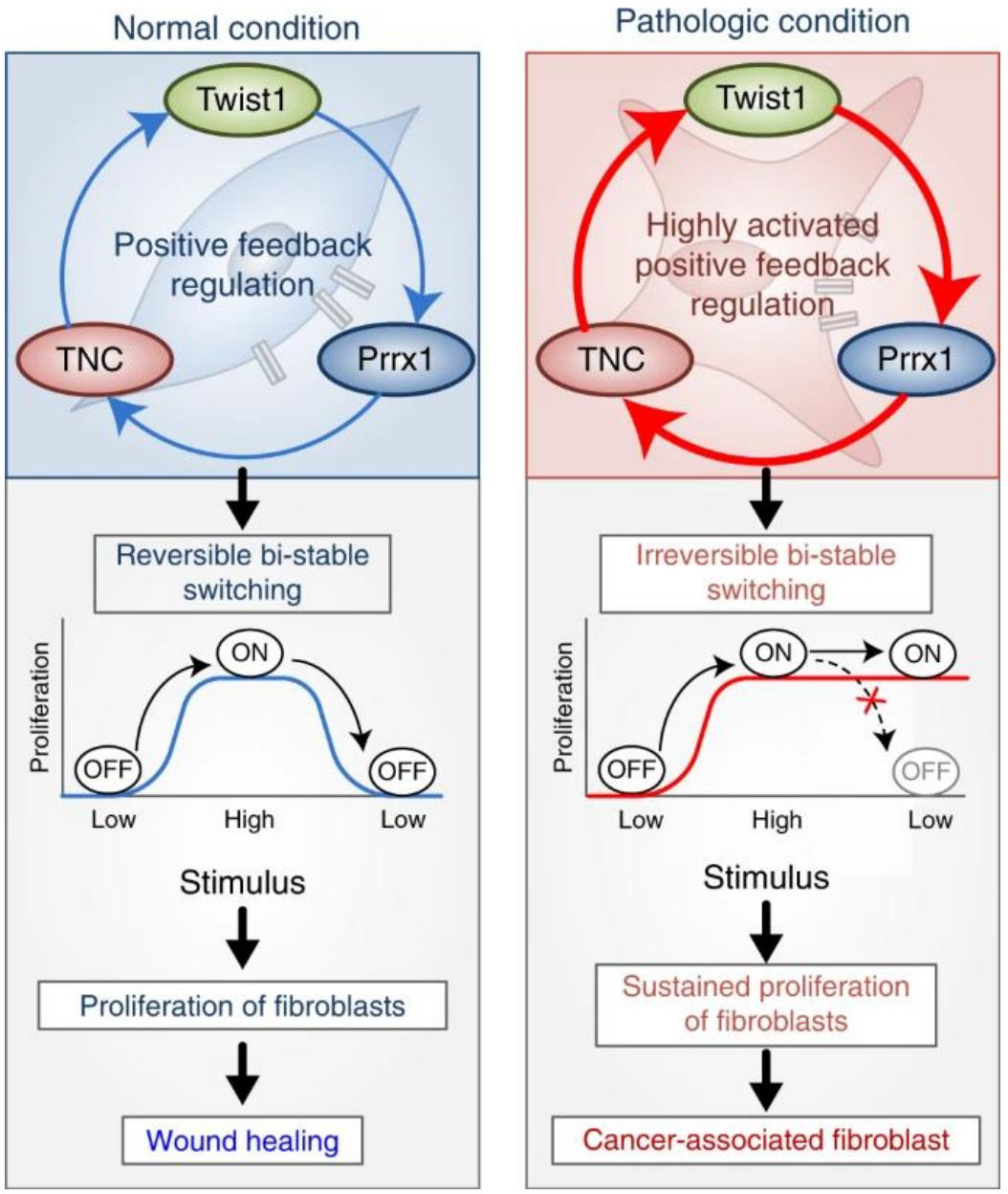
- Early in tumor growth, a dynamic and **reciprocal relationship** develops between cancer cells and components of the tumor microenvironment.
- Tumor cells **stimulate** significant molecular, cellular and physical changes within their **host** tissues to support tumor growth and progression.
- **Cancer cells recruit stromal cells** from neighboring tissue during tumorigenesis.
- **TME includes immune cells, stromal cells, blood vessels, and extracellular matrix (ECM) and can have anti-tumor or pro-tumor effects.**
- The stromal cell composition varies between tumor types but includes endothelial cells, fibroblasts, adipocytes, and stellate cells. The TME orchestrates **angiogenesis, proliferation, invasion, and metastasis** through the **secretion of growth factors and cytokines.**
- The tumor ECM is typically characterized by **increased cross-linking and density**, enzymatic modifications, and altered molecular composition, which collectively orchestrate—in part via **integrin receptors for ECM motifs—stiffness-induced signaling** and gene-expression networks that elicit invasiveness and other hallmark characteristics.
- **Acidic metabolic waste** products accumulate in the tumor microenvironment because of high metabolic activity and insufficient perfusion. The pH of TME influences cancer and stromal cell function, their mutual interplay, and their interactions with the ECM.





Inflammation

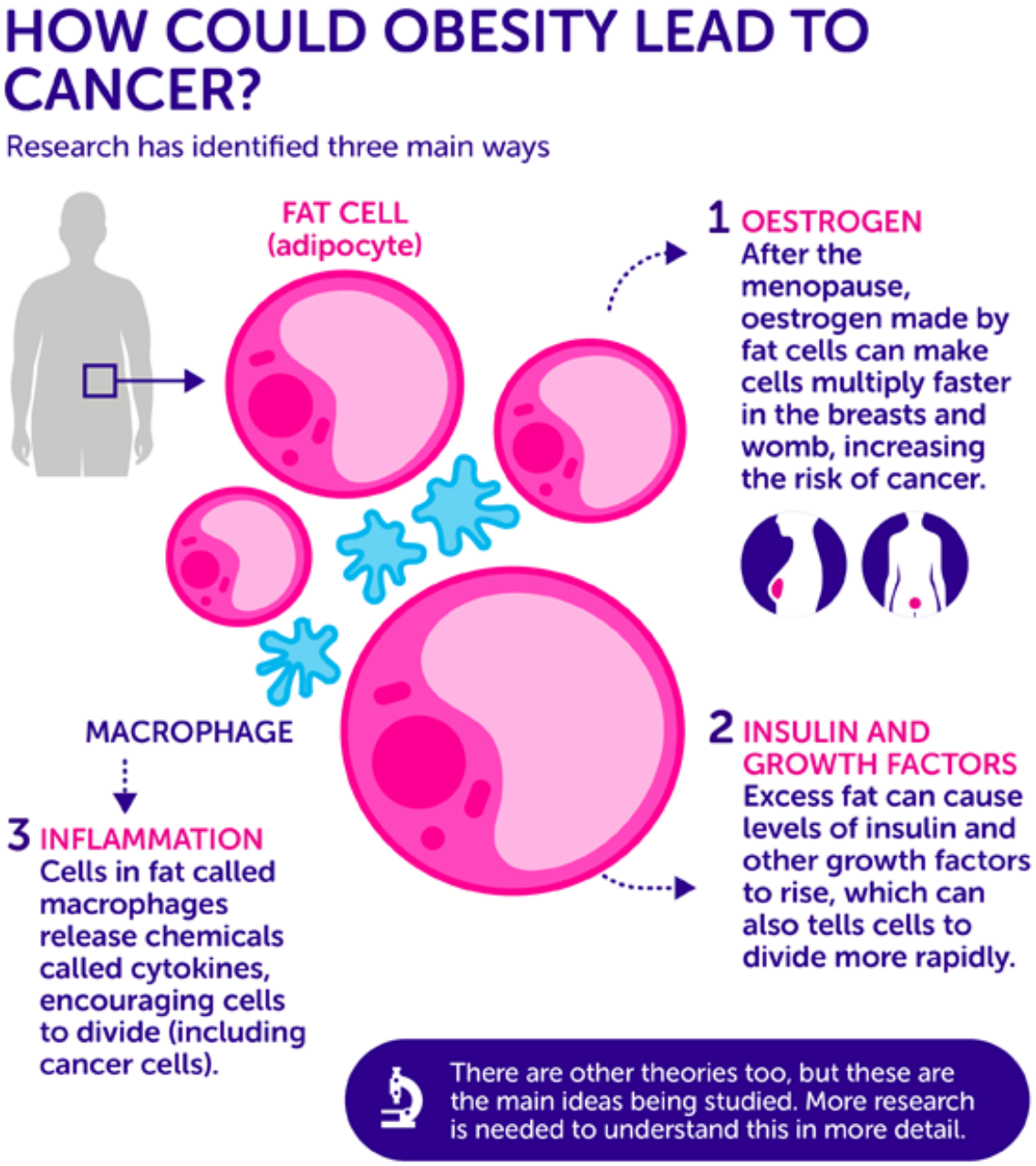
- There are important similarities between tumors and the inflammatory response associated with wound healing
- “**Tumors: Wounds that do not heal**”
- Many cancers arise from sites of infection, chronic irritation, and inflammation.
- Chronic inflammation can cause DNA damage and permanent activation of fibroblasts.



Under normal conditions, the positive feedback loop (PFL) acts as a reversible bistable switch by which the activation of fibroblasts is "ON" above a sufficient level of stimulation and "OFF" for the withdrawal of the stimulus. However, this switch can be permanently turned on under pathologic conditions by continued activation of the PFL, resulting in sustained proliferation of fibroblasts

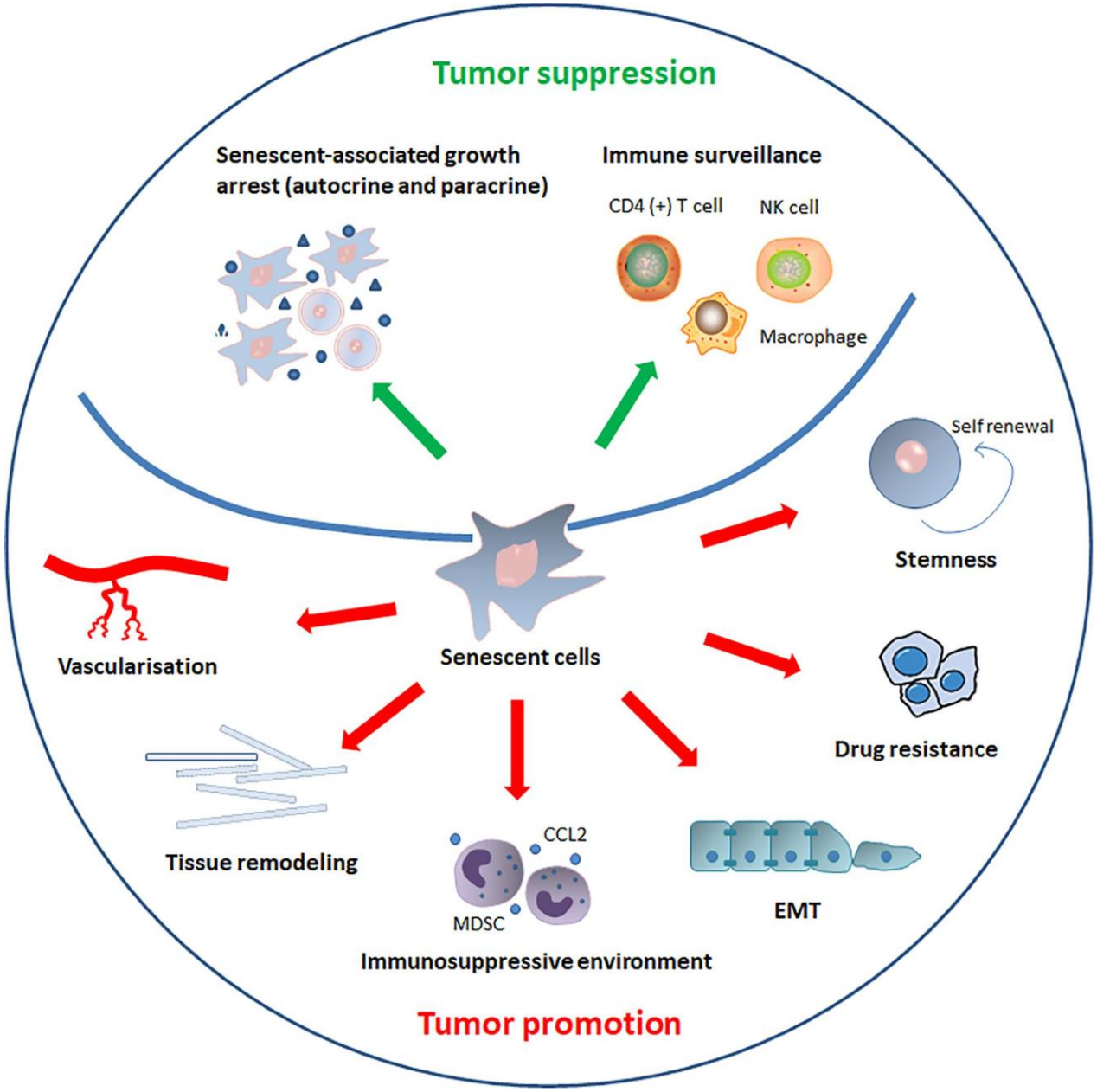
Inflammation and obesity

- As people become obese more fat cells are build up in their tissues and macrophages are recruited to clear up dead fat cells. The number of macrophages in obese fatty tissue can be substantial–**four in 10 cells.**
- Macrophages release cocktail of cytokines that can trigger chronic inflammation.
- Obese people tend to have higher levels of inflammatory cytokines in their blood.
- **Fat isn't just padding: it's like another organ it is essentially a huge gland** sending out biological information that affect the rest of body. Oestrogen and growth factors produced by fat cells increase the risk of cancer.



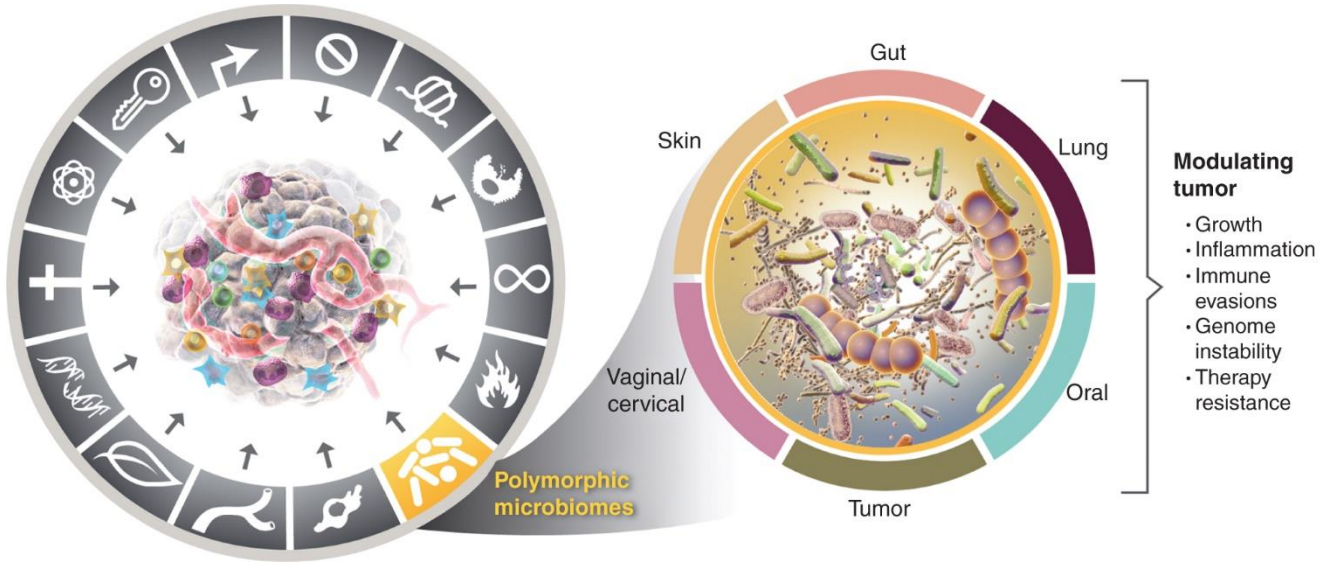
Senescent cells

- In addition to shutting down the cell cycle, the senescence program evokes **changes in cell morphology and metabolism** and, most profoundly, the activation of a **senescence-associated secretory phenotype** (SASP) involving the release of a plethora of bioactive proteins, including chemokines, cytokines, and proteases.
- SASP components can directly or indirectly promote **tumor cells growth, invasion and metastasis by promoting tumor vascularization, maintaining stem-cell features, creating an immunosuppressive environment, remodeling tissue structure, inducing drug resistance, and stimulating epithelial-mesenchymal transition** (EMT).



Polymorphic microbiomes

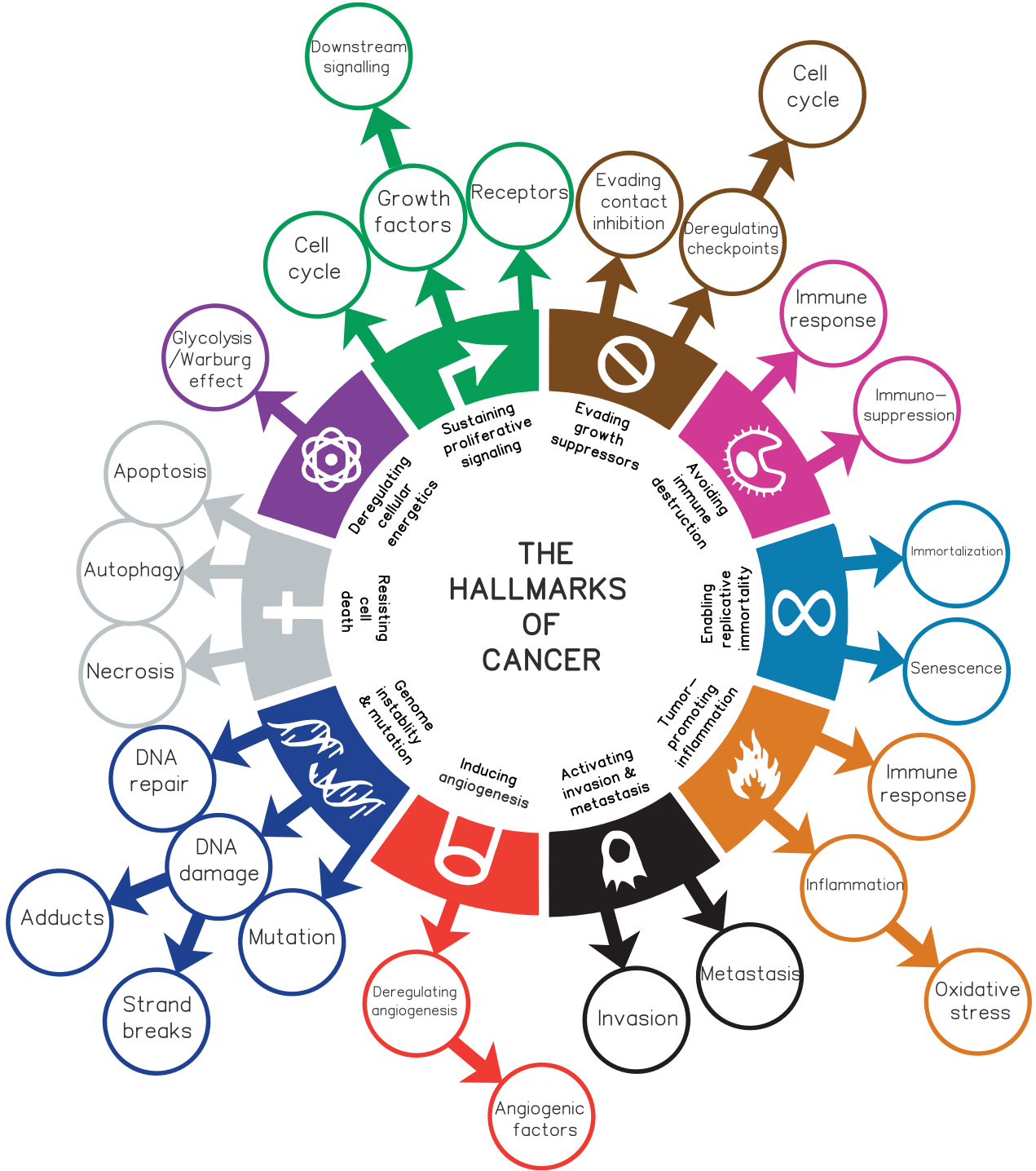
- For cancer, the evidence is increasingly compelling that polymorphic variability in the **microbiomes between individuals** in a population can have a profound impact on cancer phenotypes.
- There are both **cancer-protective and tumor-promoting microbiomes**, involving particular bacterial species, which can modulate the incidence and pathogenesis of tumors.
- A mouse model of colon carcinogenesis populated with bacteria *Porphyromonas* developed more tumors than mice lacking such bacteria.



Hallmarks of cancer

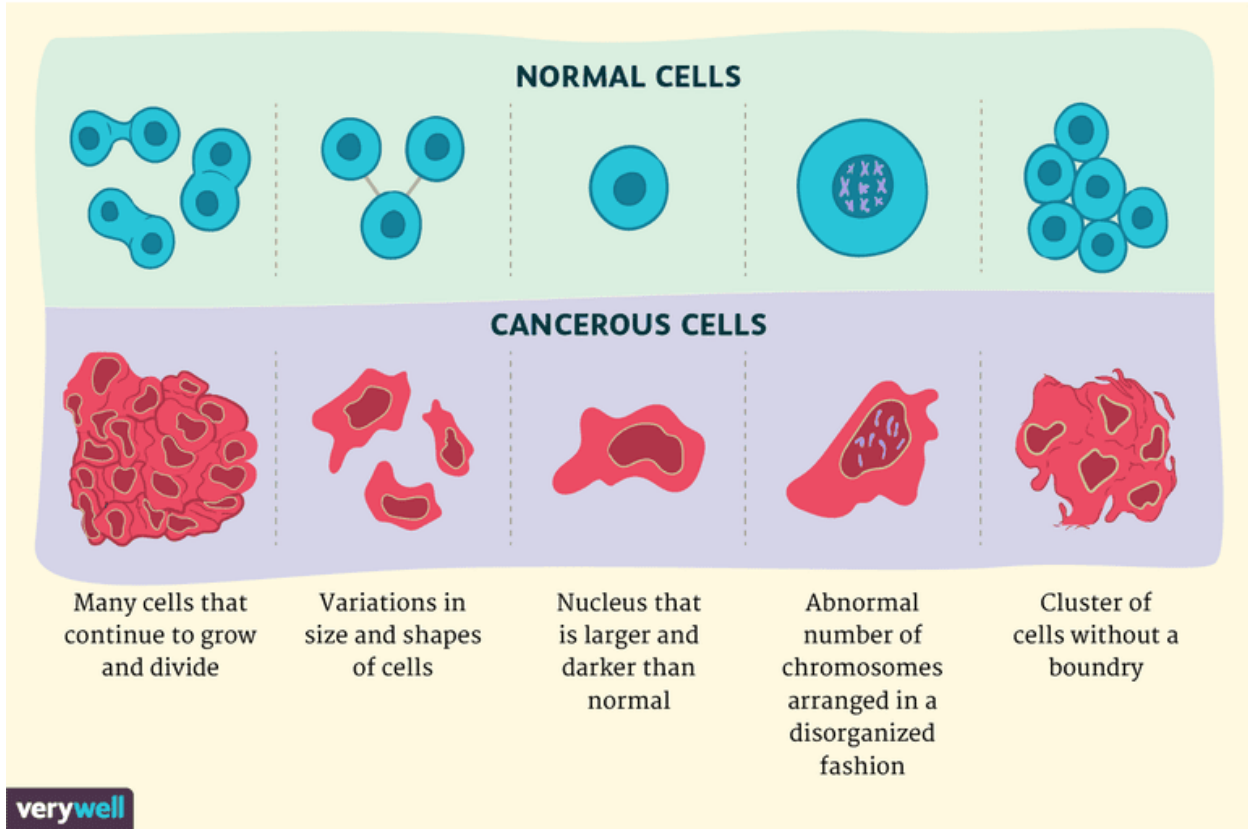
- Continual unregulated proliferation of cancer cells (sustaining proliferative signaling and evading growth suppressors)
- Replicative immortality
- Genome instability
- Resisting cell death and senescence
- Inducing angiogenesis
- Inflammation
- Avoiding immune destruction
- Altered metabolism
- Invasion and metastasis

- All these features do not have to be newly evolved, because they are part of physiological processes such as embryogenesis and wound healing. Cancer cells only use these processes in wrong intensity, time, and place. **Cancer is a disease of regulation.**



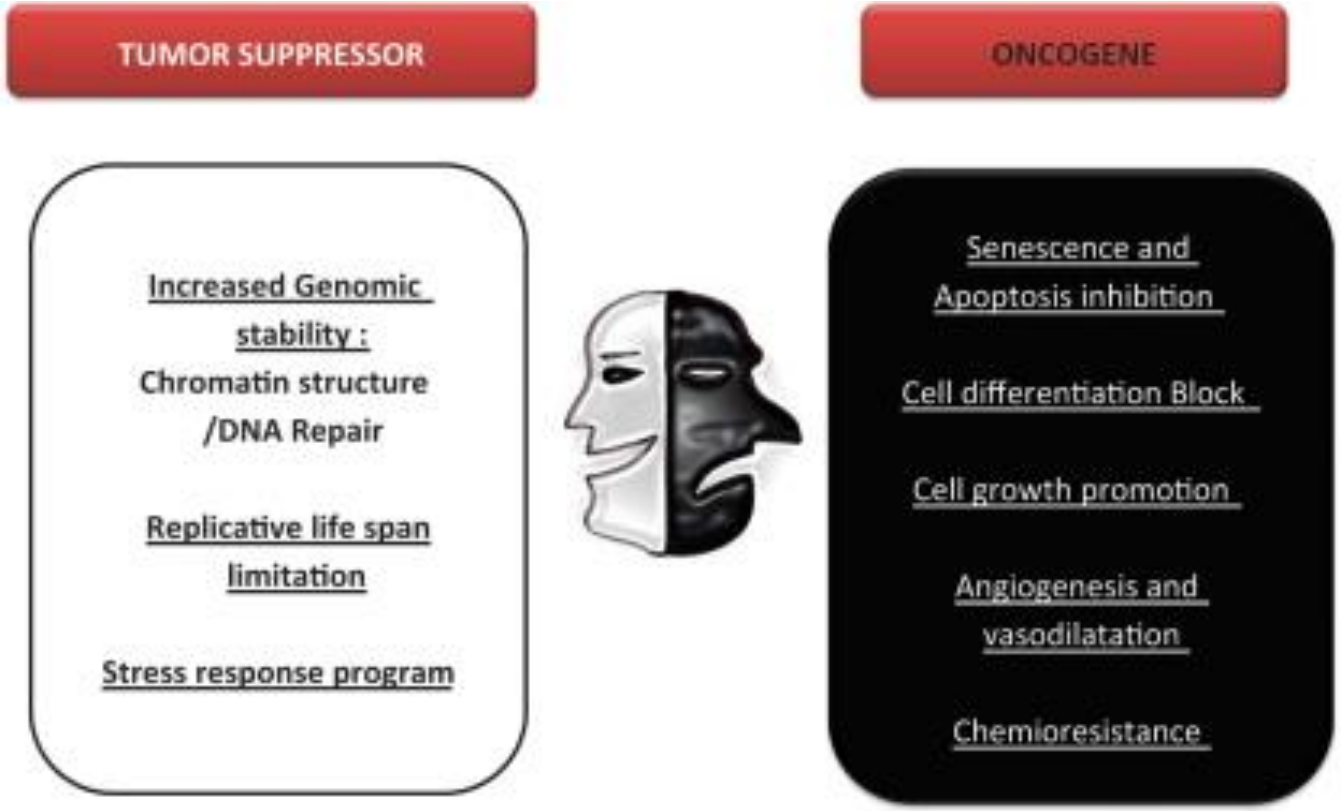
Cancer cell

Cancer cells divide excessively - they have too many “GO” signals or not enough “STOP” signals and can also ignore “DIE”, “ DIFFERENTIATE “, or “GROW OLD” signals.

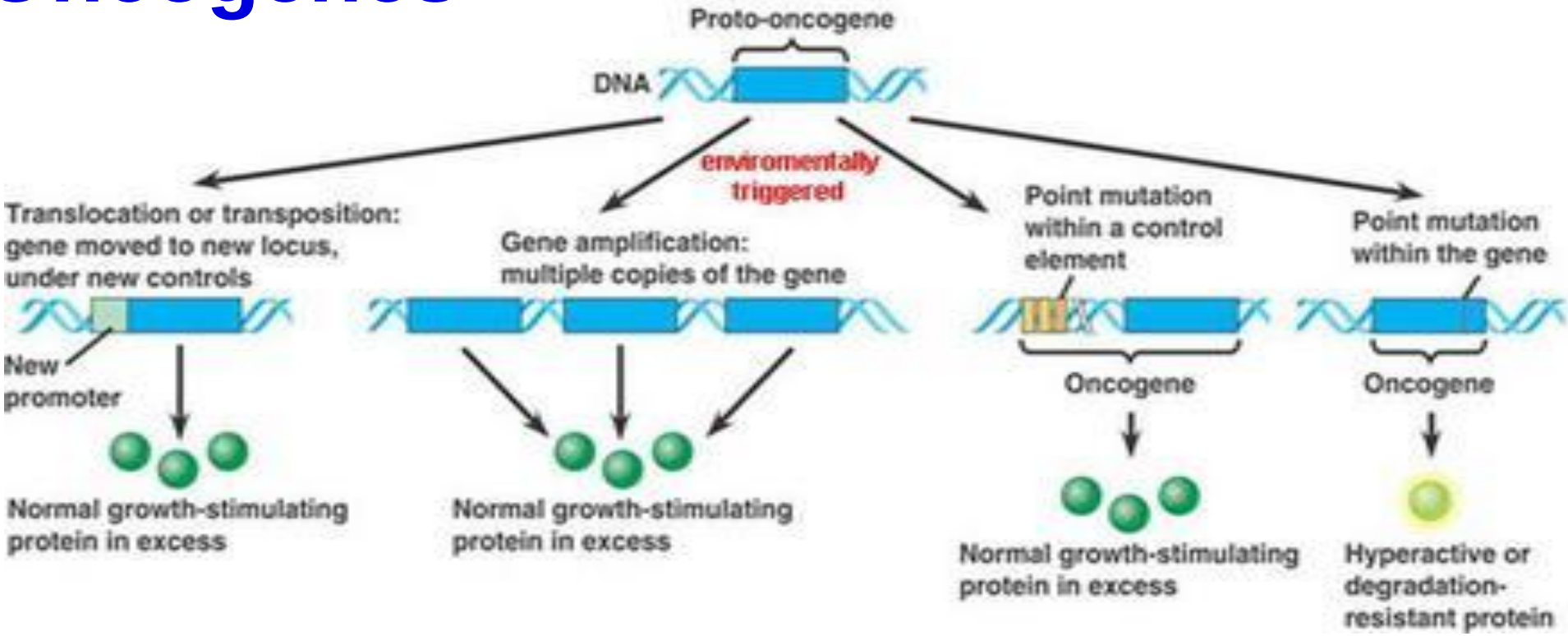


Oncogenes and tumor suppressors

Proto-oncogenes – Genes whose products encode components of the molecular cascades that mediate cell growth, cell survival, and block cell defferentiation.
The abnormal, **mutated** form of the proto-oncogenes that lead to excessive cell proliferation and cancer are called **oncogenes**.
Proteins encoded by **tumor suppressor genes** inhibit cell proliferation or survival and support cell differentiation.



Oncogenes



Oncogenes differ from proto-oncogenes in three basic ways:
1. timing and quality of expression
2. structure and function of protein products
3. degree to which their protein products are regulated by cellular signals

Uncontrolled growth

In cancer cells, a number of alternative mechanisms operate to ensure that cell proliferation is not constrained.
Cancer cells produce growth factors that stimulate their own proliferation (**autocrine growth stimulation**) and **hijack cellular mitogenic signals**.

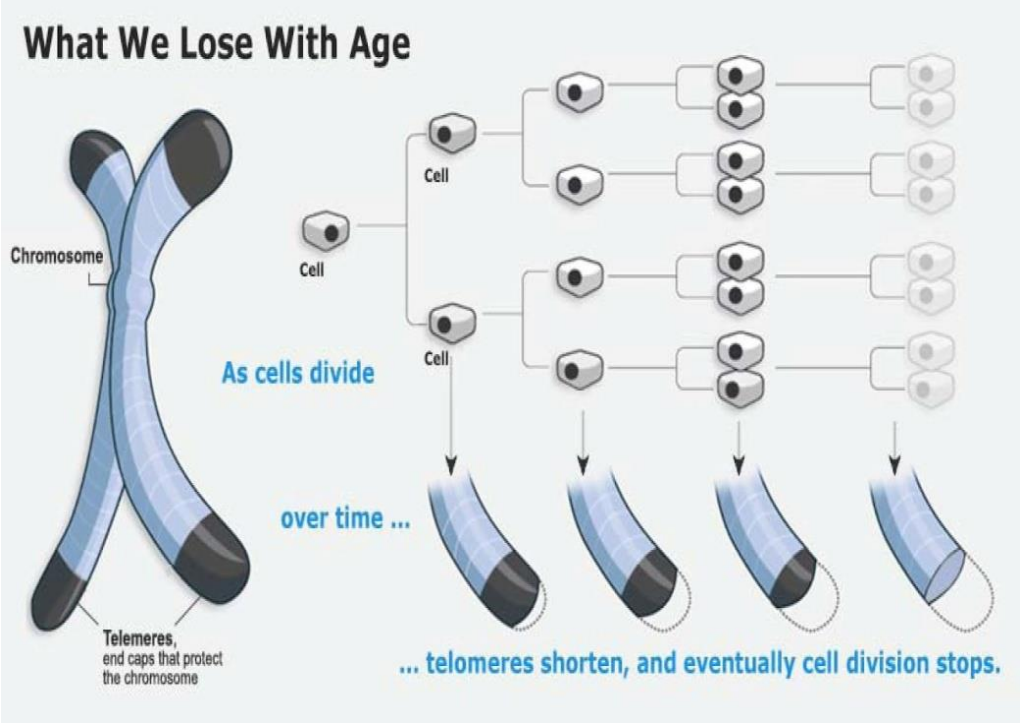
Uncontrolled growth - “GO” signals

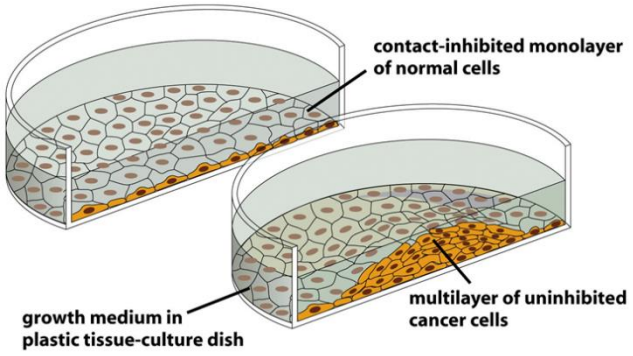
“GO” signals = main mitogenic signals include:

1. growth factors (e.g. EGF, VEGFA, PDGF)
2. growth factor receptors (e.g. the receptors for epidermal growth factor EGF (EGFR) and its close homologue HER2/neu (ERBB2)
3. receptor-coupled signal transduction molecules (RAS family)
4. proteinkinases (SRC,ABL)
5. transcription factors (MYC, MYB, FOS, JUN)
6. cyclins
7. cyclin-dependent kinases (cdk)

Contact inhibition and immortalization

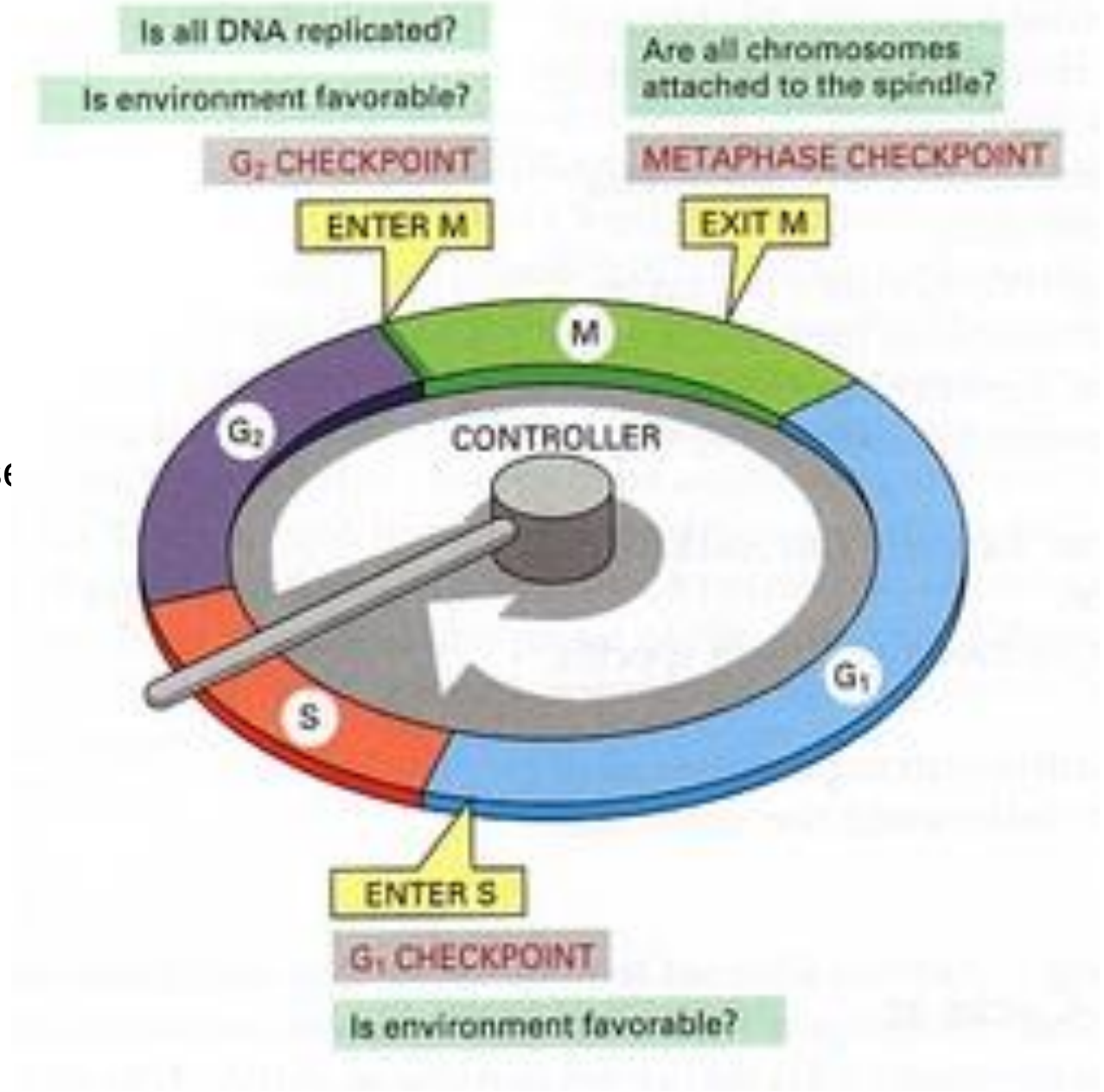
Proliferation of many normal cells is inhibited by cell-cell contact (**contact inhibition)** and by erosion of telomeres (**Hayflick limit)**, but cancer cells are characteristically insensitive to such inhibition of growth.
Most pre-malignant cells escape from Hayflick limit by stabilizing their telomeres (**telomerase**, hTERT).
Cells that have stabilized their telomeres can proliferate indefinitely and are therefore said to be **immortalized**. Immortal cells are not necessarily transformed (tumorigenic) cells.





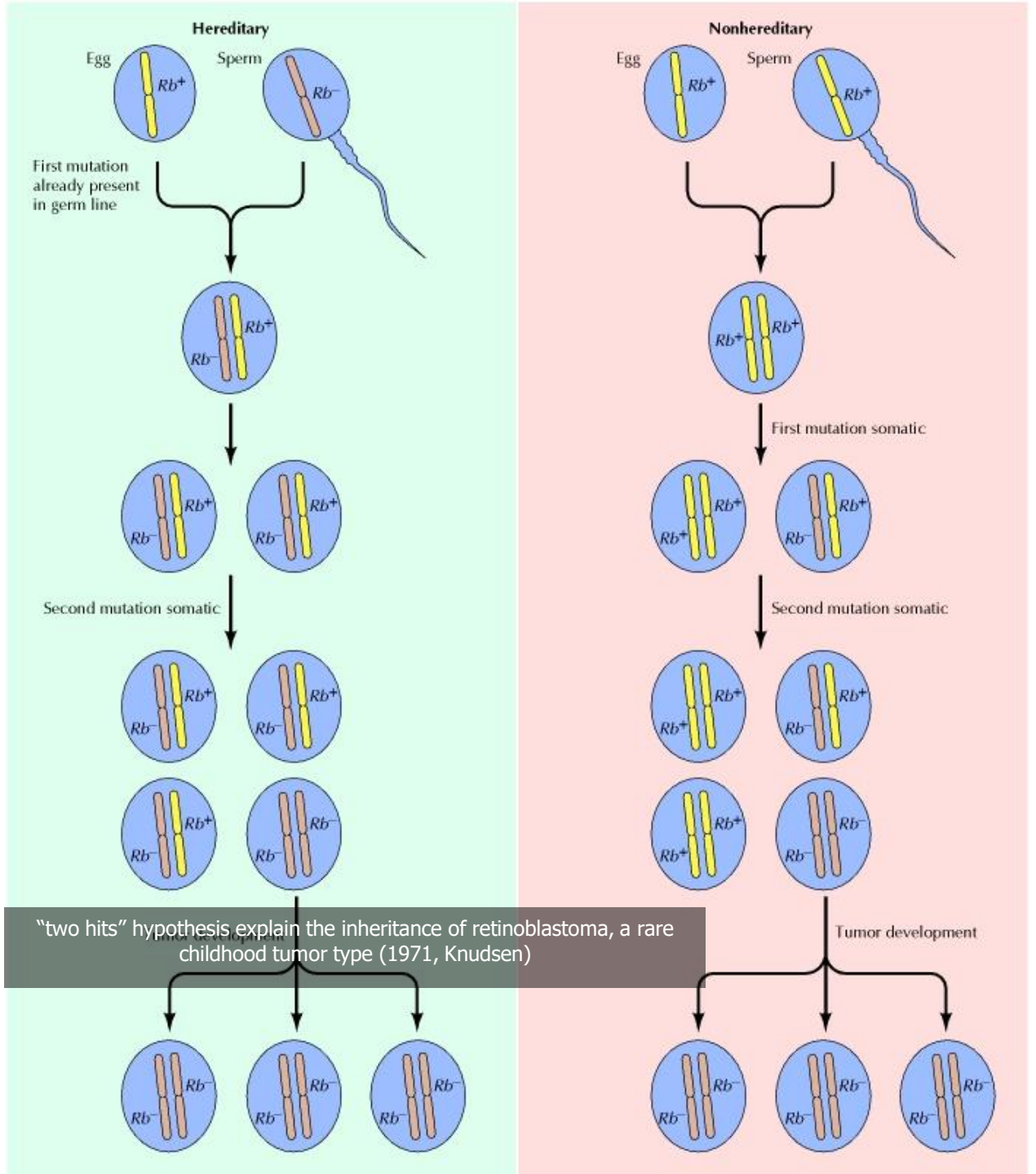
Uncontrolled growth – loss of “STOP” signals

- The critical decisions concerning growth versus quiescence are made in the G1 phase of the cell cycle.
- Growth of normal cells is controlled by signals from the external environment (extracellular matrix, surface of adjacent cells) and from the inside of the cell (DNA damage, cell damage, mitotic spindle damage).



Tumor suppressors

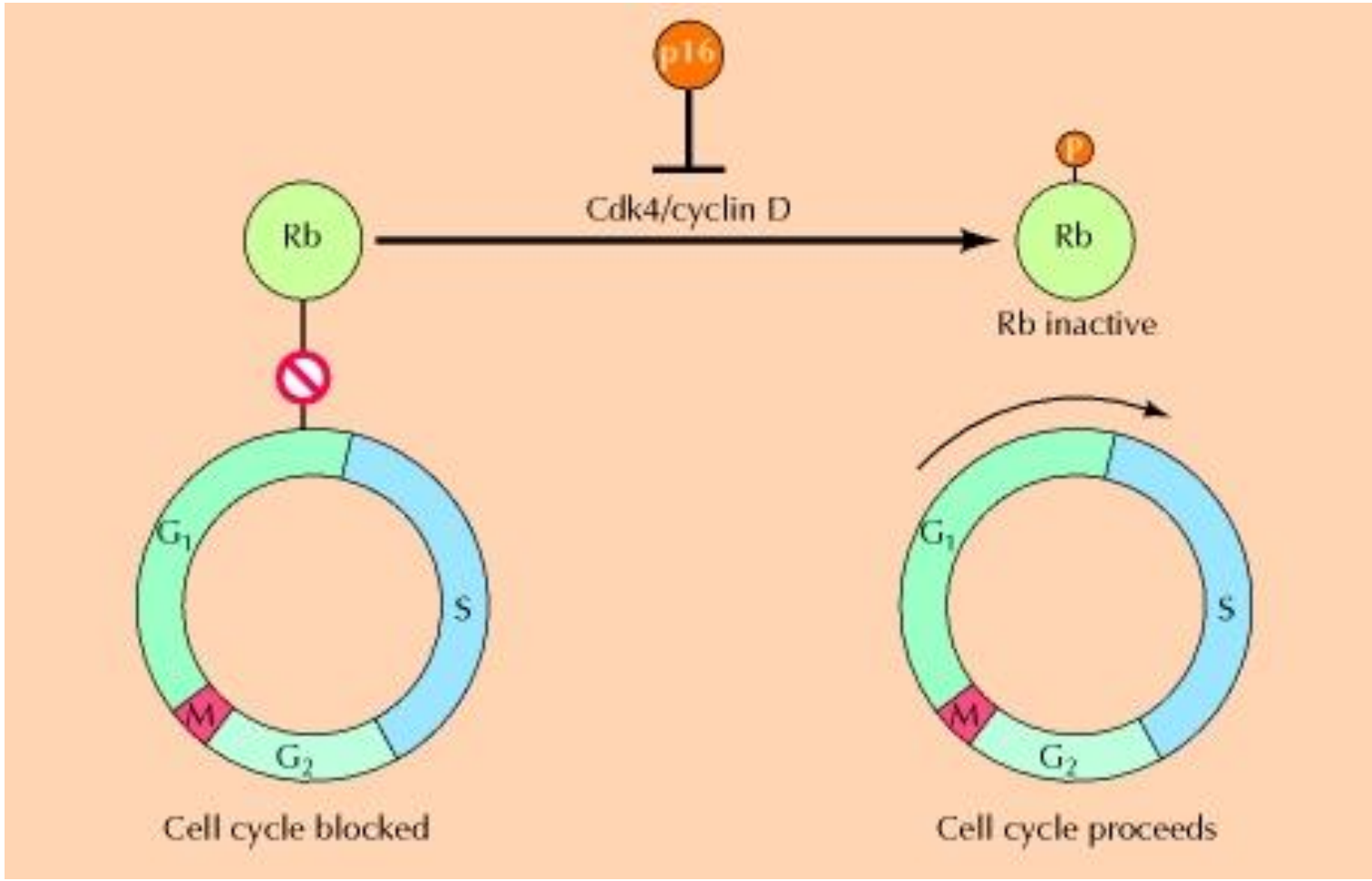
- In many tumors are lost or inactivated.
- tumor suppressor proteins inhibit the same cell regulatory pathways that are stimulated by the products of oncogenes.
- Most **familial cancer syndromes** are inherited as a recessive trait and correspond to the constitutive inactivation of an important tumor suppressor gene.
- Tumor suppressors are often named according to the type of tumor developing due to their loss of function.
- Rb (= retinoblastoma)
- WT (= Wilm's tumor)
- NF1 and NF2 (= neurofibromatosis)
- APC (= Adenomatous Polyposis Coli)
- DCC (= Deleted in Colon Cancer)
- VHL (= von Hippel-Lindau syndrome)



"two hits" hypothesis explain the inheritance of retinoblastoma, a rare childhood tumor type (1971, Knudsen)

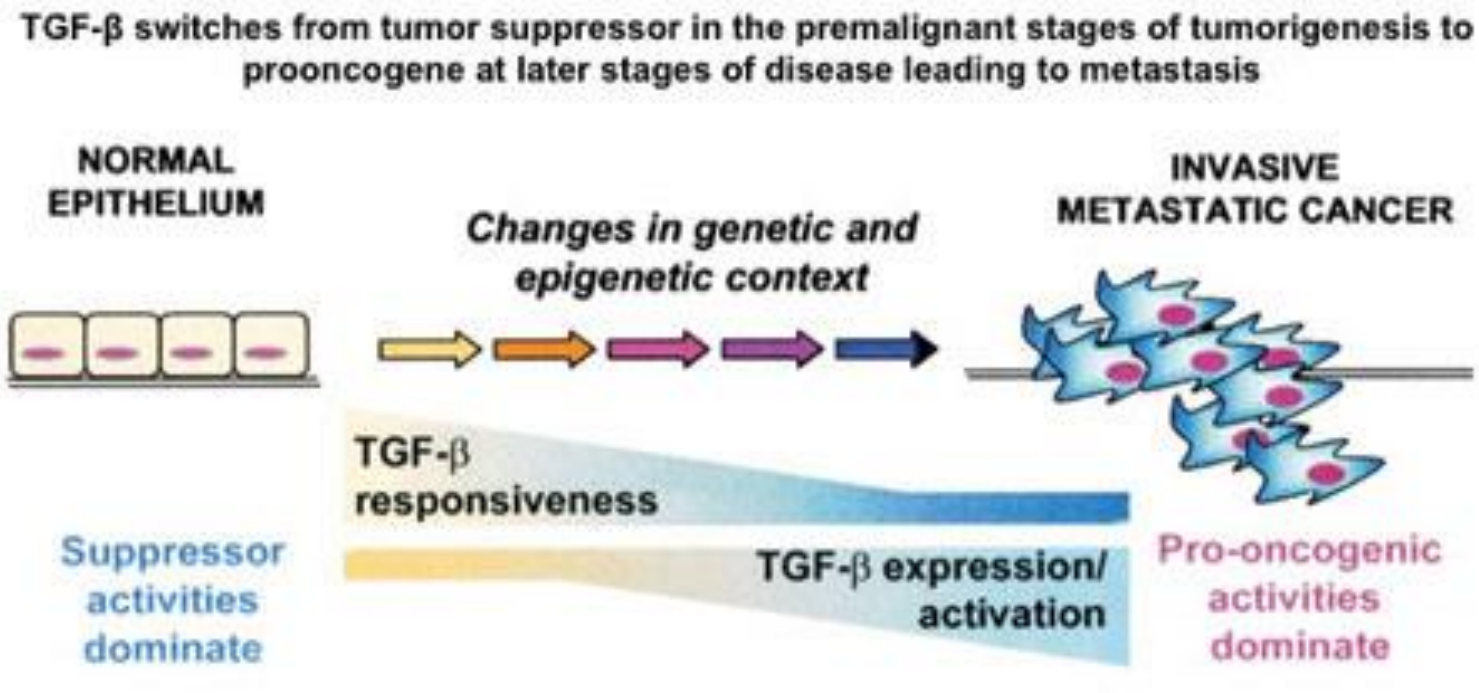
Rb protein–true tumor suppressor

- Rb is a main inhibitor of cell cycle and controls the transition from G1- to S-phase.
- Rb inhibits the transcription factor E2F, which upon release from Rb ↑ expression of S phase genes (e.g. DNA replication enzymes).
- Rb is present all the time, its activity is modulated by phosphorylation.
- – phosphorylated Rb = inactive
- – dephosphorylated Rb = active
- *Rb* mutations are also involved in tumors of adults (bladder, breast, and lung carcinomas).
- The significance of the *Rb* tumor suppressor gene thus extends beyond retinoblastoma.



Will you be my tumor suppressor for ever?

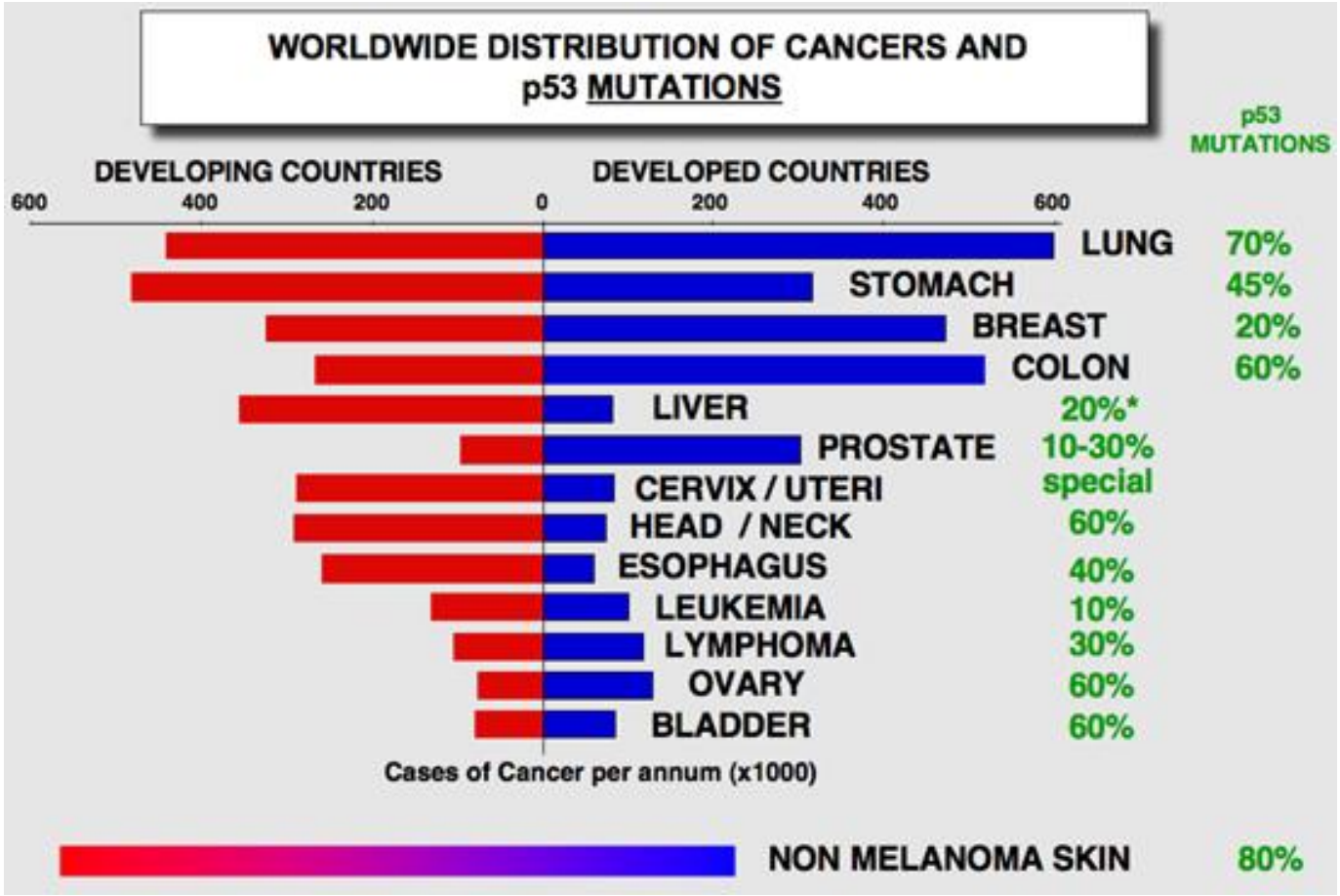
- Tumor suppression is context-dependent.
- TGF-β (transforming growth factor- β) has an antiproliferative effect and maintains genomic stability. As cancer progresses, tumor cells alter their responsiveness to TGF-β.
- At late-stage tumors, TGF-β promotes cell migration, invasion of cancer cells, and becomes a pro-survival factor.



Other “ STOP“ signals

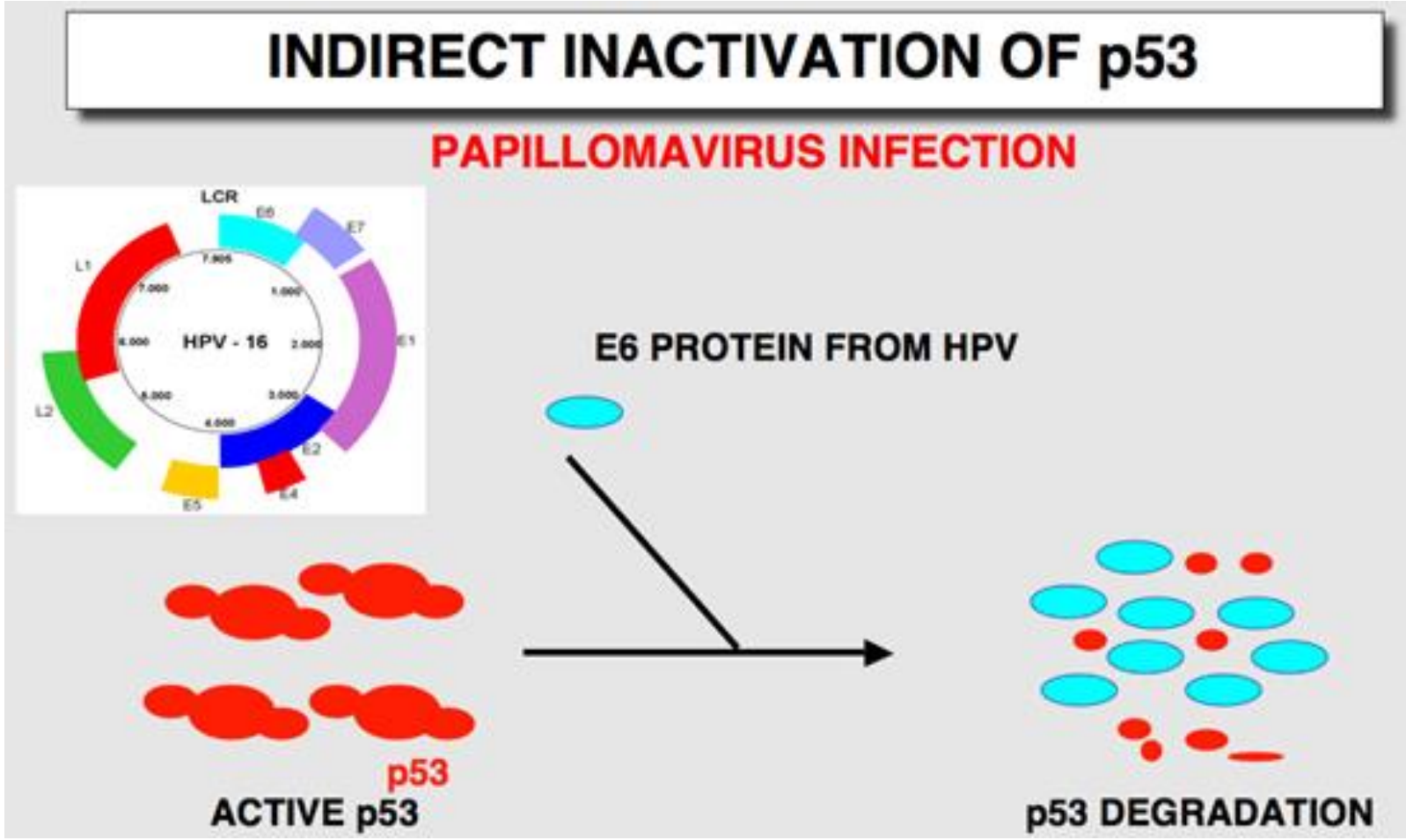
p53 protein (ch. 17p13)
“guardian of the genome” – active in G1 and G2 checkpoints
DNA damage increases expression of p53
acts as a transcription factor for DNA repair and apoptosis genes
inhibitors of cyclin-dependent kinases (e.g. p21, p27, p16, etc.)
p21 is the main target of p53 = inhibitor of Cdk – cell cycle arrest in G1 phase by inhibition of Cdk2/cyclin E complex

percentage of tumors with mutated p53



HPV and p53

- The E6 viral protein expressed by HPV specifically binds to the p53 protein and induces its degradation. This observation explains the rarity of p53 mutations in HPV-positive cervical cancers.



Cell death

- **Apoptosis**

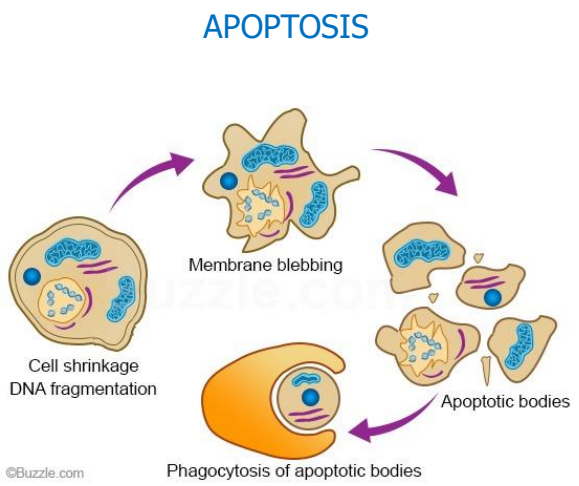
Active (=needs energy), programmed cell death. The action of caspases and other apoptotic enzymes (proteases and nucleases) leads to cell fragmentation to apoptotic bodies that are removed by macrophages.

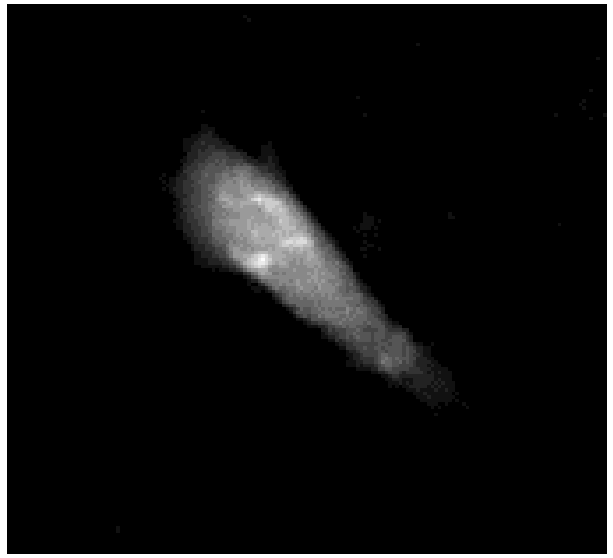
- **Necrosis**

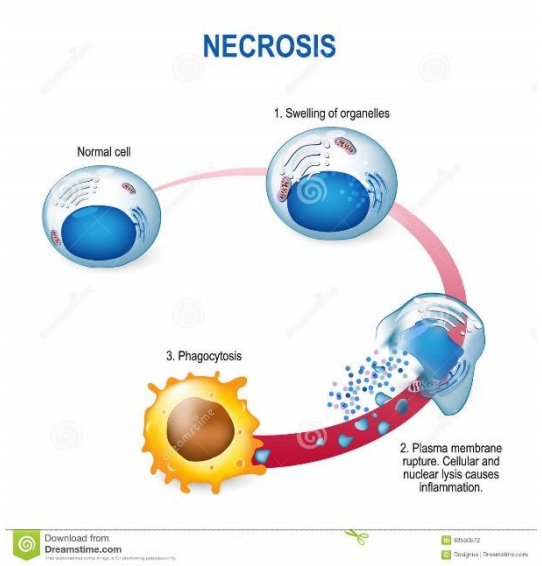
Accidental cell death caused mainly by external factors (infections, toxins, etc.). Cellular content is released into the environment and damage surrounding tissues. Necrosis has pro-inflammatory and tumor-promoting potential.

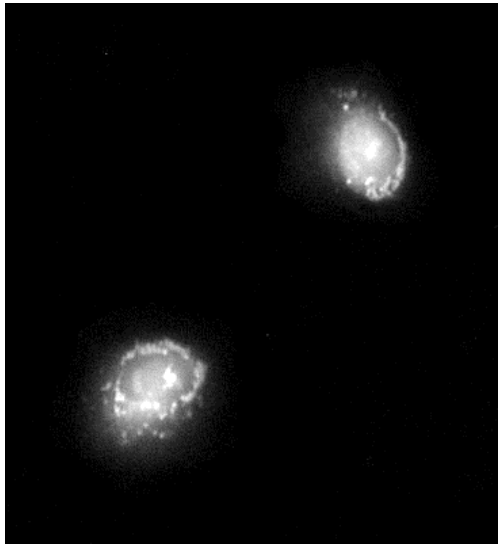
- **Regulated necrosis**

1. **Necroptosis** (driven by kinases RIP1 and RIP3).
2. **Ferroptosis** (dependent on iron and characterized by the accumulation of lipid peroxides).
3. **Parthanatos** (dependent on the activity of poly (ADP-ribose)-polymerase (PARP)).
4. **MPT-driven necrosis** (induction of the mitochondrial membrane permeability transition (MPT), can lead to mitochondrial swelling and cell death).
5. **Pyroptosis** (Pyroptosis is an inflammatory cell death usually caused by microbial infection, accompanied by activation of inflammasomes and maturation of pro-inflammatory cytokines interleukin-1β and interleukin-18. Proteins from Gasdermin family are the executors).



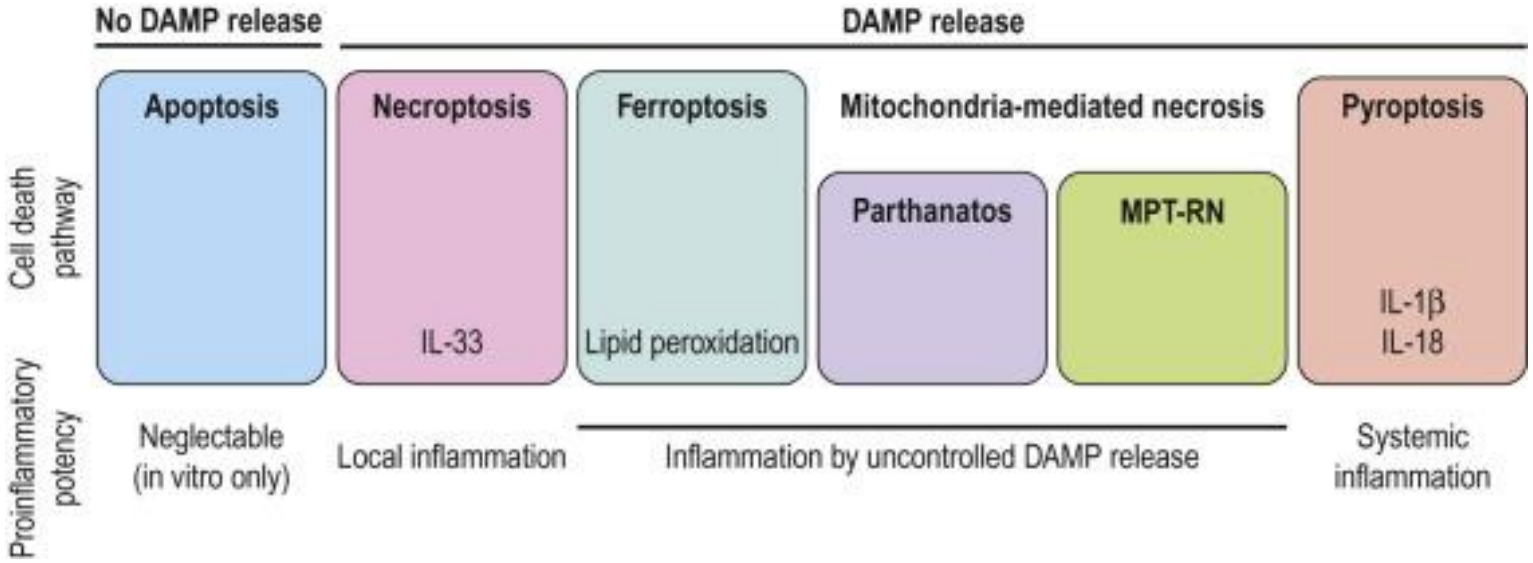






Immunogenicity of different types of cell death

- **The loss of plasma membrane integrity** that occurs during regulated necrosis leads to the **release of molecular damage-associated molecular patterns** (DAMPs) into the extracellular space. During necroptosis, anti-inflammatory cytokines (IL-33) may be released in a specific context. **IL-33 promotes the recruitment of regulatory T-lymphocytes to the intestinal mucosa**, which may limit immunogenic response in necroptosis.
- In contrast, during ferroptosis or MPT-driven necrosis, no active production of cytokines or immunomodulatory factors has been described that could attenuate the immunogenic effect of DAMPs.
- **The most immunogenic form of regulated necrosis is pyroptosis**, which involves the active production of pro-inflammatory cytokines (IL-1β, IL-18) leading to the systemic inflammatory response.

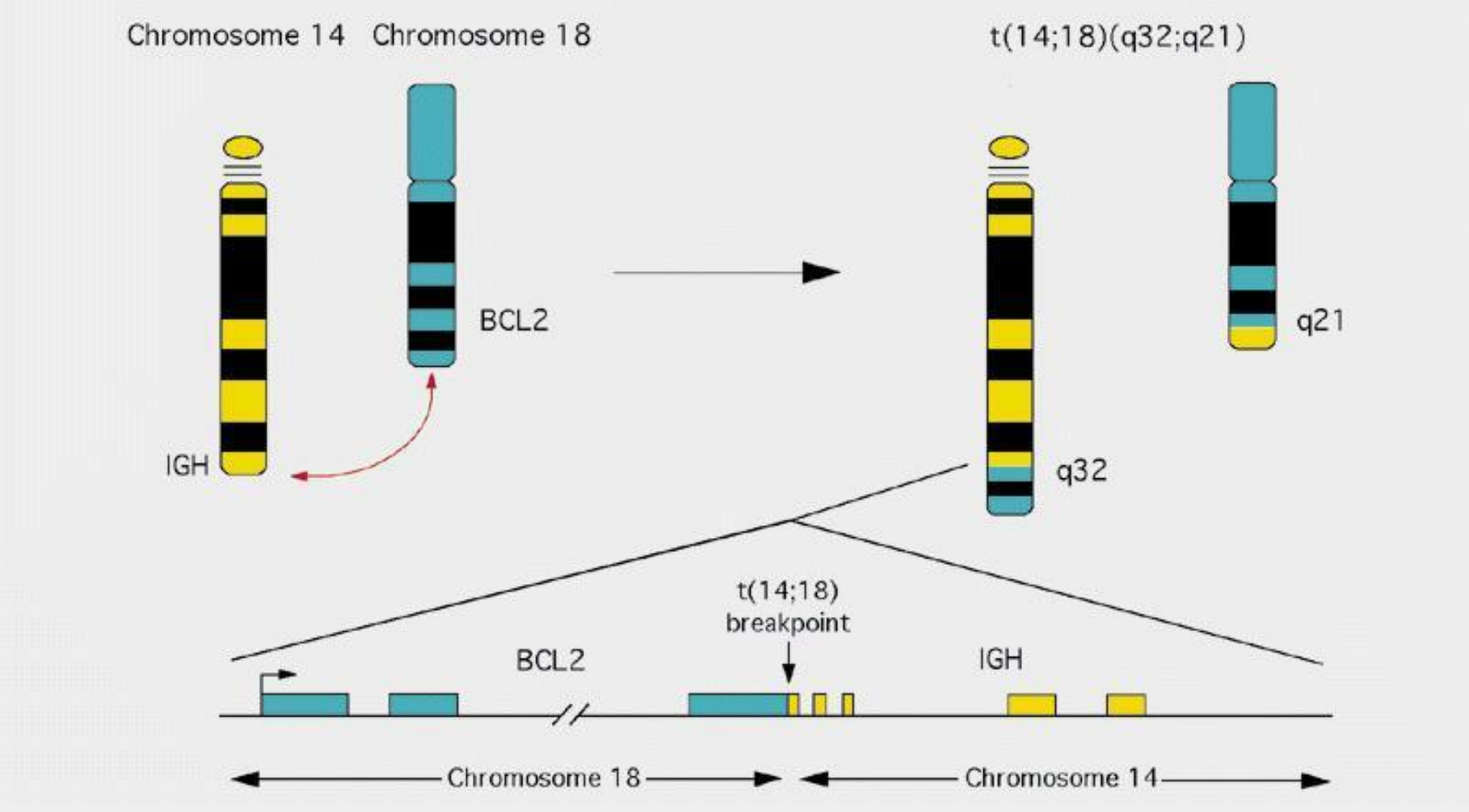


Resisting apoptosis

- Tumor cells evolve a variety of strategies to limit cell death. Most known are:
- loss of **p53**
- **increased expression of antiapoptotic** regulators (Bcl-2, Bcl-xL) and survival signals (insulin-like growth factors; Igf1/2)
- **downregulating of proapoptotic** factors (Bax, Bim, Puma)

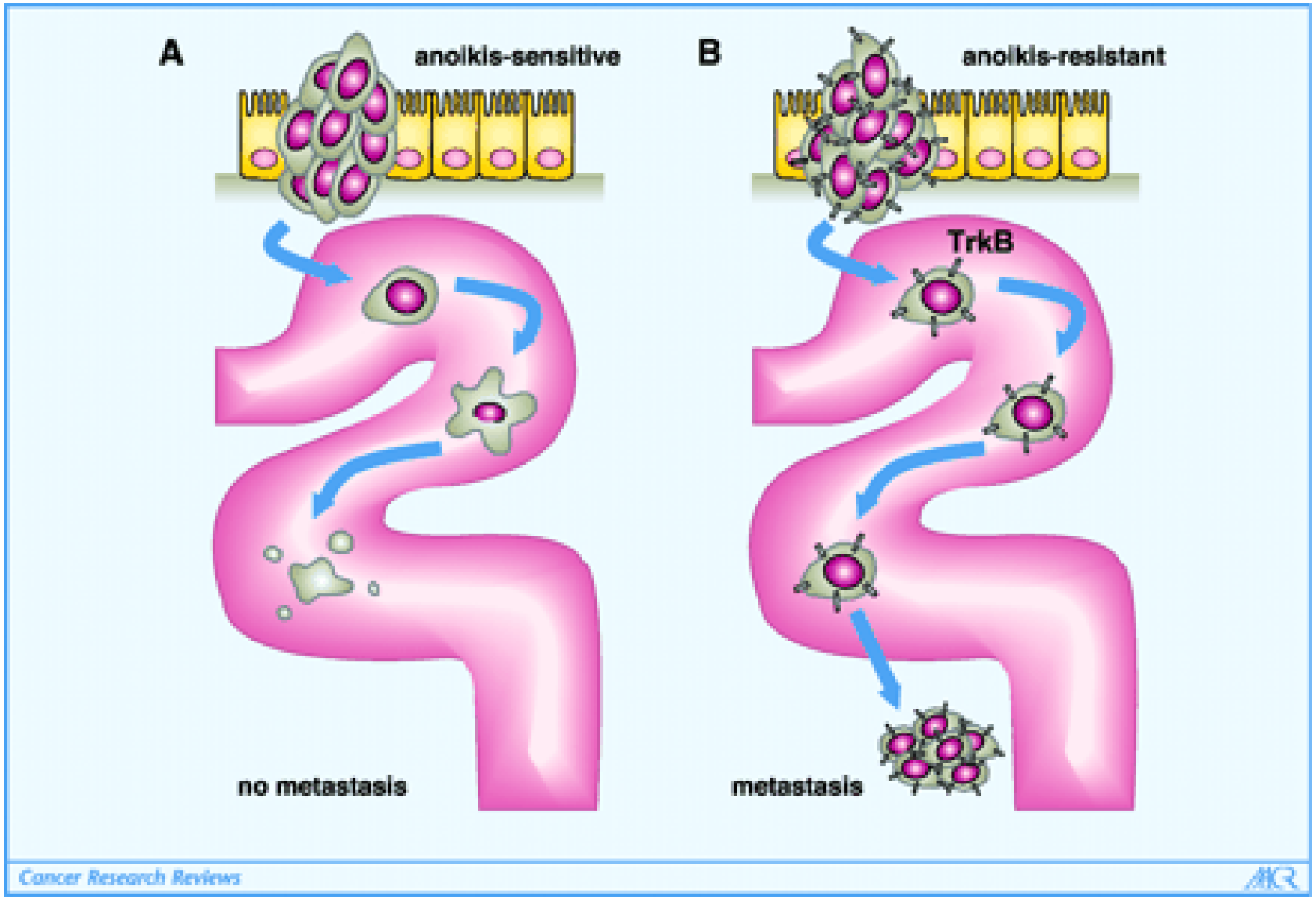
Resisting apoptosis

Chromosomal translocation associated with B-cell lymphomas.
The Bcl-2 gene is translocated behind a potent immunoglobulin gene promoter. Increased epression of Bcl-2 gene is associated with inhibition of apoptosis.



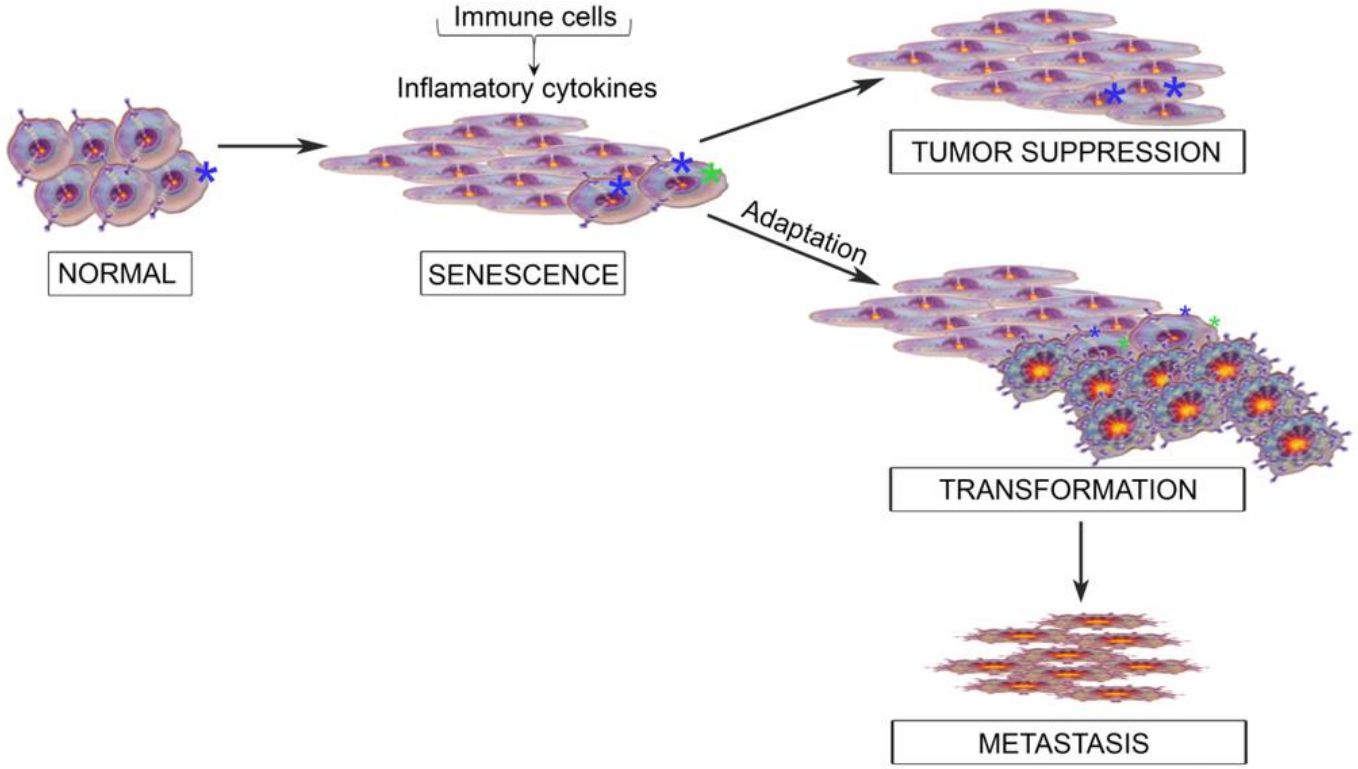
Resistence to anoikis

Anoikis is a form of programmed cell death that occurs in anchorage-dependent cells when they detach from the surrounding extracellular matrix.
barrier to metastasis
circulating tumor cells are anoikis resistant
TrkB (neurotrophic receptor) overexpression protects disseminated, circulating tumor cells from undergoing anoikis.



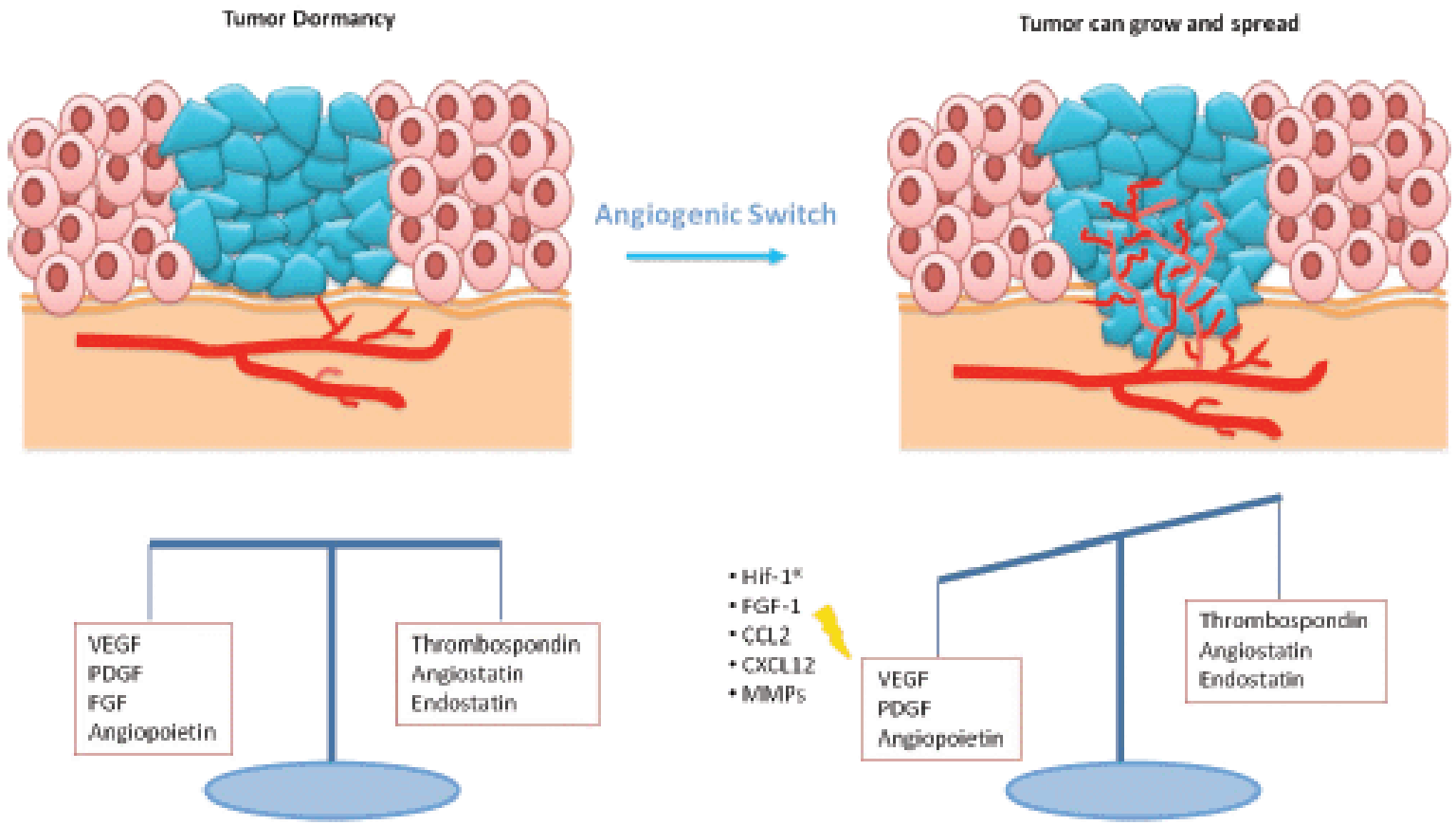
Resisting oncogene-induced senescence

- Cellular senescence is a growth-arrest program that limits the lifespan of cells and **prevents unlimited cell prolife**ration.
- Certain mitogenic oncogenes or the loss of anti-mitogenic tumour-suppressor genes induce senescence. This is known as **oncogene-induced senescence**.
- Many cancer cells either do not have fully active senescence programs or develop bypass mechanisms to regain proliferation capabilities (c-myc overexpression).



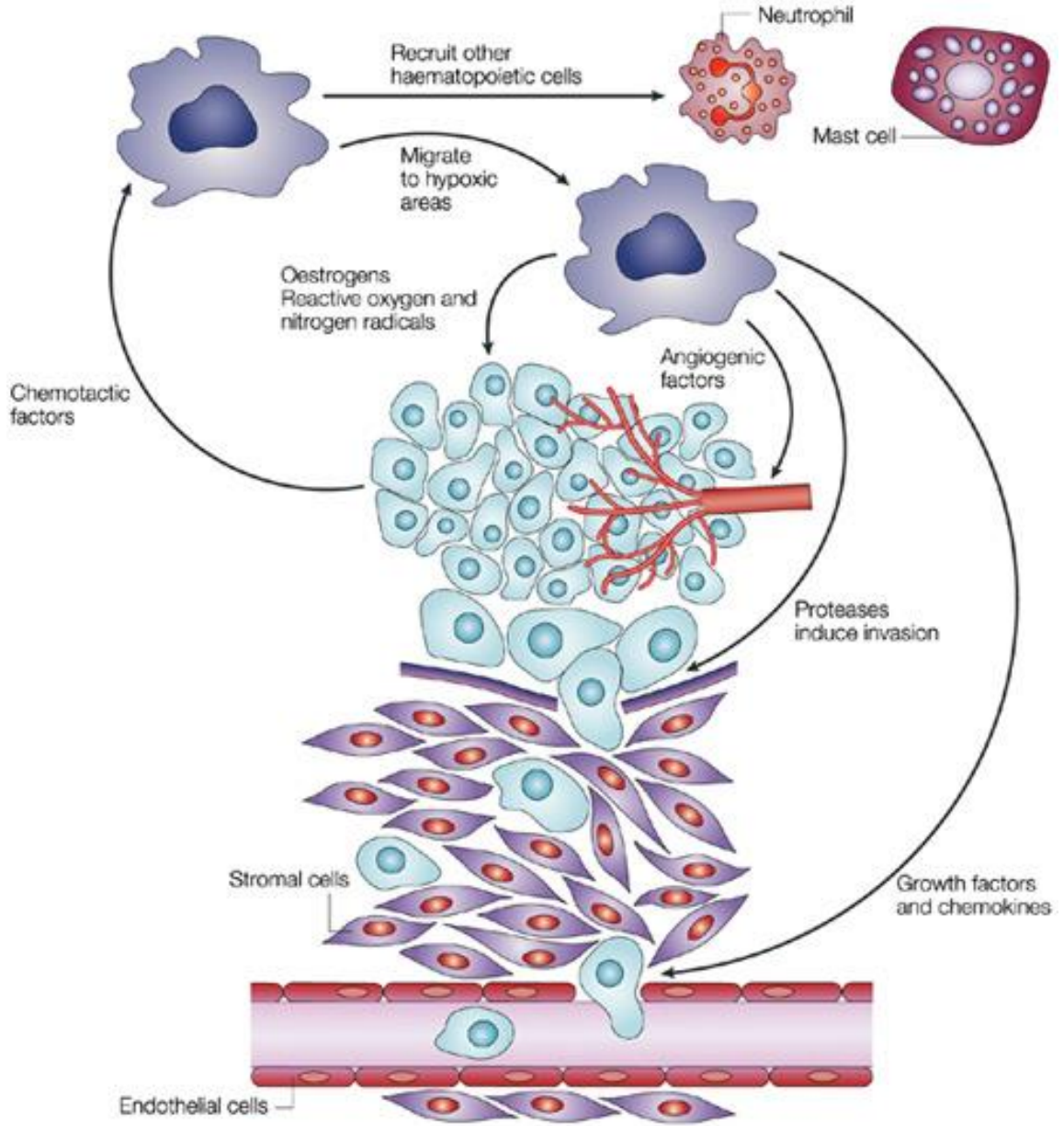
Inducing angiogenesis

Like normal tissues, tumors need nutrients and oxygen.
Tumor without blood circulation grew to 1–2 mm^3. In the absence of vascular support, tumors may become necrotic.
Up-regulation of the activity of angiogenic factors is not sufficient for angiogenesis of the neoplasm. Negative regulators of vessel growth need to be downregulated.
New vessels enable invasion of tumor cells into circulation and creation of distant metastases.



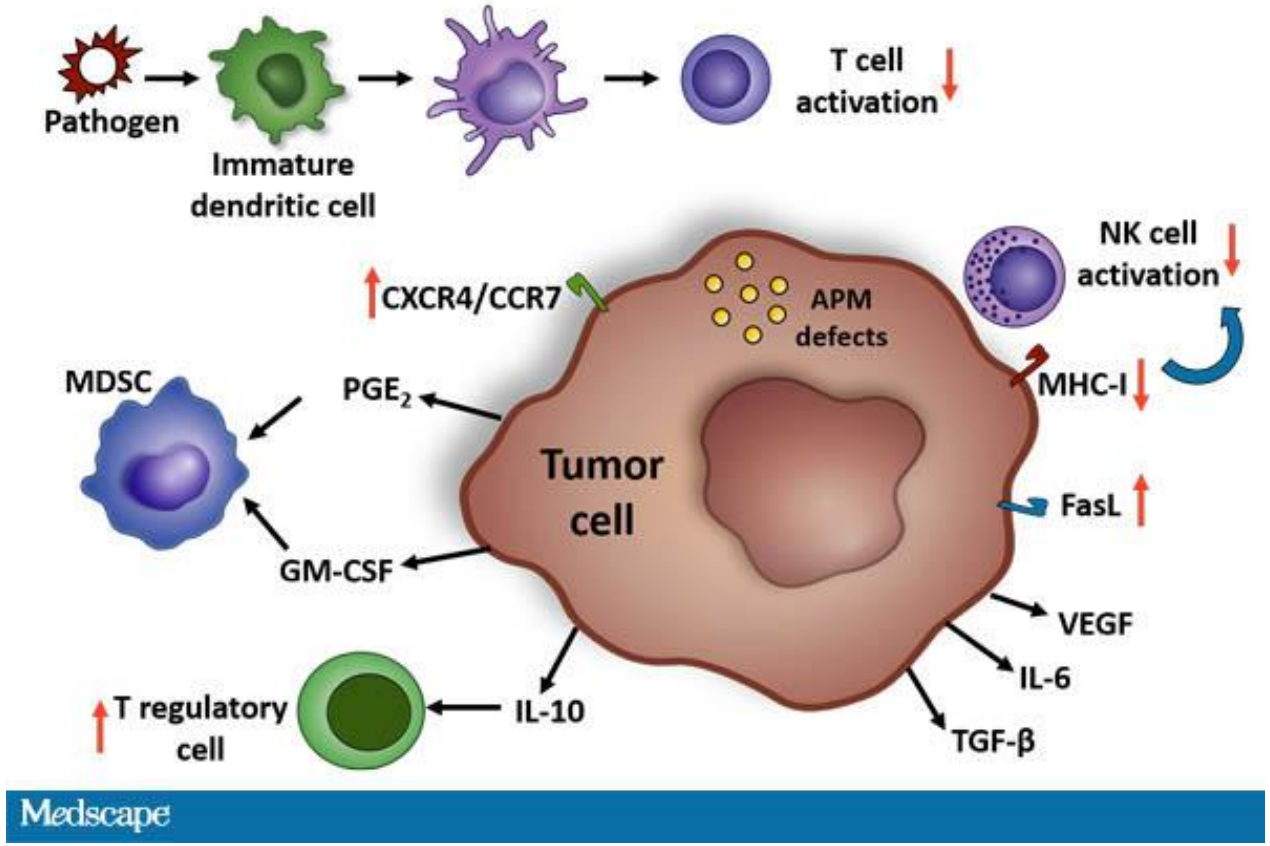
Inducing angiogenesis

Cells of the innate immune system (macrophages, neutrophils, mast cells, and myeloid progenitors) can infiltrate premalignant lesions and contribute to tumor angiogenesis.
Vascular endothelial growth factor (VEGF) production by stromal fibroblasts plays an important role in tumor angiogenesis.



Evading immune destruction

- **Defective antigen presentation** due to down-modulating antigen-presenting machinery (↓ major histocompatibility complex, MHC).
- **Immune suppression** in the tumor microenvironment, mediated by CD4+CD25+ FoxP3+ regulatory T cells (**Tregs**), or other types of suppressive cells.
- **Paralyzing cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells** via production of immuno-suppressive cytokines (by the cancer cells or by the non-cancerous cells in the tumor microenvironment). TGF-β is a chief mediator of this activity.
- **Down regulation of death receptors** prevents death ligand-mediated killing of tumor cells by both CTLs and NK cells.

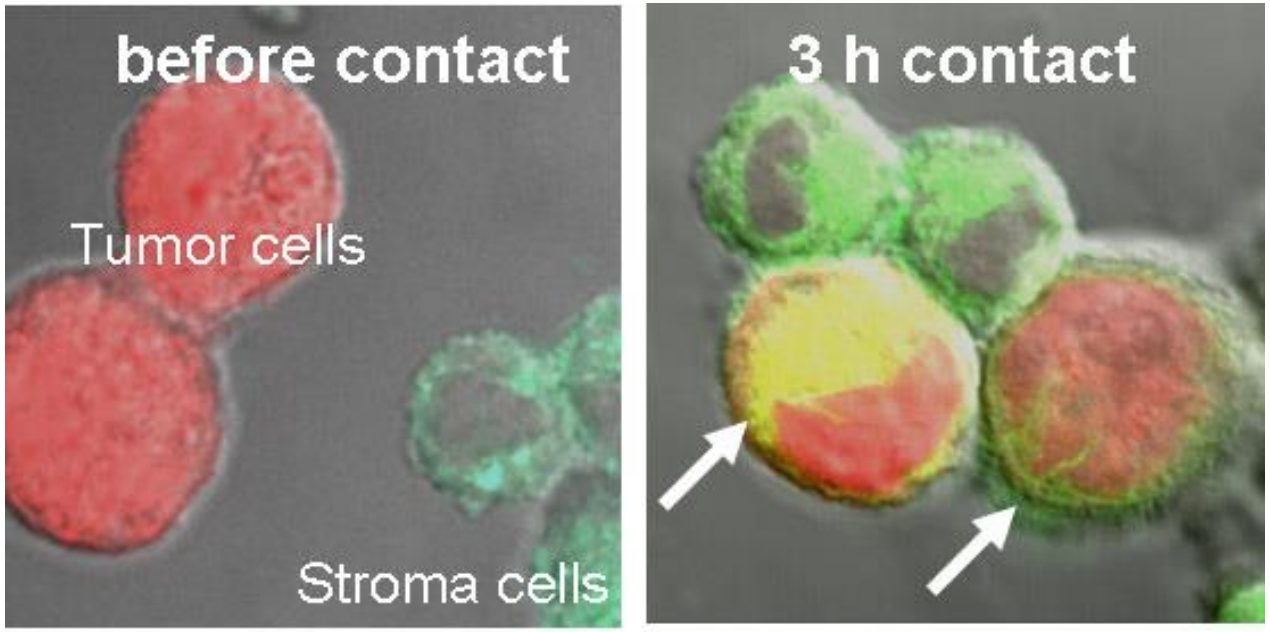


Cancer Neoantigens: A Promising Source of Immunogens for Cancer Immunotherapy

- Somatic mutations in tumor genes could be reflected in proteins. Missense or frameshift mutation has the potential to generate **tumor-specific antigens** (TSAs), which are theoretically recognized as “non-self” by the host immune system.
- TSAs, also known as “**cancer neoantigens**”, have the potential to be utilized as biomarkers predicting clinical responses to immunotherapy and outcomes, as well as serving as targets for immunotherapy.
- Neoantigens are also expressed by fetal organs. Older fetal organs (21 weeks) and adult organs do not express an immunogenic neoantigens.

Oncological trogocytosis-the way how to get rid off antigens

Intercellular exchange of intact membrane patches.
Exchange of membrane molecules/antigens.
Human epidermal growth factor receptor 2 (HER2) could be transferred from cancer cells to monocytes via trogocytosis.

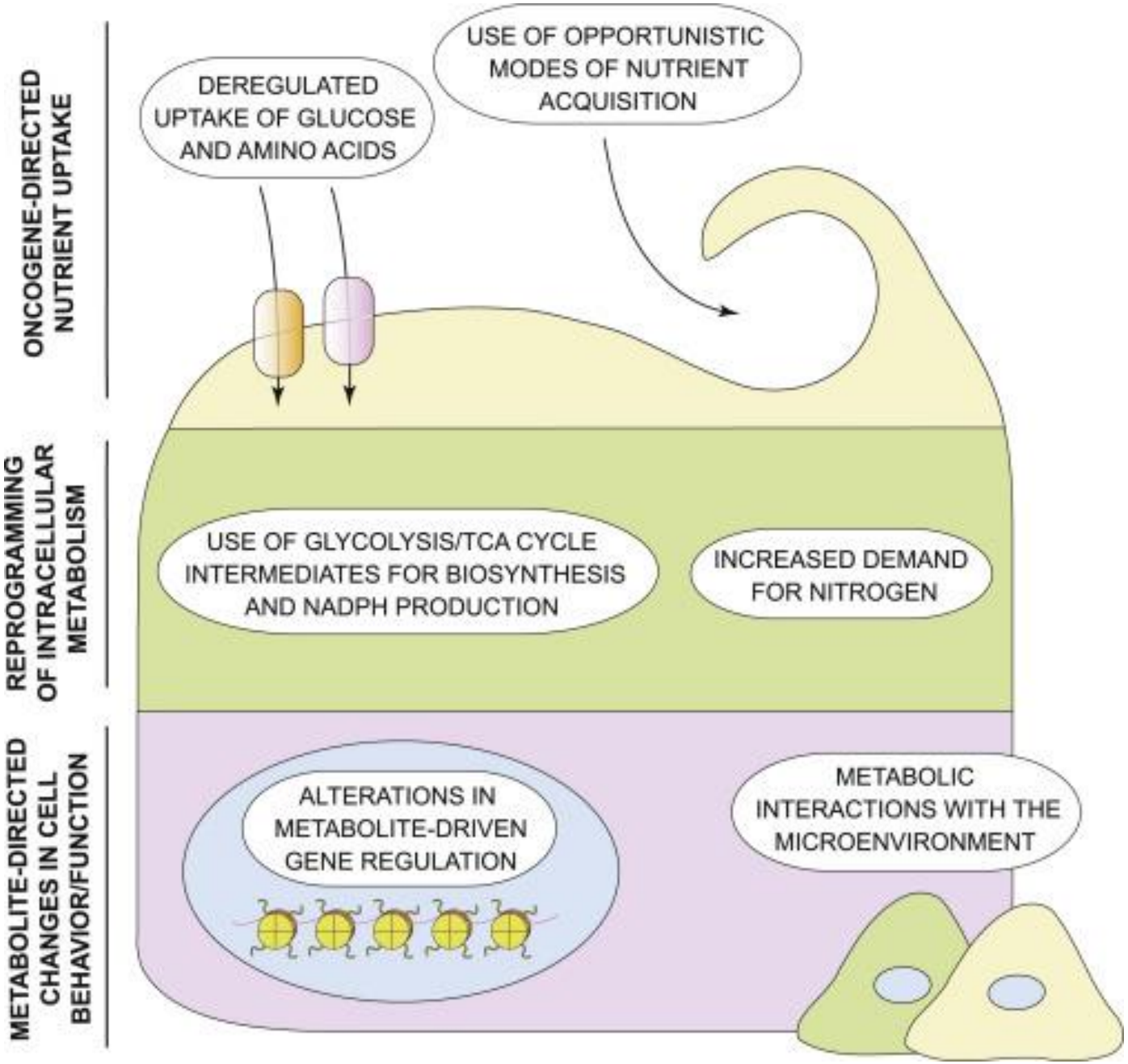


Altered metabolism

- the ability to acquire necessary nutrients from **a nutrient-poor** (low glucosis) and **hostile** (hypoxia, oxidative stress) environment and utilize these nutrients to maintain viability and build new biomass.
- cancer-associated metabolic reprogramming have profound effects on gene expression, cellular differentiation, and the tumor microenvironment.
- These adaptations involve an ability to access normally inaccessible nutrient sources.

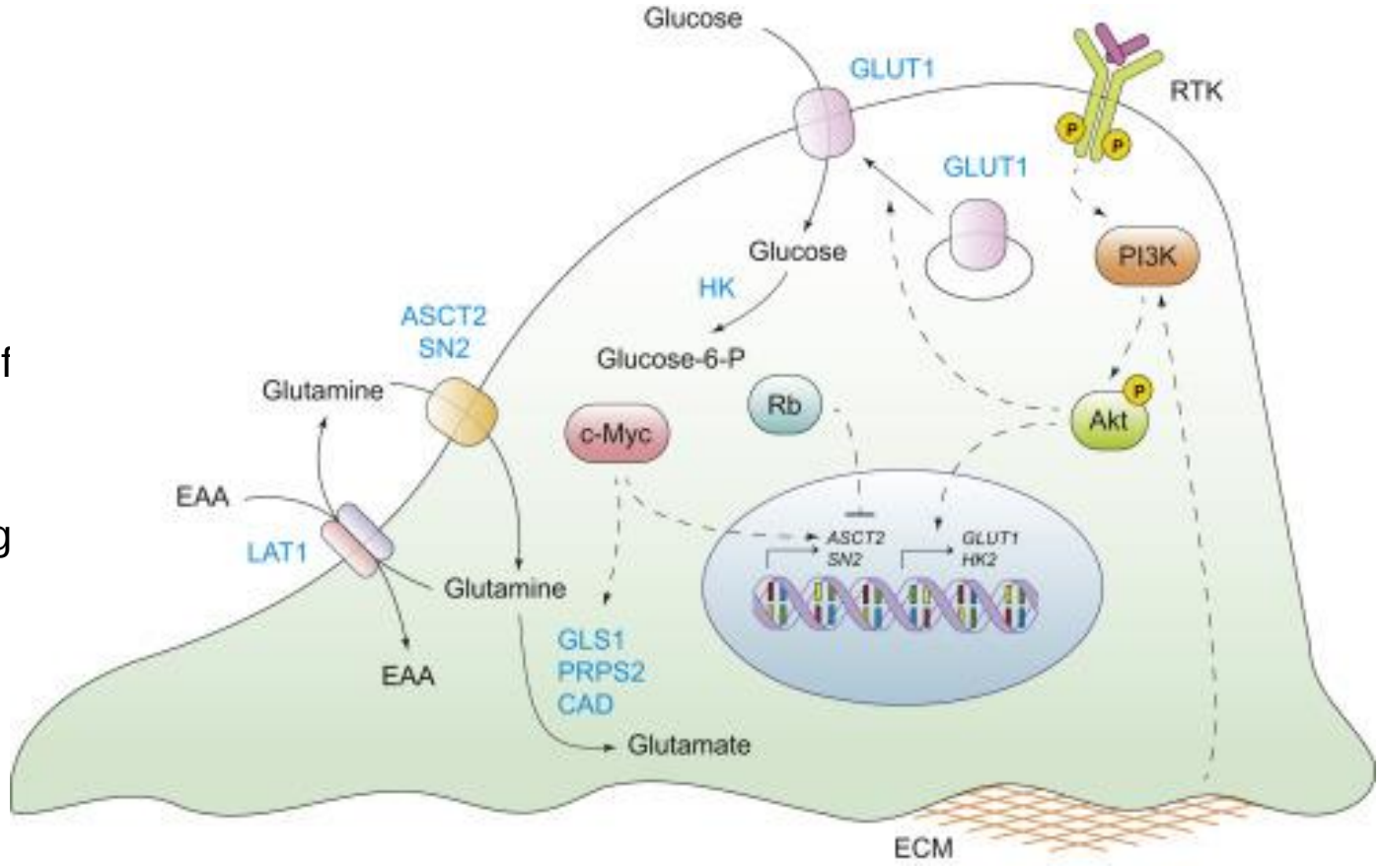
Hallmarks of cancer metabolism

(1) deregulated uptake of glucose and amino acids (Warburg effect, glutaminolysis)
(2) use of opportunistic modes of nutrient acquisition (cannibalism)
(3) use of glycolysis/TCA cycle intermediates for biosynthesis and NADPH production
(4) increased demand for nitrogen
(5) alterations in metabolite-driven gene regulation – metabolites influence enzymes involved in deposition and removal of epigenetic marks.
(6) metabolic interactions with the microenvironment (lactate, tomor acidosis)



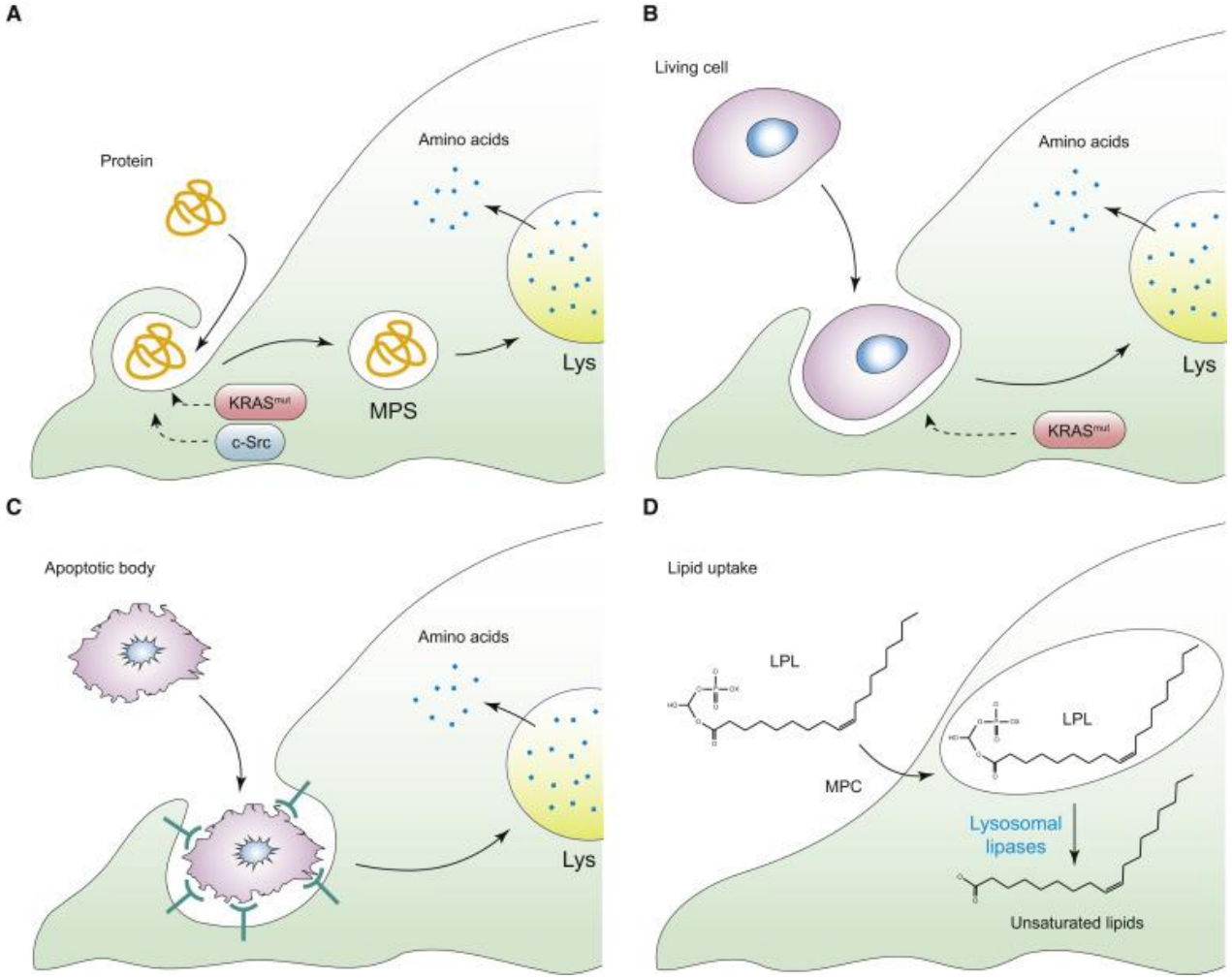
Altered metabolism

- Two principal nutrients that support survival and biosynthesis are **glucose** and **glutamine**.
- Glutamine provides the nitrogen required for the biosynthesis of purine and pyrimidine nucleotides and nonessential amino acids.
- **Warburg effect -** a markedly increased consumption of glucose by some tumors in comparison to the nonproliferating normal tissues.
- **Positron emission tomography** (PET)-based imaging of the uptake of a radioactive fluorine-labeled glucose analog, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has been successfully used in the clinic for tumor diagnosis.
- Oncogenic signaling proteins—Ras upregulate *GLUT1* mRNA expression and increase cellular glucose consumption.



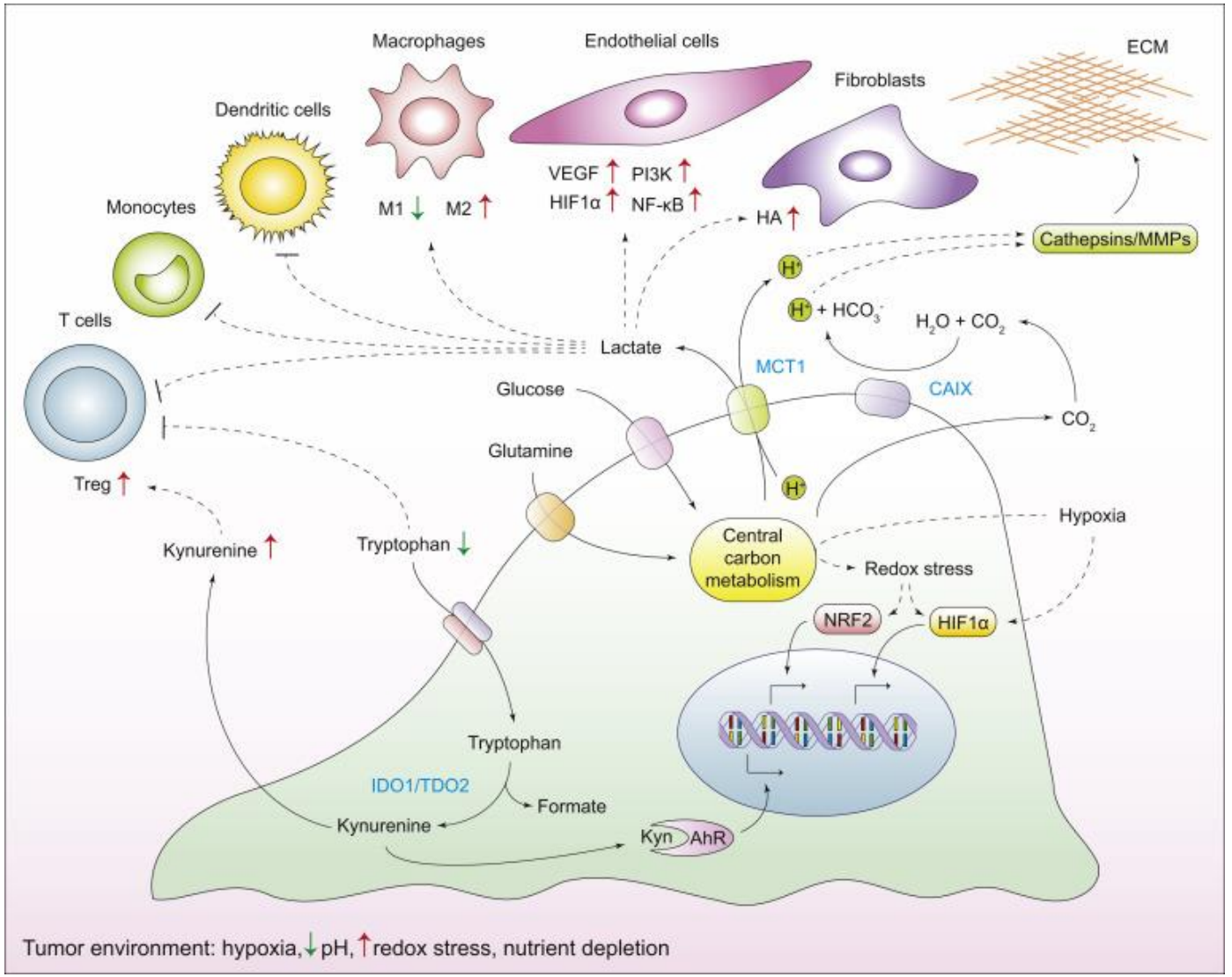
Use of opportunistic modes of nutrient acquisition

Ras or c-Src oncogenes allow to recover free amino acids through the **lysosomal degradation of extracellular proteins**.
Macropinocytosis.
Macroautophagy (autophagy cannot supply cells with new biomass and thus cannot support proliferation in nutrient-poor conditions).
Phagocytosis of apoptotic cellular corpses.
Cannibalism.



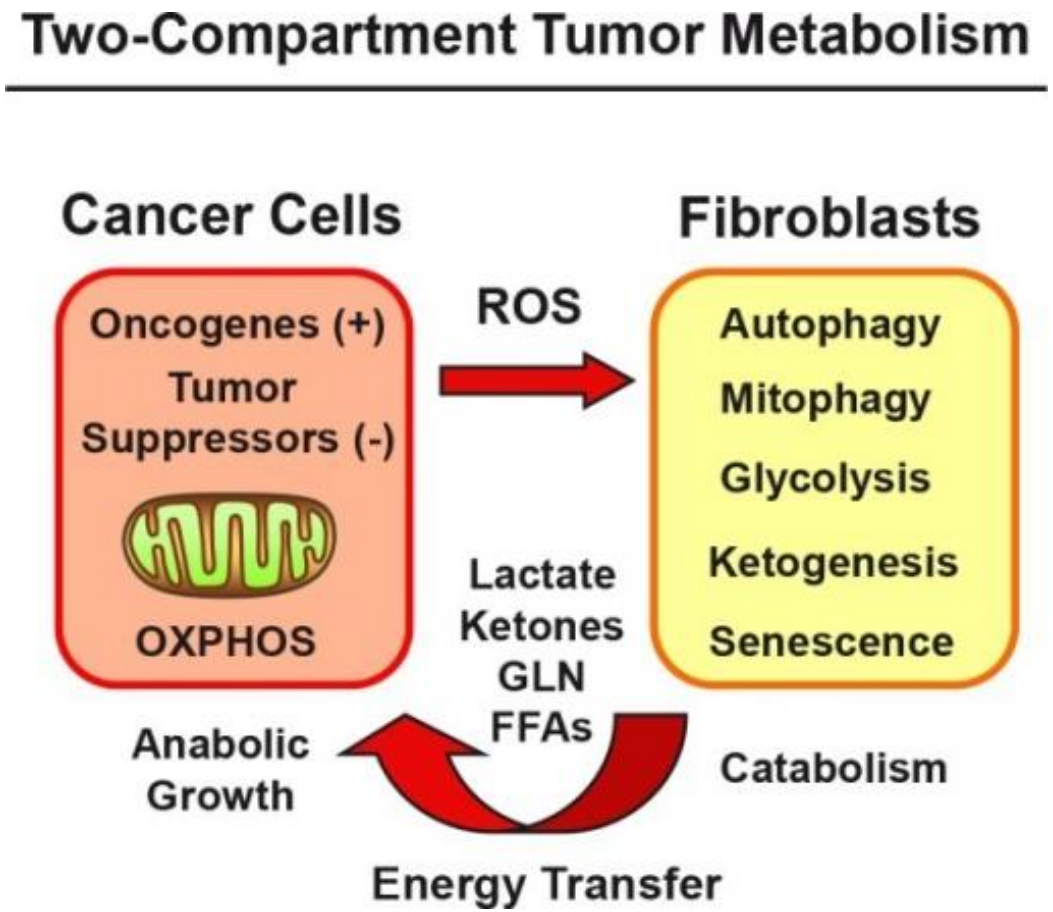
Metabolic interactions with the microenvironment

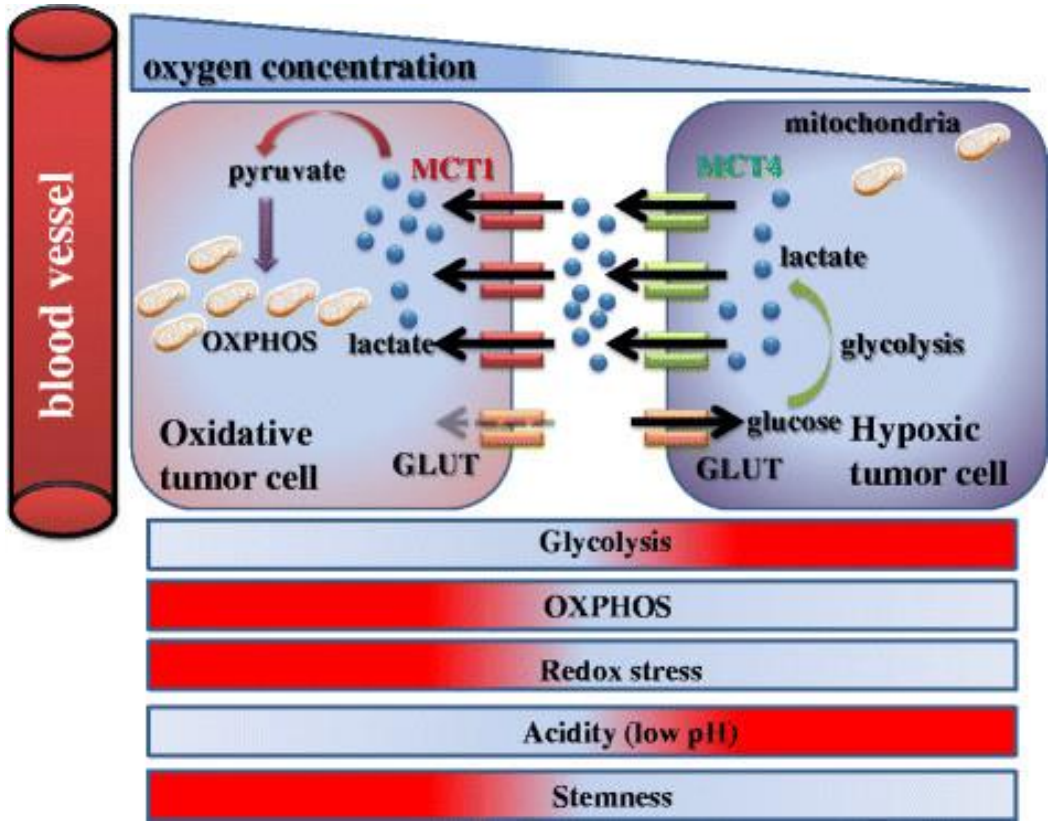
- Cancer cells alter the chemical composition of the extracellular milieu, which exerts **pleiotropic effects** on the phenotypes of normal cells that reside in the vicinity of the tumor.
- Reciprocally, the microenvironment affects the metabolism and signaling responses of cancer cells.
- The high metabolic demand of cancer cells leads to an accumulation of H+ ions in tumor microenvironment – **acidosis**.



Metabolic symbiosis

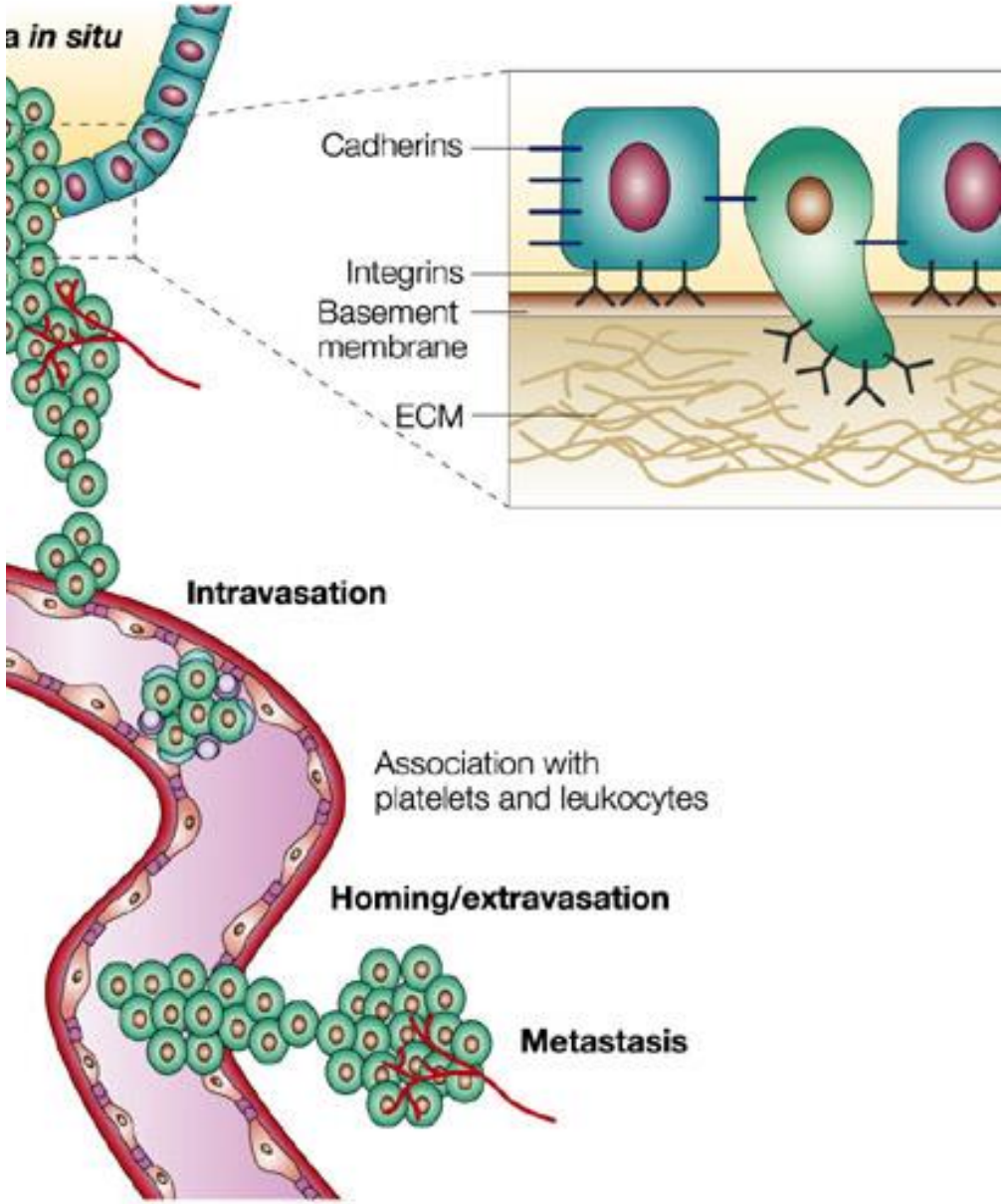
Catabolic fibroblasts are rich source of energy and biomass for the growth and survival of anabolic cancer cells.
A linear path of clonal succession oversimplifies the reality of cancer; number of **genetically distinct subclones** of cells coexist within a single tumor mass: intra-tumor heterogeneity - oxidative and glycolytic tumor cells in one tumor.





Invasion and metastasis

- Cancer cells lose **E-cadherin** dependent intercellular adhesions, acquire a **migratory phenotype** (anoikis resistence, epithelial-mesenchymal transition=EMT), penetrate the basement membrane, and invade the interstitial matrix (production of MMPs).
- Tumour angiogenesis allows cancer cells to enter the bloodstream (circulating tumor cells), either directly or through the lymphatic system, by a process called **intravasation.**
- In the circulation, tumour cells form small **aggregates with platelets and leukocytes**.
- After stopping in the microcirculation of the target organ, tumour cells exit the bloodstream, by a proces called **extravasation**, and undergo local expansion.



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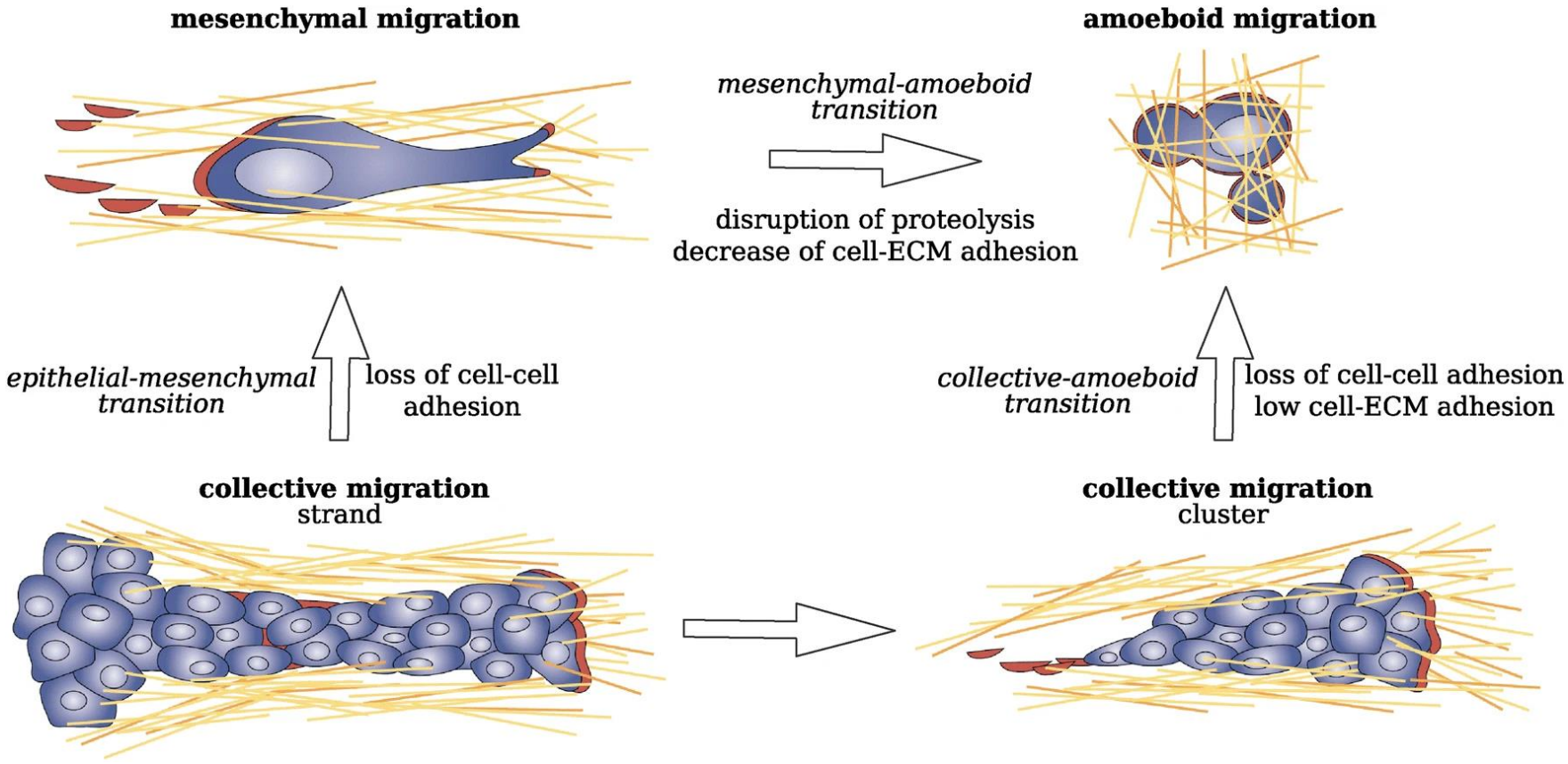
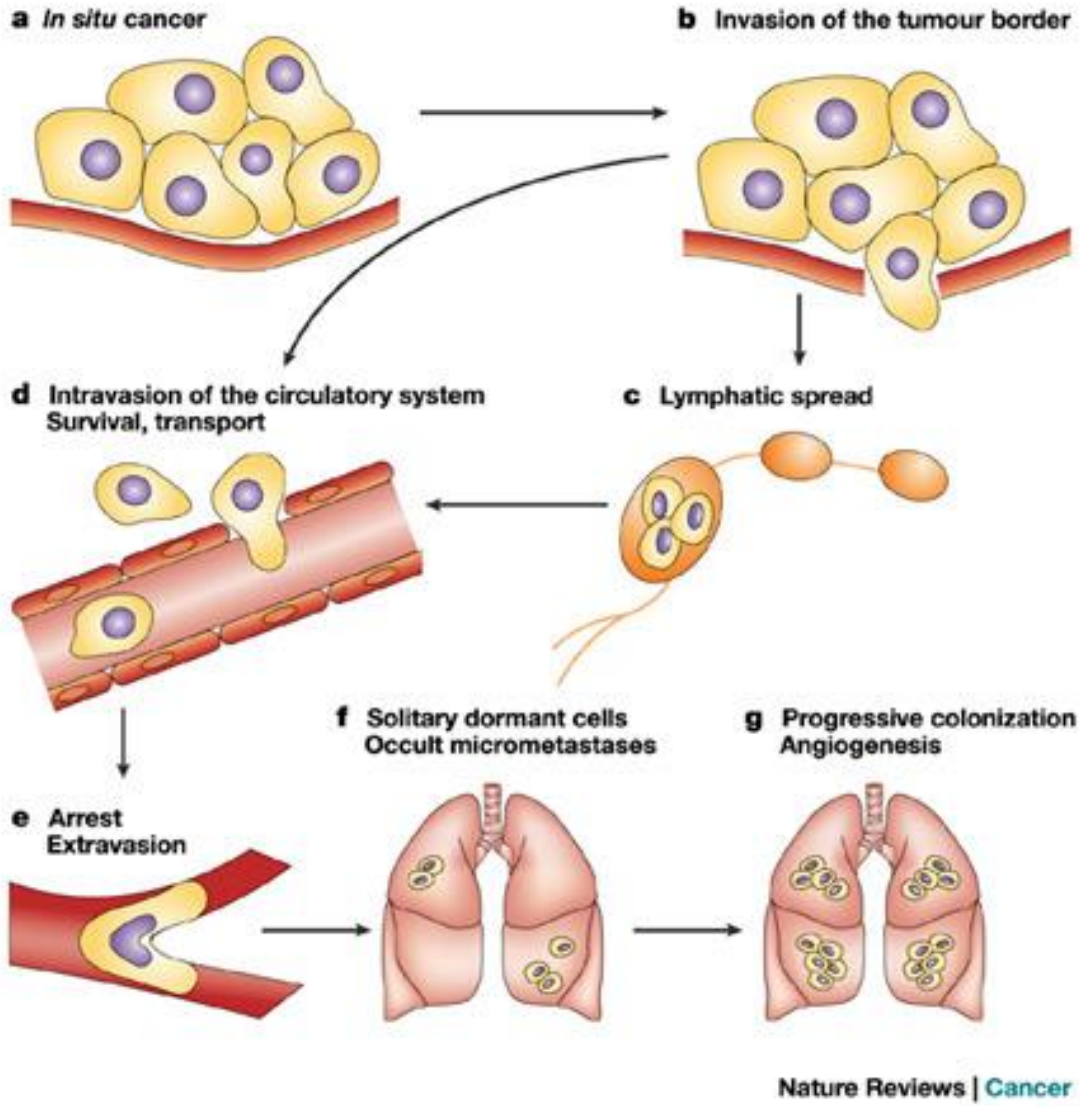
Migratory phenotype

- Cell migration can be classified into single-cell migration modes (mesenchymal, amoeboid) and collective migration modes (cell strands, sheets, clusters).
- These migration modes are associated with cellular energetic status, a characteristic structure of the cytoskeleton, specific use of integrins, matrix-degrading enzymes, and cell-cell adhesion molecules.
- Mesenchymal cell migration is a motility mode characterized by the elongated, spindle-like shape of cells, high cell polarization, and in the case of too-tight spaces in ECM, by proteolytic ECM remodeling by matrix metalloproteinases and serine proteases. In migrating cancer cells, mitochondria localize at the leading edge to support enhanced cell migration by providing local sources of energy.



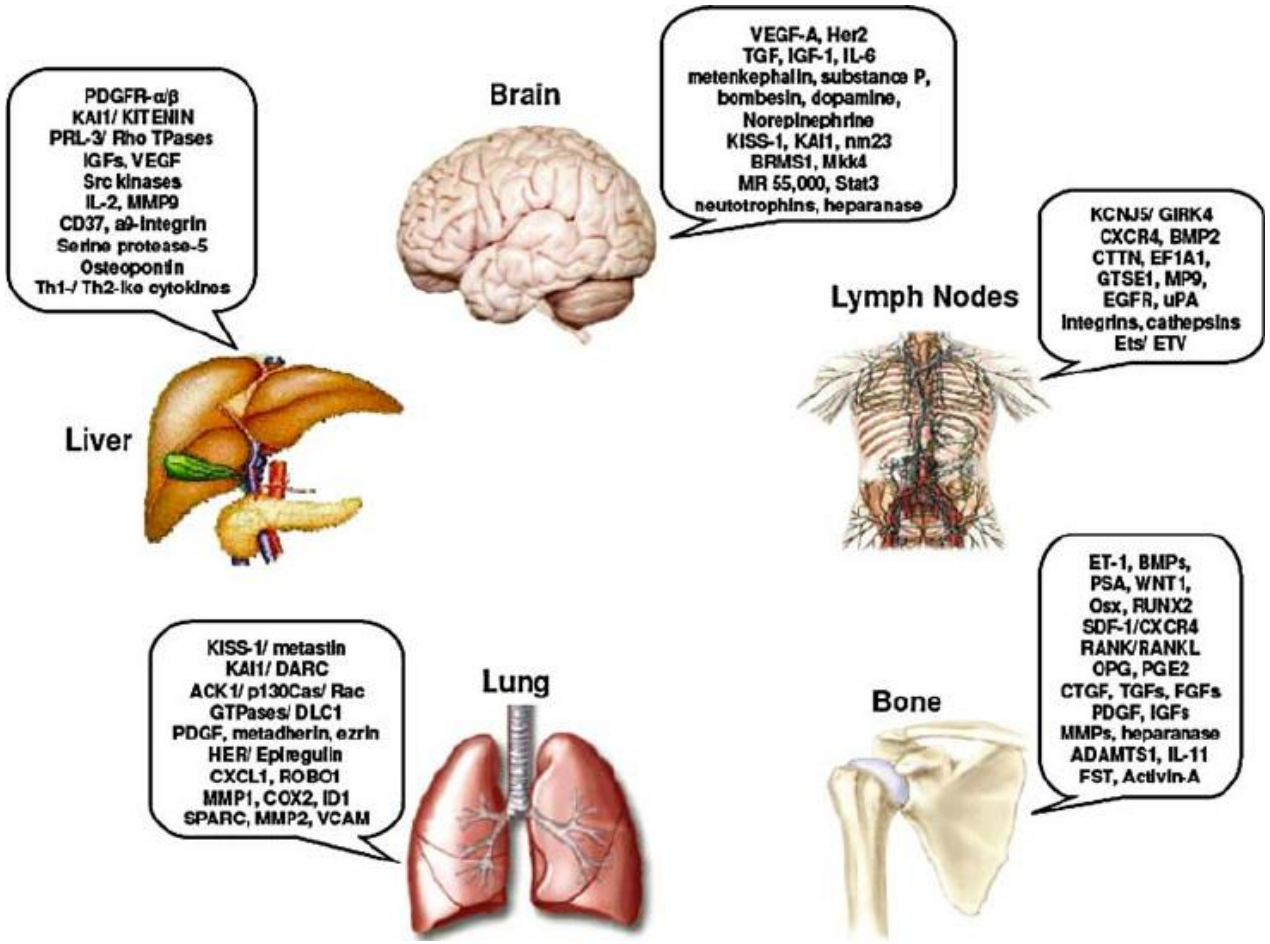
Invasion and metastasis

- Tumors that breach the basement membrane and invade underlying tissue are **malignant**. An even further degree of abnormality is metastasis, the seeding of tumor colonies to other sites in the body. Metastasis requires not only **invasiveness** but also **motility** and **adaptation** to foreign tissue environments.
- several ways of spreading:
- – **blood** (very often in the direction of flow from GIT to the liver by venous blood to the lungs from lungs by artery blood to bones and brain)
- – **lymphatic** (first neighboring lymph nodes, then distant)



Seed and soil hypothesis – permissive microenvironment

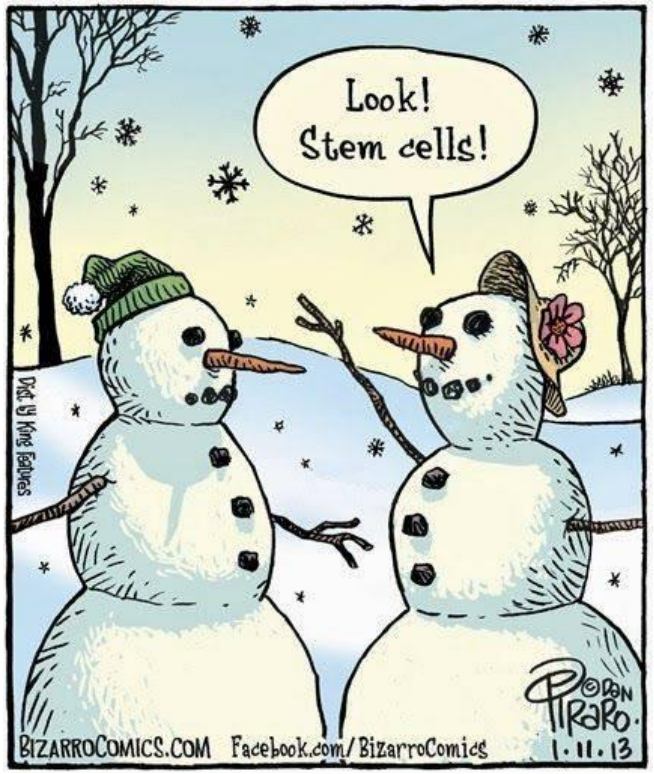
Tumor cell-intrinsic metastatic propensities are not sufficient for metastatic seeding.
Metastasis is dependent on the interactions between 'seeds' (the cancer cells) and the 'soil' (the host microenvironment).
Different cancers have preferential sites of metastasis=**organotropism** (prostate cancer - the bone and the liver).
Tumour-secreted factors and tumour-shed extracellular vesicles enable the 'soil' at distant metastatic sites to encourage the outgrowth of incoming cancer cells.
Pre-metastatic niches (PMNs) are sites of immune deregulation, owing to the presence of a pro-tumorigenic, inflammatory milieu induced by tumour-secreted factors, which creates immunosuppression and coagulation disorders.

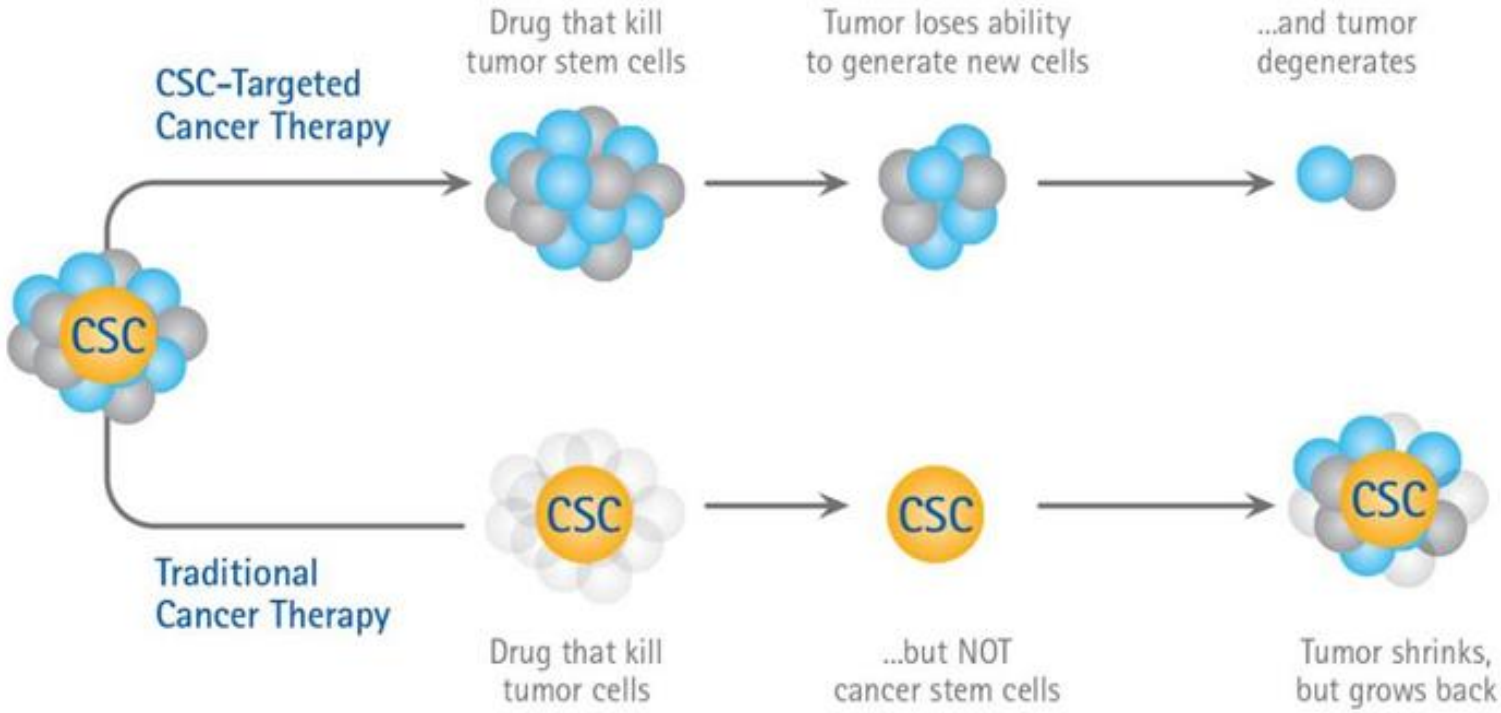


factors influencing organ-specific metastases to the liver, lung, brain, bone and lymph nodes

Cancer stem cell (CSC) hypothesis

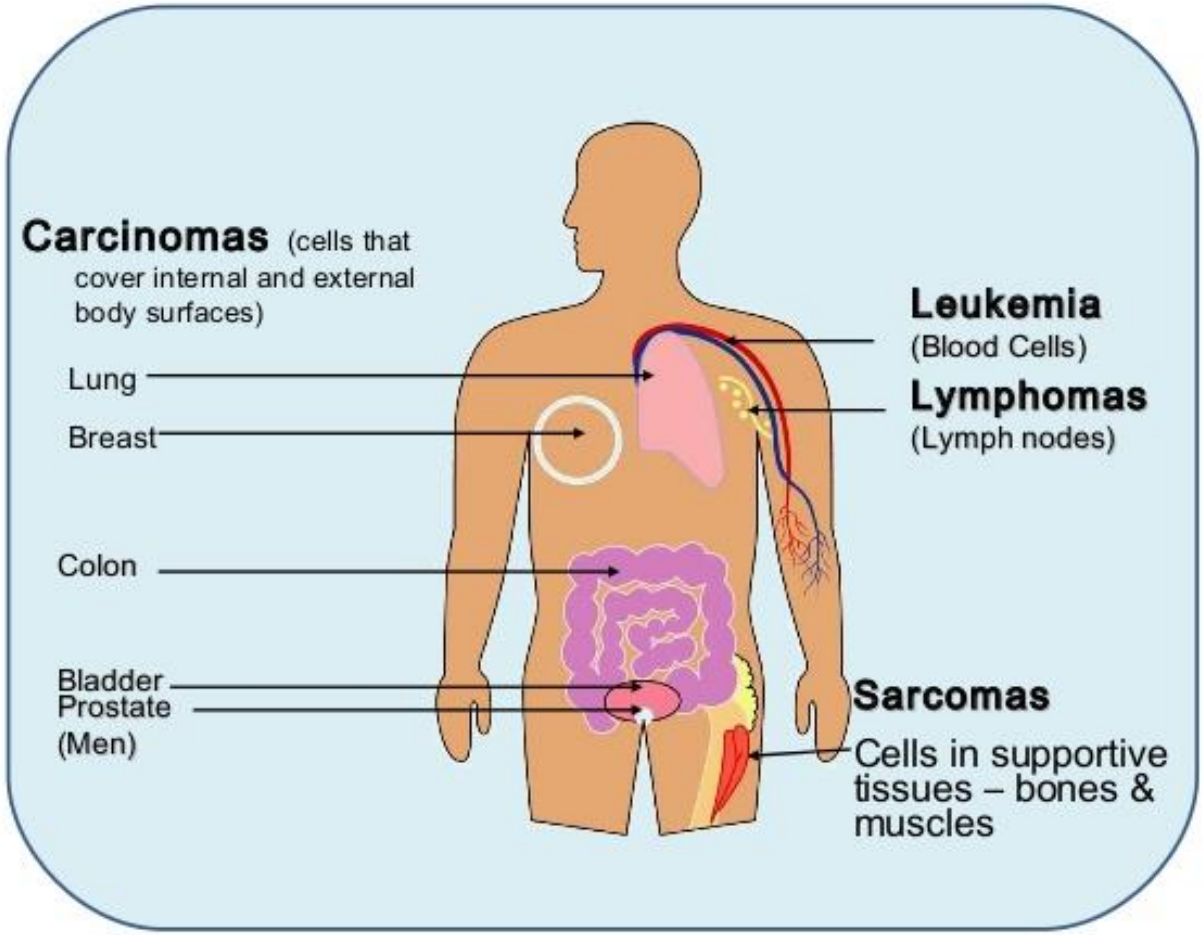
Cancer stem cells are rare **immortal** cells within a tumor that can both self-renew by dividing and give rise to many cell types that constitute the tumor.
CSCs are **tumorigenic**, associated with metastasis and relaps.
Enhanced resistance to therapy and cell stress.
Such cells have been found in various types of human tumors and might be attractive targets for cancer therapy.





Tumor clasification

the most common human cancers are of epithelial origin- the **carcinomas**. two main categories**: squamous cell carcinomas** (from epithelia that form protective cell layers) and **adenocarcinomas** (from secretory epithelia) Nonepithelial malignant tumors include: **sarcomas** (from mesenchymal cells); **hematopoietic cancers** (from the precursors of blood cells); and **neuroectodermal tumors** (from components of the nervous system).

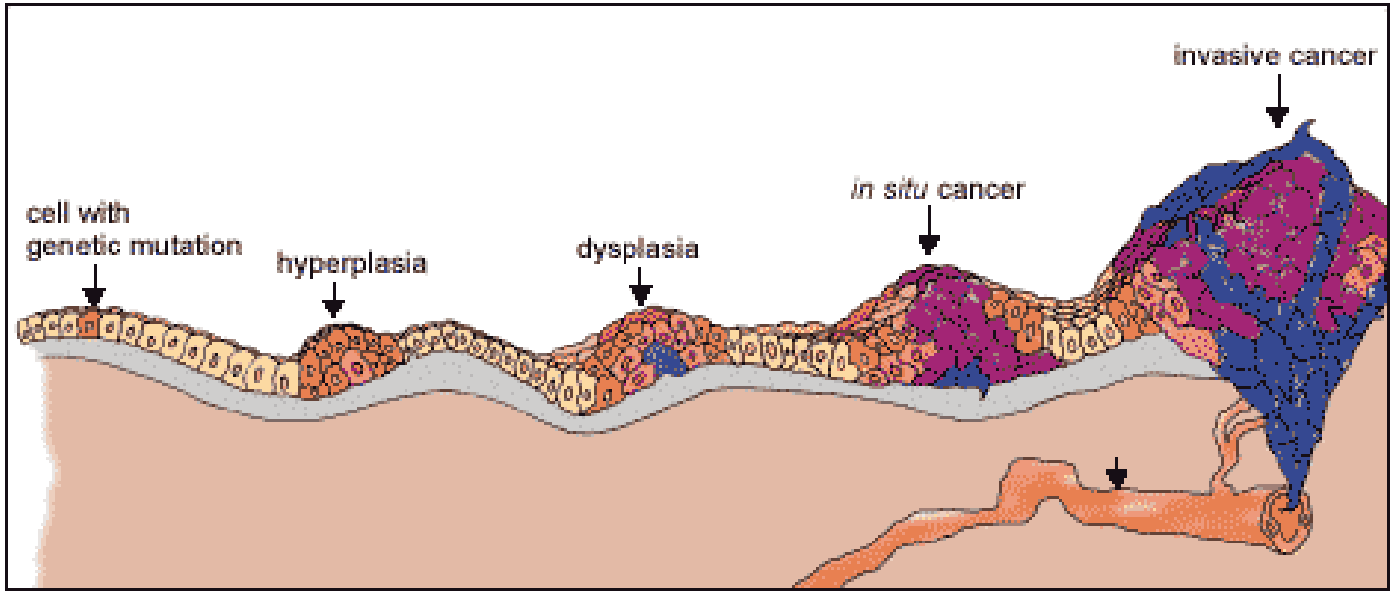


Tumor clasification

- If a tumor’s cells have dedifferentiated (lost all tissue-specific traits), its origin can not be readily identified; such tumors are said to be **anaplastic**.
- Benign tumors may be **hyperplastic** or **metaplastic**. Hyperplastic tissues are normal except for an excessive number of cells, whereas metaplastic tissues show displacement of normal cells by normal cell types not usually encountered at that site.
- **Dysplastic tumors** contain cells that are cytologically abnormal. Dysplasia is a transitional state between completely benign and premalignant.
- **Adenomas, polyps, papillomas, and warts** are dysplastic epithelial tumors that are considered to be benign because they respect the boundary created by the basement membrane.

Tumor clasification

typing = histological type
grading = benign × malignant
staging = TNM classification (T = tumor, N = node, M =metastasis)



Interaction of tumor with the host

local effect of tumor
mechanical compression (eg. brain tumors)
obstruction (e.g. carcinoma of the ductus choledochus)
bleeding, bruise (leukaemia)
chronic blood losses into GIT (gastric and intestinal tumors)
oedema (e.g. lymphomas)
coughing (lung carcinoma)
thromboses
difficult swallowing (oesophageal ca)
loss of vision (compression of optic nerve by hypophyseal adenoma)
voice changes (laryngeal carcinoma)
pathological fractures (myeloma)

Interaction of tumor with the host

systemic effects of tumor

anemia (supression of bone marrow) – effect of proinflammatory cytokines

fever - production of cytokines (pyrrogens) by tumor (IL-1, TNFα)

tumor cachexia – anorexic mediators (TNFα)

paraneoplastic syndromes – some tumors produce hormones (adenomas); important diagnostically!

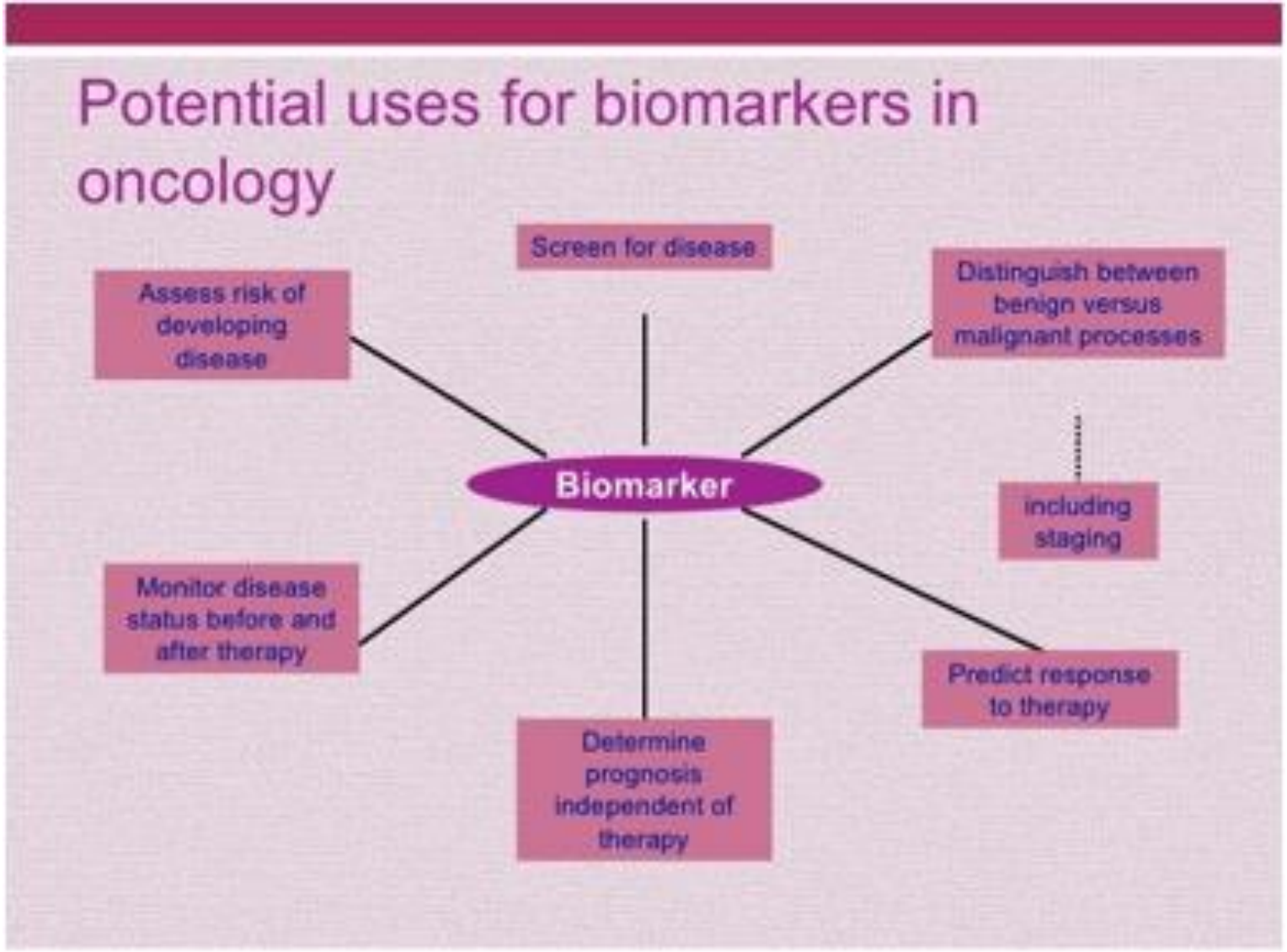
- –pigmentation
- –endokrinopathy (Cushing sy.,hypercalcaemia).

Cancer biomarkers

Cancer biomarkers are substances that are produced in response to cancerogenesis.
These substances can be found in the blood, urine, stool, tumor tissue, or bodily fluids.
Most cancer biomarkers are proteins. However, patterns of gene expression and changes in DNA can be used.

Cancer biomarkers

Cancer biomarkers can be classified into the categories based on their usage:
Predictive biomarkers predict response to specific therapeutic interventions (positivity/activation of *HER2* that predicts response to trastuzumab in breast cancer).
Prognostic biomarkers aim to inform regarding the risk of clinical outcomes such as cancer recurrence or disease progression.
Diagnostic biomarkers are used to identify whether a patient has a specific disease.



Cancer biomarkers – clinically relevant examples

Alpha-fetoprotein (AFP)

Cancer types: Liver cancer and germ cell tumors

Tissue analyzed: Blood

How used: To help diagnose liver cancer and follow response to treatment; to assess stage, prognosis, and response to treatment of germ cell tumors

BCR-ABL fusion gene (Philadelphia chromosome)

Cancer type: Chronic myeloid lukemia, acute lymphoblastic leukemia, and acute myelogenous leukemia

Tissue analyzed: Blood and/or bone marrow

How used: To confirm diagnosis, predict response to targeted therapy, and monitor disease status

Cencer antigen (CA) 15-3

Cancer type: Breast cancer

Tissue analyzed: Blood

How used: To assess whether treatment is working or disease has recurred

Cancer biomarkers - examples

HER2/neu gene amplification or protein overexpression
Cancer types: Breast cancer, gastric cancer
Tissue analyzed: Tumor
How used: To determine whether treatment with certain targeted therapies is appropriate
Prostate-specific antigen (PSA)
Cancer type: Prostate cancer
Tissue analyzed: Blood
How used: To help in diagnosis, assess response to treatment, and look for recurrence
Carcinoembryonic antigen (CEA)
Cancer types: Colorectal cancer and some other cancers
Tissue analyzed: Blood
How used: To keep track of how well cancer treatments are working or check if cancer has come back

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