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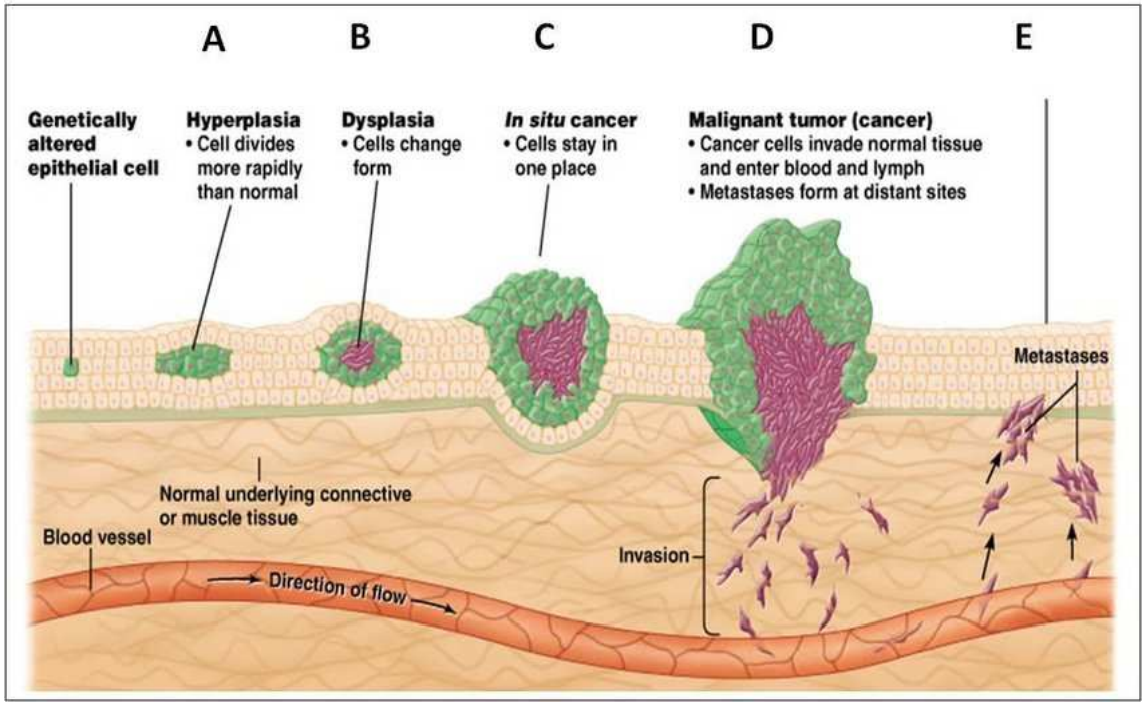
Malignant transformation

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.

Cancerogenesis



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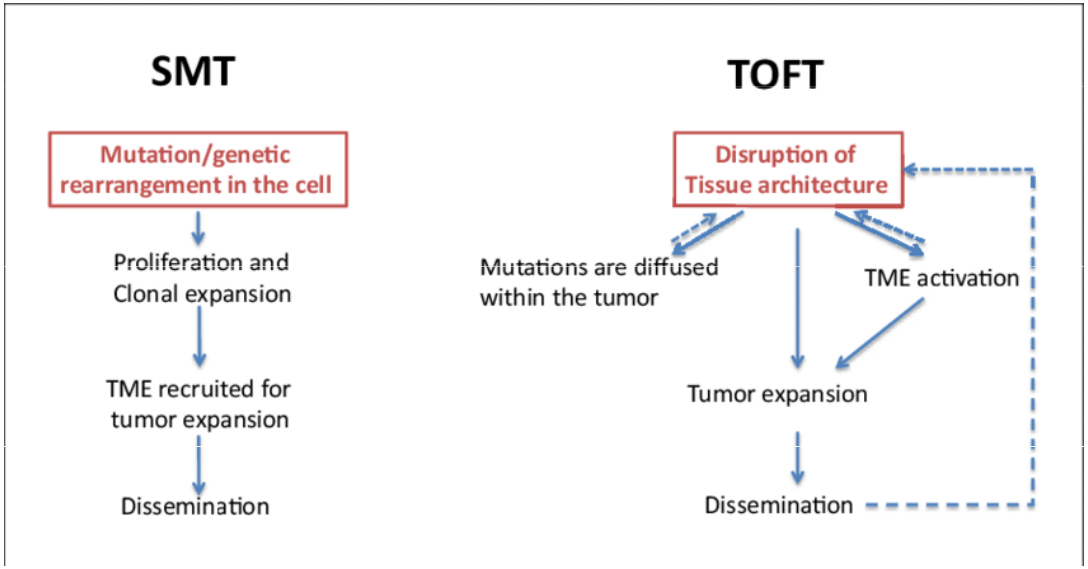
Theories of carcinogenesis

Tissue Organization Field Theory (TOFT)

- Carcinogenesis is “development gone awry.”
- Normal tissue blocks the proliferation and motility of cells (tissue homeostasis).
- Disruption of the normal tissue organization 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.

Somatic Mutation Theory (SMT)

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



Somatic mutations versus tissue organization

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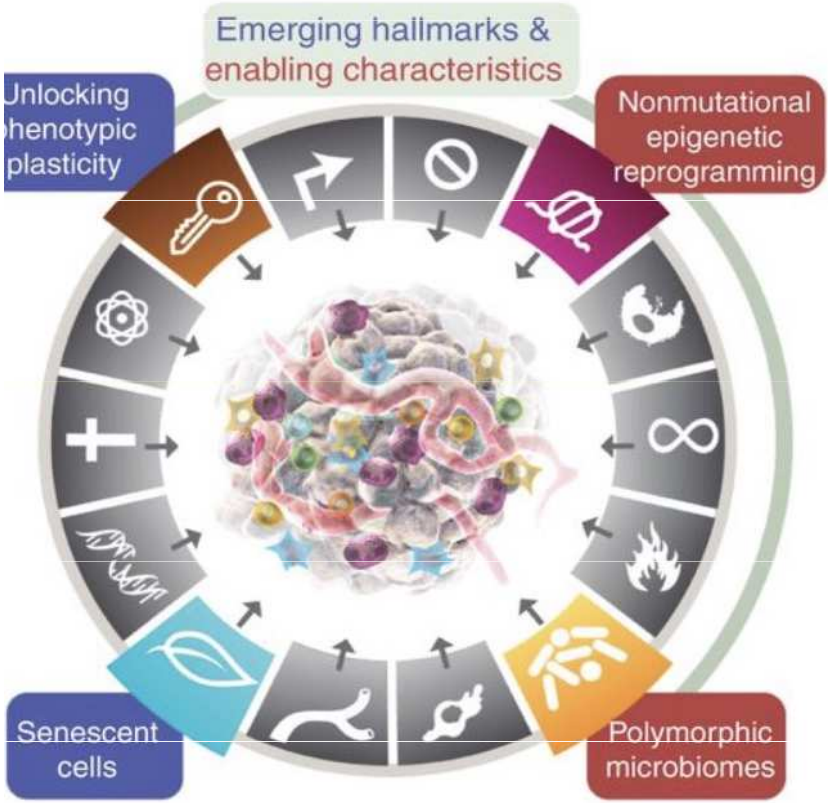
Enabling characteristics of cancer

- Genomic instability and nonmutational epigenetic reprogramming
- Unlocking phenotypic plasticity
- Tumor microenvironment
- Polymorphic microbiomes



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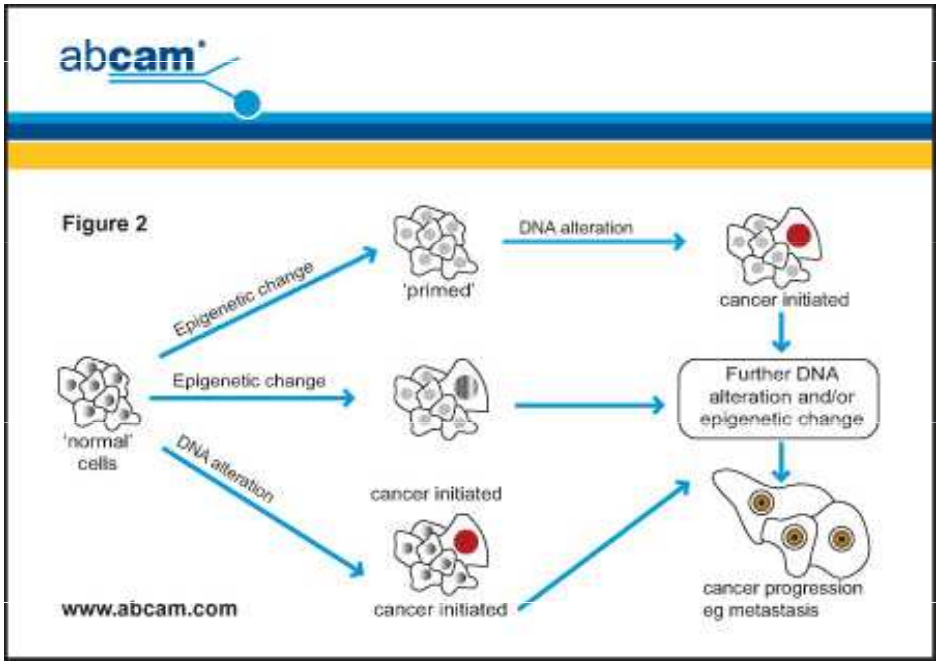
Genomic instability and non-mutational epigenetic reprogramming

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



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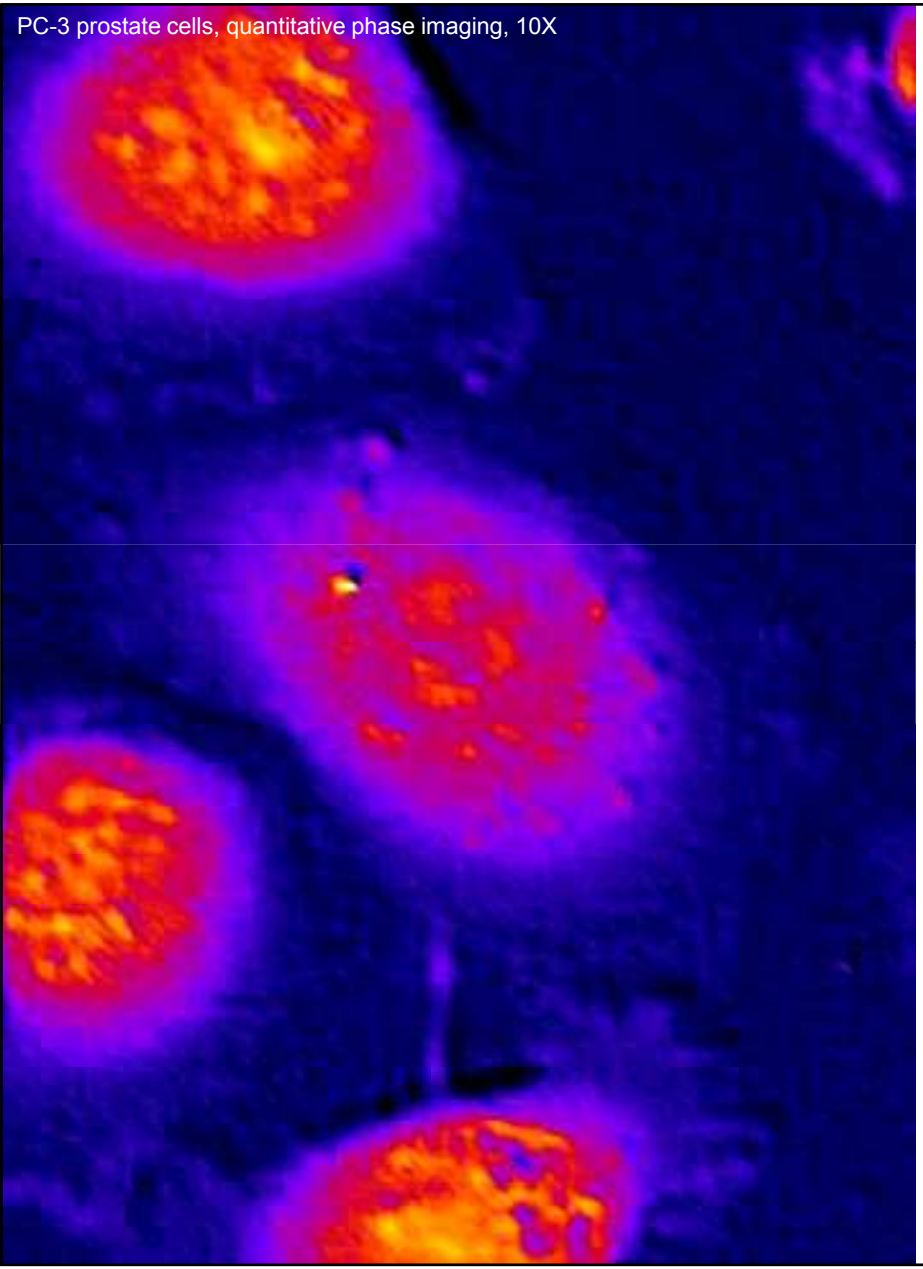

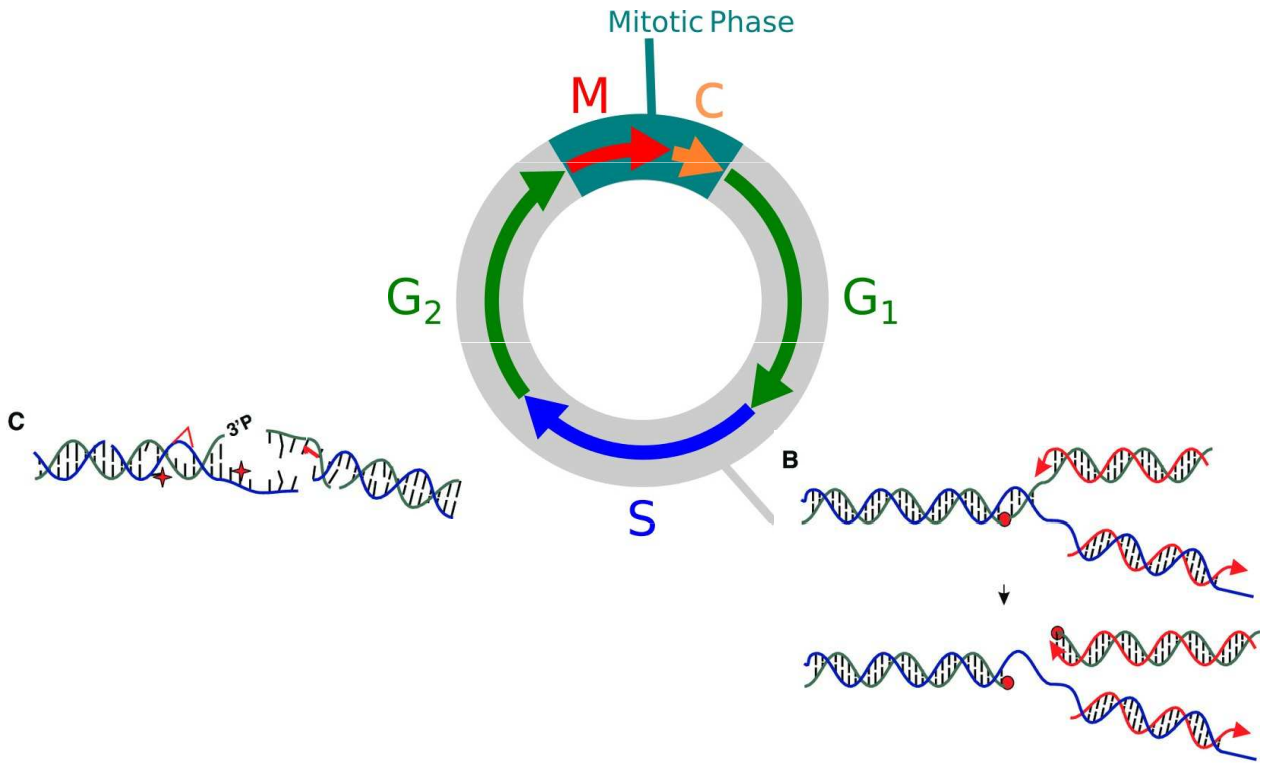

double DNA strand break ← single DNA strand break

50/cell cycle	5000/cell cycle

30 000 000 000 000 breaks/day in human

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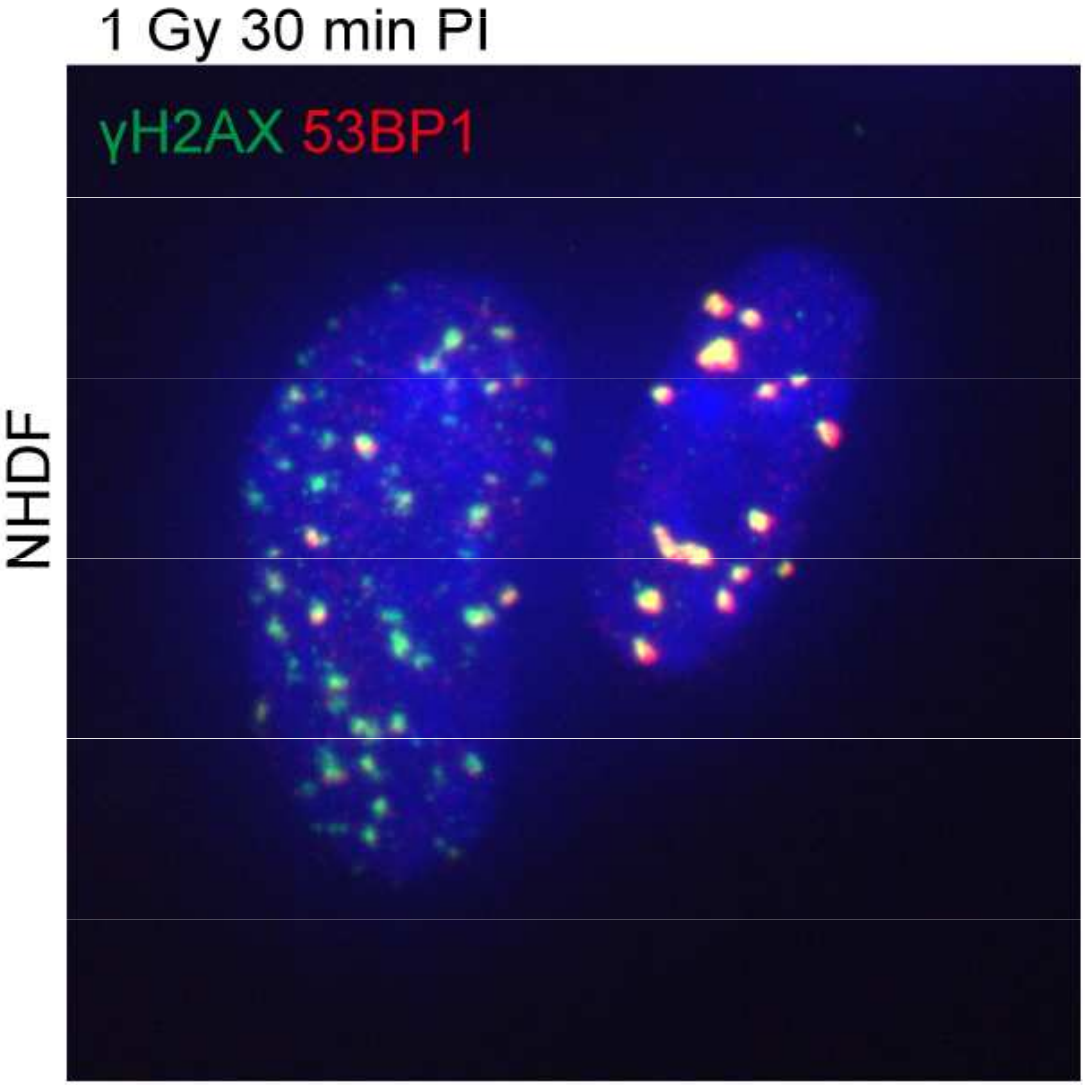
Double strand breaks – most serious DNA damage



repair of 1 double strand break = 10^4 ATP molecules

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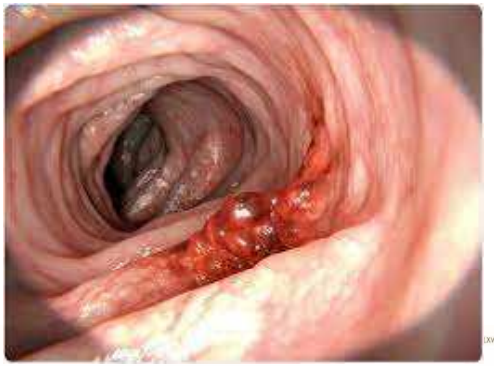
DNA repair genes/proteins

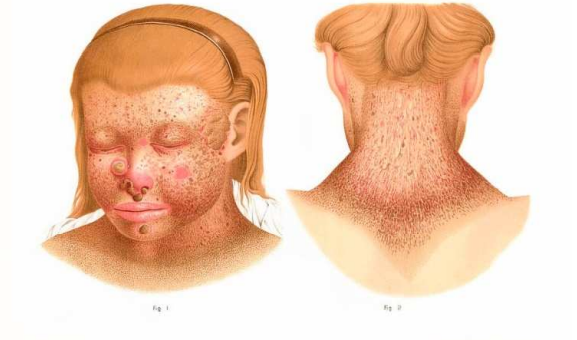
MMR genes/proteins (“Mismatch repair”)

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.



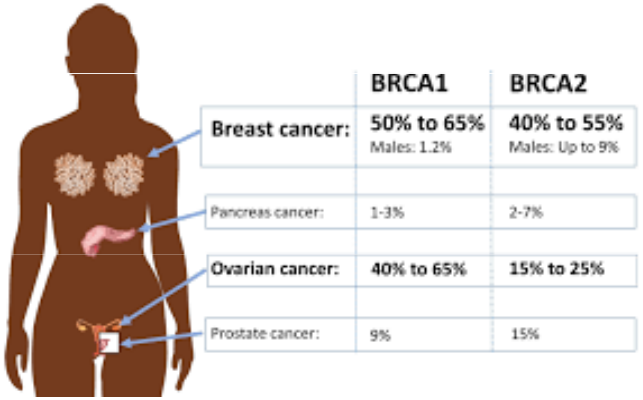
Nucleotide excision repair genes/proteins (“single strand break repair”)

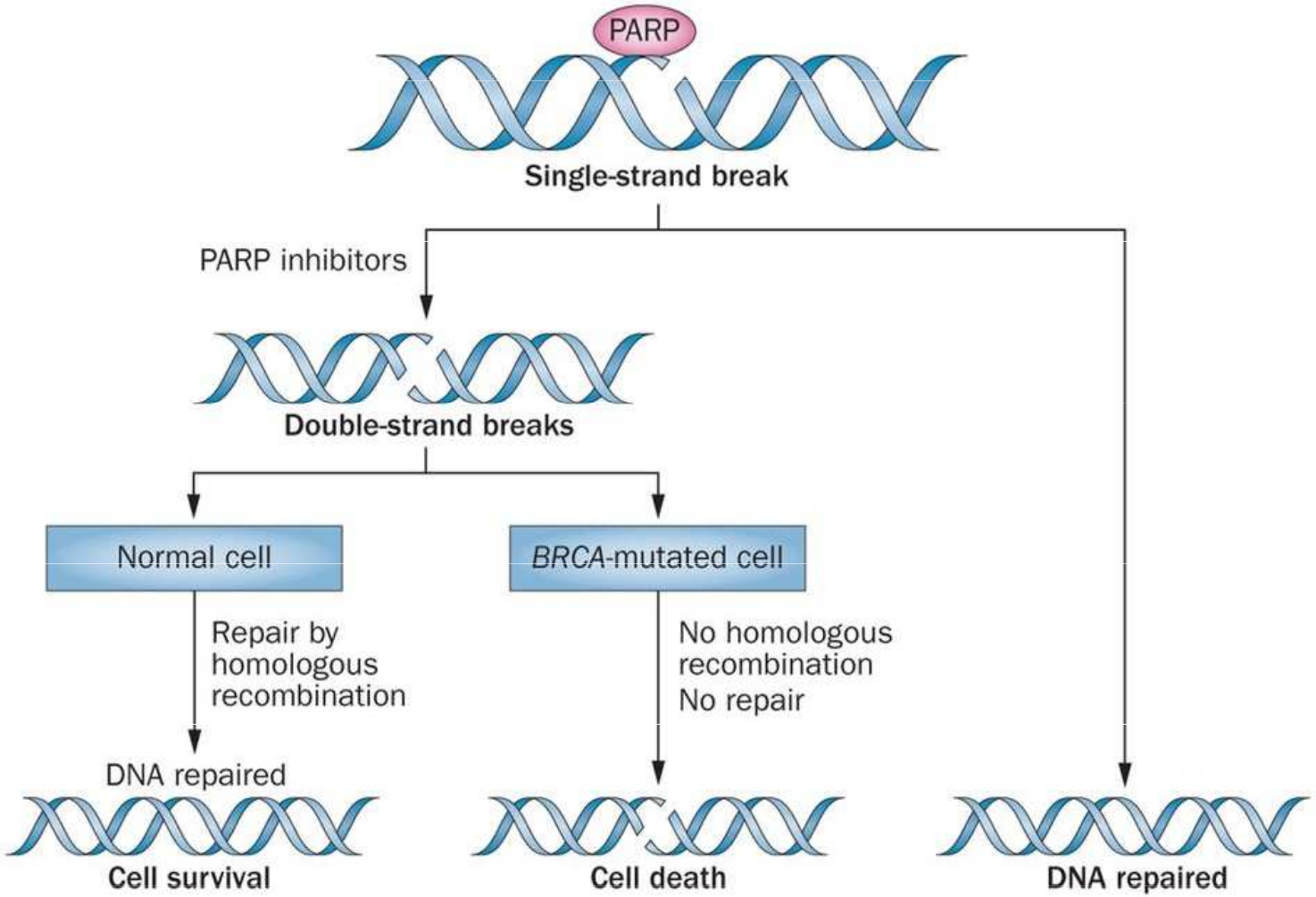
NER-defects cause xeroderma pigmentosum (XP). XP patients show severe sun sensitivity and develop skin cancers during childhood.



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")




PARP
Single-strand break
PARP inhibitors
Double-strand breaks
Normal cell
BRCA-mutated cell
Repair by homologous recombination
No homologous recombination
No repair
DNA repaired
Cell survival
Cell death
DNA repaired

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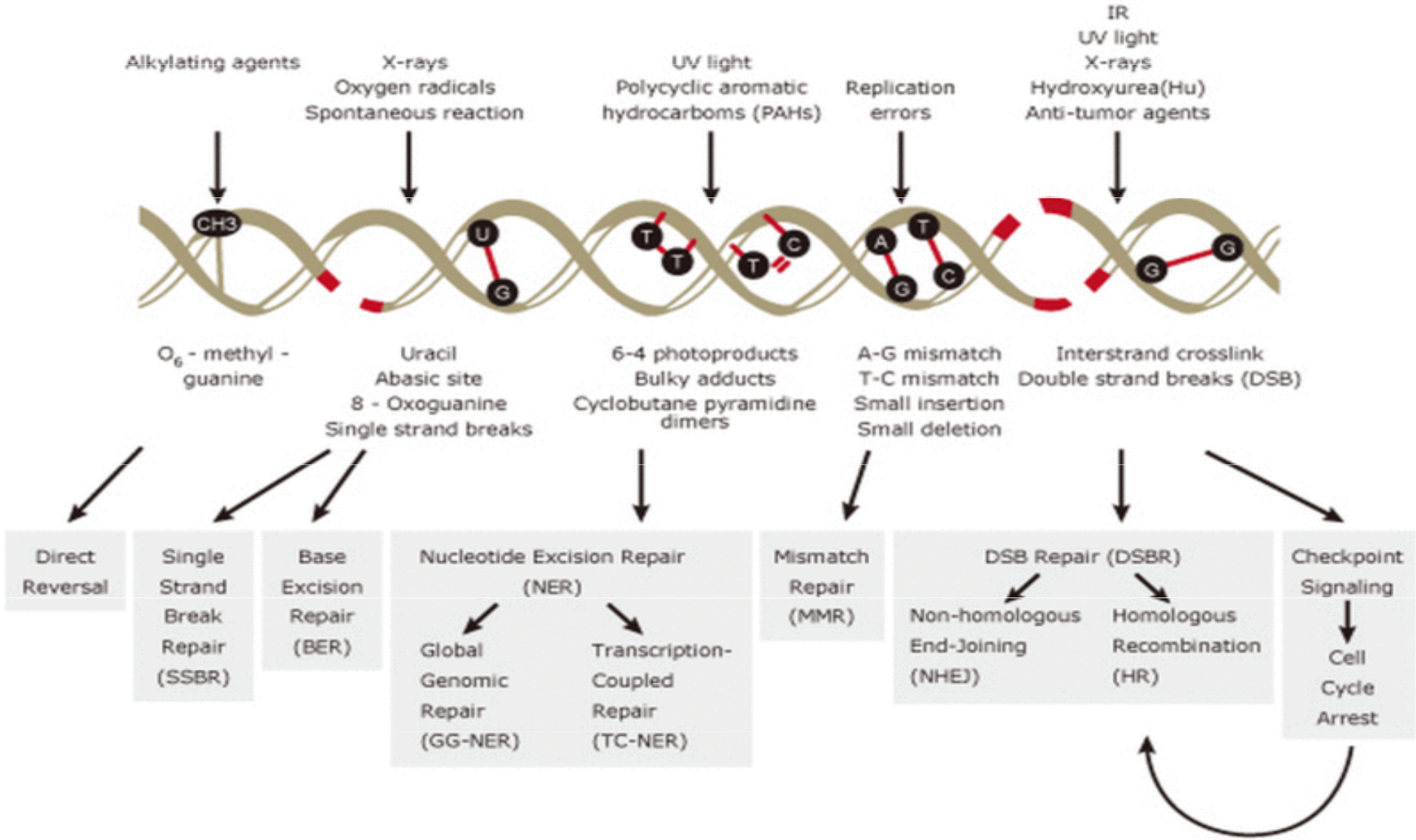
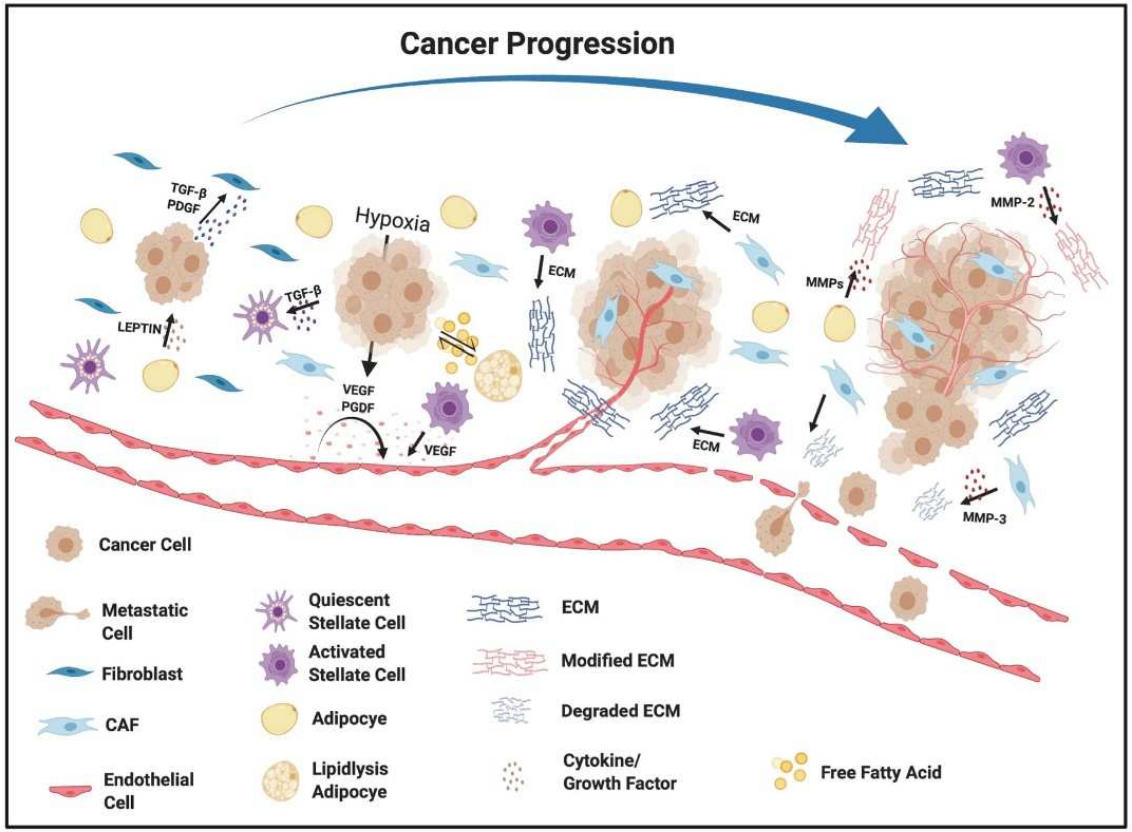

Alkylating agents
X-rays
Oxygen radicals
Spontaneous reaction
UV light
Polycyclic aromatic
hydrocarboms (PAHs)
Replication
errors
IR
UV light
X-rays
Hydroxyurea(Hu)
Anti-tumor agents
CH3
U
G
T
T
T
C
A
T
G
C
G
G
O6 - methyl -
guanine
Uracil
Abasic site
8 - Oxoguanine
Single strand breaks
6-4 photoproducts
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

Tumor microenvironment

- **reciprocal relationship** between **cancer cells and components of the TME**
- 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 **an 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.

- 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.



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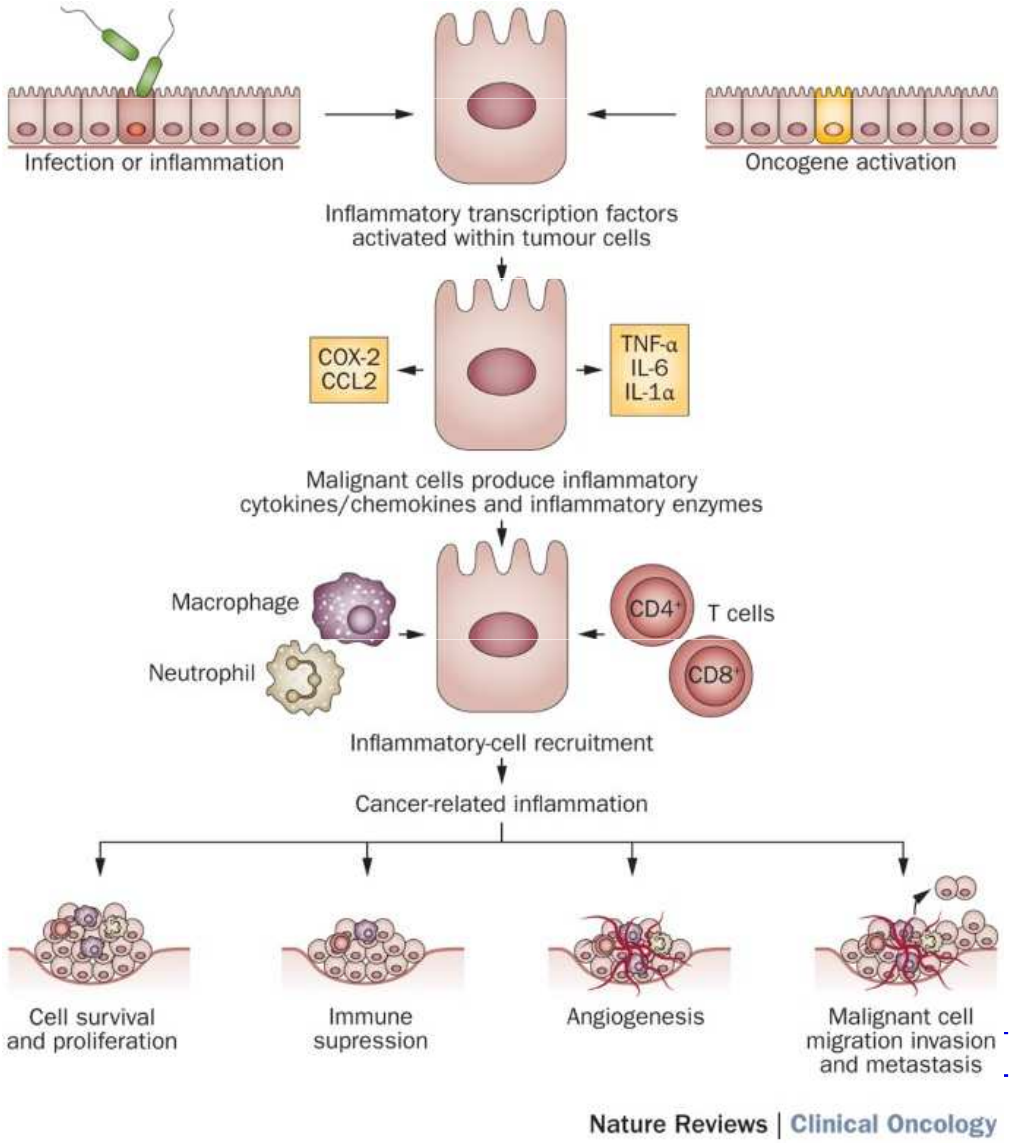
Inflammation

- 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.

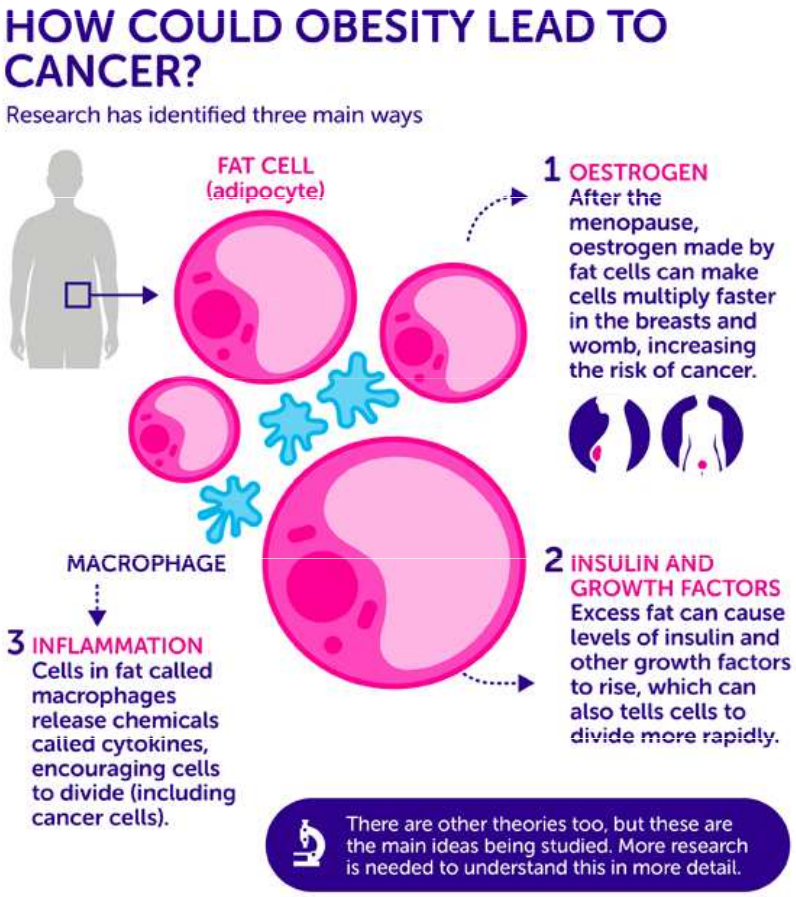


Inflammation and obesity

- 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– 4 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 that is essentially a huge gland sending out biological information that affects the rest of the body. Oestrogen and growth factors produced by fat cells increase the risk of cancer.



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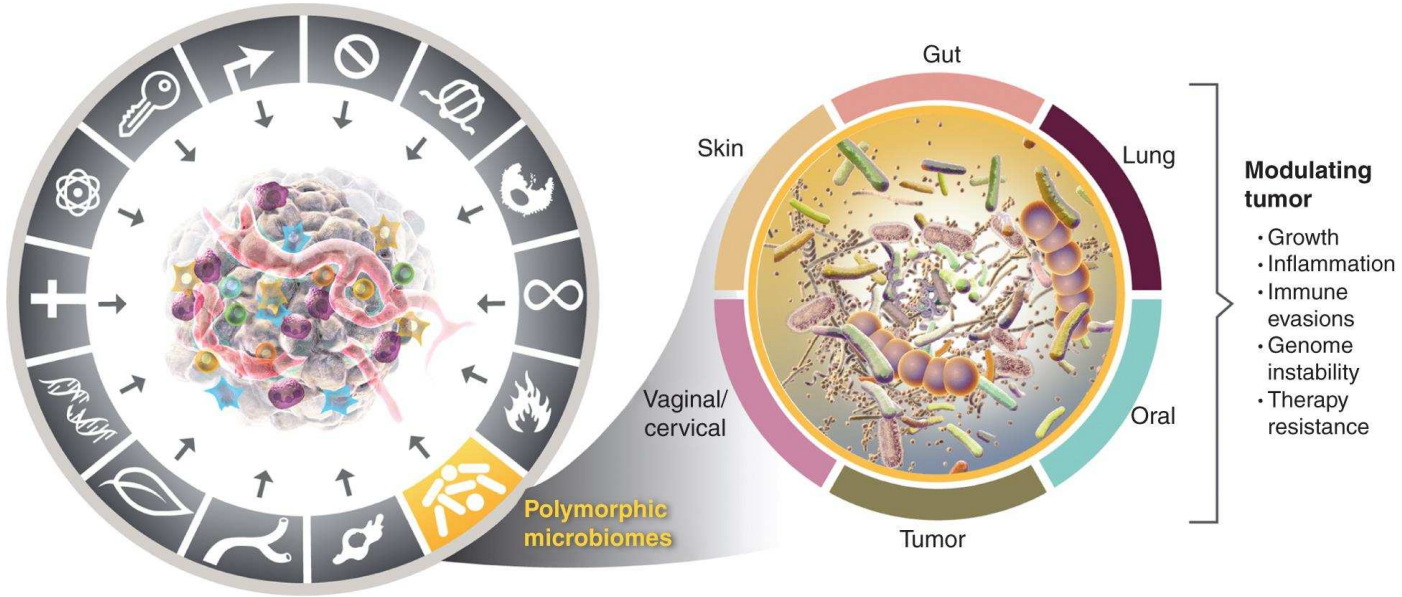
Polymorphic microbiomes

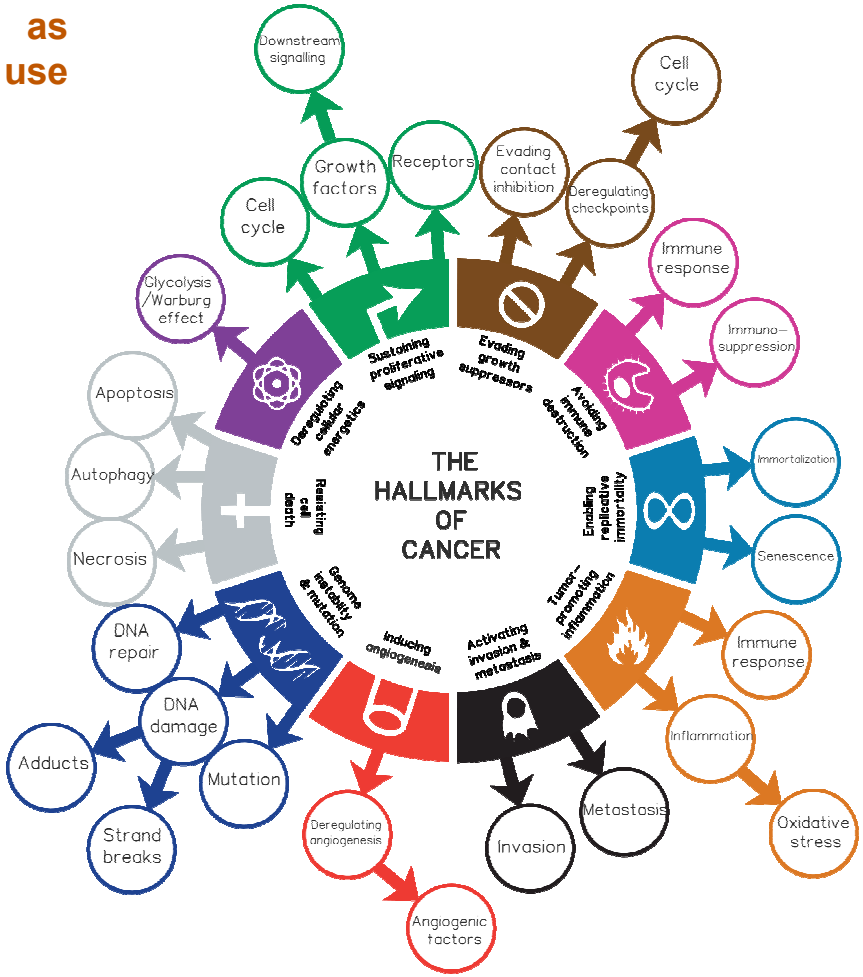
- The evidence is increasingly compelling that polymorphic variability in the microbiomes between individuals in a population can have a profound impact on cancer phenotypes.
- There are both cancer-protective and tumor-promoting microbiomes, involving particular bacterial species, which can modulate 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

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 at the wrong intensity, time, and place.
Cancer is a disease of regulation.

- Continual upregulated 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



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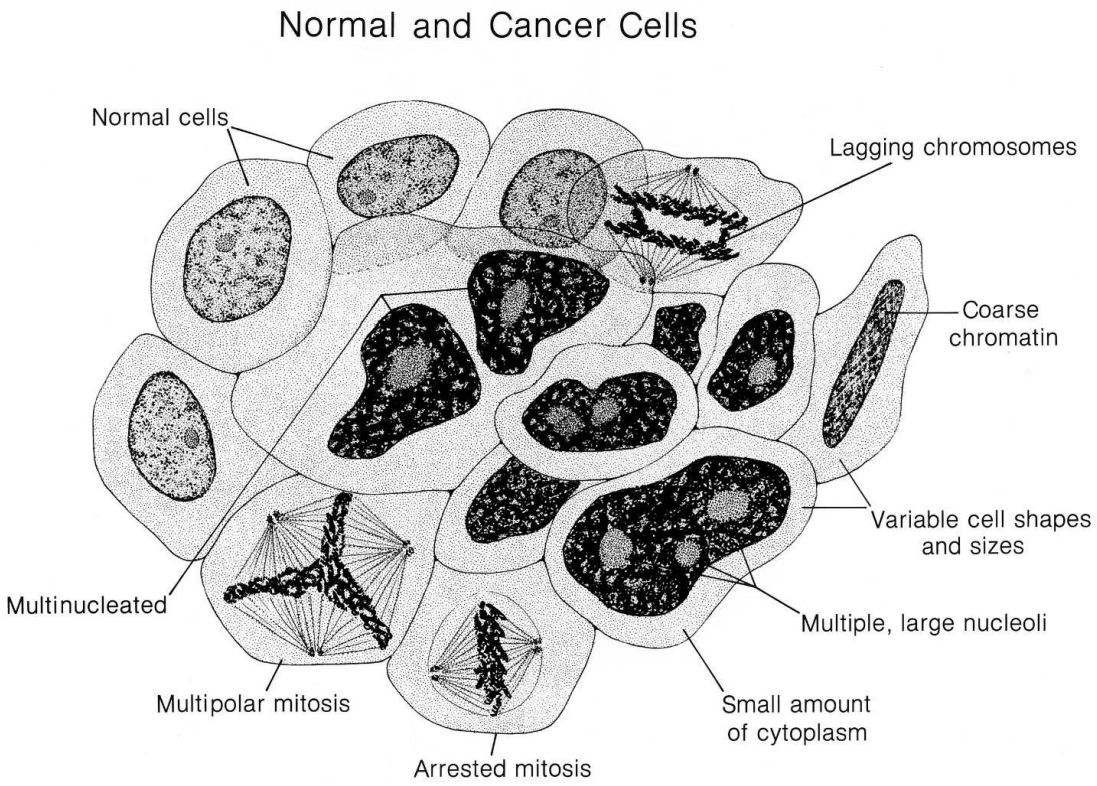
Cancer cell

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.



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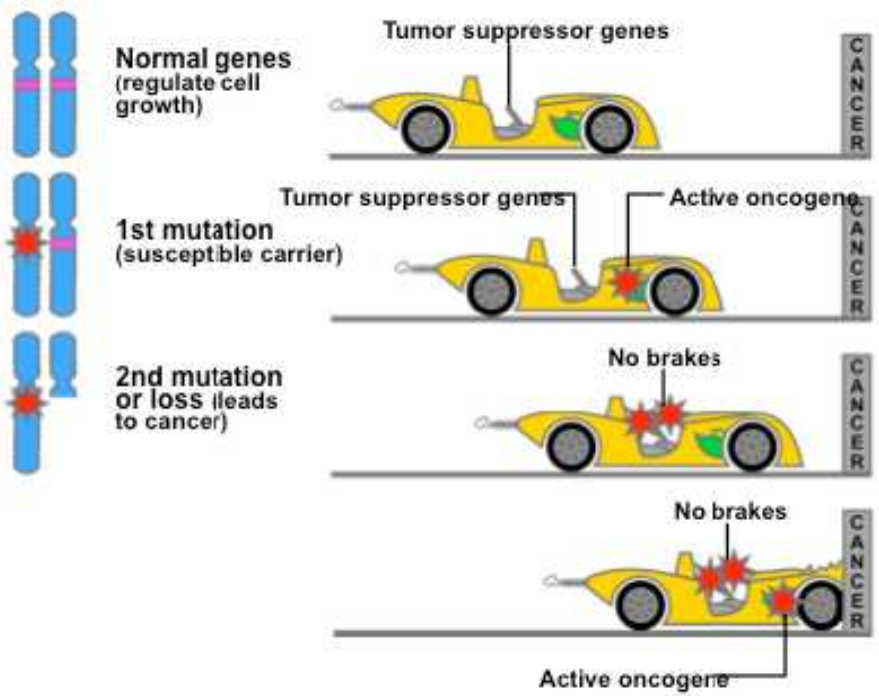
Oncogenes and tumor suppressors

- **Proto-oncogenes** – Genes whose products encode components of the molecular cascades that mediate cell growth, cell survival, and block cell differentiation.
- 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.



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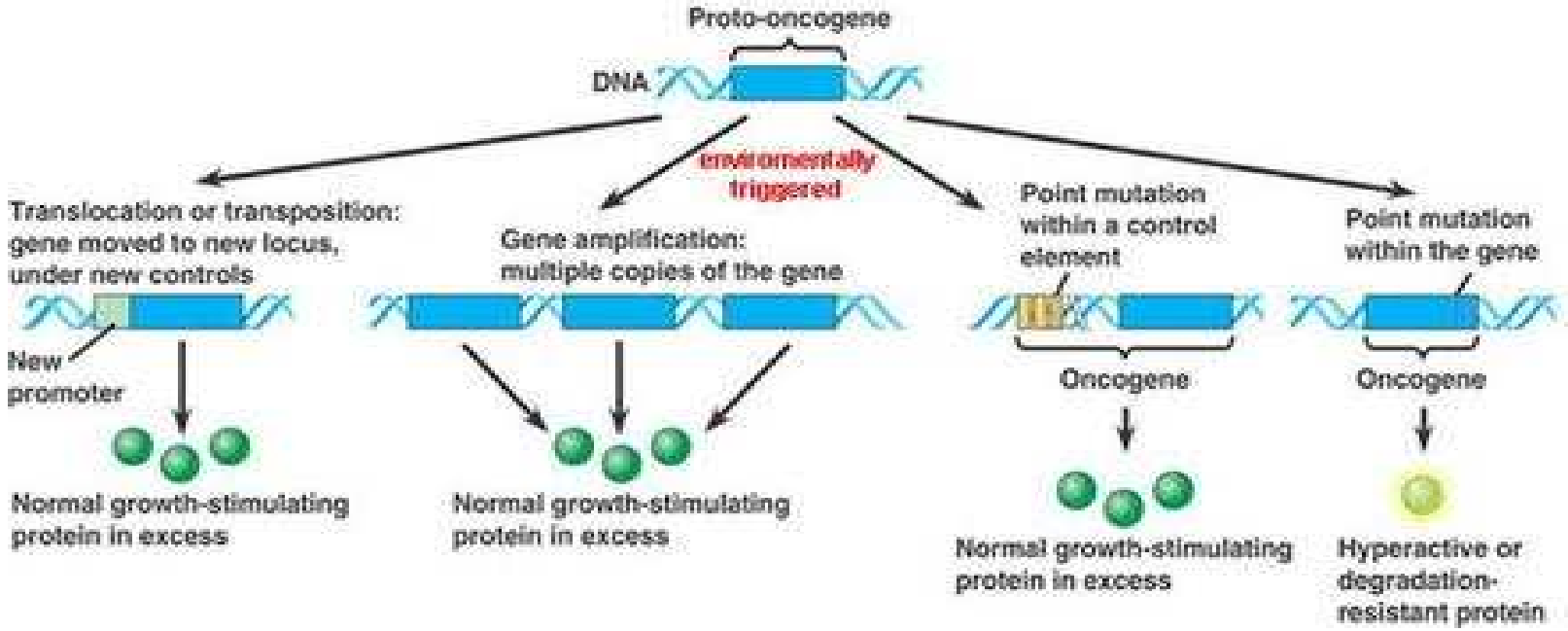
Oncogenes

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



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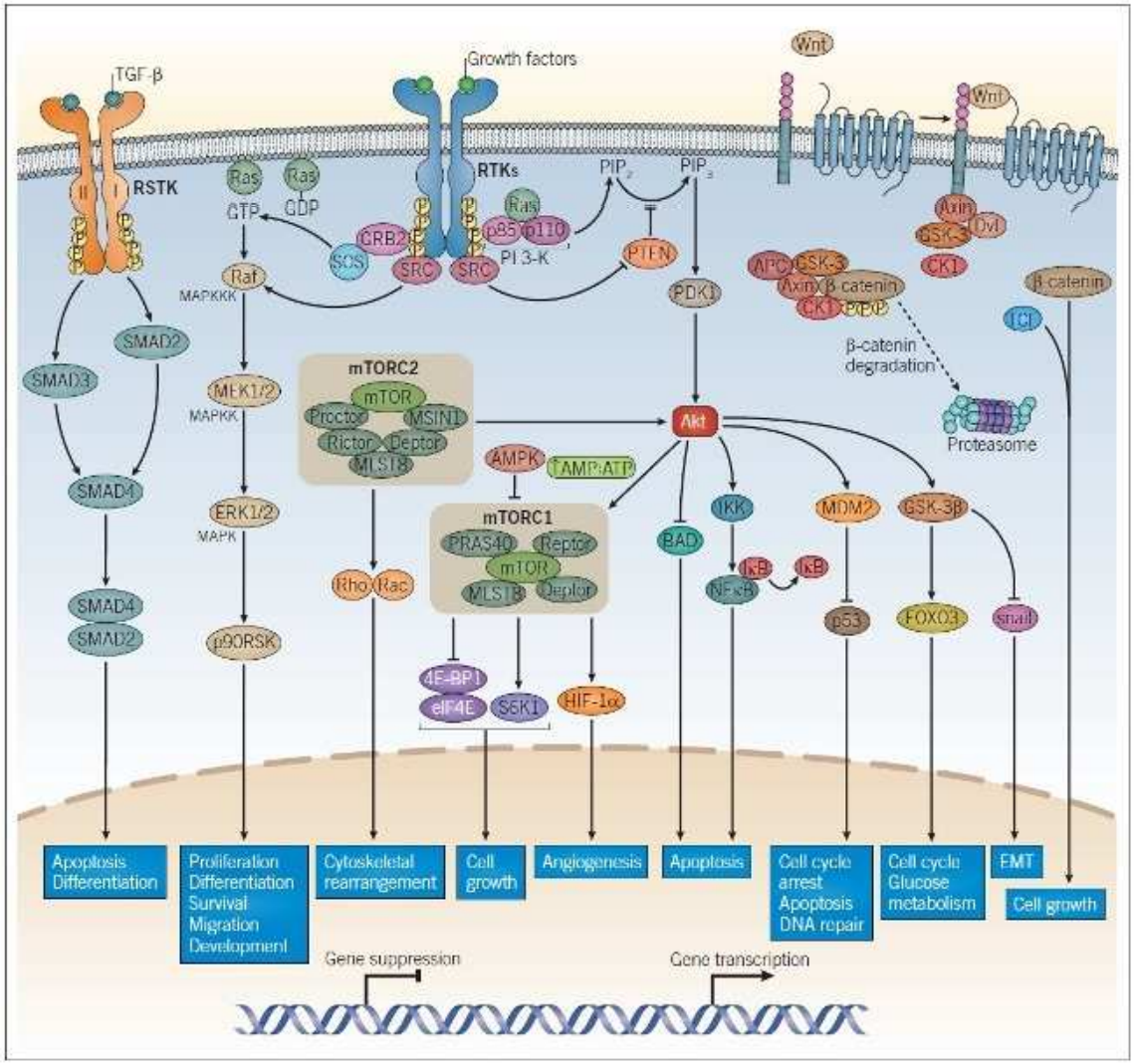
Uncontrolled growth - “GO” signals

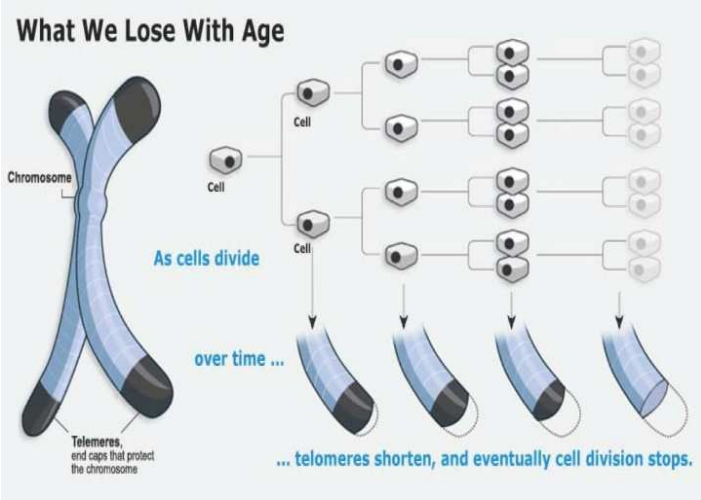
“GO” signals = main mitogenic signals include:

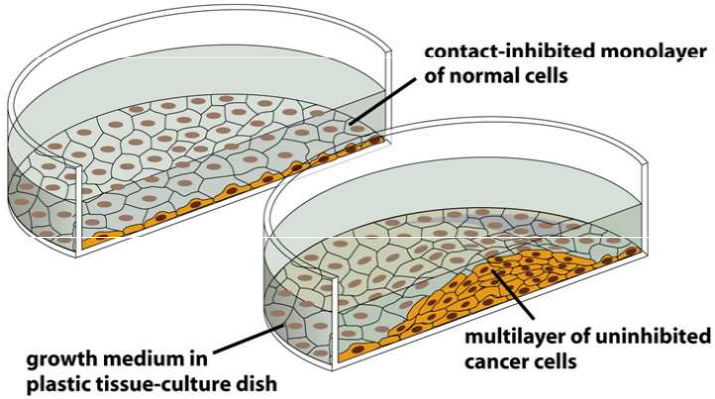
1. **growth factors** (e.g. EGF, VEGFA, PDGF)
2. **growth factor receptors** (e.g. the receptors for epidermal growth factor EGF (EGFR) and its close homologue HER2/neu (ERBB2)
3. **receptor-coupled signal transduction molecules** (RAS family)
4. **proteinkinases** (SRC,ABL)
5. **transcription factors** (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.





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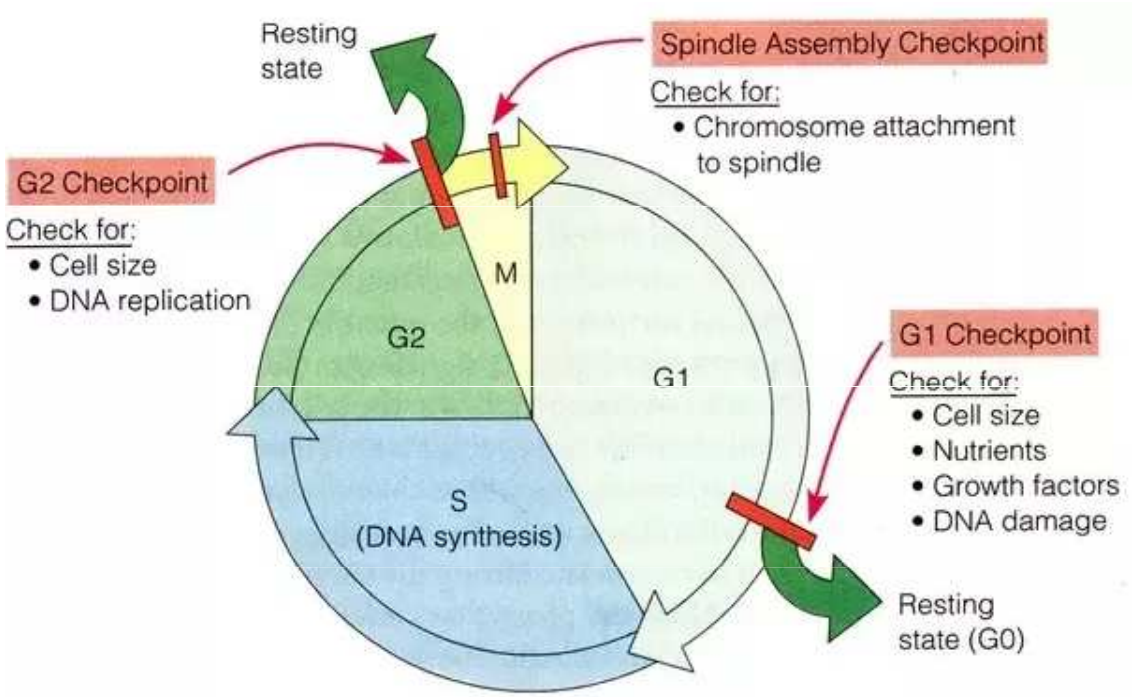
Uncontrolled growth – loss of “STOP” signals

- 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).



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Tumor suppressors

- 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.
- In many tumors suppressors are lost or inactivated.

Tumor suppressors are often named according to the type of tumor developing due to their loss of function.

Rb (= retinoblastoma)

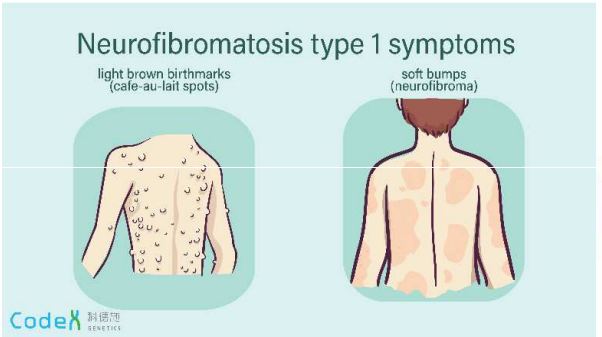
WT (= Wilm's tumor)

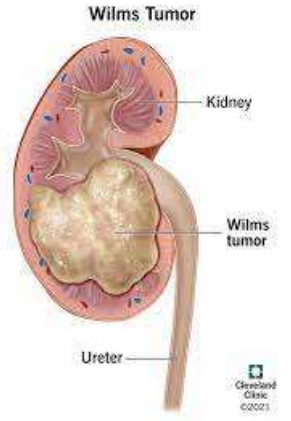
NF1 and NF2 (= neurofibromatosis)

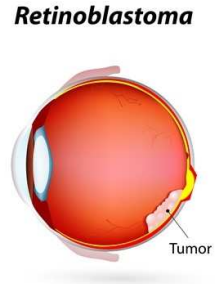
APC (= Adenomatous Polyposis Coli)

DCC (= Deleted in Colon Cancer)

VHL (= von Hippel-Lindau syndrome)







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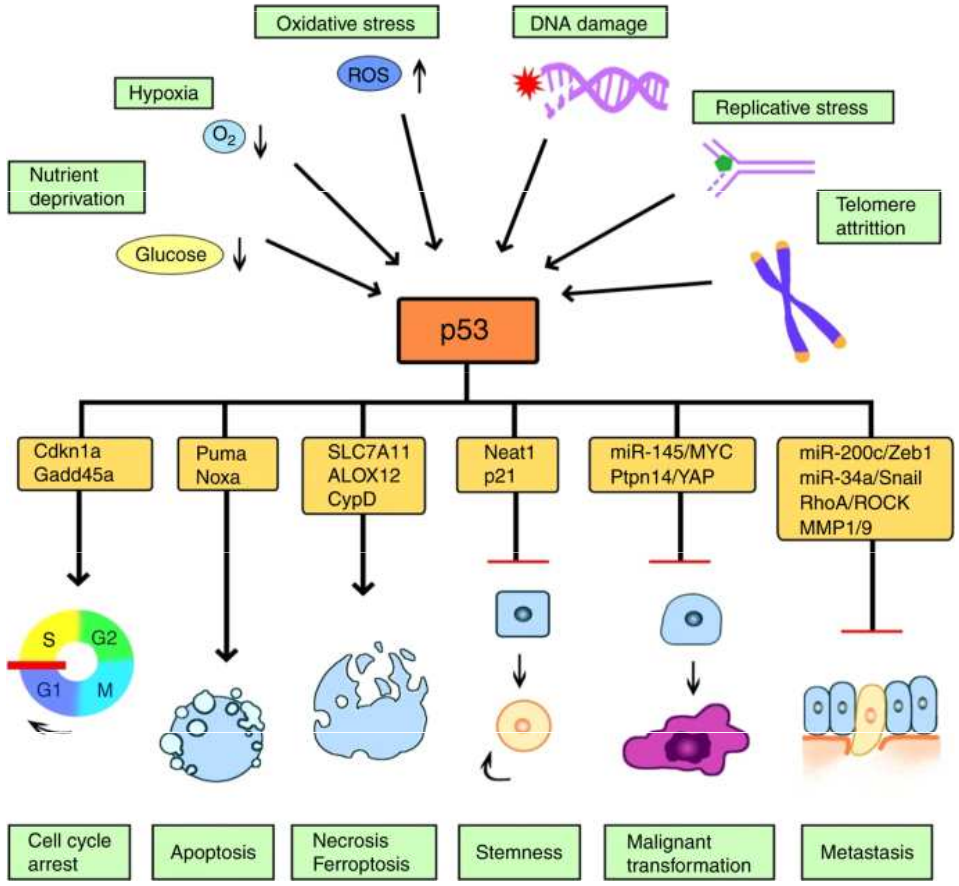
p53 – the guardian of the genome

Located at 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, apoptosis and other genes
- Li-Fraumeni syndrome – inherited TP53 mutation

Inhibitors of cyclin-dependent kinases (e.g. p21, 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



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Rb protein–true tumor suppressor

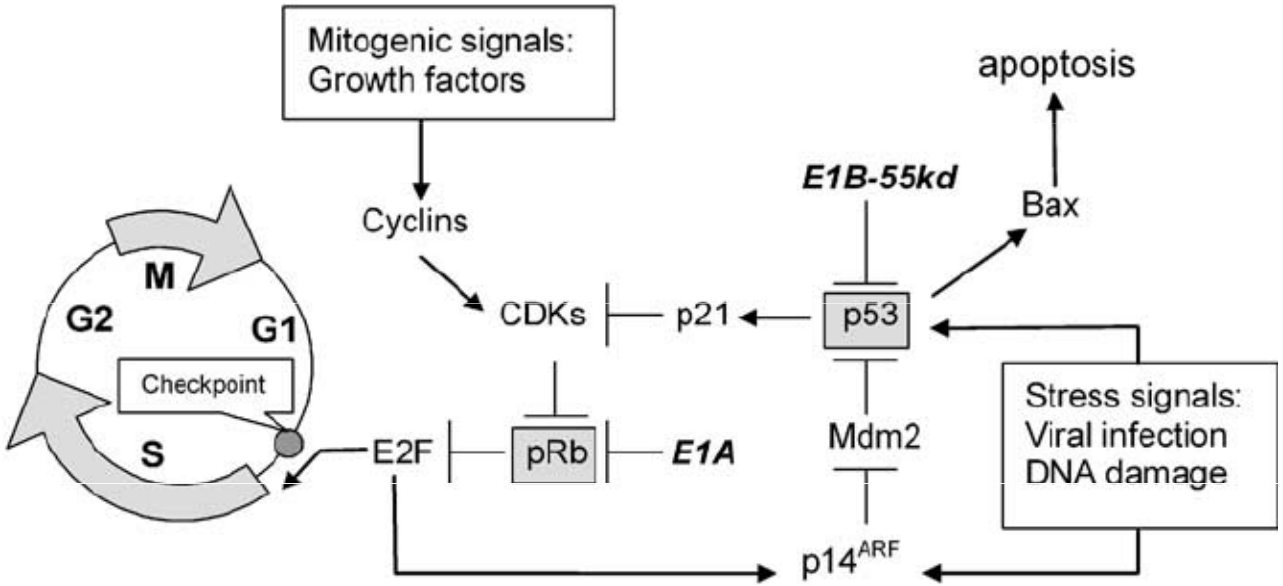
- Rb is a main inhibitor of the cell cycle and controls the transition from G1- to S-phase.
- Rb inhibits the transcription factor E2F, which upon release from Rb ↑ expression of S phase genes (e.g. DNA replication enzymes).

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.



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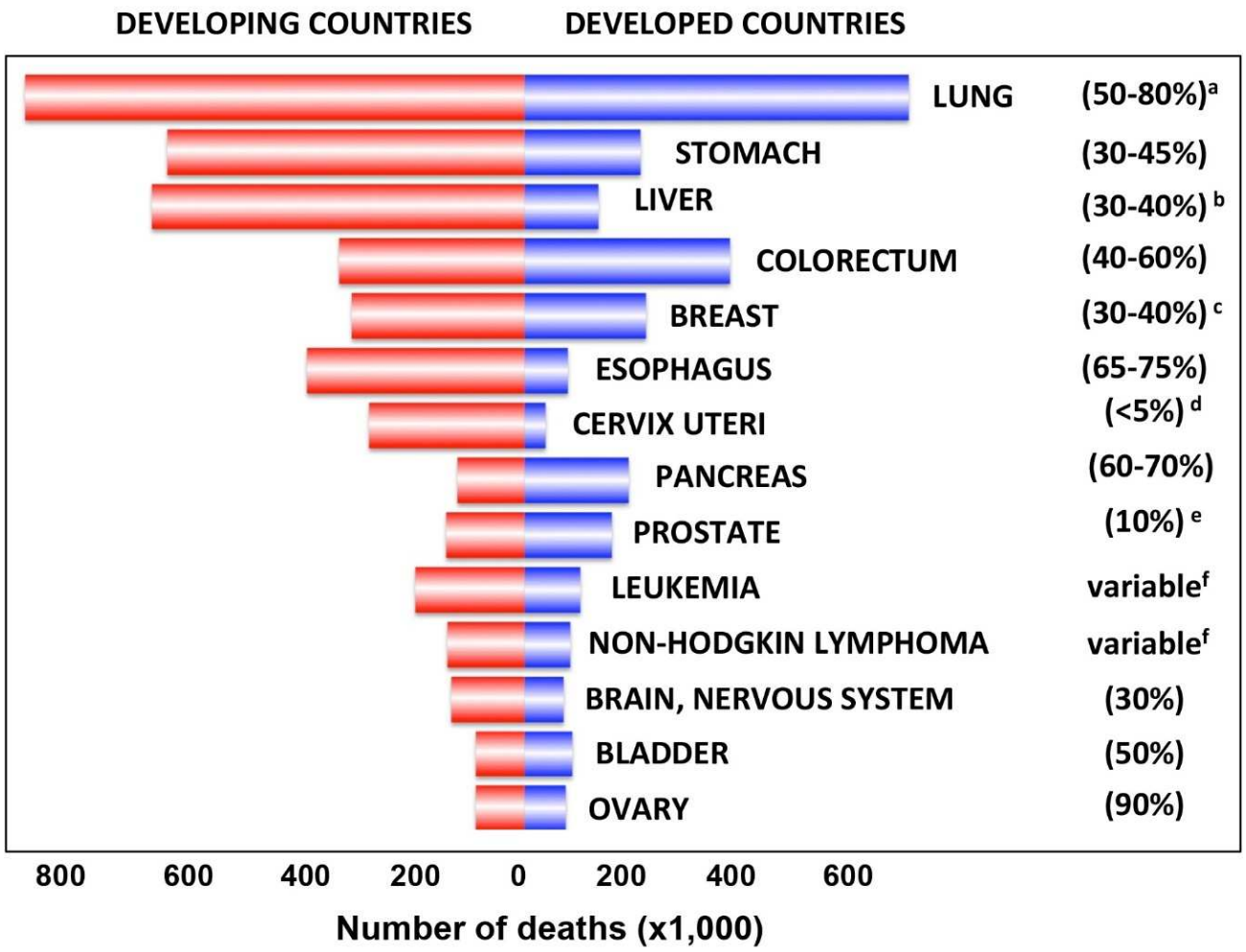
Percentage of tumors with mutated p53



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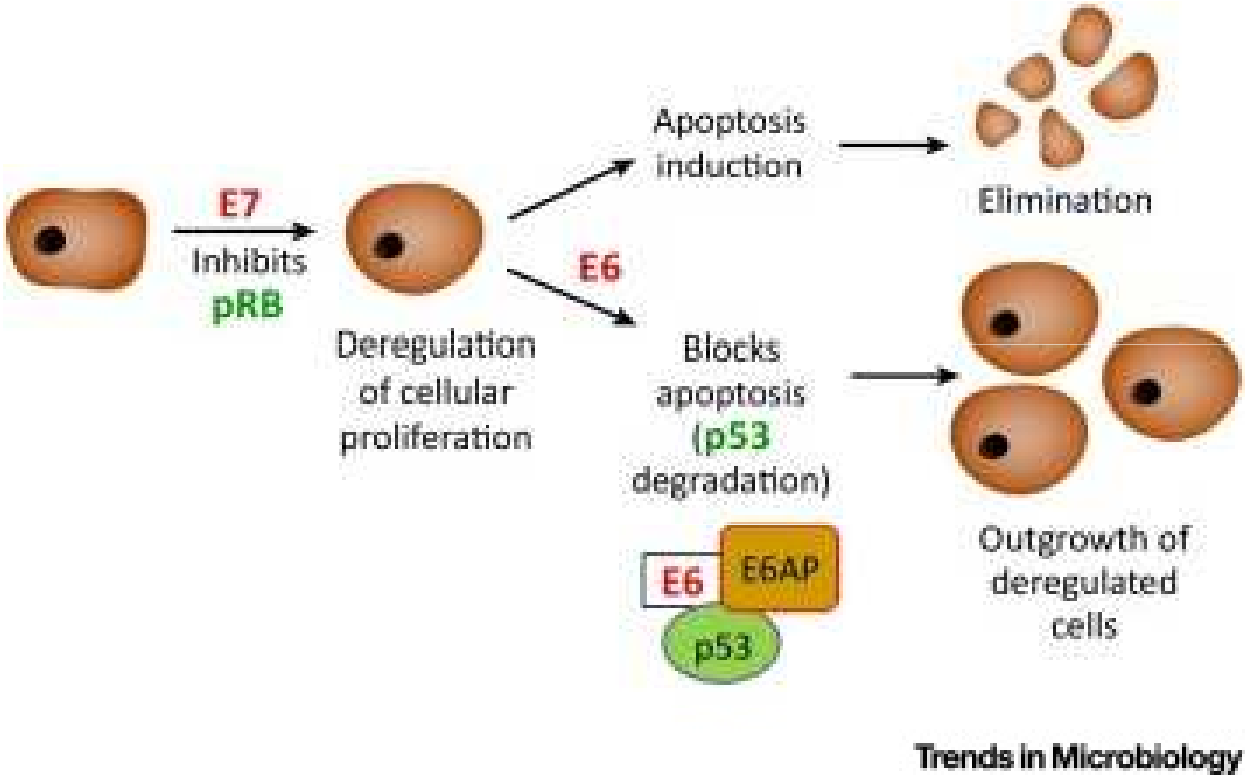
HPV and p53

– 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.



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Cell death

- **Apoptosis**

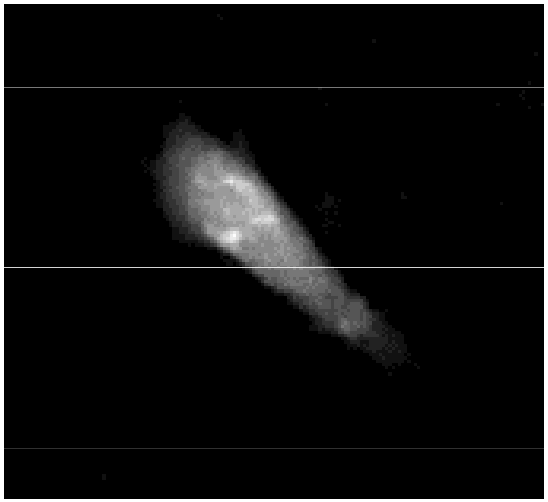
– Active (=needs energy), programmed cell death. The action of caspases and other apoptotic enzymes (proteases and nucleases) leads to cell fragmentation to apoptotic bodies that are removed by macrophages.

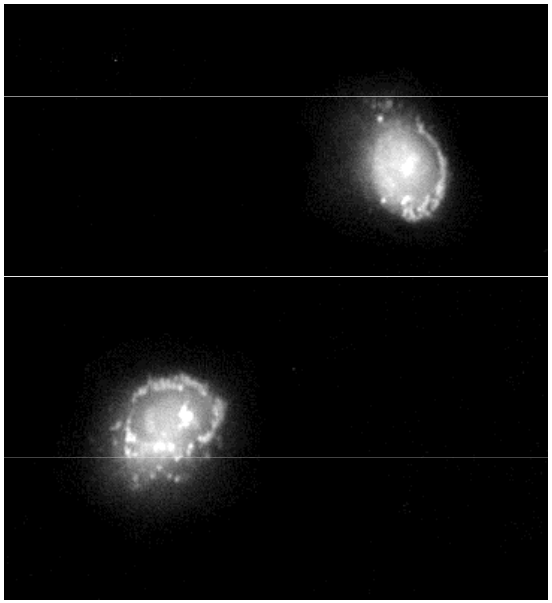
- **Necrosis**

– Accidental cell death caused mainly by external factors (temperature, pH). 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).





Apoptosis

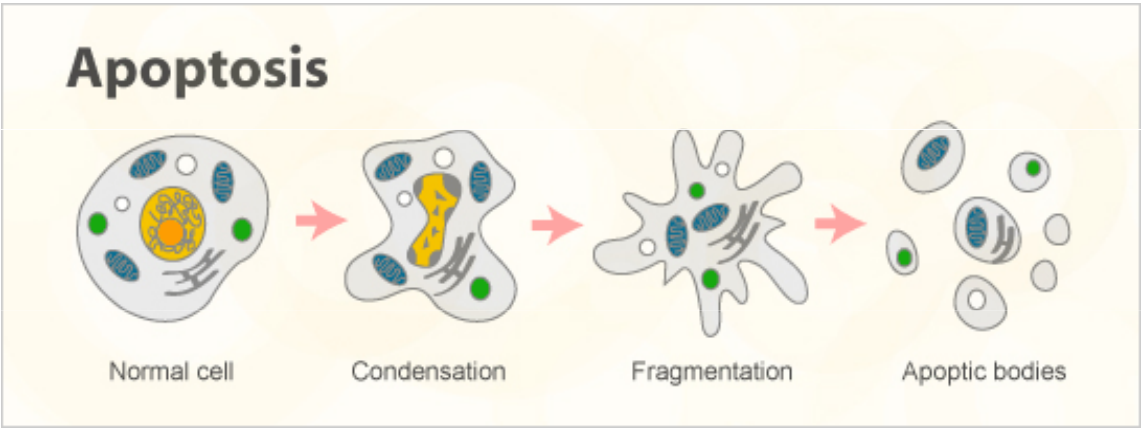
https://www.youtube.com/watch?v=DR80Huxp4y8&ab_channel=WEHImovies

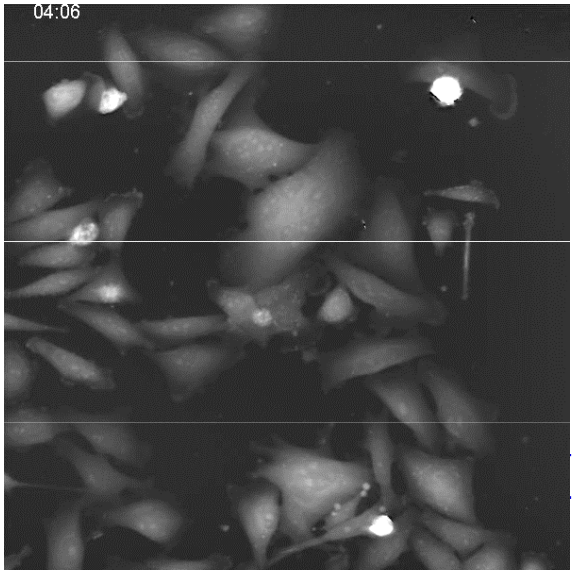
- Apoptosis is the first described form of programmed cell death, and it plays a critical role in tissue homeostasis.
- It contributes to cell turnover, the proper functioning of the immune system, and embryonic development.
- There are several **key characteristics of apoptosis**:

cellular, organelle, and DNA fragmentation and formation of apoptotic bodies

active, energy consuming process executed by a subset of cellular proteins

Even though, in general, this **process is immunological silent**, apoptosis has been shown to be involved in inflammatory pathologies as well.





Apoptosis

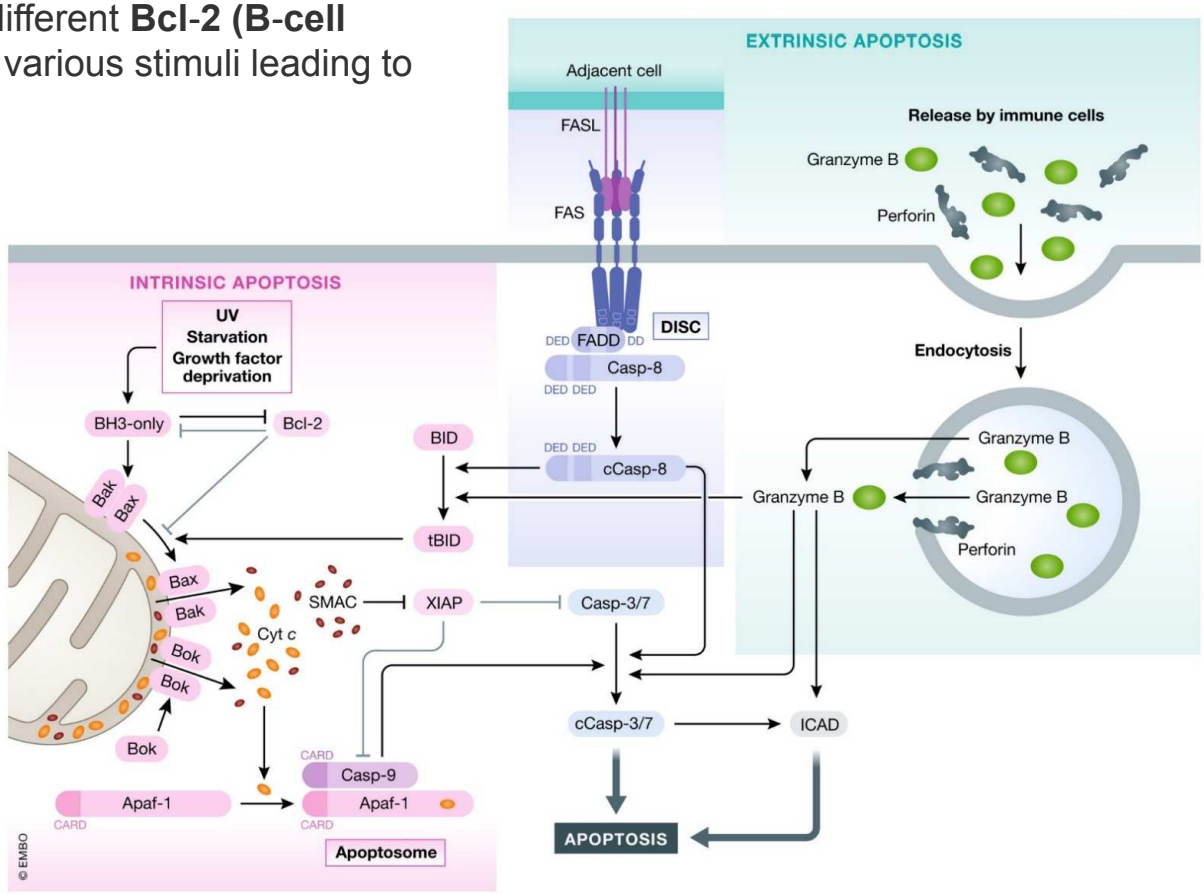
There are two (or 3) major pathways that mediate apoptosis: intrinsic and extrinsic pathways.

During **extrinsic apoptosis**, **TNF** (tumor necrosis factor) superfamily (TNFSF) can induce cell death by binding to their cell surface receptors and activating a deathly signaling cascade causing extrinsic apoptosis.

Intrinsic apoptosis is controlled by the equilibrium of the different **Bcl-2 (B-cell lymphoma 2) family members** which can be disrupted by various stimuli leading to cell death.

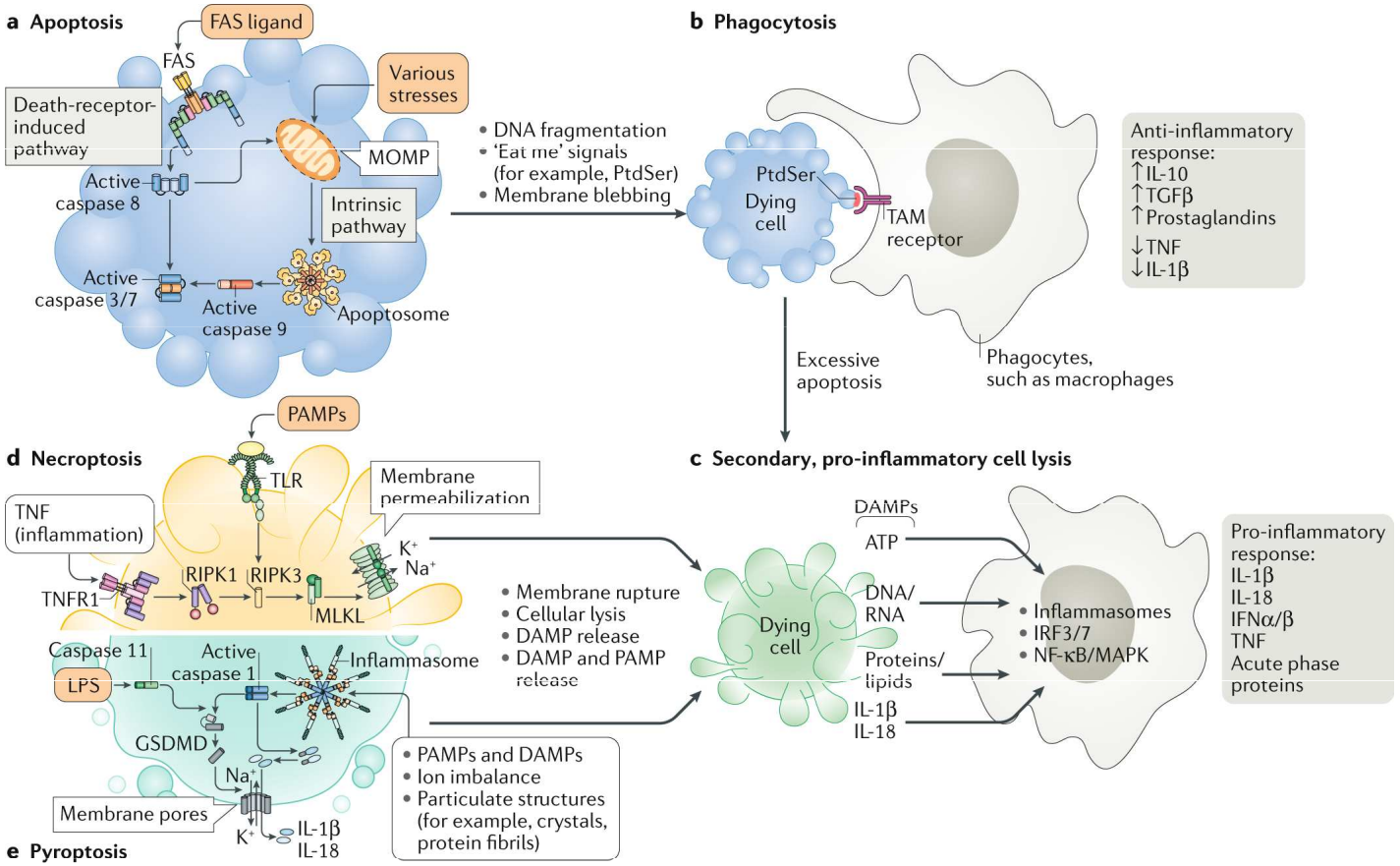
The third modality of apoptosis induction is **cell-based**. **Cytotoxic T cells** can engage cells that present non-self-antigens leading to cell death induction by **proteases called granzymes**.

All apoptotic pathways converge on the central proteases of this pathway: **caspases**, which are either playing a role in transmitting cell death stimulus **(initiator caspases)** or in the execution **(effector caspases).**



Immunogenicity of different types of cell death

- **Non-lytic cell death, apoptosis (the integrity of plasma membrane is sustained).**
- **Plasma membrane rupture (PMR) is the final cataclysmic event in lytic cell death (regulated or accidental necrosis).**
- **PMR releases intracellular molecules known as damage-associated molecular patterns (DAMPs) that propagate the inflammatory response.**



Bedoui, S., Herold, M.J. & Strasser, A. Emerging connectivity of programmed cell death pathways and its physiological implications. *Nat Rev Mol Cell Biol* **21**, 678–695 (2020). https://doi.org/10.1038/s41580-020-0270-8

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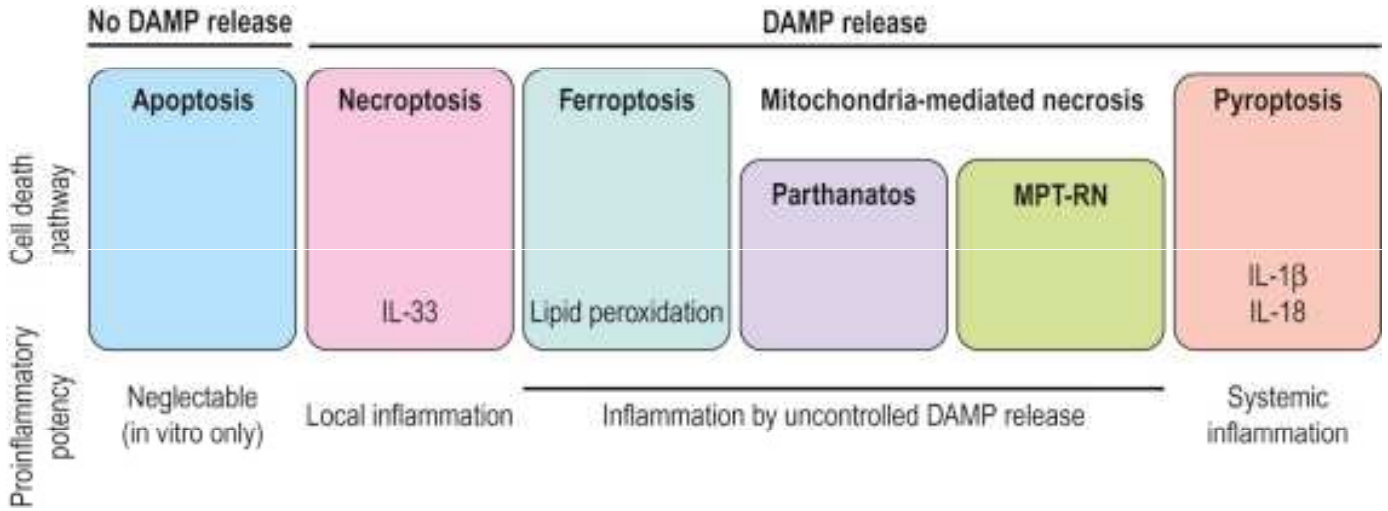
Immunogenicity of different types of cell death

- 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 (IL33) may be released in a specific context. IL33 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.



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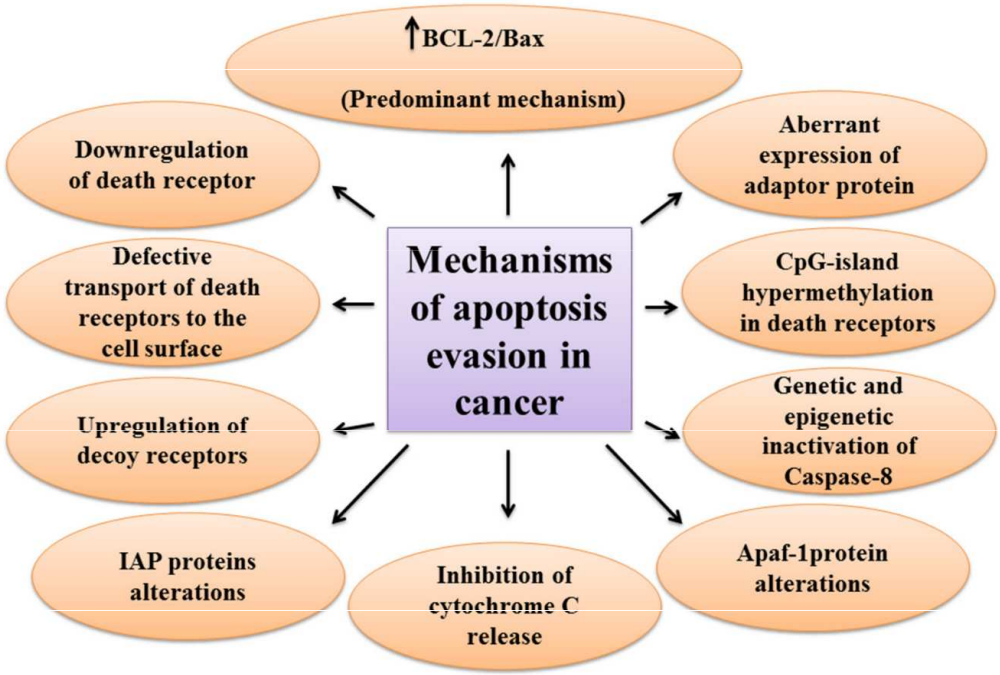
Resisting apoptosis

Tumor cells evolve a variety of strategies to limit cell death.

Most known are:

- **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)
- loss of **p53**



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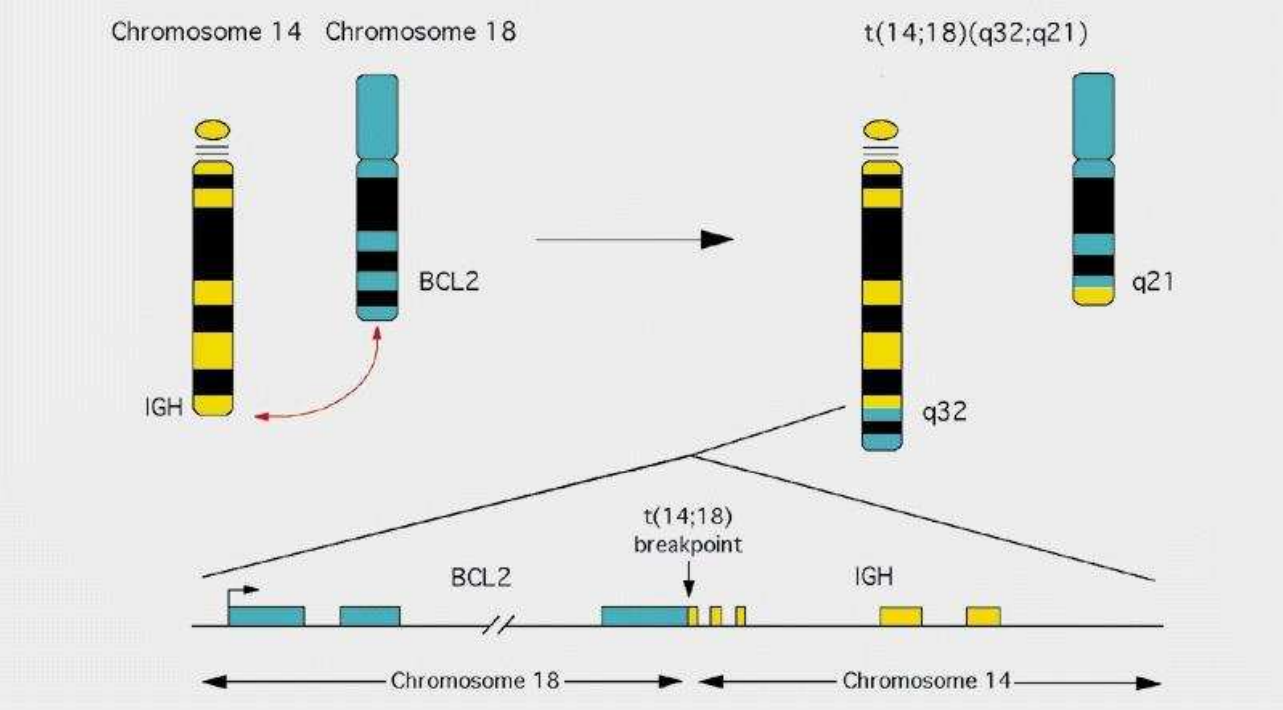
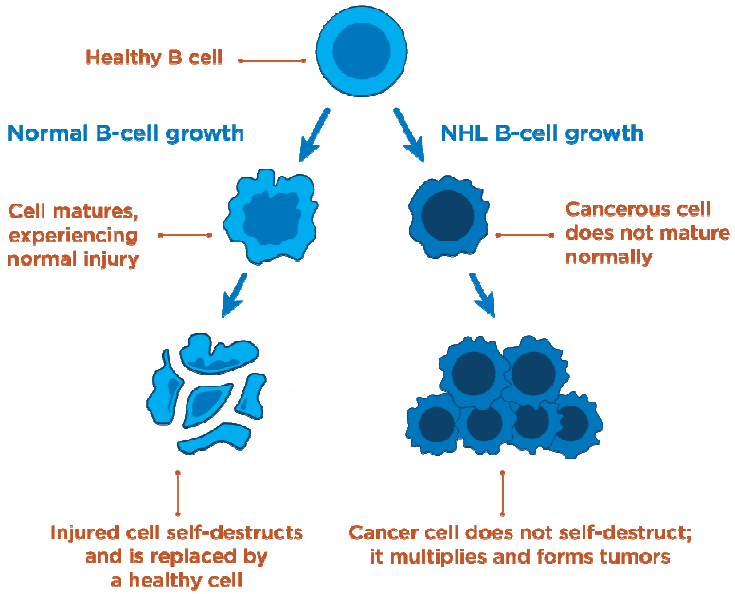
Resisting apoptosis

https://www.youtube.com/watch?v=tzwaPWElklo&t=4s&ab_channel=WEHImovies

Chromosomal translocation associated with B-cell lymphomas.

The Bcl-2 gene is translocated behind a potent immunoglobulin gene promoter. Increased expression of Bcl-2 gene is associated with inhibition of apoptosis.





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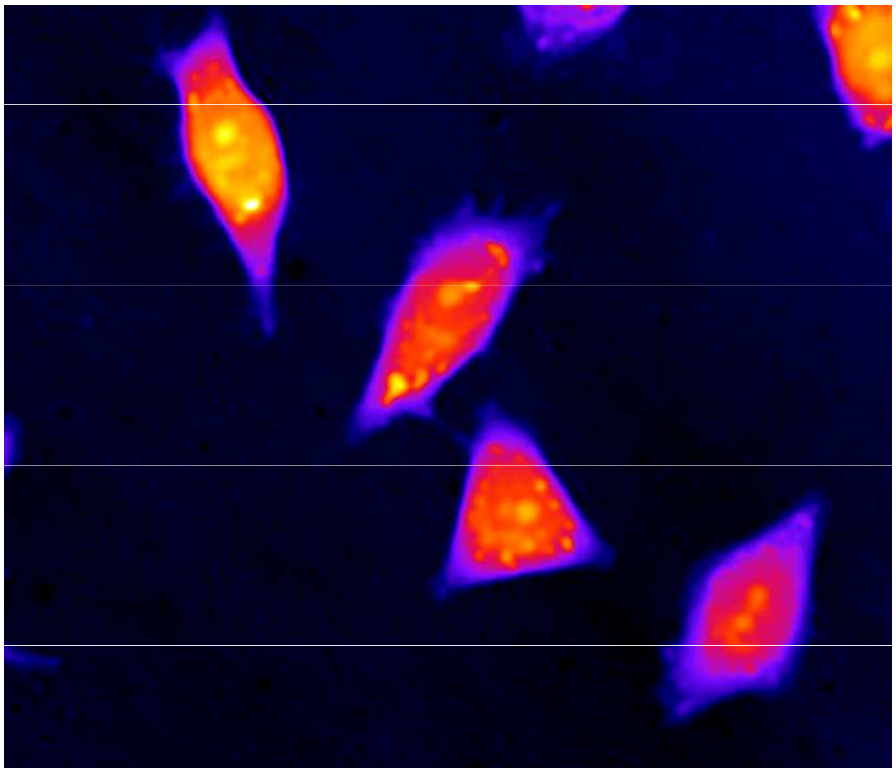
Resisting cell death by cell fusion



– opportunistic behavioral patterns (cell fusion)

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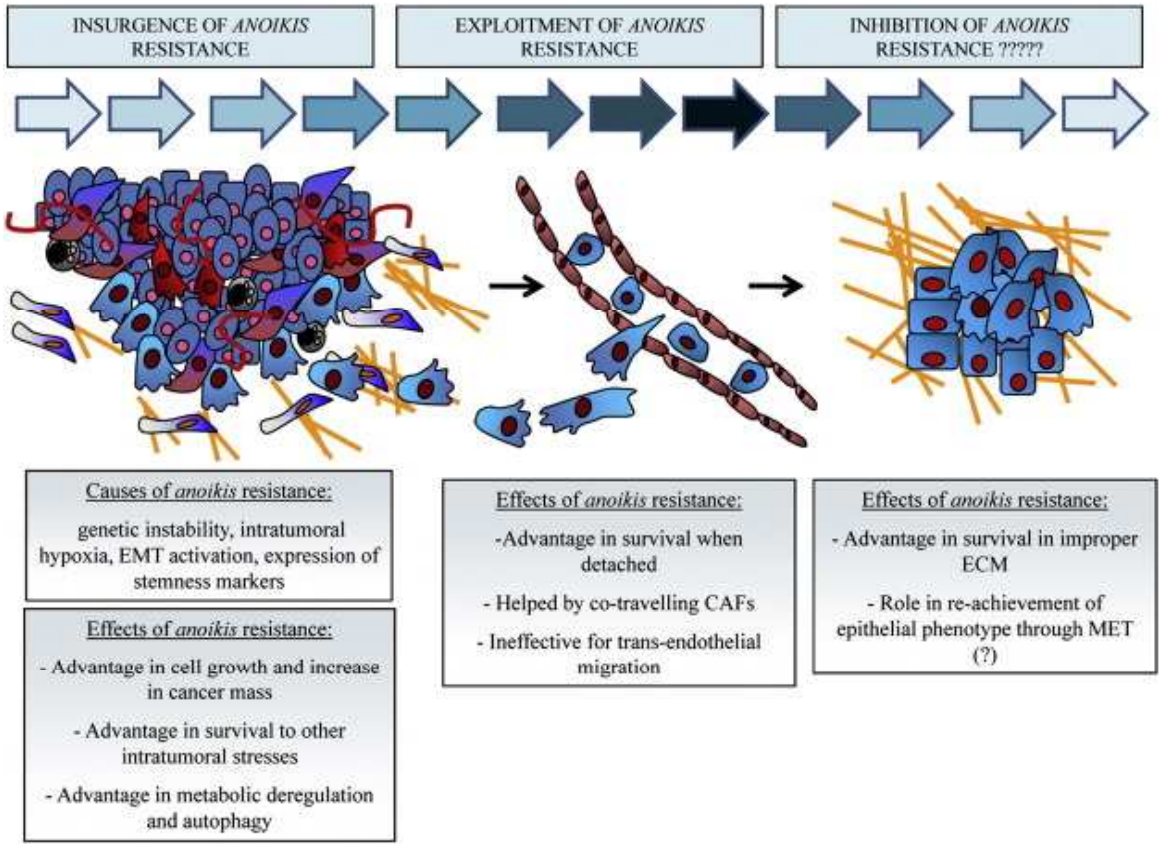
Resistance to anoikis

- **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.



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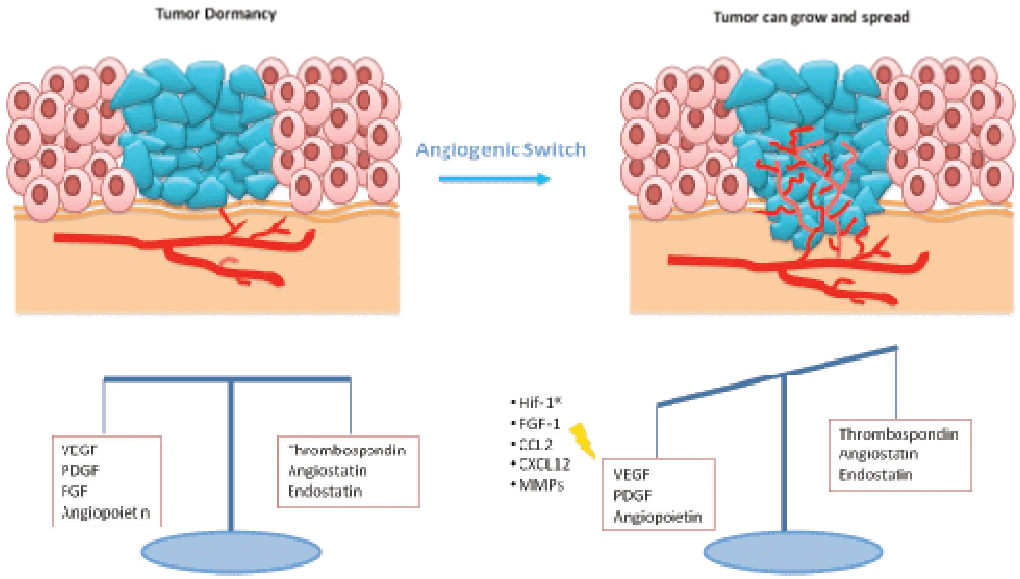
Inducing angiogenesis

- 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 the invasion of tumor cells into circulation and the creation of distant metastases.



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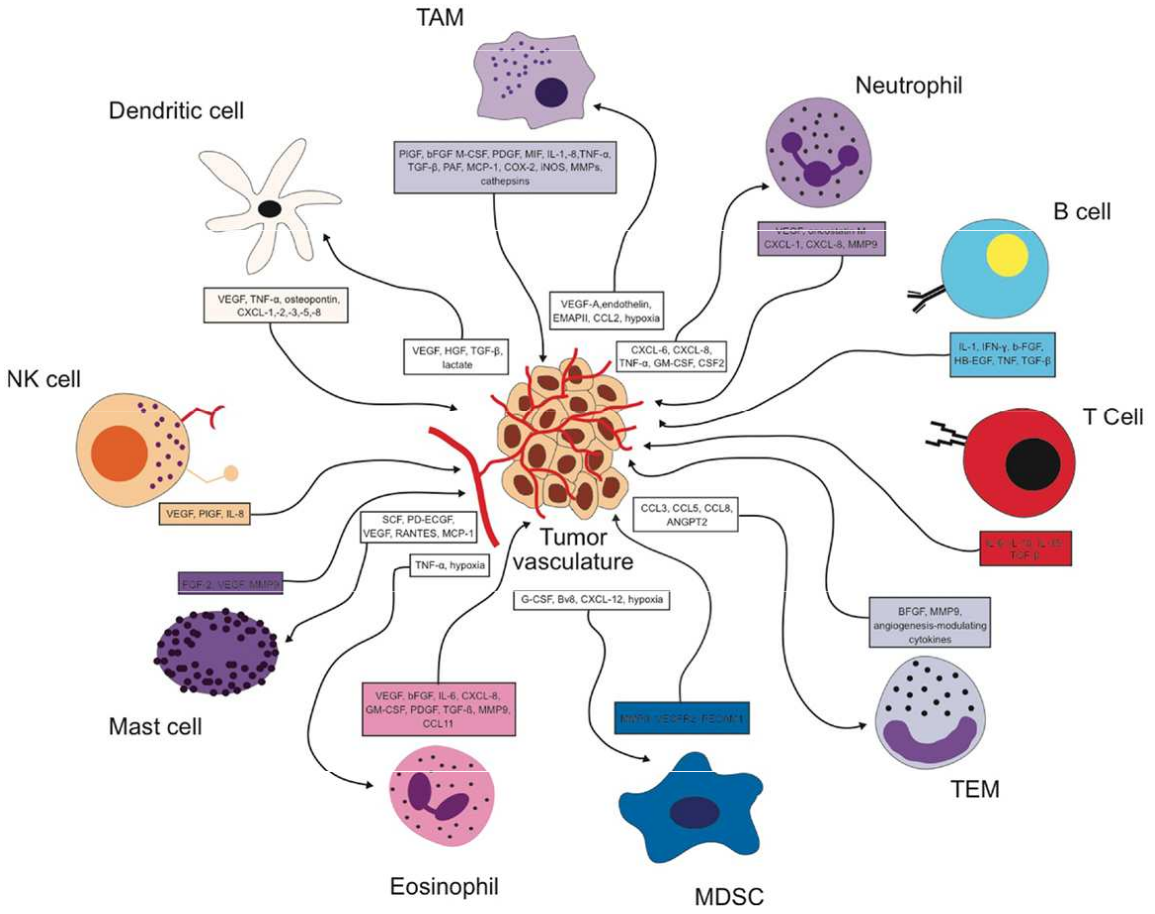
Inducing angiogenesis

- 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.



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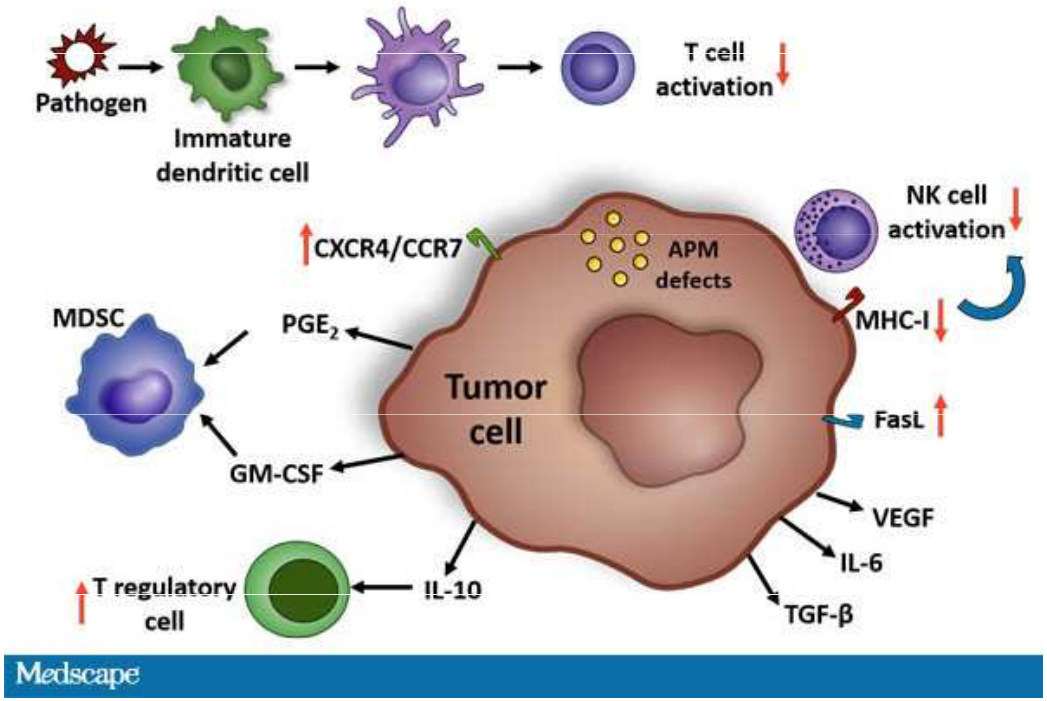
Evading immune destruction

- **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.



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Altered metabolism of cancer cells

- 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)

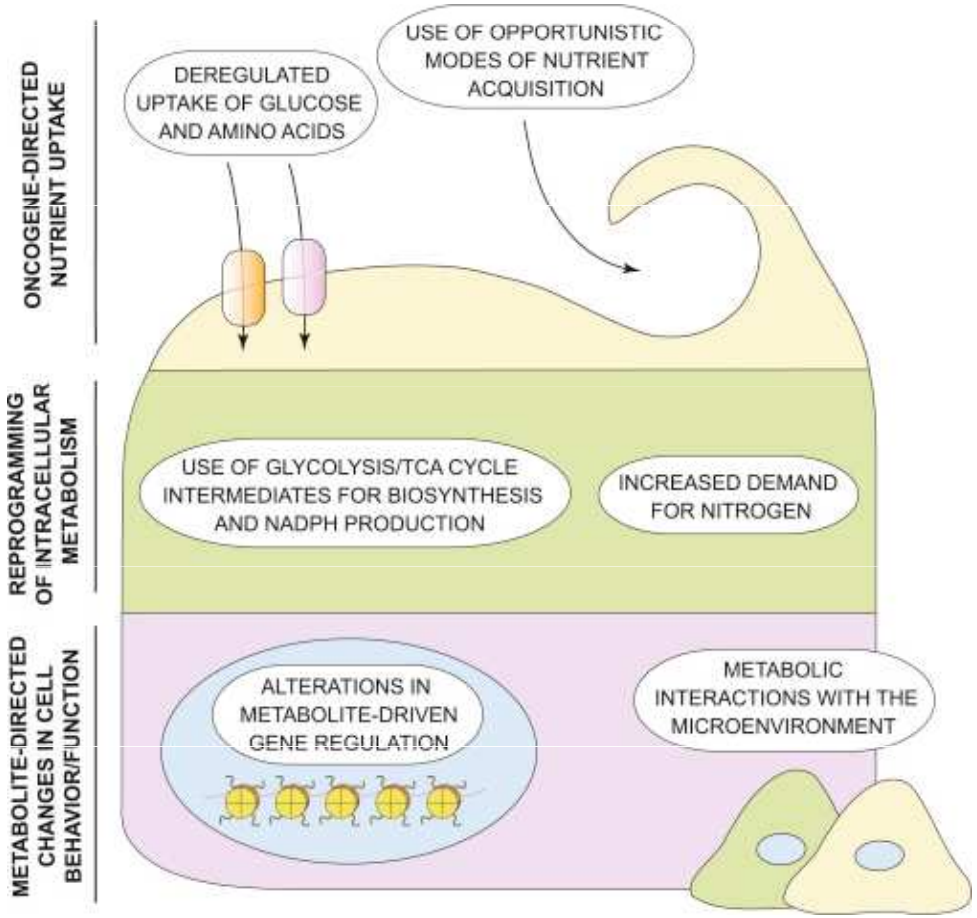
(2) use of opportunistic modes of nutrient acquisition (cannibalism)

(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)



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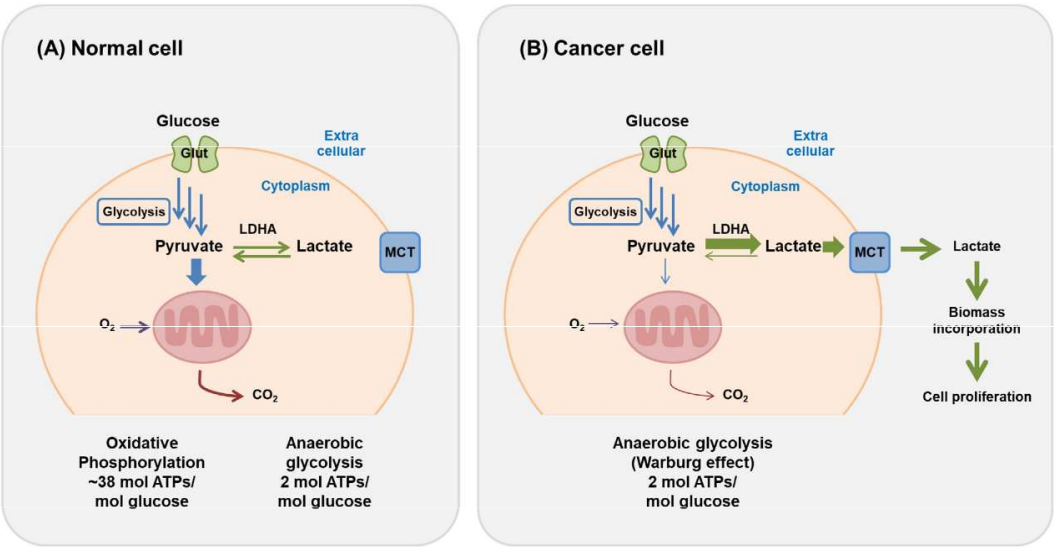
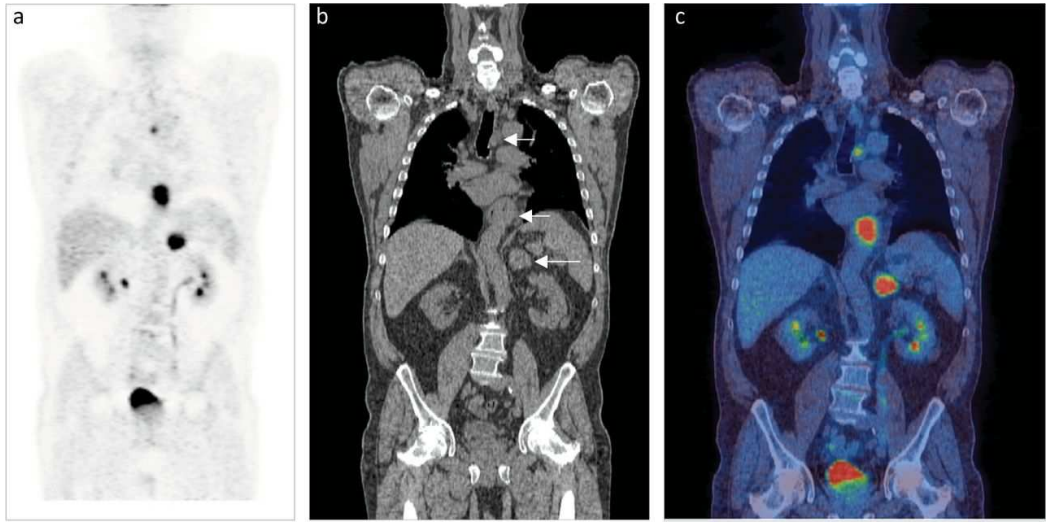
Altered metabolism

- 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.





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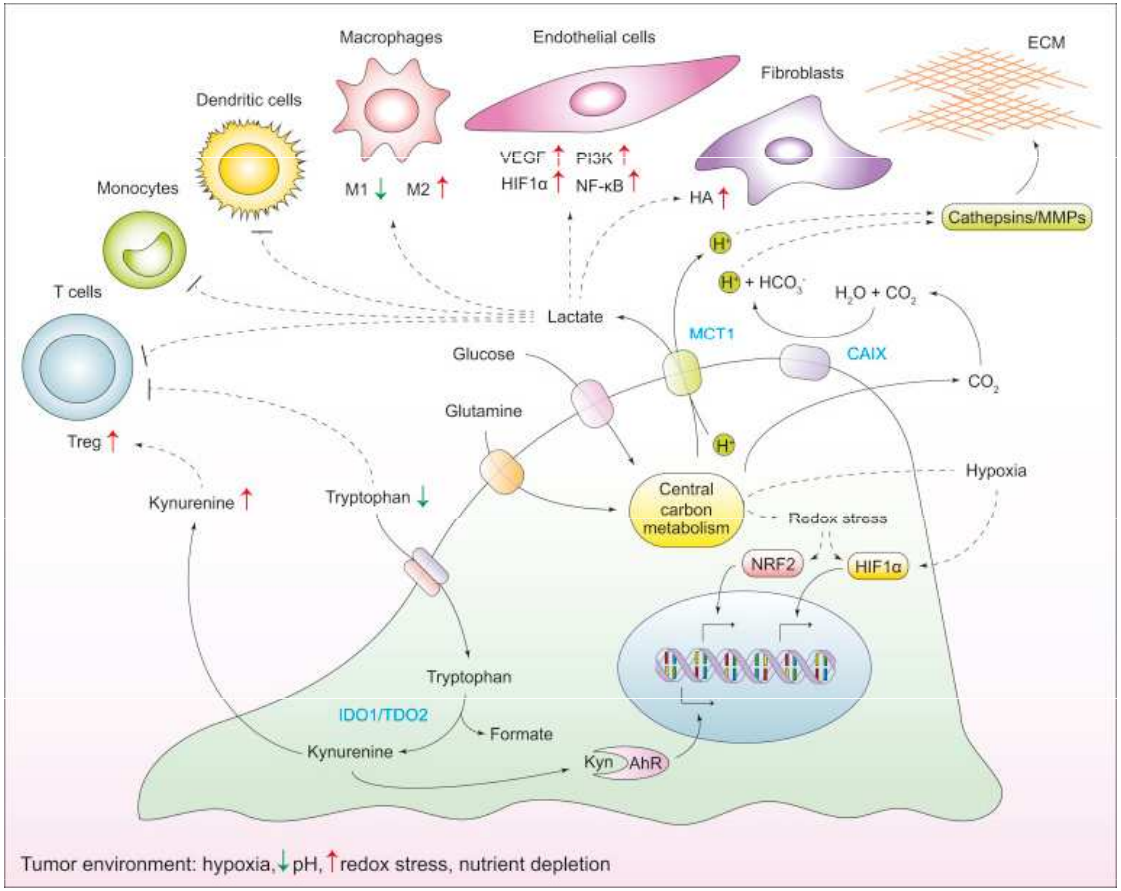
Metabolic interactions with the microenvironment

- 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 the TME– **acidosis**.



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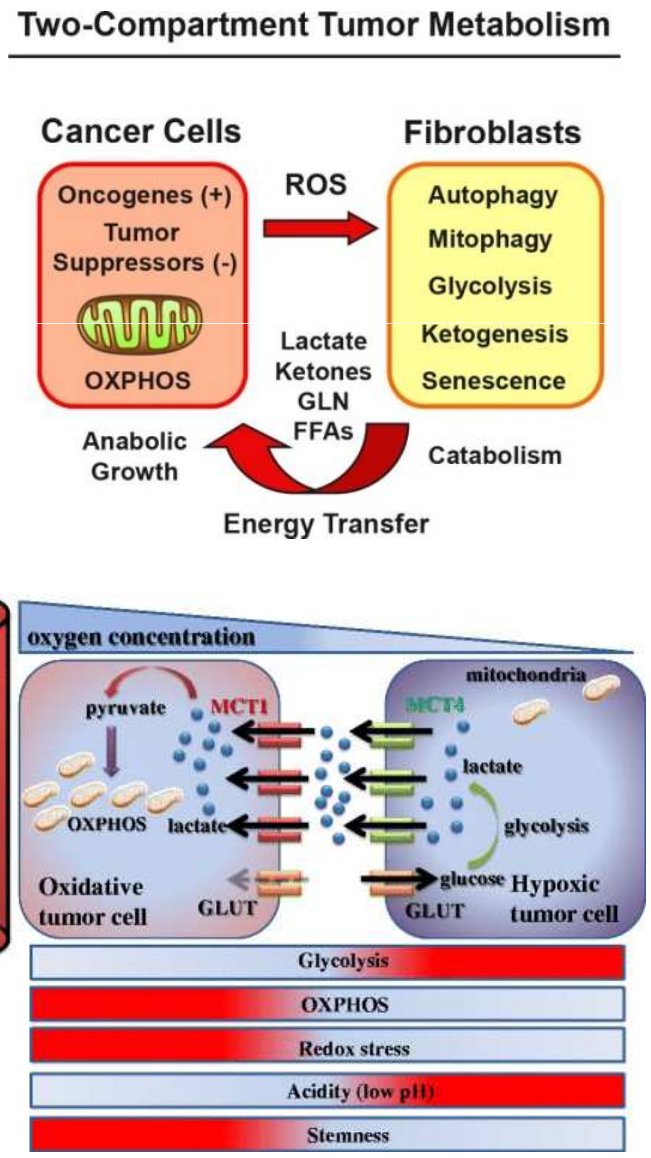
Metabolic symbiosis

- Catabolic fibroblasts are a 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; a number of **genetically distinct subclones** of cells coexist within a single tumor mass: intra-tumor heterogeneity - oxidative and glycolytic tumor cells in one tumor.



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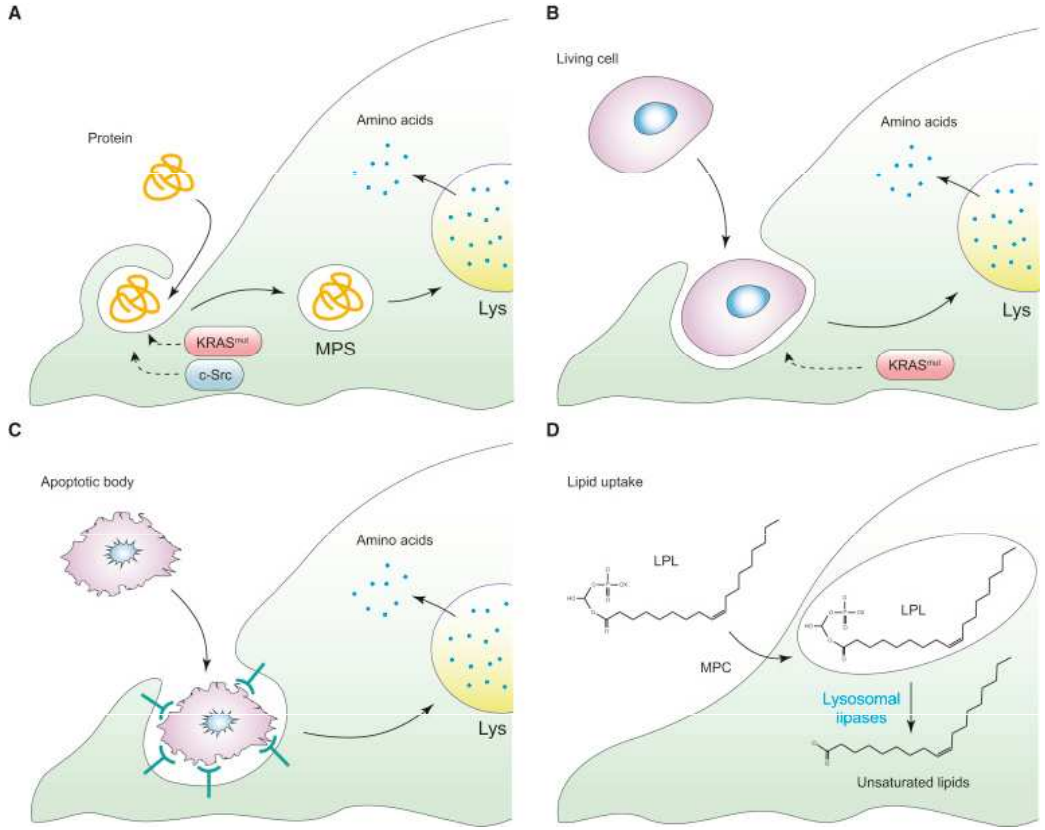
Use of opportunistic modes of nutrient acquisition

- 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**.



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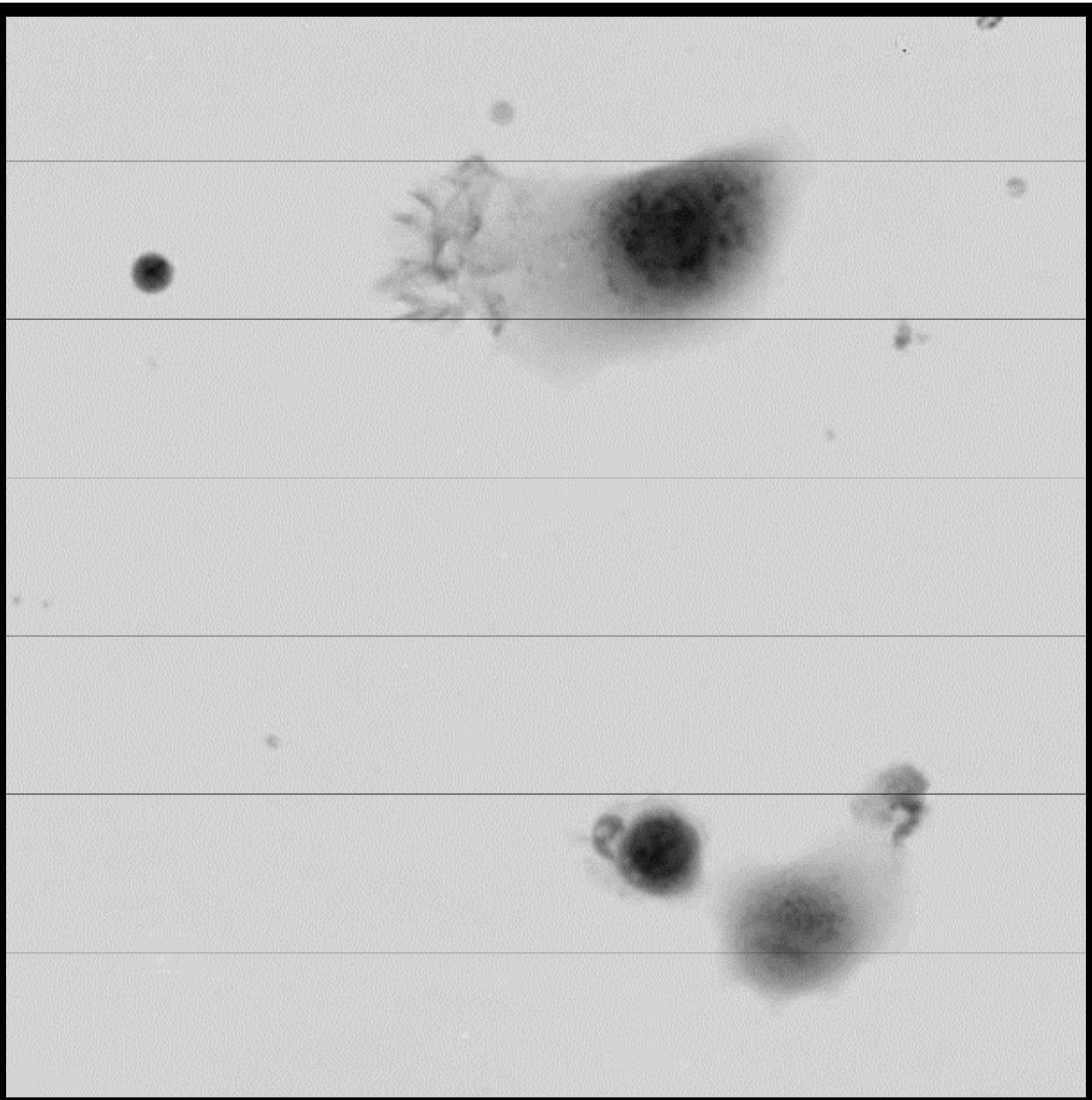
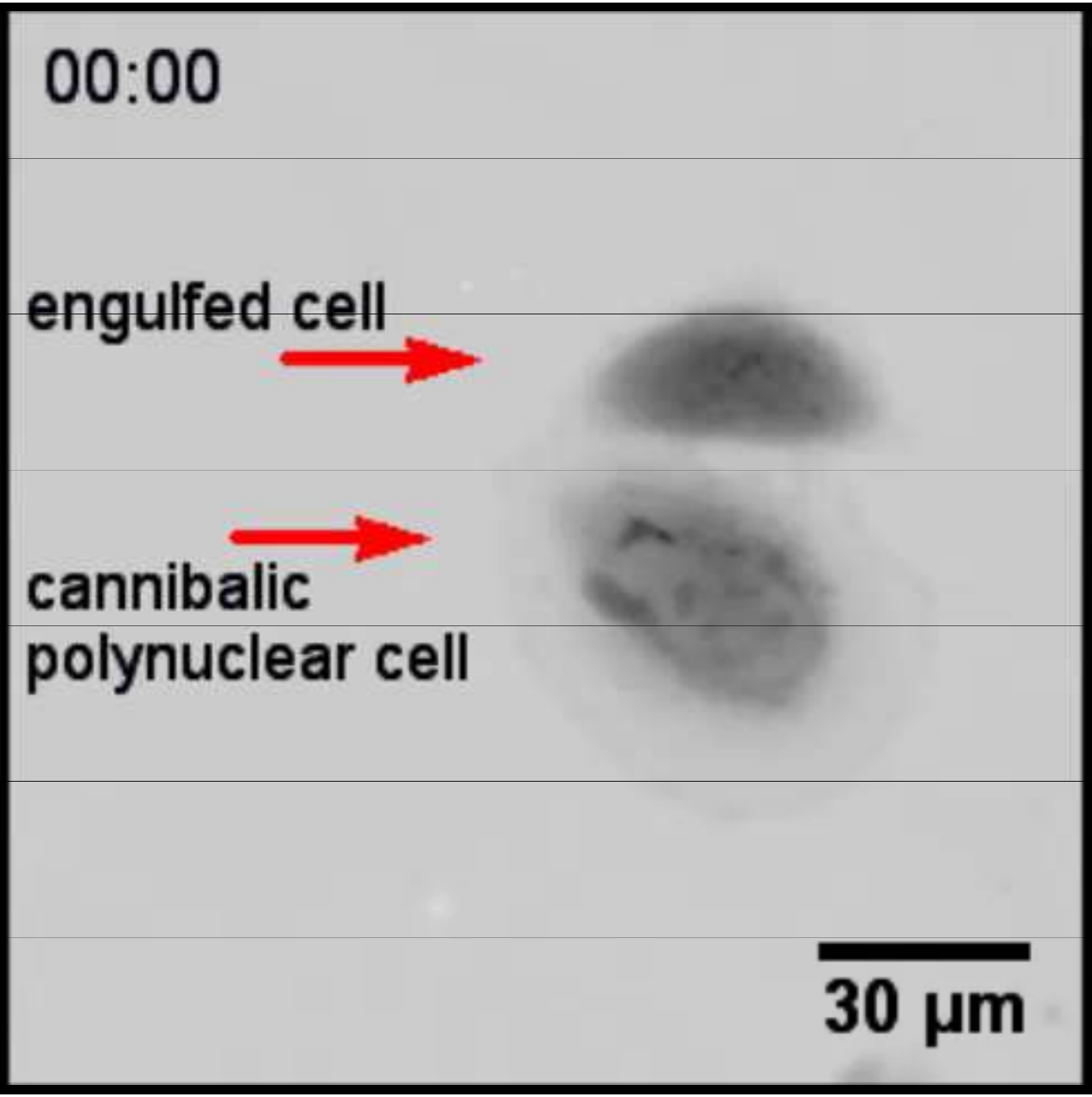



00:00
engulfed cell
cannibalic
polynuclear cell
30 µm

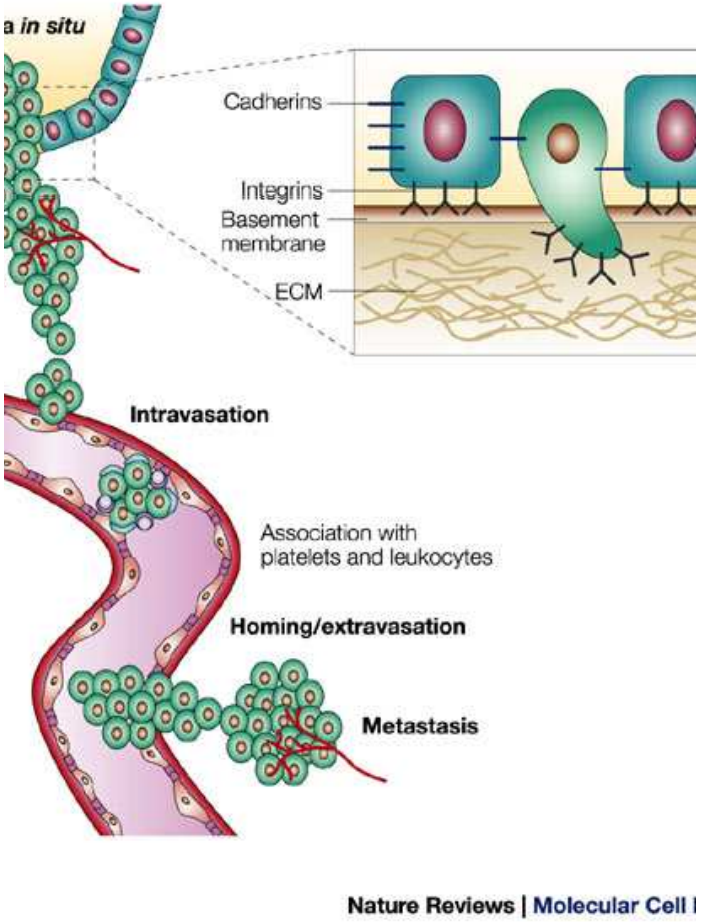
Invasion and metastasis

- Cancer cells lose **E-cadherin-dependent** intercellular adhesions, acquire a **migratory phenotype** (anoikis resistance, 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.**

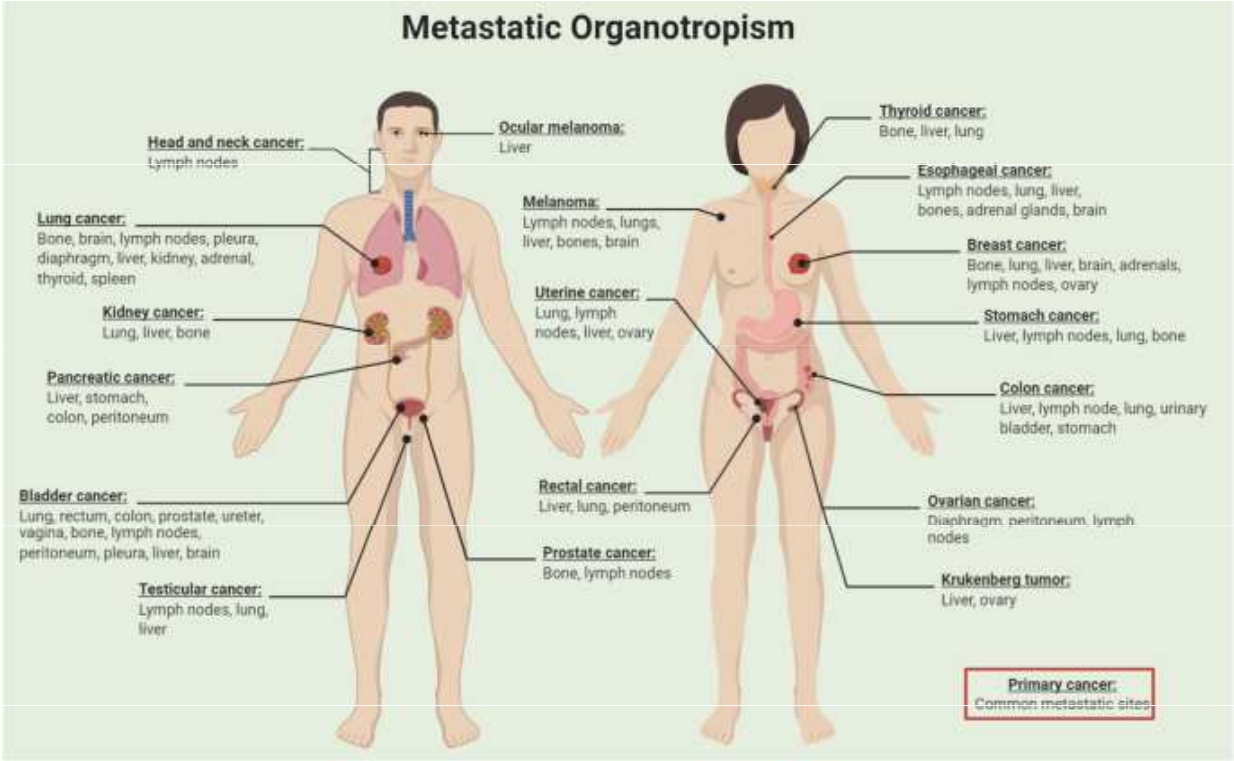
- In the circulation, tumour cells form small **aggregates with platelets and leukocytes**.

- After stopping in the microcirculation of the target organ, tumour cells exit the bloodstream, by a process called **extravasation**, and undergo local expansion.



Seed and soil hypothesis –permissive microenvironment

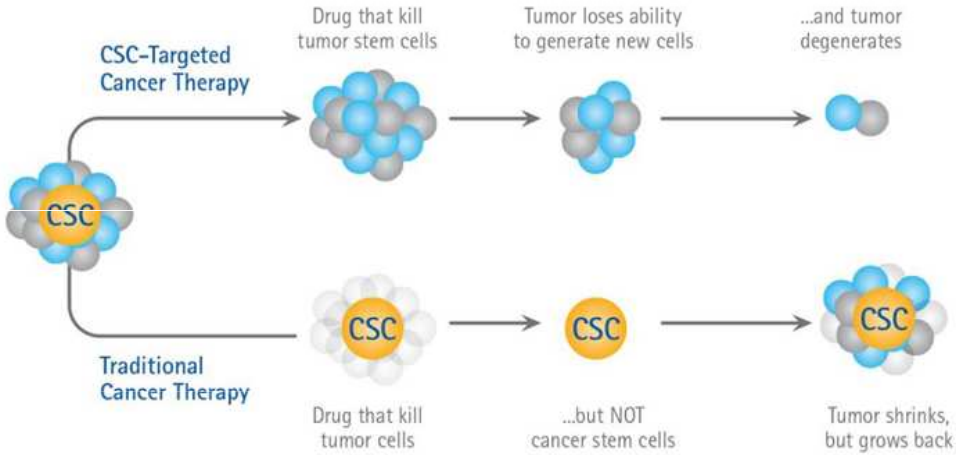
- Metastasis is dependent on the interactions between 'seeds' (the cancer cells) and the 'soil' (the host microenvironment).
- Different cancers have preferential sites of metastasis=**organotropism** (prostate cancer - the bone and the liver).
- Tumour-secreted factors and tumor-shed extracellular vesicles 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 tumor-secreted factors, which creates immunosuppression and coagulation disorders.

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 responsible for tumor initiation and growth.
- CSCs are associated with metastasis and relapse.
- 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.



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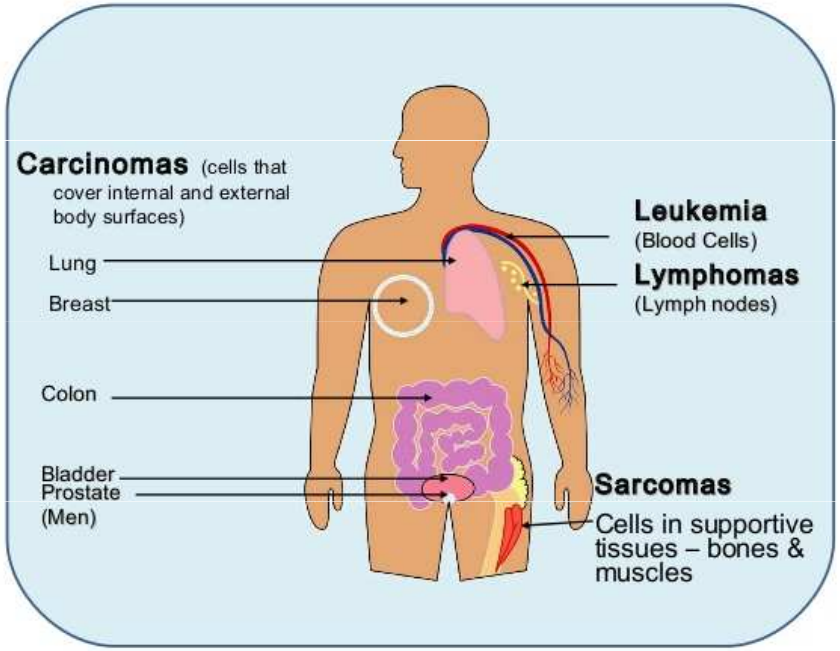
Tumor clasification

- the most common human cancers are of epithelial origin—**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).



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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.

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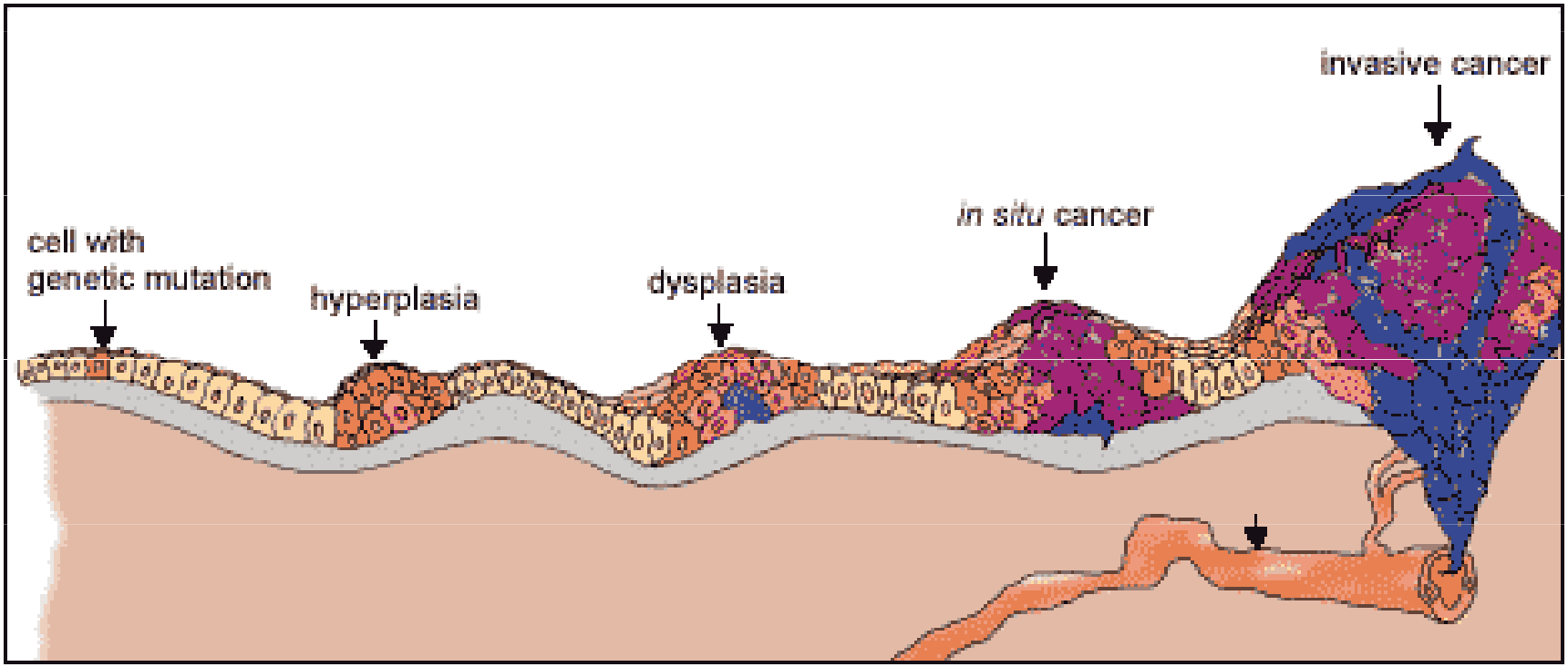
Tumor clasification

- **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** (suppression of bone marrow) – effect of proinflammatory cytokines
- **fever** - production of cytokines (pyrogens) by tumor (IL-1, TNFα)
- **tumor cachexia** – anorexic mediators (TNFα)
- **paraneoplastic syndromes** – some tumors produce hormones (adenomas); important diagnostically!
  - –pigmentation
  - –endocrinopathy (Cushing sy., hypercalcemia).

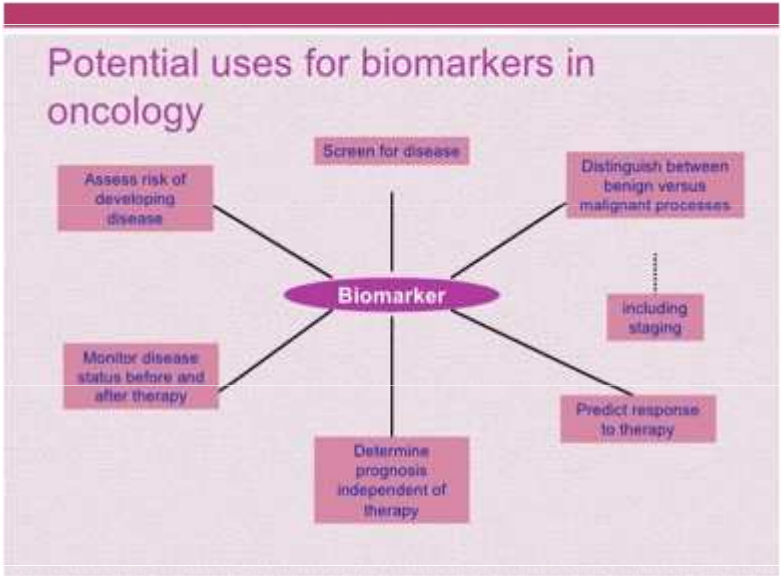
Cancer biomarkers

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

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.



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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 (lung, breast)
- Tissue analyzed: Blood
- How used: To assess response to treatment, and look for recurrence

Thank you for your attention

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