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Bi4025en

Molecular Biology

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Lecture 10

- Molecular basis of carcinogenesis – oncogene versus suppressors

Tumor associated facts

- Every third person in the Czech Republic gets cancer.
- One in four people dies because of it.
- In 2015, there were almost 542,000 people living in the Czech Republic who had been diagnosed with an oncological disease in that year or earlier.
- Every year, about 27,000 people die of cancer in the Czech Republic.
- Mortality from malignant tumors shows stagnation in absolute numbers!
- Increase in prevalence (number of patients with a given tumor living in a given year).

Incidence of malignancies in Czech Republic

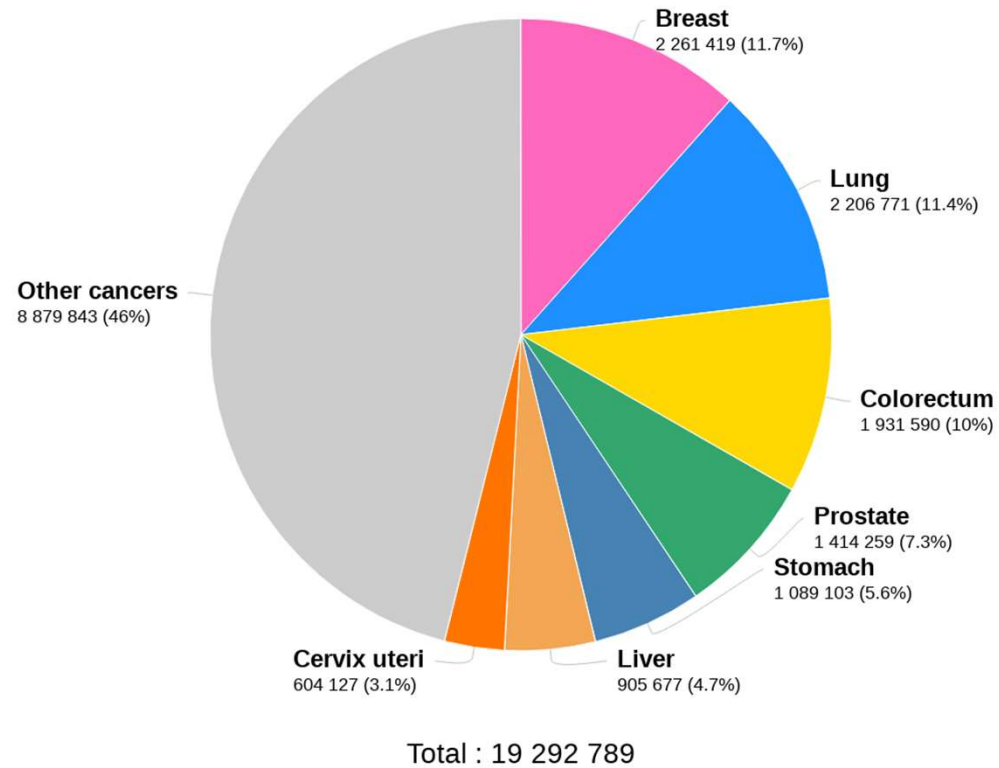
- Every 20 minutes, one person dies of cancer in the Czech Republic.
- In the number of oncological patients - leading places in Europe.
- The most common newly diagnosed malignant diseases in 2011-2015 were skin tumors (excluding melanoma), colorectal cancer, breast cancer in women, and malignant tumors of the prostate and lung.
- Main factors responsible for high incidence of malignant disease in Czech Republic:
 - Significant demographic aging of the Czech population.
 - New treatment technologies and their success: prolonging survival of cancer patients.
 - Subsequent malignancies in oncological patients.

Incidence of malignancies as a global problem

- Tumors 12% of all deaths (56 million in 2000).
- In 2000 - 5.3 million men and 4.7 million women were diagnosed, 6.2 million died of tumor.
- Prediction – 10 million new cases in 2000 to 15 million in 2020 – aging population – smoking and poor lifestyles.

Incidence of malignancies as a global problem

Estimated number of new cases in 2020, worldwide, both sexes, all ages

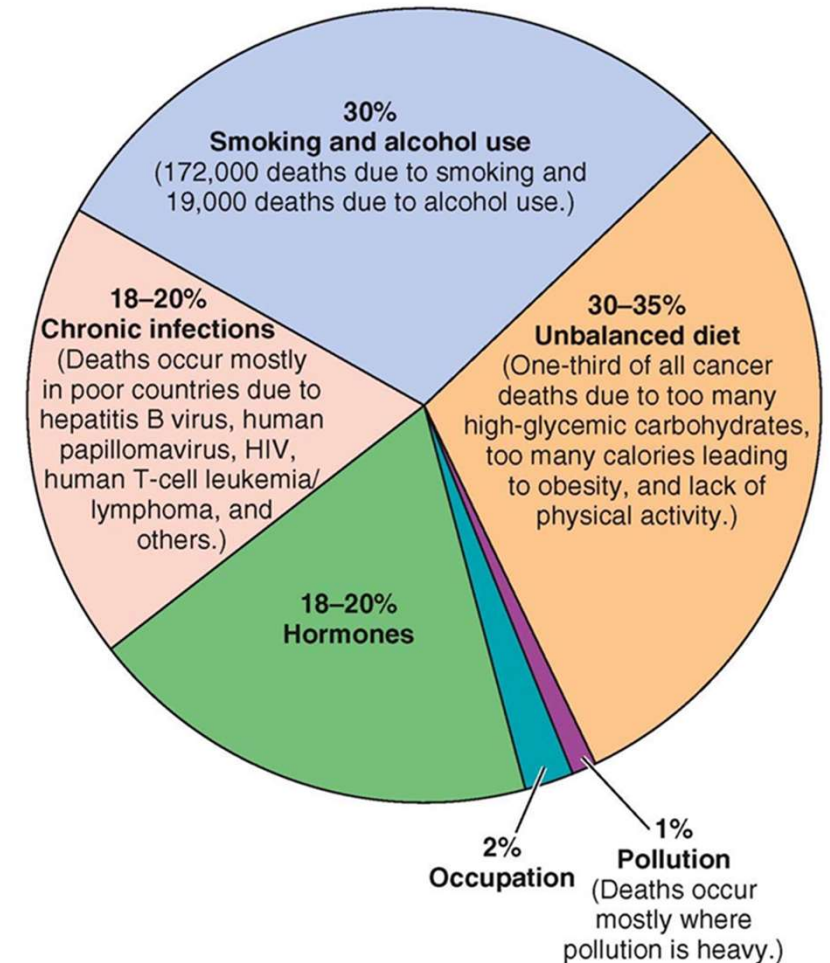


Data source: Globocan 2020
Graph production: Global Cancer
Observatory (<http://gco.iarc.fr>)

International Agency for Research on Cancer
World Health
Organization

Important facts

- About 1/3 of tumors are associated with **obesity**, poor diet and low physical activity.
- **Smoking** – 30% of all deaths from tumors, 87% of deaths from lung tumors.
- Obesity increases the risk of breast tumors in postmenopausal women by 50% and 40% in bowel tumors in men.



Cancers and rates

Global cancer rates

The ten worst countries and the UK cancer rate, per 100,000 of the population

| | | |
|----|----------------|-------|
| 1 | Denmark | 326.1 |
| 2 | Ireland | 317 |
| 3 | Australia | 314.1 |
| 4 | New Zealand | 309.2 |
| 5 | Belgium | 306.8 |
| 6 | France | 300.4 |
| 7 | US | 300.2 |
| 8 | Norway | 299.1 |
| 9 | Canada | 296.6 |
| 10 | Czech Republic | 295 |
| 22 | UK | 266.9 |

SOURCE: WORLD CANCER RESEARCH FUND



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Tumor

- Uncontrolled growth of cells in the tissue of higher organisms.
- Does not have a physiological function.

- Clonal expansion characteristics.

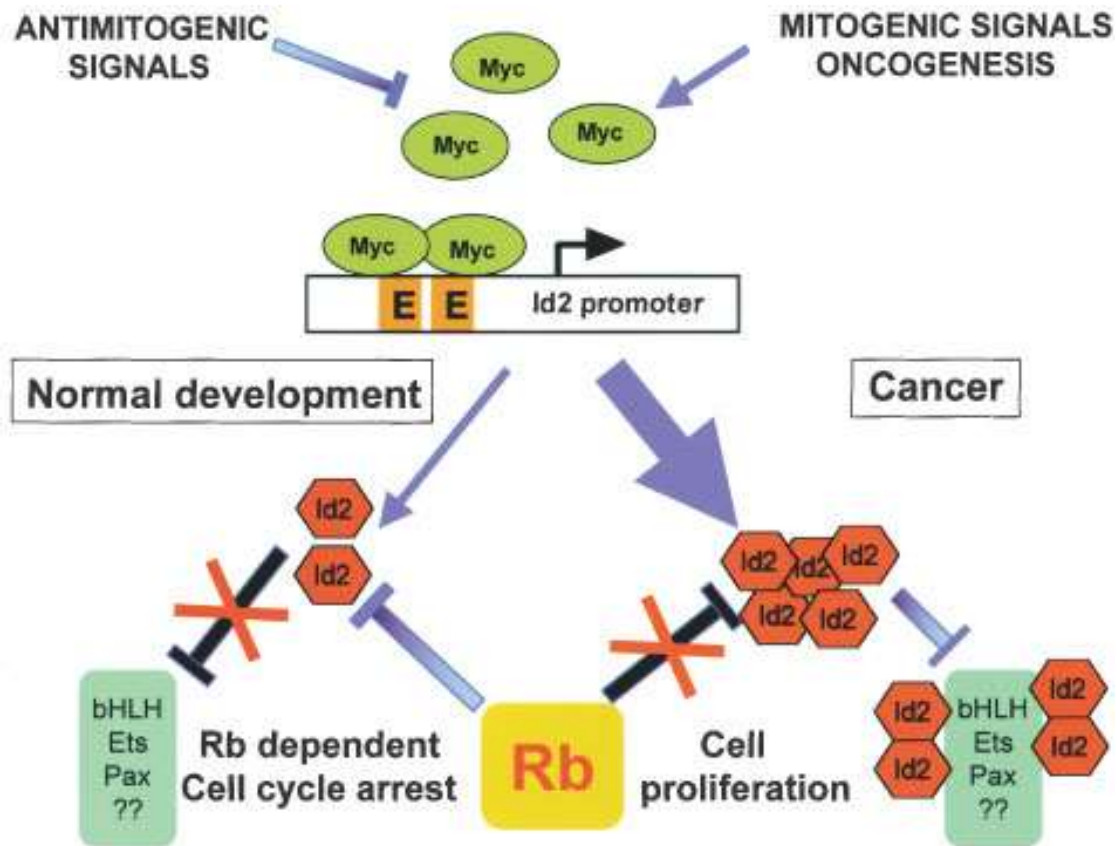
- Disrupts the balance in the body.

- Critical two types of genes:
- **Oncogenes** (gain of function).
- Tumor **suppressors** (loss of function).
 - All of these genes generally have other primary functions.
 - Genes may be tumor suppressor or oncogene in one tissue, at one time point, NOT in other.
 - Effects of such genes are subject to tradeoffs with other functions.

Tumor oncogenes

- 1970 - *src* – chicken retrovirus Rous sarcoma virus (Dr. Martin, UC Berkley).
- 1976 - Stehelin, Vermus, Bishop – oncogenes are activated proto-oncogenes.
- **Proto-oncogene** – a gene that encodes proteins that affect growth, differentiation and/or, signal transmission.
- Protooncogene activation – is the conversion of proto-oncogene into oncogene. Mutation or increased expression or amplification – oncogene **Ras, Myc, ERK.**
- Proto-oncogene mutations are:
 - **Activating.**
 - **Dominant.**
 - **Occur in somatic cells and rarely in germ cells.**

Tumor oncogenes



Tumor suppressors

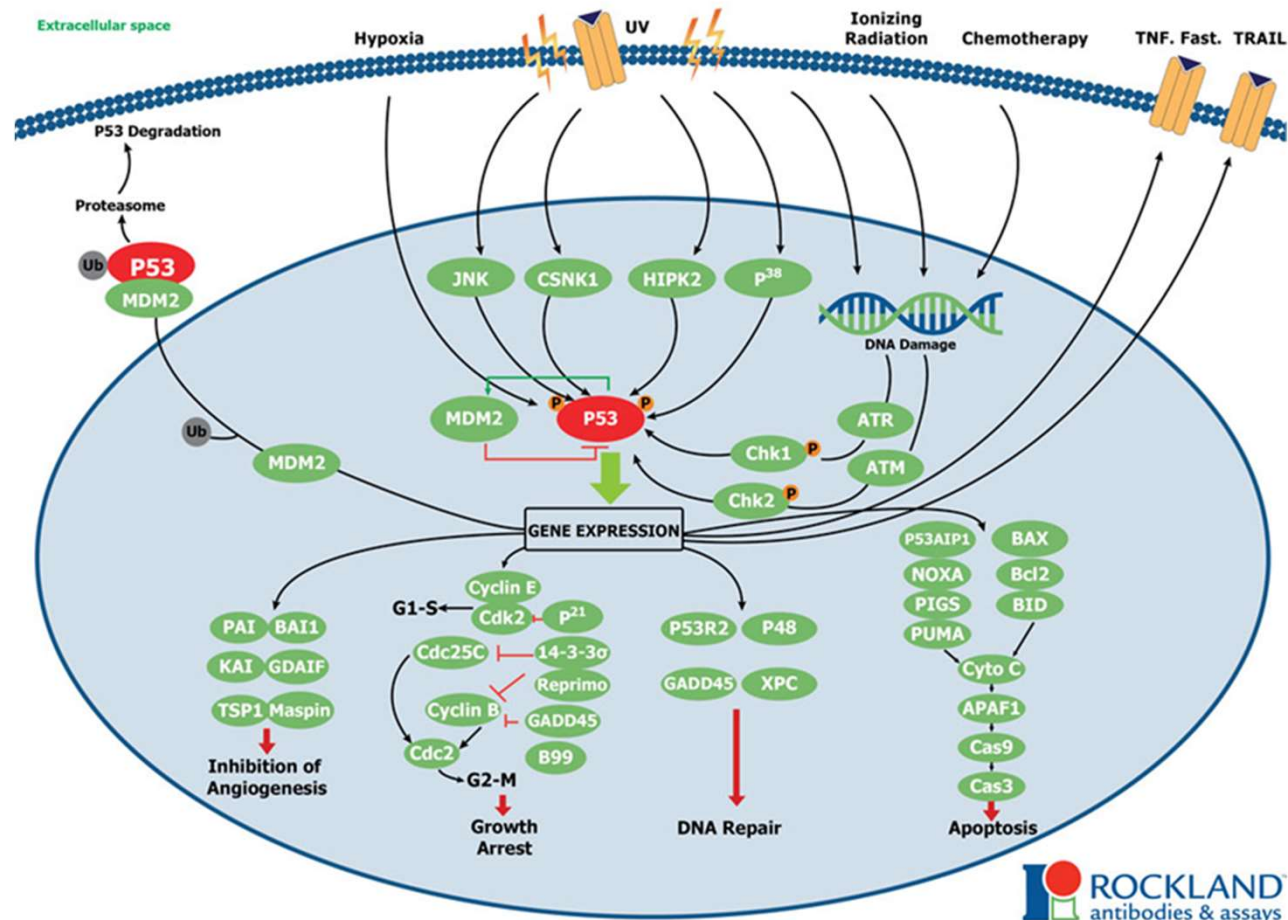
- The products of genes for tumor suppressors (**antioncogenes**) in normal cells do not cause proliferation, but, on the contrary, suppress it and keep the cells at rest (G0). Their loss is manifested by unregulated proliferation.
- Mutations of tumor suppressors are:
- **Inactivating**.
- **Recessive** (associated with Loss Of Heterogeneity) ("recessive oncogenes").
- Occur in somatic and also in germ cells.

Tumor suppressor

- p53 – guardian of the genome.
- 17p13.1, 53 kDA.
- Proliferation, apoptosis, DNA repair, angiogenesis, replication, cell division...
- Rapid degradation.
- Regulated MDM2 protein – transfer to cytoplasm, inactive.
- Induction of expression after cell exposure to stress.
- Cell cycle arrest, apoptosis.
- Mutations in more than 50% of human tumors.
- Li Fraumeni syndrome – hereditary tumor syndrome, germ mutation p53.
- Mutations of inactivating, recessive, somatic and germ cells.

Tumor suppressor

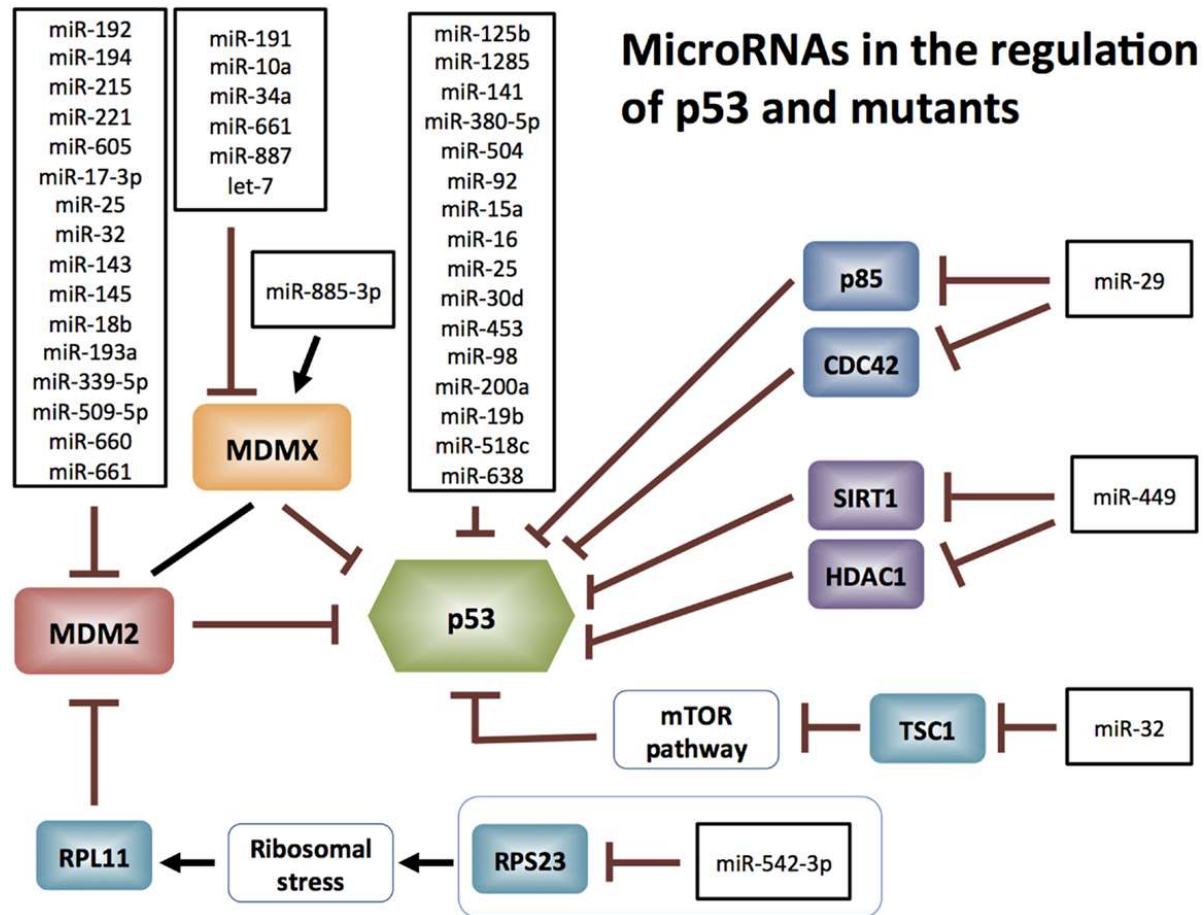
p53 Signaling



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Tumor suppressor



Types of genes mutated in cancers

- **Gatekeeper genes** - genes that regulate growth and differentiation; include oncogenes and tumor suppressor genes.
- **Caretaker genes** - genes that help to maintain genetic integrity; their loss of function mutations lead to:
 - Microsatellite instability (due to mismatch repair deficiency).
 - Chromosomal instability (gain or loss of chromosomes or parts thereof).
- (3) **Landscaper genes** - genes that when mutated lead to abnormal extracellular or intracellular environment that contributes to carcinogenesis.

Risk factors

- The risk of developing a tumor increases with increasing age.
 - Exposure to chemicals.
 - Viruses.
 - Mutations.
 - Lifestyle?
-
- Early diagnosis and treatment important.
 - Identification of persons at risk.

Chemicals increase risk of cancer

- Asbestos.
- Pesticides.
- Herbicides.
- Benzene.
- Radioactive substances.
- Chemicals in food – herbicides, pesticides, E-numbers.

Oncogenic (Cancerogenic) viruses

- Retroviruses (RNA viruses): contain an **oncogene** (acutely transforming viruses) in their genome or activate the **proto-oncogene** next to which they have integrated (slowly transforming).
- **DNA oncogenic viruses** use a different transformation strategy: they do not contain oncogenes, but encode proteins that interact with **tumor suppressors** (RB, p53, p300/CBP) of the host cell and thus push the host cell into the S phase:
 - SV40 - large T antigen interacts with p53, RB, p300/CBP through different domains.
 - Adenovirus - E1A interacts s RB a p300/CBP; E1B associates s p53.
 - Papillomavirus HPV-16, HPV-18 - E6 interacts with p53, p300/CBP; E7 interacts with RB.

Oncogenic viruses and human diseases

- RNA viruses:
- human lymphotropic virus type I (HTLV-1) causes adult T-cell leukemia (ATLL)

- DNA viruses:
- Epstein-Barr Viruses (EBV) – Burkitt's lymphoma (BL), Hodgkin lymphoma (HD), Lymphomas, Nasopharyngeal carcinomas (NPC).
- Hepatitis B virus (HBV) - Hepatocellular carcinoma (HCC).
- Human papillomaviruses (HPV 16, 18,..) - anogenital tumors, oral tumors, warts.
- Human herpesvirus type 8 (HHV8) - Kaposi sarcoma (KS).

Historical perspective

- 400 BC **Hippocrates** described tumors as long prominences.
- Grece: karkinos = crayfish; onkos = crab
- Latin cancer = crayfish.

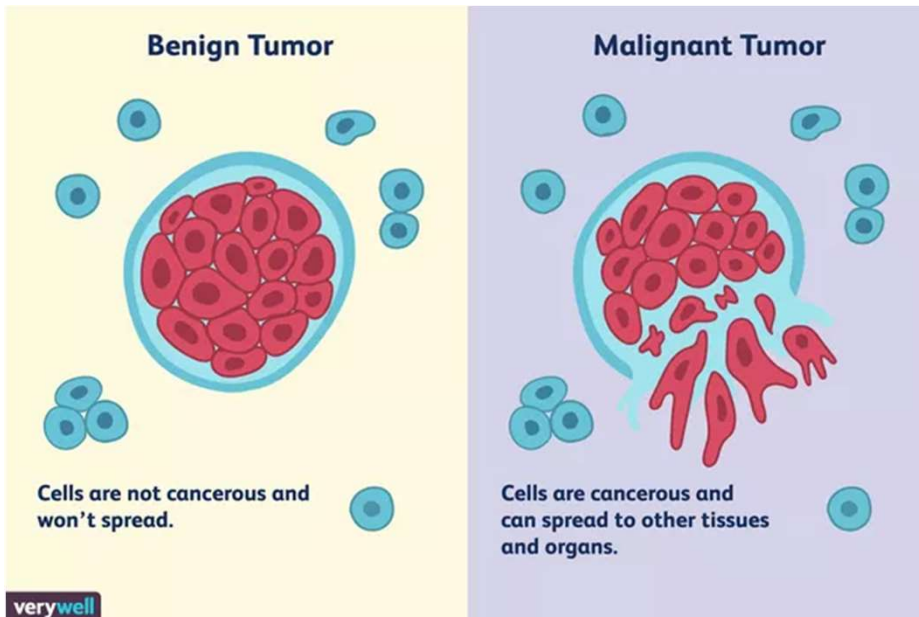
- Descriptive knowledge:
- 1848 - increased incidence of breast cancer in nuns (childlessness, non-breastfeeding).
- 1902 - Connection of X-rays and cancer induction .
- 20th century - occurrence of familiar type of tumors.

Classification of tumors

- Based on their ability to invade other tissues.
- **Benign** - they remain at the place of their origin, do not migrate, do not invade other tissues.
- **Malignant** - they invade into surrounding tissues and, through the blood and lymphatic system, throughout the body, in new tissues they provoke the formation of secondary tumors (metastases).
- From this point of view, tumors can be classified into **primary** and **secondary** as well.

Classification of tumors

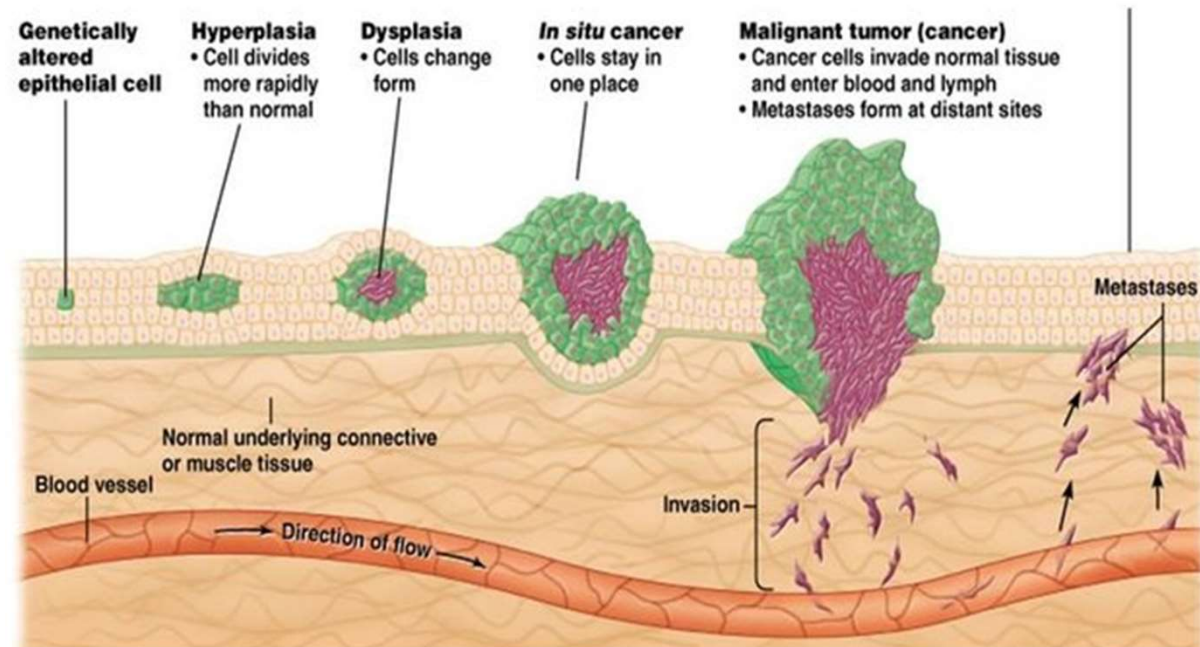
- Based on their ability to invade other tissues.



| Benign Tumors | Malignant Tumors |
|---|---|
| <ul style="list-style-type: none">• Small• Slow-growing• Non-invasive• Well-differentiated• Stay localized<ul style="list-style-type: none">• Stay where they are.• Can't invade or metastasize. | <ul style="list-style-type: none">• Large• Fast-growing• Invasive• Poorly-differentiated• Metastasize<ul style="list-style-type: none">• Infiltrate, invade, destroy surrounding tissue.• Then metastasize to other parts of body. |

Stages of tumor development

- **Hyperplasia** - is the stage where genetically altered or abnormal cells show uncontrolled and rapid growth.
- **Dysplasia** - stage of tumor development where overgrowing cells change their original form. It consists of more immature cells than mature.
- **In situ cancer** - represent neoplastic lesion where cells do not go into the process of maturation, lost their tissue identity and grow without regulation.
- **Malignant tumor** - overgrowing cells invade other areas by rupturing basal membrane.
- Metastases occur when cancer cells reach to the distant parts through lymphatic system and blood circulation.



Classification of tumors

- **Based on their origin** – from which cell types and tissues.
- **Carcinomas** – tumors of epithelial cells (about 90% of human tumors).
- **Sarcomas** – solid tumors of connective tissues – muscles, bones, cartilage.
- **Leukemia and lymphomas** - derived from hematopoietic cells and cells of the immune system.
- **Gliomas** - tumors derived from nervous tissue.

Classification of tumors

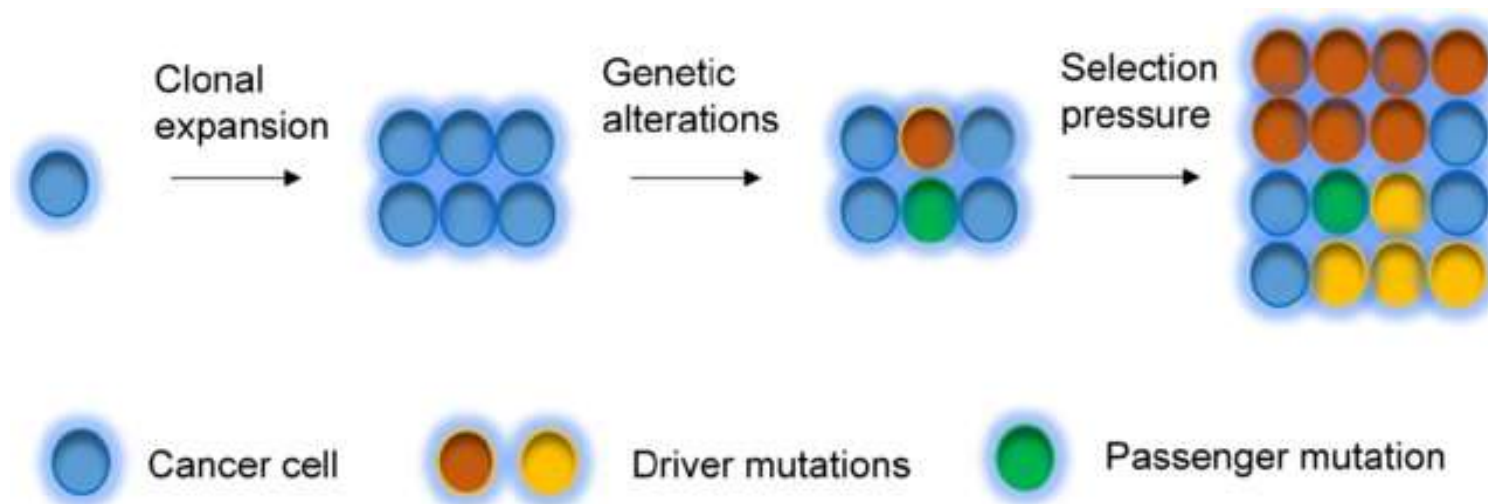
- Based on the **invading organ**.
- lung cancer
- colorectal cancer
- breast tumor
- acute myeloid leukemia
- and many other types

Cancerogenesis

- **Cancerogenesis** or **Carcinogenesis** - is the process of **tumor formation and development**. It could also be defined as the process of **tumor onset and progression**.
- The essence of carcinogenesis is the **gradual accumulation of genetic (and epigenetic) changes – mutations**.
- It is a multistage process.
- **Neoplastic transformation** - is the transformation of a somatic cell into a tumor cell.

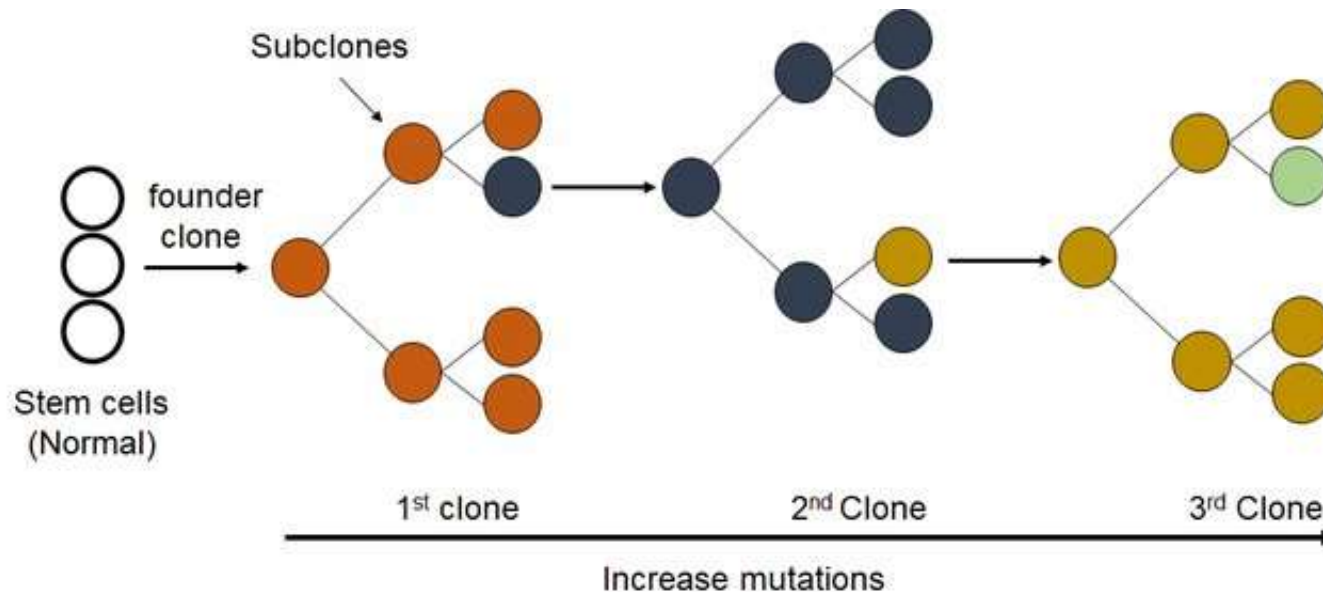
Cancerogenesis

- Carcinogenesis - accumulation of genetic mutations and epigenetic) changes.
- Under selection pressure, earlier **driver** mutations, and also **passenger** mutations obtain advantage for outgrowth of clones and drive tumors grow.



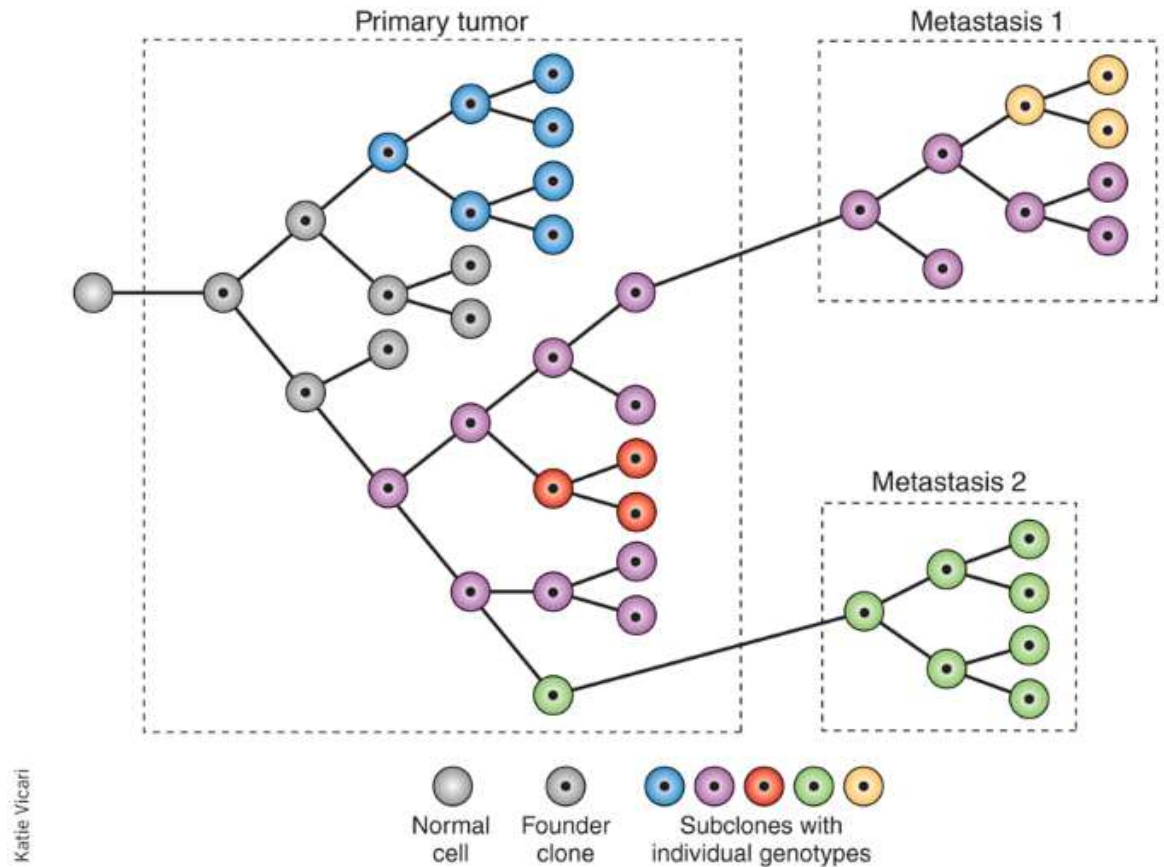
Cancerogenesis

- The **clonal expansion** of a population of mutated cells (cancer cells) from an individual single-cell causes tumor heterogeneity in pathology and molecular profiles.
- Tumor **heterogeneity** within tumors is created by genetic and epigenetic changes.



Cancerogenesis

- Nowell's theory of tumor evolution.
- The tumor arises from a single cell.
- Dominance of one clone.
- Aggressive clones spread, passive ones perish
- Selection, clonal expansion.
- Clonal diversity is accompanied by genetic heterogeneity.



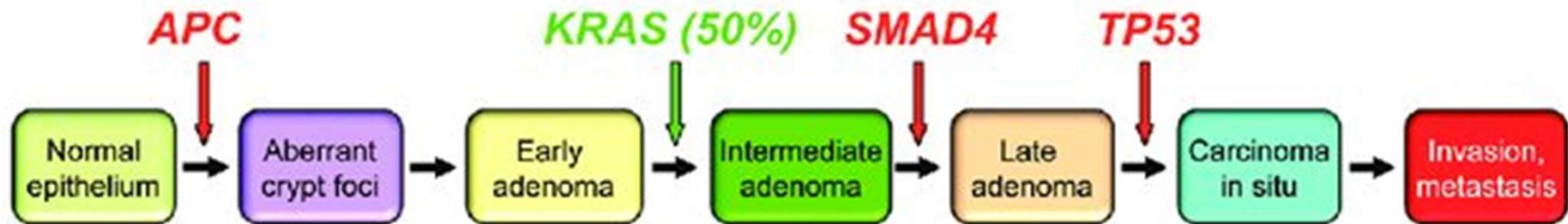
Nature Biotechnology volume 30, pages408–410 (2012)

Science. 1976 Oct 1;194(4260):23-8.

Blood. 2012 Aug 2;120(5):927-8.

Cancer multistage process

- Colonic epithelial cells undergo a histologic transition from normal to malignant state that is driven by specific genetic events including inactivation of tumor suppressors (APC, SMAD4 and TP53) and activation of the KRAS oncogene.
- The three stages of adenomas represent tumors of increasing size, dysplasia, and villous content.



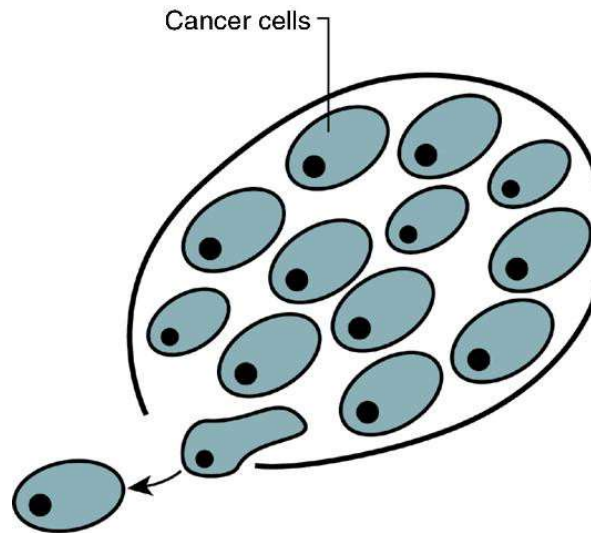
Tumor – histology

- All tumors, benign and malignant, have two basic components:
- **Stroma** - supporting, host-derived, non-neoplastic, made up of connective tissue, blood vessels, and host-derived inflammatory cells.
 - Crucial to the growth of the neoplasm.
 - Carries the blood supply.
 - Provides support for the growth of parenchymal cells.
- **Parenchyma** - made up of transformed or neoplastic cells.
 - Largely determines its biologic behavior.
 - Tumor derives its name.

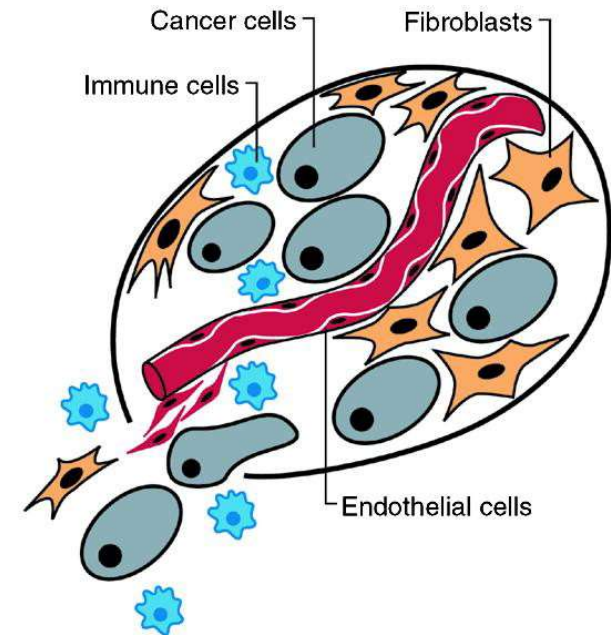
Tumor is a complex tissue

- The interactions between the genetically altered malignant cells and these supporting coconspirators proves to be critical in cancer onset and progression – microenvironment.

The Reductionist View



A Heterotypic Cell Biology



- The Hallmarks of Cancer

The hallmarks of cancer

- Hanahan and Weinberg

Avast SafeZone | Přihlášení | The hallmarks of cancer. - x +

www.ncbi.nlm.nih.gov/pubmed/10647931

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Format: Abstract

Cell. 2000 Jan 7;100(1):57-70.

The hallmarks of cancer.

Hanahan D¹, Weinberg RA

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Review [Studies of growth, differentiation and neoplastic transformati [Postepy Biochem. 1988]

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The hallmarks of cancer

- Robert Weinberg
 - 1982 – Discovered Ras, the first human oncogene
 - isolated Rb for the first time in his lab
 - MIT
-
- Doug Hanahan
 - MIT, UCSF
 - Director of École Polytechnique Fédérale de Lausanne
 - 1983- SOB medium for bacteria



Robert Weinberg









Douglas Hanahan

What genes are altered in cancer?

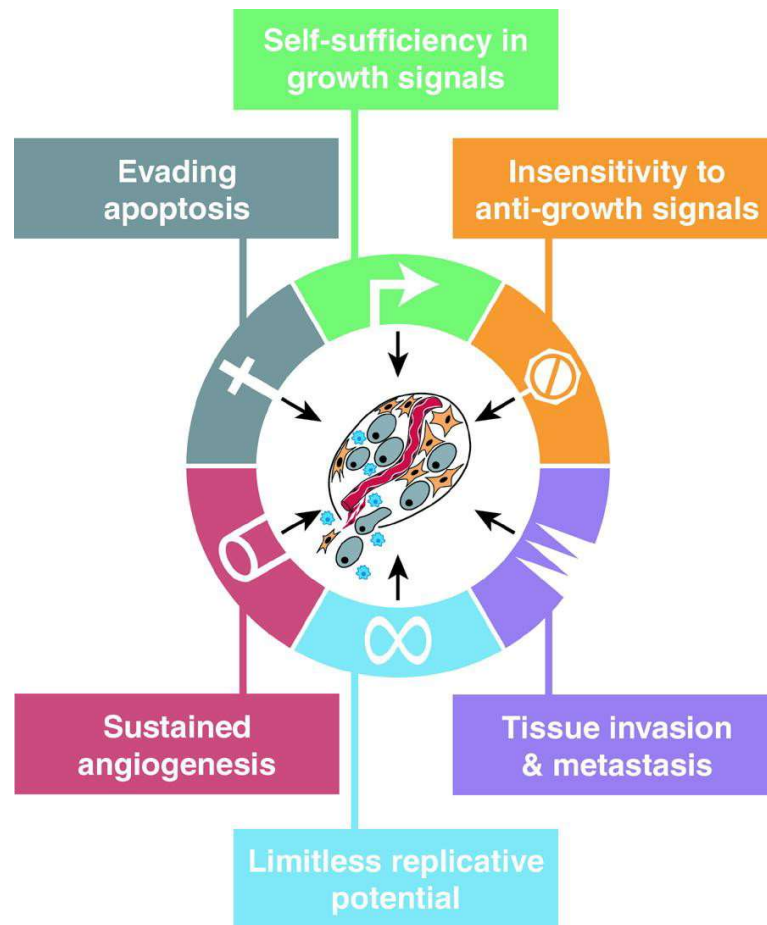
- A tumor is not a monogenic disease.
- It is estimated that 4 - 7 events (interventions) are necessary for the development of the tumor.
- There are dozens of specific genes that can be altered during carcinogenesis.
- In general, there are six (seven?) basic acquired features of a fully malignant tumor.

Tumors must acquire the same hallmarks capabilities

- Weinberg & Hanahan
- Genome instability as a necessary condition for the accumulation of all necessary mutations?

| Component | Acquired Capability | Example of Mechanism |
|---|--------------------------------------|--------------------------------|
|  | Self-sufficiency in growth signals | Activate H-Ras oncogene |
|  | Insensitivity to anti-growth signals | Lose retinoblastoma suppressor |
|  | Evading apoptosis | Produce IGF survival factors |
|  | Limitless replicative potential | Turn on telomerase |
|  | Sustained angiogenesis | Produce VEGF inducer |
|  | Tissue invasion & metastasis | Inactivate E-cadherin |

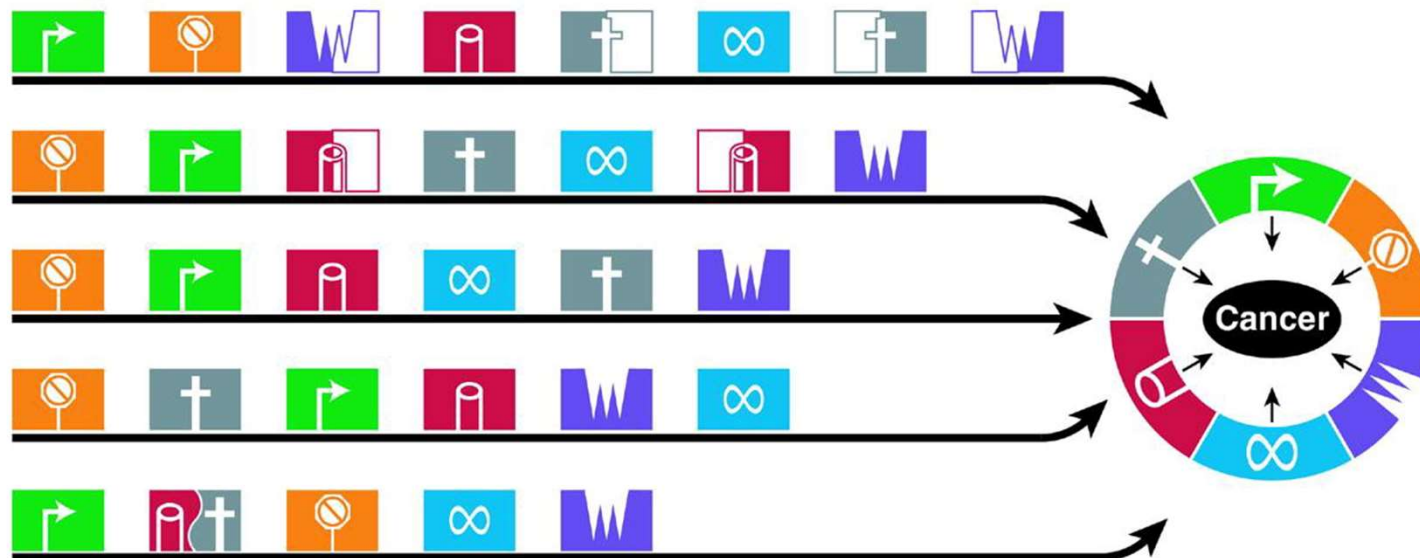
Tumors must acquire the same hallmarks capabilities




- Genome instability as a necessary condition for the accumulation of all necessary mutations?

Cancerogenesis has an individual course

- Thus, the order in which these capabilities are acquired seems likely be quite variable across the spectrum of cancer types and subtypes.
- In some tumors, a particular genetic lesion may confer several capabilities simultaneously, decreasing the number of distinct mutational steps required to complete tumorigenesis.



Tumors must acquire the six hallmarks capabilities

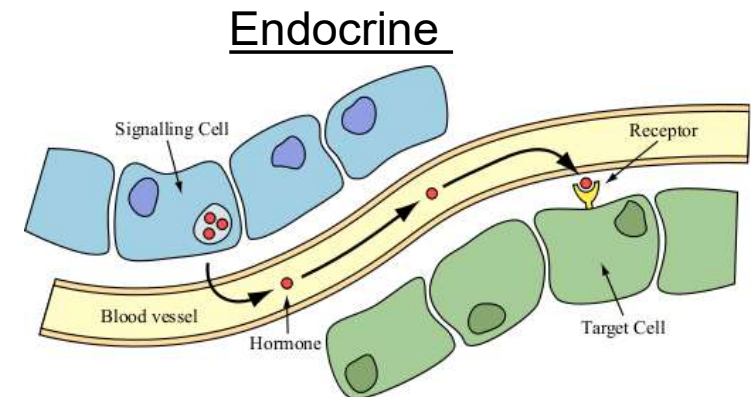
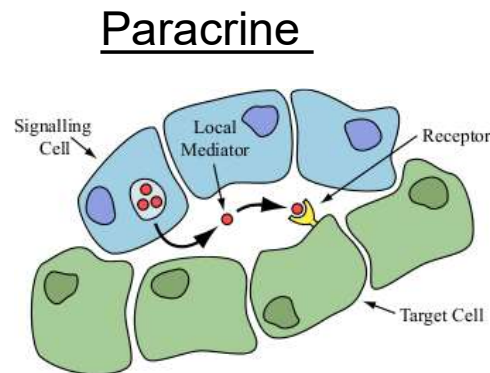
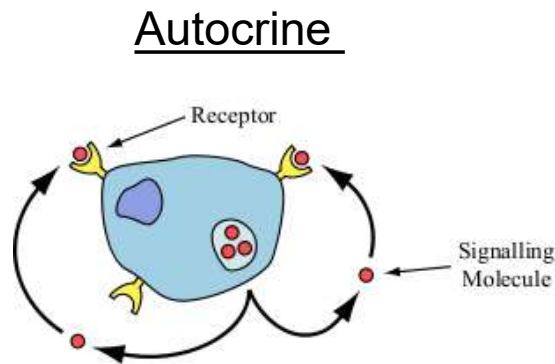
| Component | Acquired Capability | Example of Mechanism |
|---|------------------------------------|-------------------------|
|  | Self-sufficiency in growth signals | Activate H-Ras oncogene |

Sustaining cell signaling

- Healthy cells – carefully control growth and division. The signal, binding to receptor, triggering of the signaling pathway.
- Tumor cells deregulate these signals. they do not need stimulation by growth factors to proliferate.
- Tumor cells can produce:
 - Their own growth factors, such as PDGF – glioblastomas.
 - Receptor overexpression - EGFR – breast and stomach tumors.
 - Change the receptor structure – receptor does not need a ligand to activate.

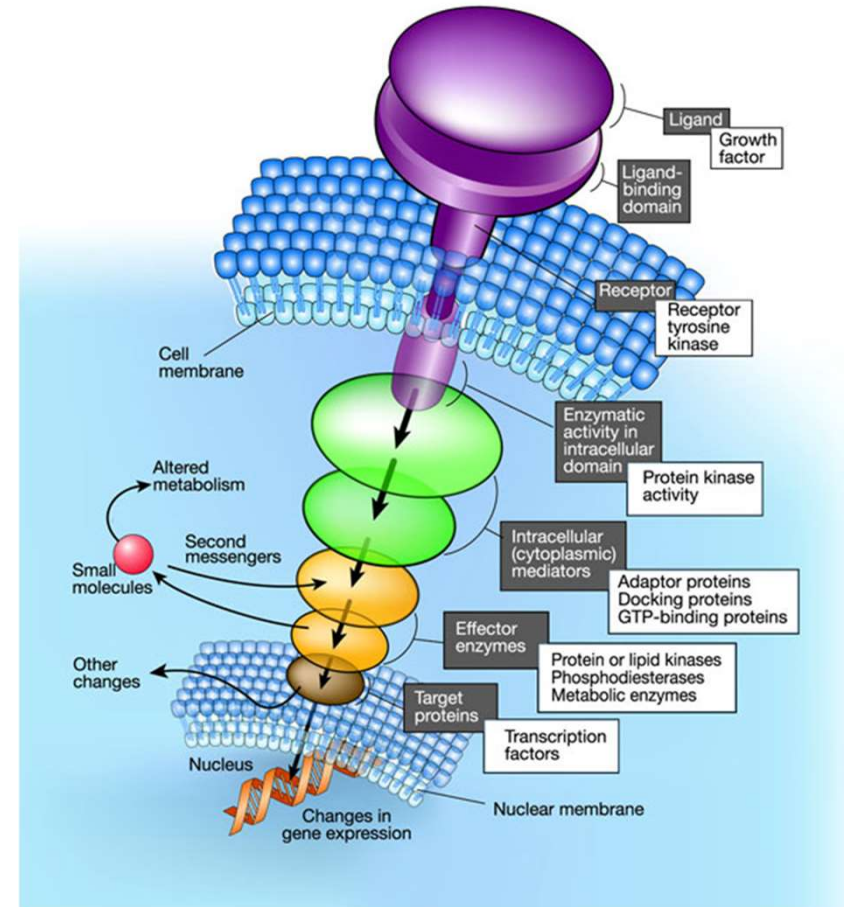
Growth factors and Receptor-tyrosine kinases

- Growth factors: Polypeptides, which are produced by cells and induce signaling to start or stop proliferation, differentiation, survival,... by activating its specific receptors on the cell surface.
- Stimulation: Three types of communication systems in biological systems differs mainly by the distance that the communication operates over.
 - Autocrine - growth factor stimulates the producing cell.
 - Paracrine - stimulation of a neighboring cell.
 - Endocrine - stimulation of distant cells.



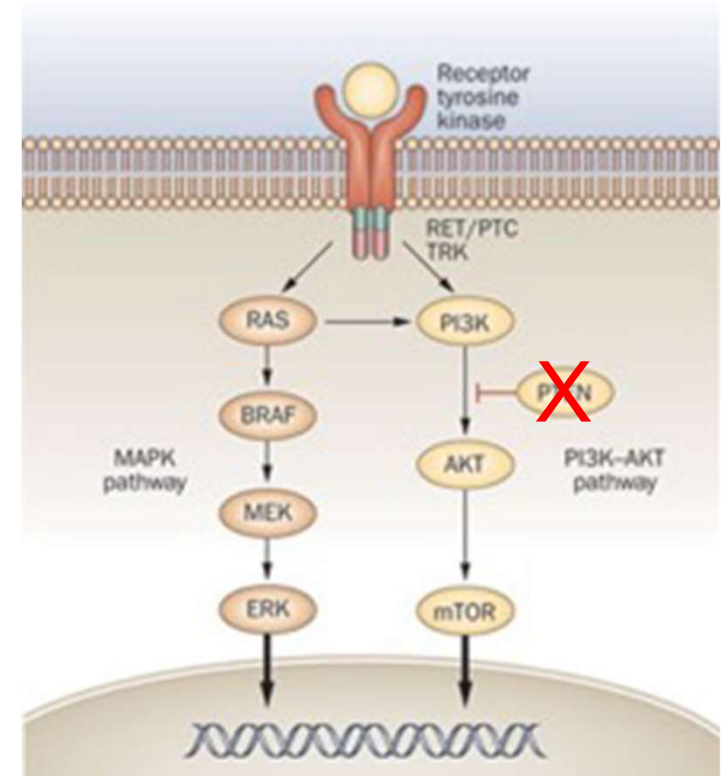
Cell signaling

- This distribution is related to the structure of the signal pathway:
- Growth factor binding to receptor.
- Activation of receptor protein kinases.
- Signal transmission to the nucleus by a cascade of protein kinases.
- Activation of the transcription factor.

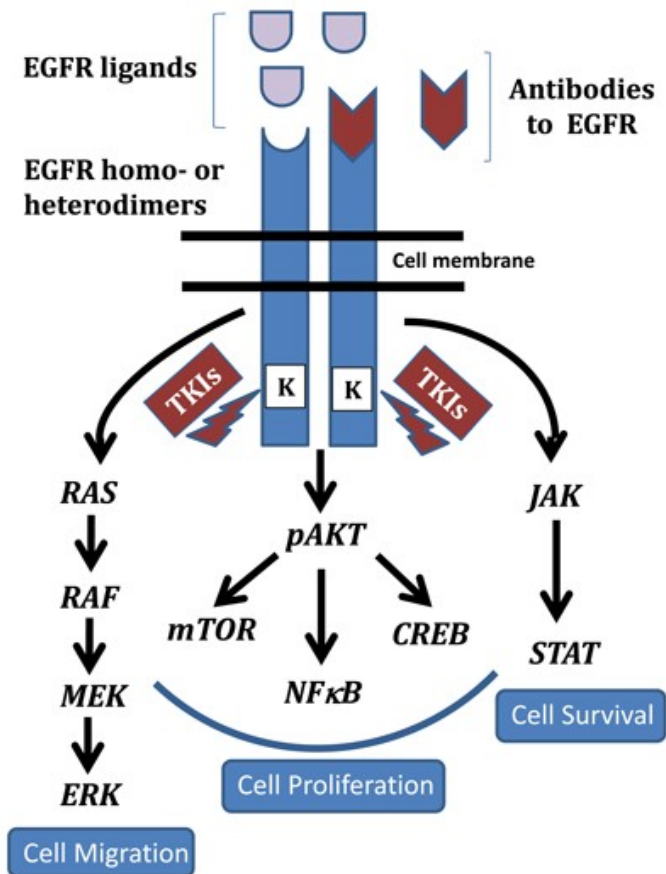


Sustaining cell signaling

- Cellular pathways critical for cell survival are deregulated in tumors.
- Mutation – activation/inactivation of the pathway leads to:
 - Uncontrollable proliferation.
 - Invasiveness.
 - Resistance to signals.
 - Angiogenesis.
 - Metastasing.
 - Resistance to apoptosis.




Sustaining cell signaling



- Activation of the EGFR pathway induces cellular survival and anti-apoptosis signals by activating transcription of genes associated with cell survival - NFκB and JAK/STAT.
- EGFR is activated either as a homo- or heterodimer resulting in regulation of multiple pathways.
- In particular the RAS/RAF/MAPK, AKT, and JAK/STAT pathways downstream of EGFR play integral roles in cell migration, proliferation, and survival, respectively.
- Anti-EGFR antibodies are targeted to the external ligand binding domains while the small molecule inhibitors or tyrosine kinase inhibitors (TKIs) target its cytoplasmic kinase domains.

Tumors must acquire the six hallmarks capabilities

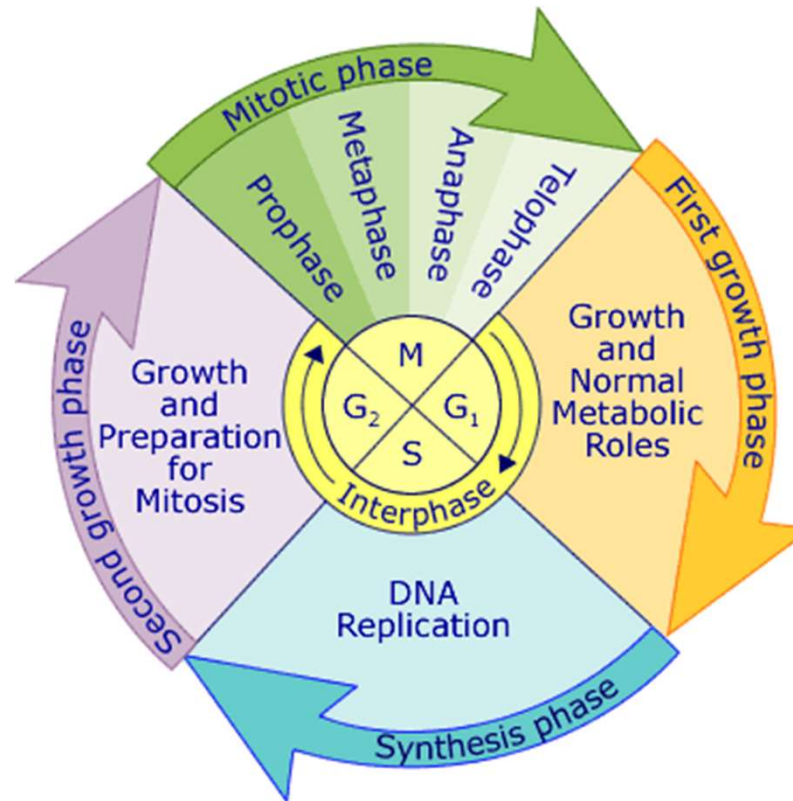
| Component | Acquired Capability | Example of Mechanism |
|---|--------------------------------------|--------------------------------|
|  | Insensitivity to anti-growth signals | Lose retinoblastoma suppressor |

Tumor as disease of the cell cycle

- Loss of the cell cycle regulation is a critical part of cell transformation.
- Loss of the cell cycle regulation is not the only part of cancerogenesis.
- When altered it is not fully transformative itself.

Cell cycle

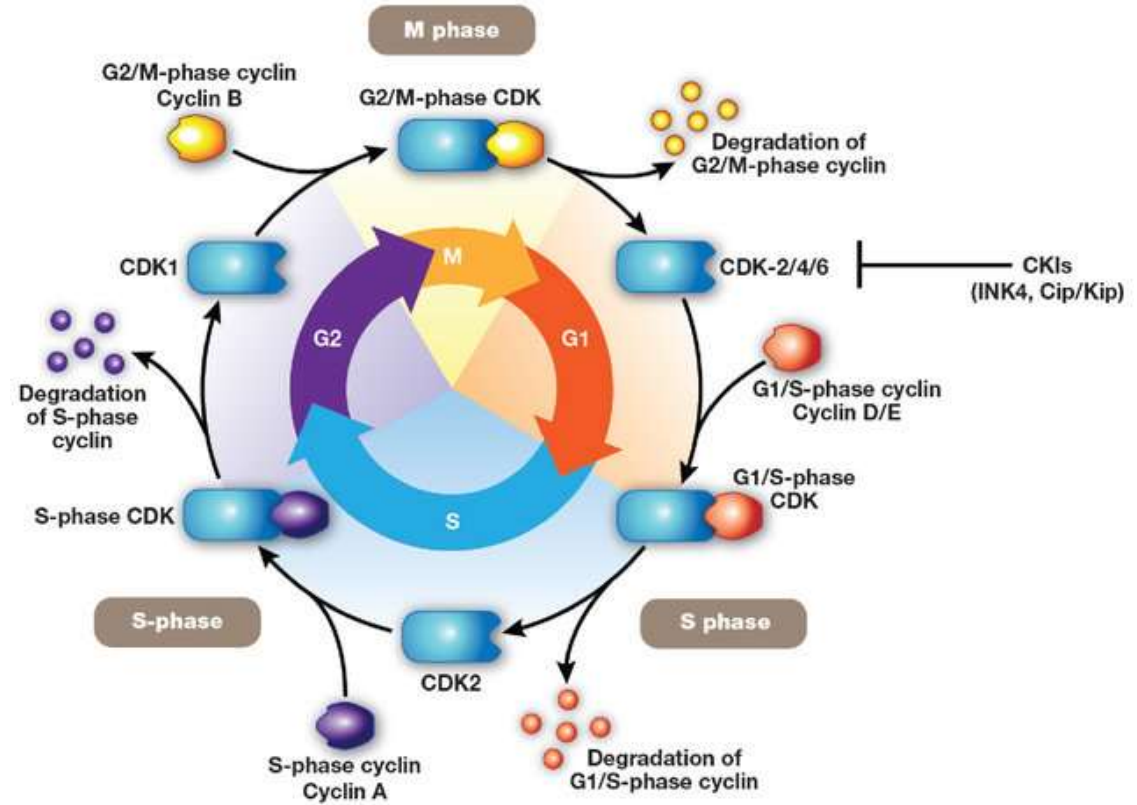
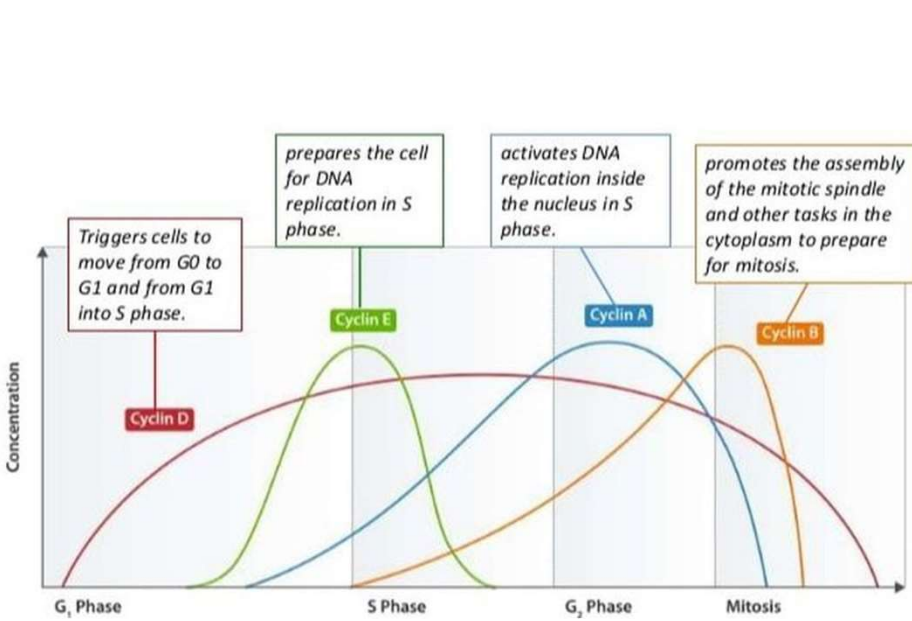
- Cell cycle:
- Interphase
- Mitosis.



Cell cycle

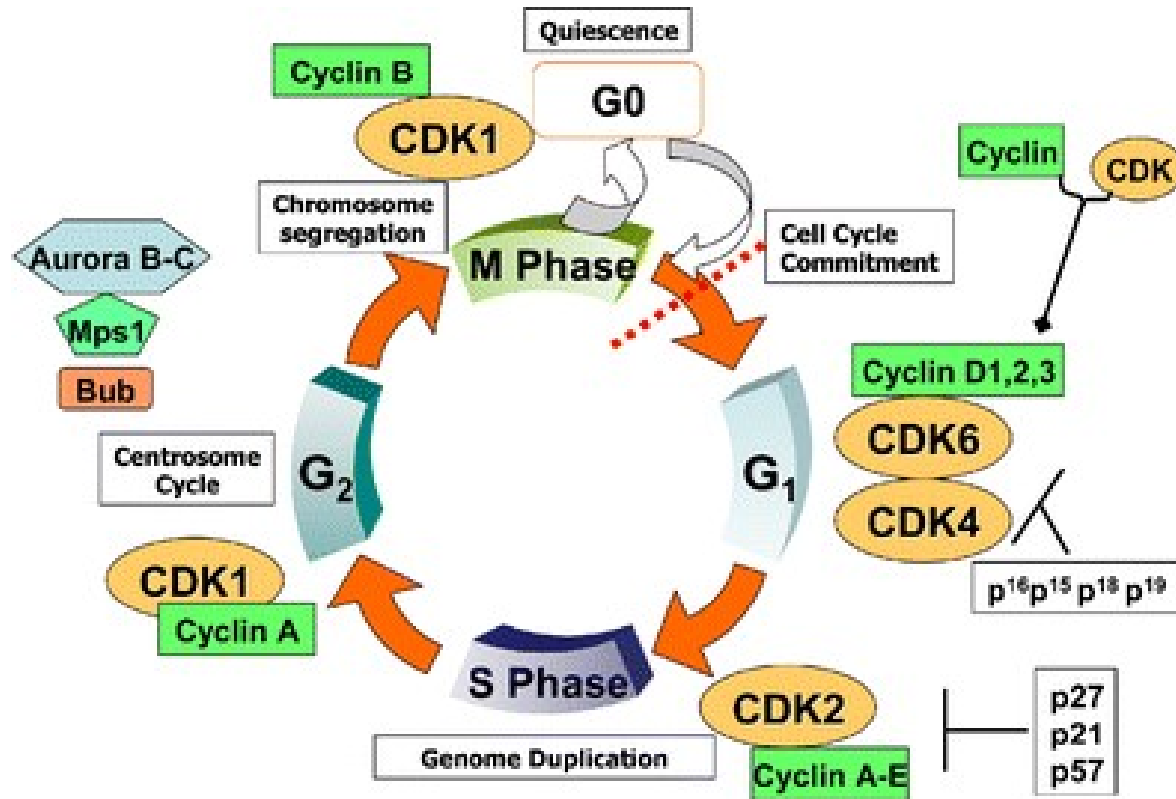
- Each phase of the cycle is catalyzed by specific cyclin-dependent kinase associated with cyclin.
- Cyklin-dependentní kinázy (CDK):
 - Phosphorylates its substrates.
 - Typically have a catalytic and regulatory subunit, activity always dependent on cyclin binding.
- Cyklins:
 - Their level fluctuates depending on the phase of the cell cycle.
 - They activate the appropriate CDK and direct it to its substrates, then they are quickly degraded.

Cell cycle



Cell cycle

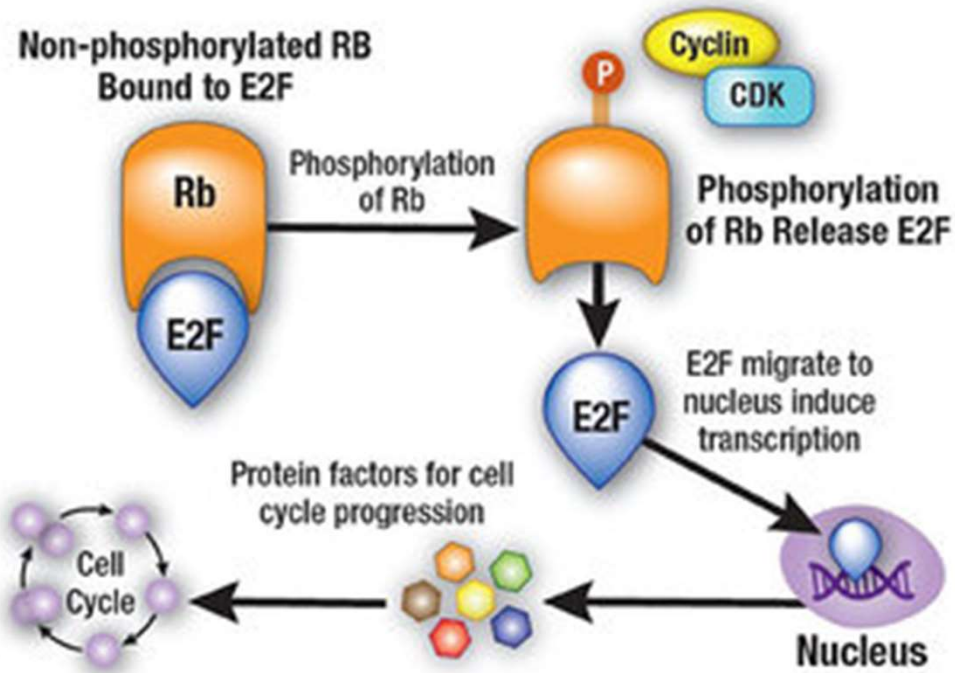
- Cell cycle.
- Interphase
- Mitosis.



pRb a principal regulator of cycle

- Retinoblastoma protein - pRB is non-phosphorylated state and blocks the passage through the G1 – S restriction point:
 - Interacts with TF family E2F.
 - Blocks their ability to transactivate their target genes - necessary for the S phase.
- Phosphorylation of pRB leads to its ability to bind E2F and passage through the restriction point is thus possible.
- Regulation of passage through the restriction point = regulation of pRB phosphorylation.

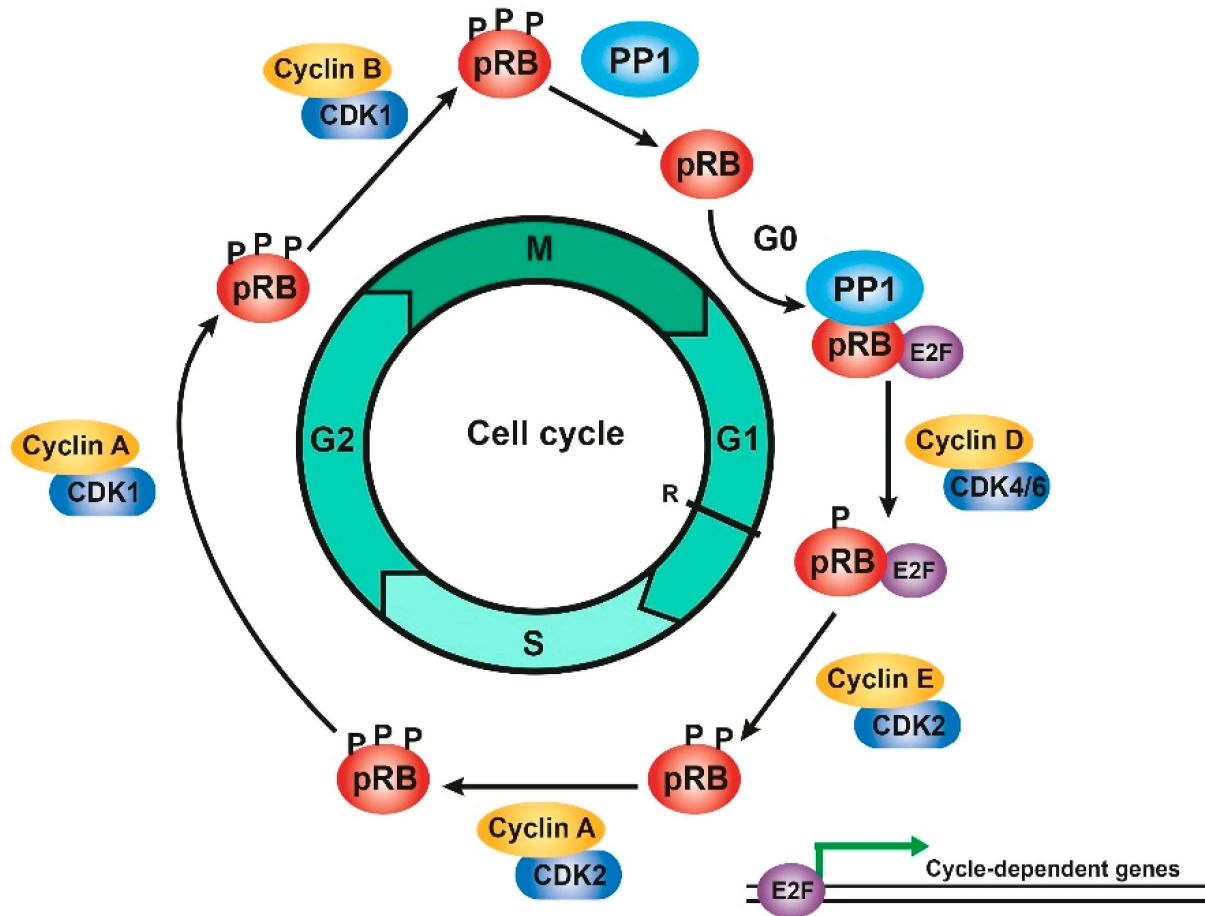
Regulation of pRb activity



Regulation of pRb activity

- The activity of pRB is positively affected:
 - Cyclins D (D1, D2 and D3) with CDK4/CDK6.
 - Cyclin E and CDK2 complexes.
- Negatively affected by cellular CDK/cyclin inhibitors:
 - Cip/Kip family proteins - p21WAF1 and p27KIP1.
 - INK4 family proteins- p15INK4B and p16INK4A.
- Mitogenic signaling leads to increased expression of cyclins D and decreased levels of inhibitors.
- Antimitogenic signaling leads to a decrease in the level of cyclins D and induction of the CDK/cyclin inhibitors.
- Mutation in Rb – often lead to an uncontrollable division due to hyperphosphorylated status of pRb.

pRb a principal regulator of cycle



Tumors must acquire the six hallmarks capabilities

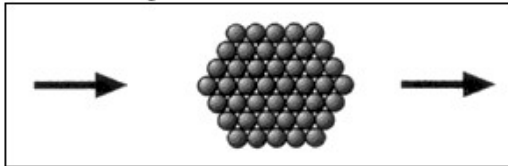
| Component | Acquired Capability | Example of Mechanism |
|-----------|---------------------|----------------------|
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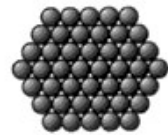
| | | |
|--|-------------------|------------------------------|
| | Evading apoptosis | Produce IGF survival factors |
|--|-------------------|------------------------------|

Cell death and tumors progression

A. Balanced proliferation and death

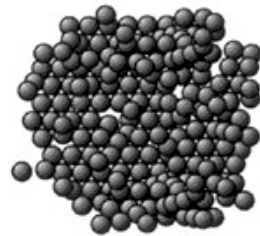
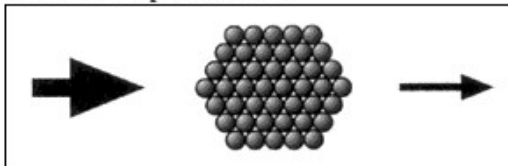


OUTCOME



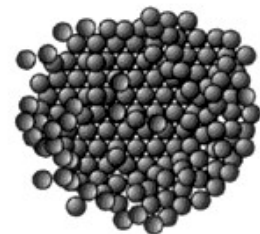
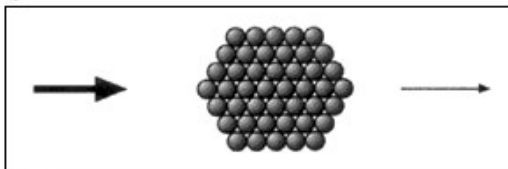
Homeostasis

B. Increased proliferation



Neoplasia

C. Decreased cell death

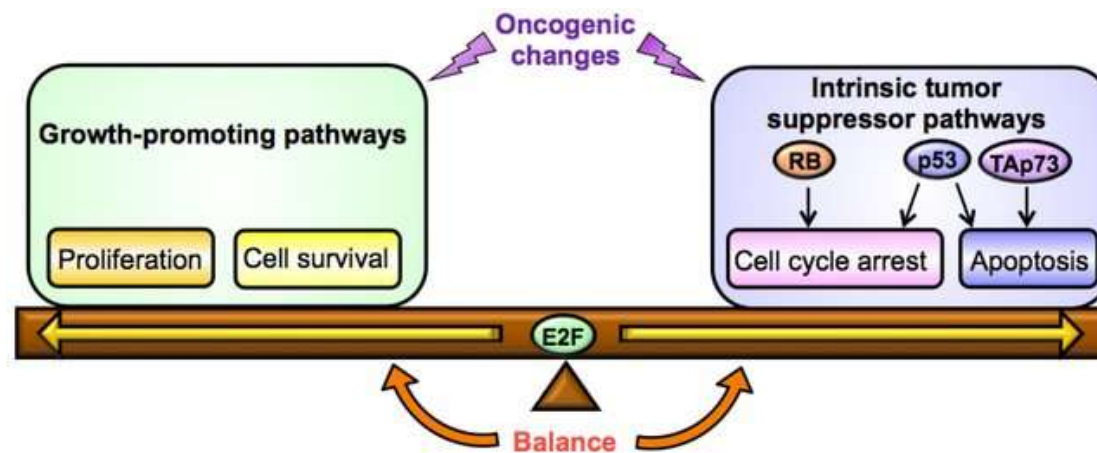


Neoplasia

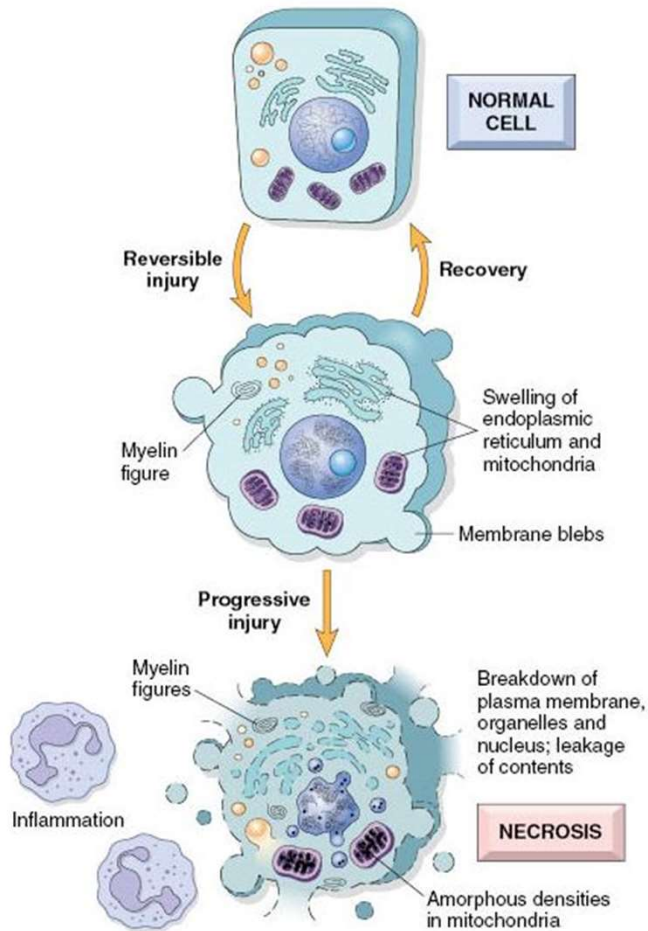
- The rate of tissue growth is determined by the rate or equilibrium of cell division and the rate of cell death.
- During homeostasis, both processes are in balance.
- In a tumor, the balance between cell division and cell death is broken.

Cell death and tumors progression

- Apoptosis:
- Cells live for a limited time.
- Then apoptosis (programmed cell death) is triggered.
- Tumor cells are resistant to the induction of cell death due to incapability to respond to death signals or they become sensitive to the oncogenic signals.



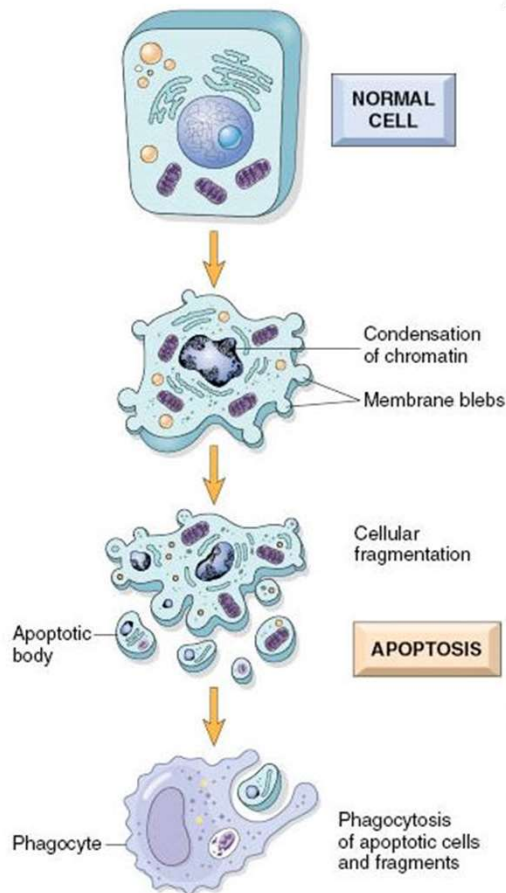
Necrosis



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- **Necrosis** refers to a group of affected cells caused by non-physiological damage (viral infection, hypothermia..), significant inflammatory reaction.
- Morphological features:
 - Begins with swelling of the cytoplasm and mitochondria organelles crumble.
 - Loss of cell membrane integrity.
- Biochemical features:
 - Loss of regulation of homeostasis.
 - Passive process without energy (runs even in 4°C).
 - Random DNA degradation.

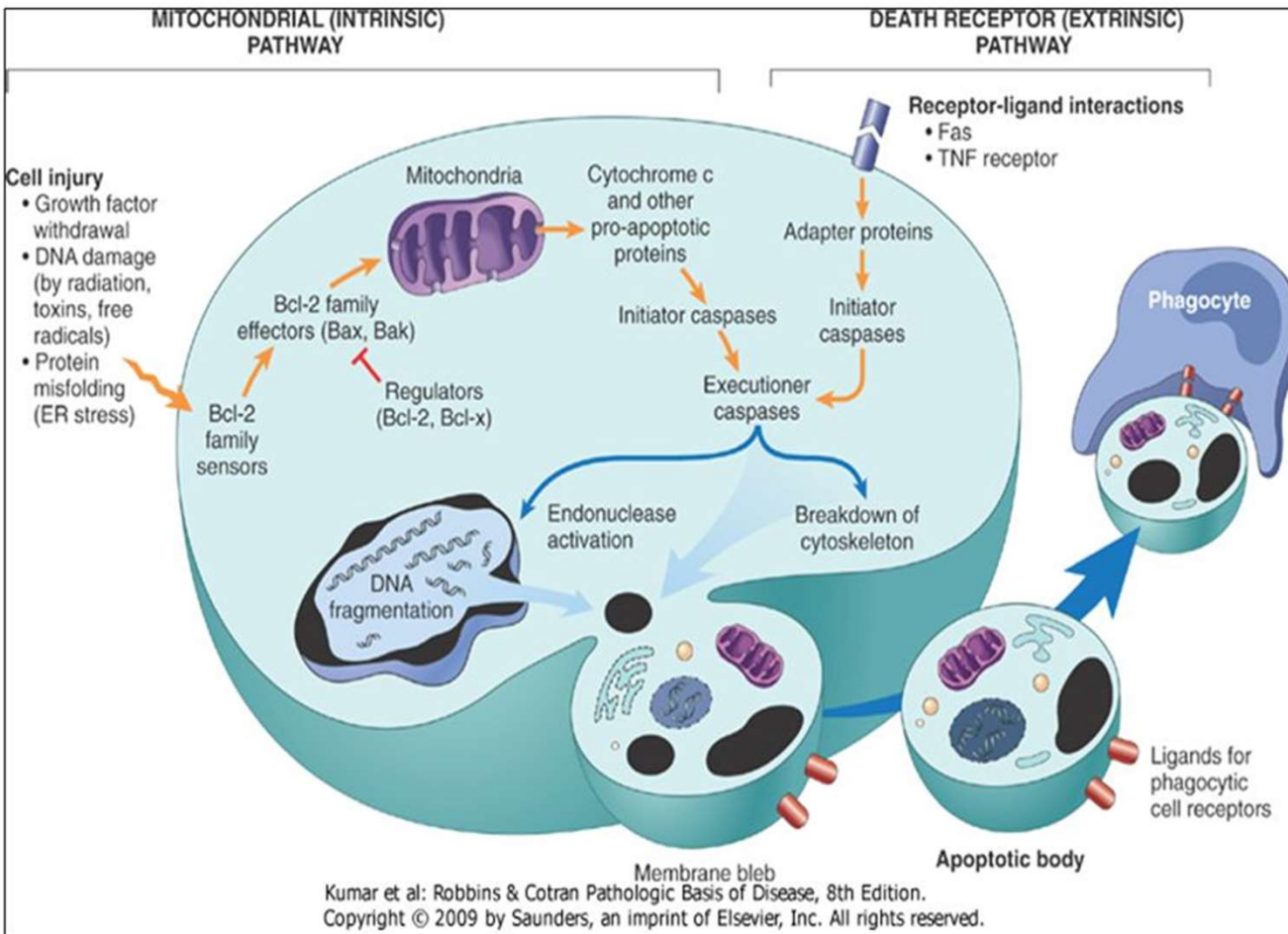
Apoptosis



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- **Apoptosis** is programmed cell death:
- Affects individual cells.
- Induced by physiological stimuli (lack of growth factors) no inflammatory reaction physiological.
- Morphological features:
 - Condensation of the cell and nucleus.
 - „Blebs“ of cell membranes.
 - Chromatin condensation.
 - Nucleus fragmentation and cell fragmentation into apoptotic bodies.
- Biochemical features:
 - Strictly regulated, active process.

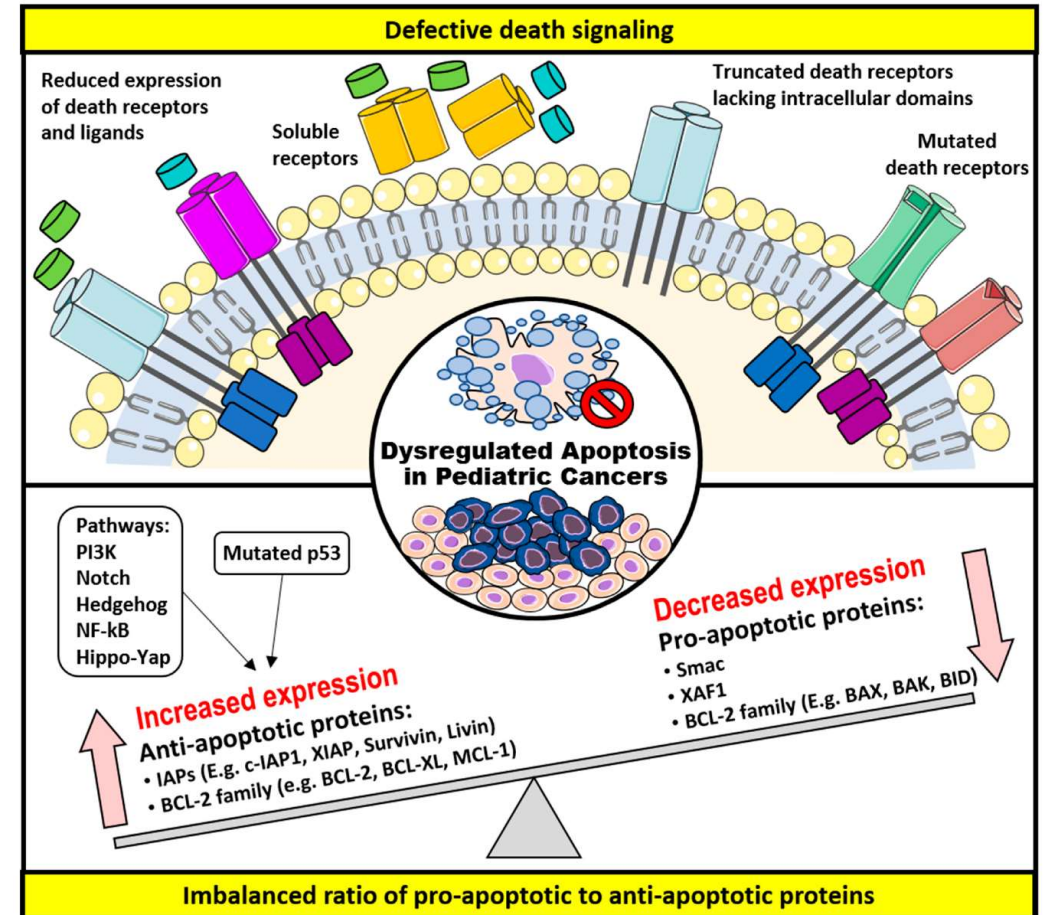
Regulation of apoptosis



- **External receptor pathway** - ligand binding to the corresponding death receptor produces a proapoptotic signal. This leads to the activation of the domain of death with the cooperation of other proteins. The goal is to activate procaspase 8.
- **Internal path** - signaling e.g. through p53 initiates an apoptotic process, the component of which is the Bcl-2/Bax system, signaling through mitochondria, the formation of a complex called apoptosome and the goal is to activate procaspase 9.

Dysregulation of apoptosis in cancerogenesis

- Apoptosis is dysregulated in cancer leading to disruptions of the delicate balance between cell proliferation and cell death.
- Examples of altered apoptotic proteins in tumors:
 - Up-regulation of Bcl-2 (chromosomal translocation) in lymphomes.
 - Up-regulation of survival factors IGF-1, IGF-2.
 - Mutation and downregulation of the Fas death receptors.
 - Mutations.
 - Activation of bax.
 - Inactivation of p53.



Tumors must acquire the six hallmarks capabilities

| Component | Acquired Capability | Example of Mechanism |
|-----------|---------------------|----------------------|
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Limitless replicative potential

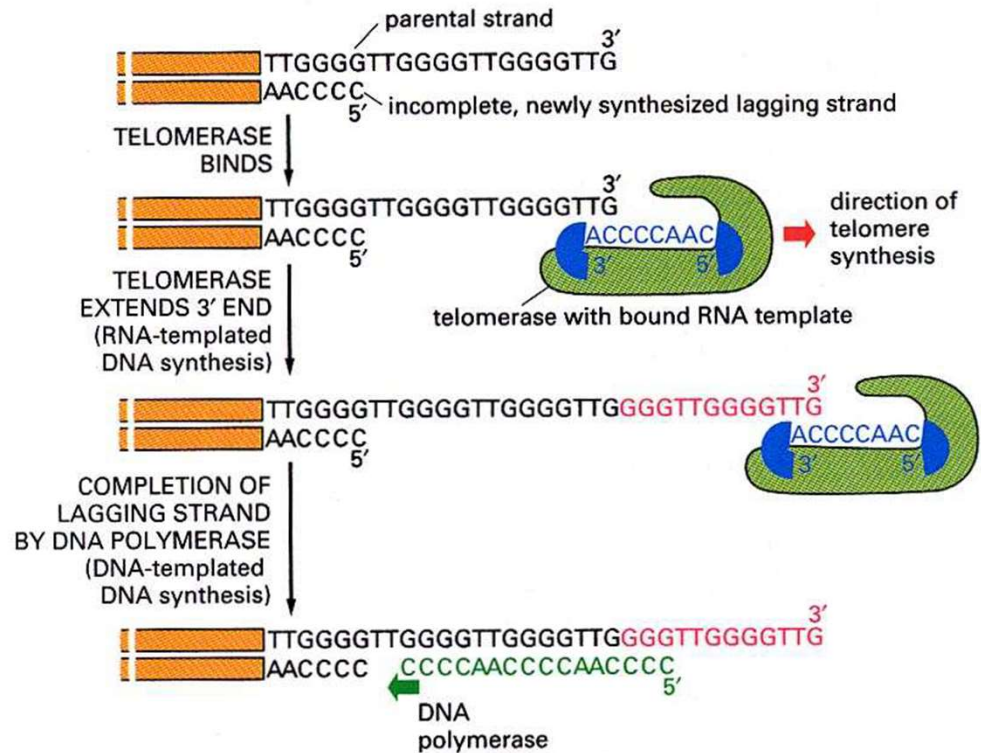
Turn on telomerase

Replication potential

- Mammalian cells have a replication potential of 60-70 divisions (Hayflick limit).
- Then they go to the stage of senescence – they change the morphology, metabolically active, do not divide, block CC – p53, Rb.
- Mutation in p53 or Rb – another 30 divisions – crisis, chromosomal aberration – apoptosis.
- If the mutation occurs with probability 10^{-7} – then there is a great chance that immortal cell will appear.
- Most tumor cells – immortal.

Telomerase hypothesis

- When the critical length of the telomeres is reached, signals are triggered that induce a state of senescence. With further division (inactivation of p53 and pRB), telomeres are further shortened and cause chromosomal instability, which provokes a crisis.
- Telomere shortening acts as a **mitotic counter** that determines the proliferative capacity of all cell types that do not have telomerase activity.

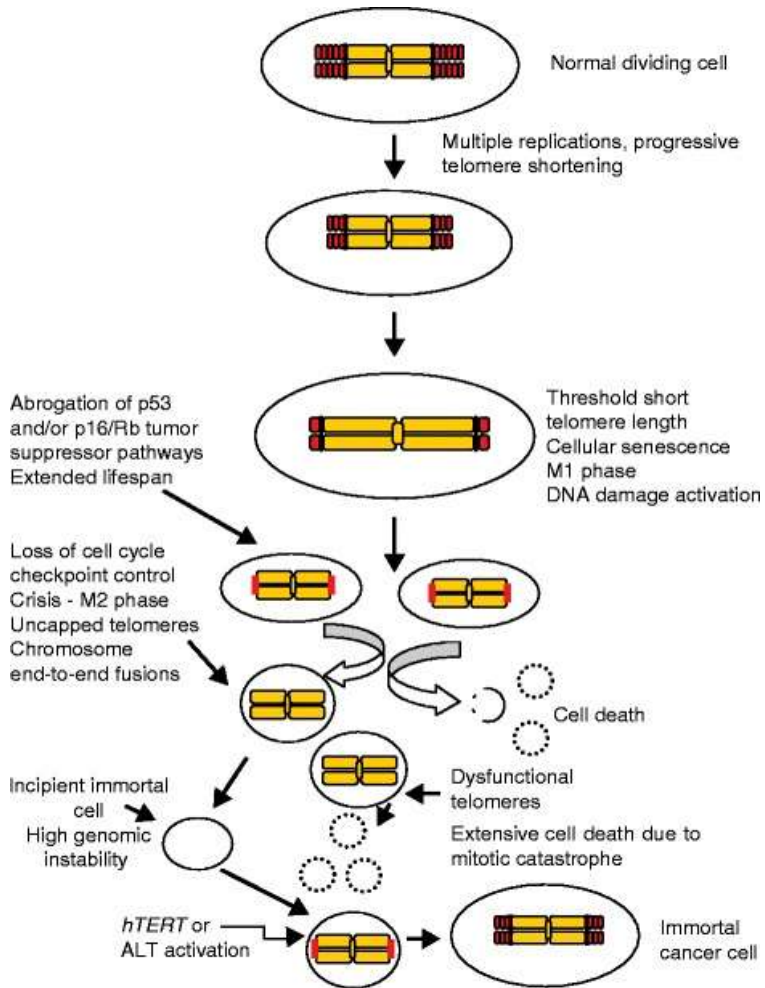


[Clear view of telomerase at last \(acs.org\)](https://acs.org)

Telomerase

- Germ cells.
- Some stem cells.
- Some somatic cells under specific conditions:
 - Lymphocytes activated by mitogens.
 - Cells in the proliferative zone of intestinal crypts.
 - Cells of the proliferative basal layer of the skin.
 - Cells of the lobular endothelium of the breast during pregnancy.

Telomerase hypothesis



- Telomere shortening is a natural consequence of cell division due to the “end replication problem”.
- In the cells undergoing replicative senescence, the p53 and p16–pRB pathways are often activated leading to essentially irreversible growth arrest.
- Cells that gain additional oncogenic changes (p53 loss) can bypass senescence and continue to divide until chromosome end-to-end fusions.
- Only a rare human cell (one in 10^5 to 10^7) can engage a mechanism to bypass crisis and become immortal.
- This is almost universally accomplished by the upregulation or reactivation of telomerase.
- A rarer telomerase negative immortalization pathway, termed ALT (alternative lengthening of telomeres), involves DNA recombination to maintain telomeres.

Tumors must acquire the six hallmarks capabilities

| Component | Acquired Capability | Example of Mechanism |
|-----------|---------------------|----------------------|
|-----------|---------------------|----------------------|

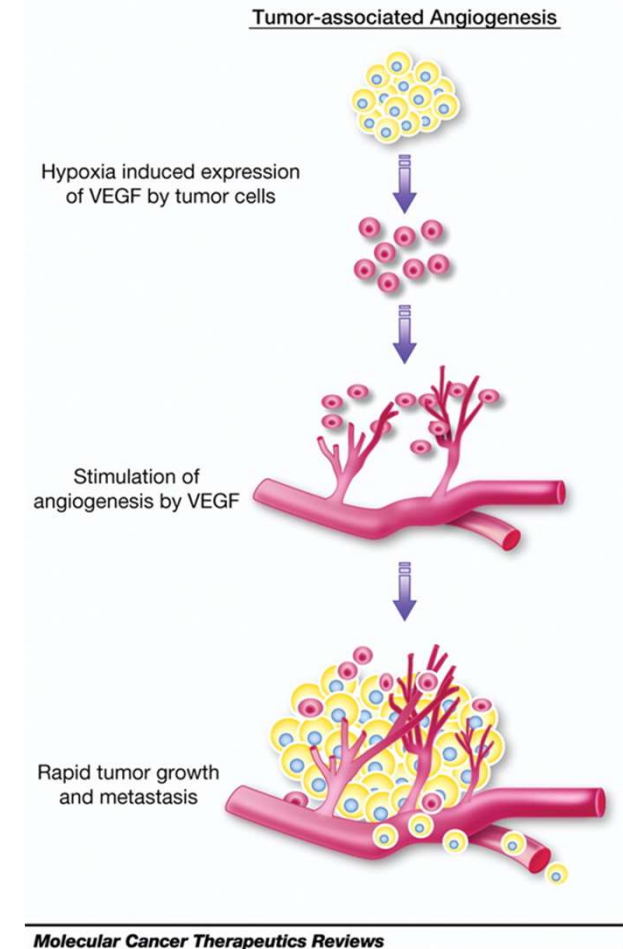


Sustained angiogenesis

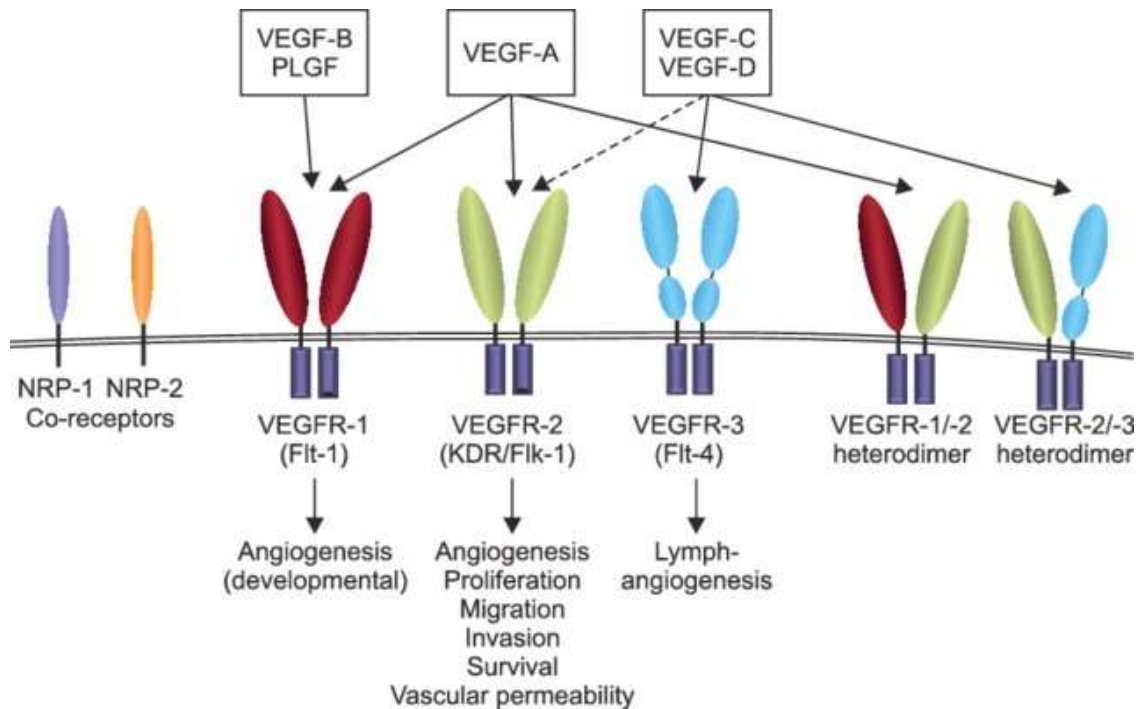
Produce VEGF inducer

Angiogenesis in cancerogenesis

- Growth of blood capillaries from the existing vasculature.
- An important step - from the dormant state of the tumor to the malignant.
- Tumor – population of rapidly and uncontrollably growing cells.
- Tumors can not grow more than 1 - 2 mm³ several million cells (lack of nutrients and oxygen).
- HIF-1 activates vascular endothelial growth factor - VEGF.
- Without angiogenesis, the tumor grows slowly and linearly, then exponentially.

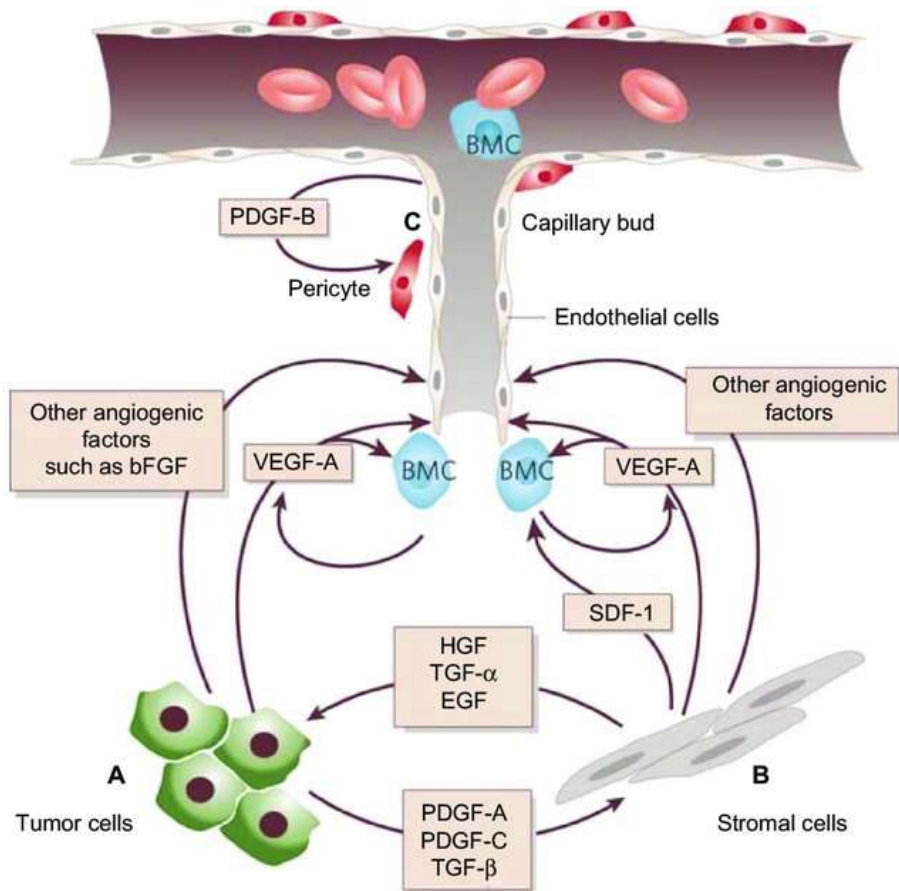


VEGF



- VEGF was the first characterized factor specific to vasculogenesis - vascular endothelial growth factor (original name - vascular permeable factor).
- It is critical for the initiation of vasculogenesis as well as for angiogenic branching.
- Today described 5 different VEGF factors and 3 different receptors.
- Interactions between VEGF and VEGF receptors orchestrate distinct biological functions.

Tumor angiogenesis

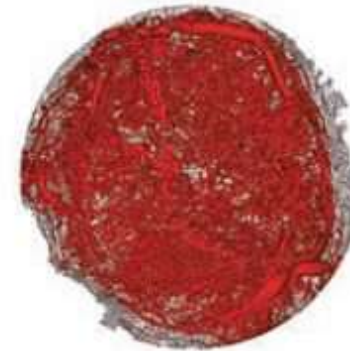


- Tumor angiogenesis:
- (A) Tumor cells produce VEGF-A and other angiogenic factors such as bFGF and angiopoietins. These stimulate endothelial cells to proliferate and migrate.
- (B) An additional source of angiogenic factors is the stroma. This is a heterogeneous compartment, comprising fibroblastic, inflammatory, and immune cells.
- (C) Endothelial cells produce PDGF- β , which promotes recruitment of pericytes in the microvasculature after activation of PDGFR- β .

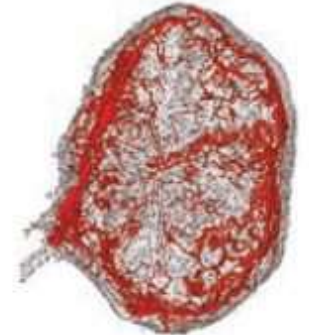
Tumor angiogenesis

- Tumor vasculature is highly disorganized.
- This can arise as a result of the uneven release of angiogenic regulators.
- The flow of blood is chaotic in different parts of the system.
- Therefore, places with hypoxia and excessive acidity are formed in the tumor.
- This circumstance may affect the effect of therapy; a space is created in which, for example, the selection and clonal expansion of cells that do not respond to hypoxia by apoptosis.

Control



+VEGF inhibitor



- Microcomputed tomography image showing effect of VEGF inhibition in a preclinical model.

Tumors must acquire the six hallmarks capabilities

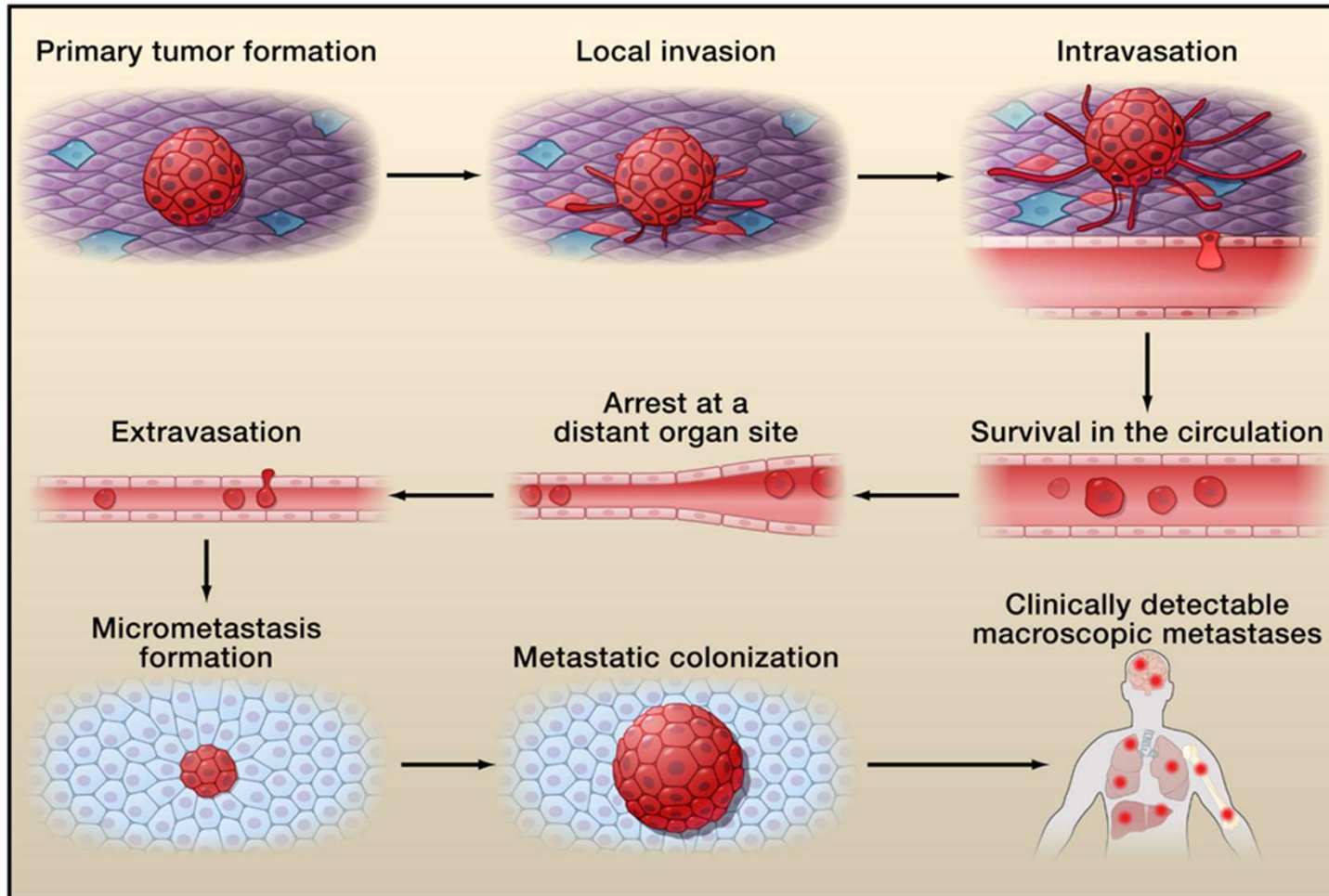
| Component | Acquired Capability | Example of Mechanism |
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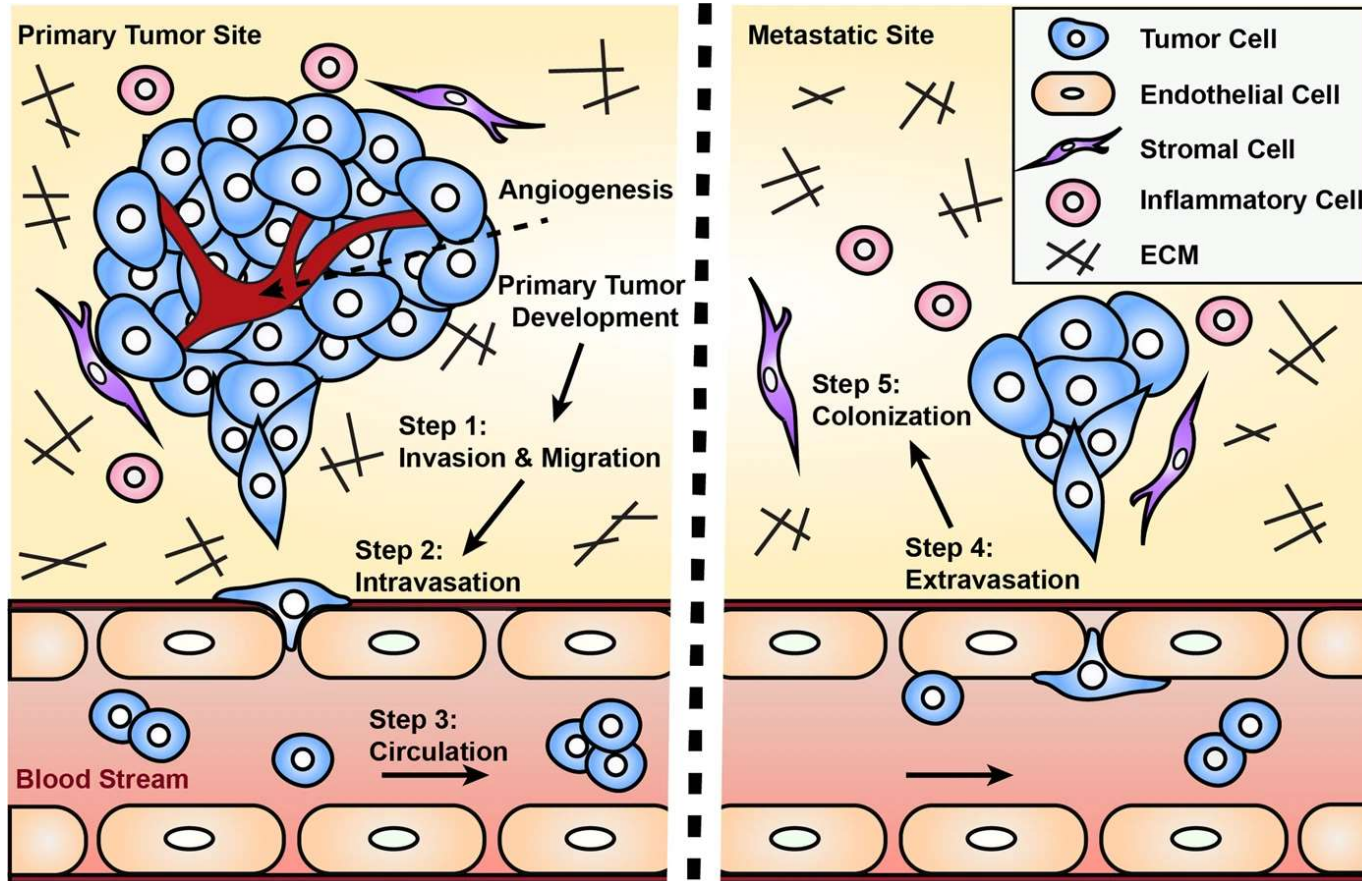
Tissue invasion & metastasis

Inactivate E-cadherin

Tumors progression

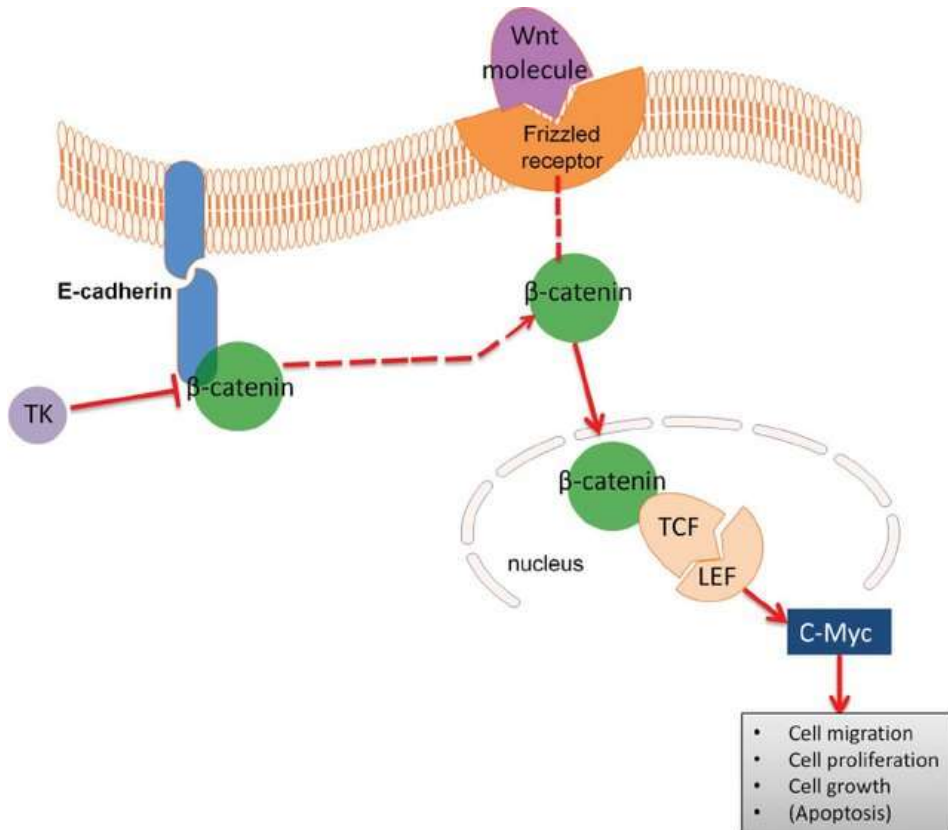


Metastatic cascade



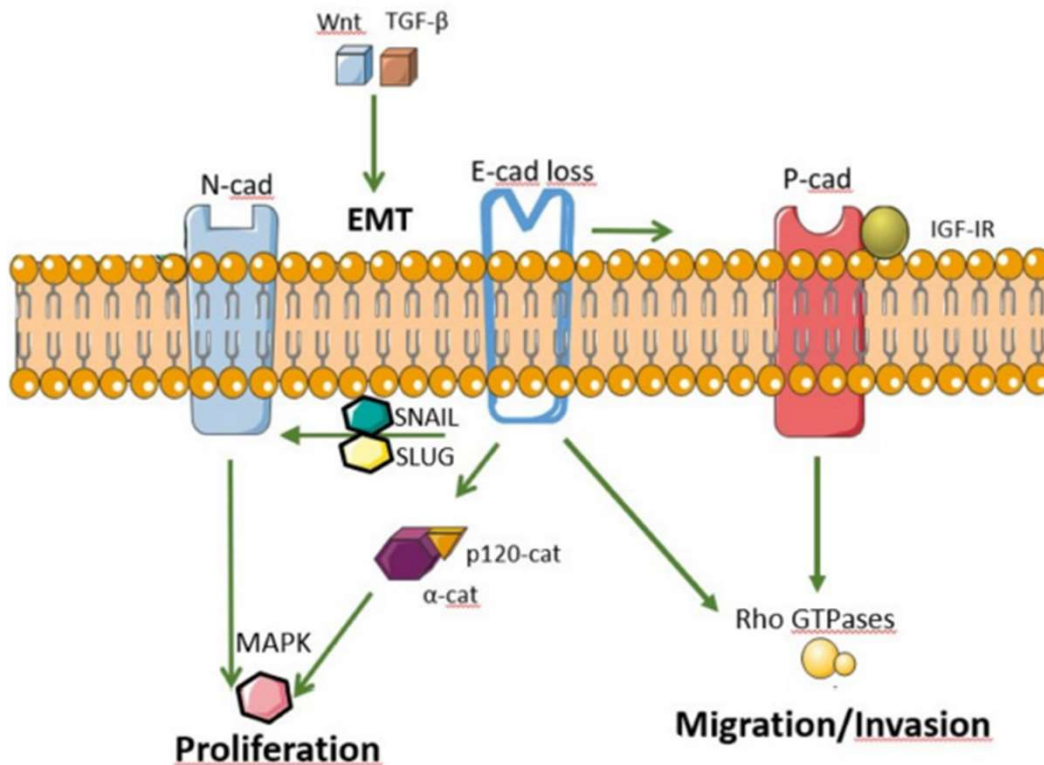
- Overview of the Metastatic Cascade.
- Step 1: Invade through basement membrane and migration.
- Step 2: Intravasation into vasculature.
- Step 3: Circulation of tumor cells in the bloodstream to blood vessels around secondary sites.
- Step 4: Extravasation through the endothelial barrier.
- Step 5: Colonization in the metastatic target organ.

The mechanism of metastasis



- Adhesive molecules – N-CAM – adhesive molecule, increased expression in Wilms tumor, neuroblastoma.
- E-cadherin – on epithelial cells, antiproliferative signals, tumors reduce expression.
- Integrins – changes in expression on migrating cells.

The mechanism of metastasis



- Glycoprotein important for cell adhesion.
- Differentiation of epithelial cells.
- Loss of expression – epithelial-mesenchymal transition, an important step in the metastatic progression of human tumors.
- Tumor suppressor.
- Decreased expression in epithelial tumors – invasiveness and worse prognosis.

- The Hallmarks of cancer: The next generation

Hallmarks of cancer: The next generation

- Hanahan and Weinberg

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Review > Cell. 2011 Mar 4;144(5):646-674. doi: 10.1016/j.cell.2011.02.013.

Hallmarks of cancer: the next generation

Douglas Hanahan¹, Robert A Weinberg

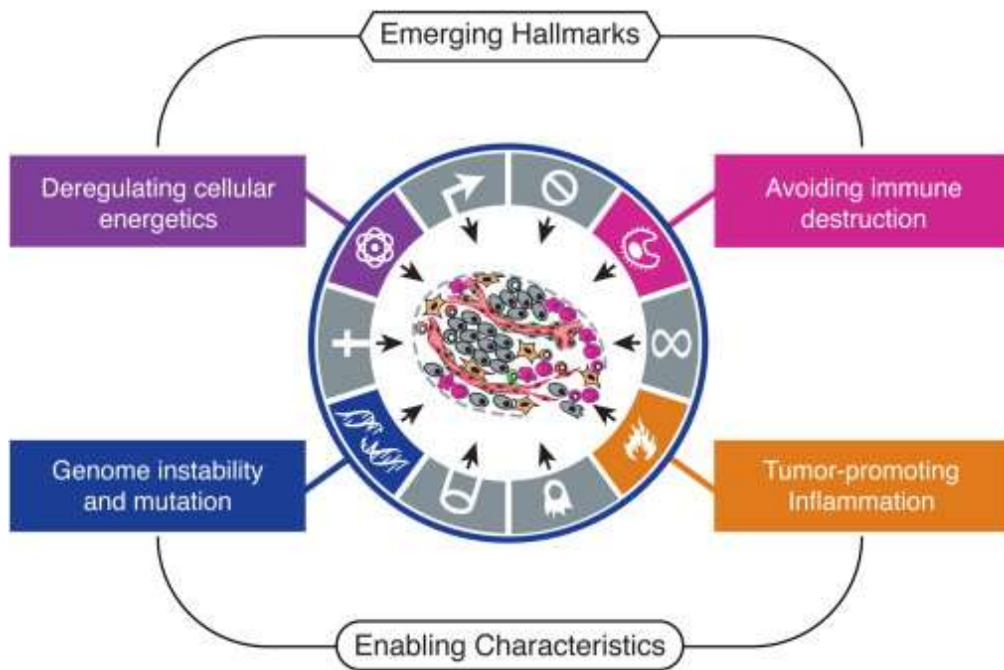
Affiliations + expand
PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013
Free article

Abstract

The hallmarks of cancer comprise six biological capabilities acquired during the multistep development of human tumors. The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks are genome instability, which

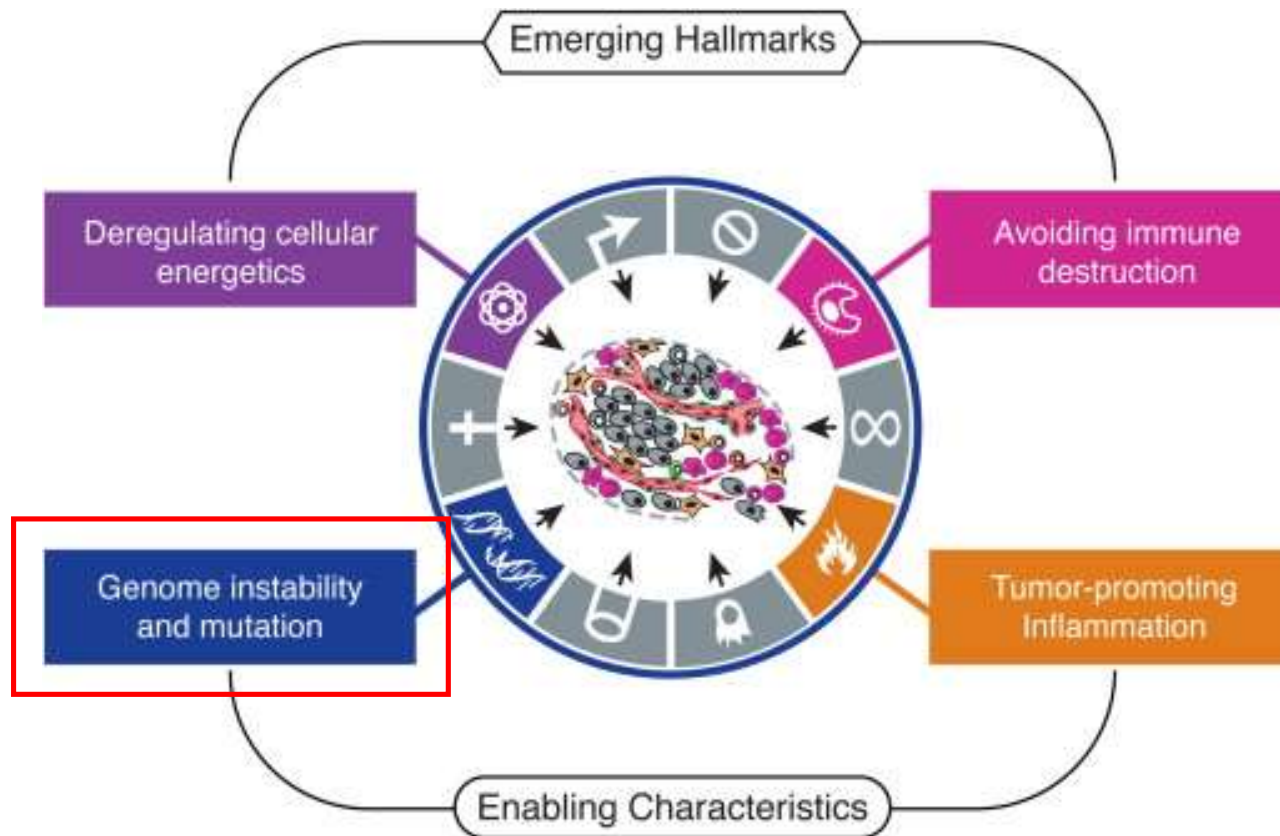
36 646 citations

Tumors must acquire additional hallmarks capabilities



- Deregulating cellular energetics – modification or reprogramming of cellular metabolism in order to effectively support neoplastic proliferation.
- Avoiding immune destruction - allows cancer cells to evade immunological destruction mediated by T and B lymphocytes, macrophages, and natural killer cells.
- Genomic instability and mutation - endow cancer cells with genetic alterations that drive tumor progression.
- Tumor-promoting inflammation - inadvertent support of multiple hallmark capabilities due to inflammatory responses of innate immune cells.

Tumors must acquire additional four hallmarks capabilities

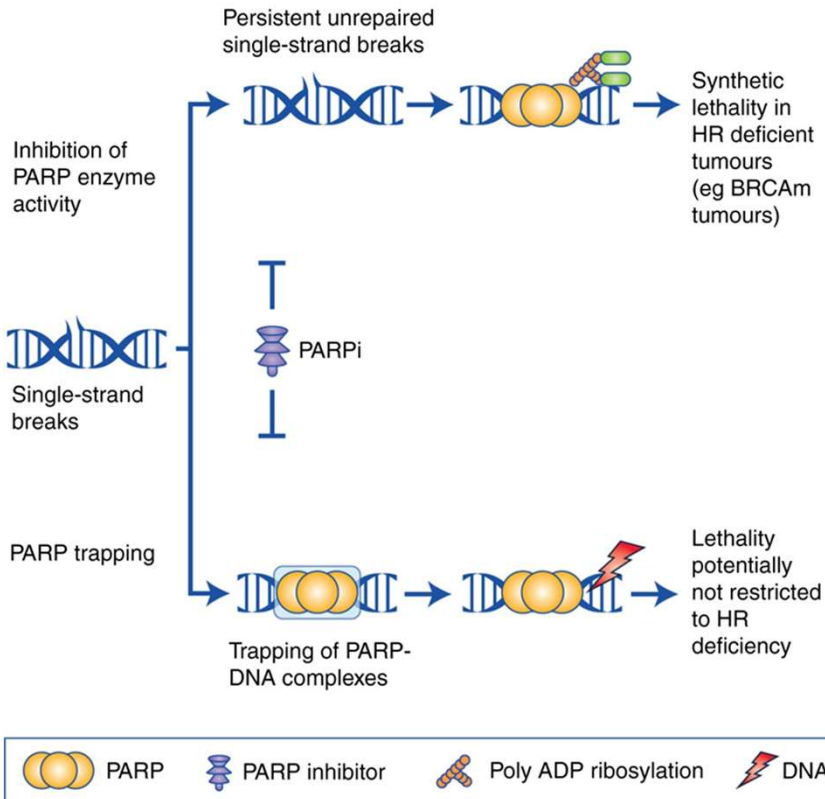


Genome instability and mutation

- Genomic instability and mutation - endow cancer cells with genetic alterations that drive tumor progression.
- This may be acquired through...
 - Clonal selection – through nonmutational changes affecting the regulation of gene expression.
 - Epigenetic mechanism - DNA methylation and Histone modifications.
- Alterations in DNA maintenance machinery due to defects in proteins involved in:
 - Detecting DNA damage and activating the repair machinery.
 - Directly repairing damaged DNA.
 - Inactivating or intercepting mutagenic molecules before they have damaged the DNA.

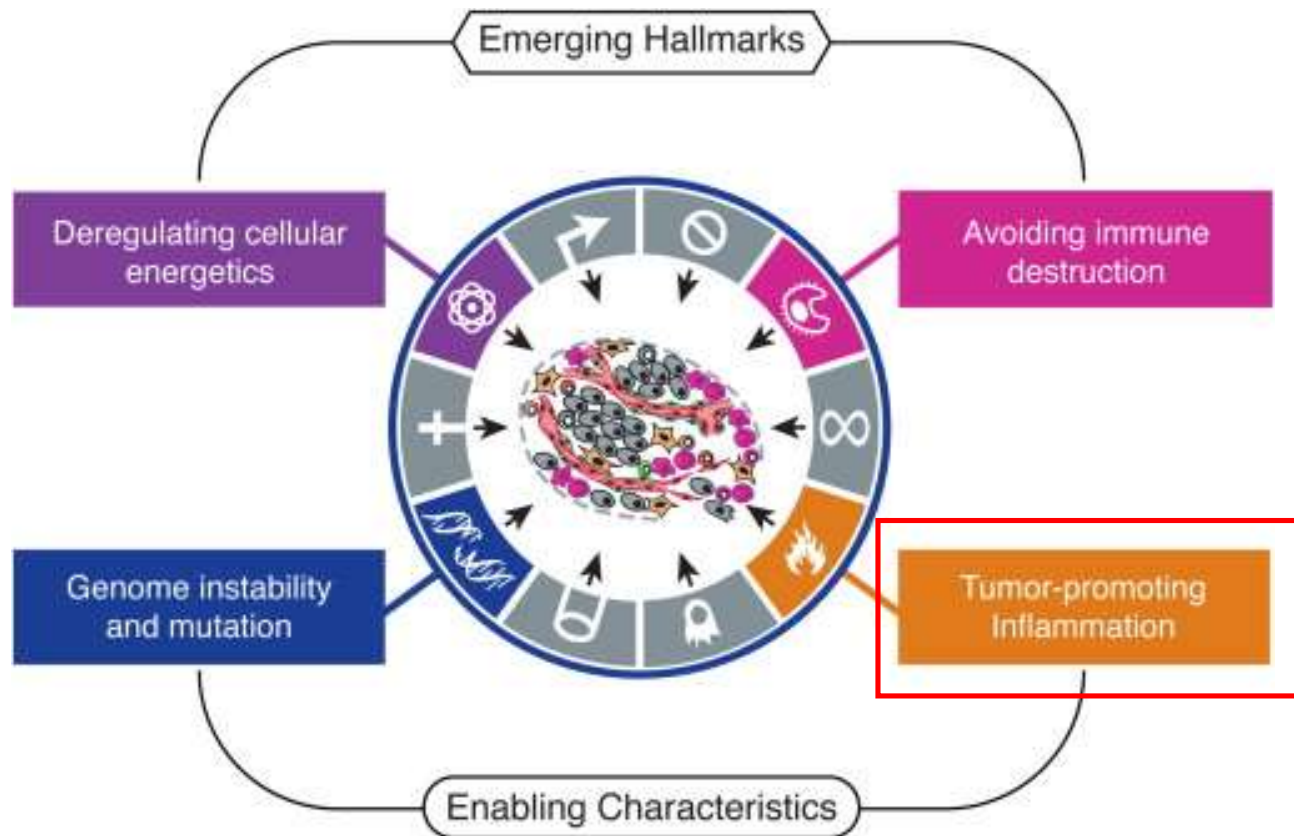
Genome instability and mutation

Potential mechanisms of action



- Inactivating or intercepting mutagenic molecules before they have damaged the DNA.
- Inhibition of PARP enzyme activity or catalytic inhibition interferes with the repair of single-strand breaks, leading to stalled DNA replication forks that requires HR repair. In HR-deficient tumors, such as those with BRCA mutations, PARP inhibition results in synthetic lethality.
- PARP trapping refers to trapping of PARP proteins on DNA, which also leads to replication fork damage, but because this pathway utilizes additional repair mechanisms, it is not restricted to tumors with HR deficiency.

Tumors must acquire additional four hallmarks capabilities

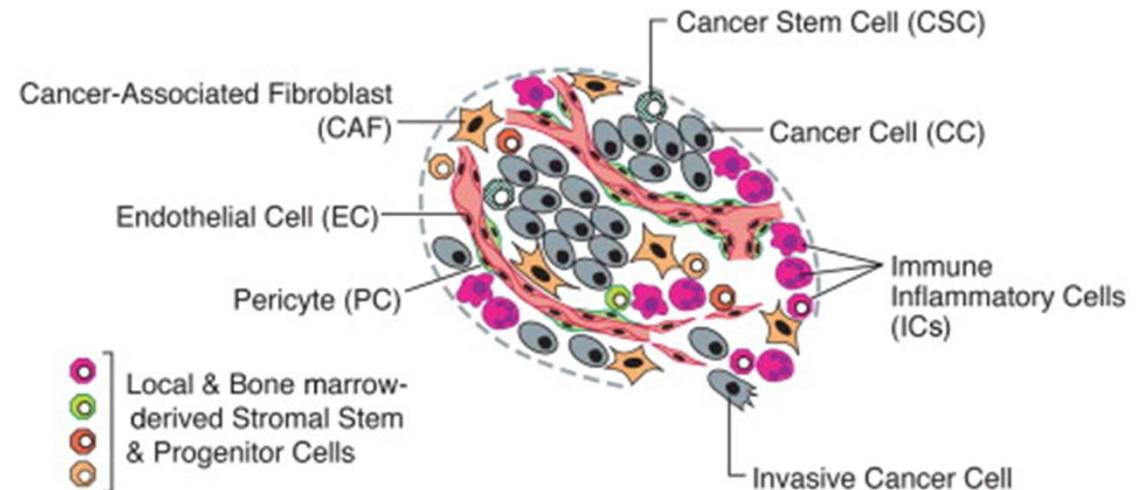


Tumor promoting inflammation

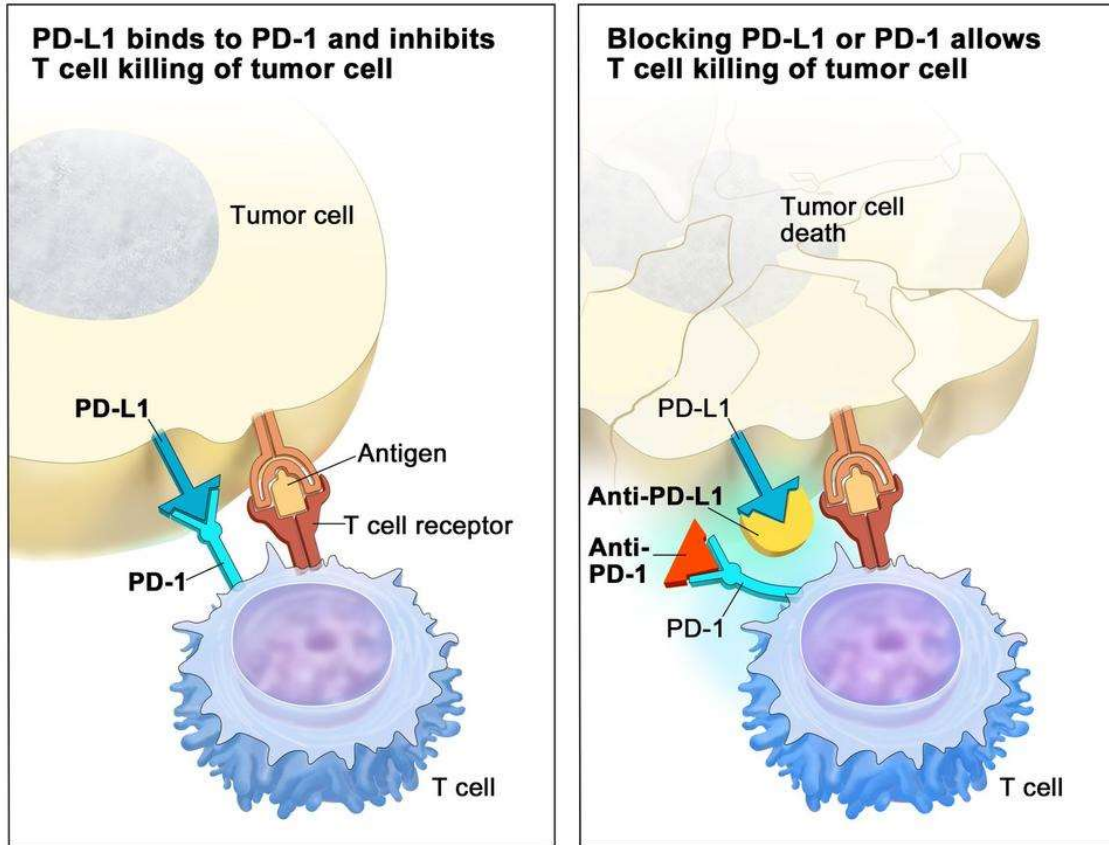
- Every neoplastic lesion contains immune cells present at densities ranging from subtle infiltrations detectable only with cell type-specific antibodies to gross inflammations.
- Inflammation contributes to multiple hallmark capabilities by supplying bioactive molecules to the tumor microenvironment, including:
 - Growth factors that sustain proliferative signaling.
 - Survival factors that limit cell death.
 - Proangiogenic factors.
 - Extracellular matrix-modifying enzymes that facilitate angiogenesis, invasion, and metastasis.
 - Signals that lead to activation of EMT.
 - Various factors facilitating other hallmarks programs.

Tumor promoting inflammation

- Most solid tumors are assembled of distinct cell types.
- Both the parenchyma and stroma of tumors contain distinct cell types and subtypes that collectively enable tumor growth and progression.
- Also, the immune inflammatory cells present in tumors can include both tumor-promoting as well as tumor-killing subclasses.



Tumor promoting inflammation

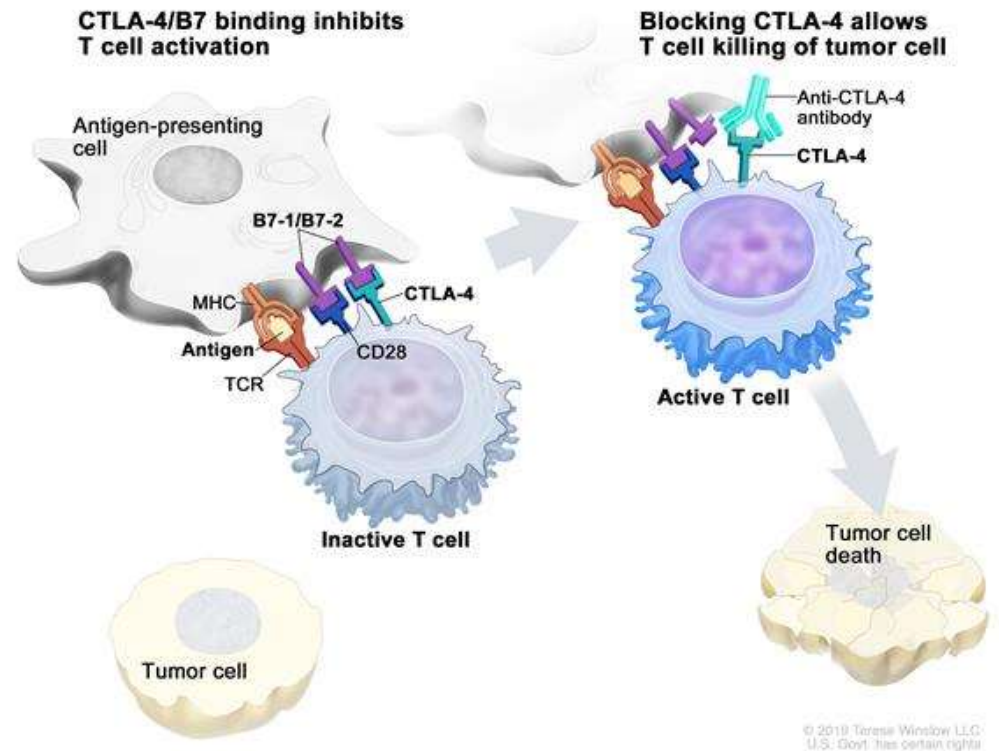


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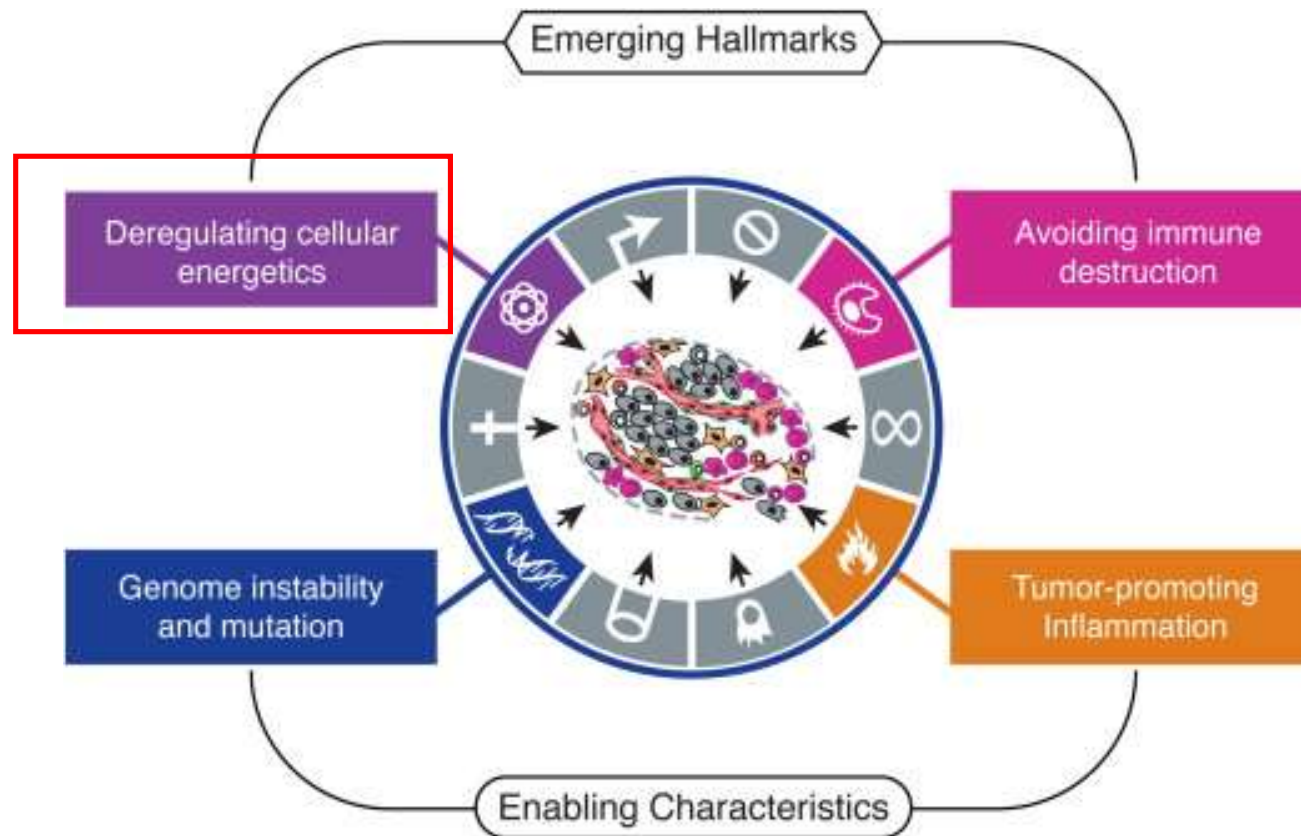
- Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep immune responses in check.
- The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body.
- Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells.

Tumor promoting inflammation

- T Cells have CTLA-4 that works as a regulating switch for T cell activity.
- By blocking the CTLA-4 pathway that T cell activation can be restored.
- Ipilimumab is a drug blocking the CTLA-4 protein. When this protein is blocked the T-cell is activated and the tumor cell is killed.



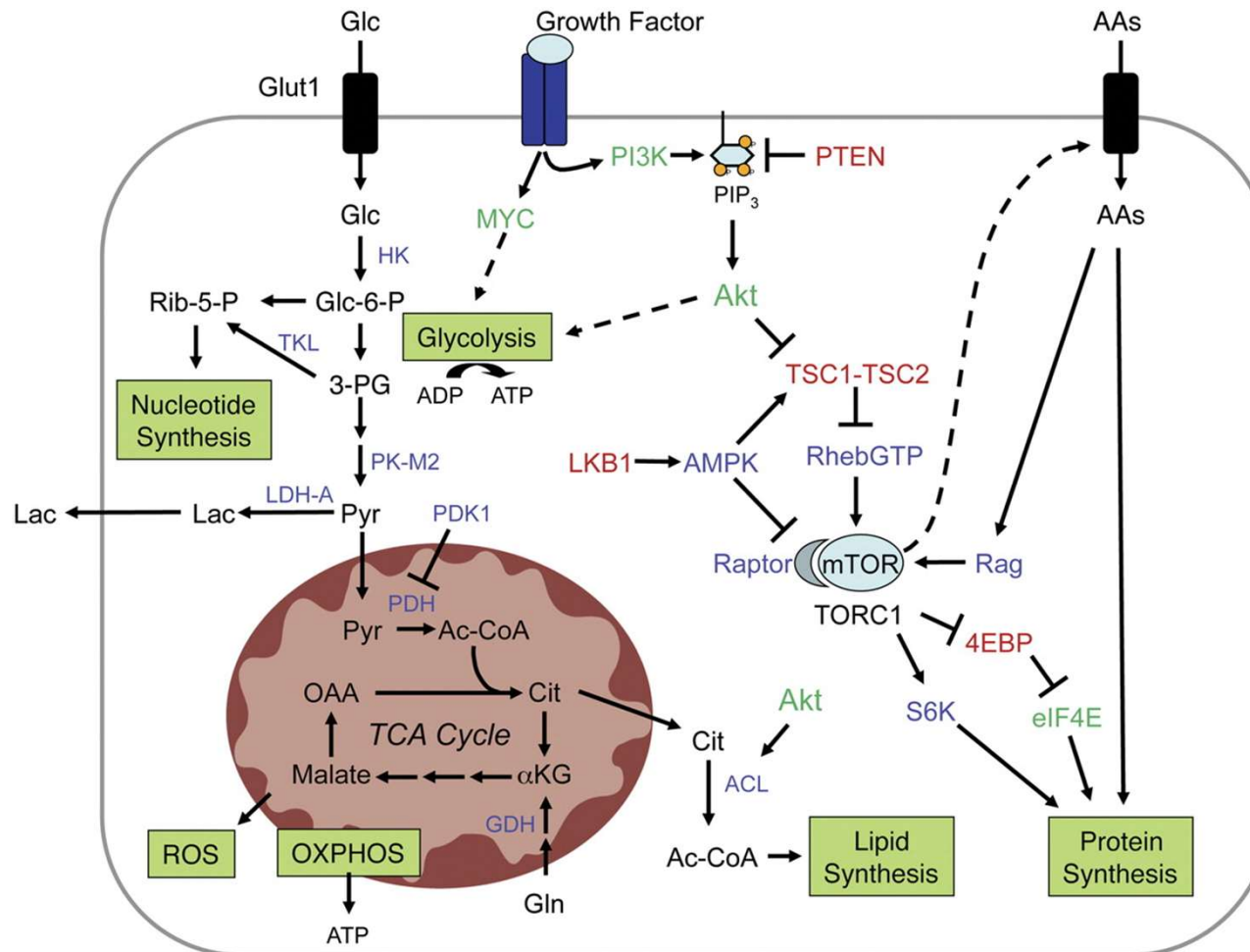
Tumors must acquire additional four hallmarks capabilities



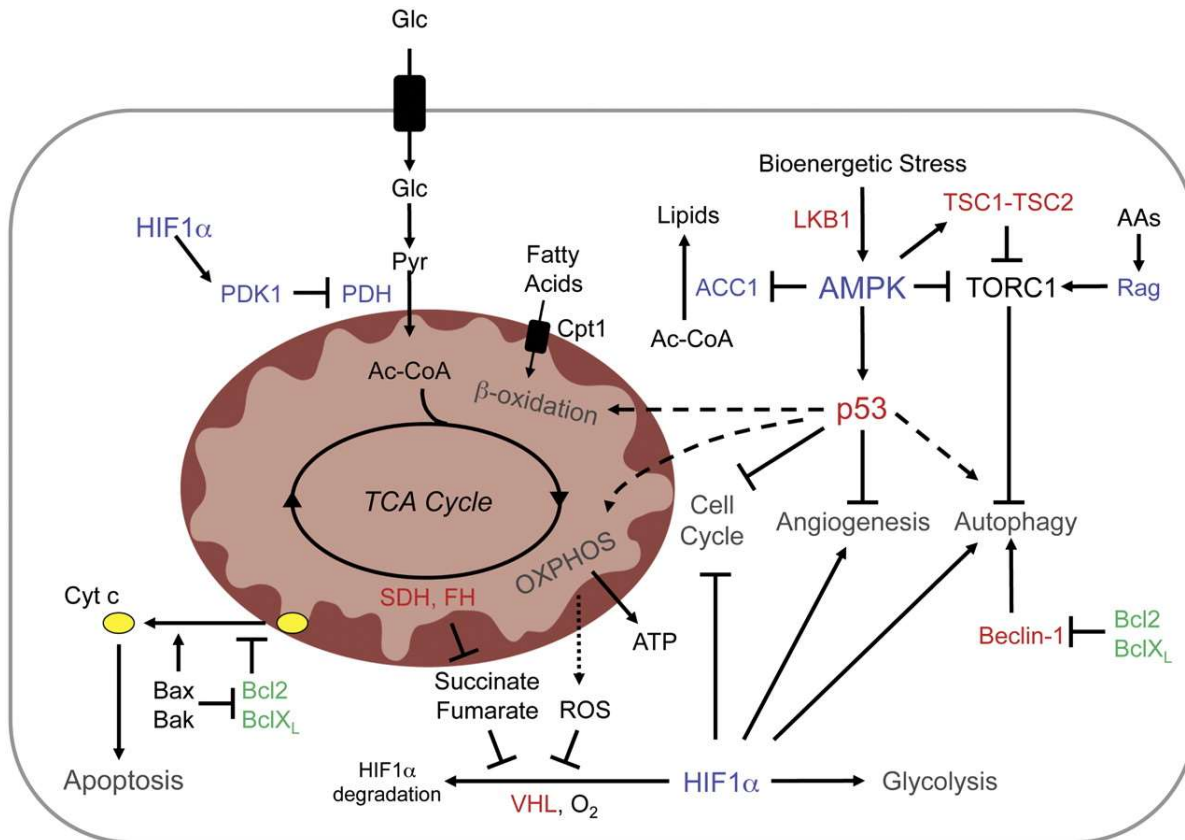
Deregulating cellular energetics

- Reprogramming energy metabolism.
- The Warburg Effect: Cancer cells reprogram their glucose metabolism, by limiting their energy production largely to glycolysis.
- The cells upregulate glucose transporters, notably GLUT1, which substantially increases glucose import into the cytoplasm.
- Growth factor-independent activation of the PI3K/Akt and c-Myc pathways facilitates increased rates of glucose uptake and glycolysis.
- The hypoxia response system acts pleiotropically to upregulate glucose transporters and multiple enzymes of the glycolytic pathway.

Deregulating cellular energetics

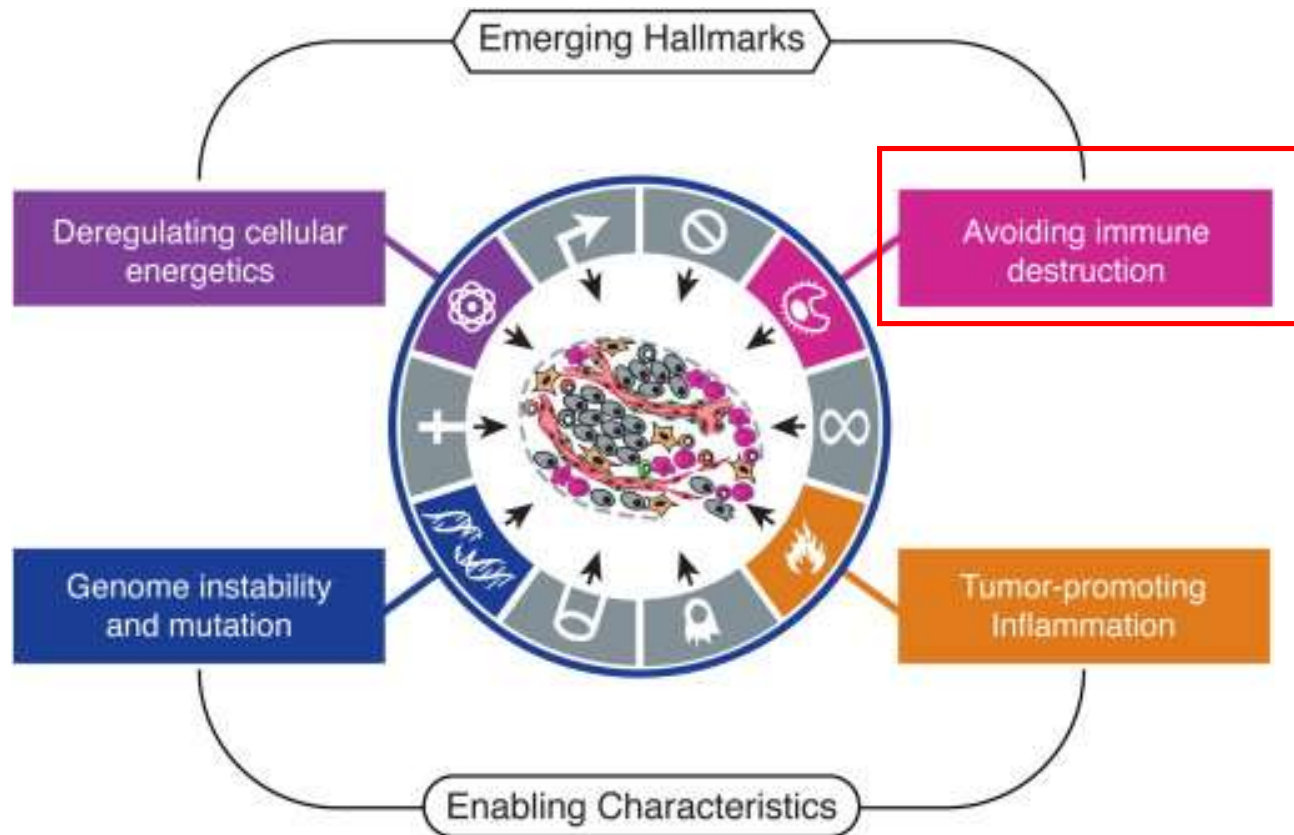


Deregulating cellular energetics



- Intracellular sensors of energy, nutrients, and oxygen promote metabolic adaptation to stress during tumorigenesis.
- Major physiological strategies of metabolic adaptation include:
 - Cell cycle inhibition.
 - Inhibition of biosynthetic pathways (lipid, protein synthesis).
 - Increases in bioenergetic pathways (β -oxidation, glycolysis, and OXPHOS).
 - Induction of autophagy.
- Oncogenes are displayed in green and tumor suppressors in red.

Tumors must acquire additional four hallmarks capabilities

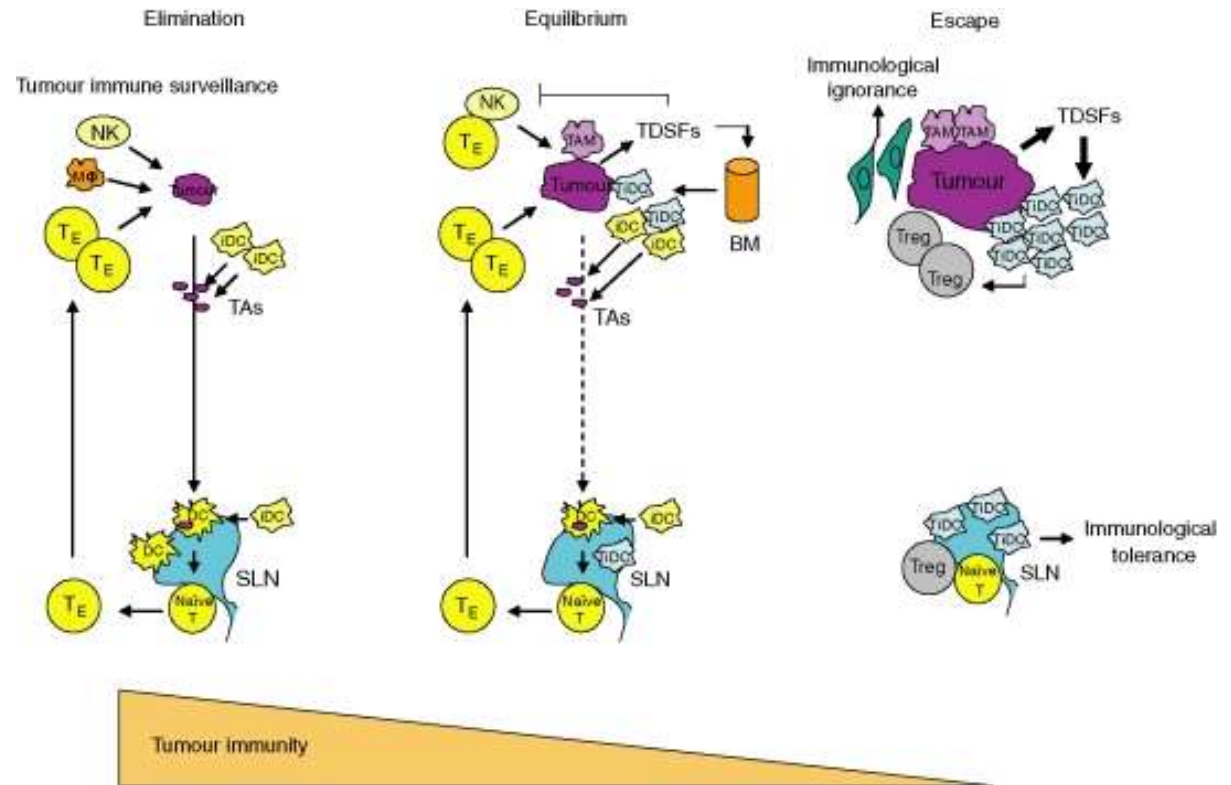


Evading immune destruction

- Cells and tissues are under constant surveillance by the immune system and immune surveillance is responsible for recognizing and eliminating the vast majority of incipient cancer cells and thus nascent tumors.
- Tumors somehow managed to avoid detection by the various arms of the immune system or have been able to limit the extent of immunological killing, thereby evading eradication.
- Immune system operates as a significant barrier to tumor formation and progression, at least in some forms of non-virus-induced cancer.
- Mice lacking NK and T cells were more susceptible to cancer development.
- Patients with higher CTLs and NK cells have a better prognosis.

Evading immune destruction

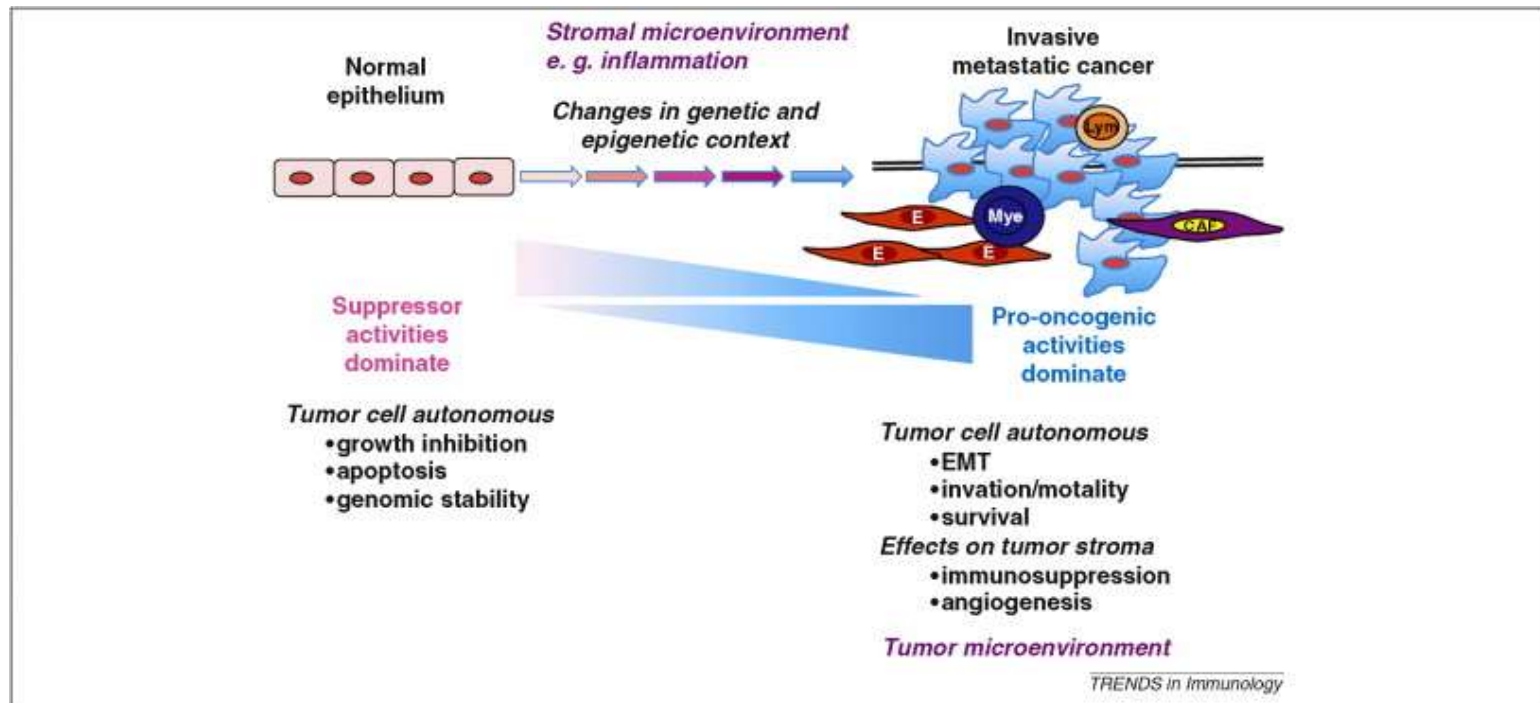
- Nascent transformed cells are directly eradicated by innate and adaptive immune responses.
- During tumor growth, tumor cells are required for angiogenesis and stromal remodeling, which produce tumor cell variants that have low immunogenicity and are resistant to immune attack.
- Tumor progression leads to the release of tumor-derived soluble factors that are involved in several mechanisms of immune evasion in the escape phase.



- iDC, immature dendritic cell; TAs, tumour antigens; SLN, sentinel lymph node; TAM, tumour-associated macrophage; TDSFs, tumour-derived soluble factors; Tregs, regulatory T cells; BM, bone marrow.

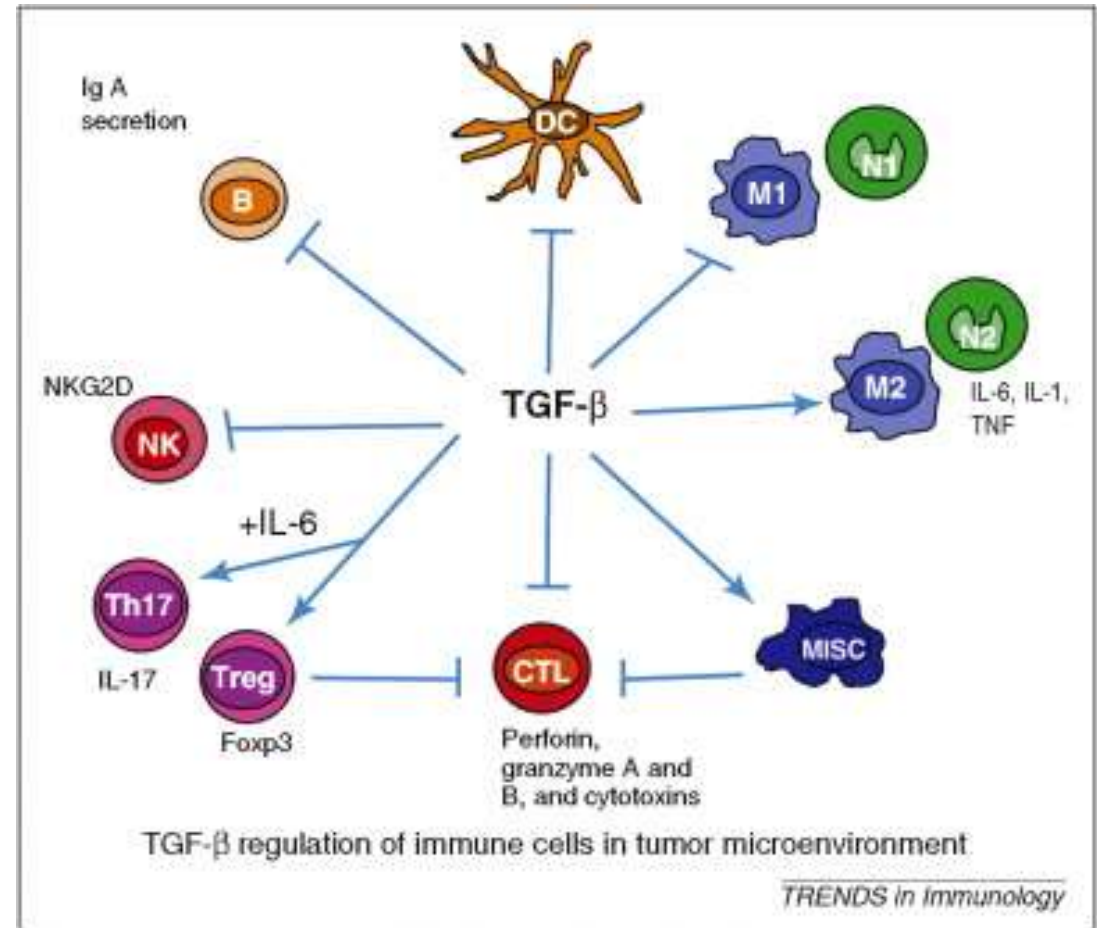
Evading immune destruction

- Progression to metastatic disease is generally accompanied by decreased or altered TGF- β responsiveness and increased expression or activation of the TGF- β ligand.

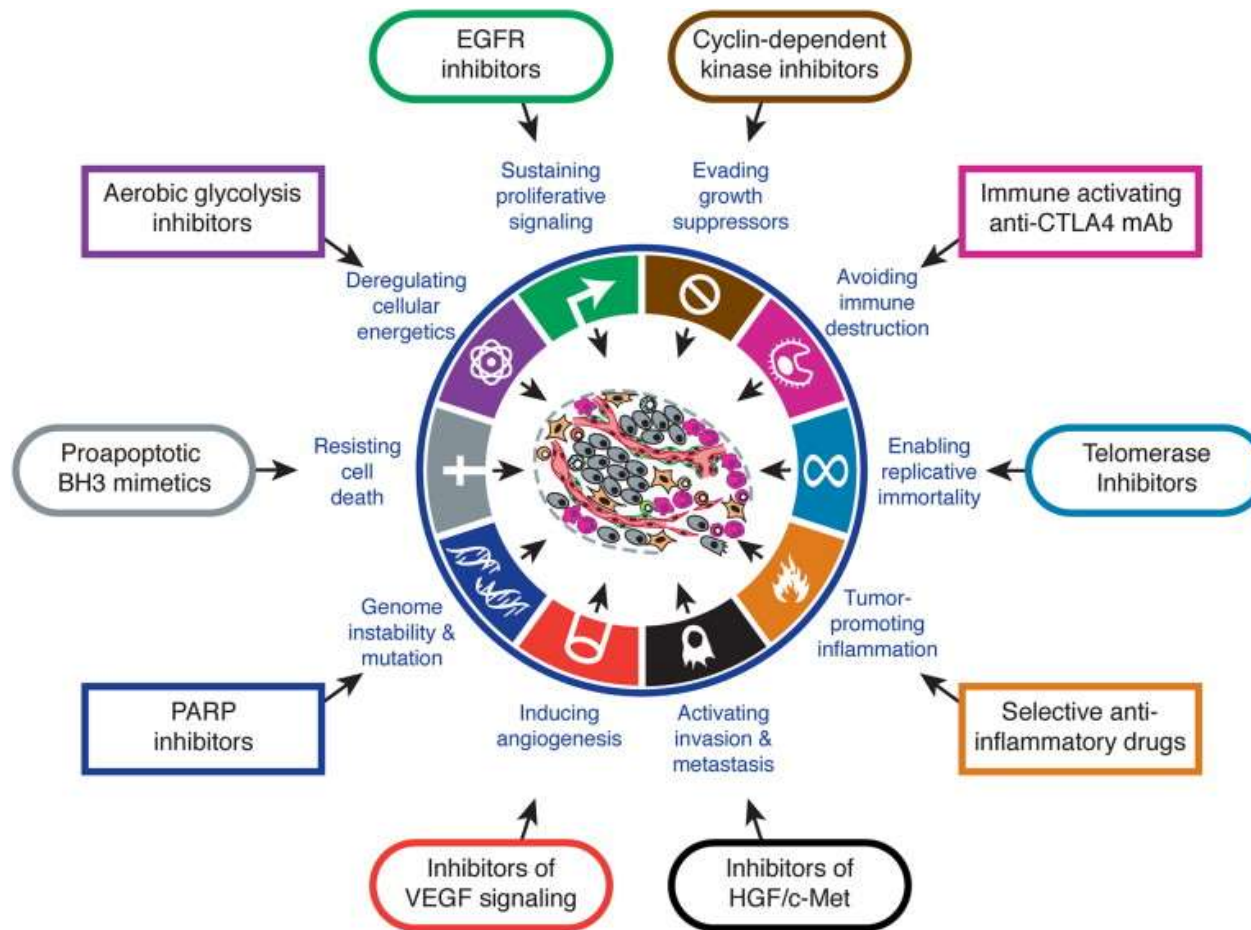


Evading immune destruction

- TGF- β affects multiple components of the immune system.
- TGF- β inhibits the function of natural killer (NK) and CD8+ CTL (cytotoxic T lymphocytes), by blocking production of perforin, granzymes and cytotoxins.
- TGF- β induces Treg and Th17 cell differentiation and inhibits B-cell proliferation and dendritic function.
- TGF- β , inhibits macrophage and neutrophil development, but promotes type II macrophages and neutrophils, and mediates the immune suppression function of MISCs.



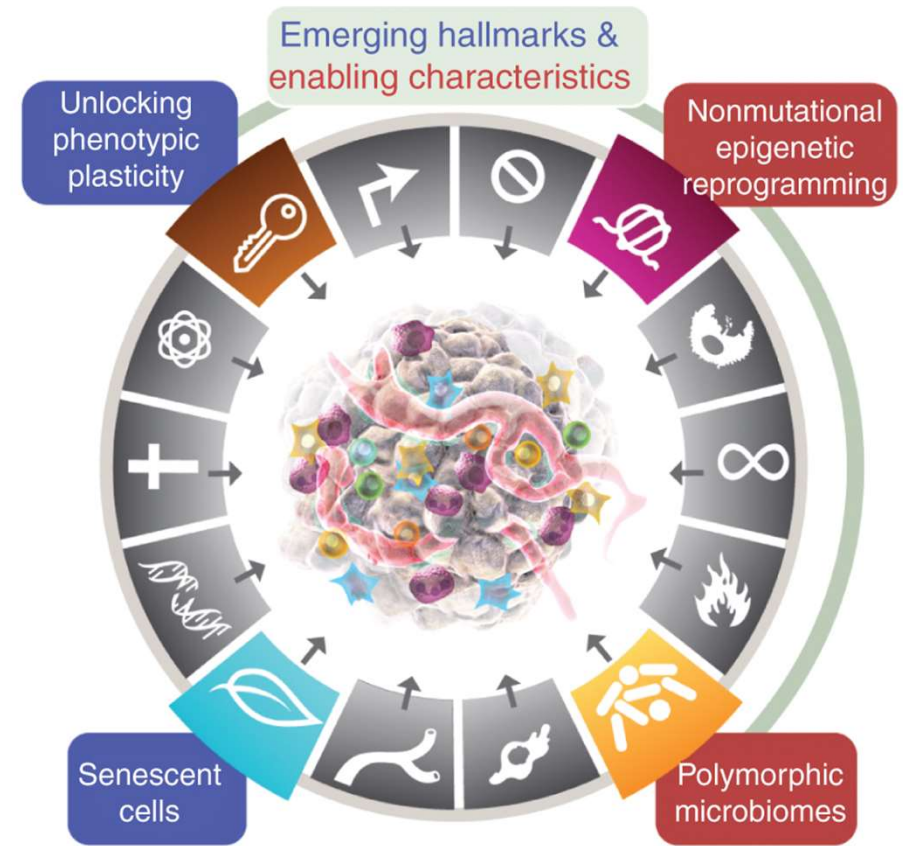
Therapeutic Targeting of the Hallmarks of Cancer



- The Hallmarks of Cancer: New Dimensions

Hallmarks of cancer: New Dimensions

- In 2022 additional emerging hallmarks and enabling characteristics of cancer were proposed:
- Unlocking phenotypic plasticity.
- Nonmutational epigenetic reprogramming.
- Polymorphic microbiomes.
- Senescent cells.

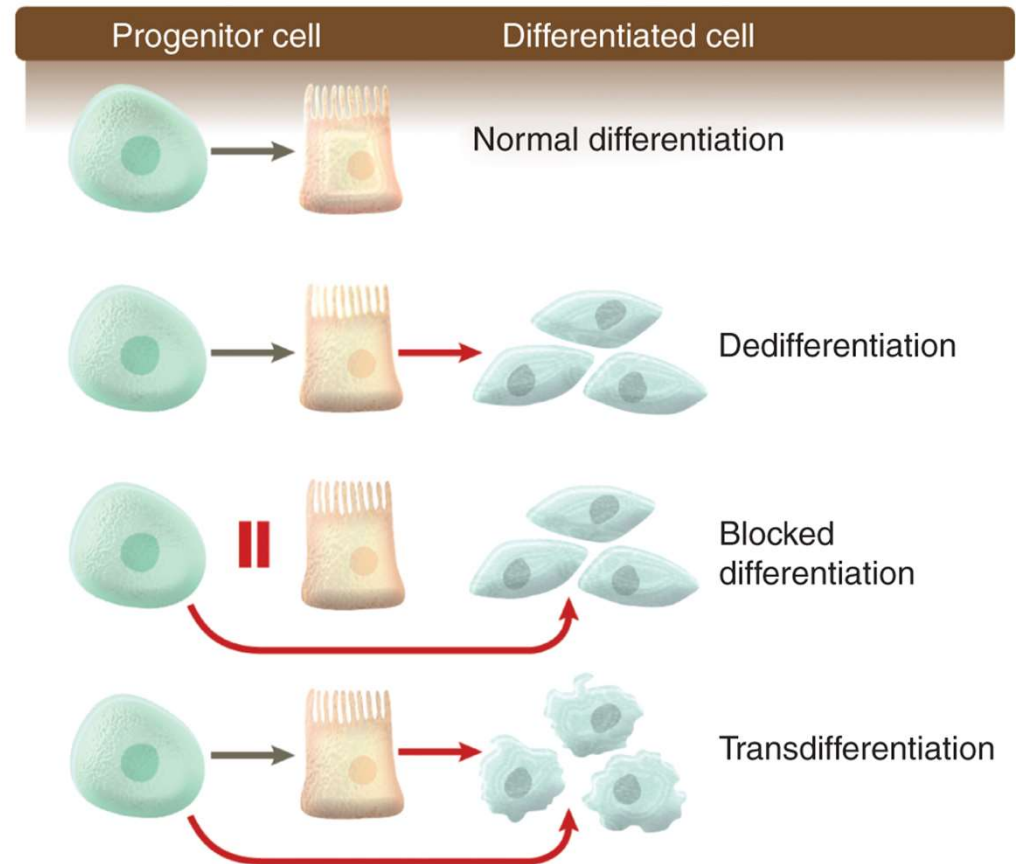


Tumors acquire additional four hallmarks capabilities



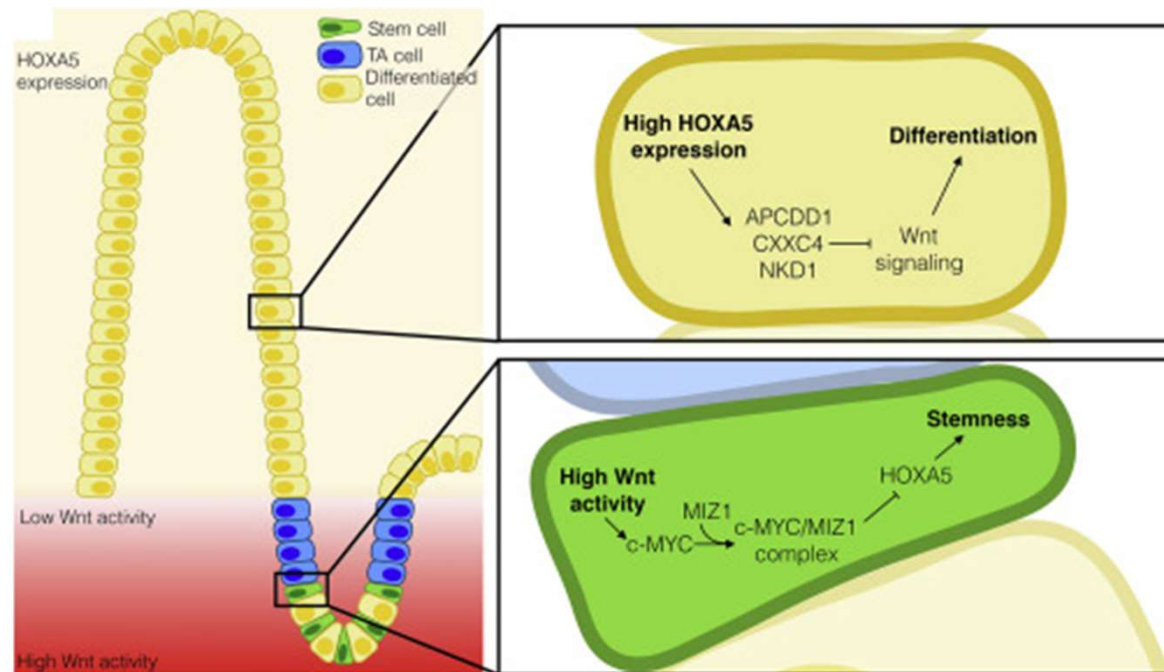
Phenotypic plasticity

- Phenotypic plasticity enables various disruptions of cellular differentiation, including:
- **Dedifferentiation** from mature to progenitor states.
- **Blocked (terminal) differentiation** from progenitor cell states.
- **Transdifferentiation** into different cell lineages.

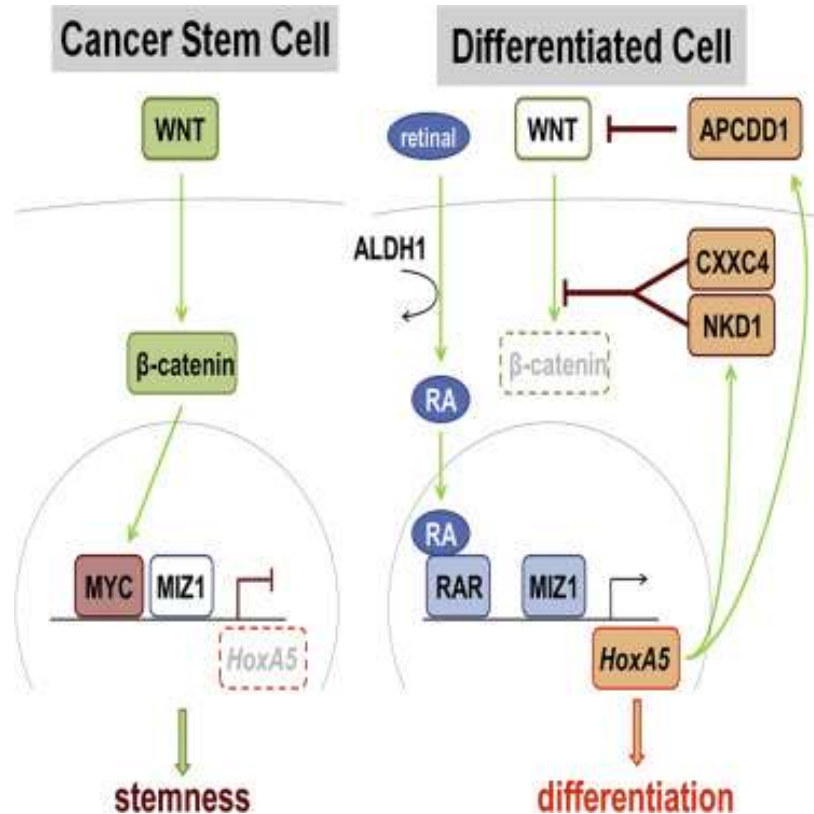


Phenotypic plasticity

- For example the developmental transcription factors HOXA5 are highly expressed in differentiating colonic epithelial cells, and typically lost in advanced colon carcinomas, which characteristically express markers of stem and progenitor cells.

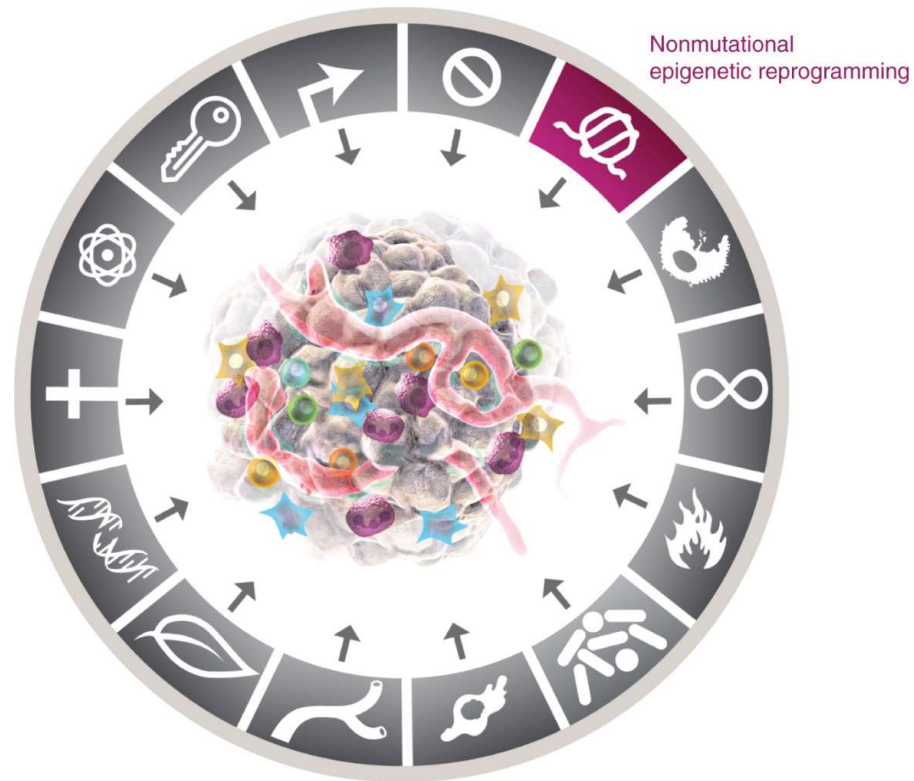


Phenotypic plasticity



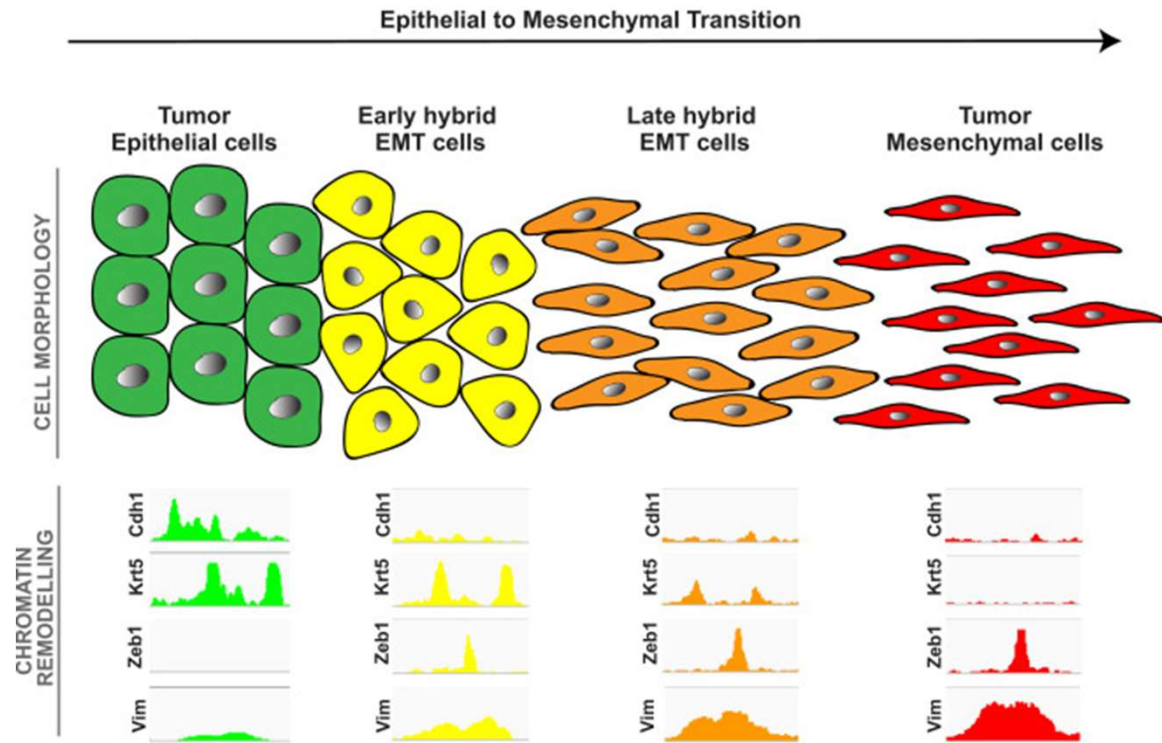
- In colon cancer, **HOXA5** is downregulated, and its re-expression induces loss of the cancer stem cell phenotype, preventing tumor progression and metastasis.
- Tumor regression by **HOXA5** induction can be triggered by retinoids, which represent tangible means to treat colon cancer by eliminating cancer stem cells.

Tumors acquire additional four hallmarks capabilities

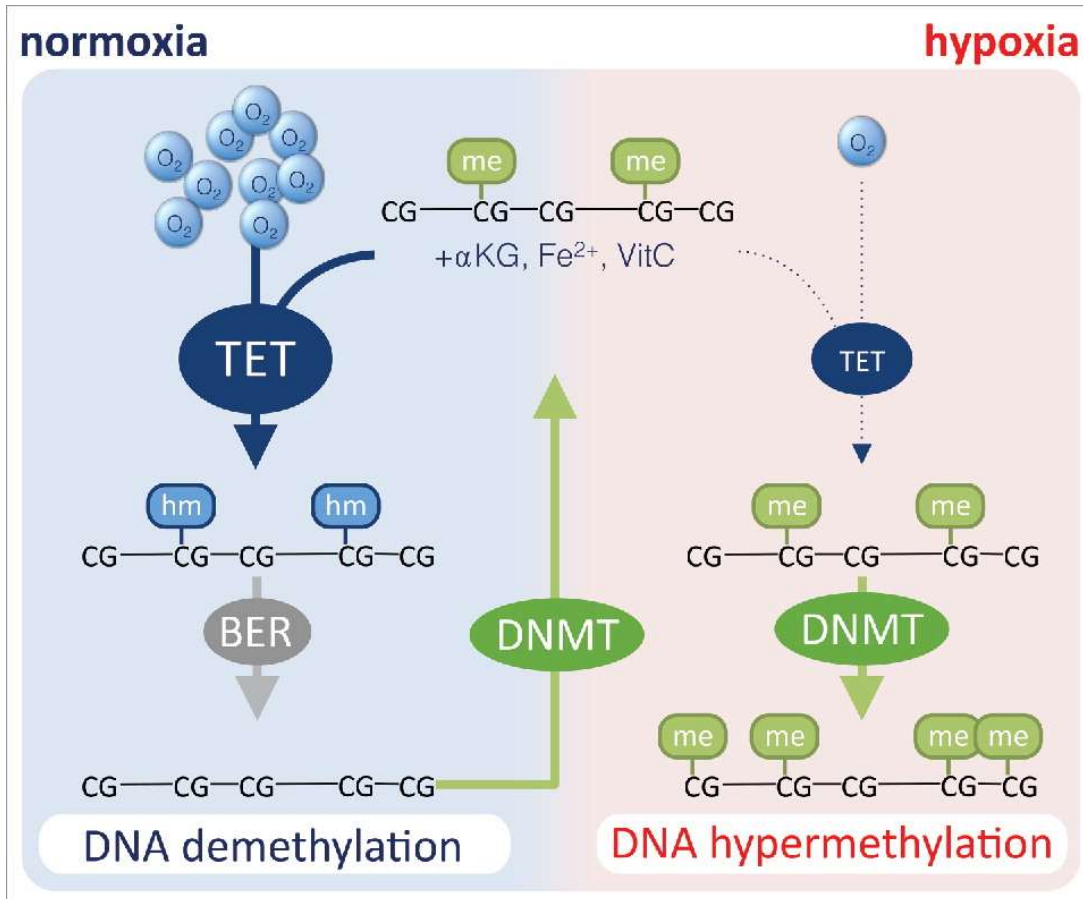


Nonmutational epigenetic reprogramming

- Nonmutational epigenetic regulation of gene expression is of course well established as the central mechanism mediating embryonic development, differentiation, and organogenesis.
- Analogous epigenetic alterations can contribute to the acquisition of hallmark capabilities during tumor development and malignant progression.



Nonmutational epigenetic reprogramming



- One common characteristic of tumors (or regions within tumors) is hypoxia, consequent to insufficient vascularization.
- Hypoxia, for example, reduces the activity of the TET demethylases, resulting in substantive changes in the methylome, in particular hypermethylation.
- Under hypoxic conditions (right) TET activity is compromised, leading to accumulation of methyl groups and causing DNA hypermethylation.

Tumors acquire additional four hallmarks capabilities

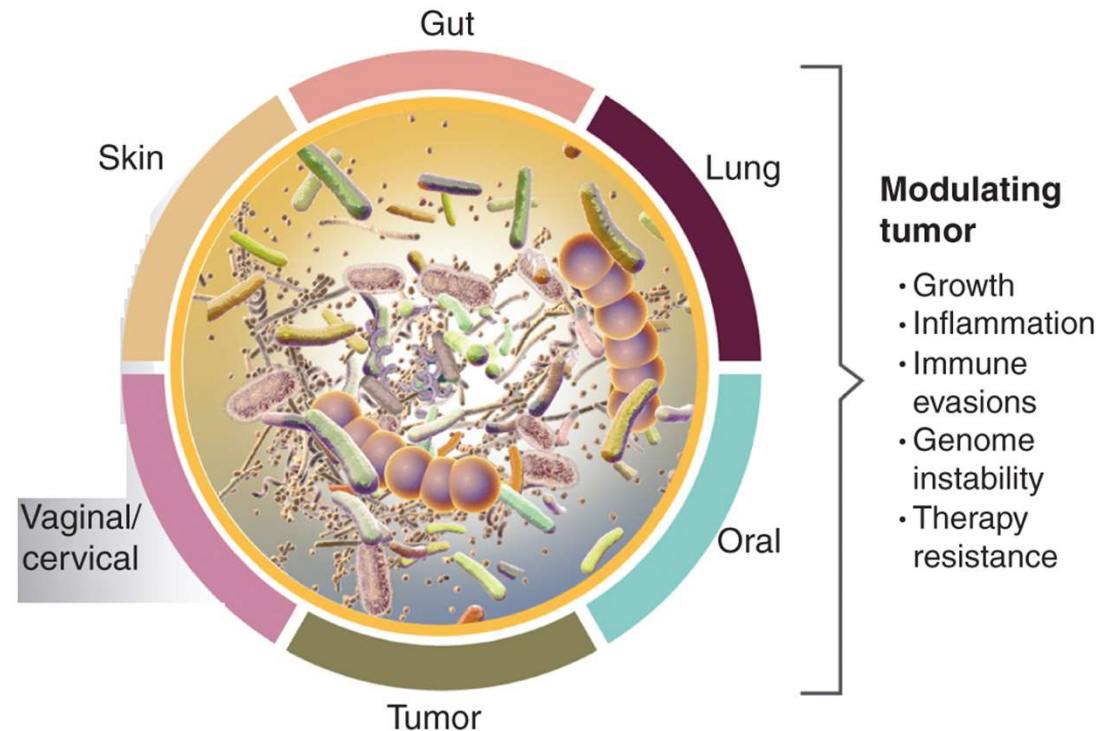


Polymorphic microbiomes

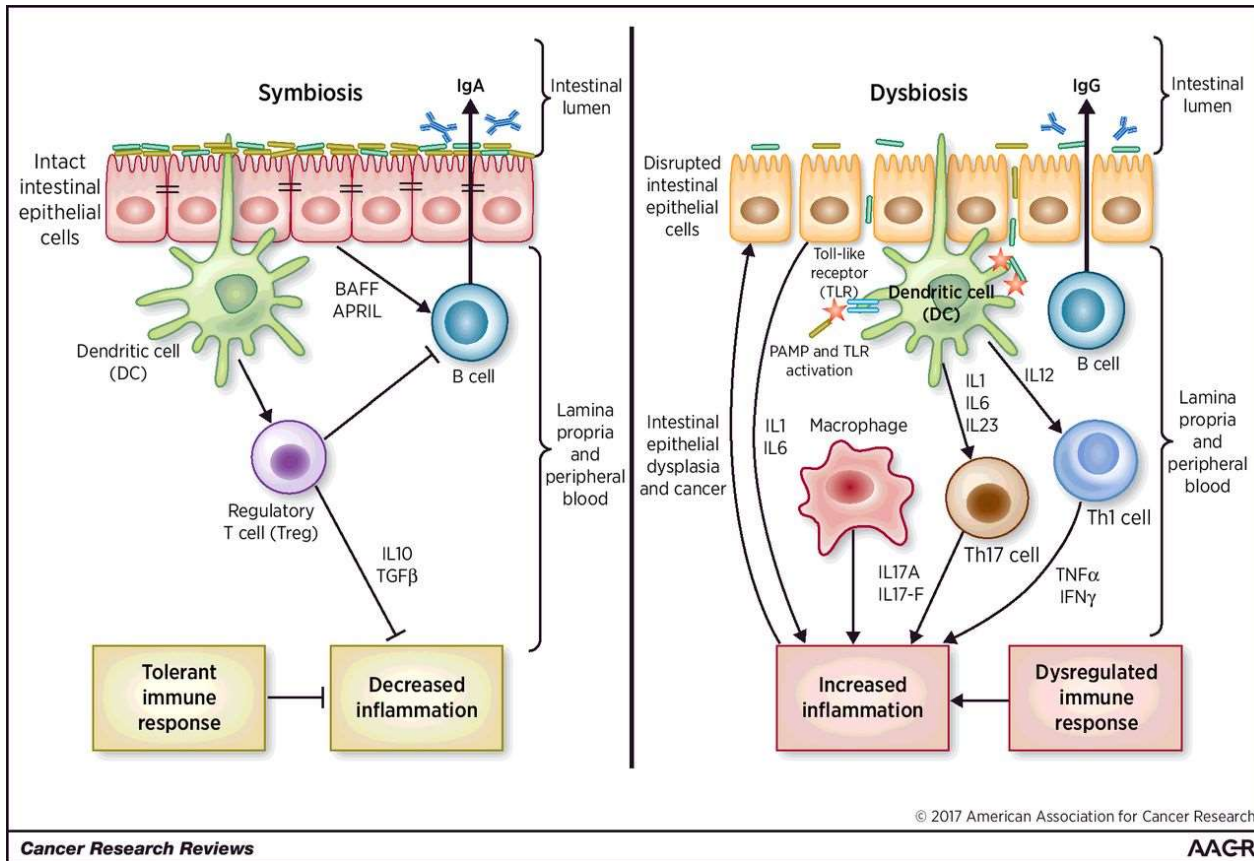
- Microbiota, that symbiotically associate with the barrier tissues of the body exposed to the external environment - the epidermis and the internal mucosa, in particular the gastrointestinal tract, as well as the lung, the breast, and the urogenital system.
- For cancer, the evidence is increasingly compelling that polymorphic variability in the microbiomes between individuals in a population can have a profound impact on cancer phenotypes.
- Microbiotic organisms have protective or deleterious effects on cancer development, malignant progression, and response to therapy.

Polymorphic microbiomes

- Polymorphic microbiomes in one individual versus another, can diversely influence—by either inducing or inhibiting—many of the hallmark capabilities.
- Tumor microbiome, are implicated in modulating the acquisition - both positively and negatively - of the illustrated hallmark capabilities in certain tumor types.



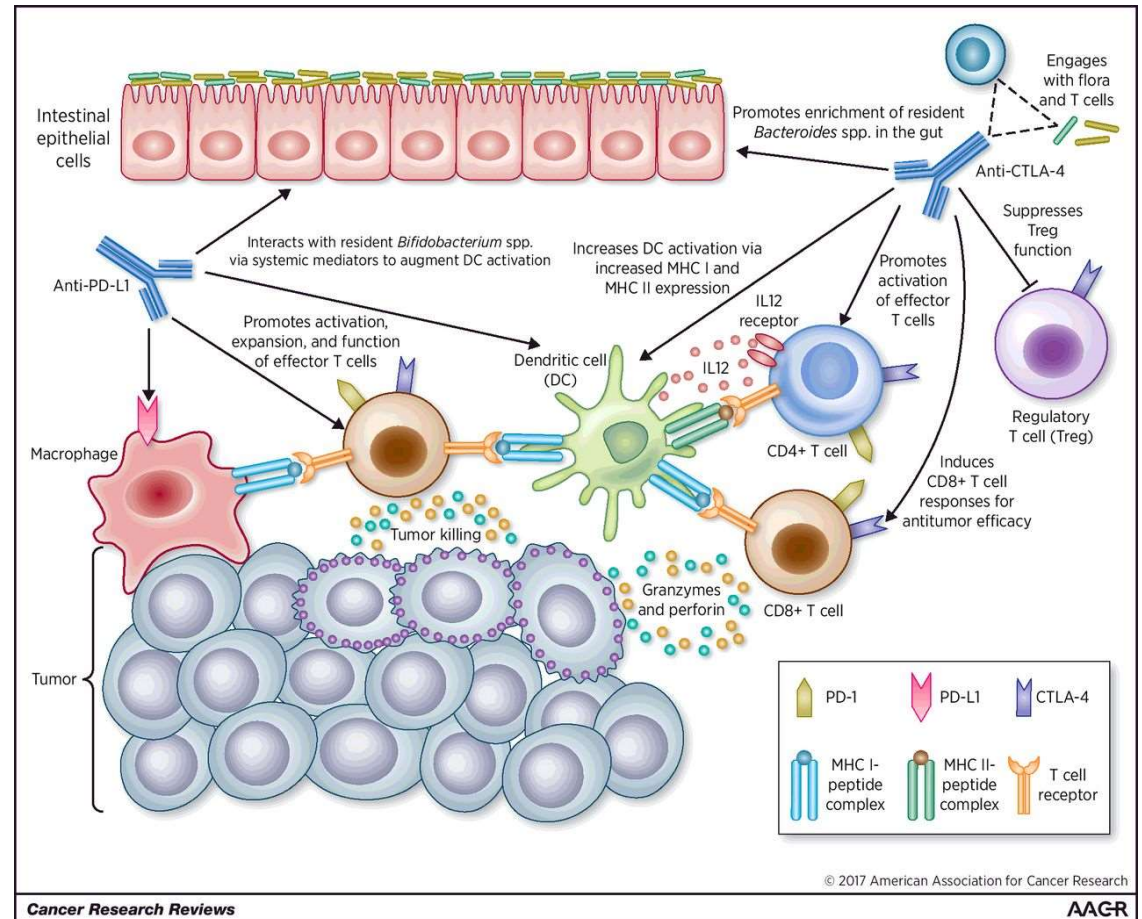
Polymorphic microbiomes



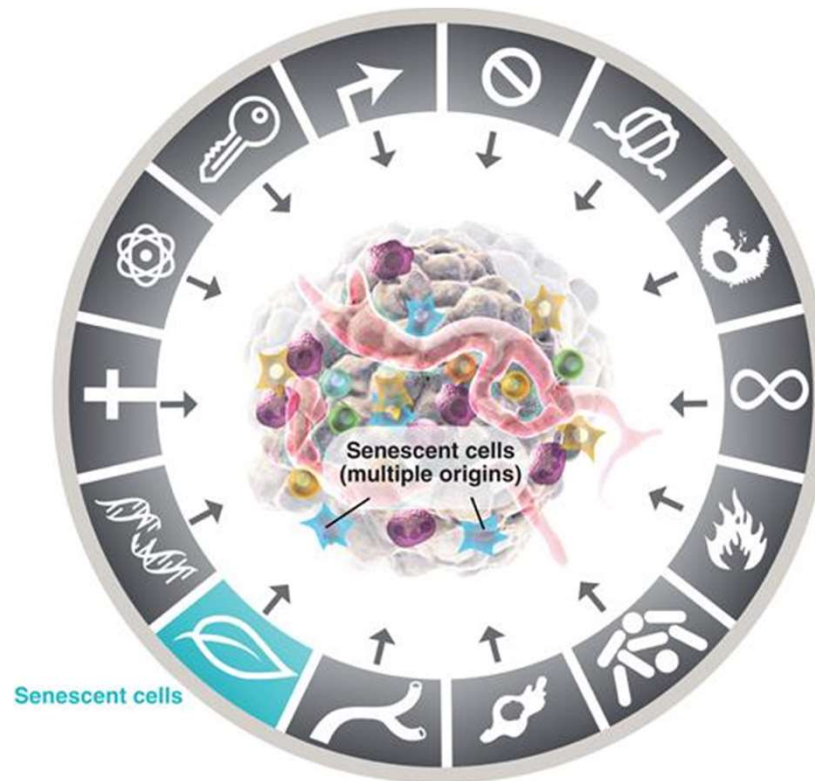
- Dysbiosis is immunocompromised state characterized by pathobiont colonization that leads to hyperinflammation, dysplasia, and tumorigenesis.
- Pathobiont overgrowth leads to the loss of barrier integrity and a breach in the intestinal epithelial cell barrier.
- The secretion of IL1 and IL6 from intestinal epithelial cells fuels a Th1 and Th17 response by DCs and macrophages and leads to higher levels of commensal-specific IgG by B cells.

Polymorphic microbiomes

- Both anti-CTLA-4 and anti-PD-L1 therapies rely on gut microbiota for efficacy in immune activation.
- Anti-PD-L1 therapy has been shown to rely on the preexistence of sufficient *Bifidobacterium* species, which are also thought to augment responses via PD-L1 binding on APCs, such as DCs and macrophages.
- Similarly, anti-CTLA-4 indirectly alters the intestinal flora and enriches the *Bacteroides* species, possibly by promoting deterioration of the intestinal epithelial cell barrier via activation of local lymphocytes.

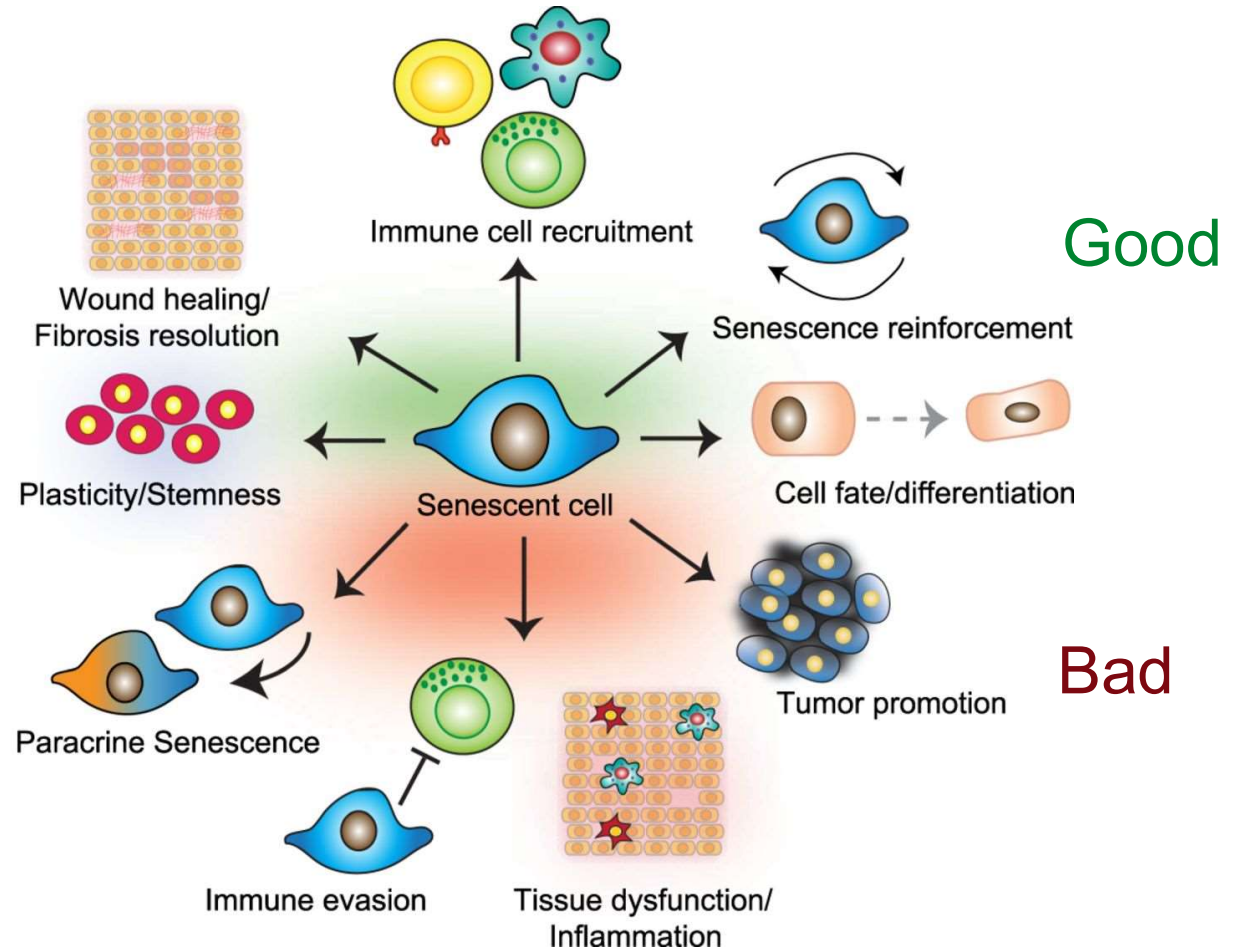


Tumors acquire additional four hallmarks capabilities

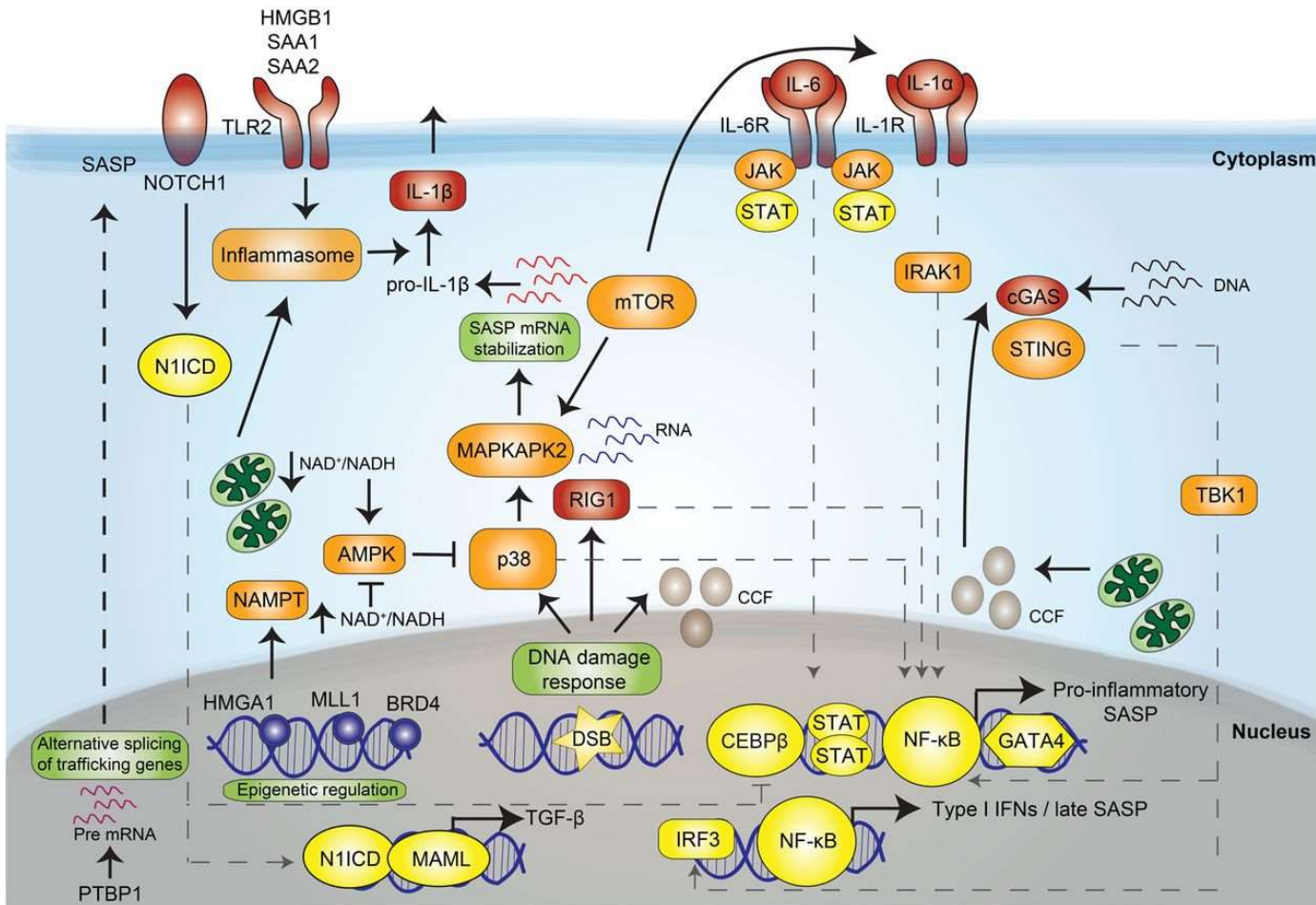


Senescent cells

- Cellular senescence is a common outcome of various anticancer interventions.
- Senescence-associated secretory phenotypes (SASPs) have pro-tumorigenic functions.
- Evidence exists of increased cellular senescence in patients treated for various types of cancer.
- Accumulation and persistence of therapy-induced senescent cells can promote tissue dysfunction and the early onset of various age-related symptoms in treated cancer patients.

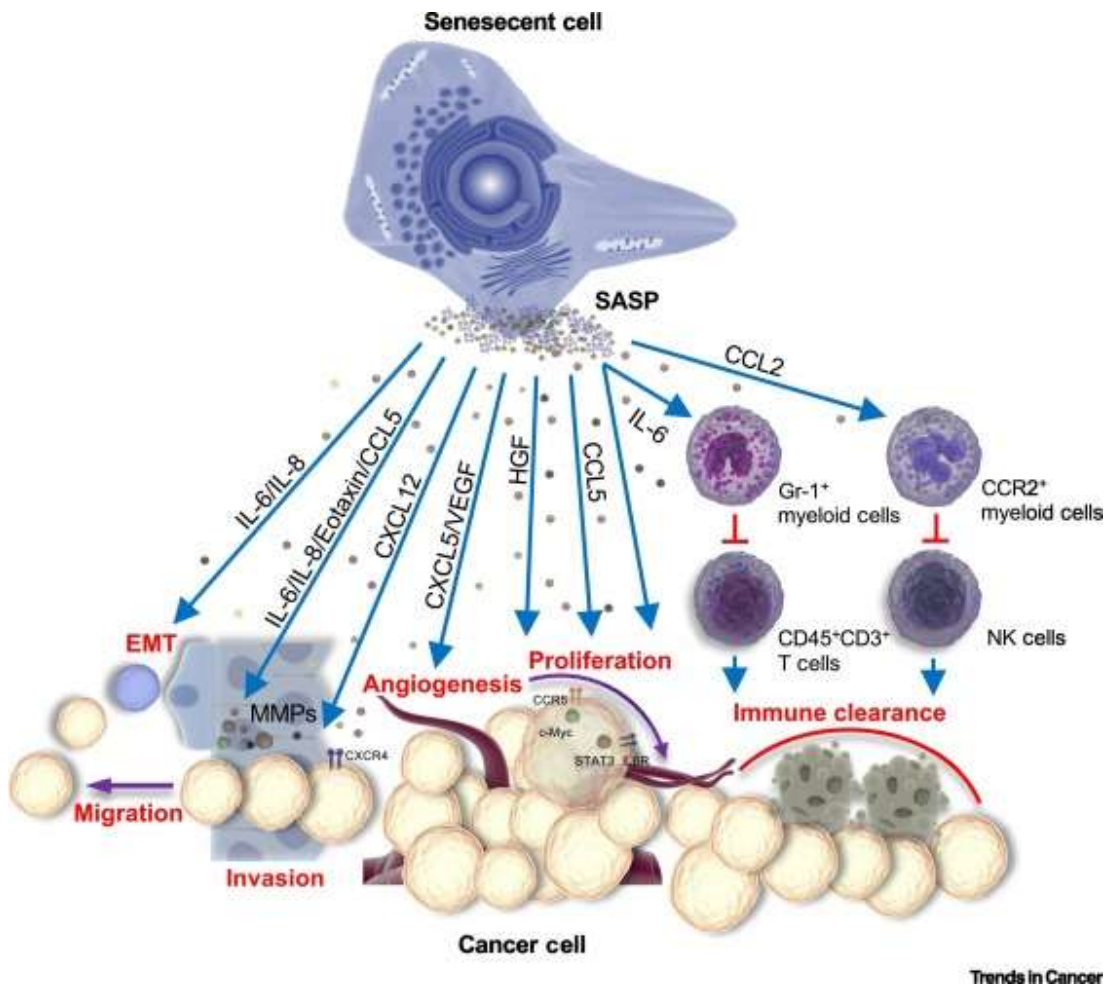


Senescent cells



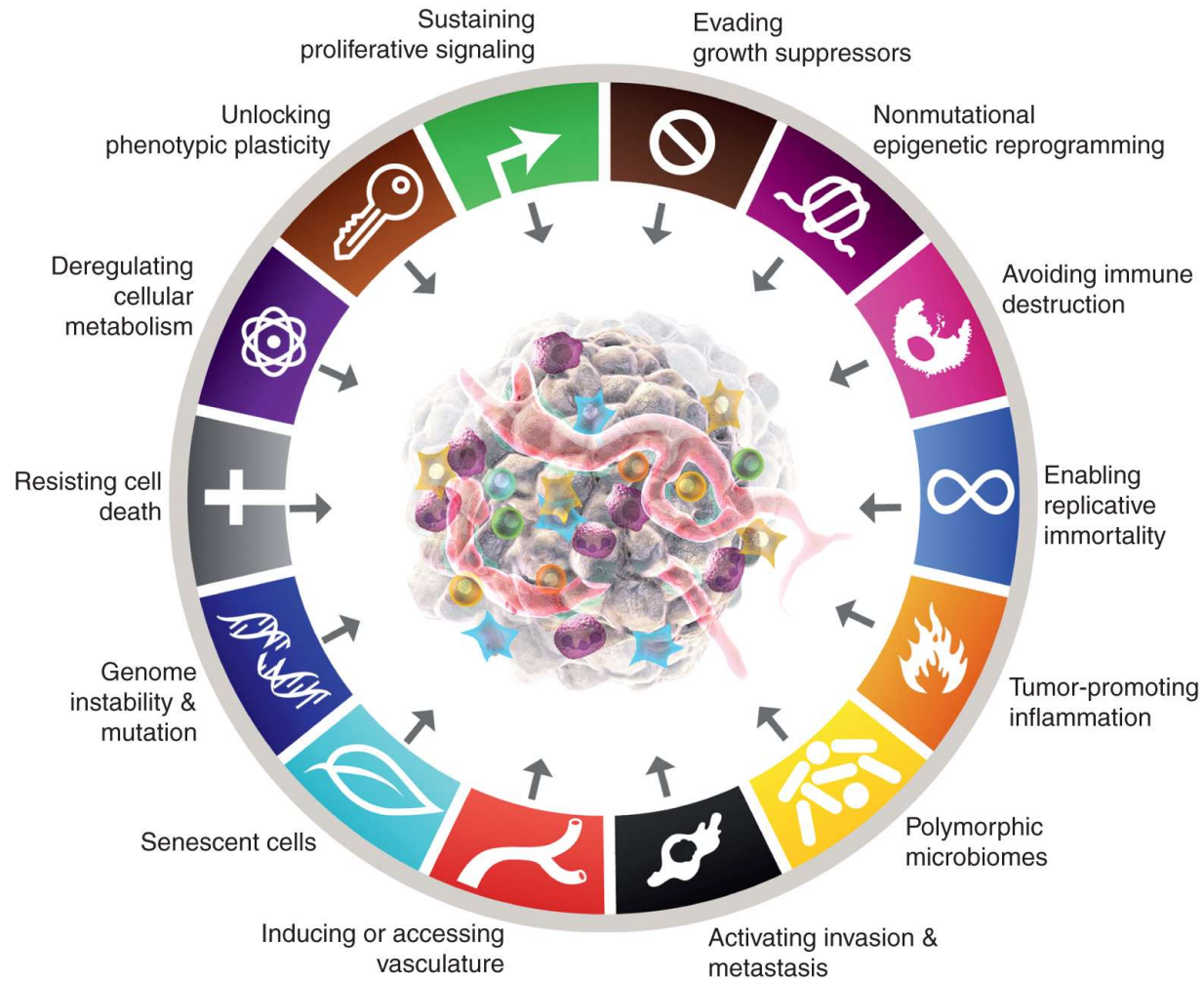
- Regulation of the senescence-associated secretory phenotype (SASP).
- Transcription factors - NF-κB, C/EBPβ, STAT, MAML (yellow).
- Intracellular signaling components – mTOR, TBK1, MAPK, JAK (orange).
- Sensors and receptors and ligands – IL-6, IL-1, TLR2, NOTCH1 (red).

Senescent cells



- Senescence-associated secretory phenotype (SASP) factors are engaged in senescent cells through the activation of the NF- κ B, C/EBP β , and p38MAPK pathways.
- SASP factors contribute to various aspects of cancer progression:
 - IL-6 and IL-8 promote EMT.
 - IL-6–IL-6R cancer cell proliferation.
 - CXCL5 and VEGF promote angiogenesis.
 - CXCL12–CXCR4 cancer cell invasion and migration.
 - IL-6 suppresses the CD45⁺CD3⁺ T cell-mediated immune clearance of cancer cells.
 - CCL2 suppresses the natural killer (NK).

Hallmarks of Cancer



THANK YOU FOR YOUR ATTENTION

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"We're looking for somebody in medical research."