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The Hallmarks of Cancer

Review

Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

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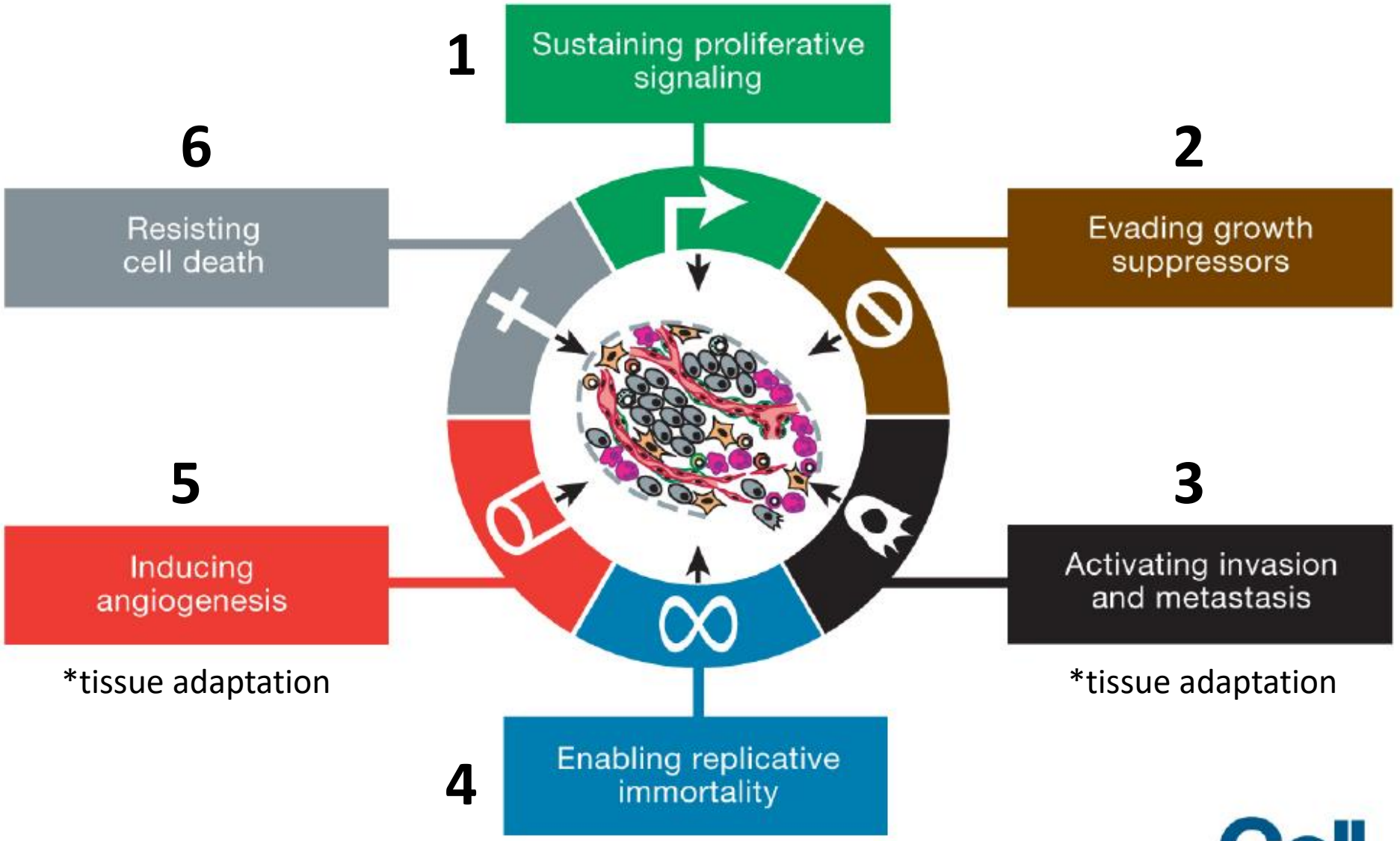
The hallmarks of cancer comprise six biological capabilities acquired during the multistep development of human tumors. The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and acti-



*tissue adaptation

*tissue adaptation

Hanahan and Weinberg, 2011

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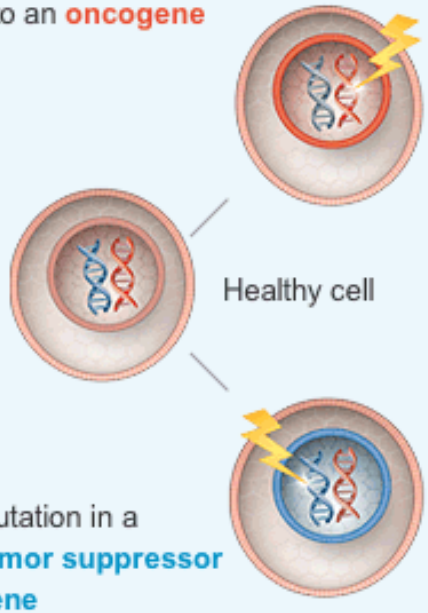
Cancer growth: genes as both the brake and gas pedals

Gain of function

Mutation of a gene into an **oncogene**



Mutations in oncogenes are like **a jammed gas pedal** in a car: they increase the speed of cell division.

Healthy cell

Cancer cells divide and grow into a tumor.

Mutation in a **tumor suppressor gene**

Mutations in tumor suppressor genes behave like **defective brakes**: the cells continue to divide uncontrollably.

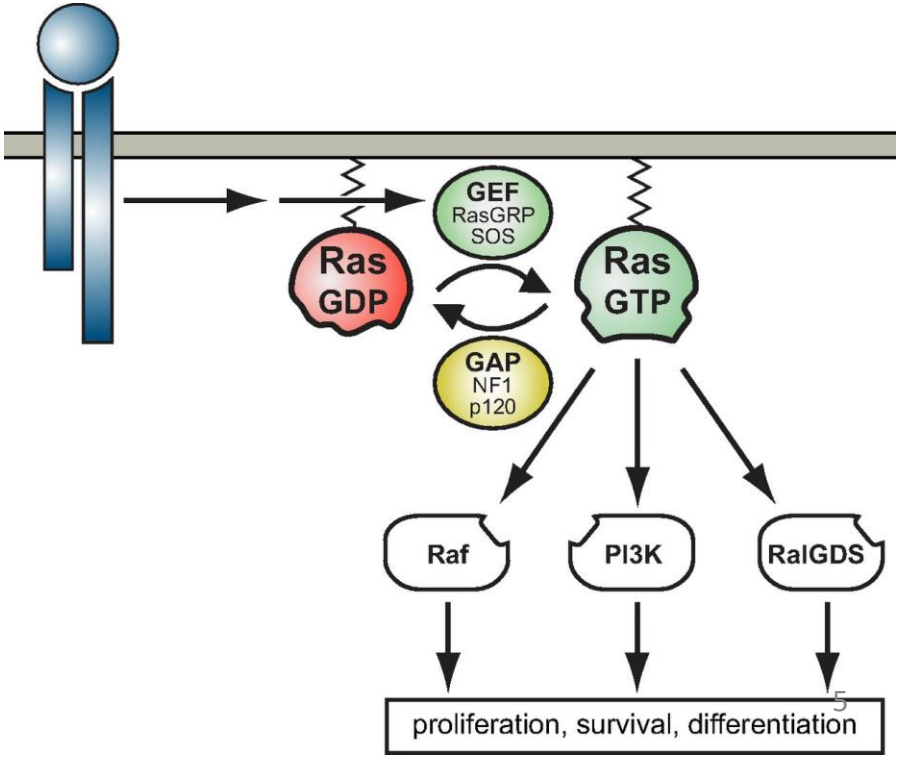
Loss of function

1: Sustaining proliferative signaling

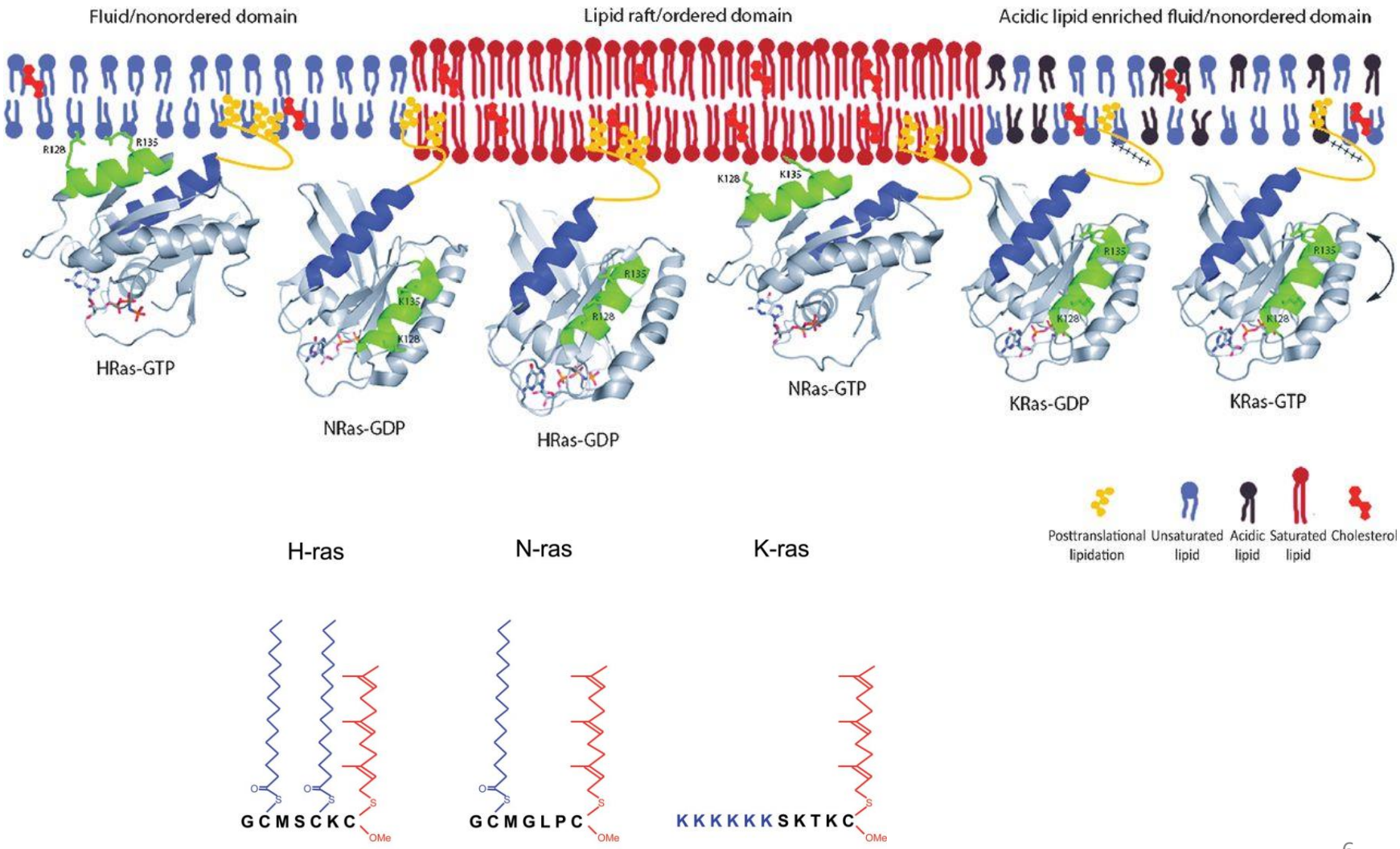
- Supporting chronic proliferation (e.g. growth hormone release)
  - Self production of growth factors (e.g. HGF)
  - Self production of cognate receptors (e.g. Tyrosine kinases)
  - Somatic mutations that activate signaling circuits (e.g. PI3-kinase)
  - Defects in negative-feedback loops (e.g. Ras)

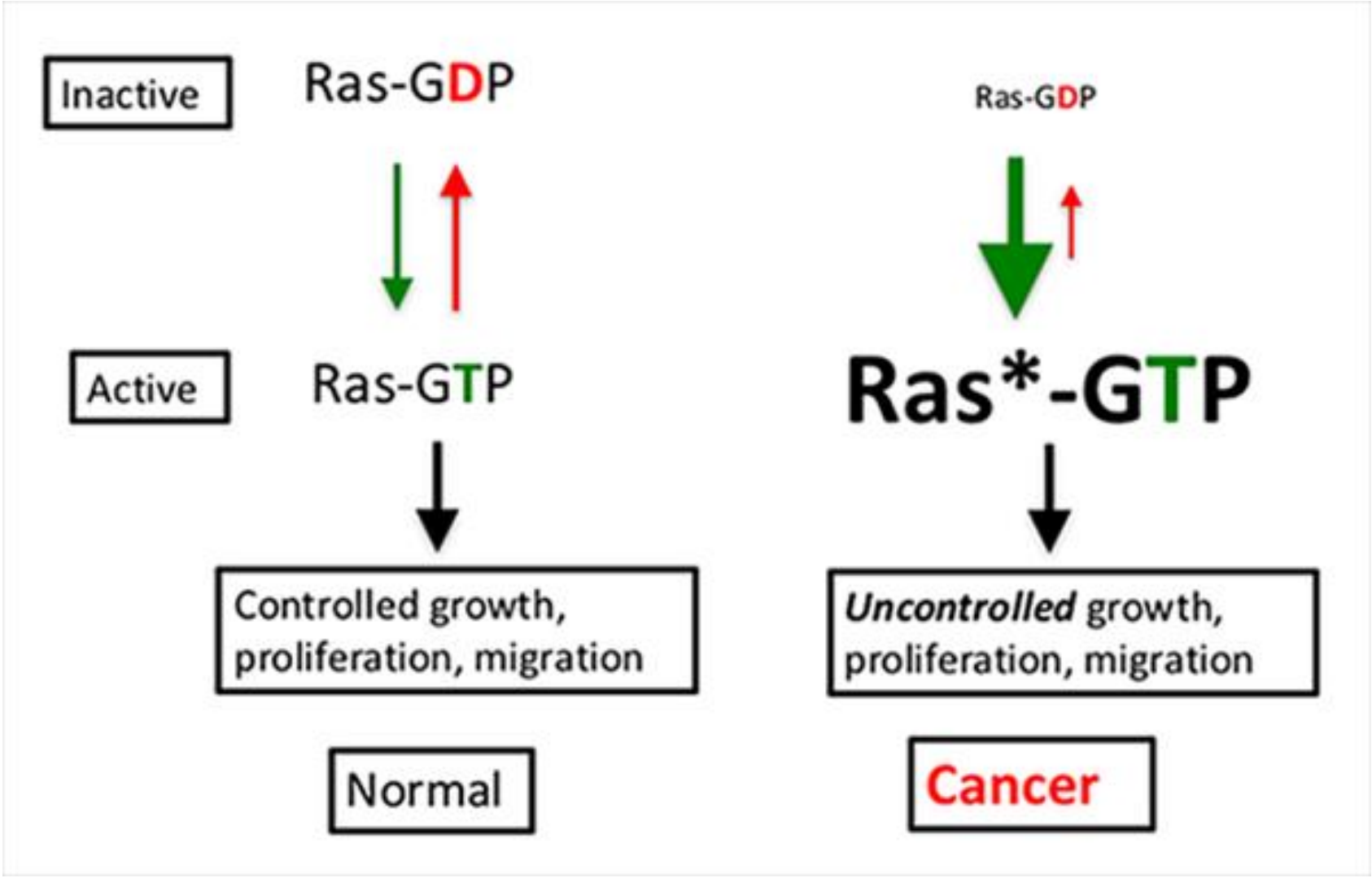
Ras signaling pathway

- Ras proteins are essential components of signaling networks controlling cellular proliferation, differentiation, and survival
- Oncogenic mutations of the H-*ras*, N-*ras*, or K-*ras* genes frequently found in human tumors (~30%)
- Oncogenic mutations are concentrated within 3 hotspots (around codons 12, 13 and 61) of the primary nucleotide sequence of all ras family members.

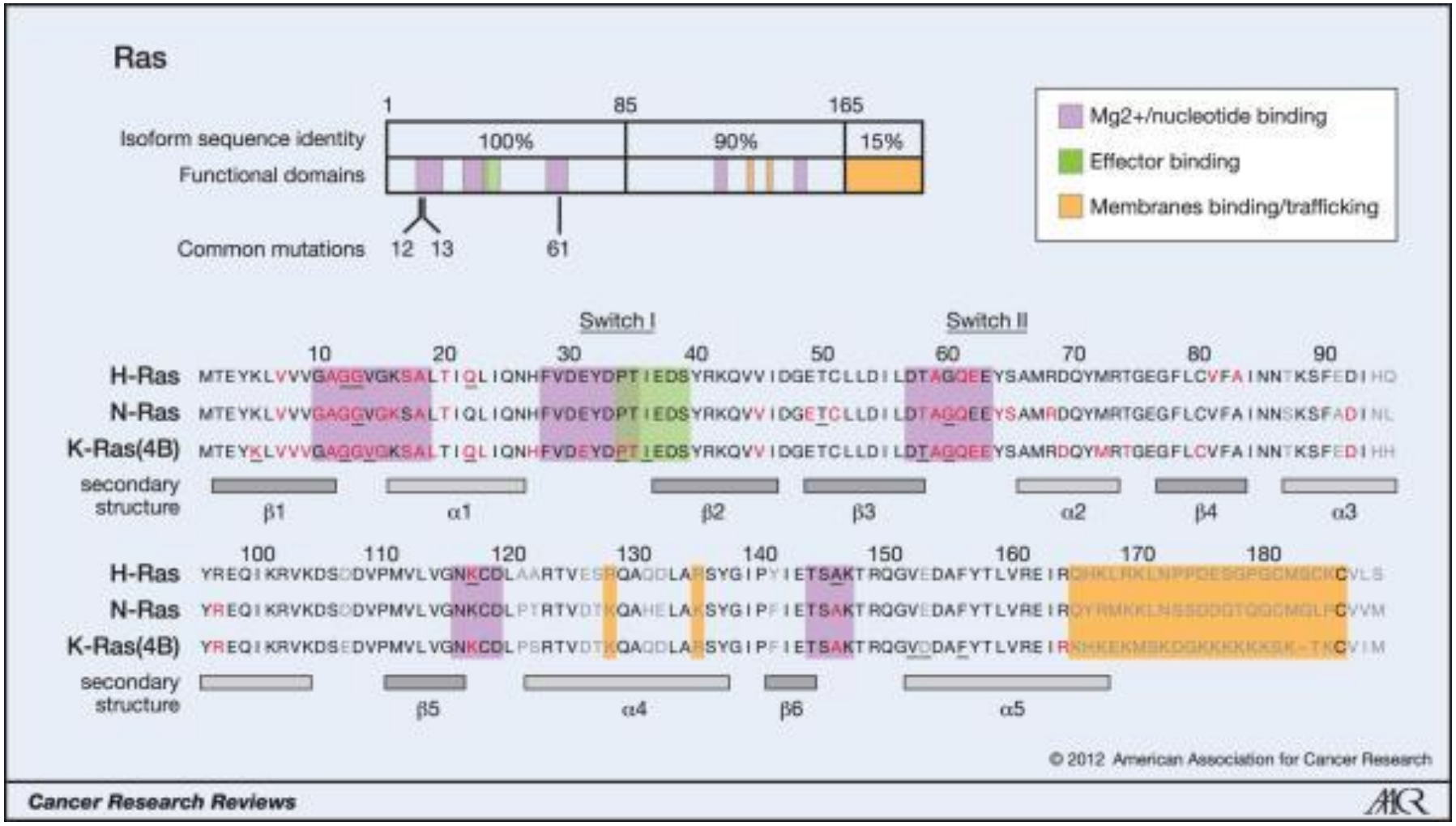


Ras isoforms and membrane insertion



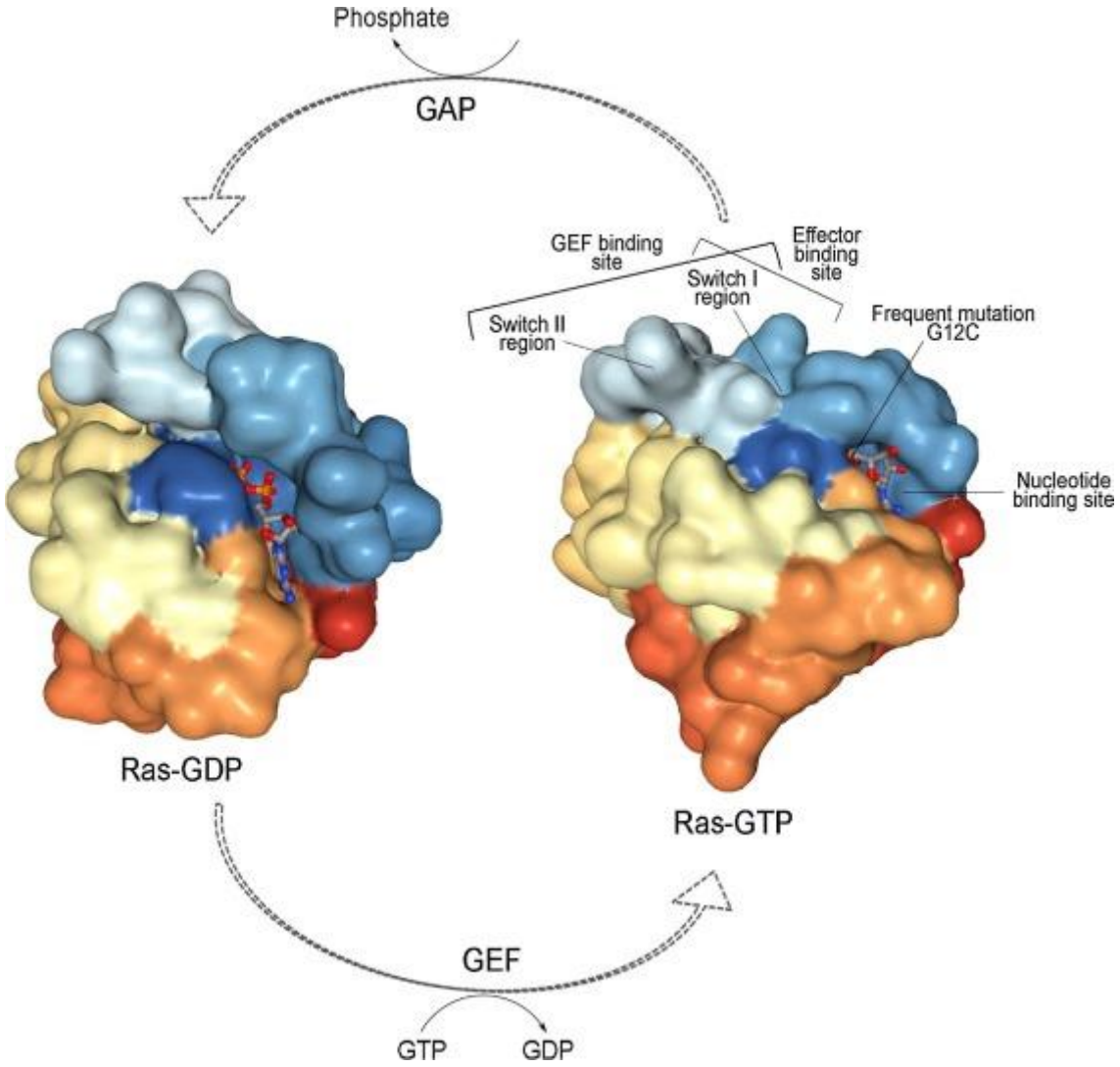

Inactive
Ras-GDP
Active
Ras-GTP
Controlled growth, proliferation, migration
Normal
Ras-GDP
Ras*-GTP
Uncontrolled growth, proliferation, migration
Cancer

Oncogenic mutations of Ras isoforms



A comprehensive survey of Ras mutations in cancer. Cancer Res. 2012

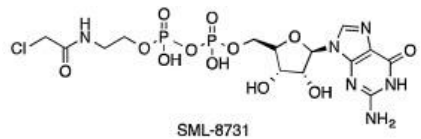
Inhibition of Ras

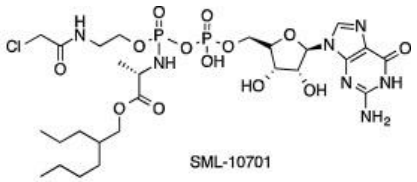


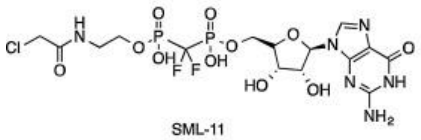
Blocking Ras inhibition as an antitumor strategy. Seminars in cancer biology. 2019

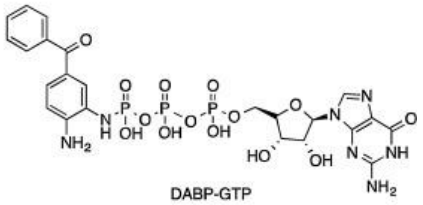
Examples of Ras Inhibitors

Nucleotide binding site inhibition

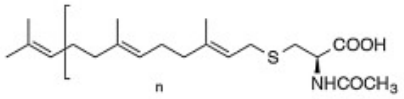


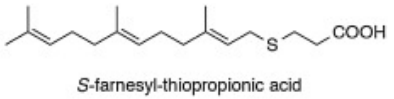


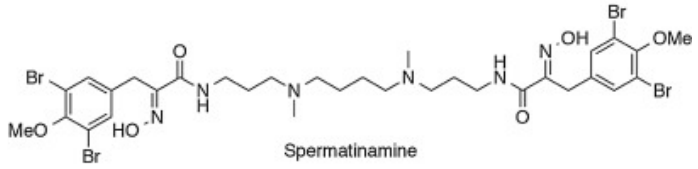




Post-translational modification inhibition





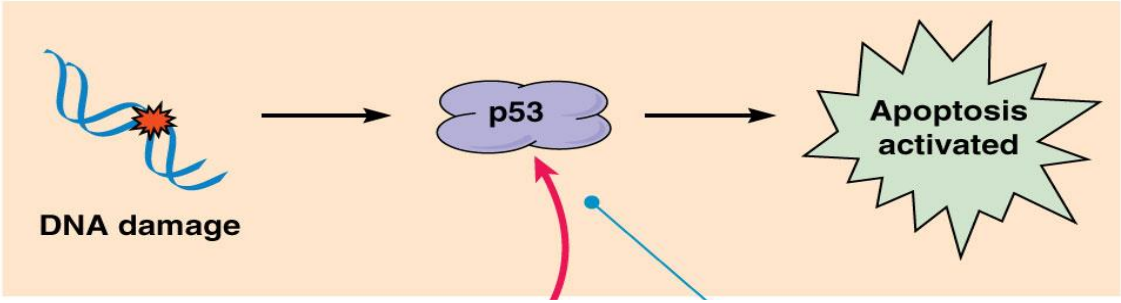


Blocking Ras inhibition as an antitumor strategy. Seminars in cancer biology. 2019

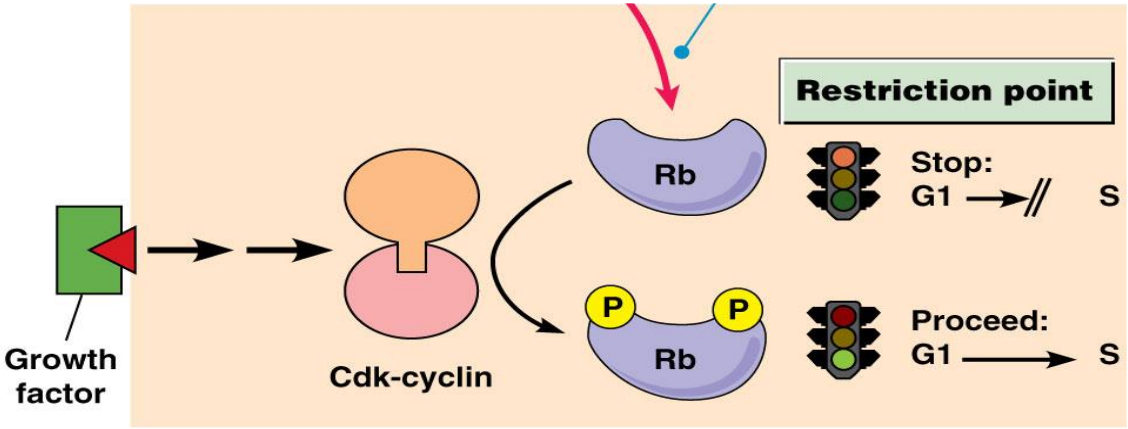
2: Evading growth suppressors

- Cancer cells adapt ways to avoid signals that negatively regulate cell proliferation
- This hallmark generally involves tumor suppressor proteins (modulate cell growth either through negative regulation of the cell cycle or by promoting apoptosis):
    - RB (Retinoblastoma) – inactivated by CDK phosphorylation
    - TP53

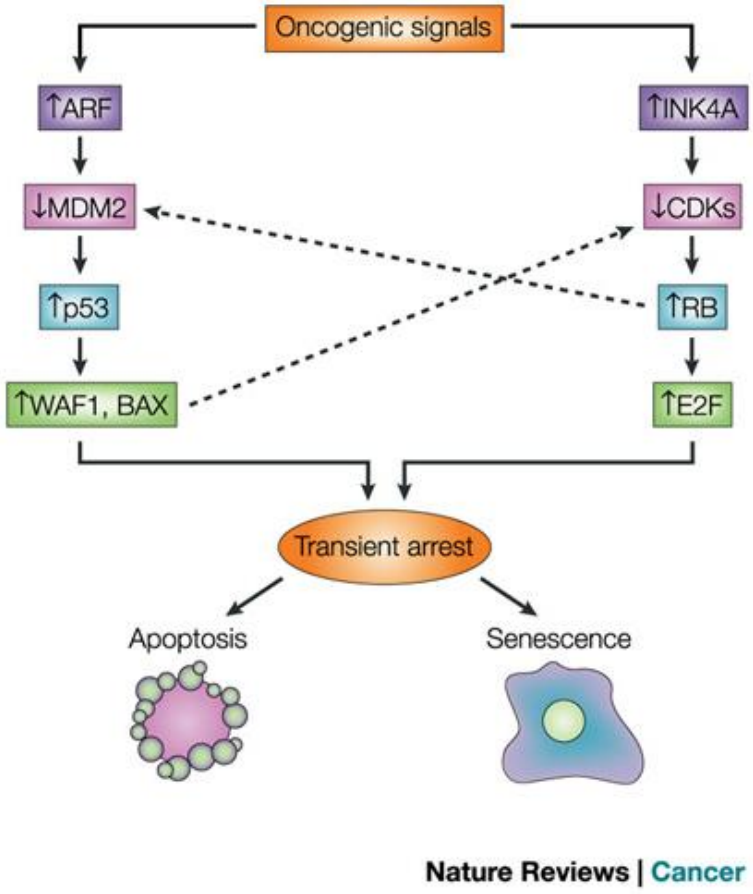
Tumor Suppressors p53 and Rb



Central nodes in apoptosis and cell proliferation



2: Evading growth suppressors



Some functional redundancy
RB null mice - free of proliferative abnormalities
P53 null mice - free of proliferative abnormalities

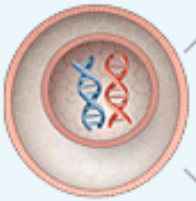
Cancer growth: genes as both the brake and gas pedals

Gain of function

Mutation of a gene into an **oncogene**

Ras

Mutations in oncogenes are like **a jammed gas pedal** in a car: they increase the speed of cell division.



Healthy cell

Mutation in a **tumor suppressor gene**

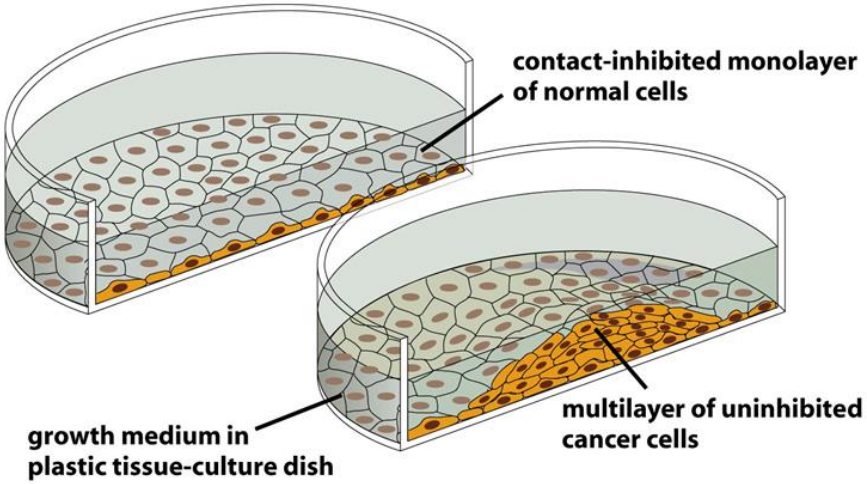
Cancer cells divide and grow into a tumor.

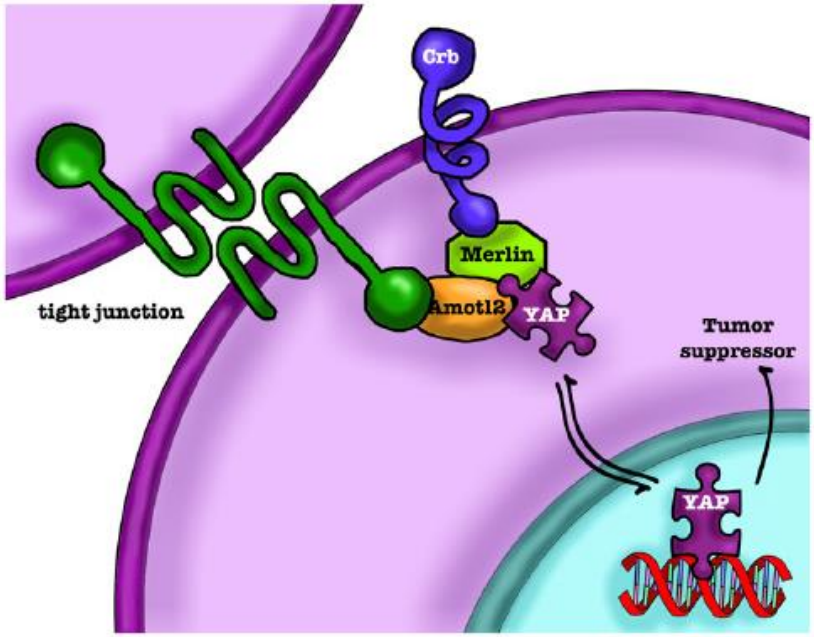
Mutations in tumor suppressor genes behave like **defective brakes**: the cells continue to divide uncontrollably.

Rb and p53

Loss of function

Loss of contact inhibition in cancer

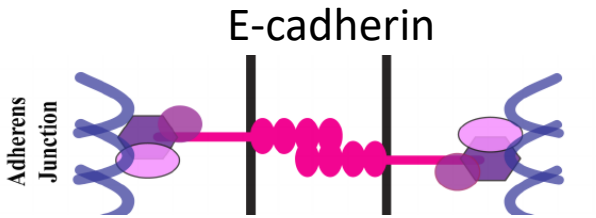




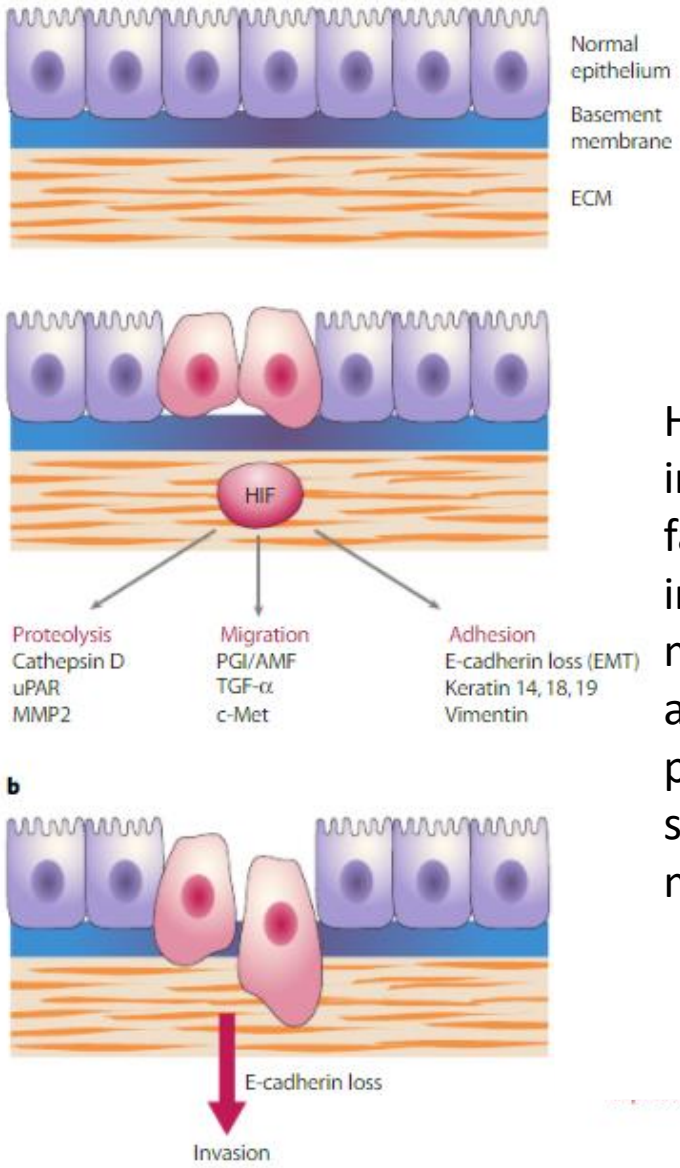
-Merlin is a membrane scaffolding protein
-mediates contact inhibition by coupling cell surface adhesion molecules
-In various cancers there is a loss of Merlin function
(e.g. it is proteasomally degraded in breast cancer)

3: Activating invasion and metastasis

- Alterations in cell-to-cell or cell-to-ECM adhesion molecules (e.g. loss of E-cadherin)
- Traits of invasion and metastasis:
  - Loss of adheren junctions
  - Expression of matrix degrading enzymes
  - Increased motility
  - Resistance to apoptosis



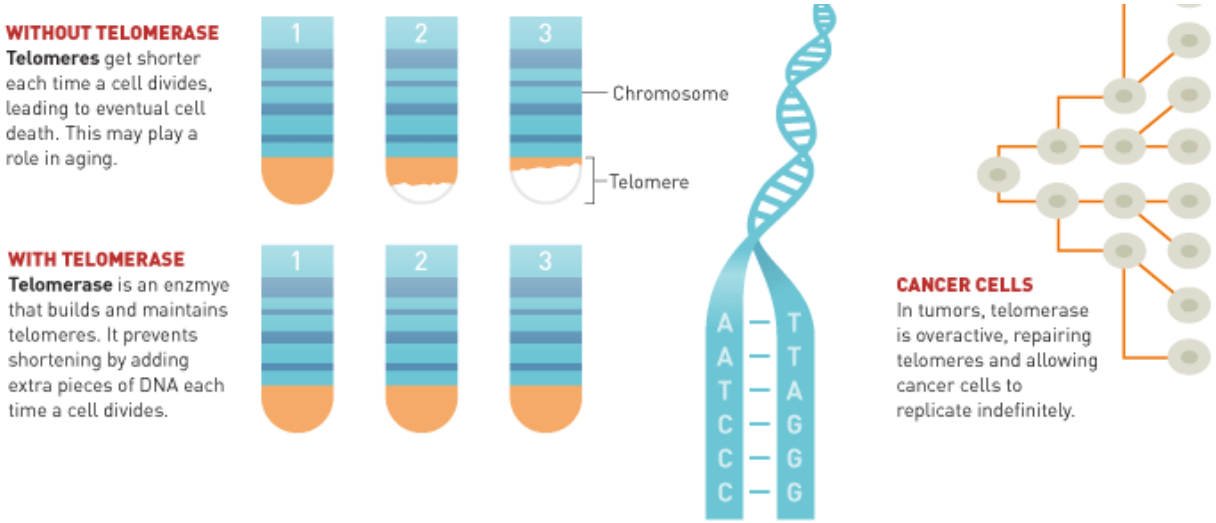
https://www.nature.com/articles/nature04871



Hypoxia-inducible factor (HIF) induces markers that activate proteolysis to stimulate migration

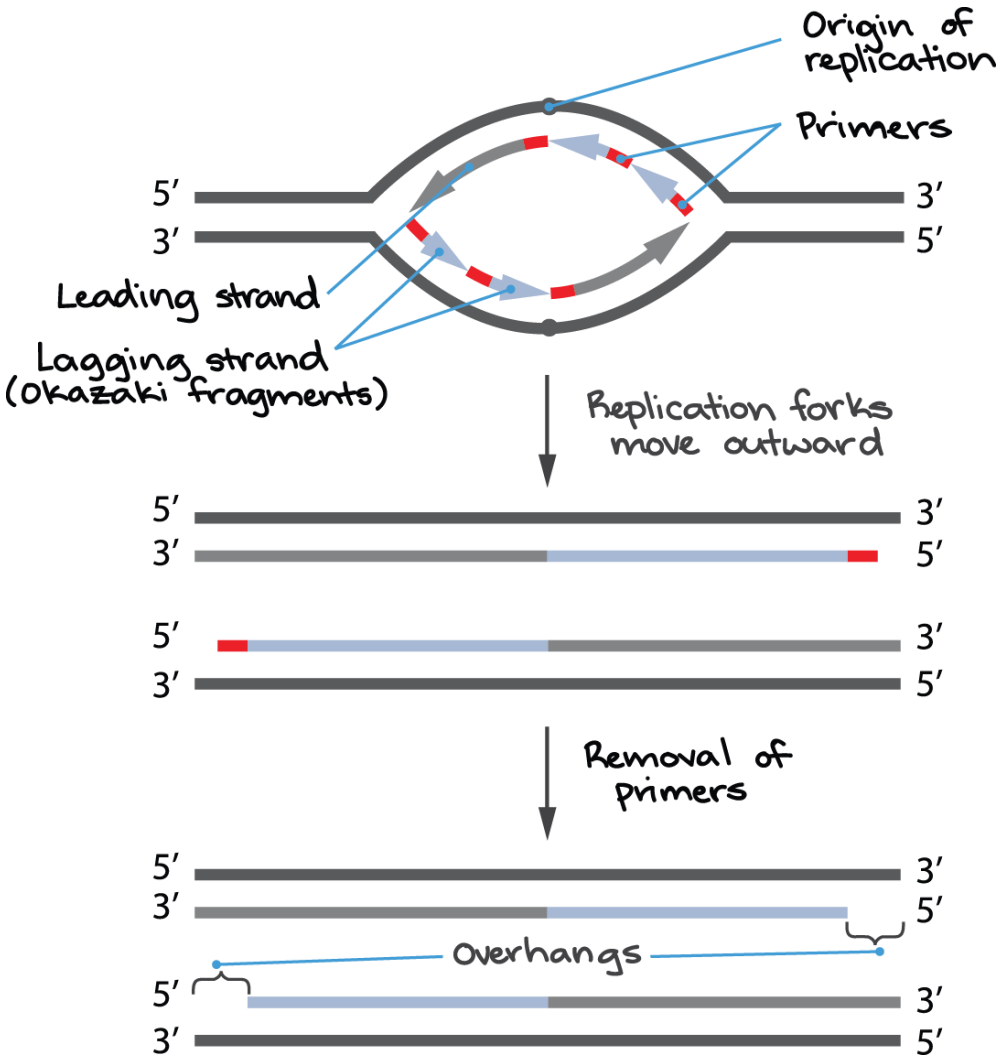
4: Enabling replicative immortality

- Telomeres protect the end of chromosomal DNA
- Composed of nucleotide repeats that shorten progressively after each round of DNA replication
- Telomerase is a DNA polymerase that lengthens the ends of telomeres
- Normal cells have low levels of telomerase and cancer cells have significantly higher levels



End replication problem

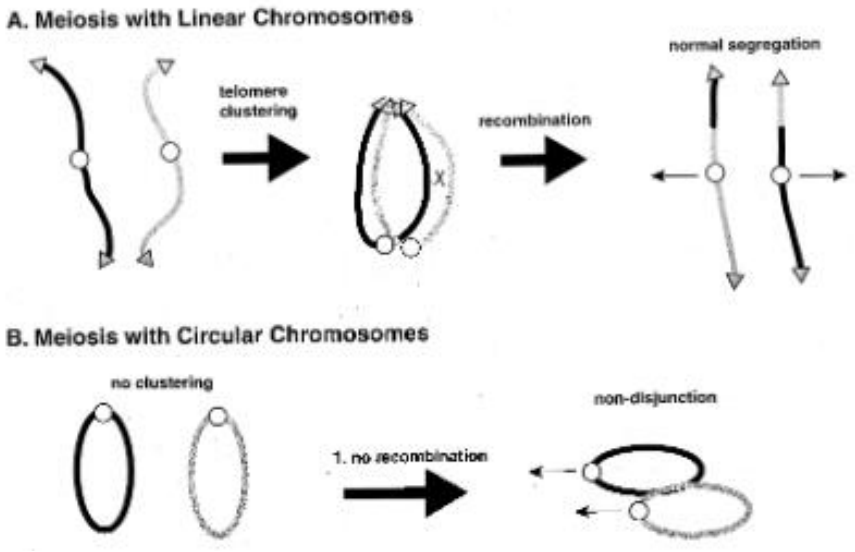
-DNA replication is bidirectional (leading and lagging)
-Polymerase moves 5’ to 3’
-RNA primer used for initiation of synthesis
-50-200 bp of DNA is unreplicated at the 3’ end/round of replication



Humans could circumvent the end replication problem with circular DNA. Why do we have linear chromosomes (advantage?)

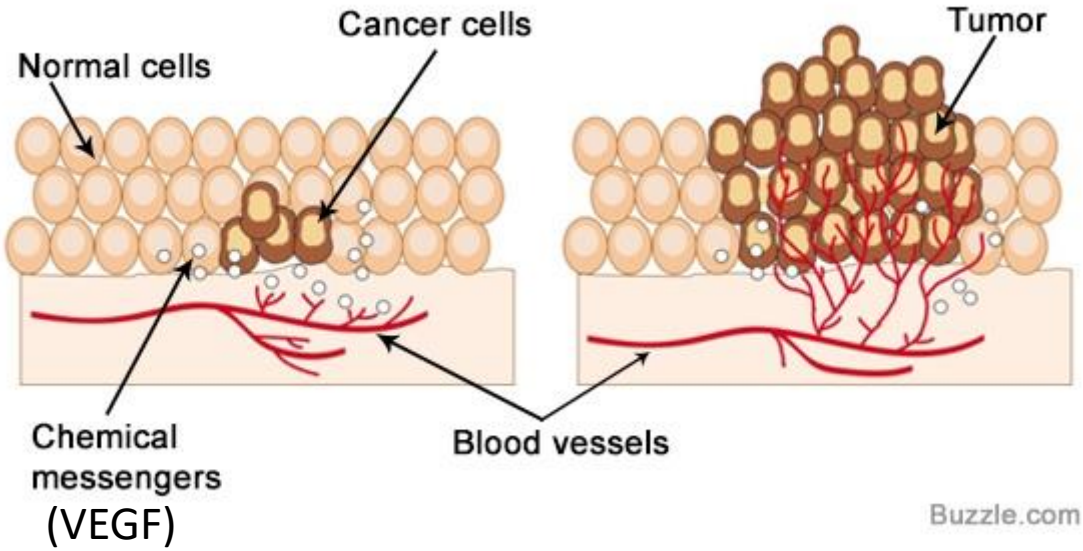
Hypothesis: small chance that all circular chromosomes are properly segregated during meiosis -telomere alignment

Meiosis is a mechanism to generate haploid cells



5: Inducing angiogenesis

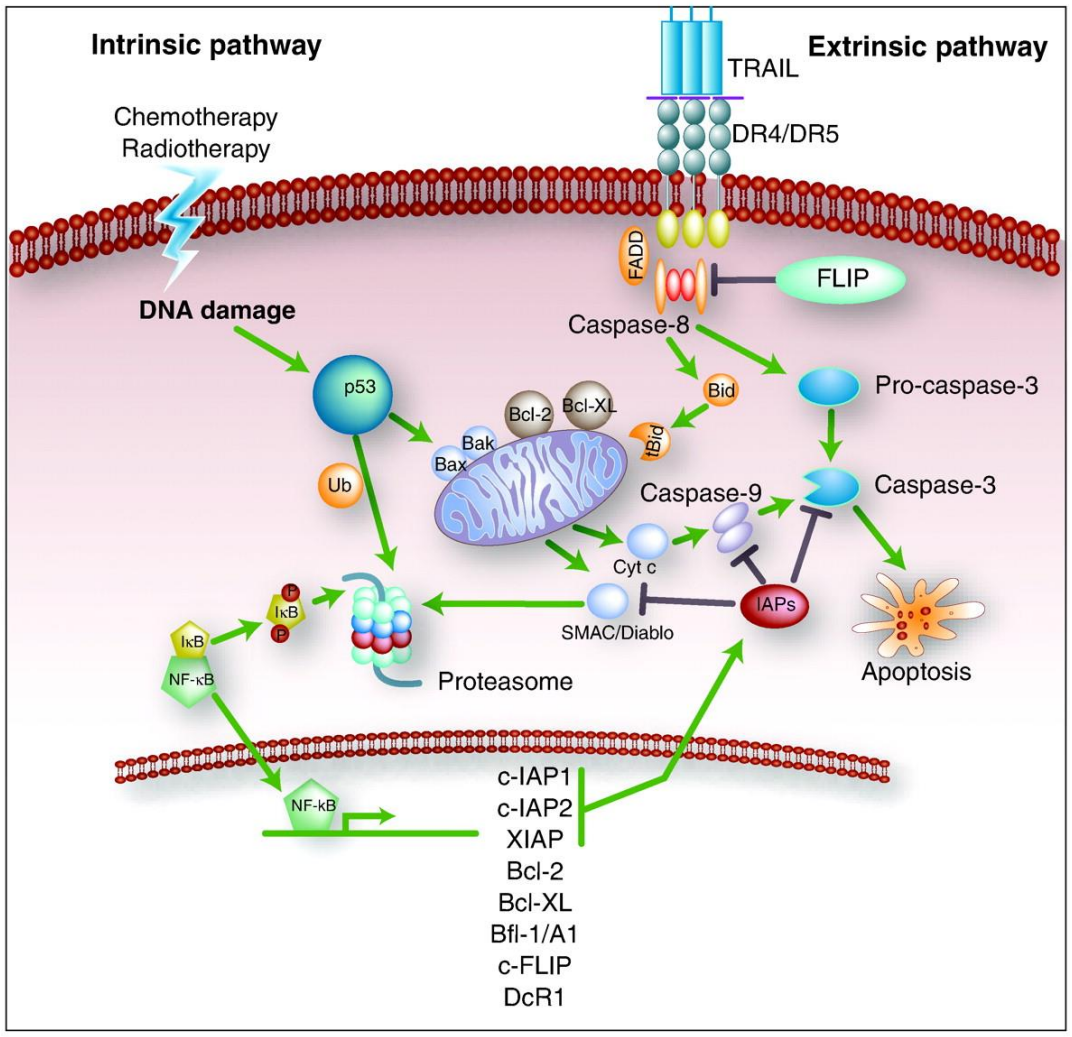
- Angiogenesis is the growth of blood vessels from pre-existing vasculature
- Cancer cells need high amounts of nutrients and oxygen as well as the ability to remove waste and CO_2



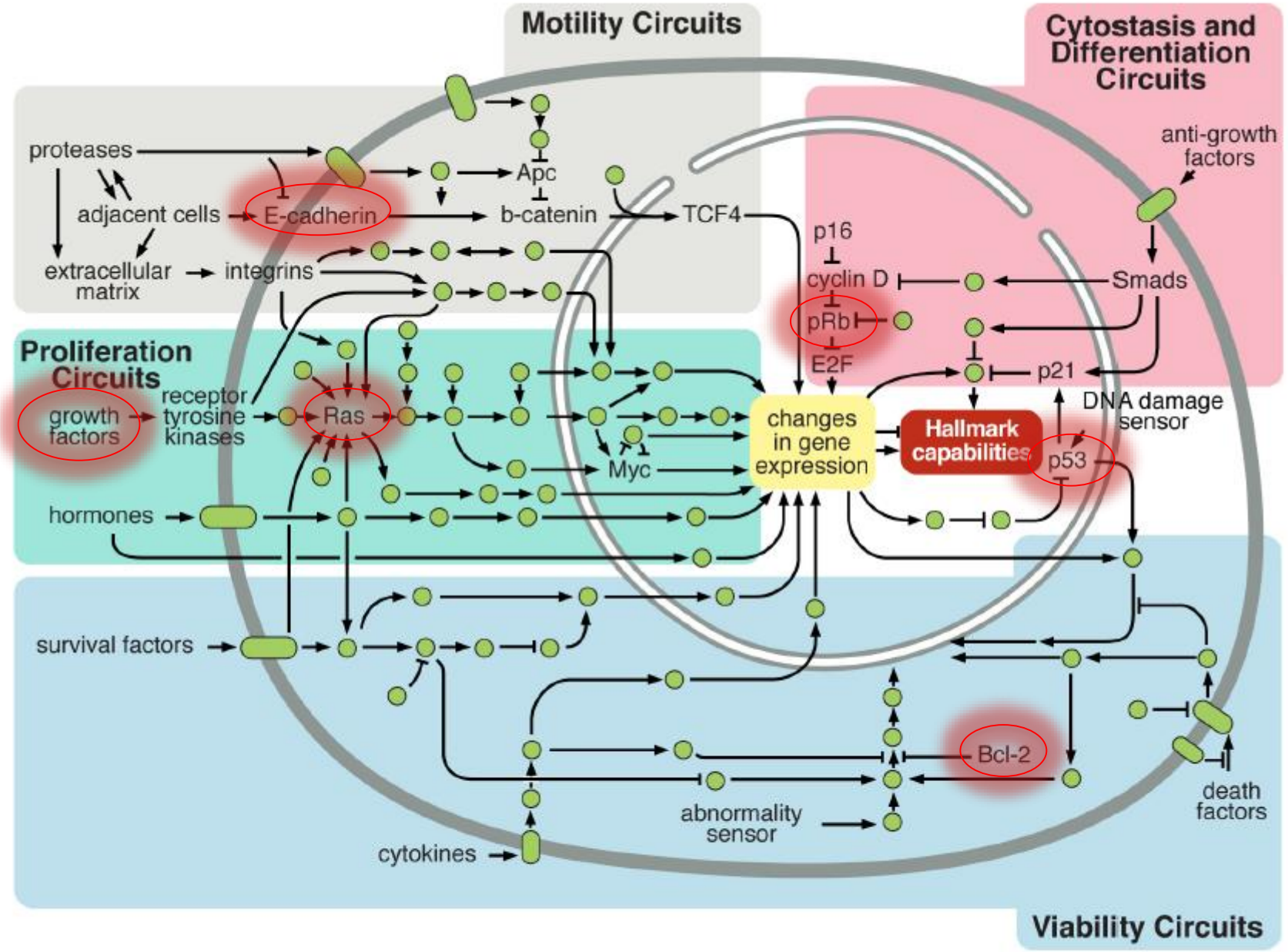
6: Resisting cell death

- Apoptosis: programmed cell death
- Cancer cells acquire mechanism that evade apoptosis
- Bcl-2 family of proteins are inhibitors of apoptosis (via binding to pro-apoptotic proteins like Bax and Bak) in the outer mitochondrial membrane.
- Bax and Bak disrupt the mitochondrial membrane to release cytochrome c to activate proteases for apoptosis.

Apoptosis pathway



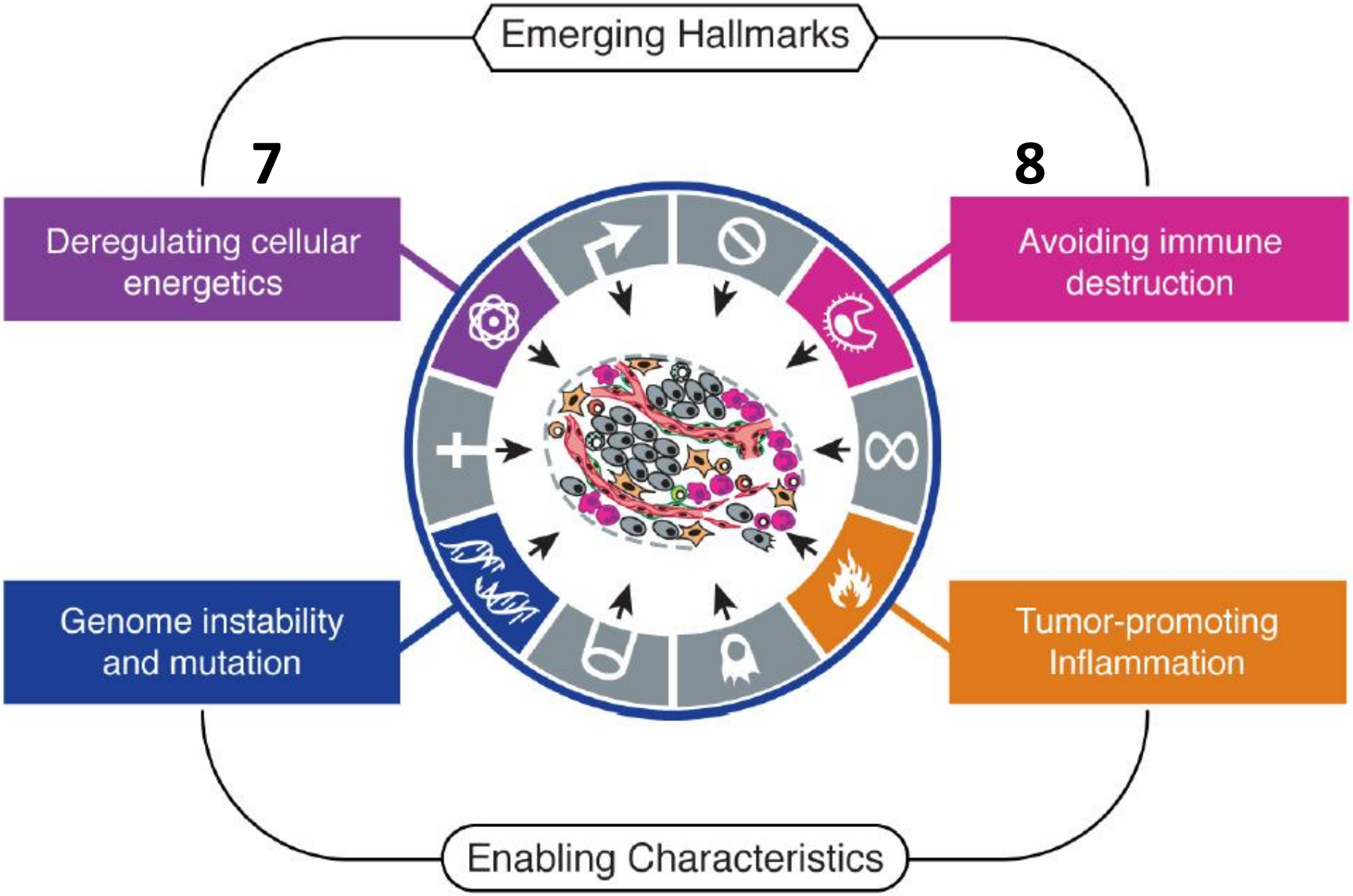
CCR Molecular Pathways



Hanahan and Weinberg, 2011

Mentimeter Poll

Ras



Hanahan and Weinberg, 2011

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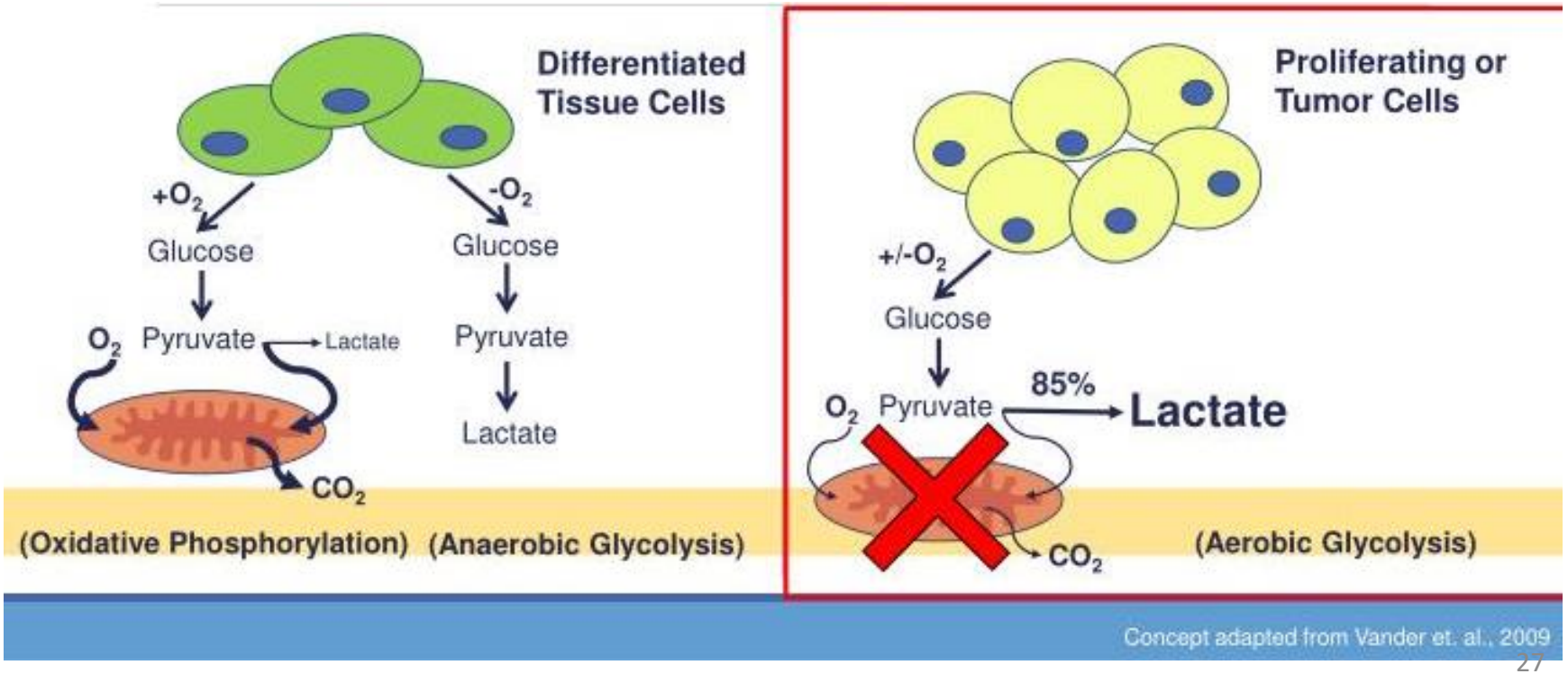
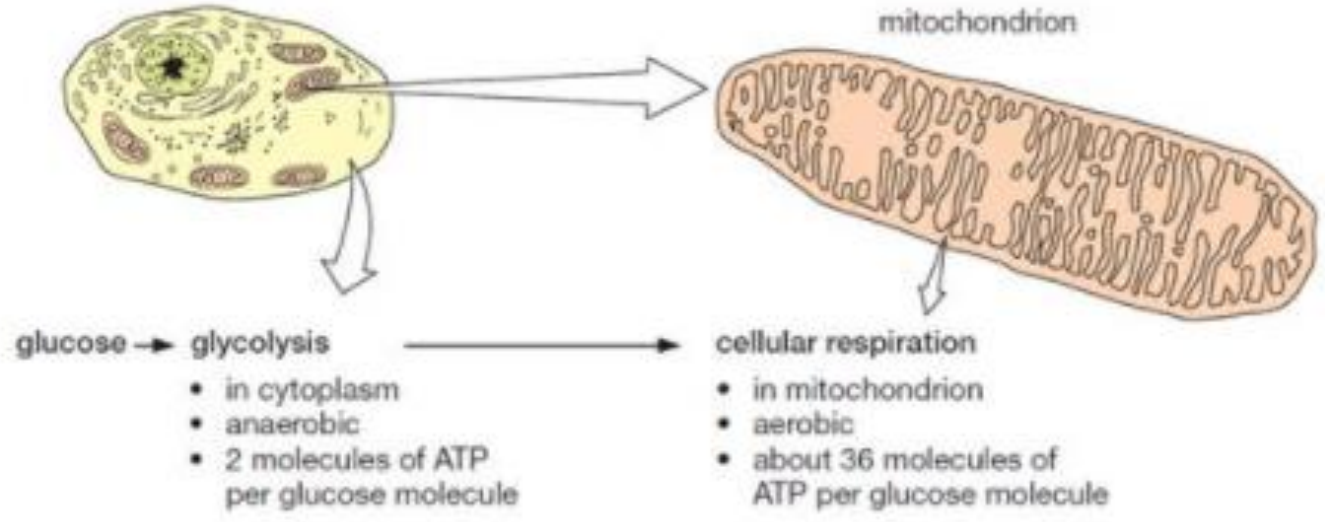
7: Deregulating cellular energetics

- Cancer cells reprogram their energy production by limiting metabolism largely to glycolysis and lactic acid fermentation (Warburg effect).



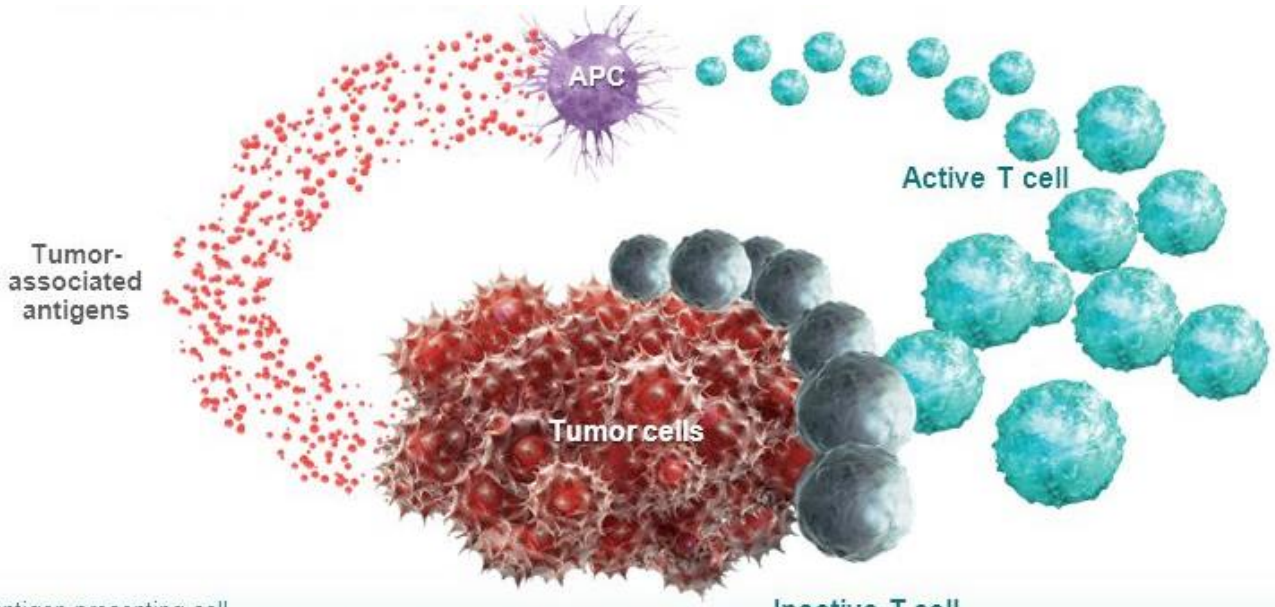
7: Deregulating cellular energetics

- Seems counterintuitive: ATP production is ~18-fold less efficient by glycolysis relative to oxidative phosphorylation. Why?
- It remains elusive…hypothesis: increased glycolysis allows for the molecular intermediates to be used in other biosynthetic pathways important for growth of new cells, e.g. generating nucleosides and amino acids.



8: Avoiding immune destruction

- Immune system provides surveillance to destroy abnormal/ cancer cells
- Some cancer cells avoid immune detection, to evade eradication



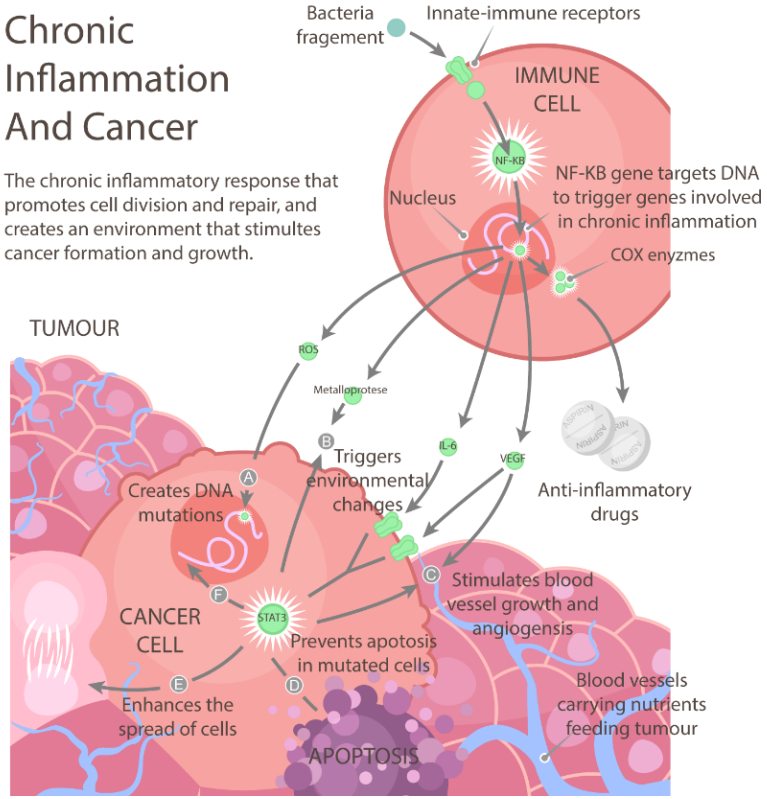
APC, antigen-presenting cell.

1. Gajewski TF et al. *Nat Immunol*. 2013;14(10):1014-1022.
2. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264.
3. Vesely MD et al. *Annu Rev Immunol*. 2011;29:235-271.

Enabling Characteristics

Genome instability and mutation

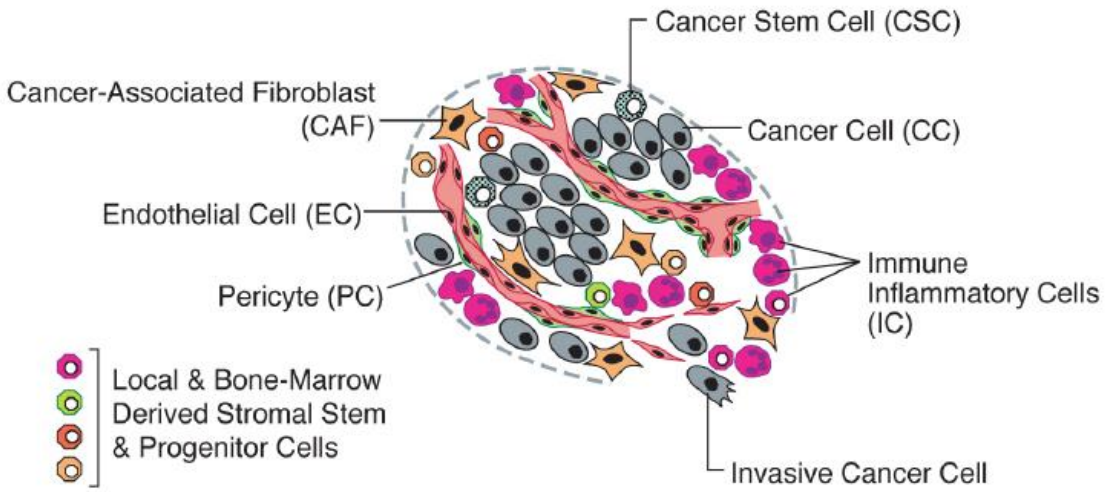
Tumor-promoting inflammation

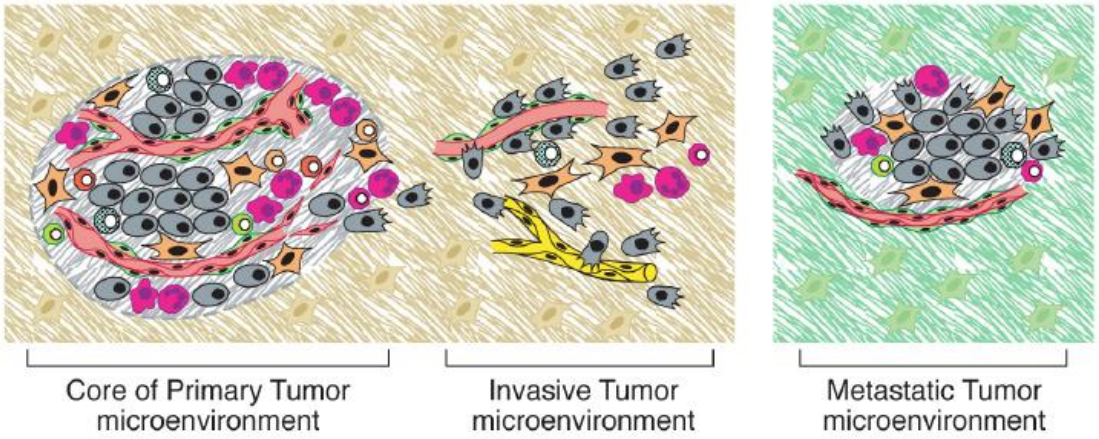


Will discuss more in future lectures….

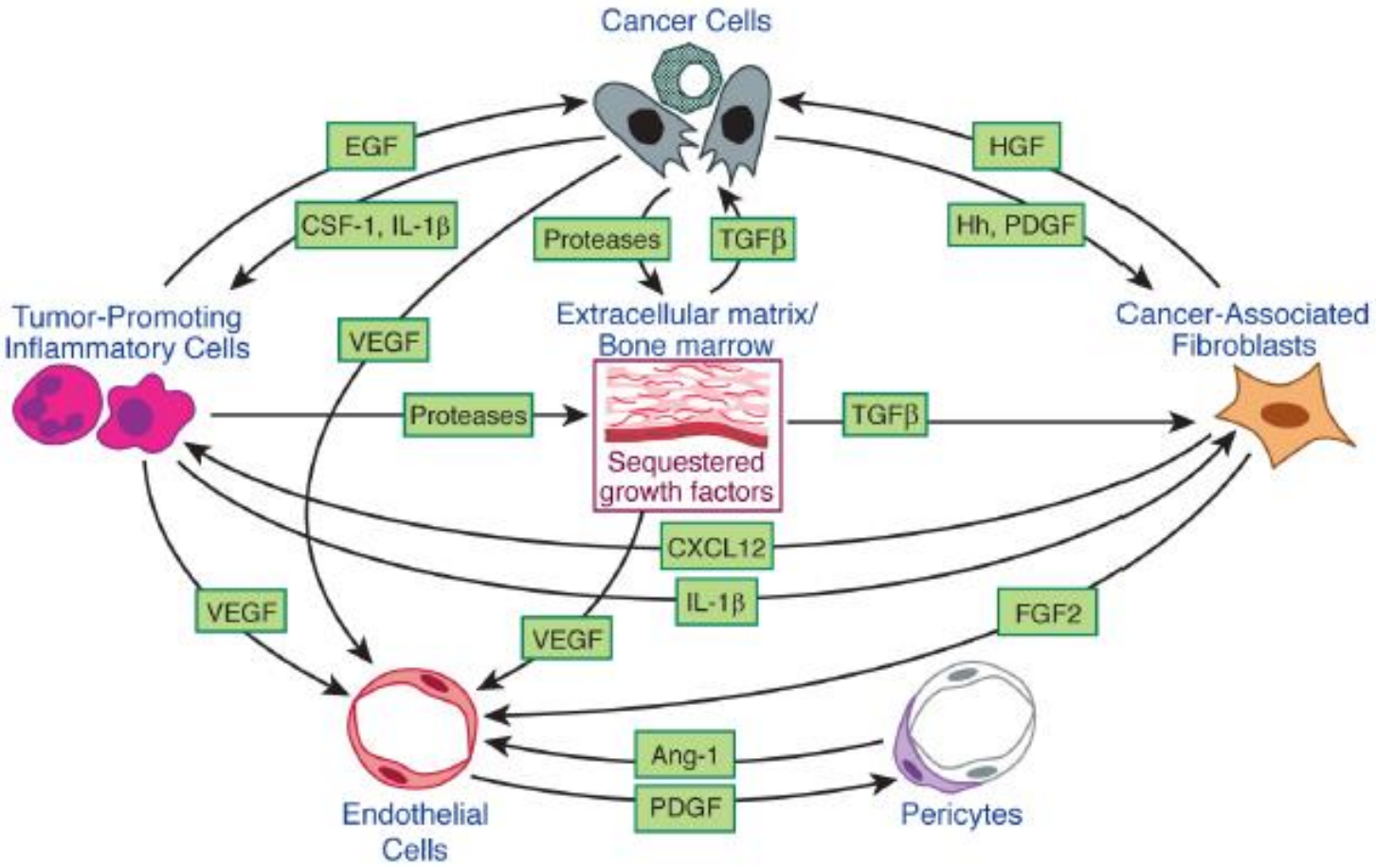
The tumor microenvironment

Tumors increasingly being recognized as organs

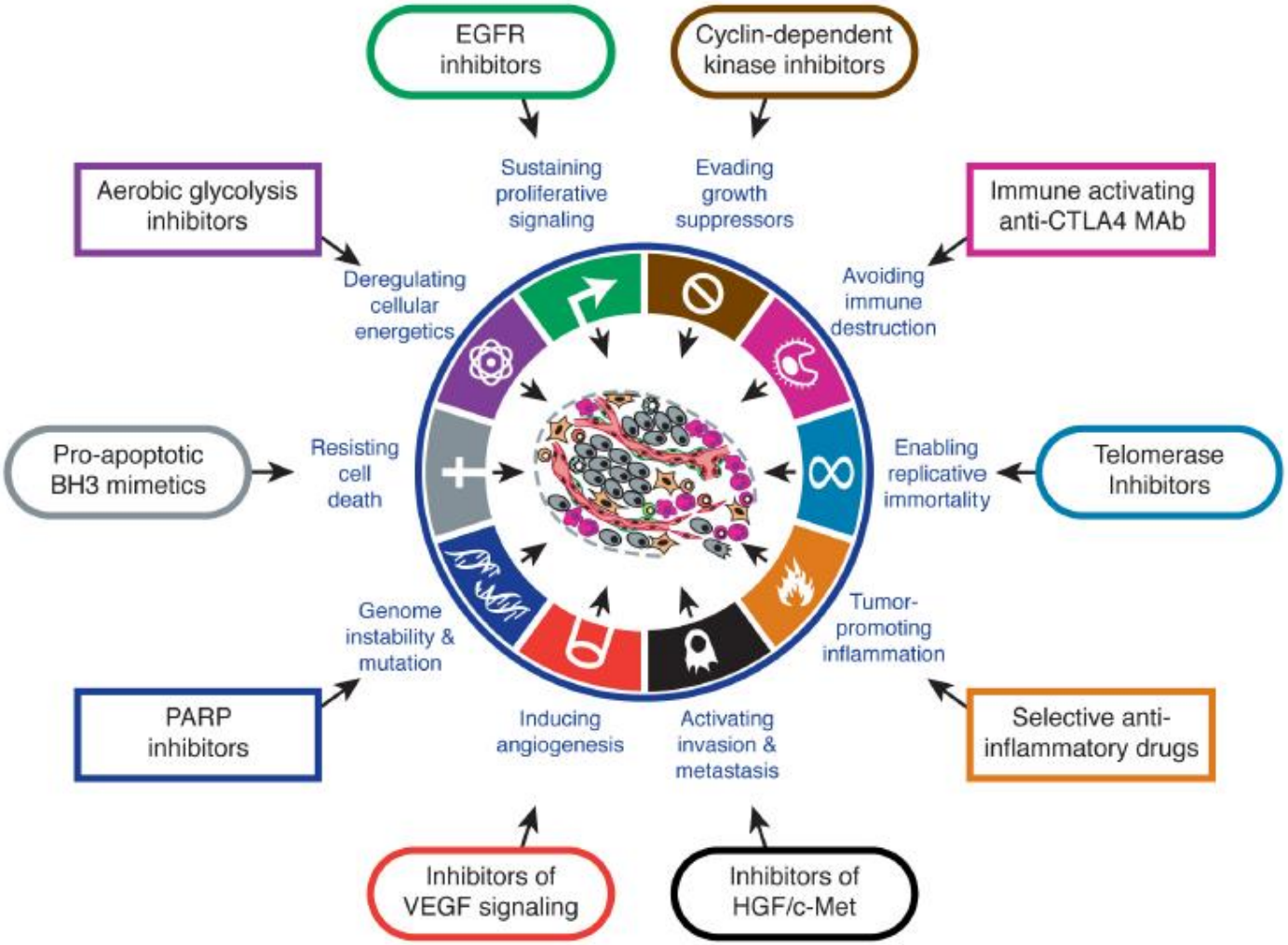




Signaling interactions in tumor microenvironment



Therapeutic Targets for Cancer



Hanahan and Weinberg, 2011

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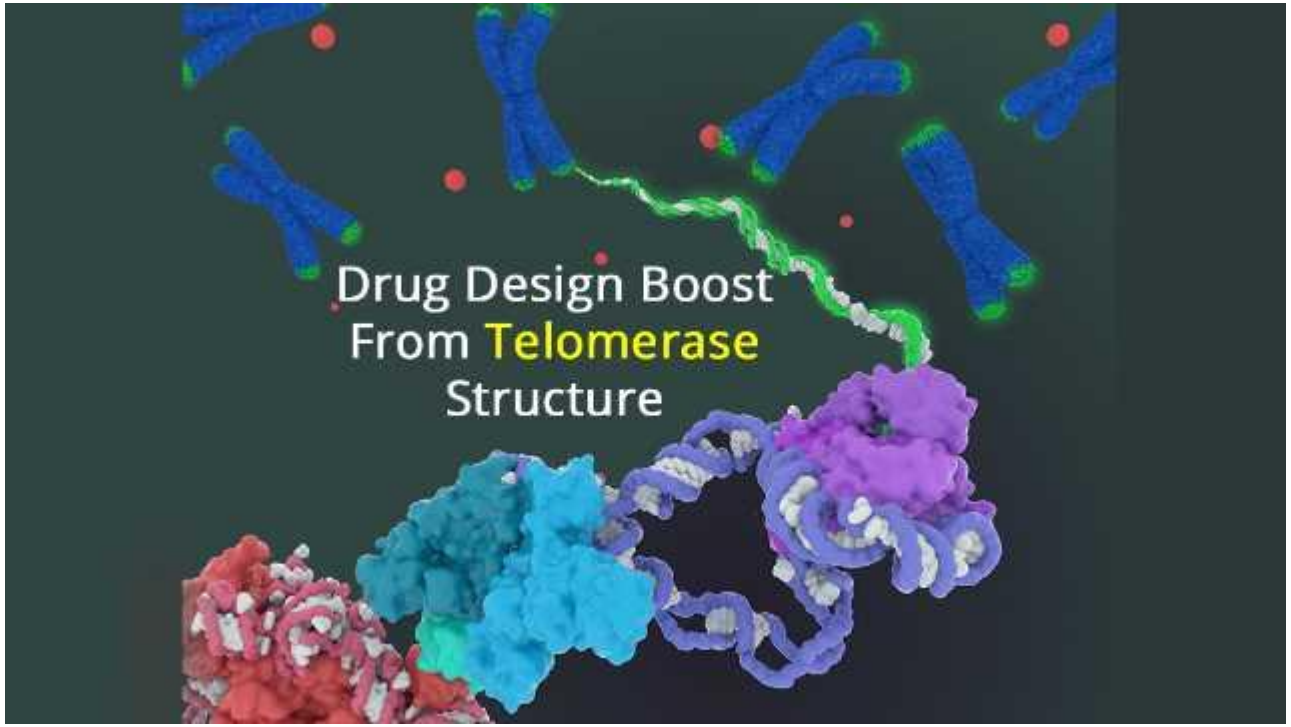
One example: Telomerase inhibition



Human telomerase enzyme, May 2018

ARTICLE

https://doi.org/10.1038/s41586-018-0062-x

Cryo-EM structure of substrate-bound human telomerase holoenzyme

Thi Hoang Duong Nguyen[1,2,3,4], Jane Tam[1], Robert A. Wu[1,6], Basil J. Greber[2,3], Daniel Toso[2], Eva Nogales[1,2,3,5]* & Kathleen Collins[1,2]*

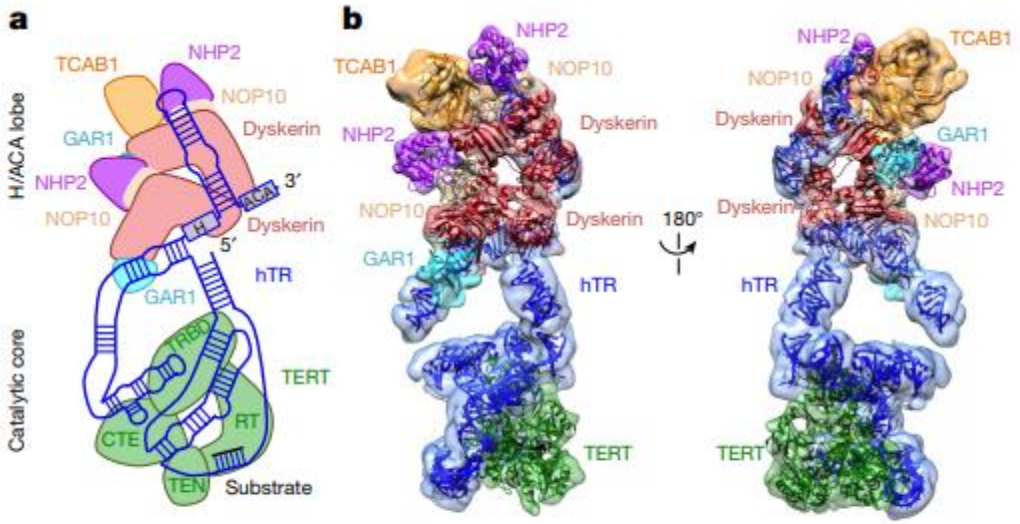


Fig. 2 | Cryo-EM structure of the substrate-bound human telomerase holoenzyme. a, Schematic of subunit arrangements. **b**, Front (left) and back (right) views of the cryo-EM reconstructions for the H/ACA lobe at 8.2 Å and the catalytic core at 7.7 Å, with fitted subunits colour-coded as indicated.

Telomerase = Ribonucleoprotein

previous images 30 Ångstroms - here 7 to 8 Ångstroms resolution using cryoelectron microscopy

Telomerase is a ribonucleoprotein polymerase that maintains telomere ends by addition of the telomere repeat TTAGGG. It binds to a ncRNA.

Clinical Trial GRN163L (Geron)

- One telomerase inhibitor on the market: Imetelstat.

- In 2005, the first Phase 1 clinical trial of, GRN163L, which later became known as imetelstat, was initiated.
- Since telomerase is upregulated in most types of human cancers, we conducted a broad program of early phase clinical trials.
- Over 500 patients have been enrolled and treated in Phase 1 and 2 clinical trials of imetelstat.

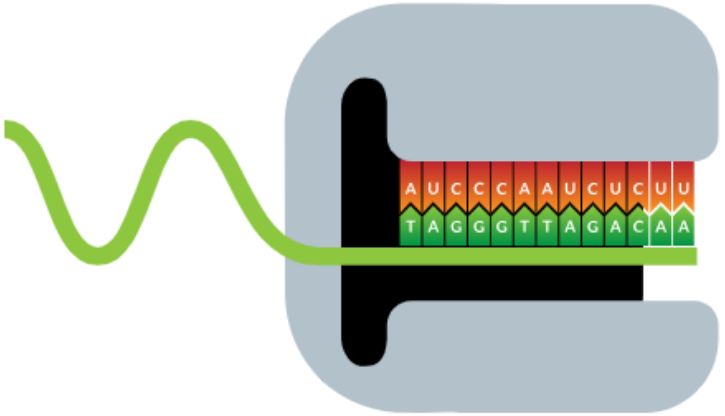
- Imetelstat used to treat hematologic myeloid malignancies.

Information from Geron website

One example: Telomerase inhibition

Imetelstat

Imetelstat Bound to Telomerase



Imetelstat binds with high affinity to the template region of the RNA component of telomerase, resulting in direct, competitive inhibition of telomerase enzymatic activity

Tips for cancer part of exam

- About half questions concern concepts from lecture and understanding in general context
- About half questions concern specific examples (i.e. carcinogenic factors, associated cancers, relevant mechanisms, important genes, key pathways)
- There will be no questions regarding global cancer incidence/statistics, often given for general interest and real world context of the molecular and mechanistic info