

Pathogenesis of solid tumors

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If you think we are going to discuss...

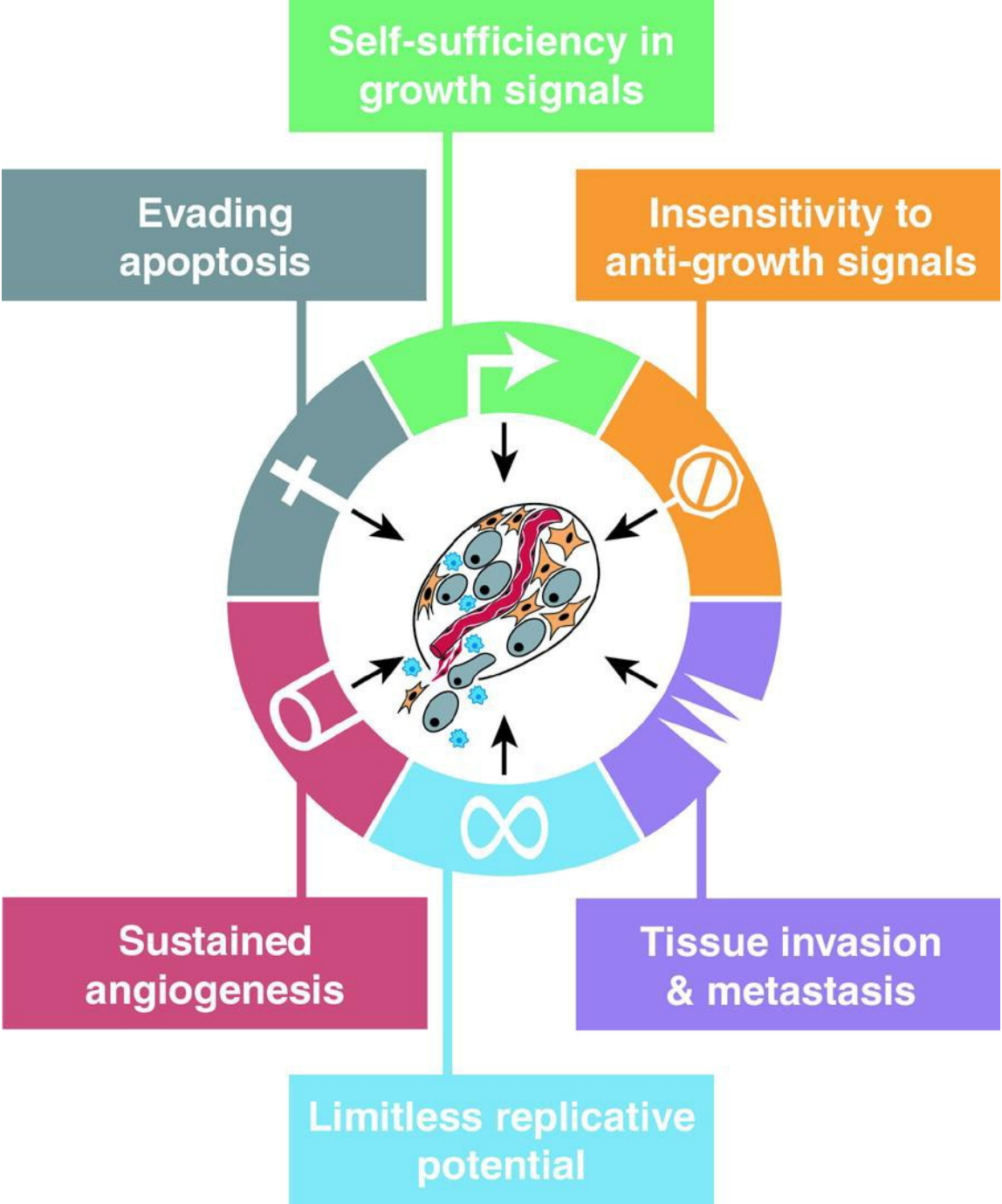
- Asbestos...mesothelioma
- Ultraviolet light...melanoma
- HPV...cervical carcinoma
- HHV8...Kaposi sarcoma
- Smoking...lung, urothelial carcinomas...
- Not to speak about oncogenes, anti-oncogenes...
- **You are wrong!**

Which of the following “hallmarks of cancer” of the following was NOT recognized before year 2000?

- A) evading apoptosis
- B) self-sufficiency in growth signals
- C) tissue Invasion and metastasis
- D) avoiding immune destruction
- E) sustained angiogenesis

The hallmarks of cancer” (Hanahan D. and Weinberg R.A. **2000**, *Cell* 100: 57-70)

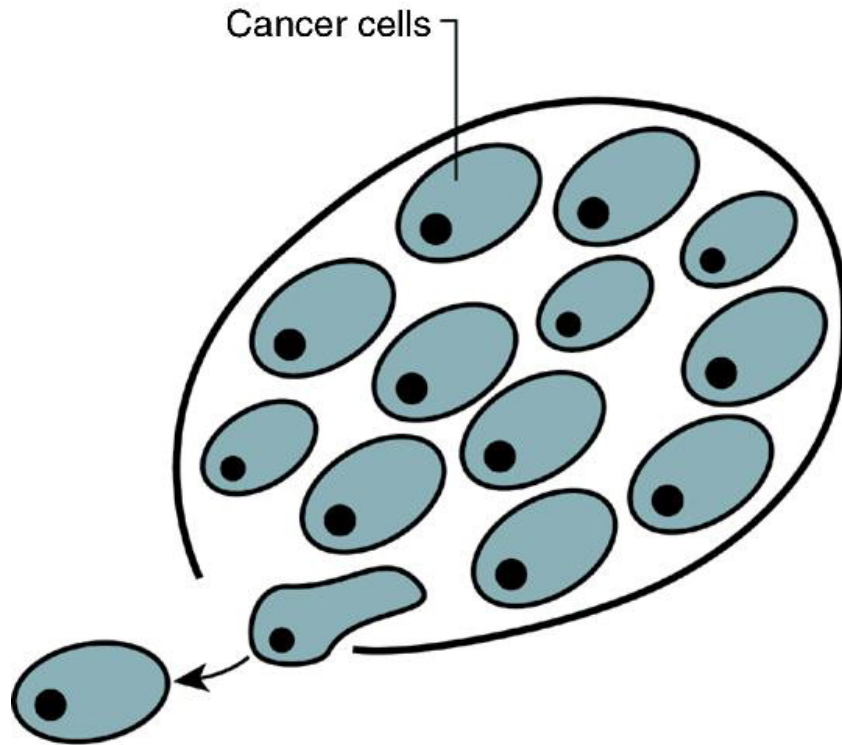




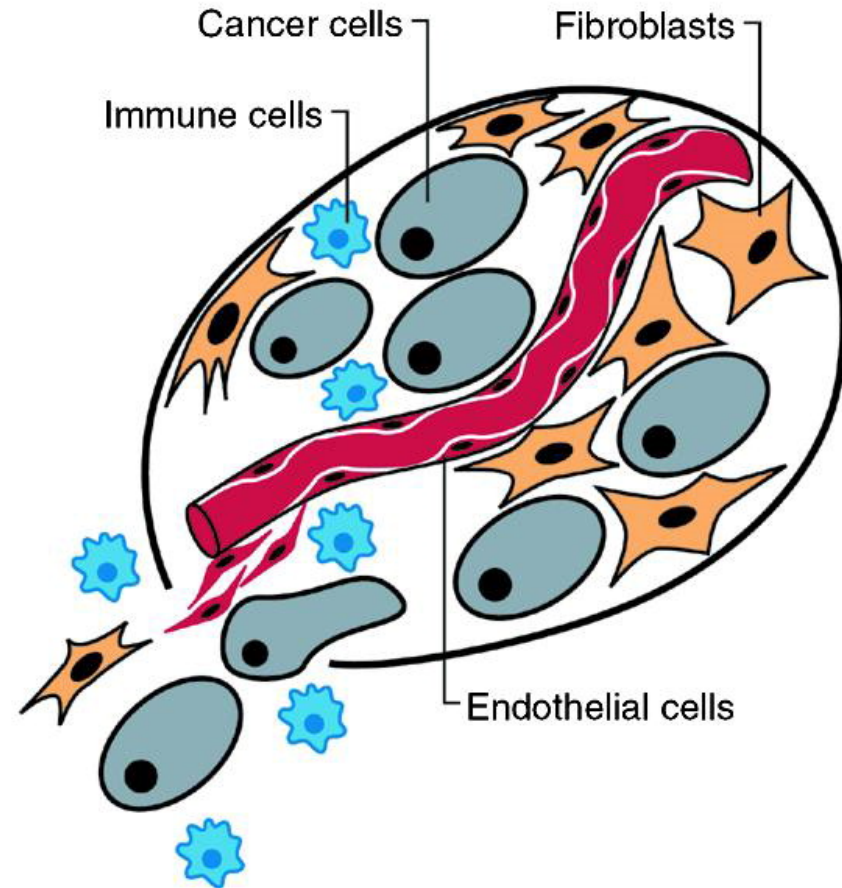
- **Self-Sufficiency in Growth Signals:** normal cells require mitogenic growth signals before they can move from a quiescent state into an active proliferative state. Cancer cells not.
- **Insensitivity to Antigrowth Signals:** within a normal tissue, multiple antiproliferative signals operate to maintain cellular quiescence and tissue homeostasis
- **Evading Apoptosis**
- **Limitless Replicative Potential**

- **Sustained Angiogenesis**
- **Tissue Invasion and Metastasis**

The Reductionist View



A Heterotypic Cell Biology



- “...a reductionist focus ... has produced ***an extraordinary body of knowledge***...new important new inroads will come from regarding tumors as ***complex tissues*** ...mutant cancer cells **have conscripted and subverted normal cell types to serve as *active collaborators* in *their neoplastic agenda***....these **supporting coconspirators** will prove **critical to** understanding cancer pathogenesis and to **the development of novel, effective therapies.**“

Molecular biology methods vs. histo(patho)logy in whole tissue examination

Molecular biology



Histo(patho)logy



A**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

B

Hallmarks of Cancer: The Next Generation

(Hanahan D. and Weinberg
R.A. **2011**, *Cell* 144: 646-
674)

Emerging Hallmarks

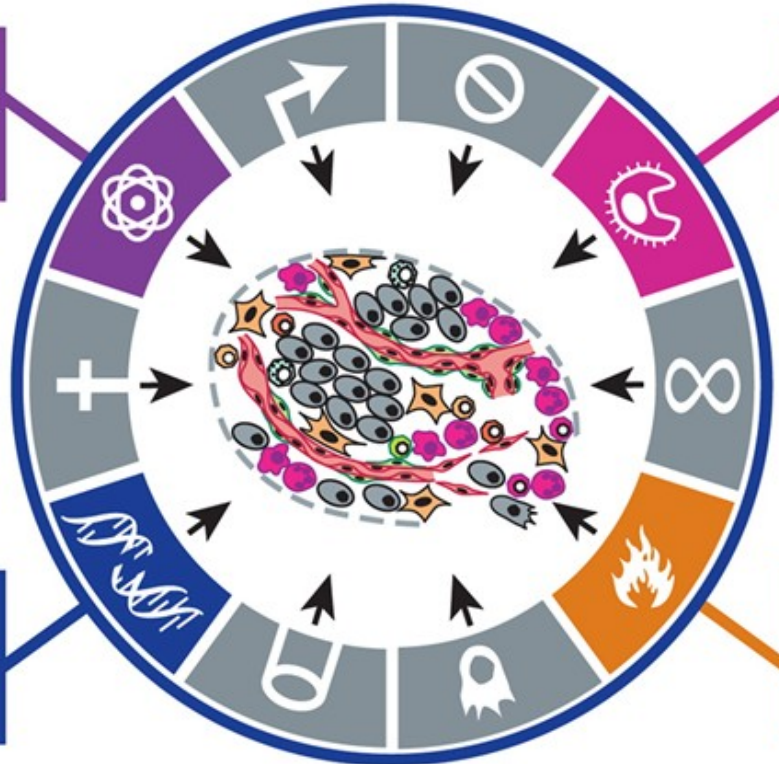
Deregulating cellular energetics

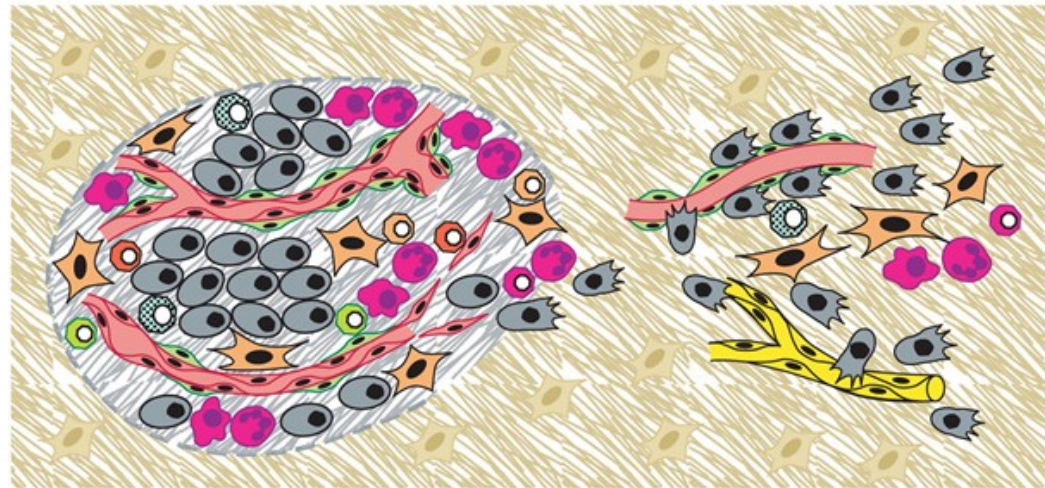
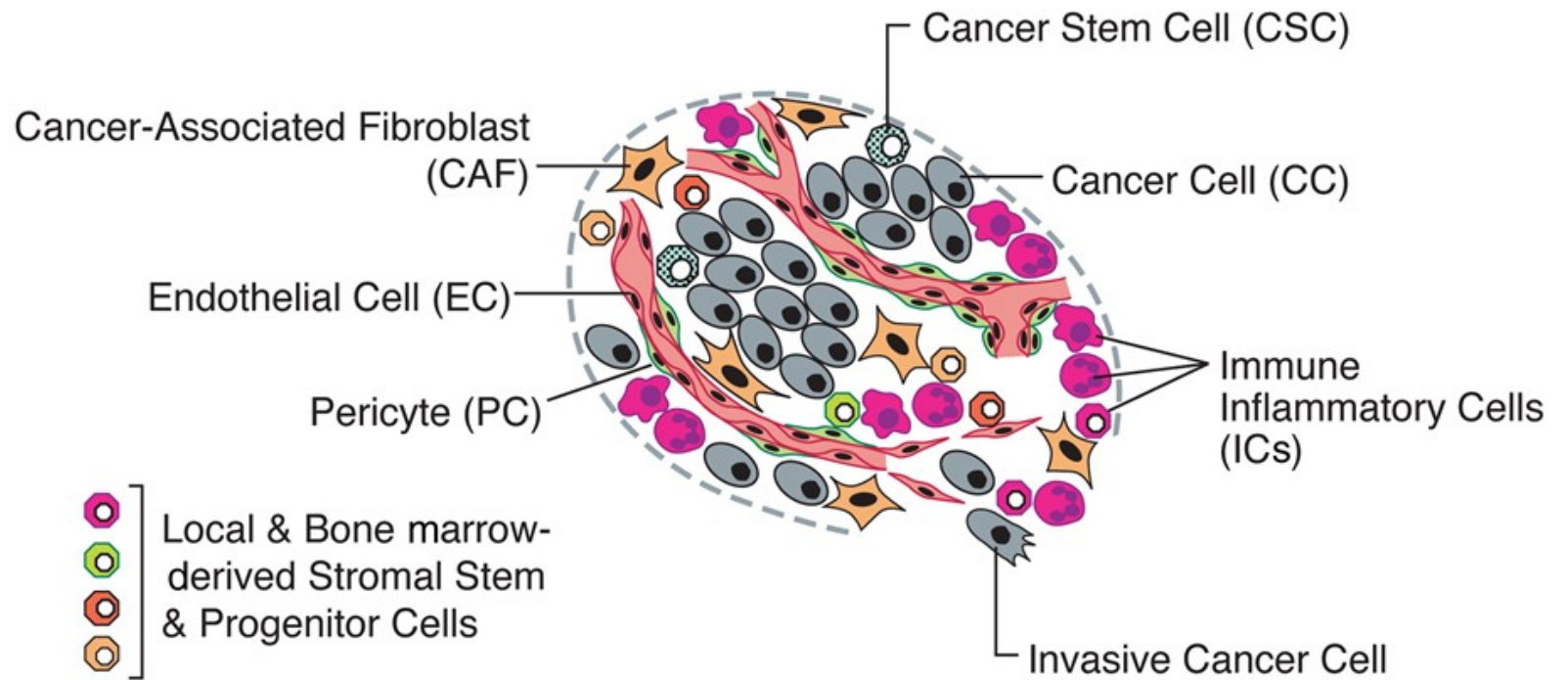
Avoiding immune destruction

Genome instability and mutation

Tumor-promoting Inflammation

Enabling Characteristics



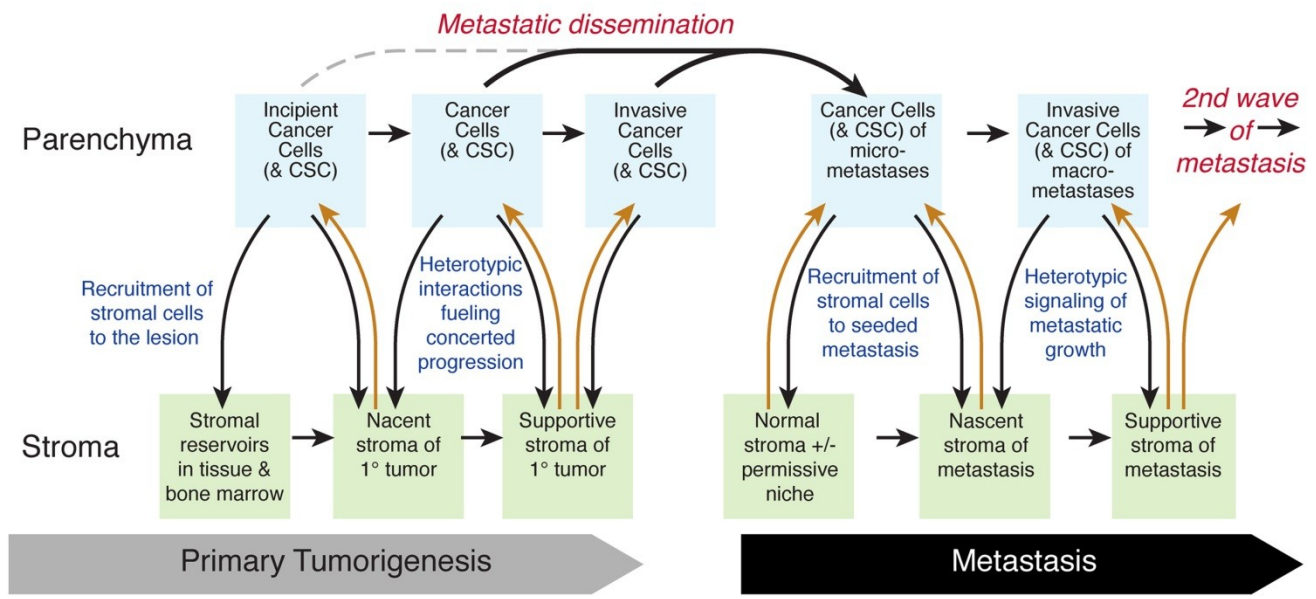
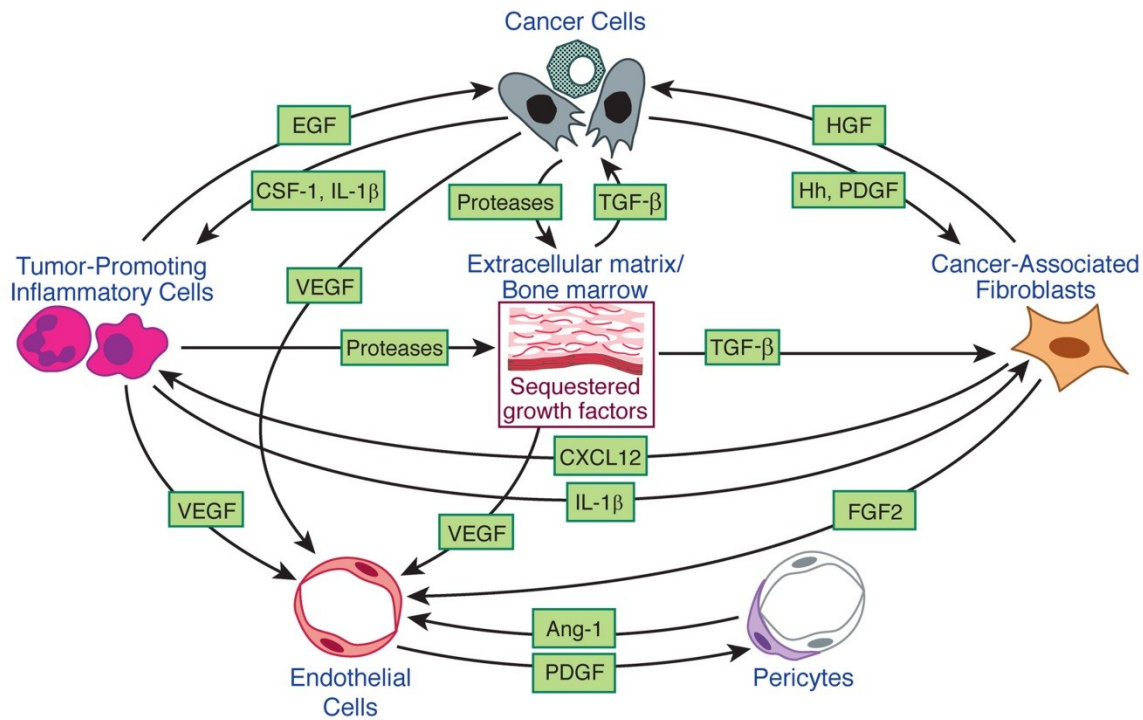


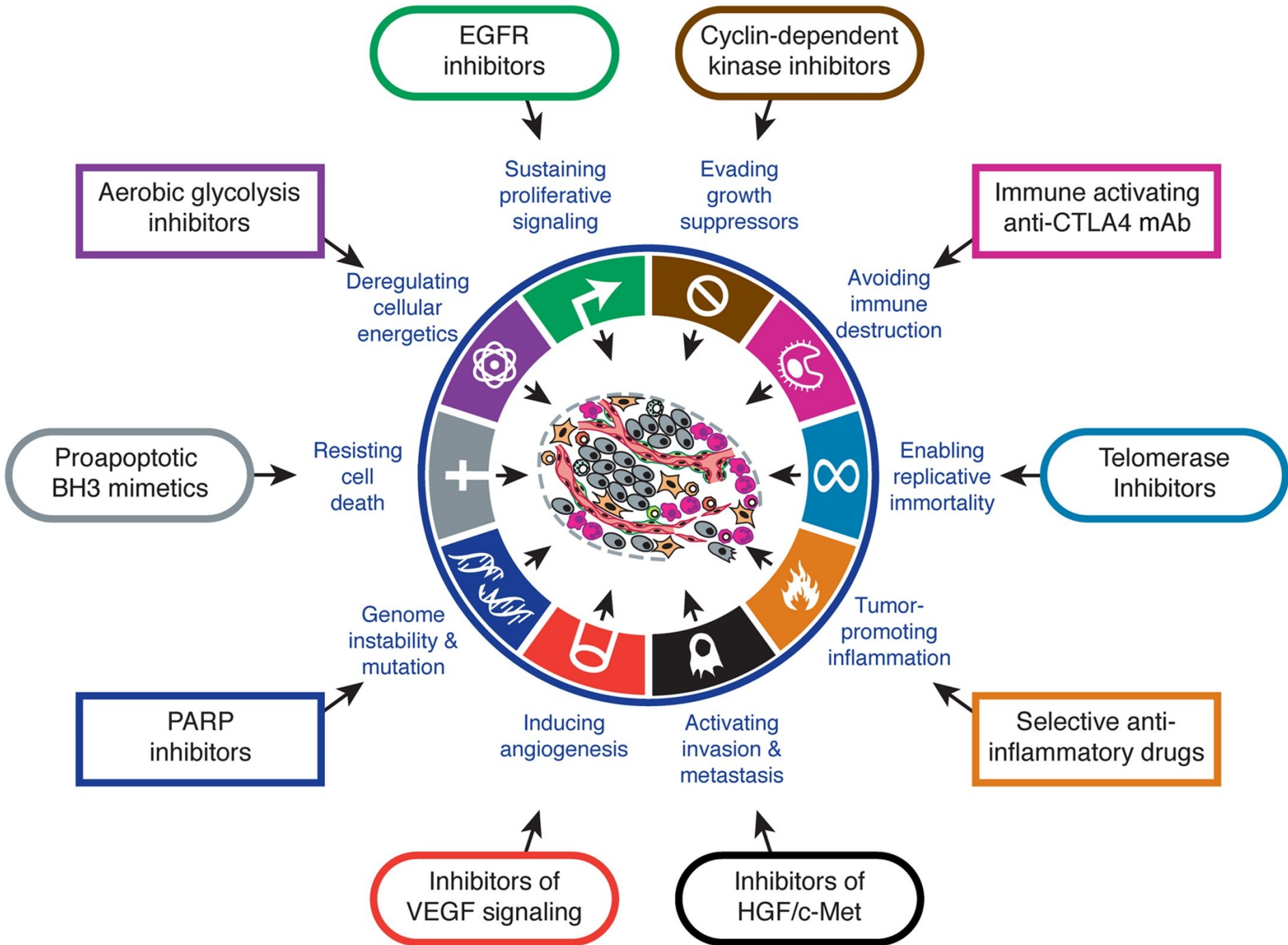
Core of Primary Tumor microenvironment

Invasive Tumor microenvironment



Metastatic Tumor microenvironment





In oncology, therapeutic blockade of CTLA-4 and PD-1 are examples of:

- A) radiotherapy
- B) chemotherapy
- C) specific immunotherapy
- D) non-specific immunotherapy
- E) adoptive cell therapy

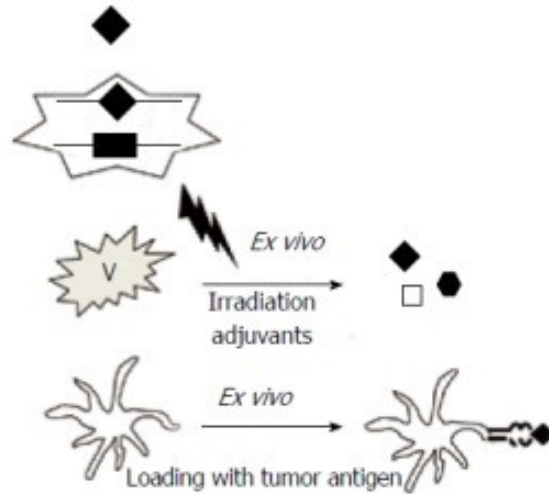
A Vaccination

Tumor antigen

Vectorized tumor antigen or DNA

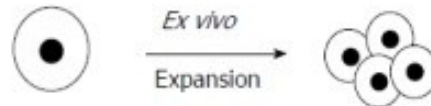
Irradiated autologous tumor cell

Autologous dendritic cells



B Adoptive cell therapy

Extracted tumor infiltrating lymphocytes

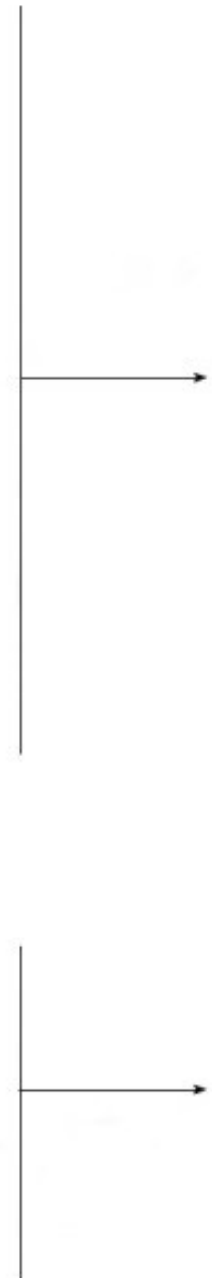


C Non specific immunotherapy

Stimulation of immunity: inflammatory cytokines



Blockade of inhibitory pathways: monoclonal antibodies

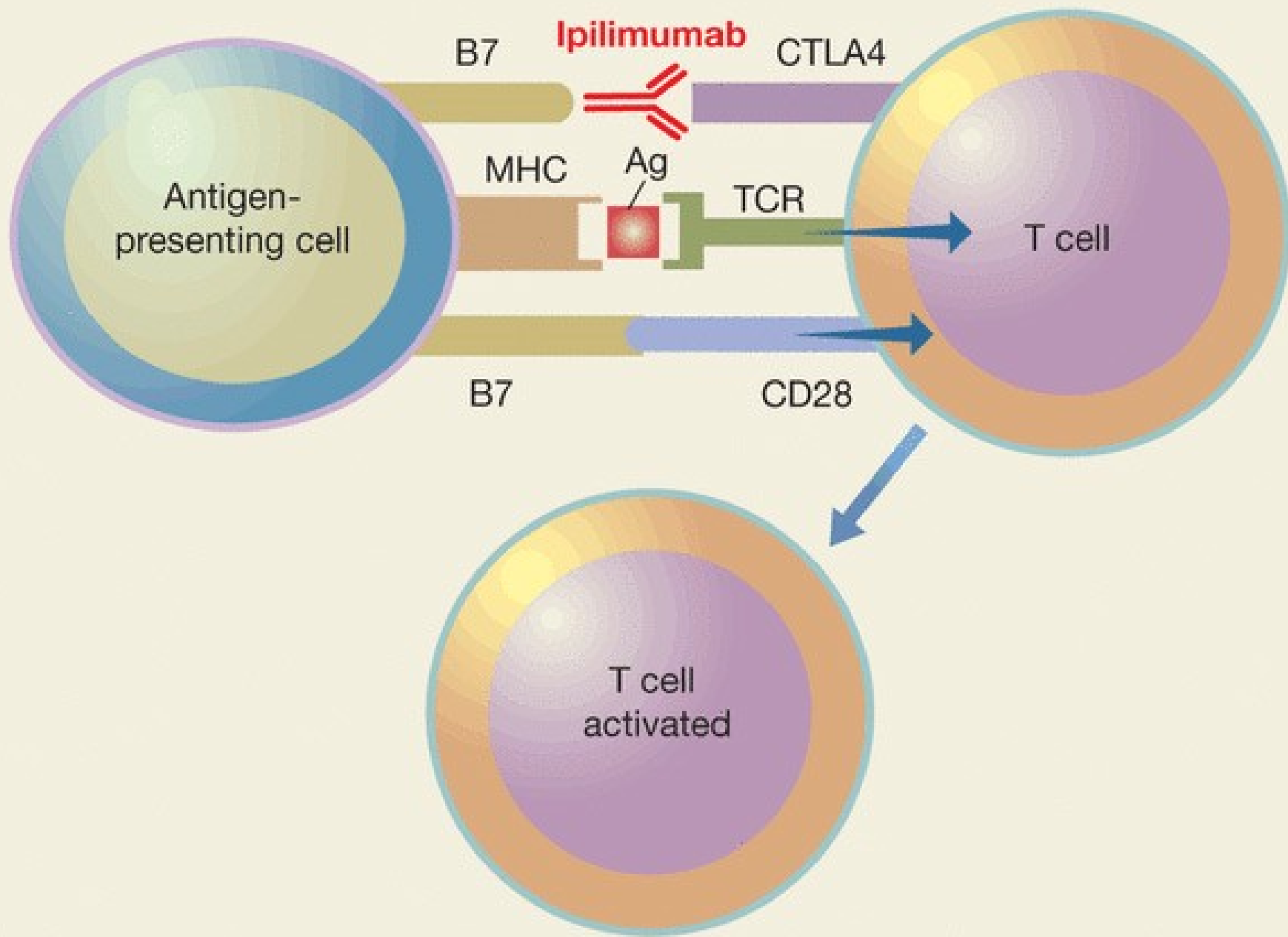


Milestones of anticancer therapy

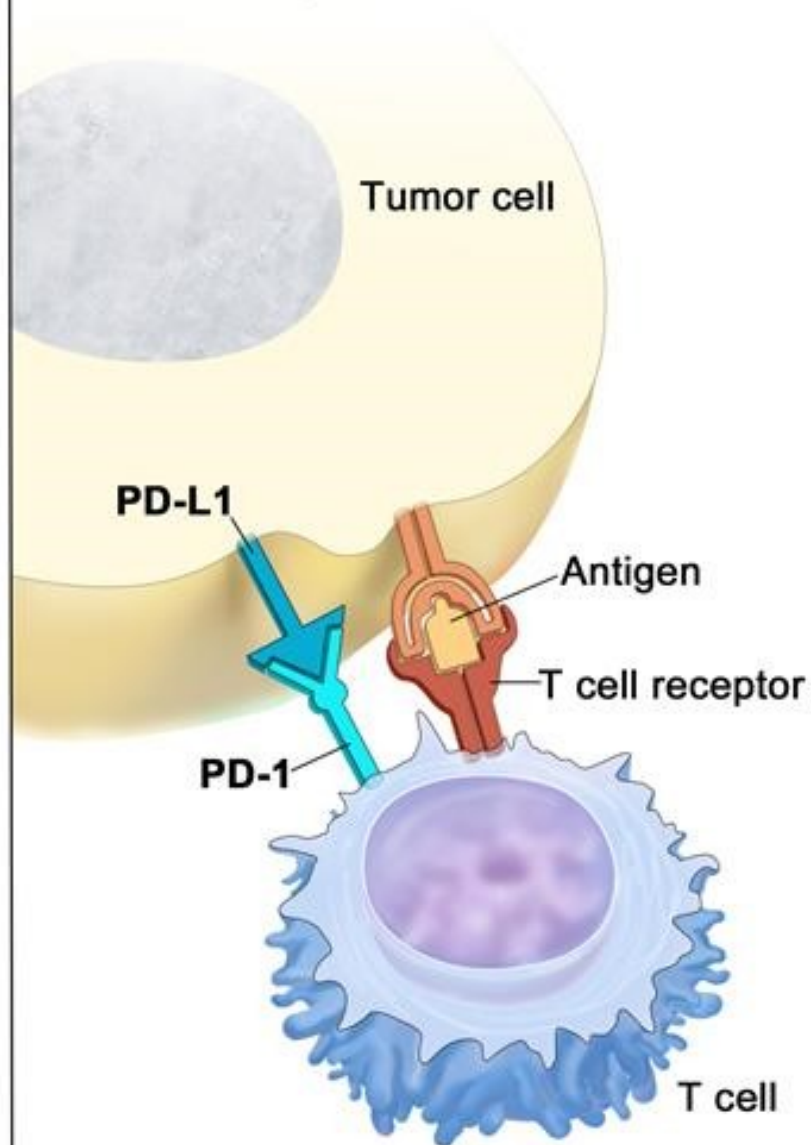
- Ionizing radiation
- Chemotherapy
- Immunotherapy (vaccines, **blockade of immune checkpoints**)
- Cancer Immunotherapy Named Science Magazine “Breakthrough of the Year” 2013

Immune checkpoints (negative feedback in immune reactions – downregulate immune responses)

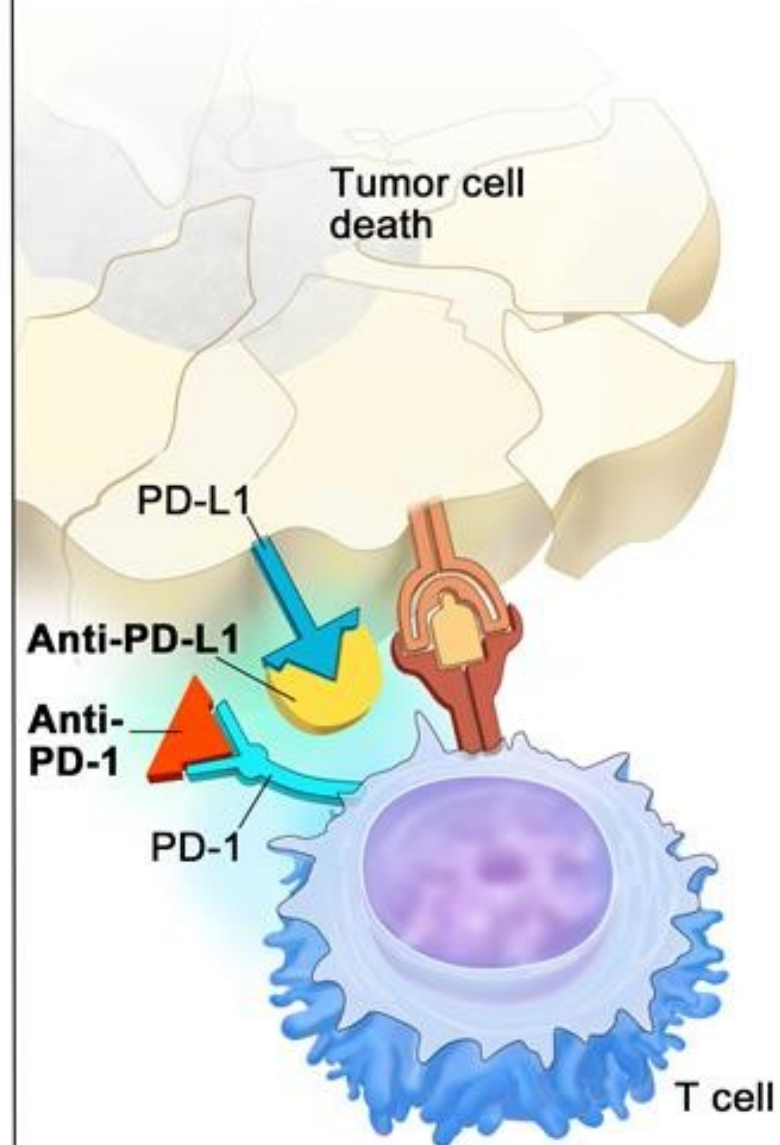
- Normally prevents autoimmune reactions
- Priming, central phase: **CTLA-4** (Cytotoxic T Lymphocyte Associated Protein 4)
- Effector, peripheral phase: **PD-1**
(Programmed Death receptor)

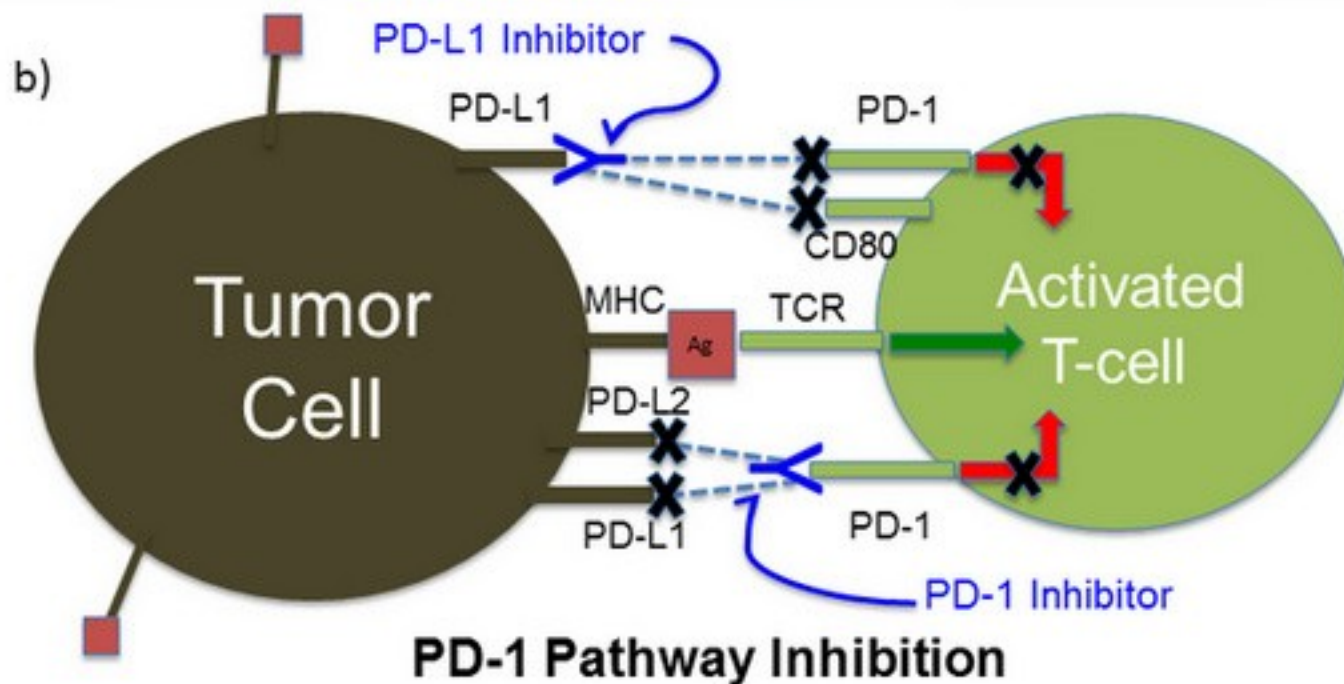
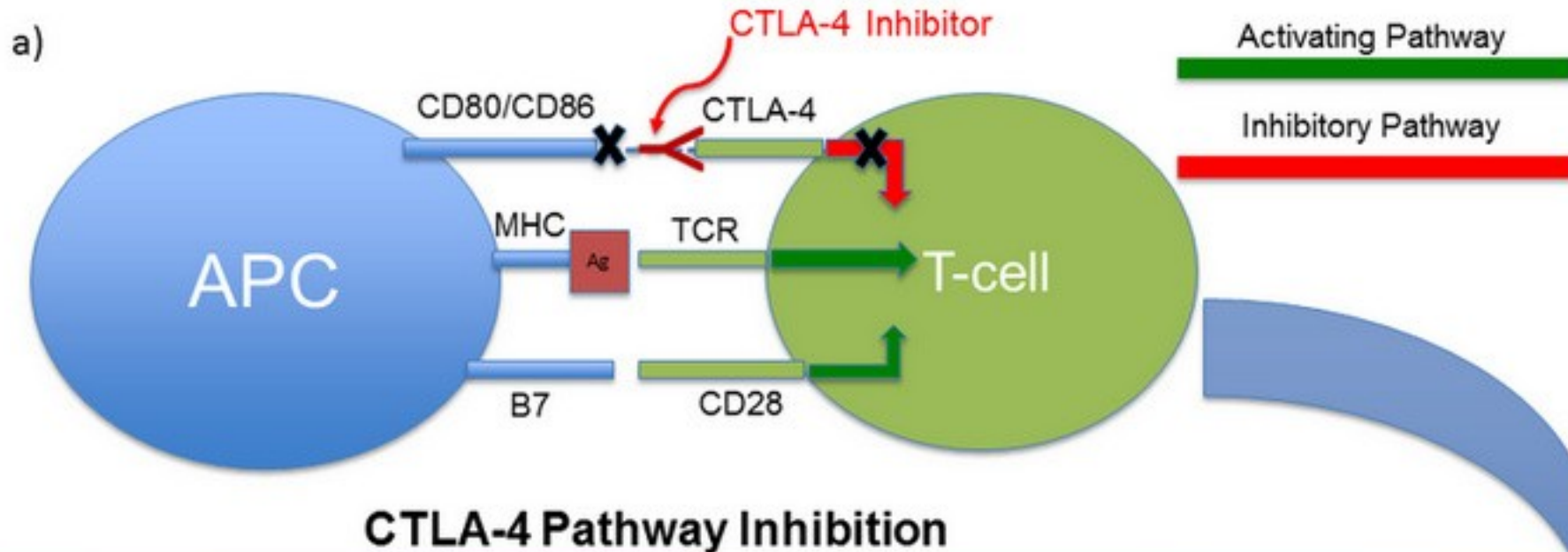


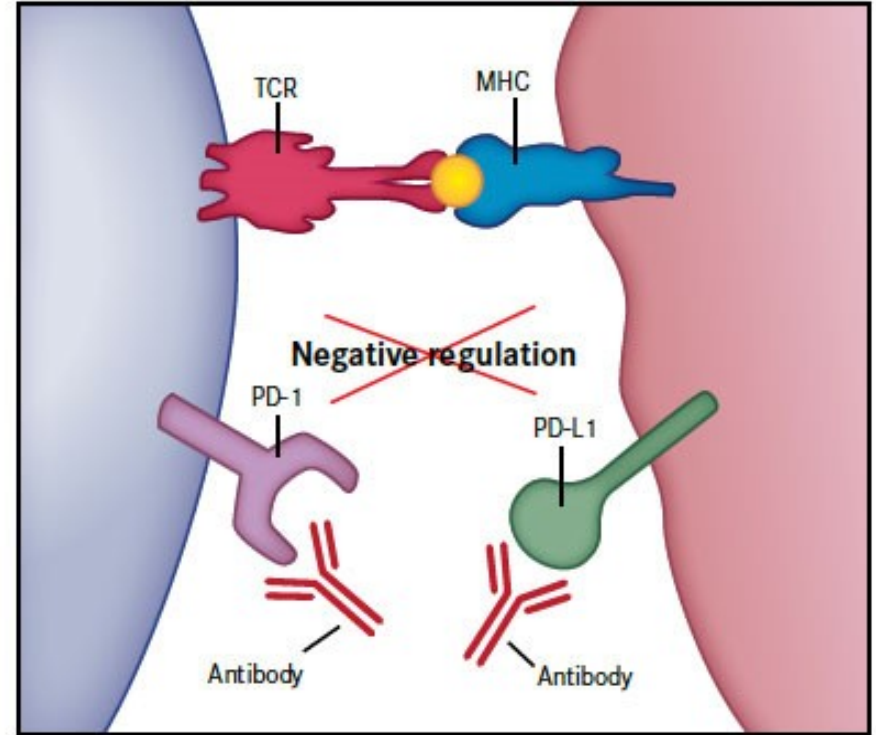
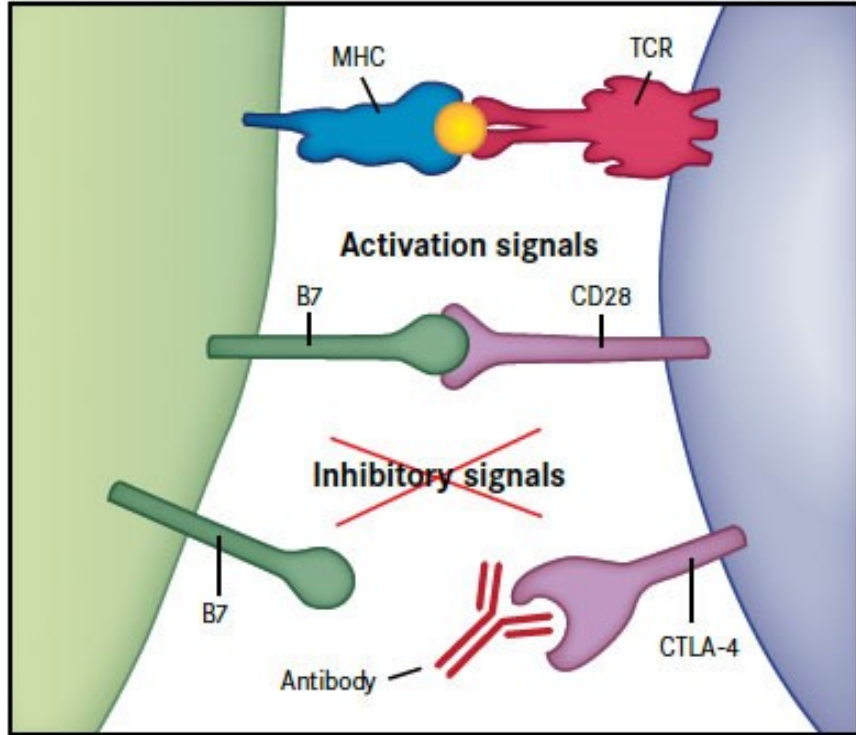
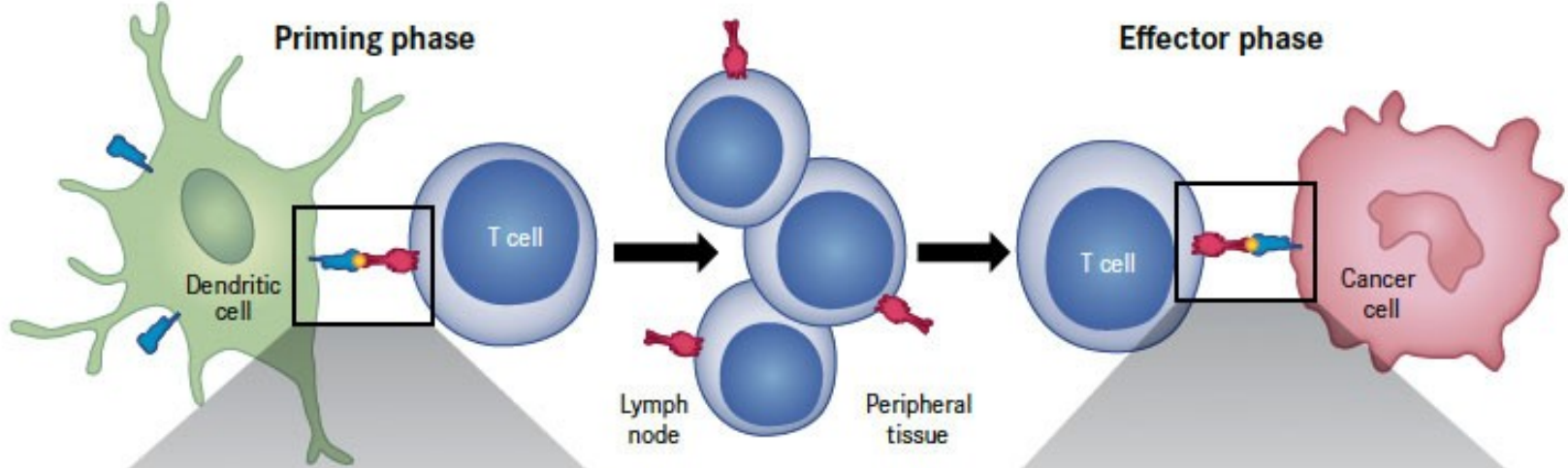
PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell

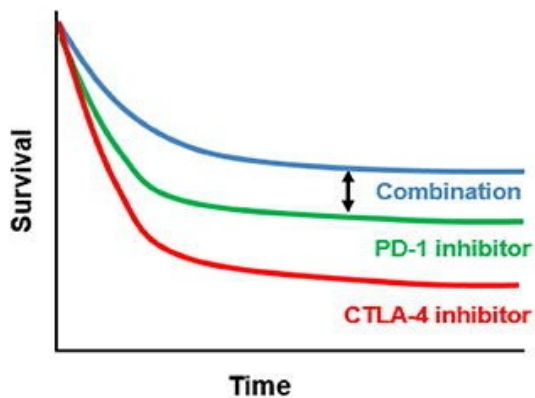
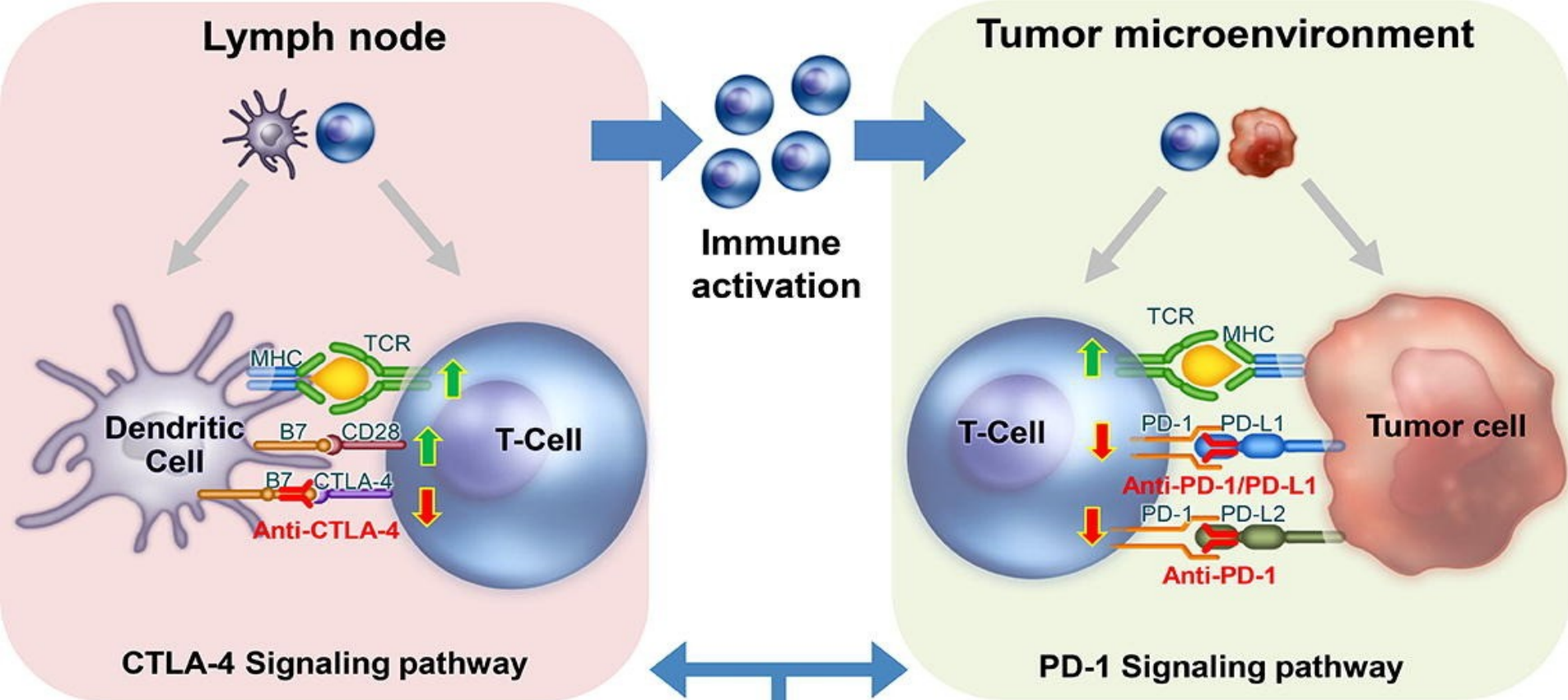


Blocking PD-L1 or PD-1 allows T cell killing of tumor cell



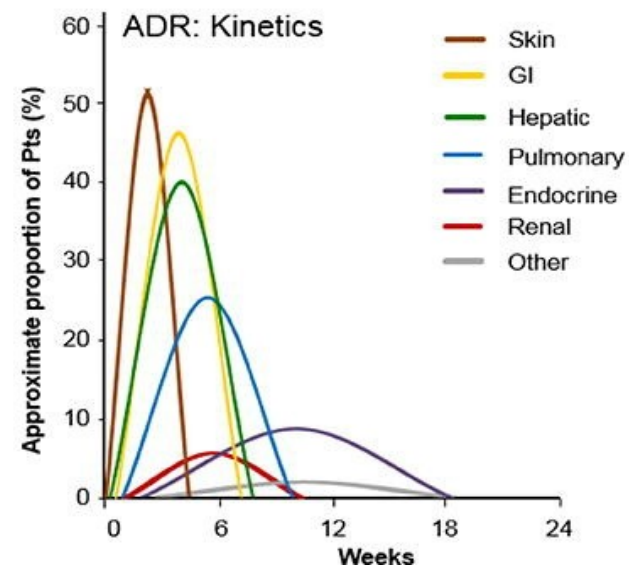






Combined ICB:

- Higher efficacy
- More frequent & more severe ADRs



- CTLA-4: ipilimumab...
- PD-L1: nivolumab...
- Disadvantages:
- So far so called financial toxicity (even in the most developed countries)
- Signs of autoimmunity

