Hallmarks of cancer

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Outline of the lecture

1. **Natural history: clinical perspective**
2. **Multistage carcinogenesis**
3. **Natural history: histological perspective**
4. **Natural history: tumor dissemination**
5. **Biology of cancer : basics**
6. **Cancer Hallmarks**

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2. Multistage carcinogenesis
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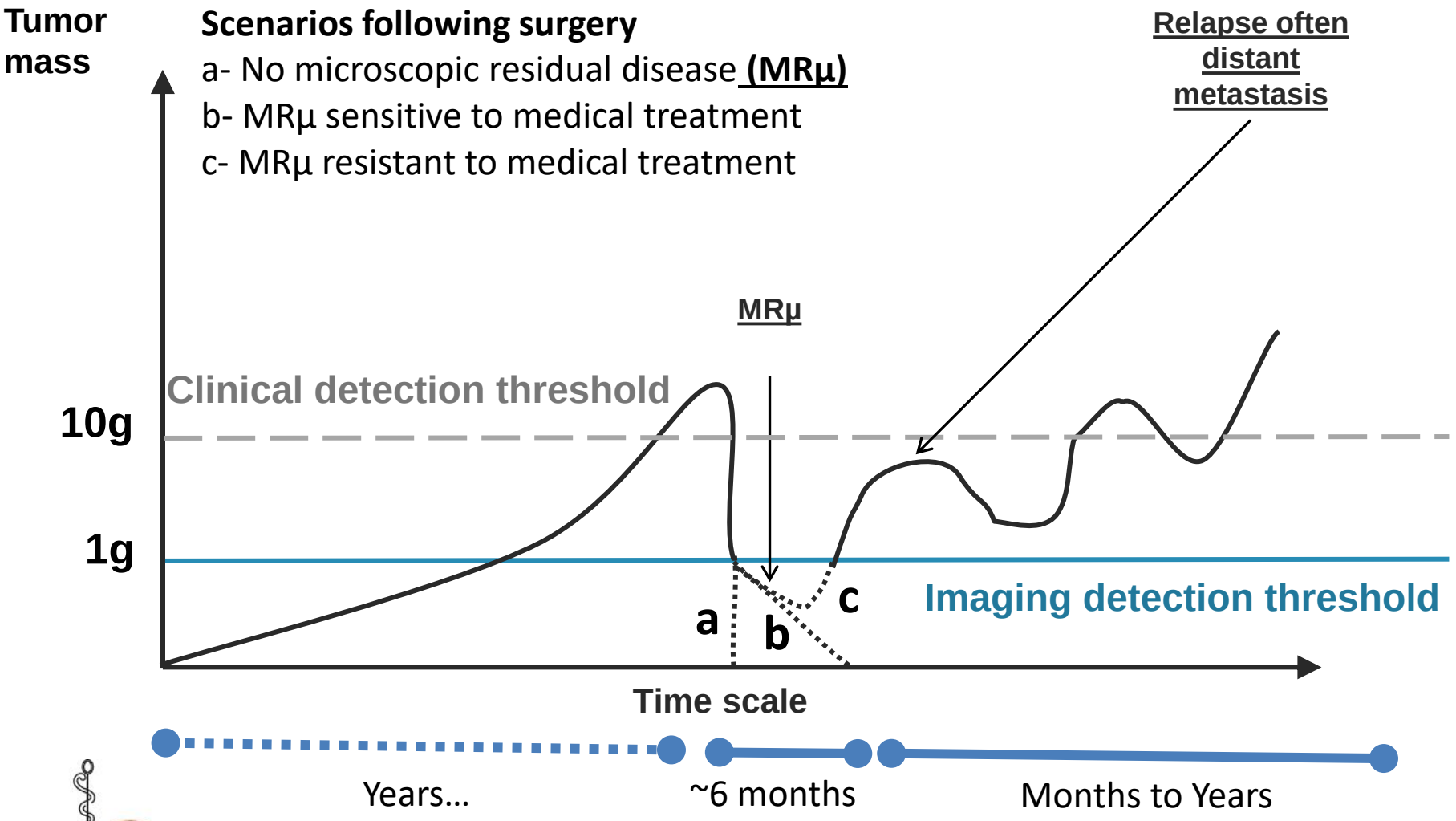
4. Natural history: tumor dissemination
5. Biology of cancer : basics
6. Cancer Hallmarks

1. Natural History: clinical perspective



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2. Multistage carcinogenesis

- **Immortalisation**
  - Loss of replicative senescence

Followed by

- **Transformation**
  - Loss of contact inhibition
  - Anchorage-independent proliferation
  - Ability to form tumors after transplantation into immunodeficient mice

2. Multistage carcinogenesis

- **Three "classical" steps**

  - **Initiation**: rapid, irreversible, and heritable DNA damage (physical, chemical, or viral factors) → precancerous lesions

  - **Promotion**: prolonged, repeated, or continuous exposure to mitogenic factors → clonal expansion

  - **Progression**: acquisition of biological characteristics ("hallmarks") promoting local and distant invasion

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3. Natural history: histological perspective

- **Stages of epithelial transformation (carcinogenesis)**
  - 'Normal'
  - Hyperplasia
  - Dysplasia (low-grade, intermediate-grade, high-grade)
  - *In situ* carcinoma
  - Invasive carcinoma

3. Natural history: histological perspective

- **Stages of epithelial transformation (carcinogenesis)**
  - 'Normal'
  - **Hyperplasia: abnormal increase in the number of cells in a tissue or organ, without alteration of architecture or cytology**
  - Dysplasia (low-grade, intermediate-grade, high-grade)
  - *In situ* carcinoma
  - Invasive carcinoma

3. Natural history: histological perspective

- **Stages of epithelial transformation (carcinogenesis)**
  - 'Normal'
  - Hyperplasia
  - **Dysplasia (low-grade, intermediate-grade, high-grade): abnormalities in cell proliferation and differentiation, leading to architectural tissue abnormalities and cytological atypia (mitoses, nuclear abnormalities); possible outcomes: stability, regression, or progression**
  - *In situ* carcinoma
  - Invasive carcinoma

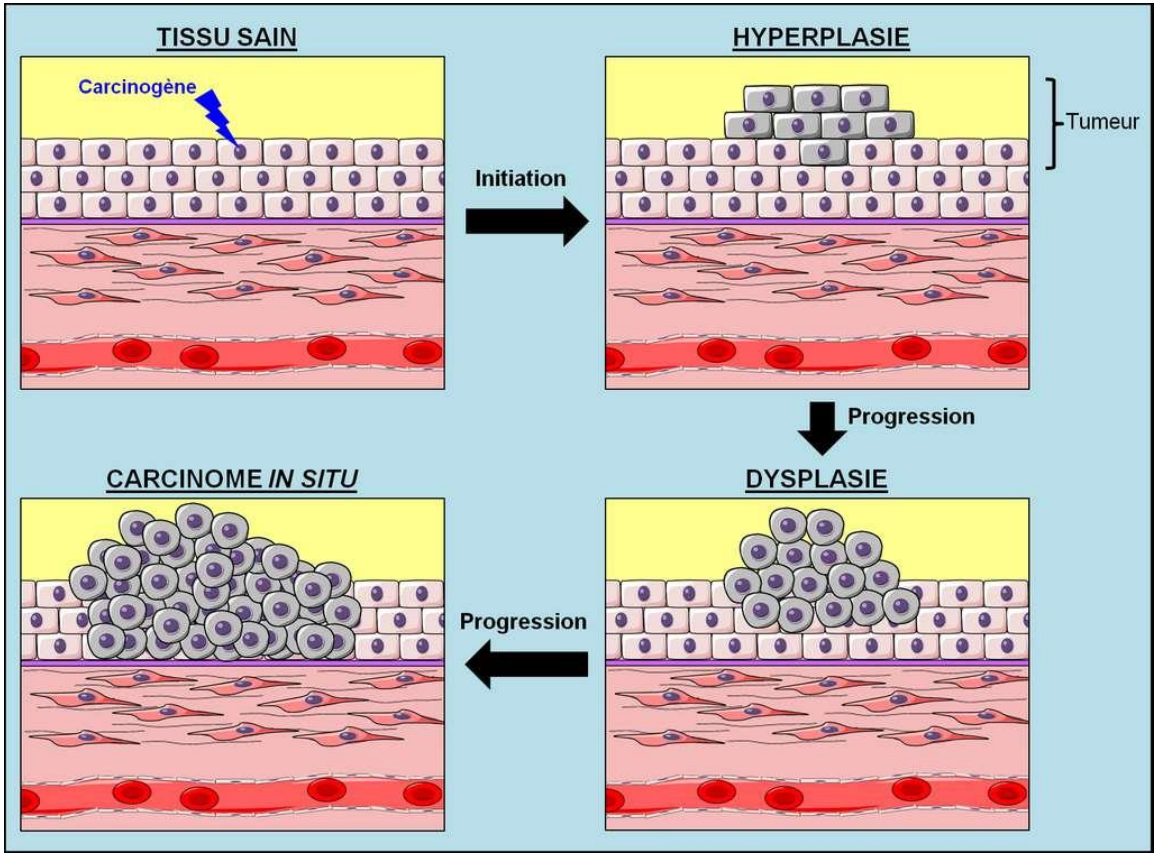
3. Natural history: histological perspective

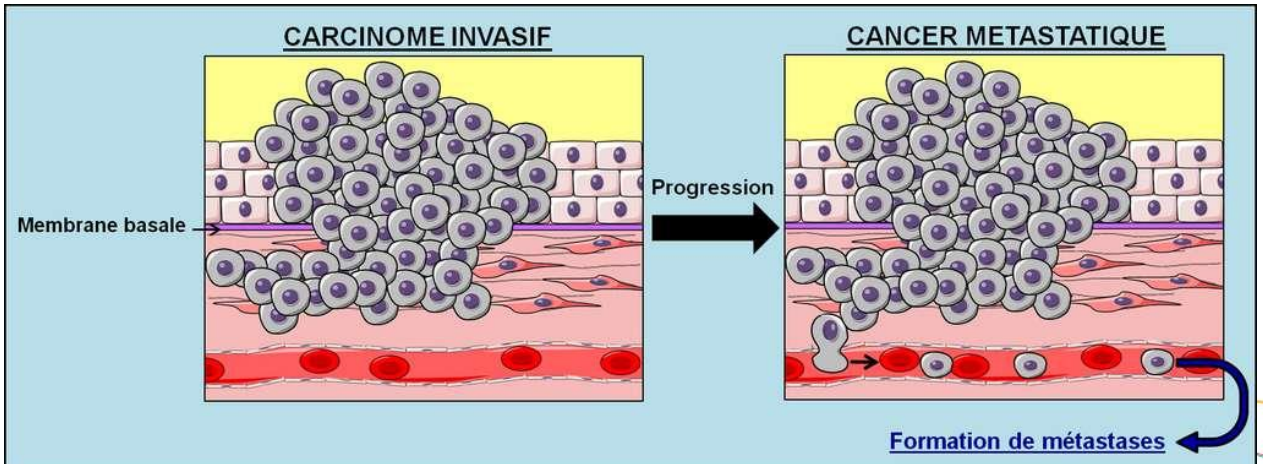
- **Stages of epithelial transformation (carcinogenesis)**
  - 'Normal'
  - Hyperplasia
  - Dysplasia (low-grade, intermediate-grade, high-grade)
  - **Carcinoma *in situ*: abnormalities in cell proliferation and differentiation associated with disorganized cellular architecture, without breaching the basement membrane (no stroma, no neoangiogenesis); possible outcomes: progression**
  - Invasive carcinoma

3. Natural history: histological perspective

- **Stages of epithelial transformation (carcinogenesis)**
  - 'Normal'
  - Hyperplasia
  - Dysplasia (low-grade, intermediate-grade, high-grade)
  - In situ carcinoma
  - **Invasive carcinoma: breach of the basement membrane and invasion of the underlying connective tissue; stroma containing mesenchymal and immune components as well as neoangiogenesis; no spontaneous regression**

Schematic histological modifications during carcinogenesis

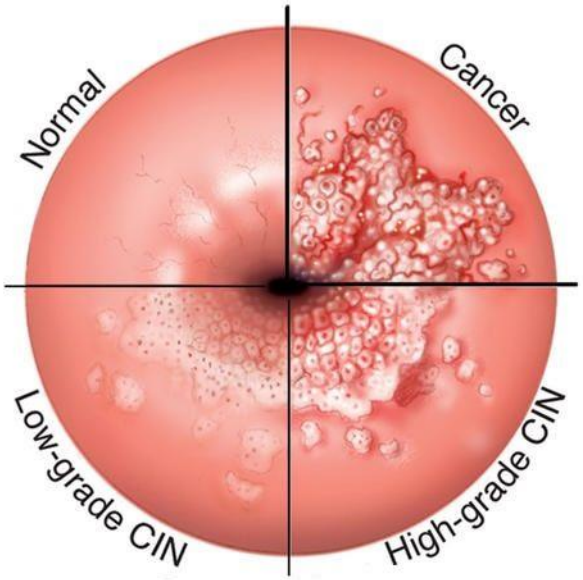


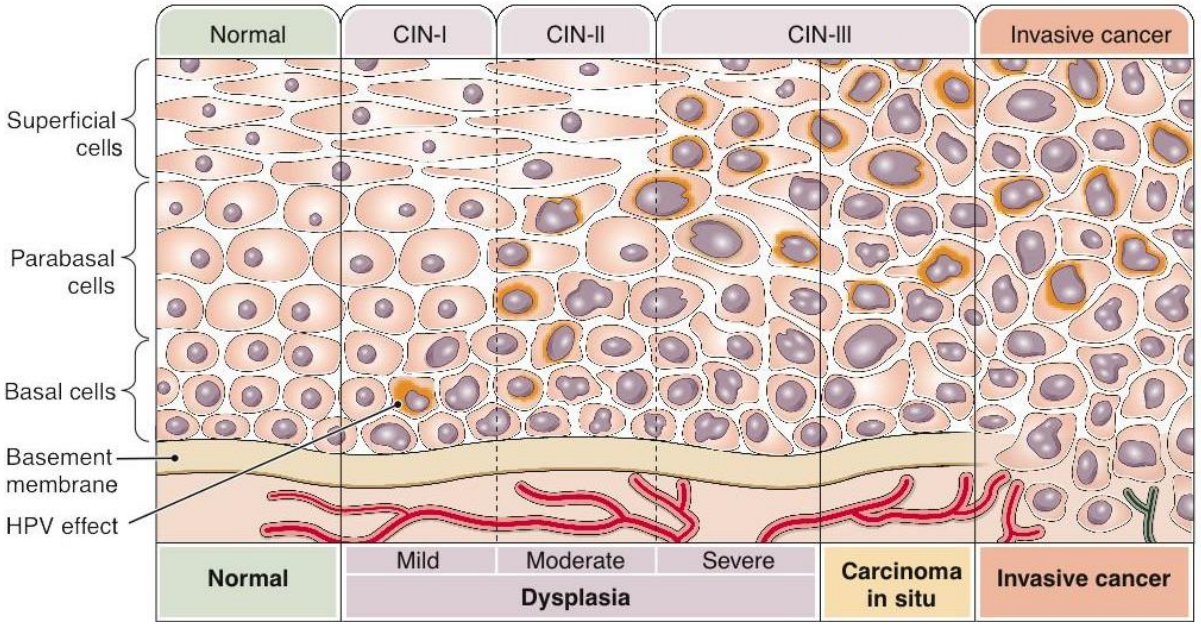


Grégory Ségala, Marc Poirot. https://www.futura-sciences.com/sante/dossiers/medecine-cancer-mecanismes-biologiques-1453/

Ex. Colposcopy and histological analysis

Cervical Intraepithelial Neoplasia (CIN)





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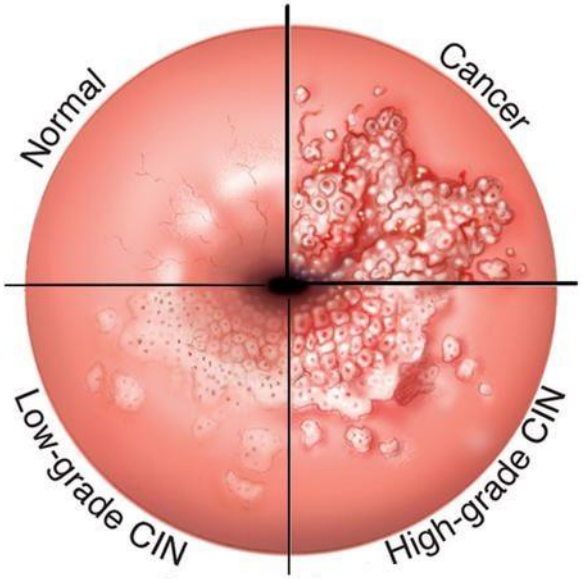

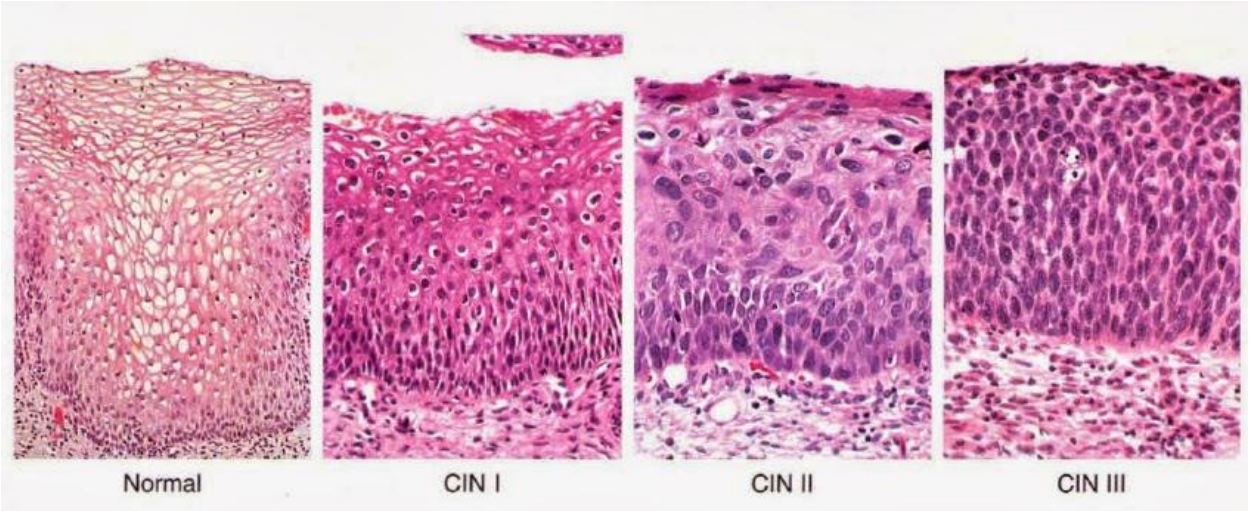

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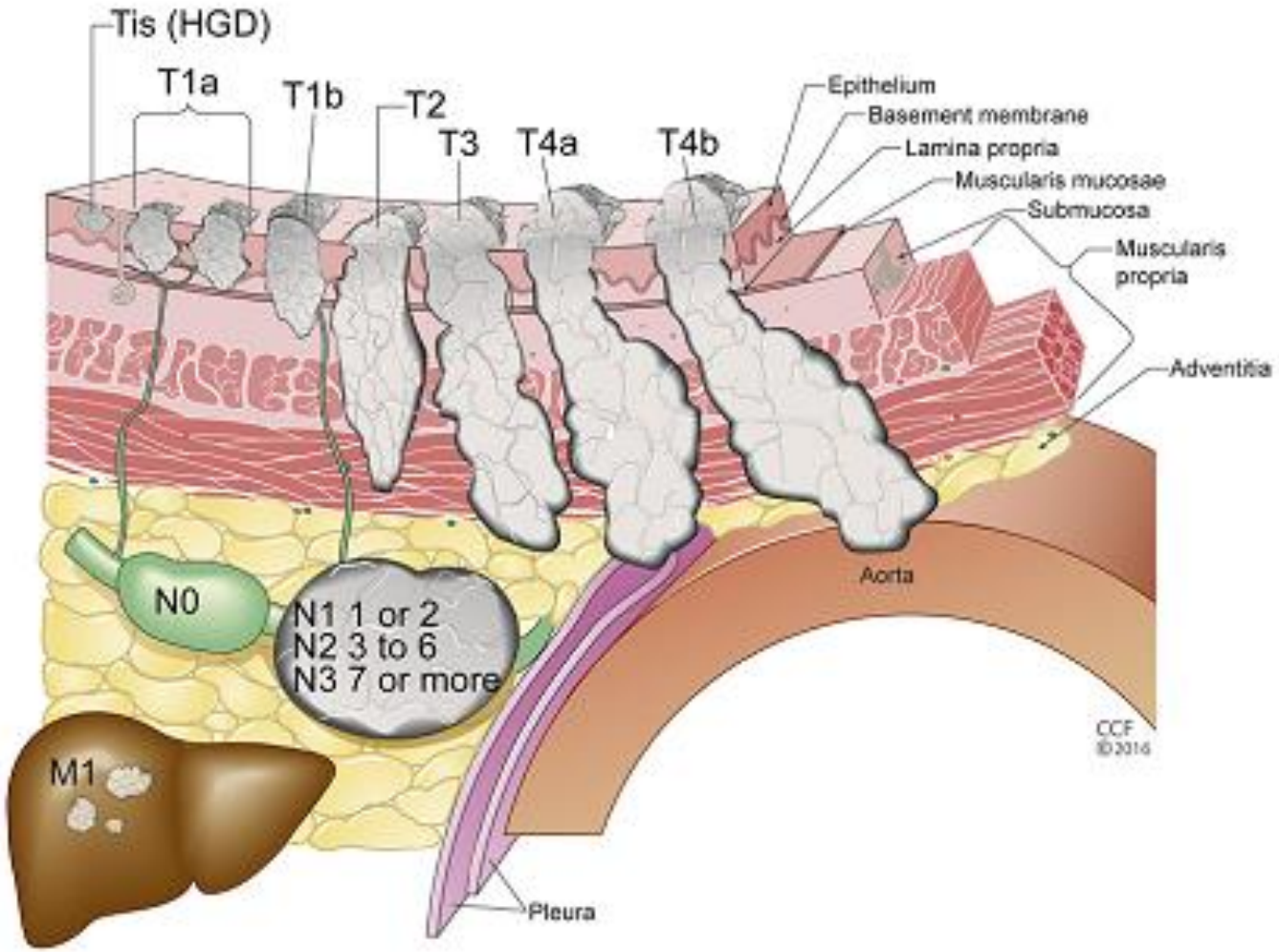
5. Natural history: tumor dissemination

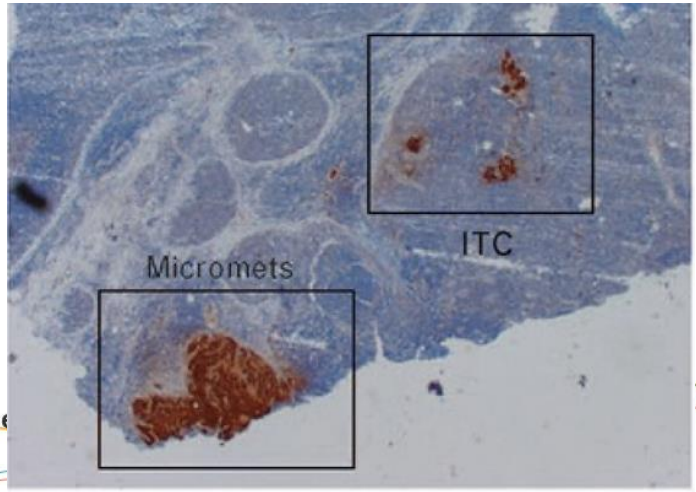
- **Locoregional invasion**
  - Invasion of adjacent tissues by contiguity
  - Invasion of blood and lymphatic vessels
  - Perineural invasion

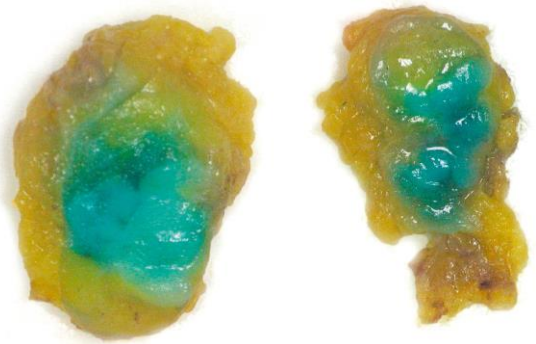
- **Dissemination and metastasis formation**
  - Via the lymphatic route: sentinel lymph node = first nodal relay
  - Via the bloodstream depending on portal or caval venous drainage
  - Intra-ductal spread (urinary tract)
  - Intra-cavitary spread (pleura, peritoneum, meninges)
  - Preferential metastatic sites depending on the primary tumor type

Dissemination et TNM classification (esophagus)



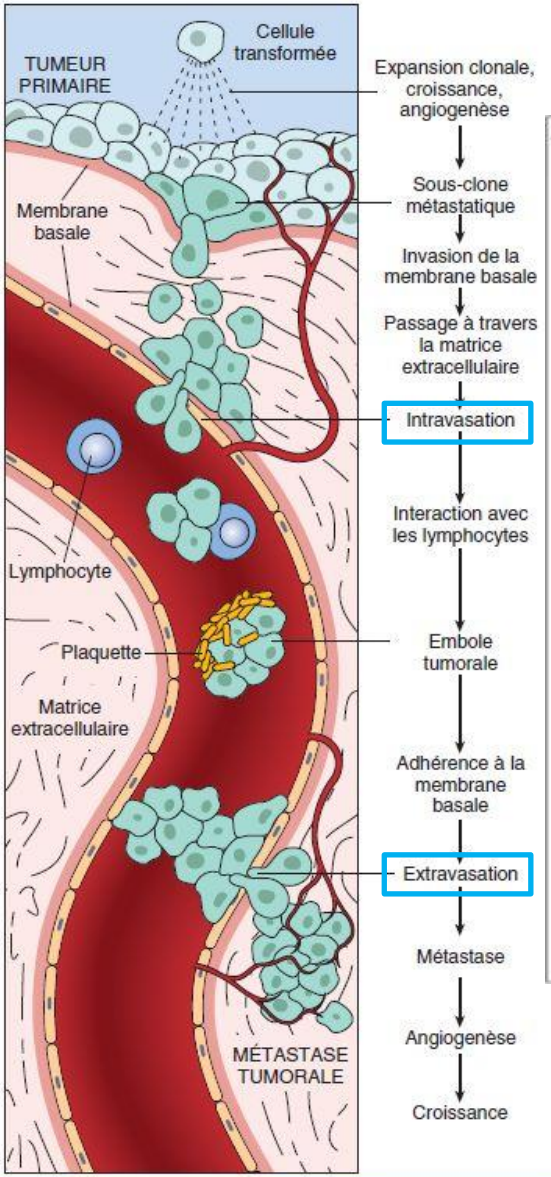
Lymphatic dissemination and sentinel node

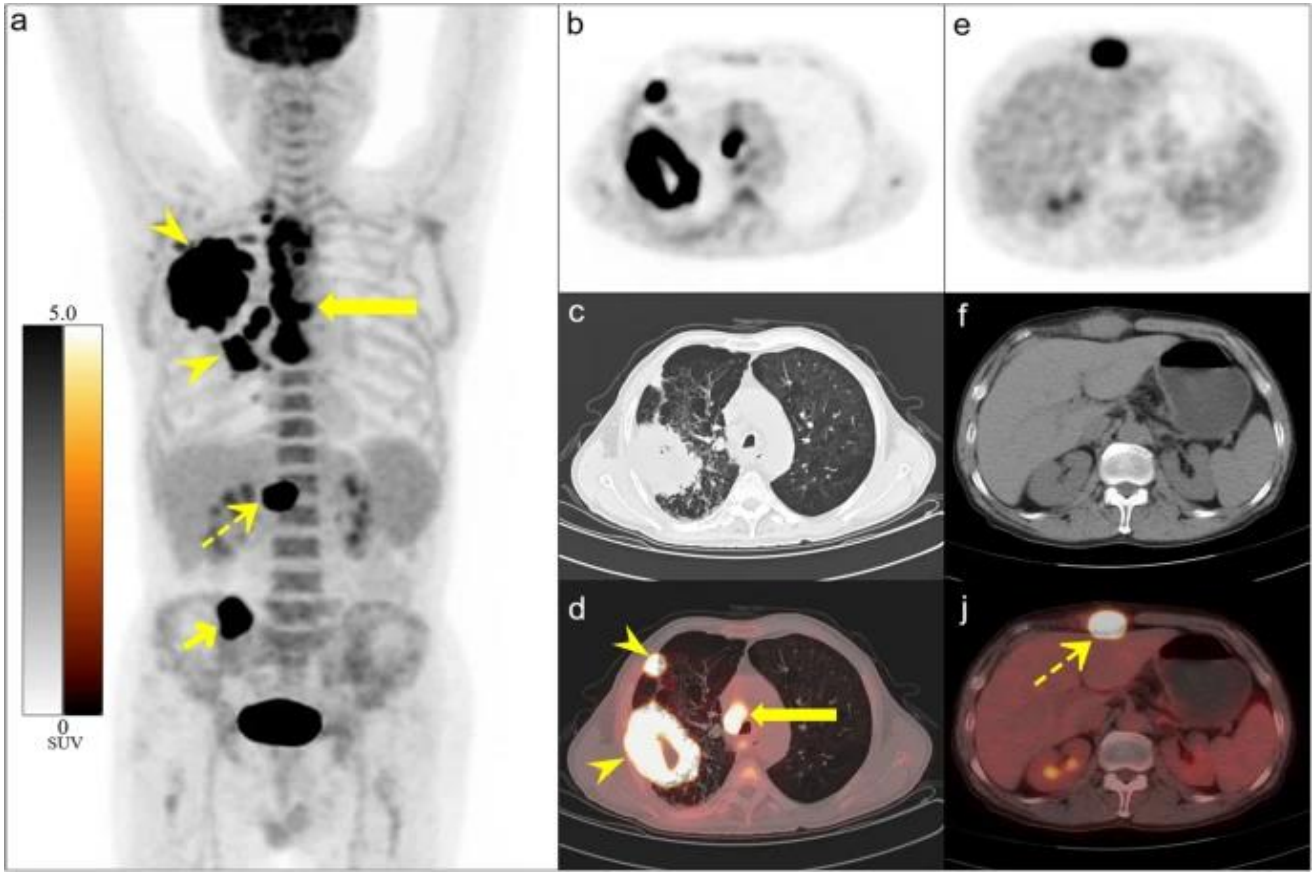




Faculté de Médecine Lyon Est

Lymphatic and blood dissemination





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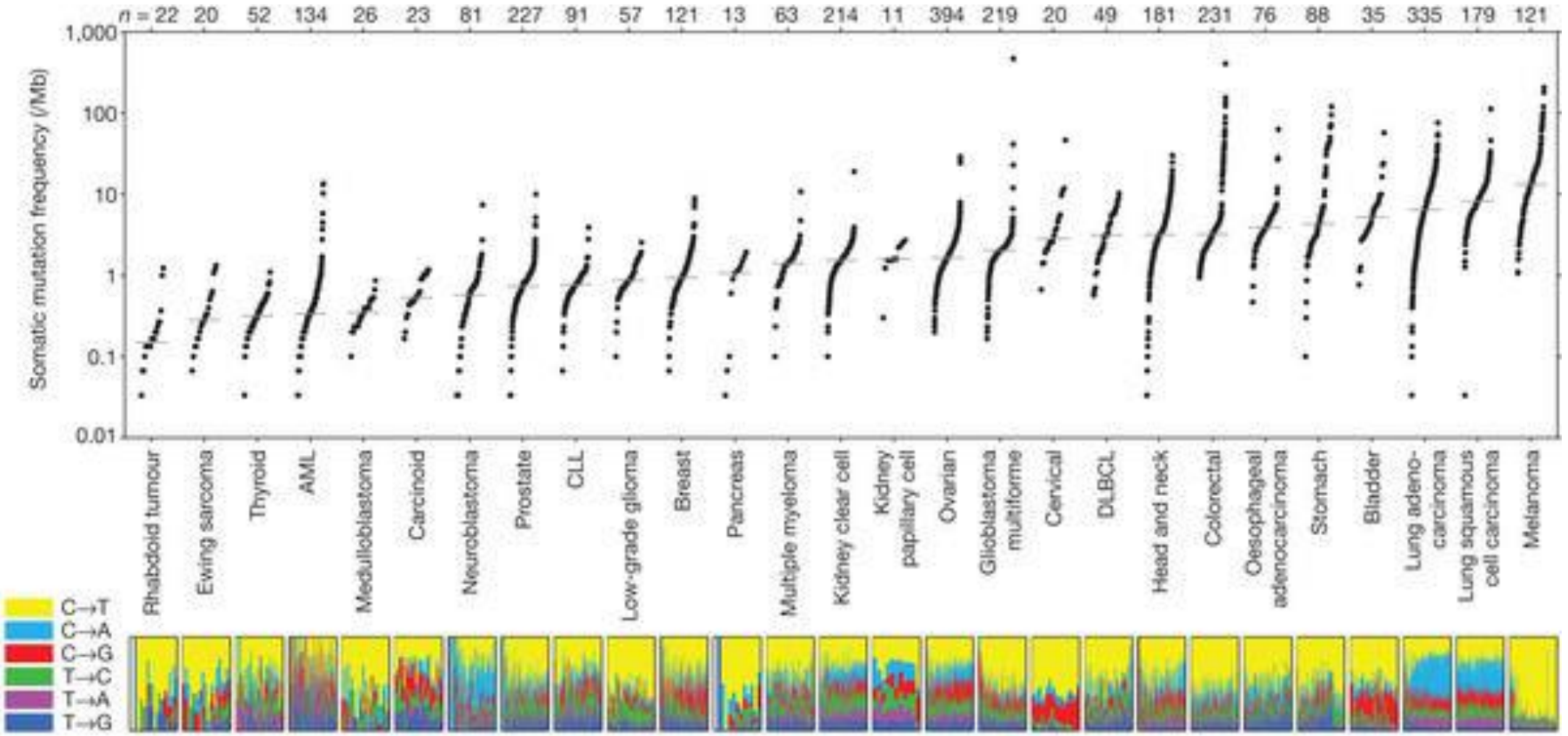
Cancer genetics (1)

- Cancer cells carry **multiple genetic abnormalities** that accumulate over successive cell divisions
- The **mutation rate varies** depending on the type of cancer; **tobacco and UV exposure** are associated with high mutational burdens
- In **some cases**, a **germ line genetic alteration** is present—inheritated from one parent, found in all cells of the individual, and predisposing to certain cancers (cancer predisposition)
- However, in **most cases**, **genetic abnormalities are somatic**, meaning they arise during the individual's lifetime and accumulate over time

Mutation burden plot



Cancer genetics (2)

- Genetic abnormalities may have **diagnostic**, **prognostic**, and **theranostic** value
- Genetic abnormalities that play a role in cancer development are called "**drivers**"; there are typically **5–10 per tumor**, affecting **proto-oncogenes** or **tumor suppressor genes**
- Other, **more frequent** genetic abnormalities reflect genomic instability and/or environmental exposures but do not contribute to cancer development; these are referred to as "**passengers**"

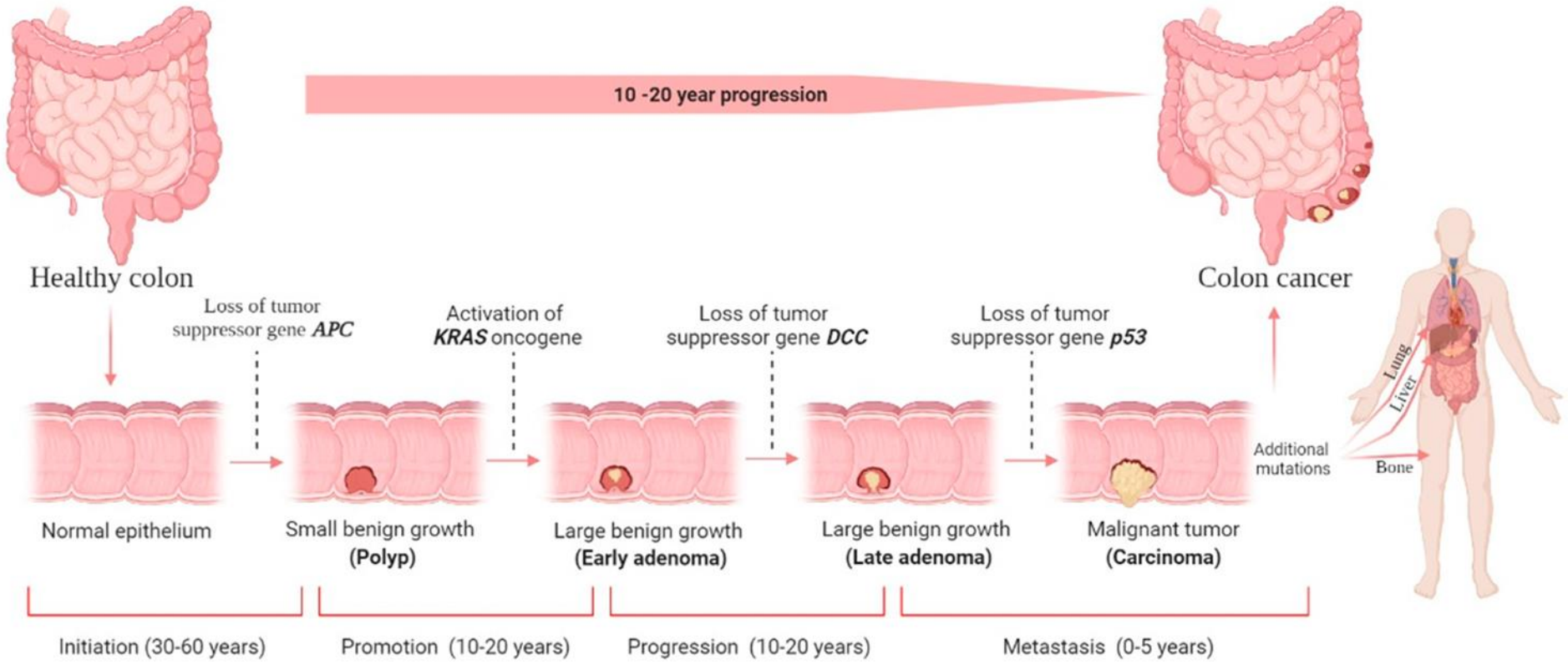
Oncogenes

- **Activated form** of a gene encoding proteins that promote the oncogenic process by inducing cell proliferation and/or survival
- **Proto-oncogene**: normal, non-mutated gene encoding proteins involved in proliferation and survival signaling (growth factors, intracellular signaling proteins, transcription factors…). Often homologous to transforming viral genes (v-onc)
- **Quantitative activation** (amplification) or **qualitative activation** (missense mutation, indel, translocation)
- A single mutated allele is sufficient: **dominant effect**
- May also be encoded by a viral genome infecting the cell

Tumor suppresor genes

- Gene whose **loss of function promotes the oncogenic process**
- Encodes proteins that:
  - **Control cell proliferation and survival**: RB1, TP53, PTEN…
  - **Regulate differentiation**: APC…
  - **Maintain genome integrity**: BRCA1…
- Inactivation may occur through **total or partial deletion**, **promoter methylation**, **nonsense mutation**, or f**rameshift mutation**
- Inactivation is generally **biallelic**
- **Tumor suppressor genes are involved in most hereditary cancer predisposition syndromes**

Combining histological and genetic of cancer perspectives



Lung adenocarcinoma

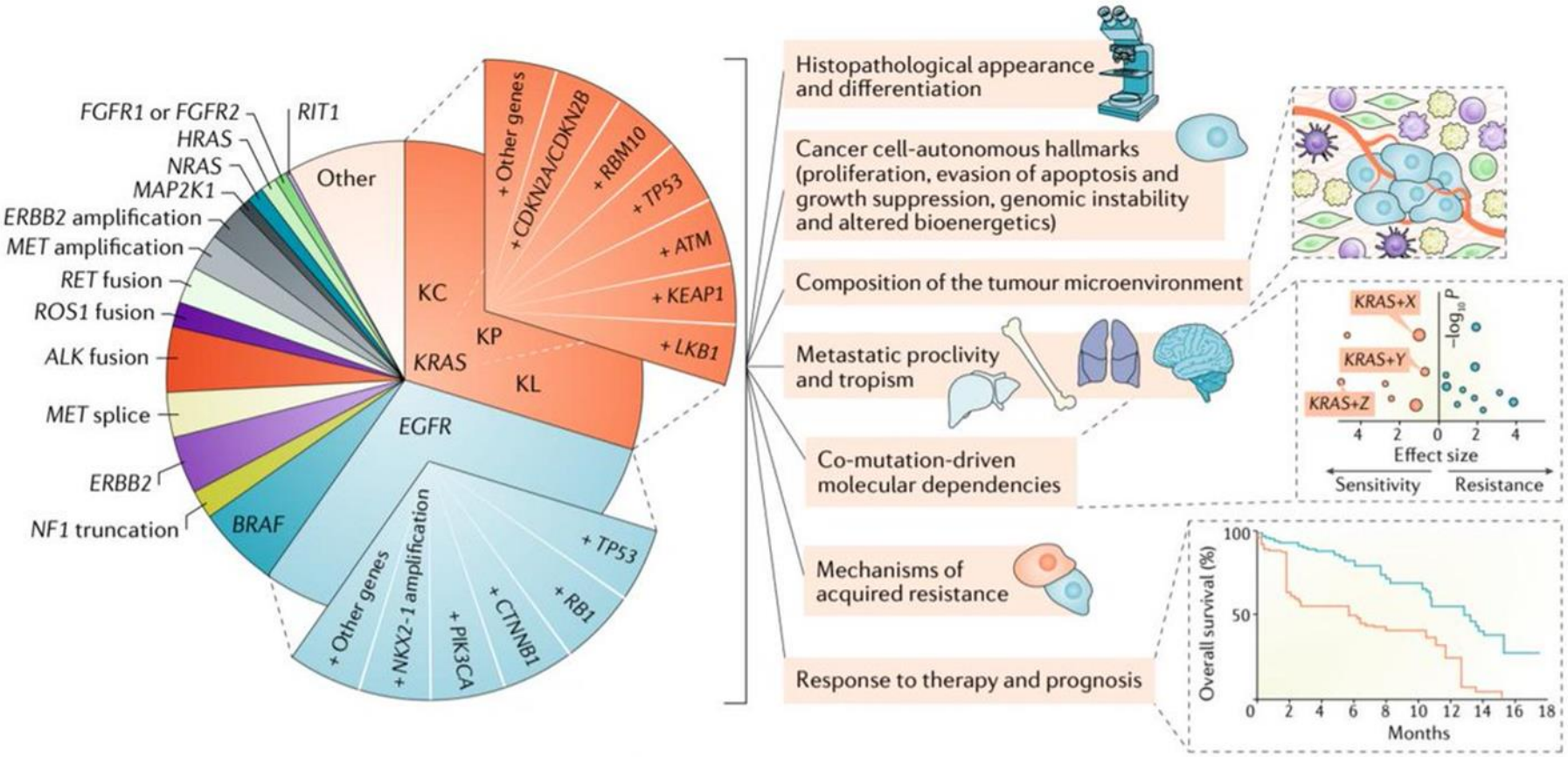
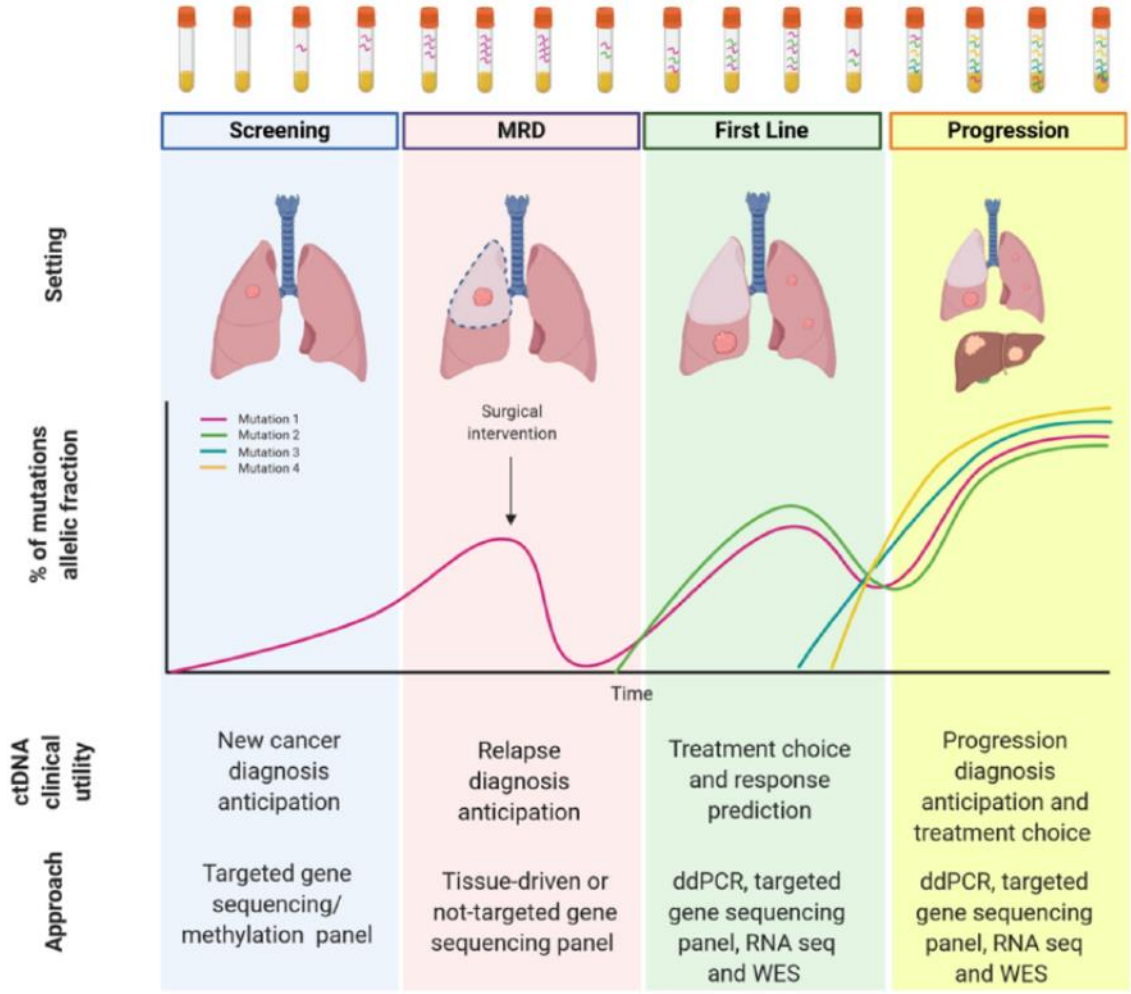


Fig. 4 | **Next-generation model for the molecular stratification of lung adenocarcinoma.** Oncogenic subgroups of


Screening
MRD
First Line
Progression
Setting
% of mutations allelic fraction
Mutation 1
Mutation 2
Mutation 3
Mutation 4
Surgical intervention
Time
ctDNA clinical utility
New cancer diagnosis anticipation
Relapse diagnosis anticipation
Treatment choice and response prediction
Progression diagnosis anticipation and treatment choice
Approach
Targeted gene sequencing/ methylation panel
Tissue-driven or not-targeted gene sequencing panel
ddPCR, targeted gene sequencing panel, RNA seq and WES
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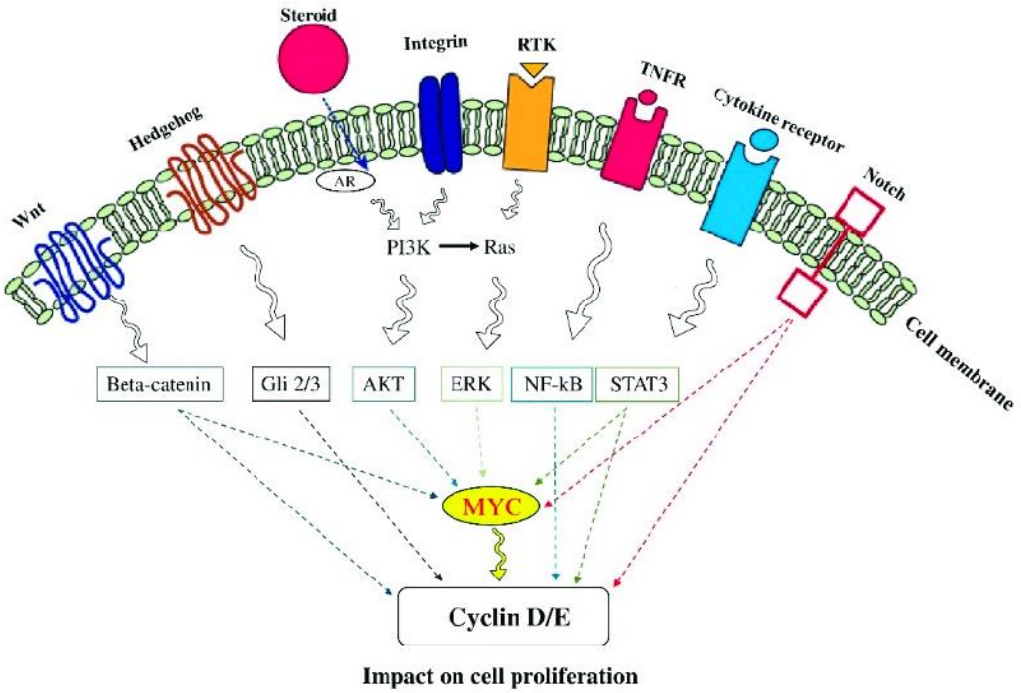
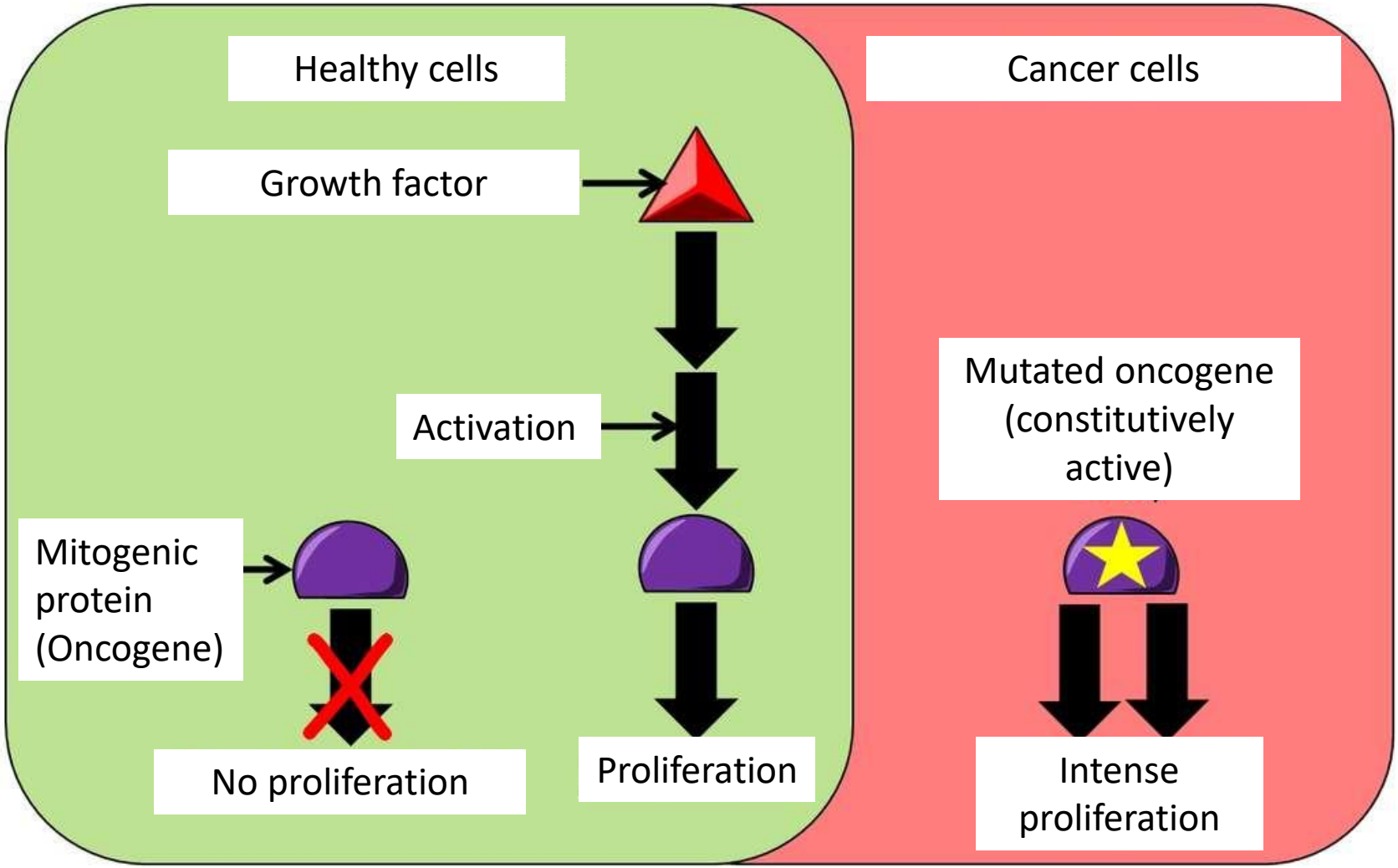
Signaling pathways regulating cell proliferation

- Proliferation is an essential step in cancer development
- The constitutive stimulation of signal transduction pathways can promote cancer development
- Abnormal cell proliferation is a hallmark of most cancers and involves the modulation of multiple signaling pathways



https://www.researchgate.net/figure/The-signaling-pathways-of-cell-proliferation-Proliferation-is-an-essential-step-in_fig3_339911022

Deregulation of cell proliferation



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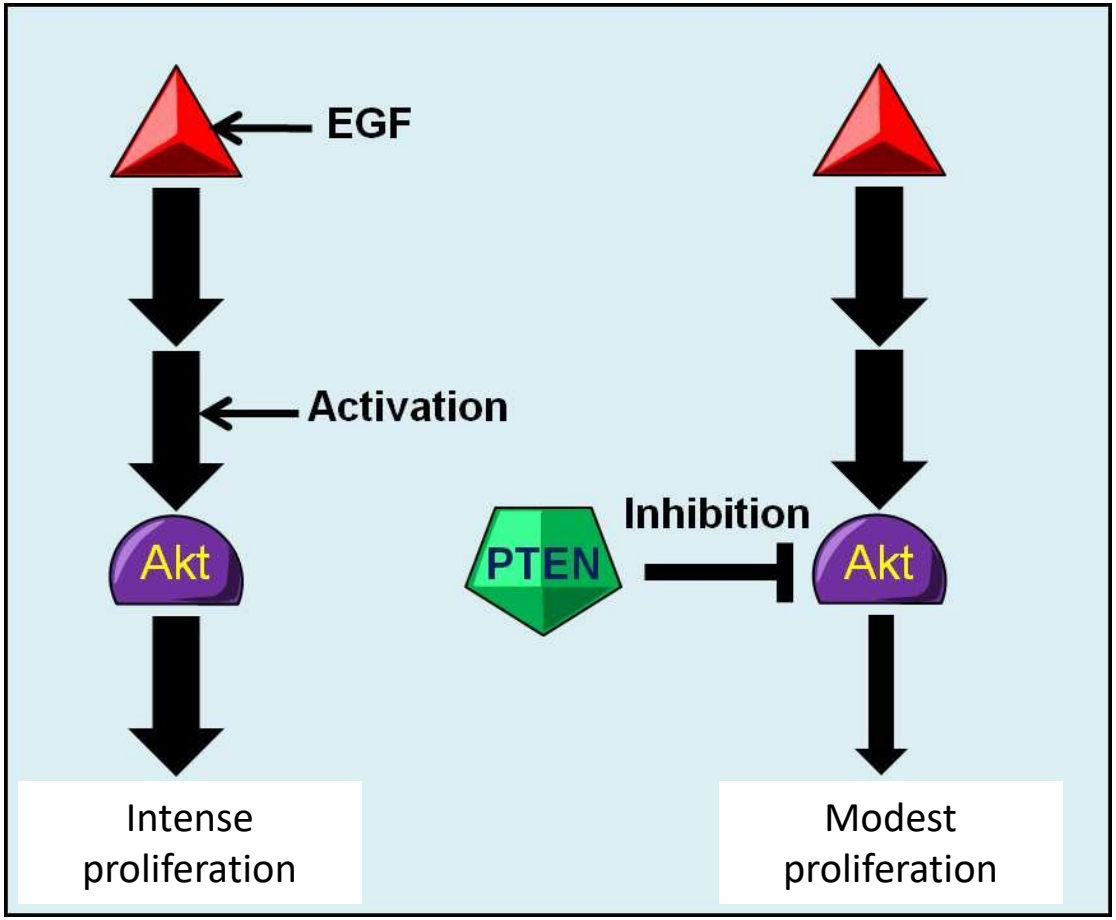
Mechanism of action of the tumor suppressor gene PTEN, a regulator of cell proliferation



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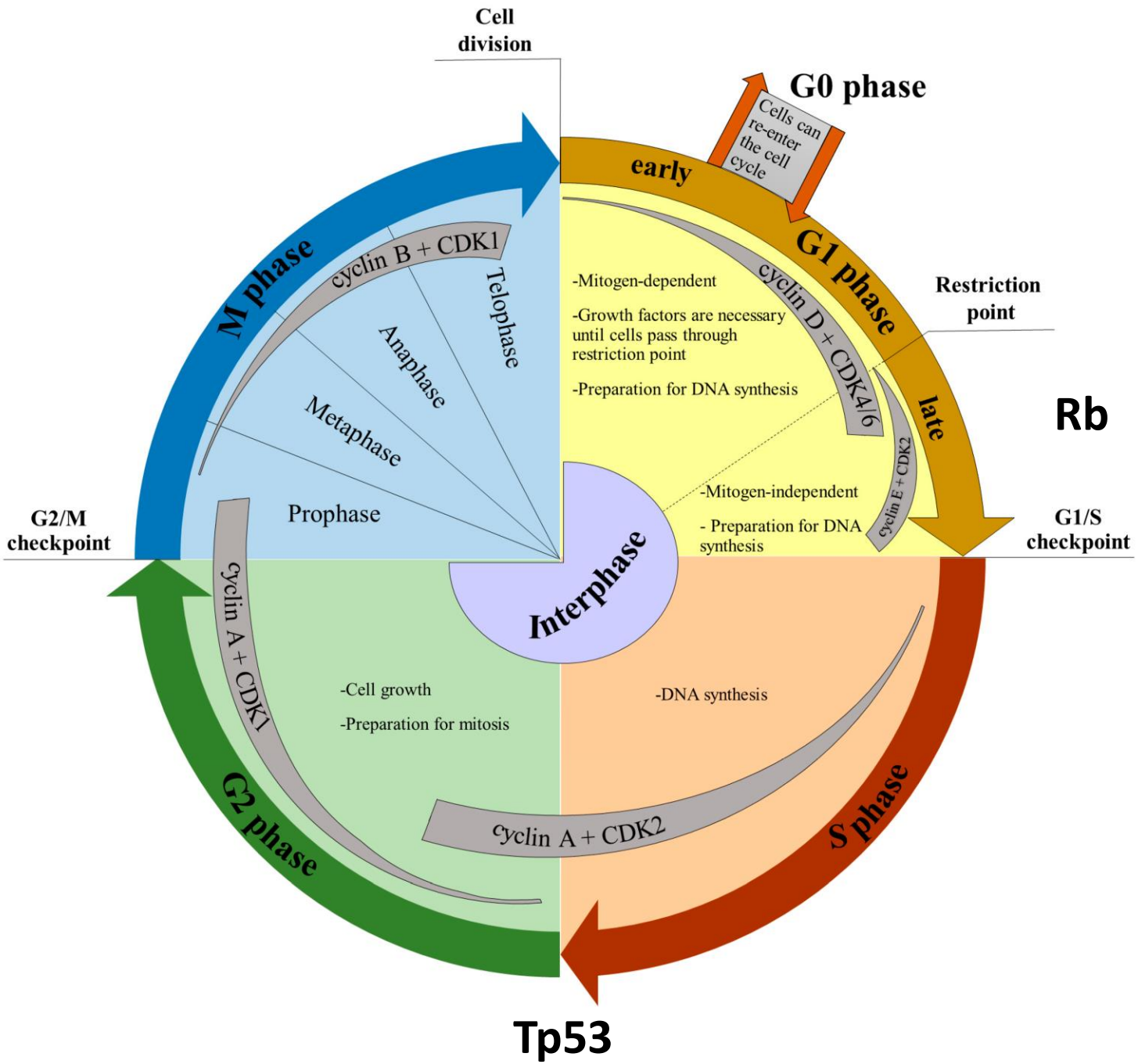
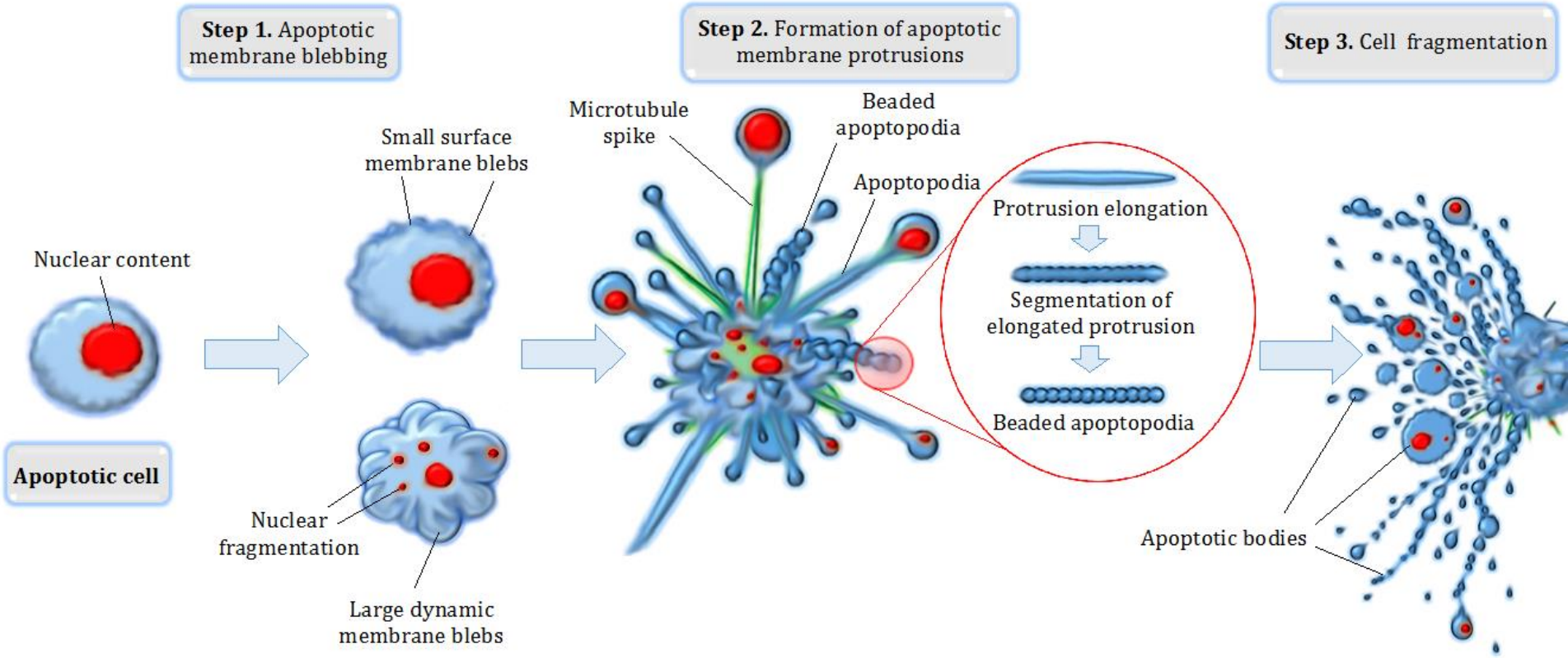
Cell cycle

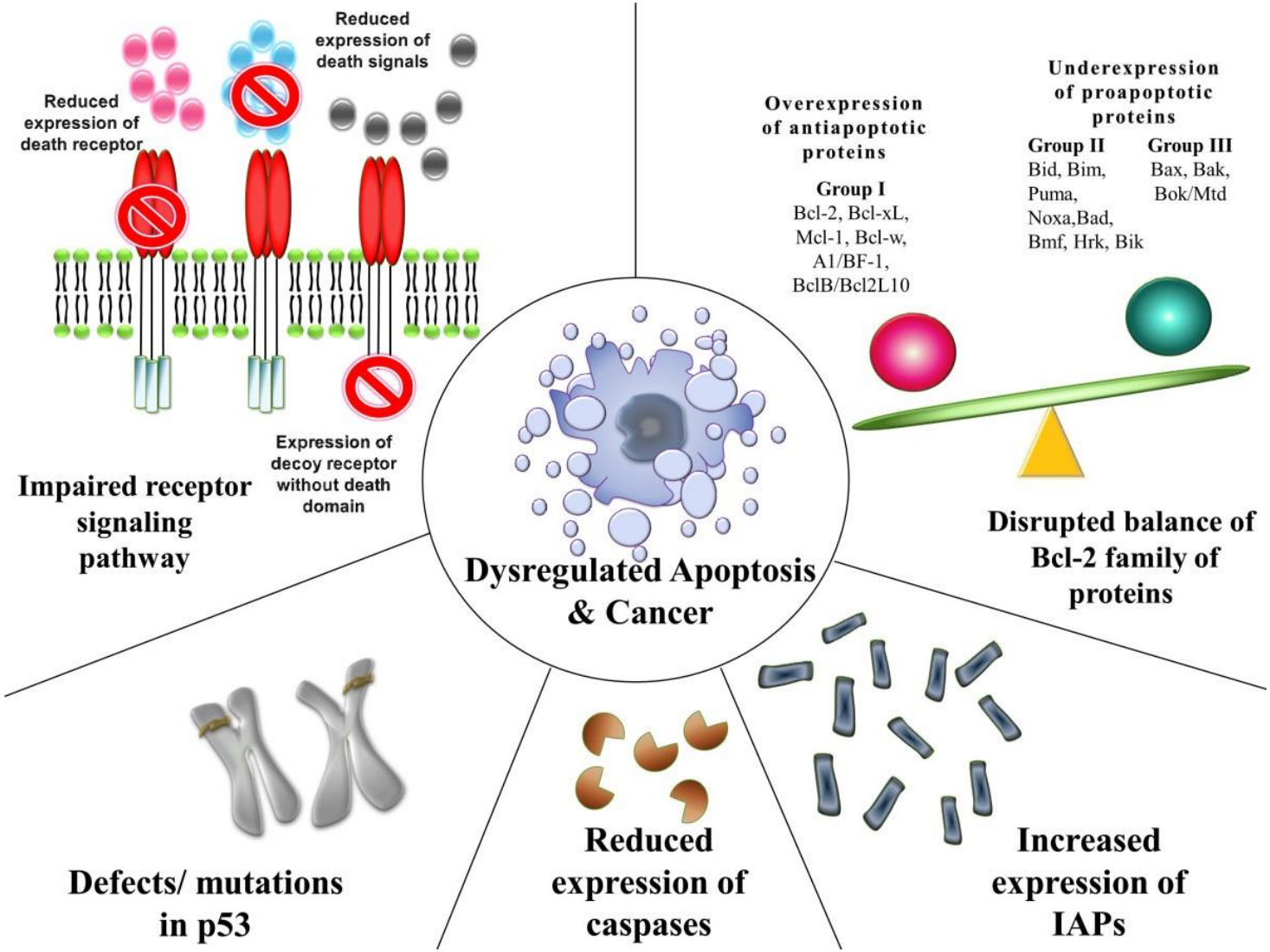


Int. J. Mol. Sci. 2023, 24(4), 3674

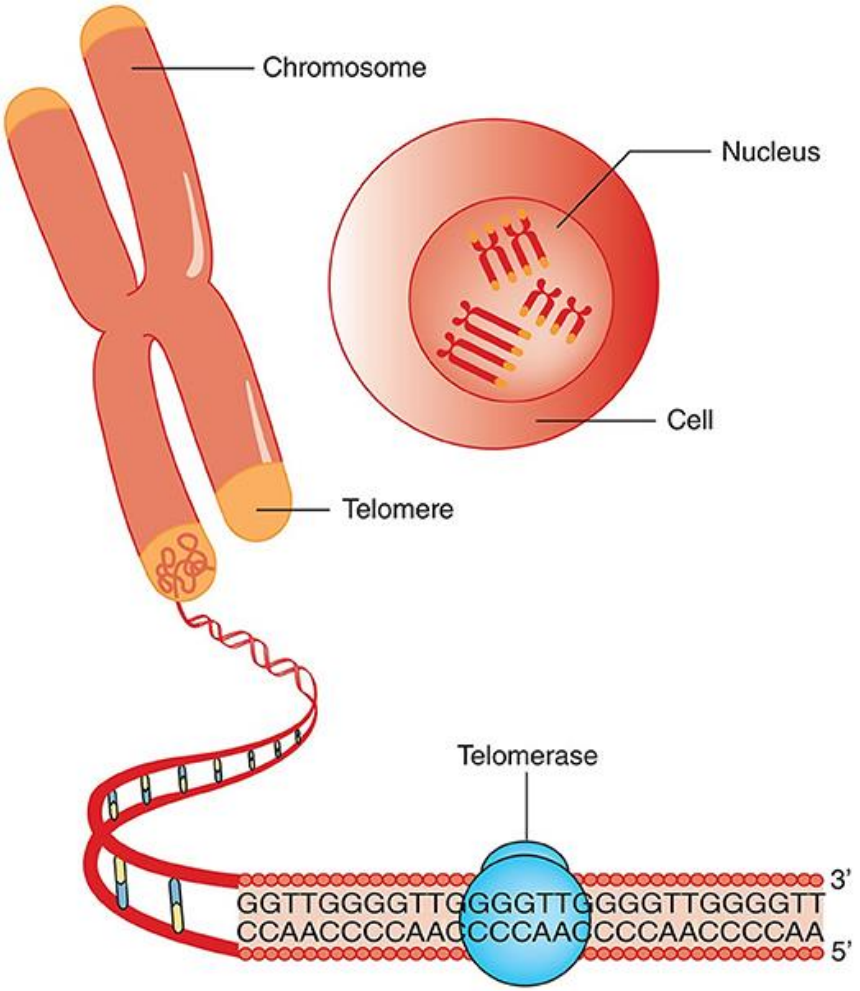
Apoptosis: a programmed cell death

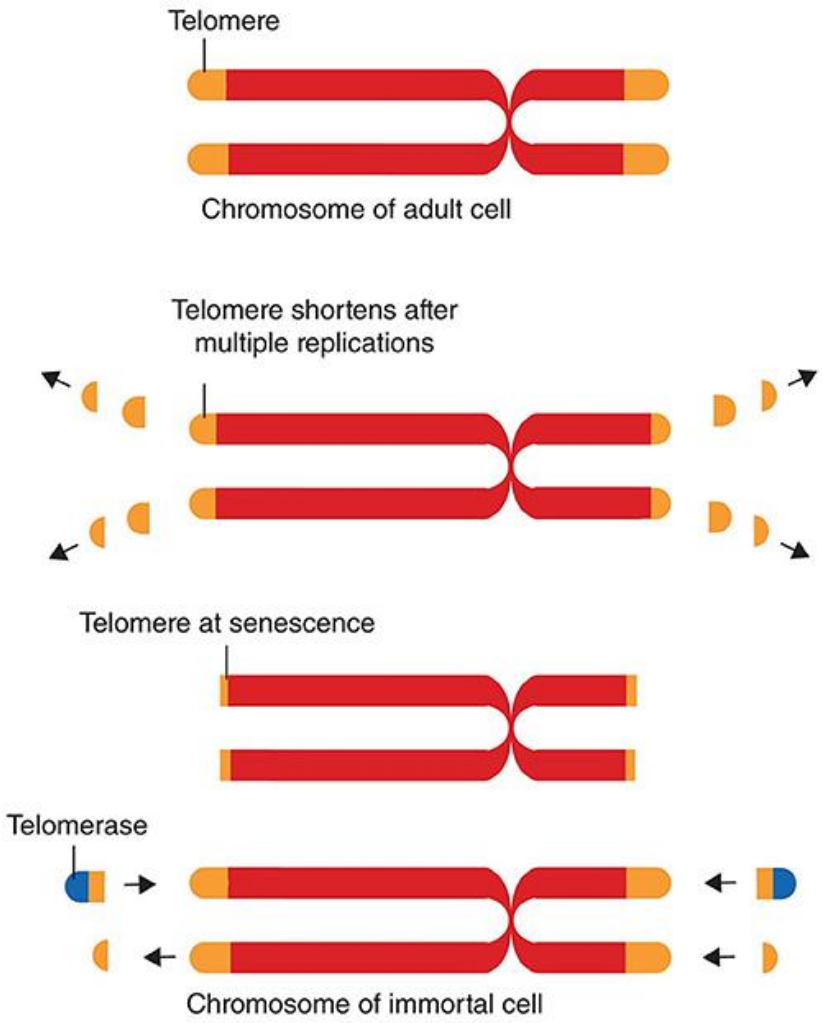


Dysregulated apoptosis & Cancer



Telomeres et telomerase





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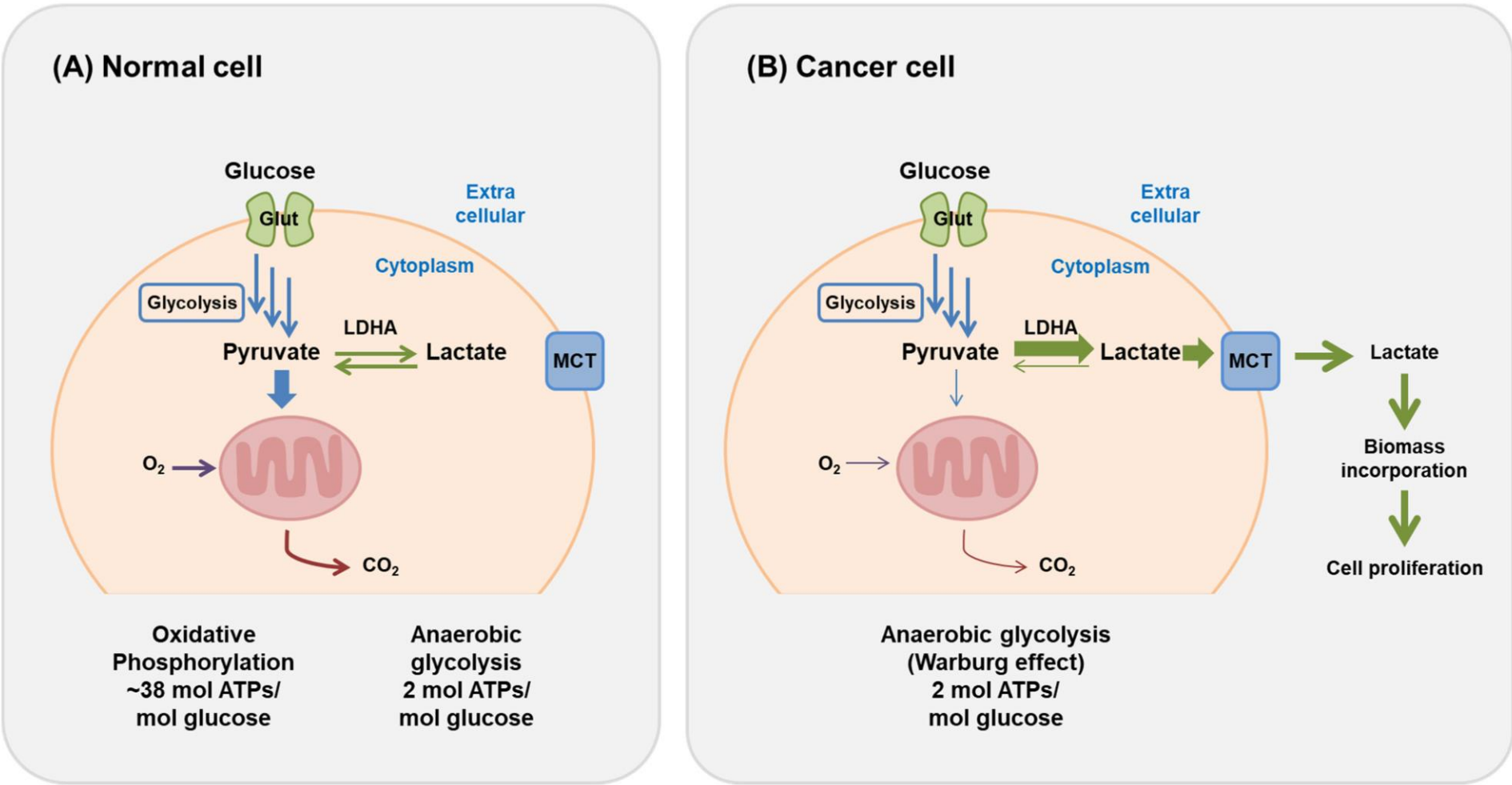
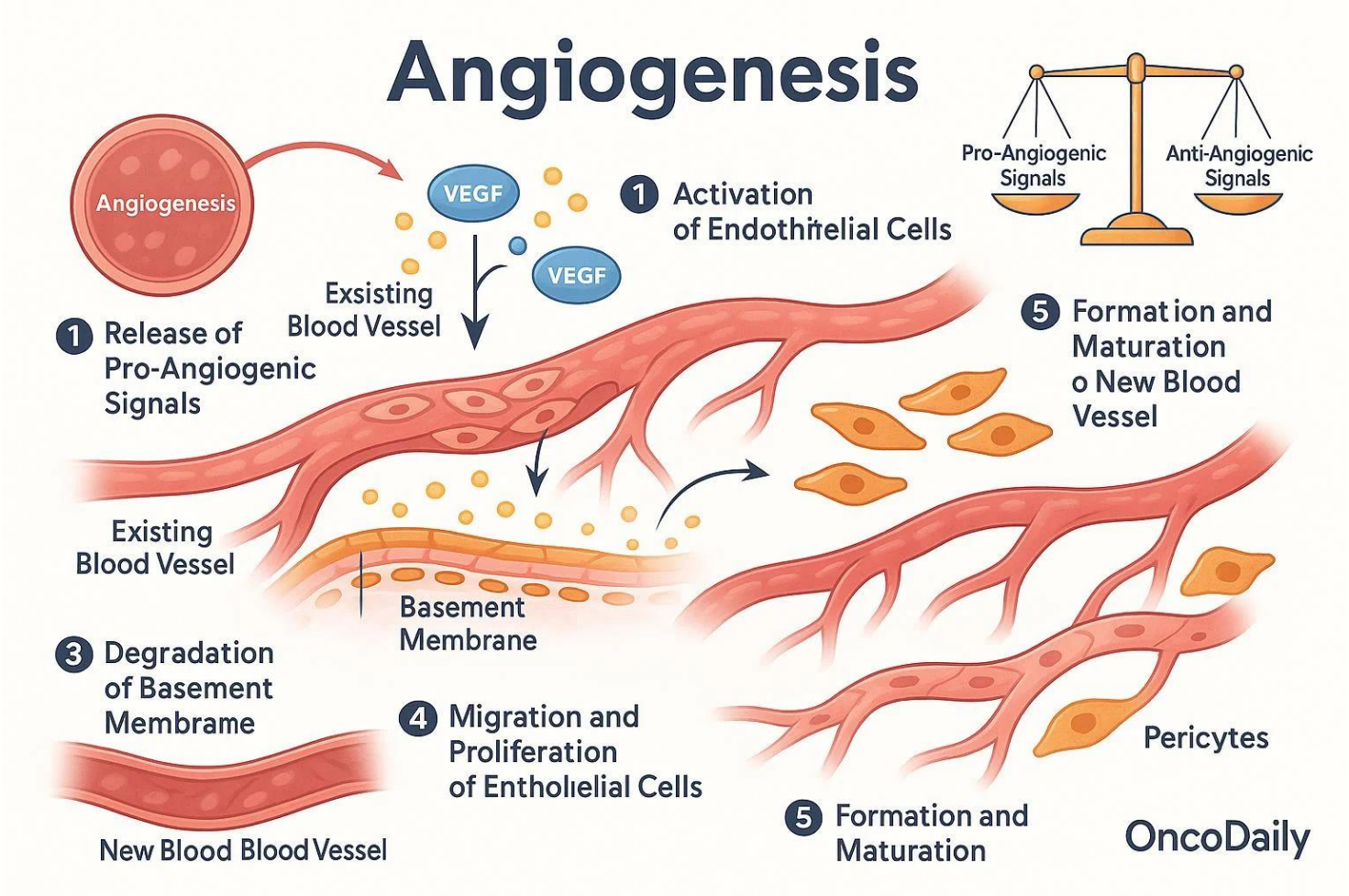
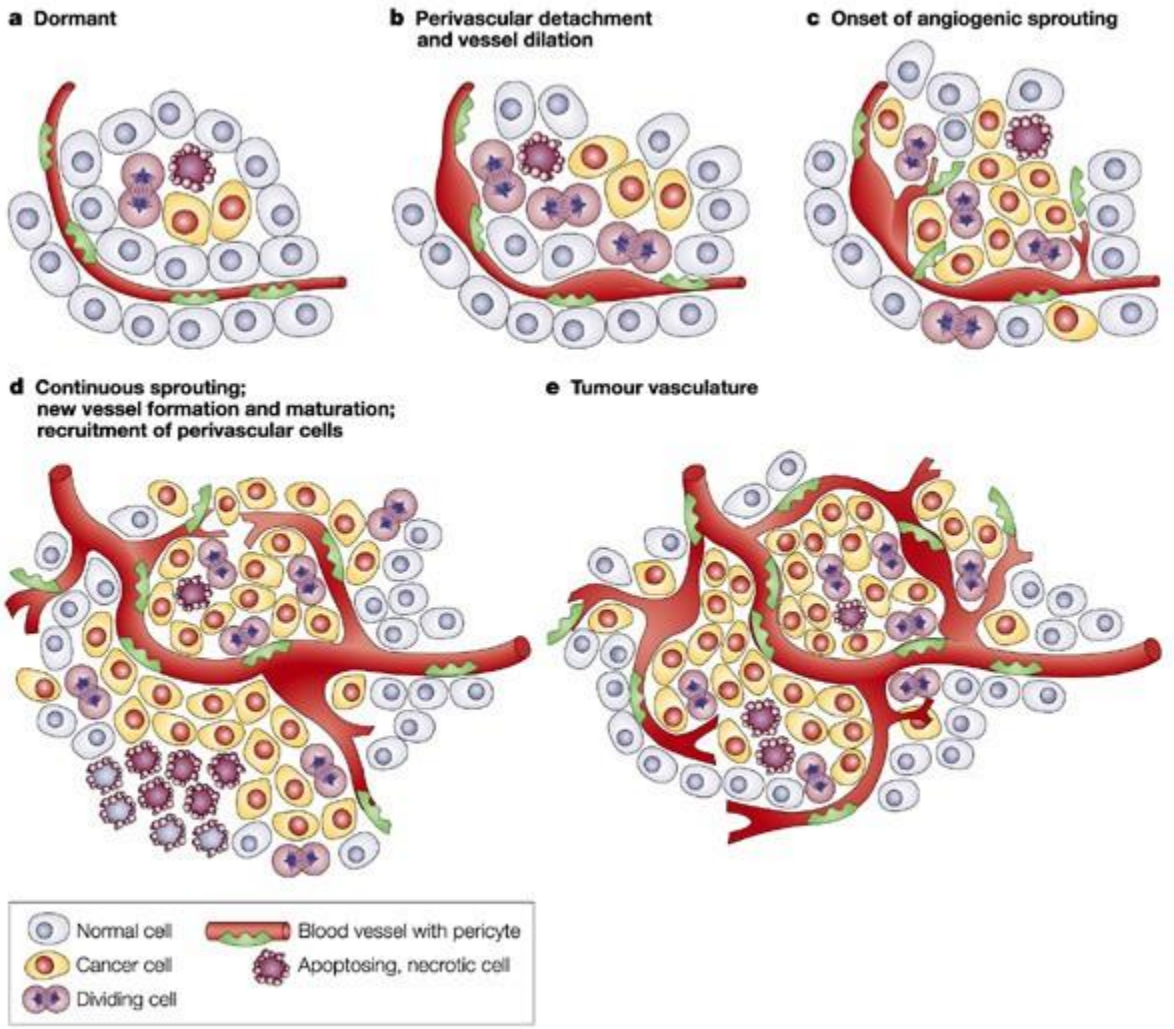
Deregulation of energy metabolism in cancer cells

Otto Warburg

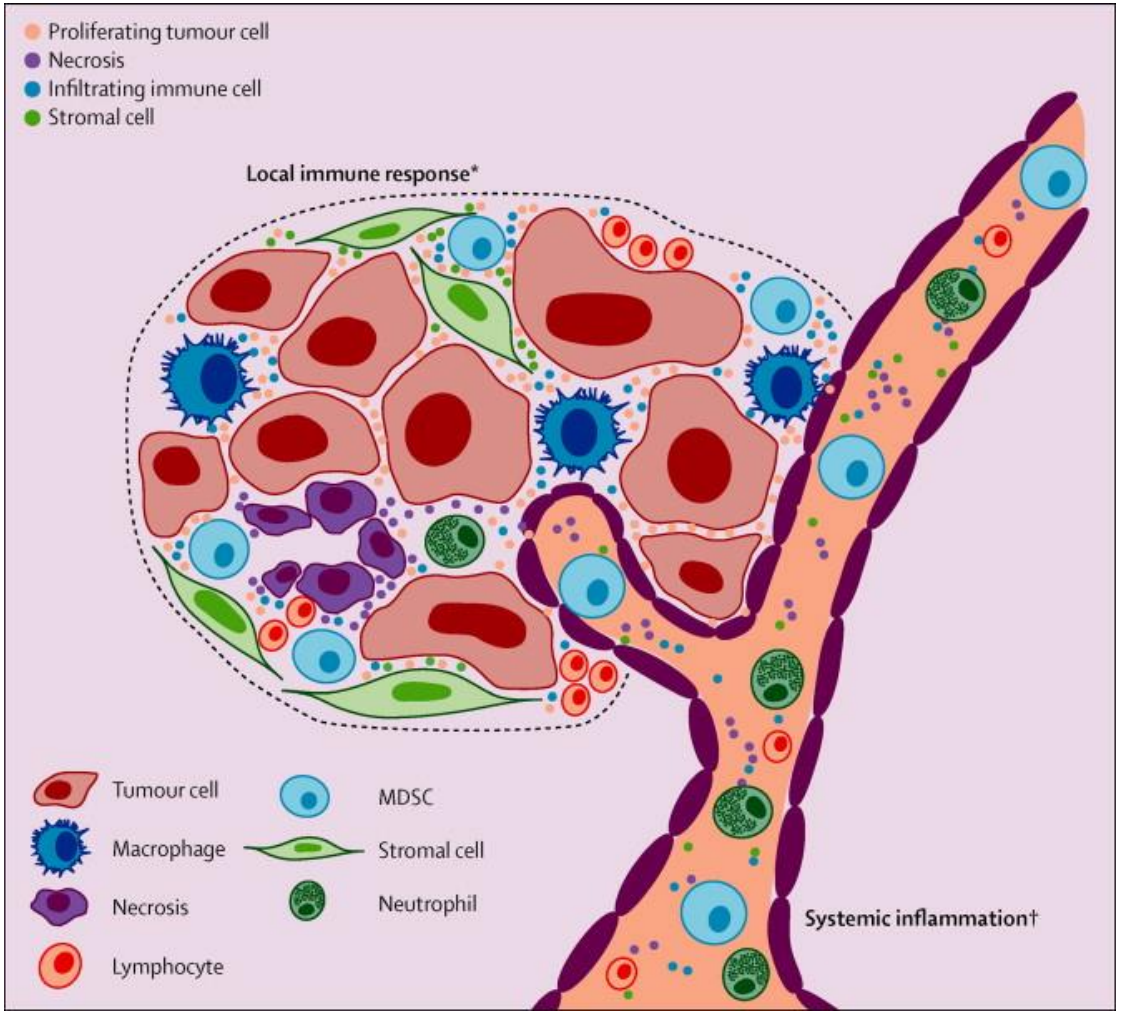



Angiogenesis
Angiogenesis
VEGF
VEGF
1 Activation of Endothitelial Cells
Pro-Angiogenic Signals
Anti-Angiogenic Signals
Exsisting Blood Vessel
1 Release of Pro-Angiogenic Signals
5 Formation and Maturation o New Blood Vessel
Existing Blood Vessel
Basement Membrane
3 Degradation of Basement Membrame
4 Migration and Proliferation of Entholıelial Cells
Pericytes
New Blood Blood Vessel
5 Formation and Maturation
OncoDaily

Tumorigenesis and the angiogenic switch



Cancer inflammation



Both Innate and Adaptive Arms of The Immune System Can Fight Tumors

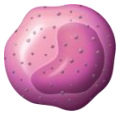
Innate Immunity

Can recognize native structures through somatic encoded receptors (PRRs*) from pathogens and nascent tumor cells and destroy them

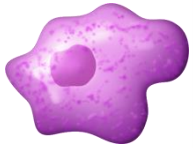
*Pattern Recognition Receptors

Non polymorphic

NK cells*

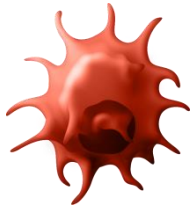


Macrophages*



Hematopoietic Stem cell

Dendritic cells*



T cells

B cells

Adaptive Immunity

Recognize and eradicate pathogens and nascent tumor cells through their antigen receptor TCR & BCR (**high diversity** due to genetic recombination)

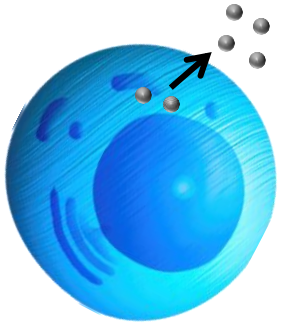
NK = natural killer.

Norvell A. In: Prendergast GC et al. Cancer Immunotherapy. 2nd ed. Elsevier; 2013:11–24

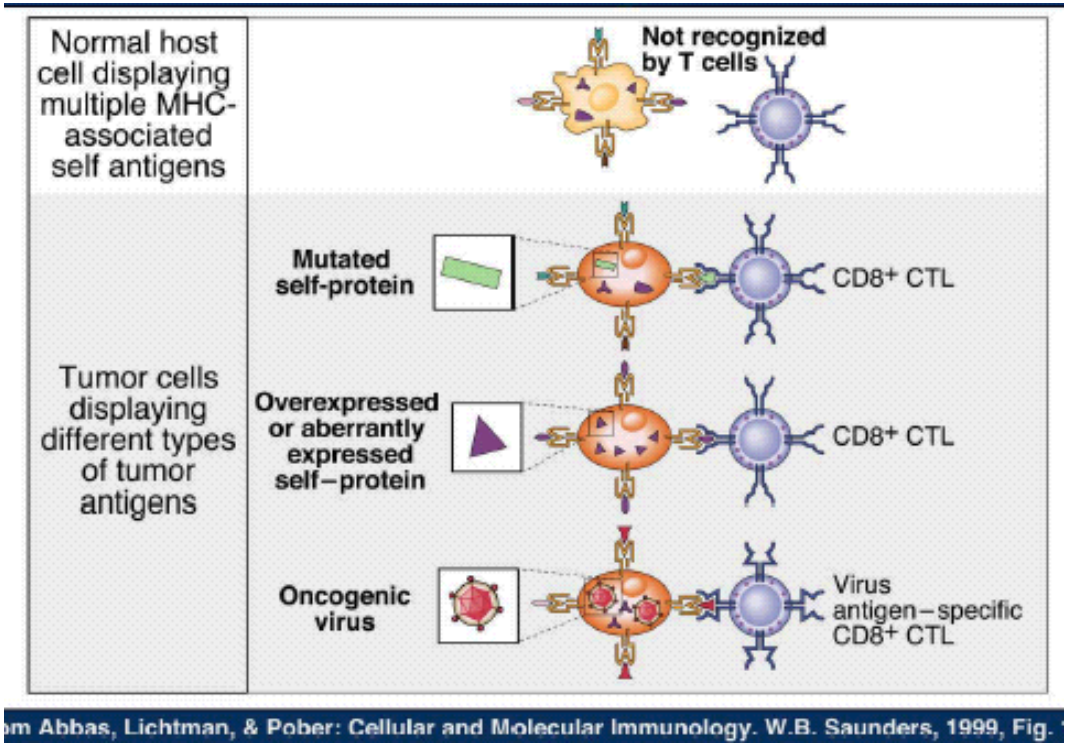
Some Tumor Cells Express Multiple Antigens That Are Not Expressed by Normal Cells

Normal cells express/release molecules that do not elicit an immune response (tolerance to normal self).

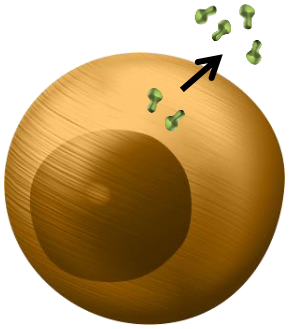
Tumor cells express/release abnormal self antigens that cause them to be recognized as foreign entities and therefore elicit an immune response.



NORMAL CELL



m Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig.

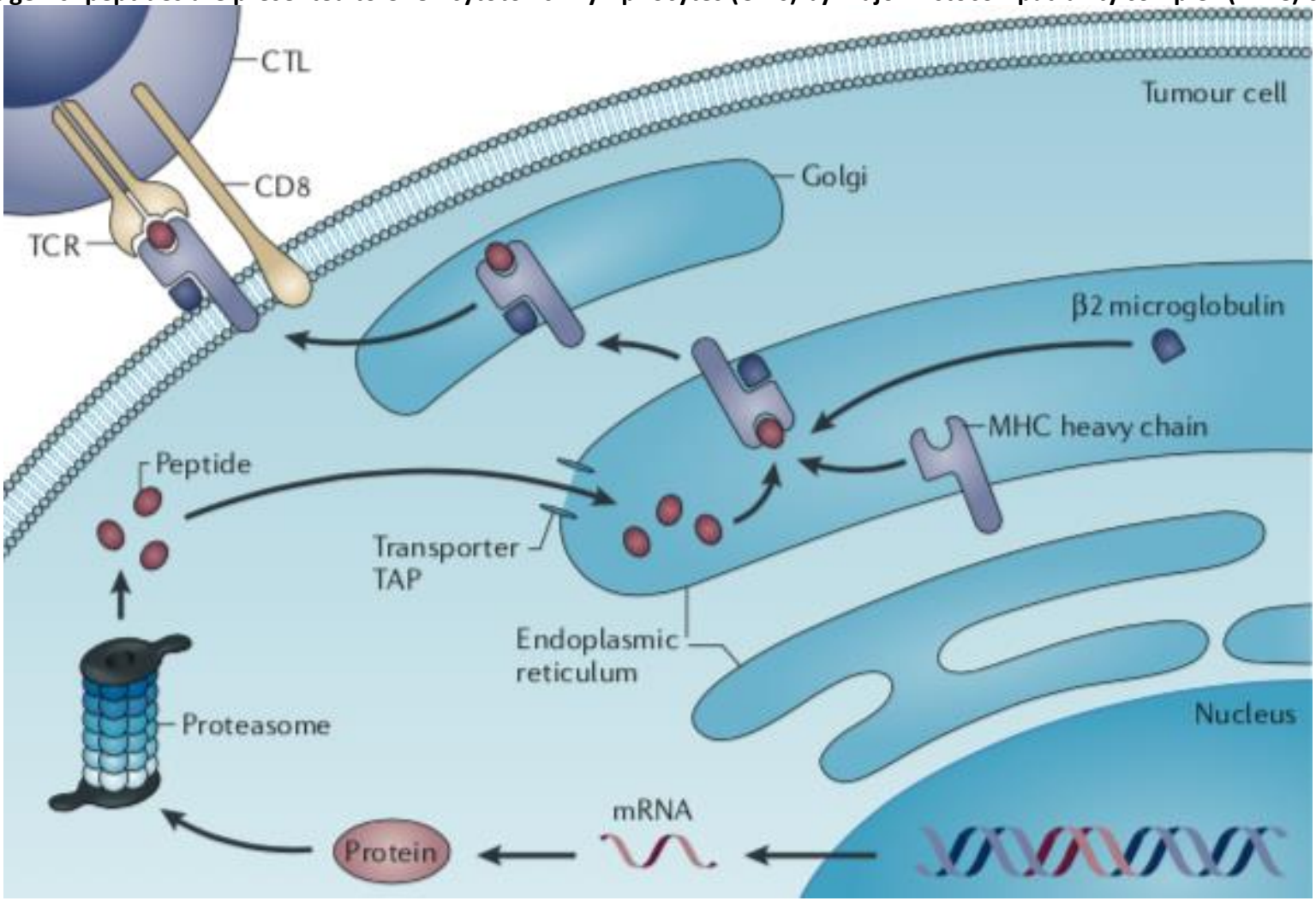


TUMOR CELL

Finn et al. N Engl J Med 2008

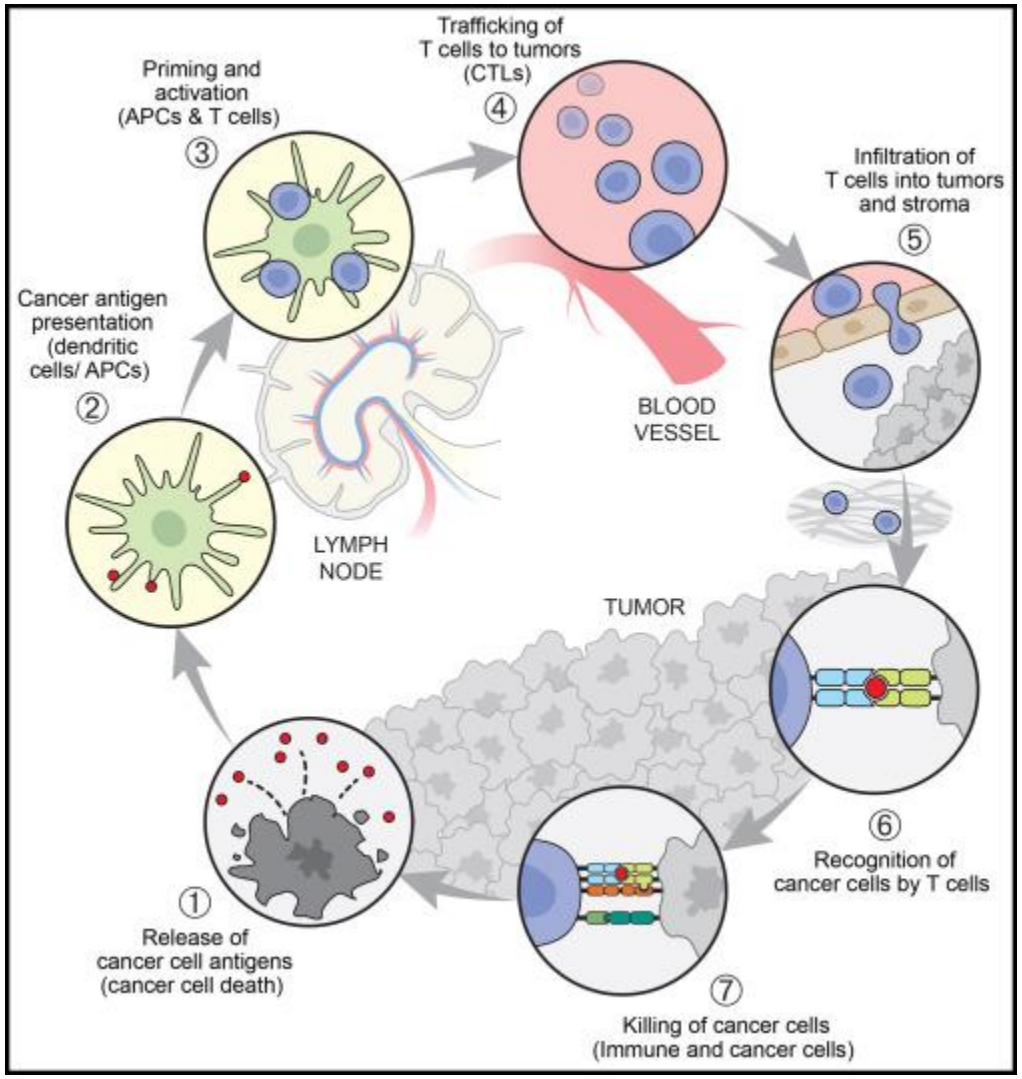
Processing of tumor antigens recognized by CD8^{+} T cells

Antigenic peptides are presented to CD8+ cytotoxic T lymphocytes (CTLs) by major histocompatibility complex (MHC) class I



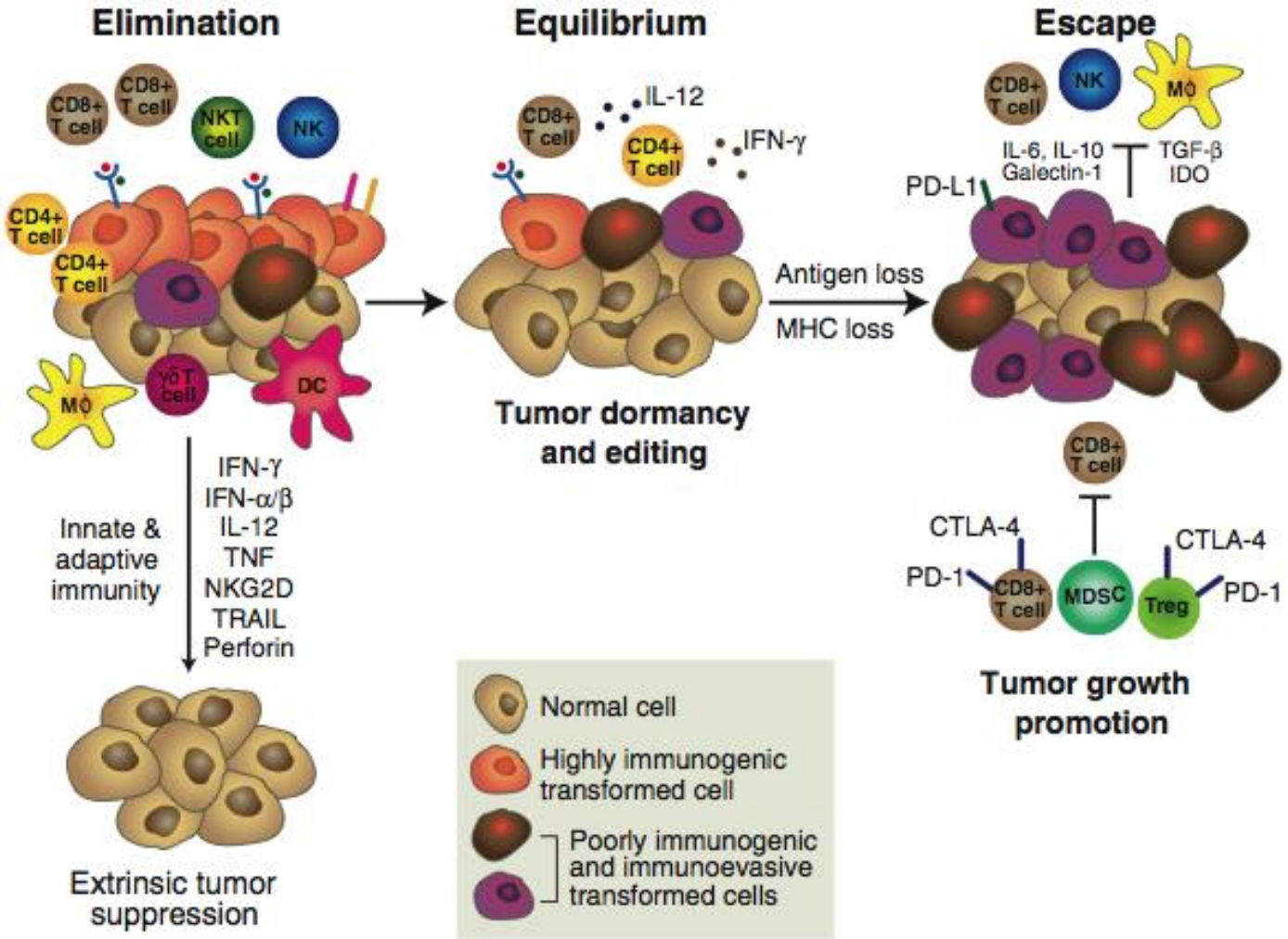
Coulie et al. Nat Rev Cancer 2014

The cancer immunity cycle



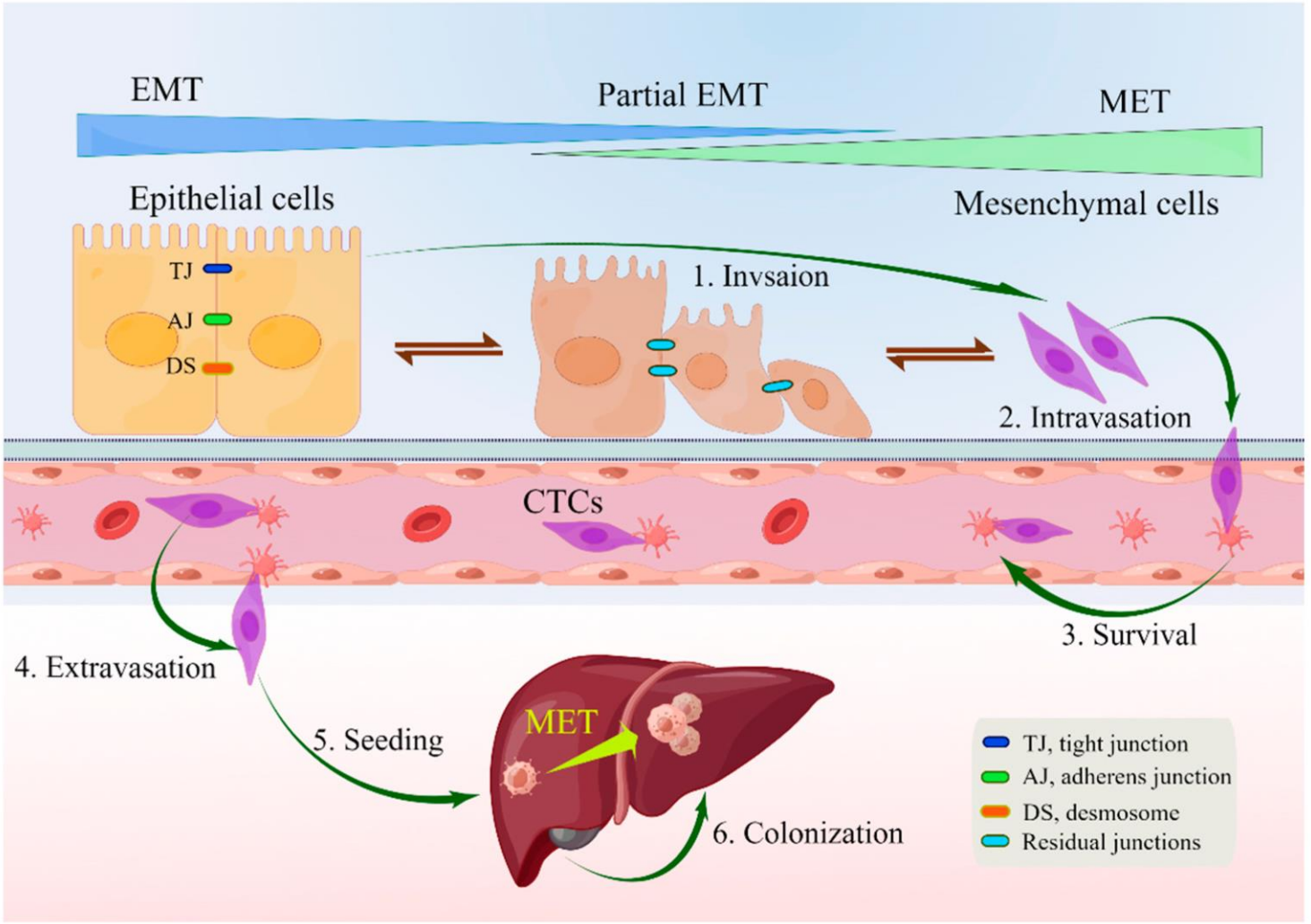
Chen and Mellman. Immunity 2013

Concept of cancer immunoediting



Adapted from Schreiber, Science 2011

Tumor invasion and epithelial–mesenchymal transition



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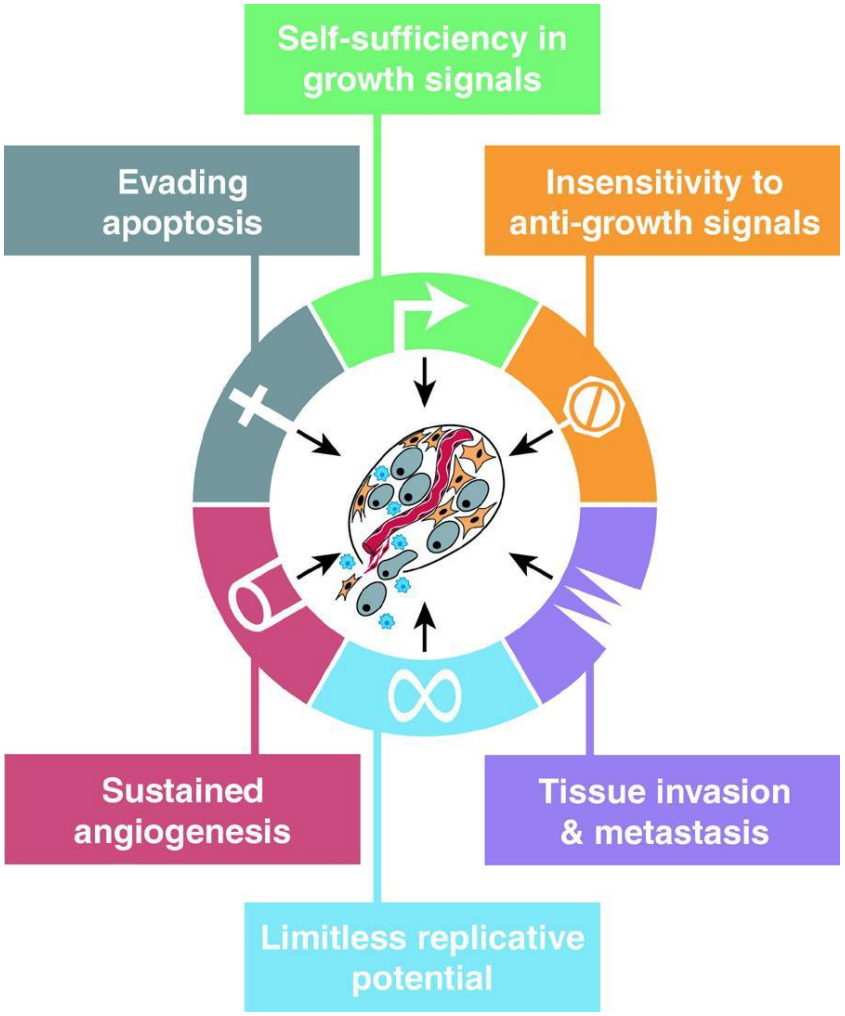
References

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

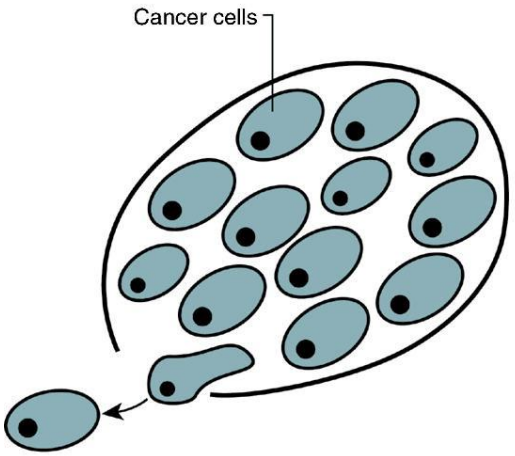
Cell 2011 Mar 4;144(5):646-74

Cancer Discov 2022;12(1):31-46

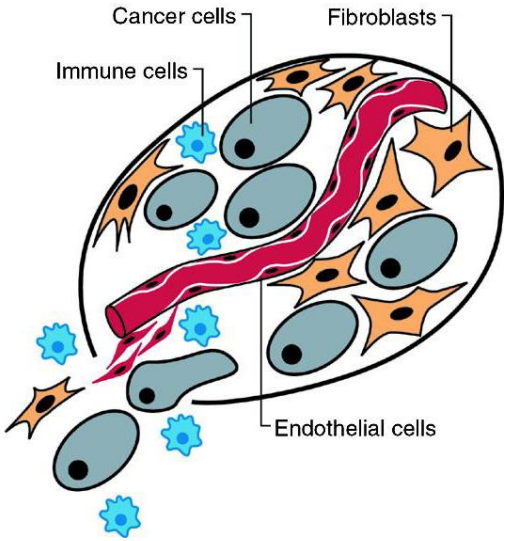
Cancer Discov 2025 Apr 2;15(4):685-701



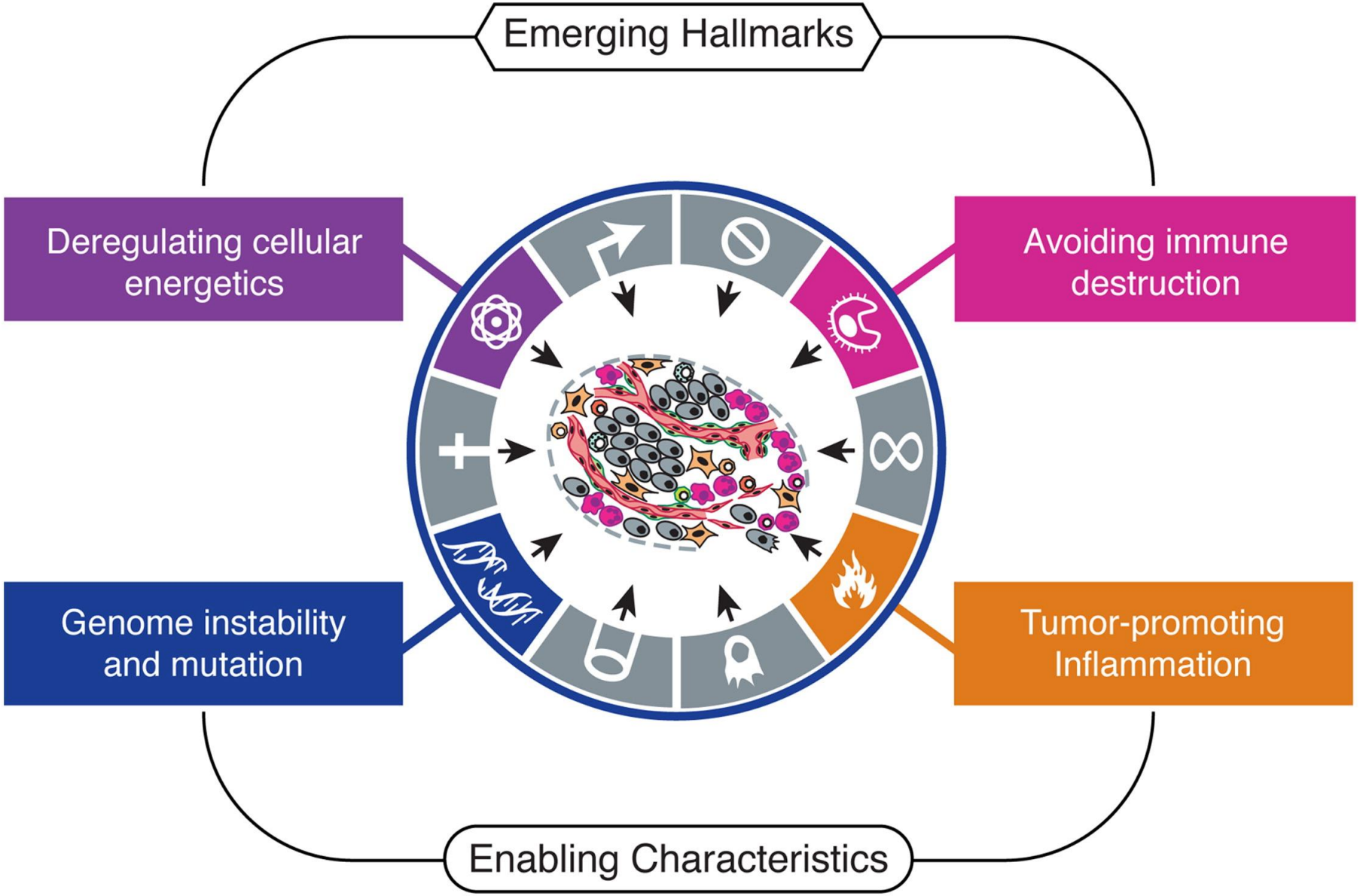
The Reductionist View



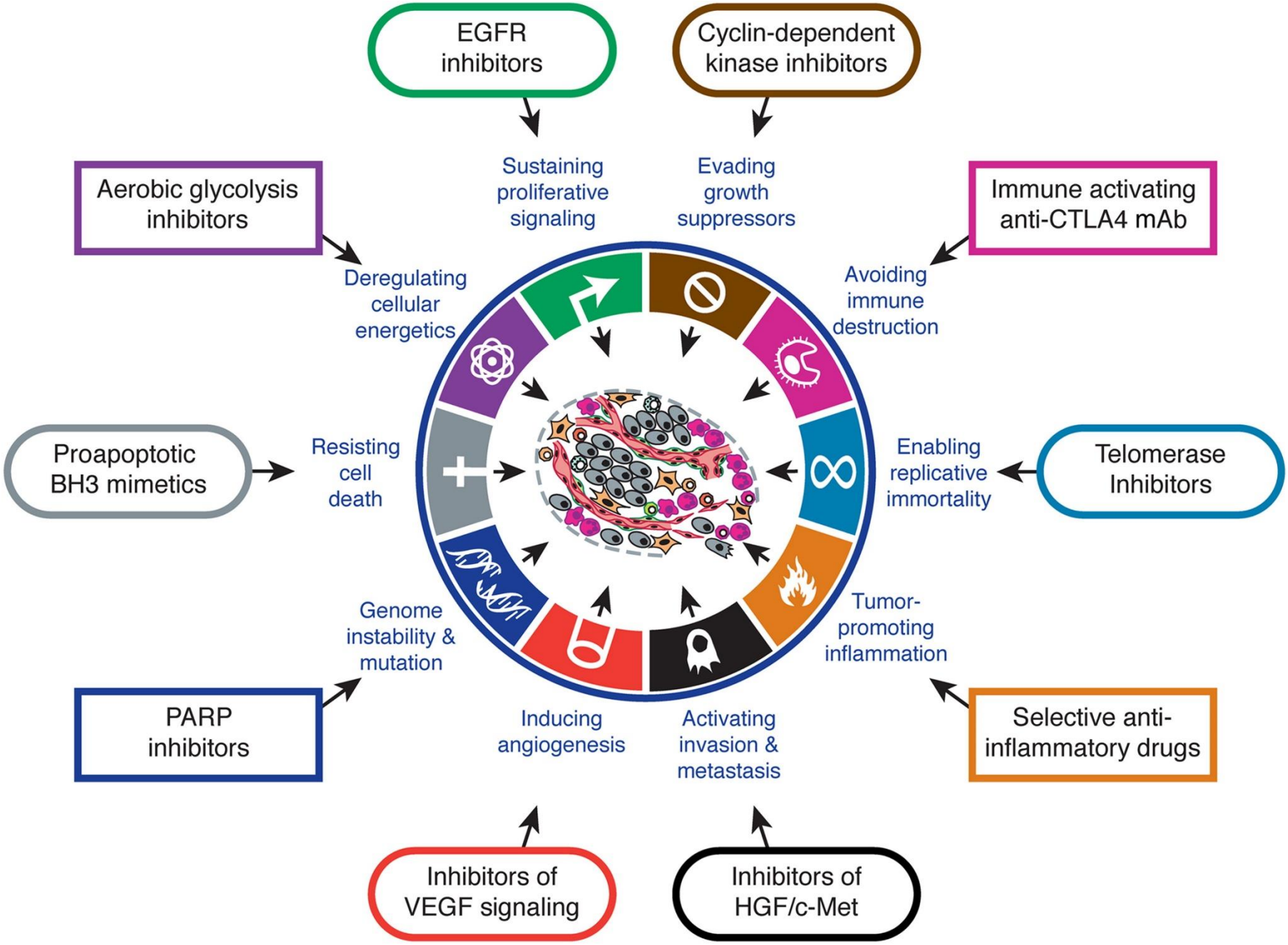
A Heterotypic Cell Biology



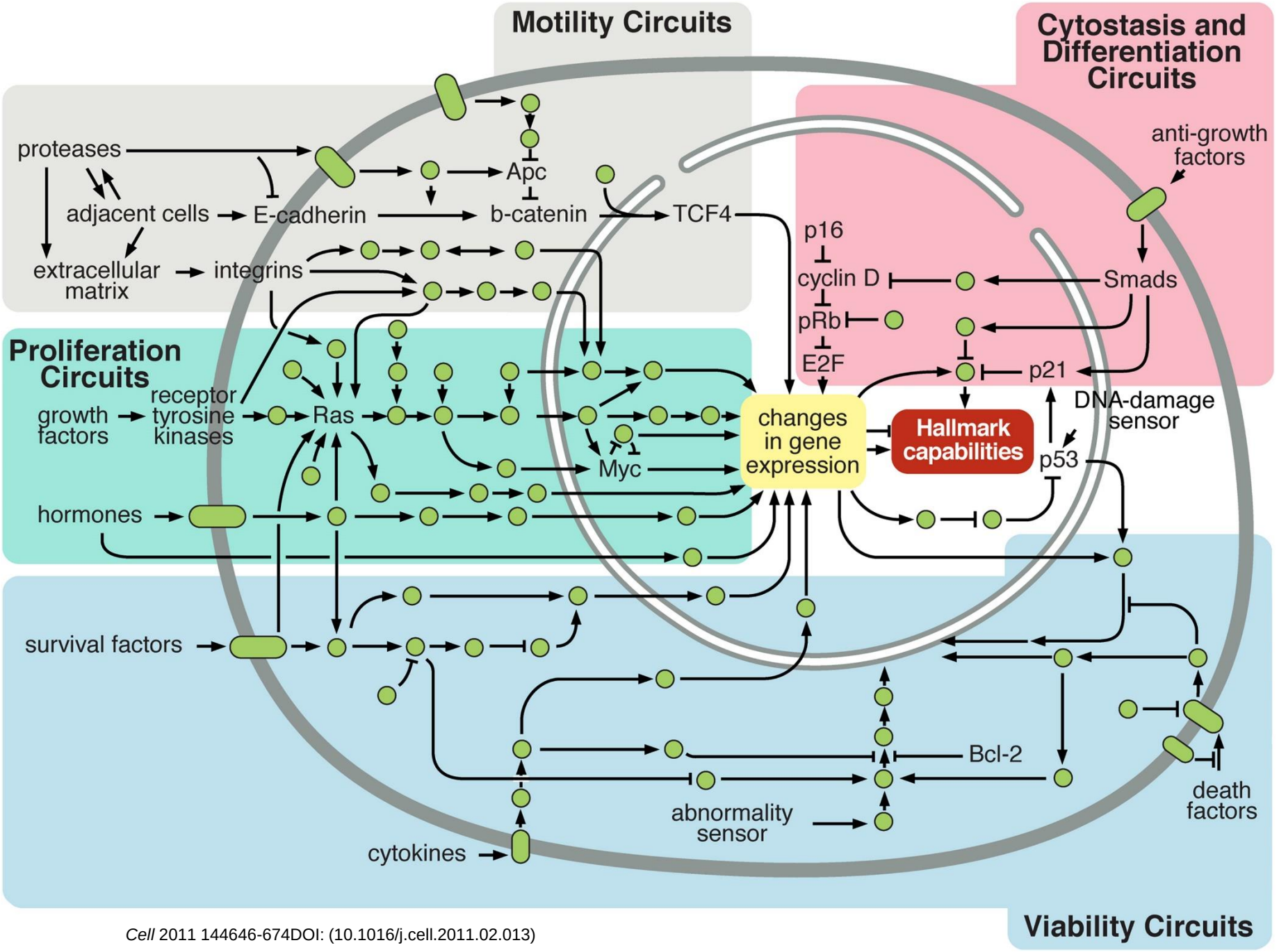
Cell 2000 Jan 7;100(1):57-70; 6 hallmarks



Cell 2011 Mar 4;144(5):646-74; 6+4 hallmarks

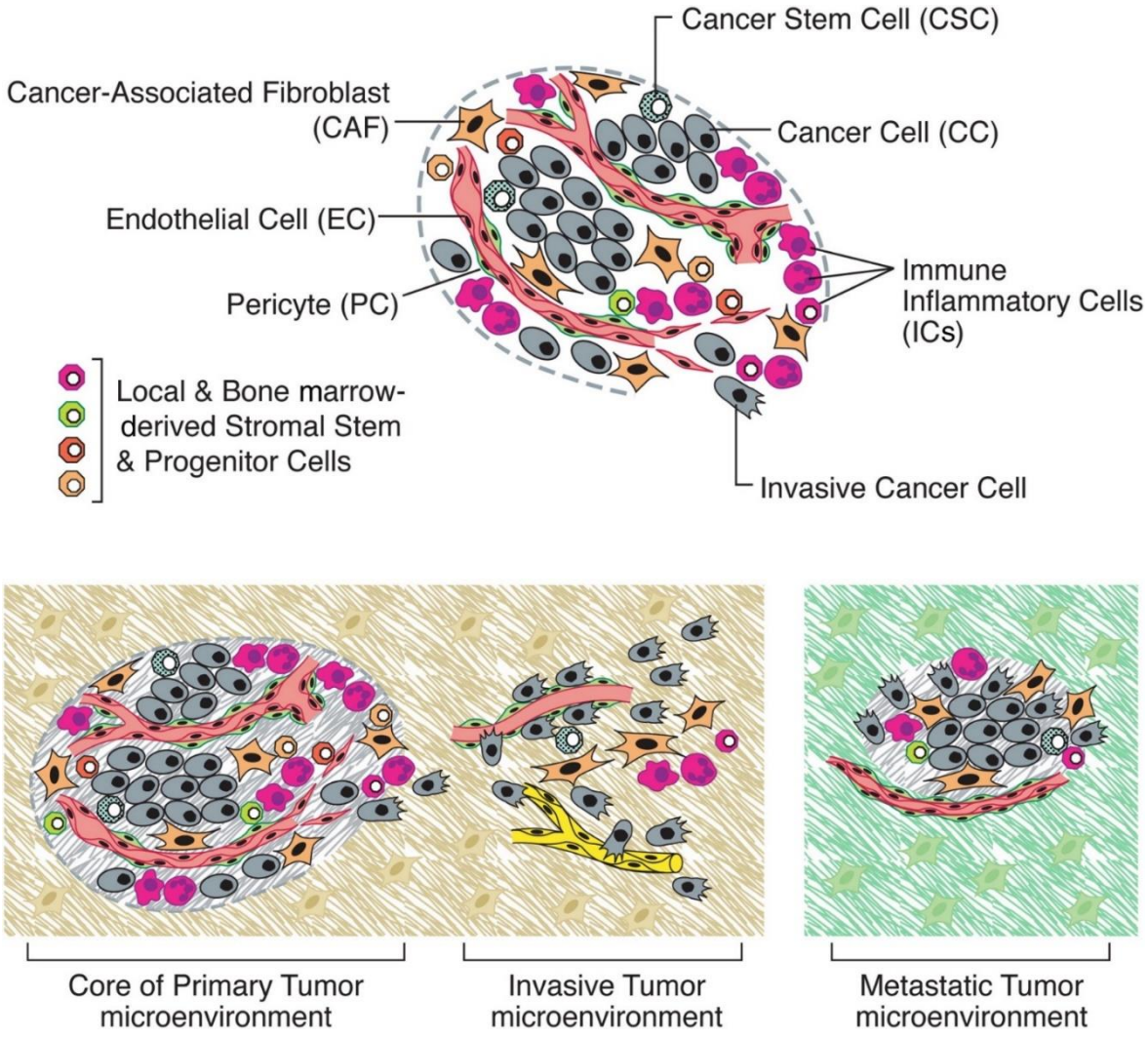


Cell 2011 144646-674DOI: (10.1016/j.cell.2011.02.013)



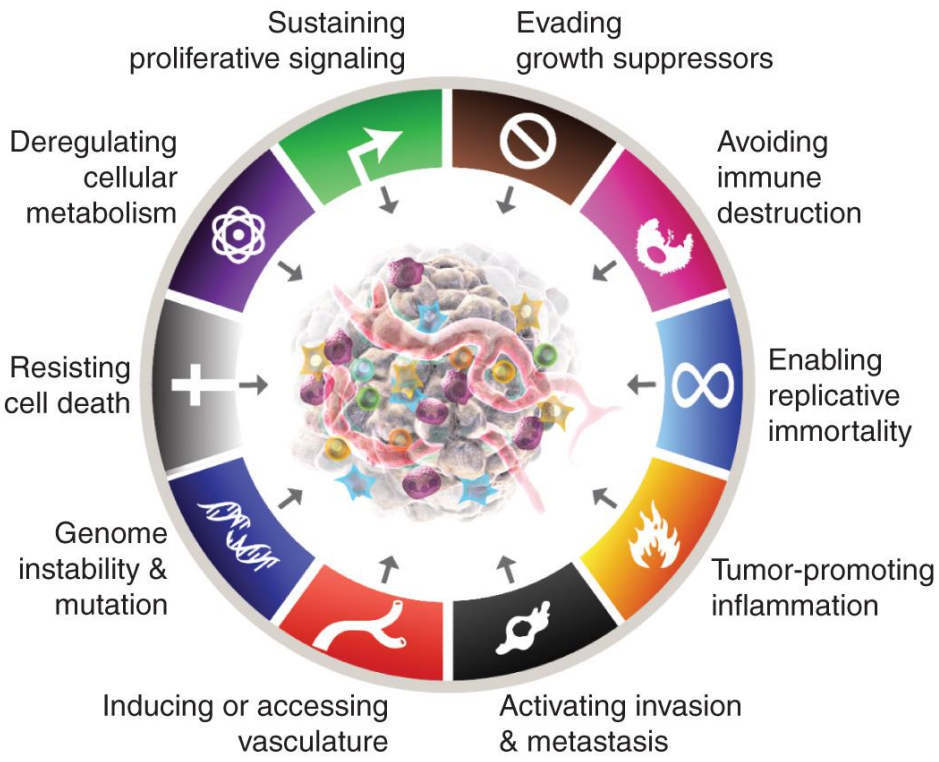
Cell 2011 144646-674DOI: (10.1016/j.cell.2011.02.013)

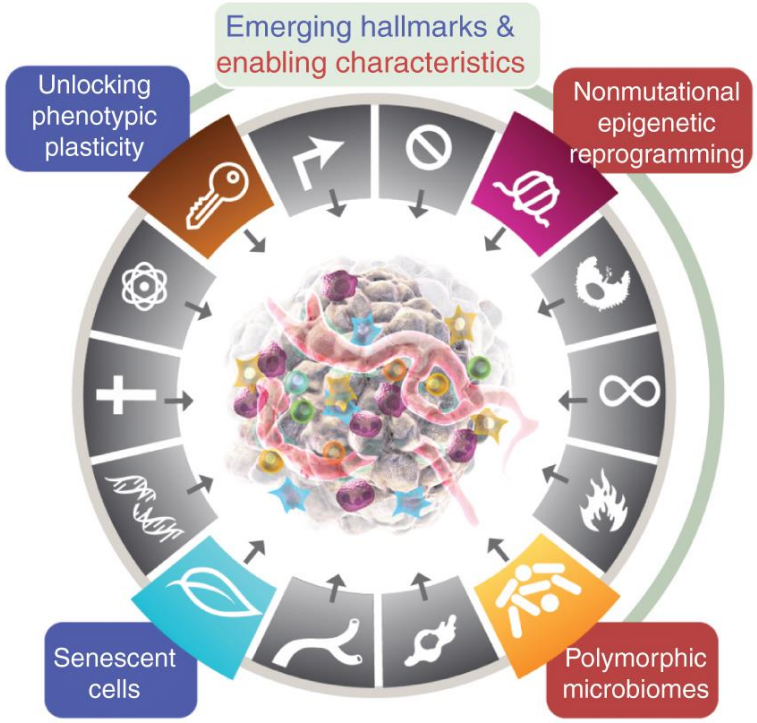
Cancer = complex and highly dynamic ecosystem



Cell 2011 Mar 4;144(5):646-74

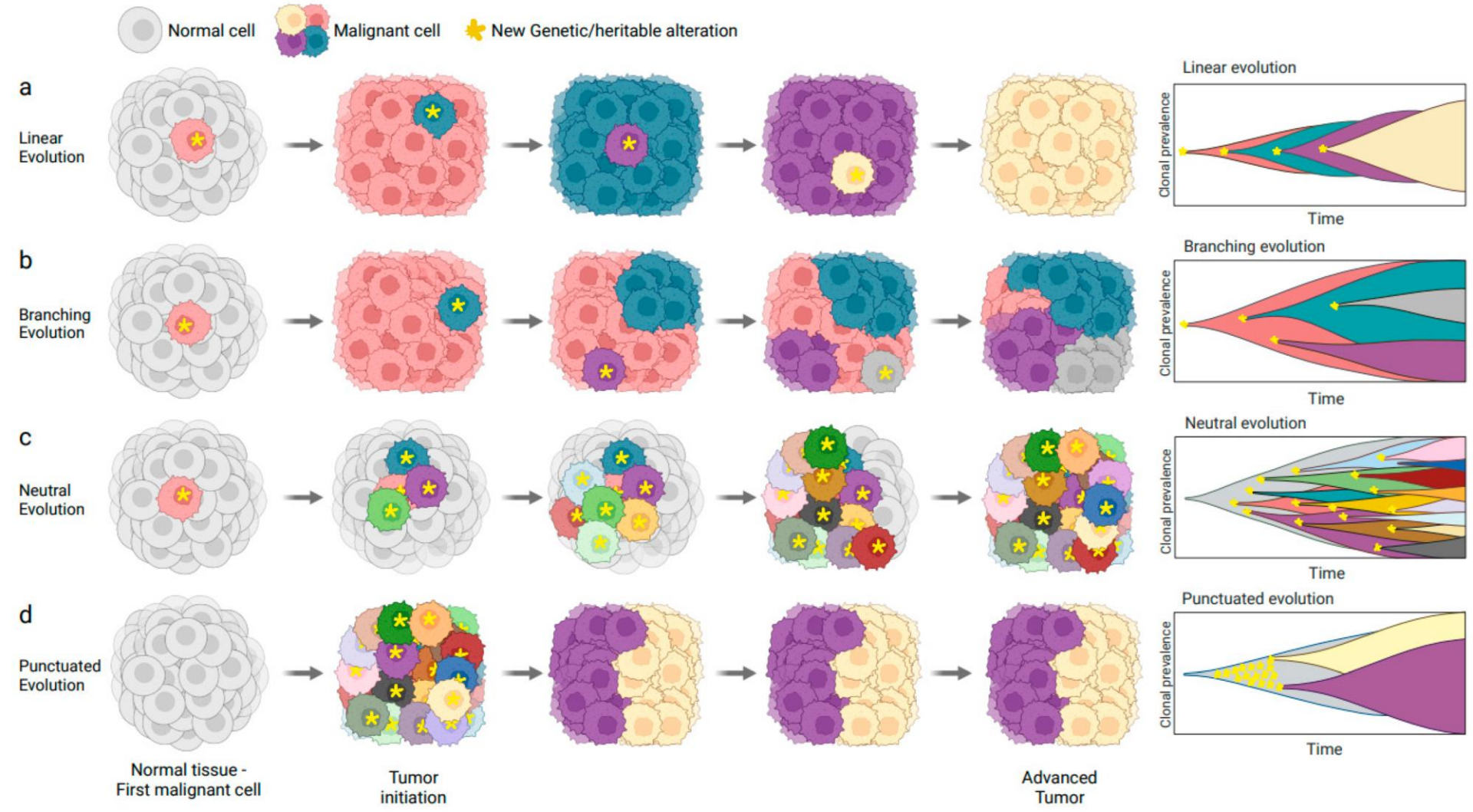
Hallmarks of Cancer (2011 -> 2022)
New Dimensions





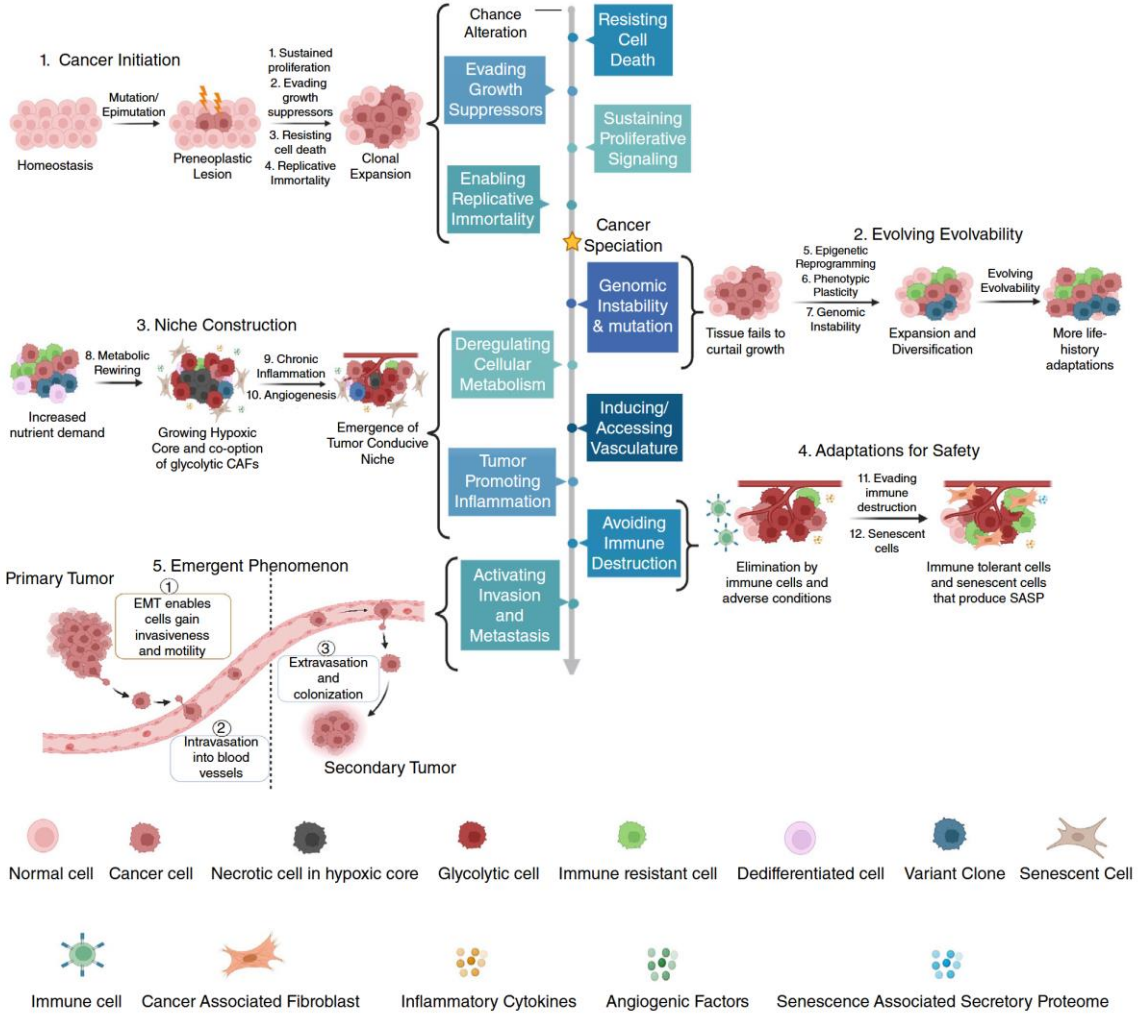
Cancer Discov 2022;12(1):31-46; 10+4 hallmarks

Decoding cancer evolution



The Hallmarks of Cancer as Eco(logy)-Evolutionary Processes

Deconstruction of the hallmarks "color wheel" into **linear**, **parallel**, and **inter-linked stages**: **cancer initiation**, **evolving evolvability**, **niche construction**, **adaptations for safety**, and **emergent phenomenon**



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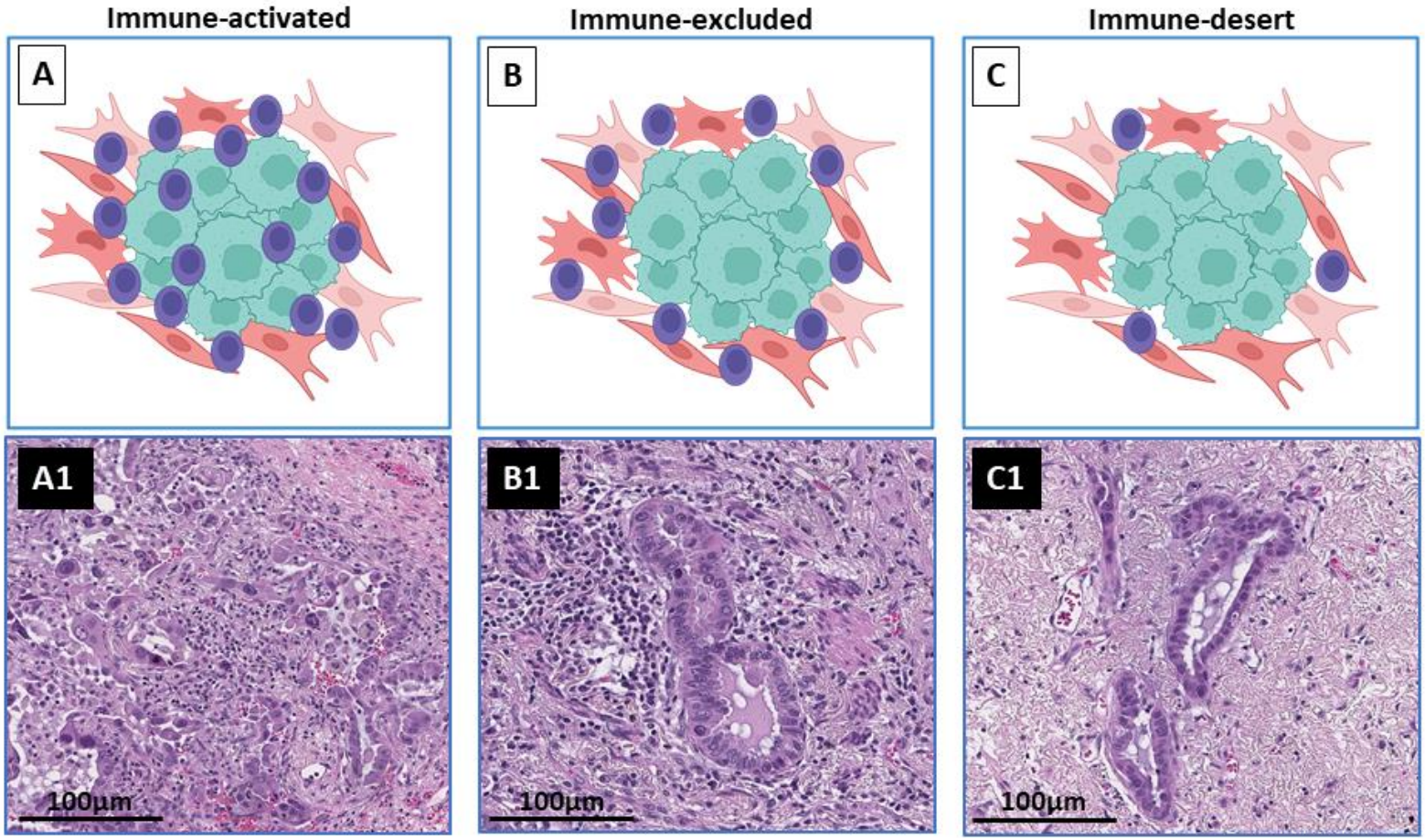
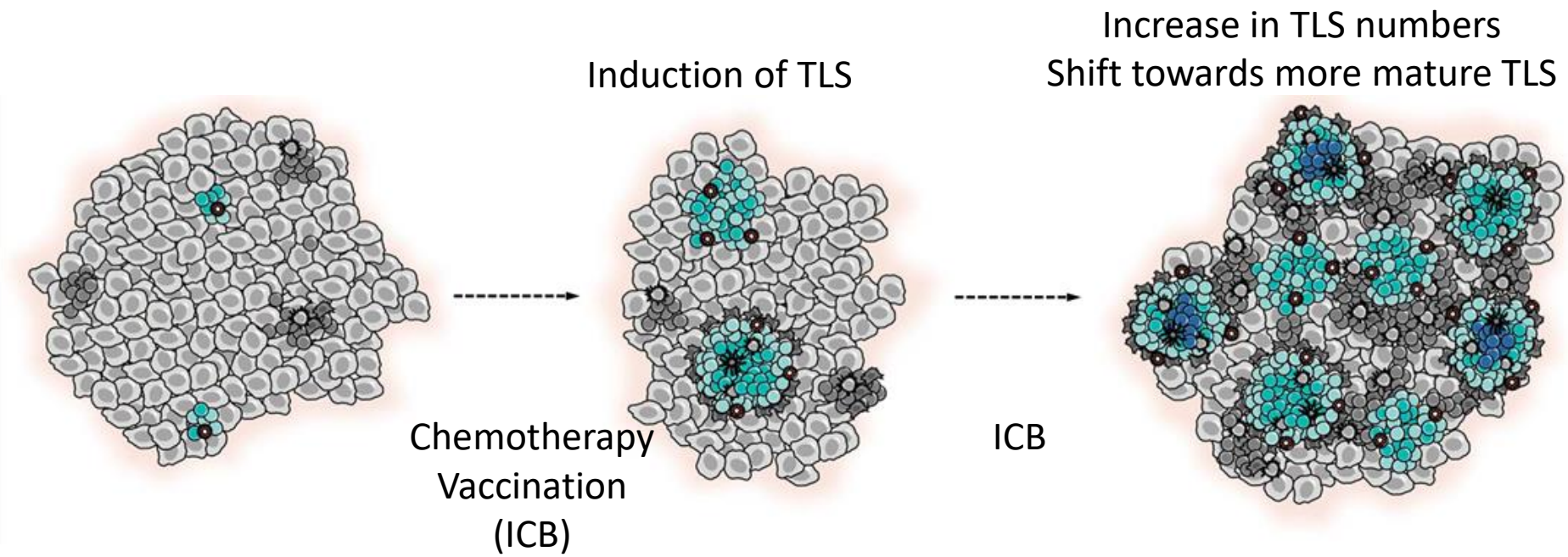
Spatial organization of the tumor ecosystem: the next cancer hallmark?

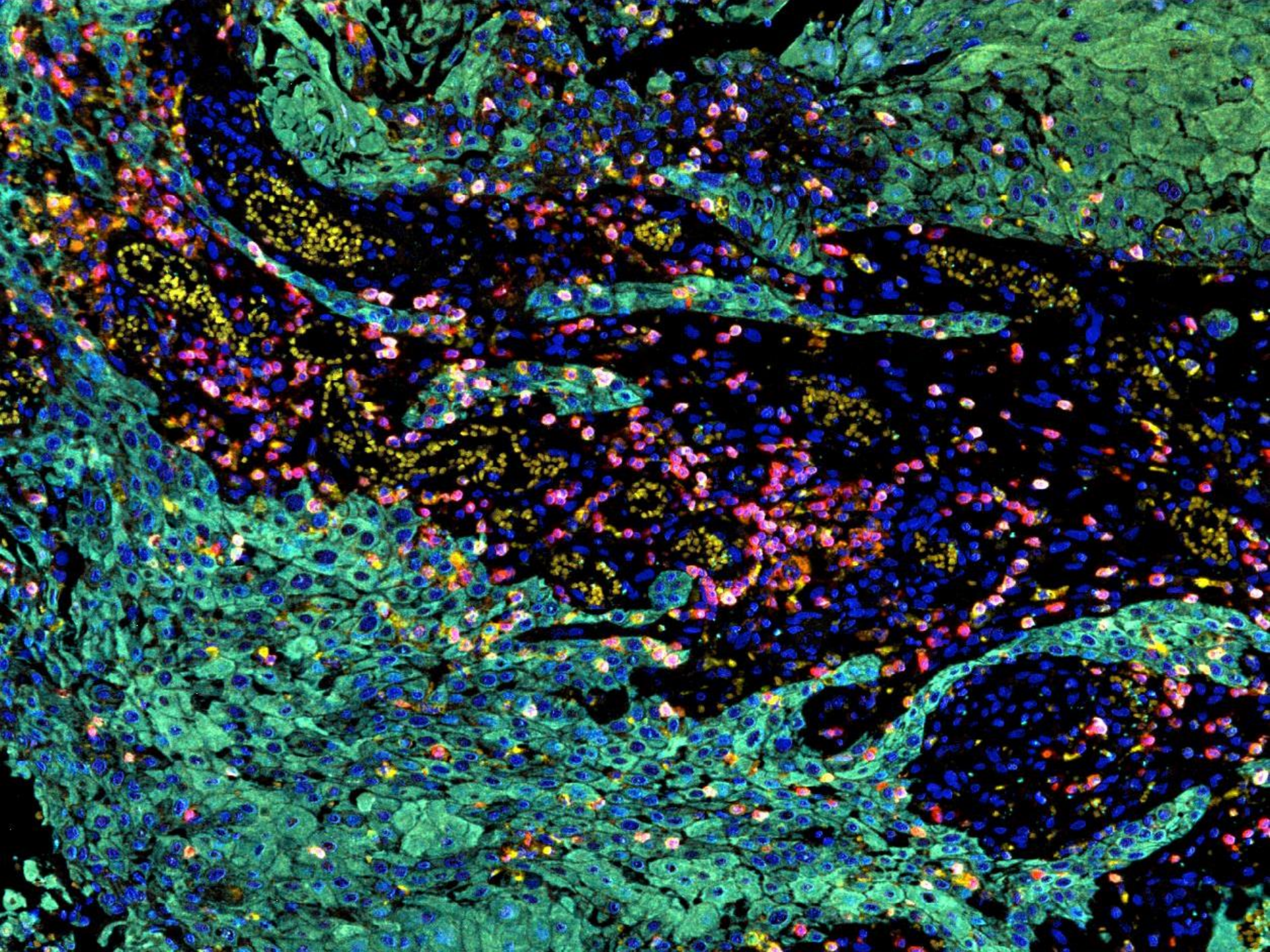


Potential impact of cancer treatment on TLSs



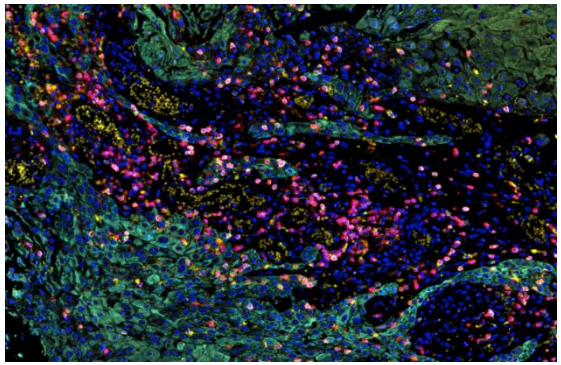
Science, 2022

Lab Invest, 2023



Analysis pipeline

Image acquisition → **Image analysis** → **Cell phenotyping**



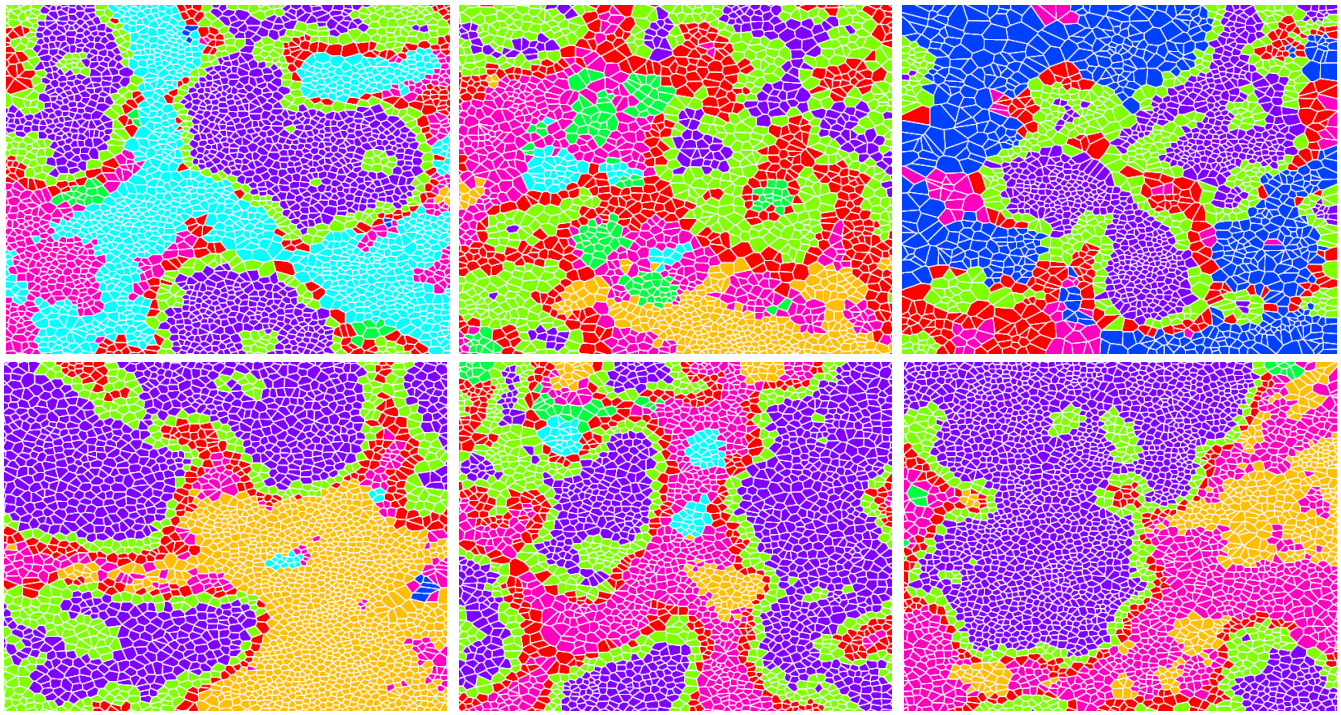
- **IMC1 : 40 markers, 15 phenotypes**
- [IMC2 : 42 markers, pending]
- mIF1 : 6 markers, XX phenotypes
- mIF2 : 6 markers, XX phenotypes
- mIF3 : 6 markers, XX phenotypes

Cell	X	Y	Marker 1 intensity	Marker 2 intensity
1	128	351	12.7	0.3
2	254	123	0.2	13.3
3	356	157	0.1	0.3

Cell	X	Y	Phenotype
1	128	351	Tumor cell
2	254	123	T CD4
3	356	157	NK

Spatial features extraction & Statistical analysis

Schürch's cellular neighborhoods (CN)



CN8-Stroma - Mac/T/mural aggregation

CN7-Tumor : Pure tumor

CN6-Stroma : Neutrophils aggregation

CN5-Stroma: Plasma cells aggregation

CN4-Stroma : Mural/mac aggregation

CN3-Internal Tumor/stroma interface

CN2-Stroma : T (CD4/CD8/reg) aggregation

CN1-External Tumor/Stroma interface

CN1-CN3-CN7 : gradient of tumor infiltration

CN2&CN8 : mixture of immune cells aggregation

CN4-CN5-CN6 : Immune monophenotypic aggregation

Thank you !