The Hallmarks of Cancer

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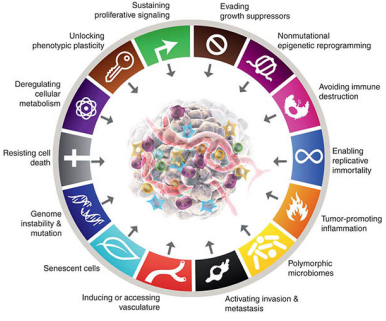

Cancer

[Kulesza et al. J. Pharmacokinetics and Pharmacodynamics, 2024]

Cancer = multiple aberrant processes across molecular, cellular, organ, and system level levels in space and time.

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A tumor is not just a mass of identical cancer cells, but rather a dynamic population of heterogeneous malignant cells that interact with each other and with their microenvironment in ways that influence their growth, survival, and evolution.

Cancer Modelling

- Multiple scales: genes, proteins, cells, tissue, microenvironment (immune cells, angiogenesis, ECM, nutrients, stroma)

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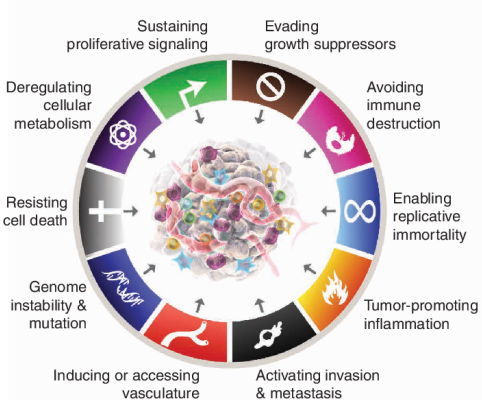
- top down: Data inform the models
- bottom up: Biological processes inform the models
- We need to strike a balance between model complexity, available data and interpretability.

The Hallmarks of Cancer

14 Hallmarks in 3 papers by Hanahan and Weinberg:

- Hanahan, Weinberg, Cell 2000
- Hanahan, Weinberg, Cell 2011
- Hanahan, Cancer Discovery, 2022

Hallmarks


Sustaining proliferative signaling
Evading growth suppressors
Deregulating cellular metabolism
Avoiding immune destruction
Resisting cell death
Enabling replicative immortality
Genome instability & mutation
Tumor-promoting inflammation
Inducing or accessing vasculature
Activating invasion & metastasis


Emerging hallmarks & enabling characteristics
Unlocking phenotypic plasticity
Nonmutational epigenetic reprogramming
Senescent cells
Polymorphic microbiomes

(1) Sustained proliferative signalling

Known growth promoters: PTEN, PIP3, PI3K, mTOR, etc.

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(2) Avoidance of growth suppression

For example loss of P53 signalling, or loss of contact inhibition

(3) Resisting cell death

P53 can signal apoptosis (cell suicide)

(4) Enabling replicative immortality

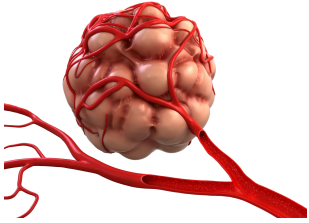
- telomerases can add telomeres to the cell's DNA and prevent aging.
- unclear: interaction of P53 with telomerase

(5) Angiogenesis

Angiogenesis is the sprouting of new blood vessels

- induced by VEGF, TSP-1 signalling
- supplied tumor with nutrients and oxygen
- supplies immune response
- opens doorway for chemical drugs

Modellers distinguish between vascular and avascular tumors.

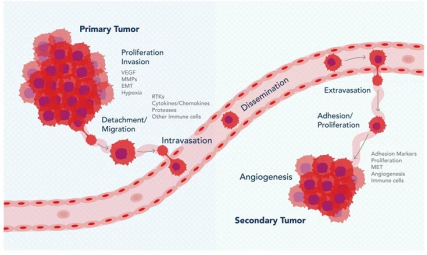


(6) Invasion and Metastasis

The metastatic cascade

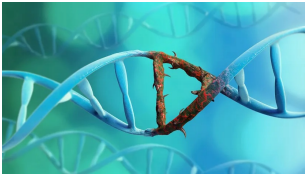
1. local invasion
2. intravasation
3. dissemination
4. extravasation
5. micrometastasis
6. Metastasis

Local invasion is based on the endothelial-mesenchymal transition (EMT)
Reverse transition MET is also possible



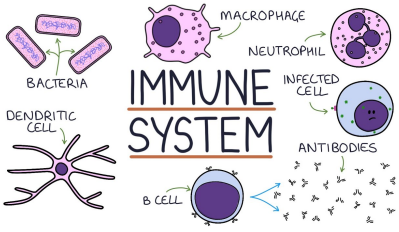
(7) Genome instability

- cancer increase rate of mutation due to loss of surveillance systems (again P53 involved)
- driver mutations: contribute to tumor initiation and progression. Give cancer a distinct evolutionary advantage.
- passenger mutations no or minimal evolutionary advantage.
- full grown cancer has 600-1000 different phenotypes.



(8) Tumor promoting inflammation

- inflammation can contribute to the first six hallmarks, growth factors, proliferative signalling, angiogenesis, metastasis, etc.
- immune response can make everything worse.
- But, Immune response is the major control for all tumors that we do not see.



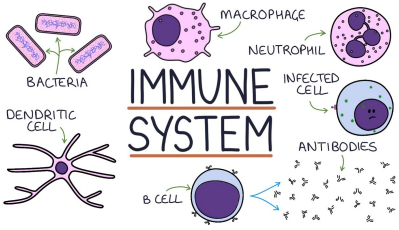
(9) Reprogramming energy metabolism

- normal: glycolysis and oxidative phosphorylation in the mitochondria, creates 30-32 ATP per reaction.
- Warburg: aerobic glycolysis, fermentation, produces 2 ATP, works in acidic conditions.
- Very little modelling in this area.

(10) Avoiding immune destruction

Cancer can reprogram the immune response

- deactivate T-cell response through expression of PD-1.
- reprogram macrophages from M1 to M2
- tumor associate fibroblasts help tumor growth
- platelets protect circulating cancer cell clusters



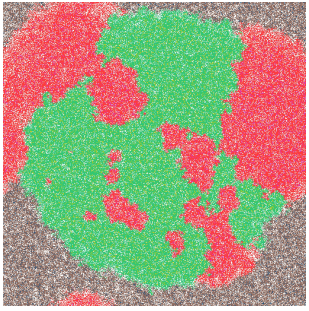
(11) Phenotypic plasticity

Cells do not follow the normal differentiation process and they use alternative progressions, like

- dedifferentiation
- blocked differentiation
- transdifferentiation

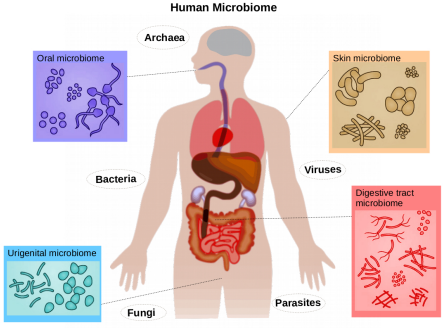
(12) Epigenetic programming

- caused by microenvironment and treatment
- leads to increased heterogeneity
- cancer field effect
- also relevant for stromal cells



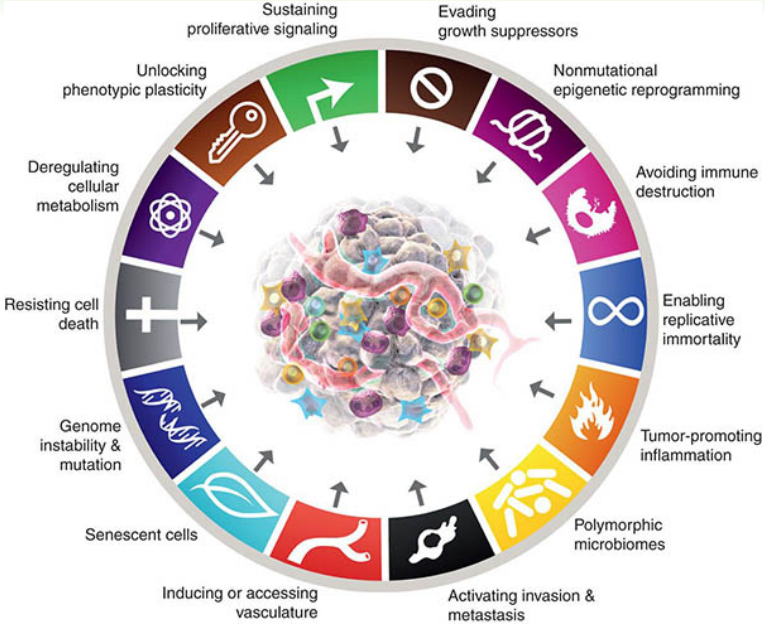
(13) Role of the microbiome

- microbiomes play important roles for the health of the gut, the lung, the skin, the reproductive organs.
- microbiome is likely to have a huge impact on cancer progression
- wide open research area.



(14) Senescent cells

- complex signalling
- avoidance of treatments and resistance
- senescent tumor associated fibroblasts are dangerous cancer initiators.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- Chronobiology Cancer growth and treatment are affected by the circadian rhythm, menstrual cycle and other periodic processes. [Clairambeault, Yea Kyong Kim]
- Metronomic therapy: repeated low-dose therapy to avoid resistance. Connection to adaptive evolutionary therapies has not been made. [Ledzewicz]