Cancer Pathobiology
11-10-25

Exogenous factors in oncogenesis ~~and therapy~~

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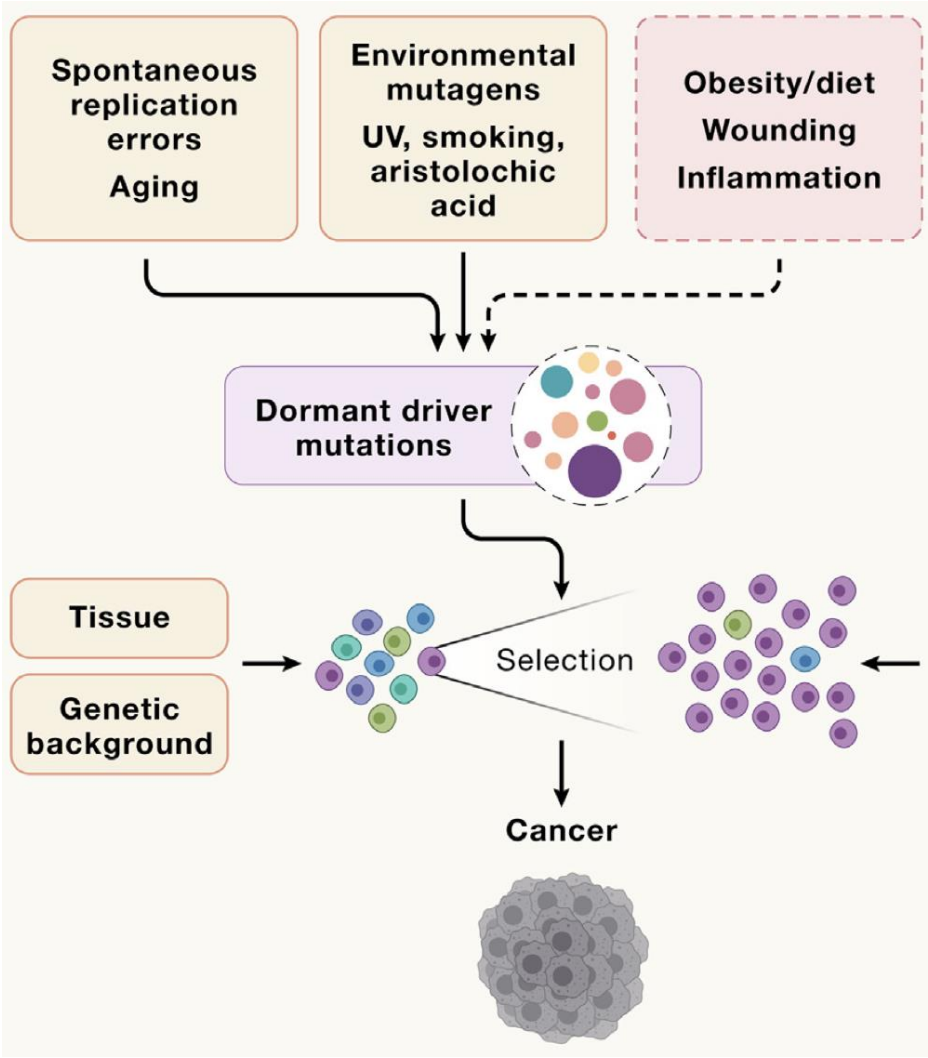
Two "opposing" but equally true statements

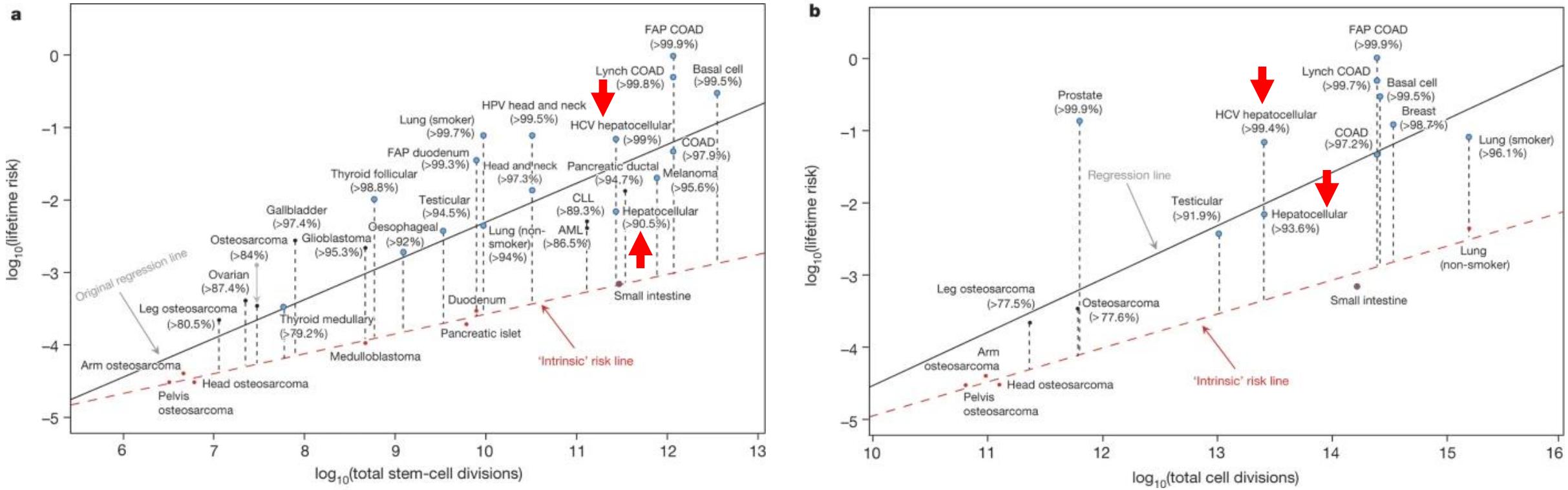
- Cancer is an extremely rare event
- Cancer is a very common disease
- 1 in 100-150 trillion cells successfully transforms



Cancer development: an extremely rare event

- Several barriers inhibit carcinogenesis and metastasis
- Mammalian cells equipped with multiple tumor suppressive mechanisms
- Each proliferative signal is opposed by multiple negative feedbacks
- Other barriers: immune evasion, stress management, metabolic requirements

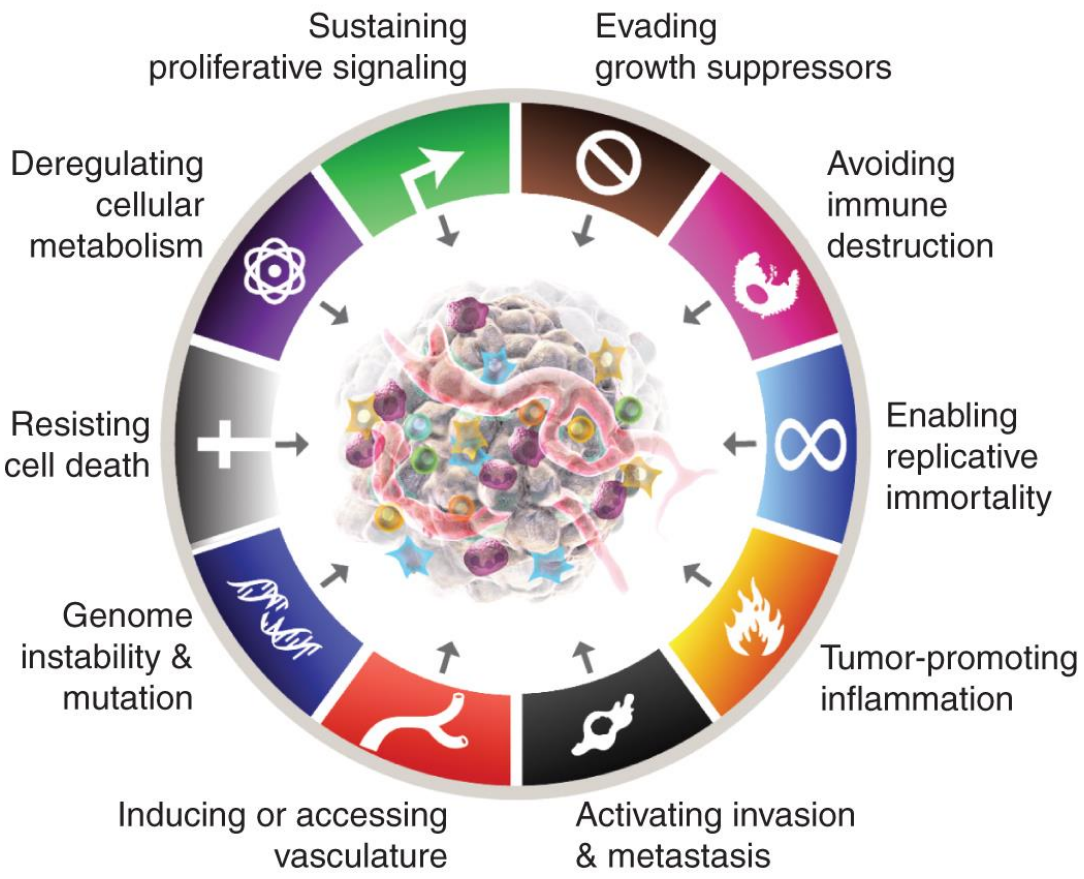
Cancer development: Intrinsic V Extrinsic drivers

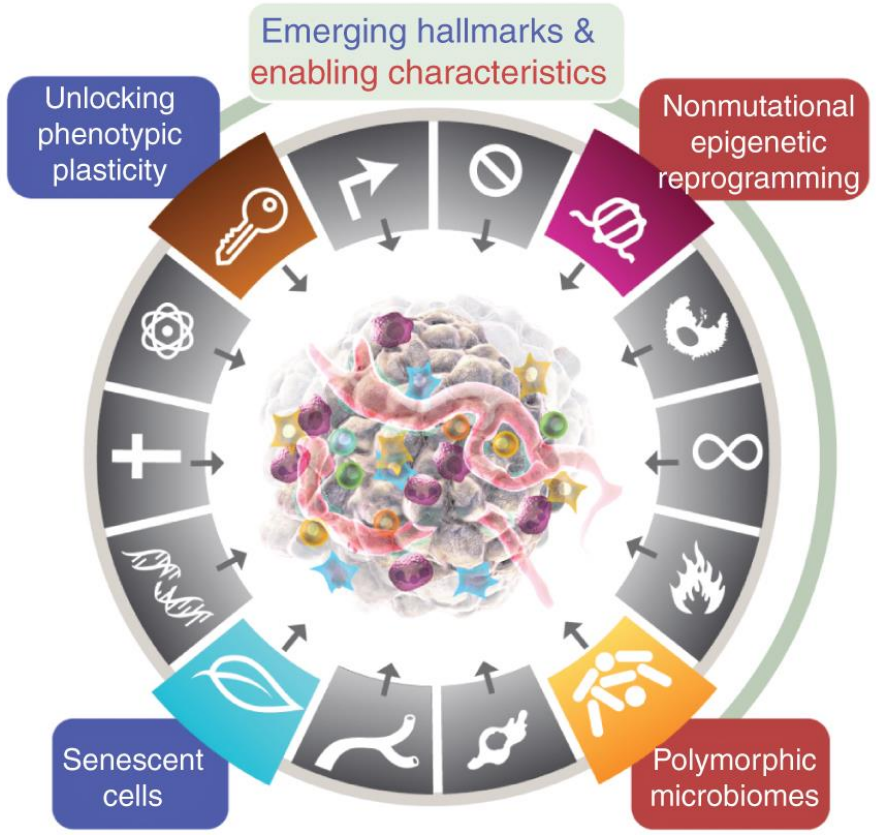


Wu *et al.*, Nature, 2015

Both models (based on stem-cell and total cell divisions) show that over 90% cancers arise due to extrinsic factors.

Hallmarks of cancer





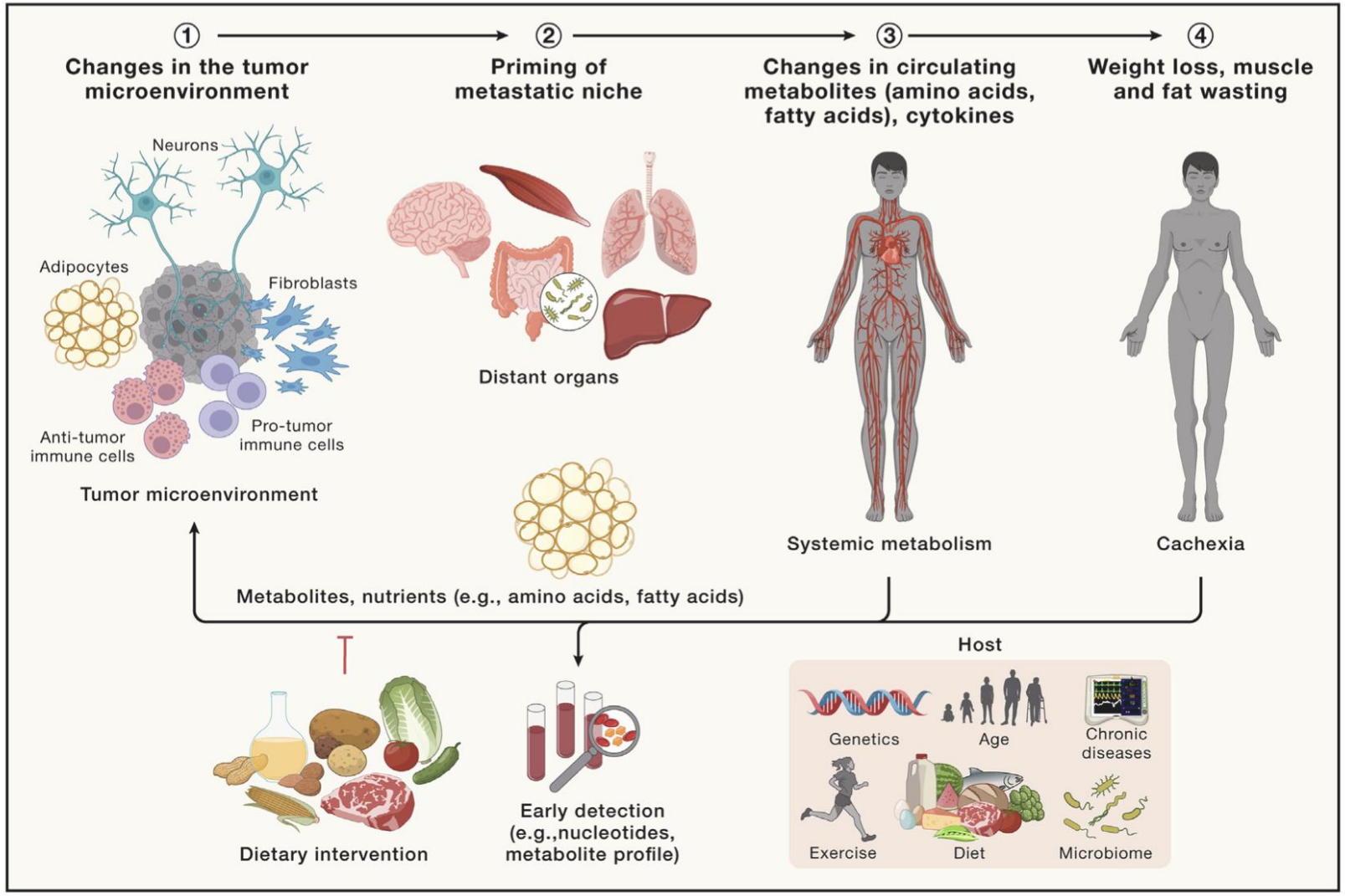
Cancer Discov. 2022;12(1):31-46. doi:10.1158/2159-8290.CD-21-1059

Cancer is a systemic disease

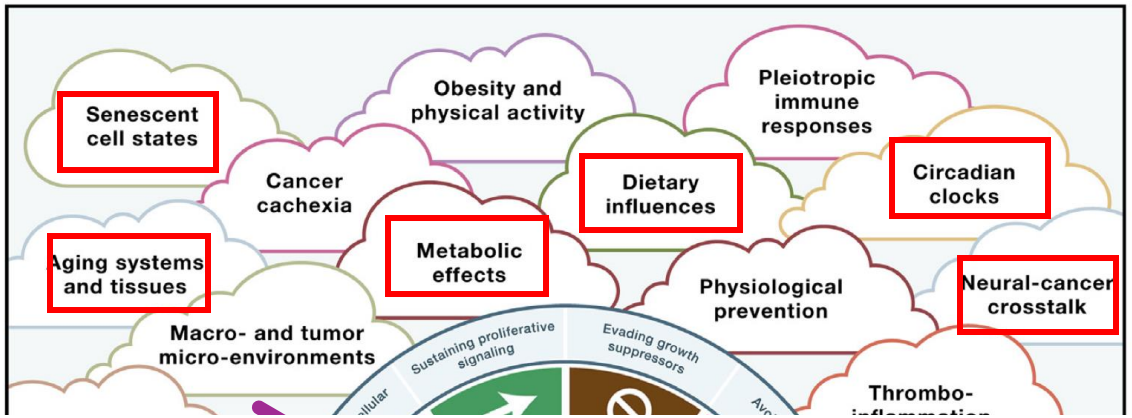
- Cancer mutations: rewire/enhance proliferative pathways and suppress cell death mechanisms

- Cancer cells require a host of external factors and signals for successful colonization and migration
    1. Growth factors
    2. Extracellular matrix proteins
    3. Cross-talk with other systems
    4. Inflammation
    5. Microbiome
    6. Micro- and macronutrients

Cancer is a systemic disease

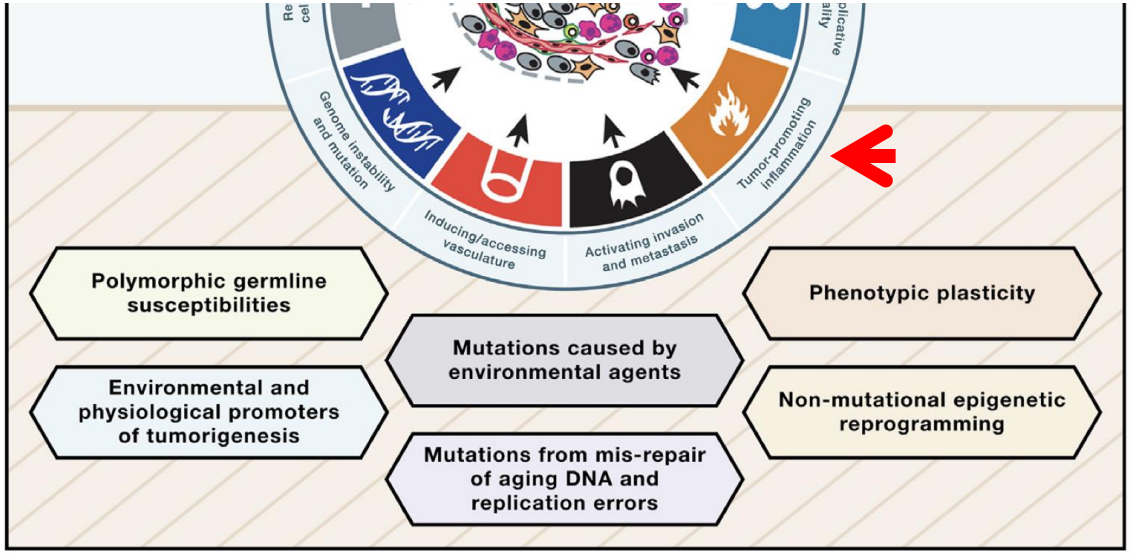


The “clouds of complexity”



- Highly tissue and context specific
- Systemic in nature
- Mutation-specific adaptations in the same organ

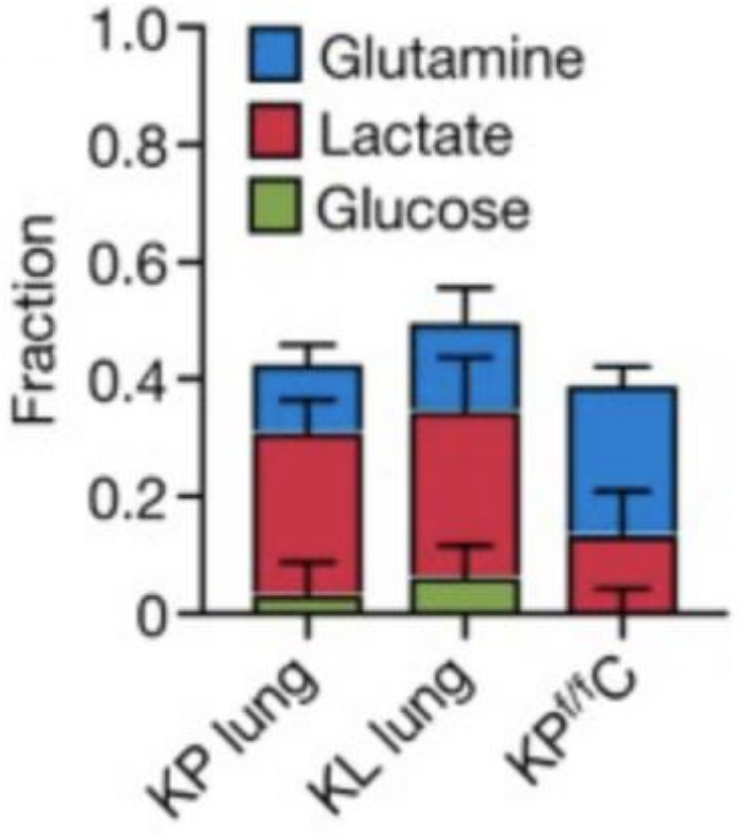
Which C source is used for energy and does that depend on mutation and anatomic location?



- background
- Driven by environmental effects and patient genetics
- Biological sex as a variable
- Highly variable effects of exogenous factors

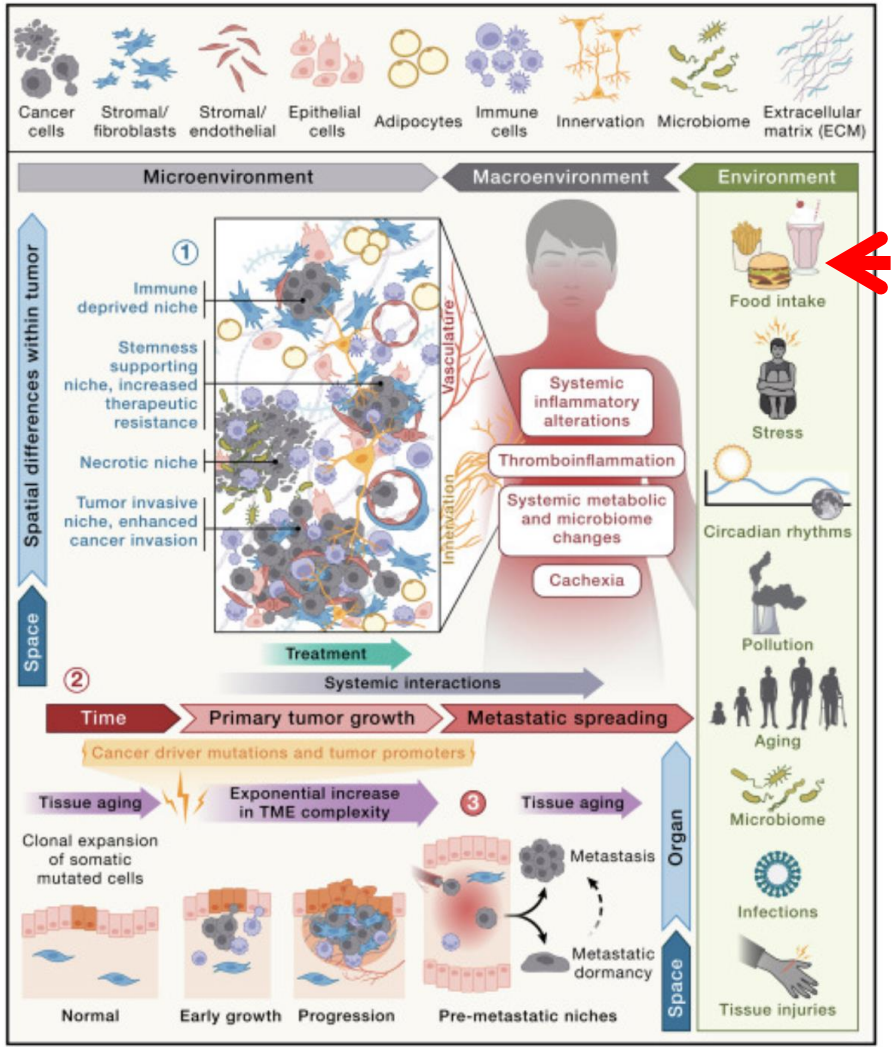
Swanton *et al.*, Cell, 2024

Circulating lactate as an energy source



Faubert *et al.*, Cell, 2017
Hui *et al.*, Nature, 2017

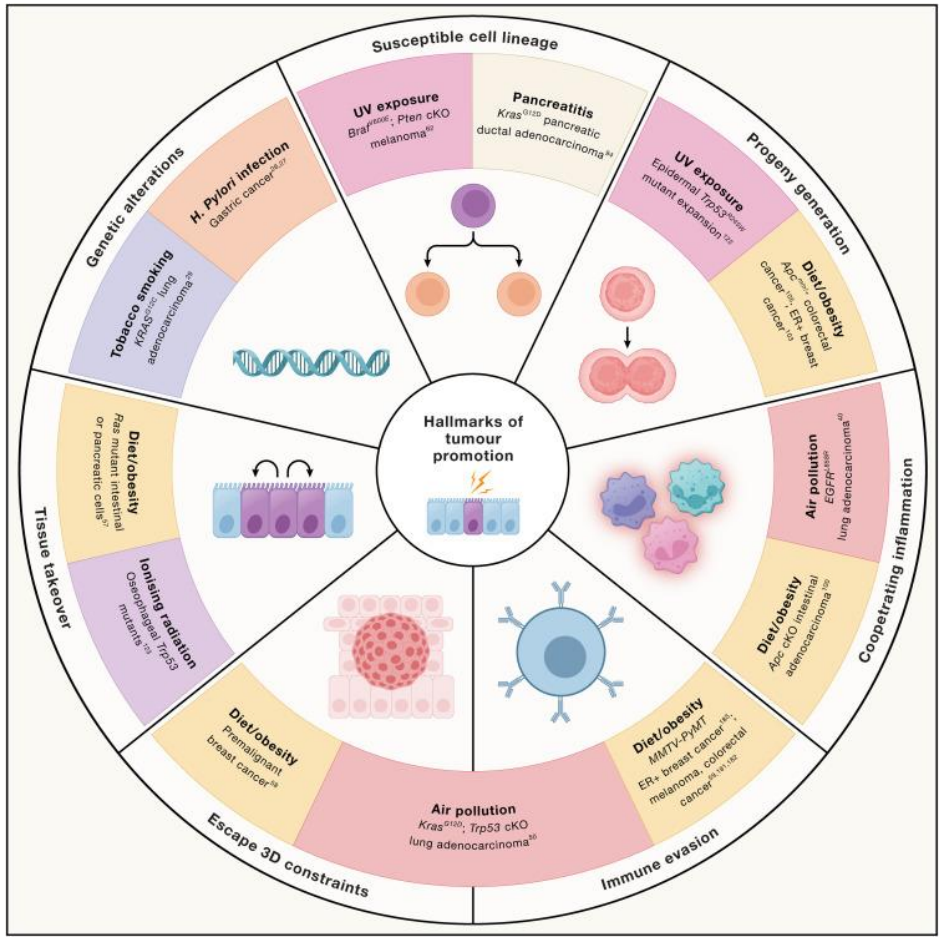
Importance of tumor micro- and macro-environment in cancer pathobiology



- TME contents: cancer cells, stromal cells, immune cells , fibroblasts, vasculature, fat, nerve cells, and extracellular matrix (ECM) components
- Spatial heterogeneity of the TME components - desmoplasia, angiogenesis, and immune modulation
- Macroenvironment: systemic inflammation, metabolic status, microbiome, etc
- Each components contribute to tumorigenesis, metastasis, and therapeutic response
- Metastasis exemplifies the role of non-cancerous cells in secondary tumorigenesis

Swanton *et al.*, Cell, 2024

Why focus on obesity and cancer?



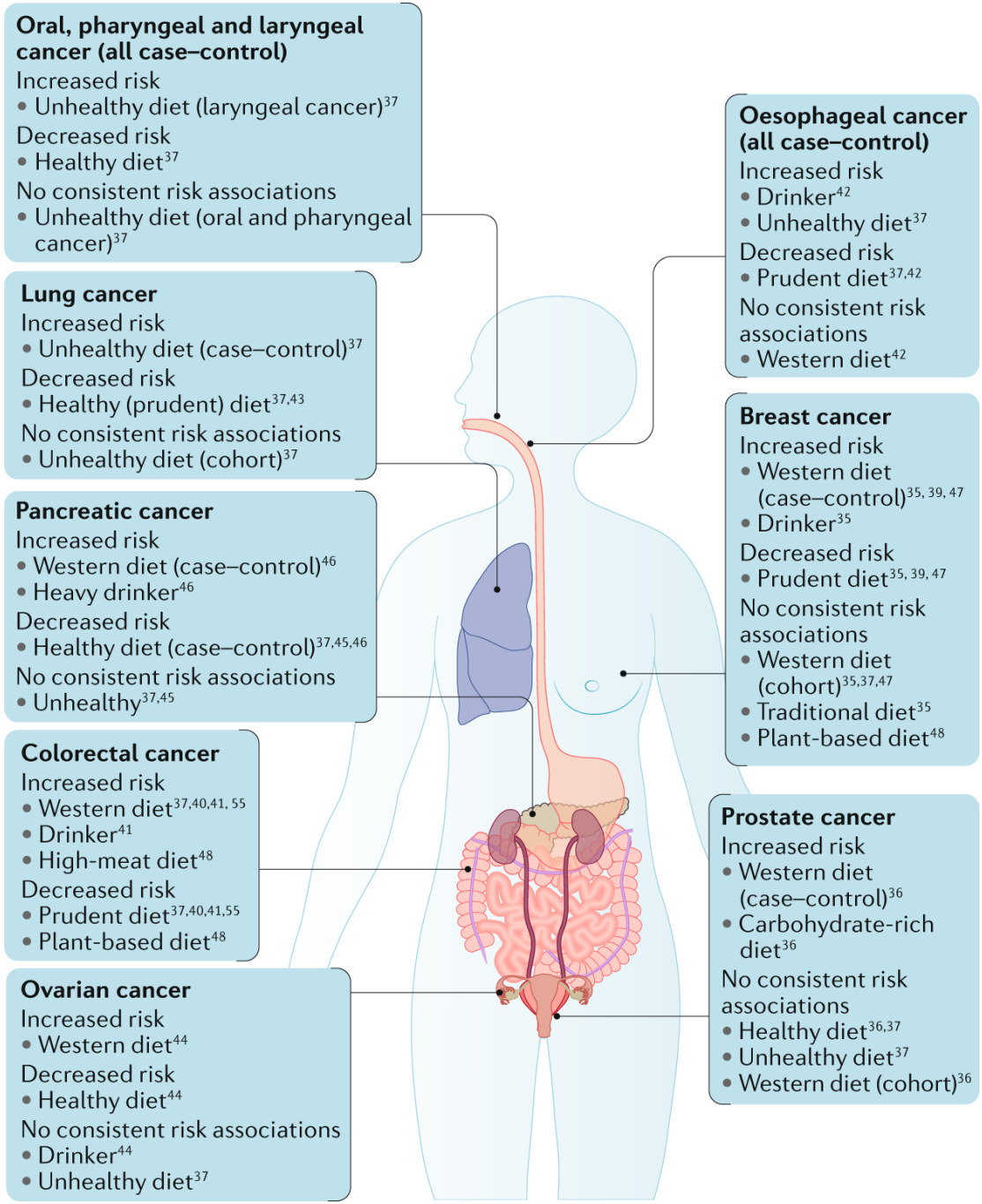
- Chronic inflammation
- Hormonal imbalance
- Metabolic dysfunction
- Immune system impairment
- Adipokines and other growth factors
- Microenvironmental changes
- Tissue permeability
- Microbiome dysbiosis
- Oxidative and other stress
- Nutritional reserves

Influence of organismal metabolism on tumorigenesis

- Cancer cells impact metabolism at the organismal level vice a versa
- Metabolic disorders and T2D are strong predisposition factor for cancer development
- T2D: Hyperglycemia plus compensatory increase in insulin/IGF-1
- High sugar/fat WD + sedentary lifestyle increases cancer incidence (liver, CRC……)

Obesity and Over-nutrition in cancer

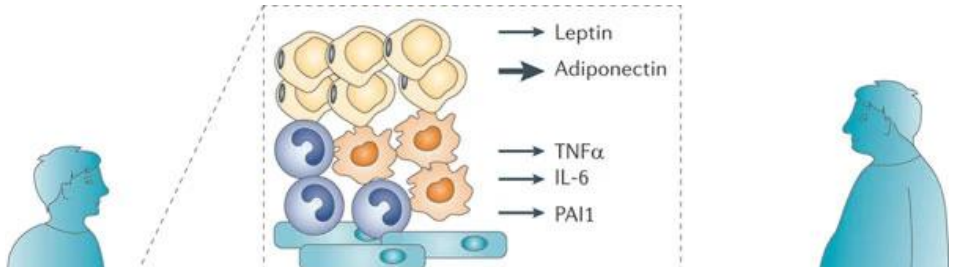
- Metabolic dysfunction is a major risk factor for cancer development – obesity, diabetes, MASLD/MASH
- 5-8% global cancers are associated with obesity and related metabolic dysfunction
- Pro-tumorigenic effects:
  - Nutritional reserves
  - Immune suppression
  - Metastatic niche
  - Drug sequestration
  - Stiffness and mechanical stress
- Anti-tumorigenic effects:
  - Delay in cachexia



- At least 14 types of cancer are linked to obesity, including endometrial cancer, esophageal cancer, and pancreatic cancer.
- Hormones, adipokines, and proinflammatory immune cells promote cancer development in obesity.
- Obesity suppresses antitumor immunity and causes metabolic and functional impairments in antitumor immune cells.
- Although obesity increases cancer risk, a higher BMI correlated with improved responsiveness to ICB in some clinical studies ('obesity paradox') but the universality of this phenomenon is still under debate.
- There is so far insufficient evidence that obesity affects adoptive cell therapies.

Steck and Murphy, Nature Reviews Cancer, 2019

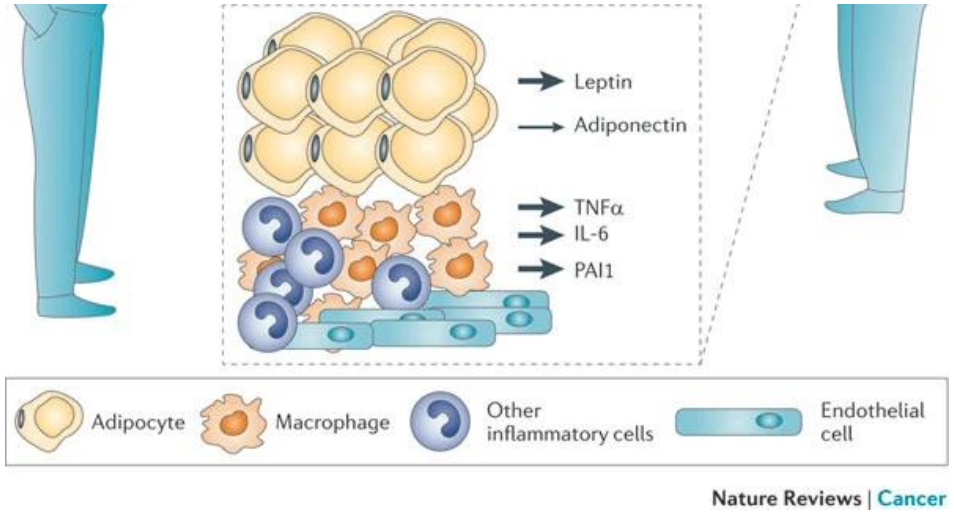
Oncogenic adipocyte dysfunction in obesity



Lean

- Low leptin
- High adiponectin
- less macrophage infiltration and

How does adipocyte dysfunction promote distant tumorigenesis?

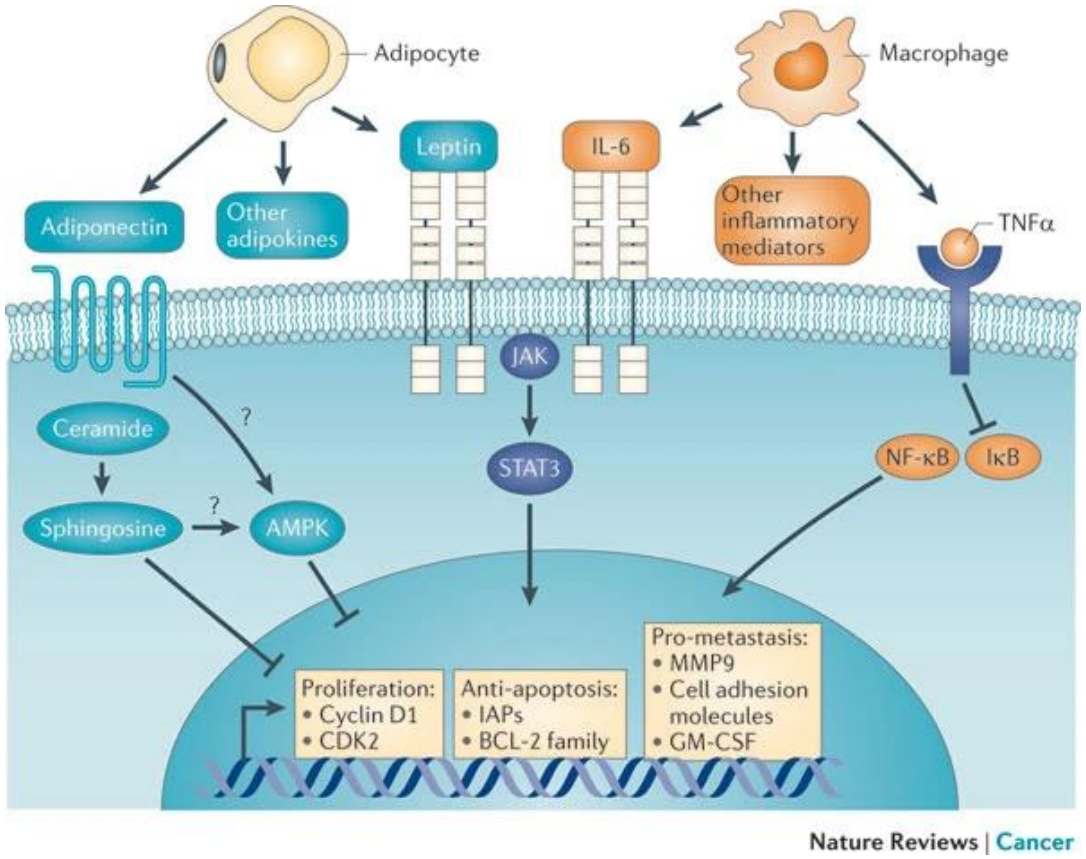


Khandekar *et al.*, Nature Reviews Cancer, 2011

Obese

- High leptin
- Low adiponectin
- Significant macrophage infiltration
- Increased cancer-promoting cytokines

Adipokine deregulation in obesity



- **Adiponectin (good adipokine)**

binds ADIPOR1/2

promotes AMPK signaling

increased sphingosine production

- **Leptin (bad adipokine)**

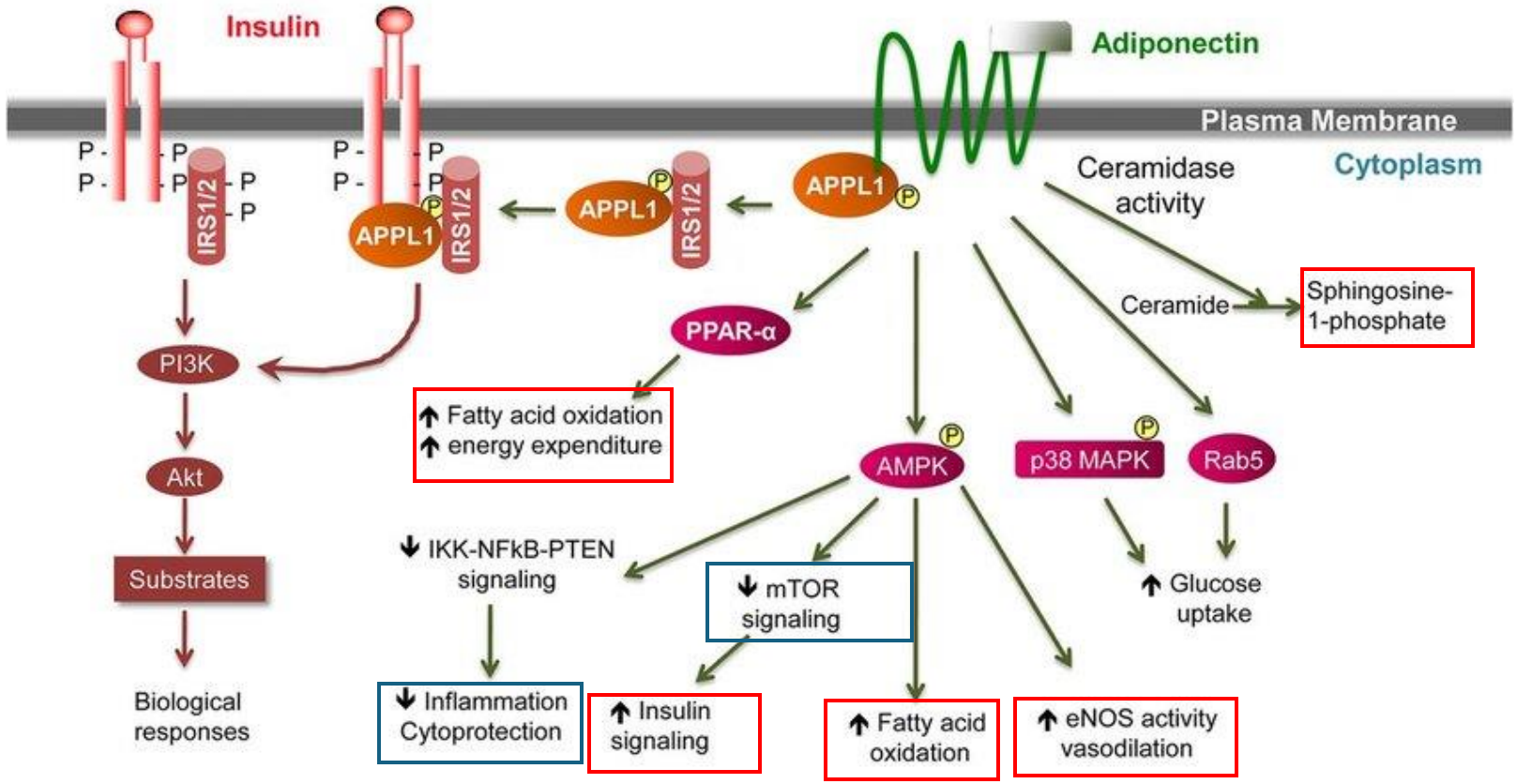
binds leptin or IL-6 receptors

drives Jak/Stat oncogenic signal transduction

Activates NFkB pathway

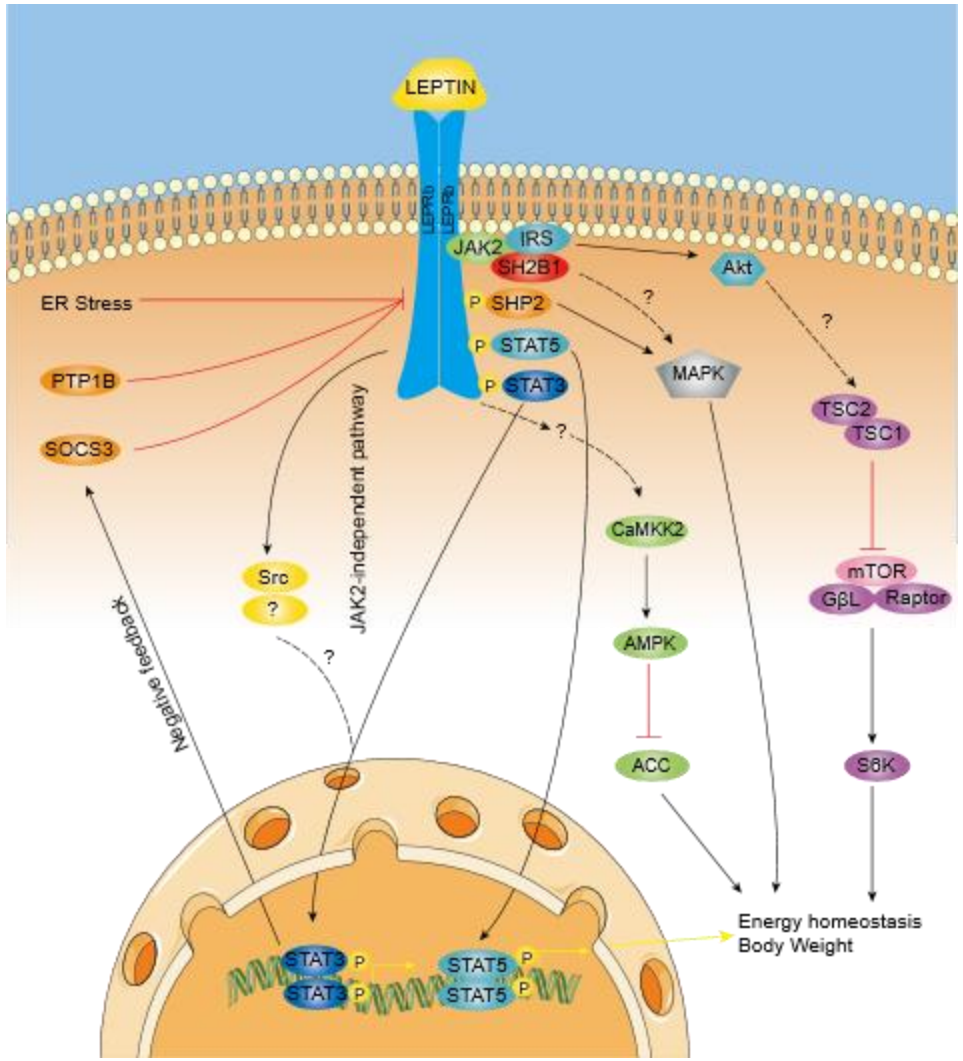
Khandekar *et al.*, Nature Reviews Cancer, 2011

Adiponectin: promotes catabolic pathways



Ruan *et al.*, JMCB, 2016

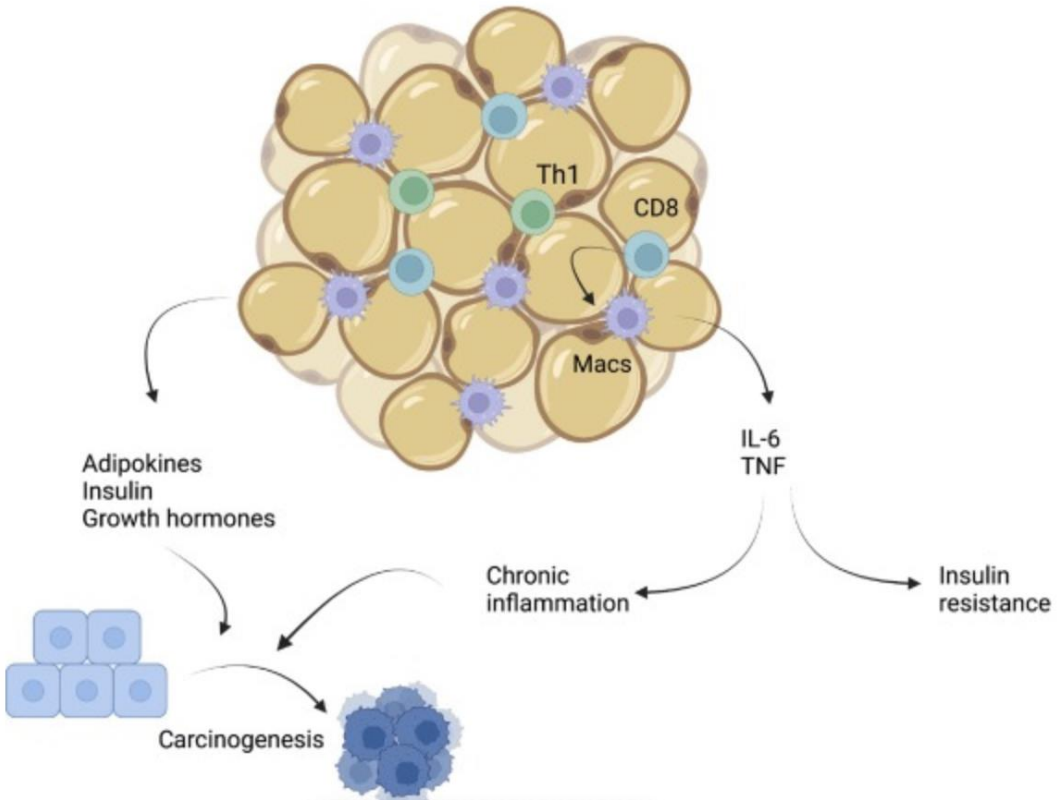
Leptin promotes anabolism and oncogenesis



https://www.creative-diagnostics.com/leptin-signaling-pathway.htm

- Leptin resistance and increased leptin levels are hallmarks of obesity
- Leptin activates mTORC1 pathway
- Leptin activates the canonical JA/STAT mechanism to drive proliferation and immune modulation.

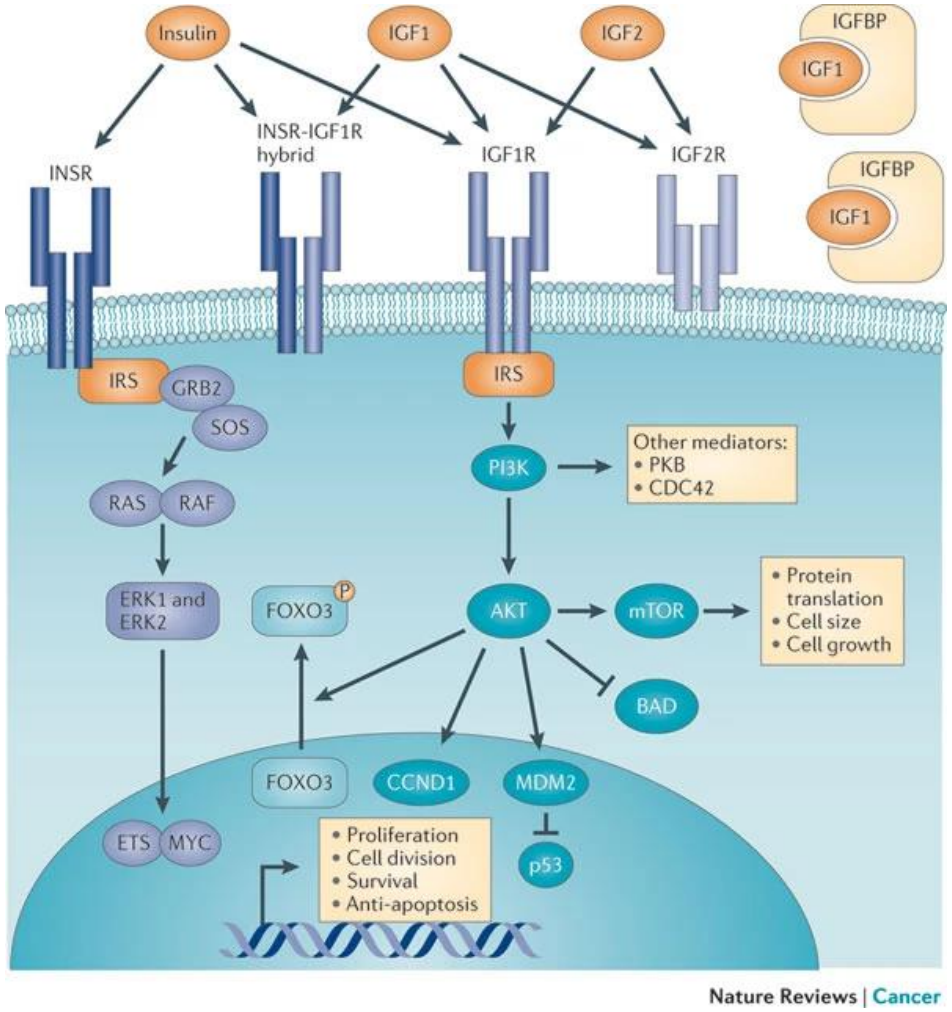
Obesity and chronic inflammation: drivers of oncogenesis



- Chronically inflamed adipose tissue are inflamed with Th1, $CD8^+$ T cells, and macrophages
- IL-6 and TNF promotes insulin resistance and chronic/systemic inflammation to drive oncogenesis
- Adipokines, macronutrients, and growth hormones contribute to carcinogenesis

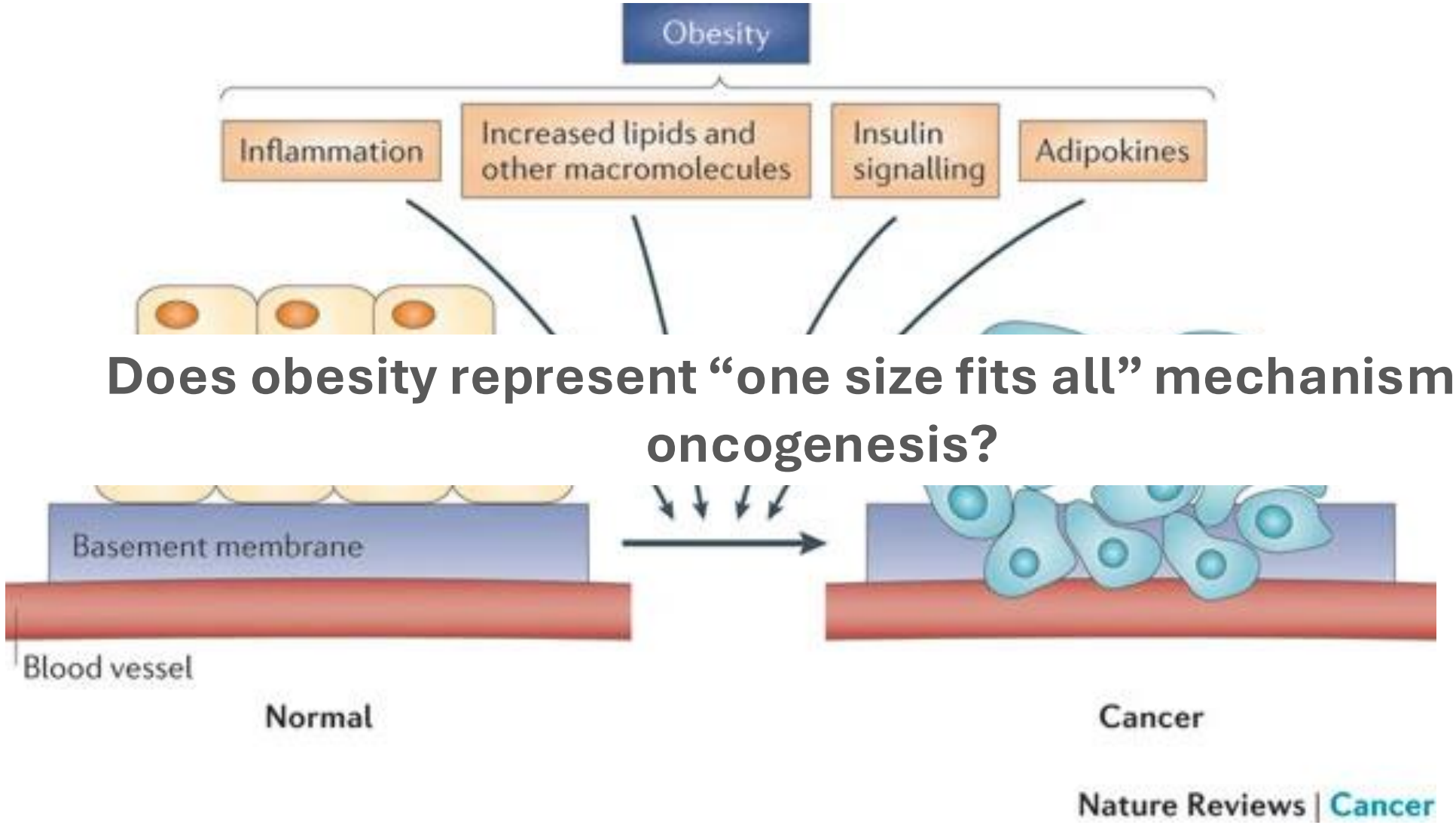
Dyck *et al.*, Trends in Molecular Medicine, 2023

Hyperinsulinemia drives oncogenic signaling



Khandekar *et al.*, Nature Reviews Cancer, 2011

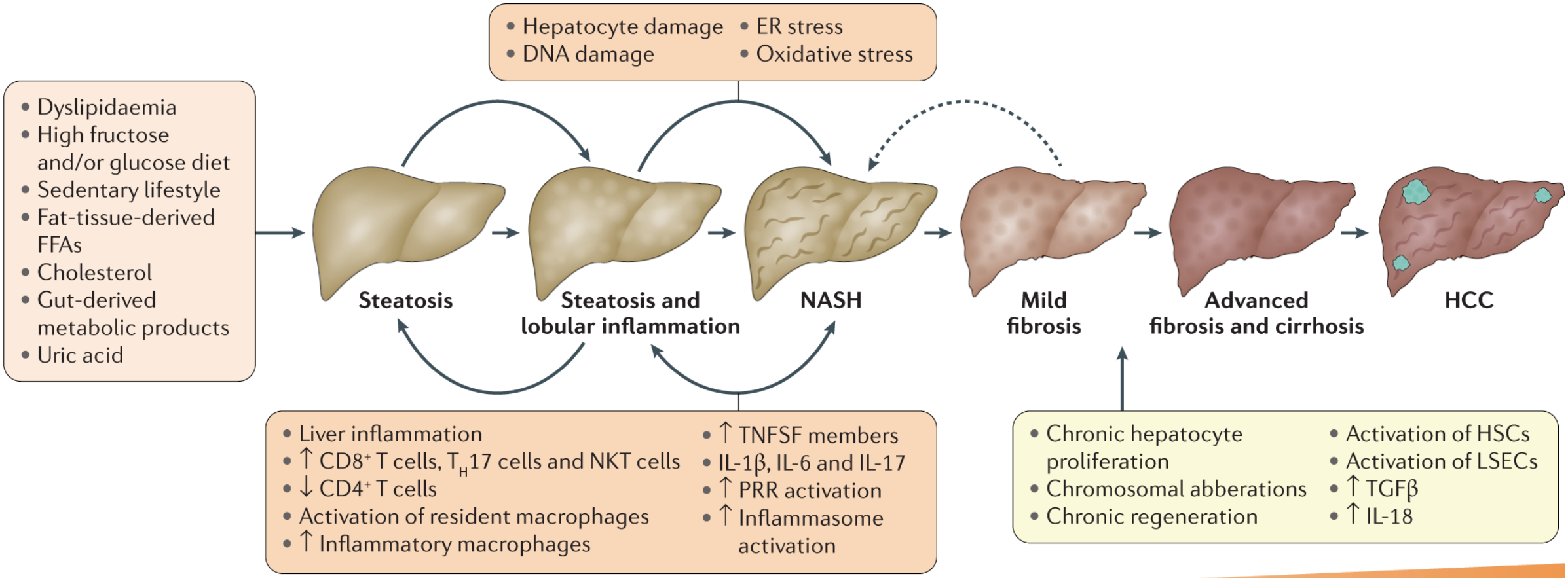
- Excess Insulin and IGF1 are hallmarks of insulin resistance
- Insulin – promotes MAPK/ERK signaling pathway
- IGF1 – promotes PI3K/AKT signaling



Does obesity represent "one size fits all" mechanism for oncogenesis?

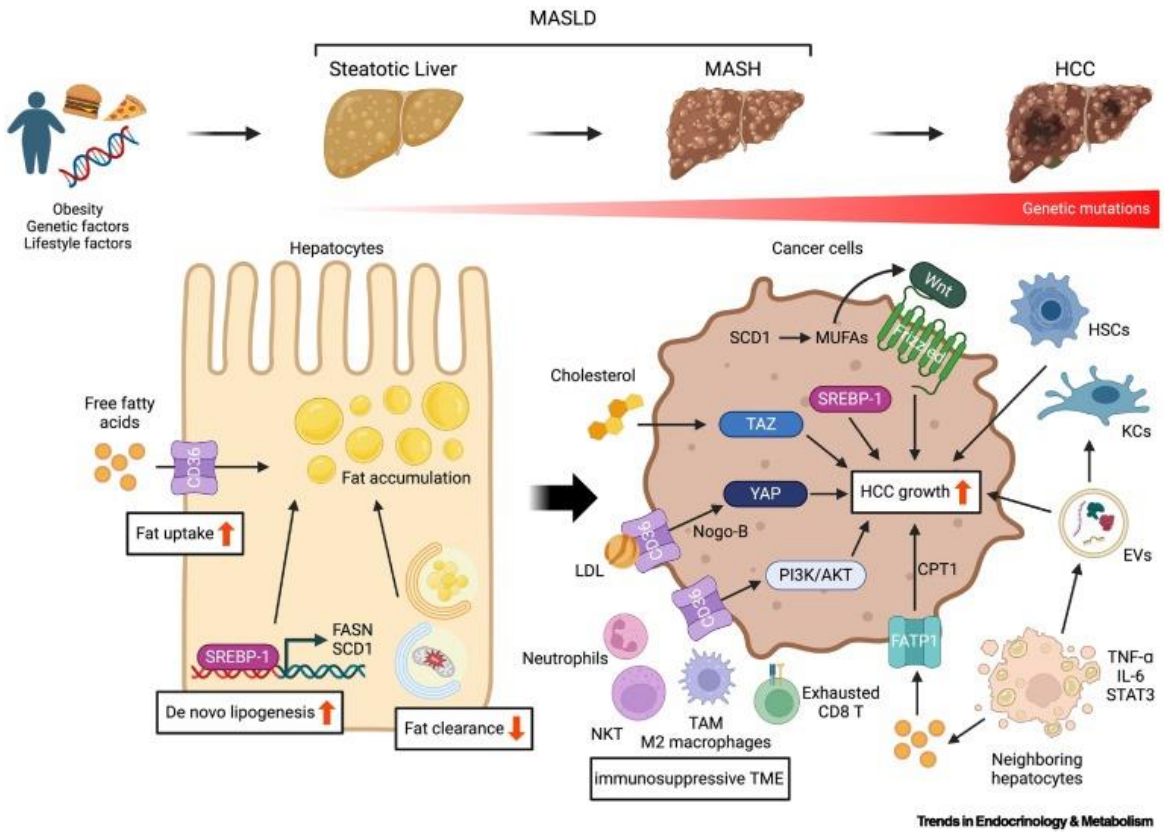
Khandekar *et al.*, Nature Reviews Cancer, 2011

Dietary insults and liver cancer



Antsee *et al.*, Nature reviews Gastro and Hepatology, 2019

MASLD-HCC pathobiology



Kim *et al.*, Trends in Endo & Met., 2024

Excess fat accumulation (steatosis) and inflammation induces liver damage

↓

Liver damage activates repair mechanisms, including HSC differentiation and activation

↓

Fibrosis

↓

Advanced fibrosis

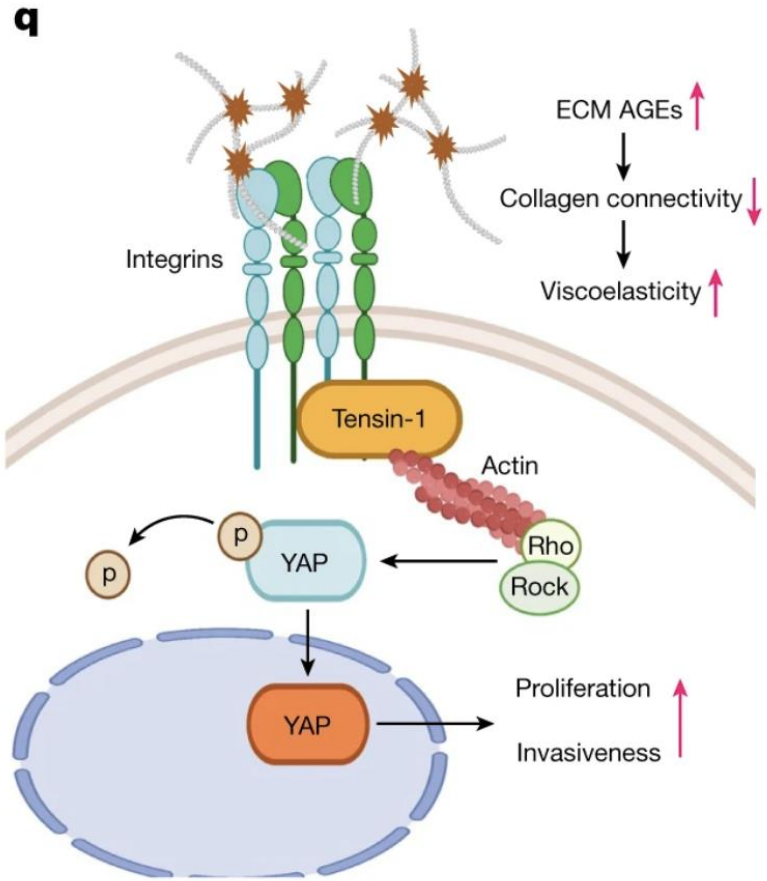
↓

Cirrhosis

↓

HCC

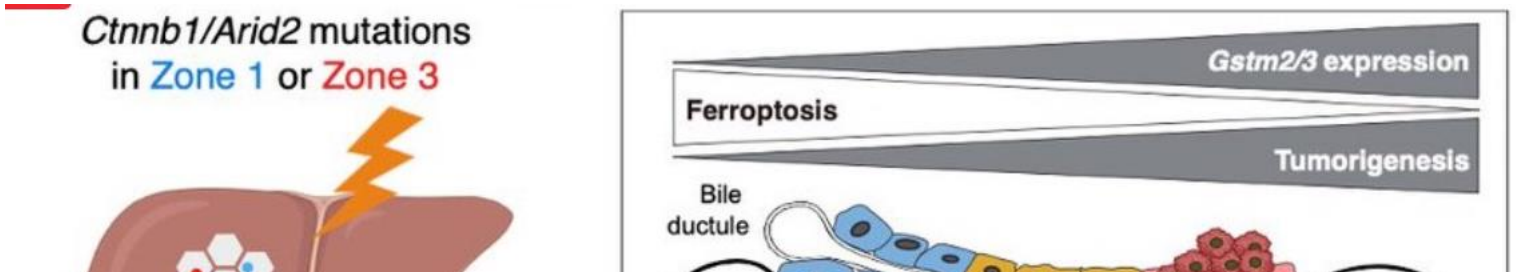
Hyperglycemia alters tissue viscoelasticity through glycation



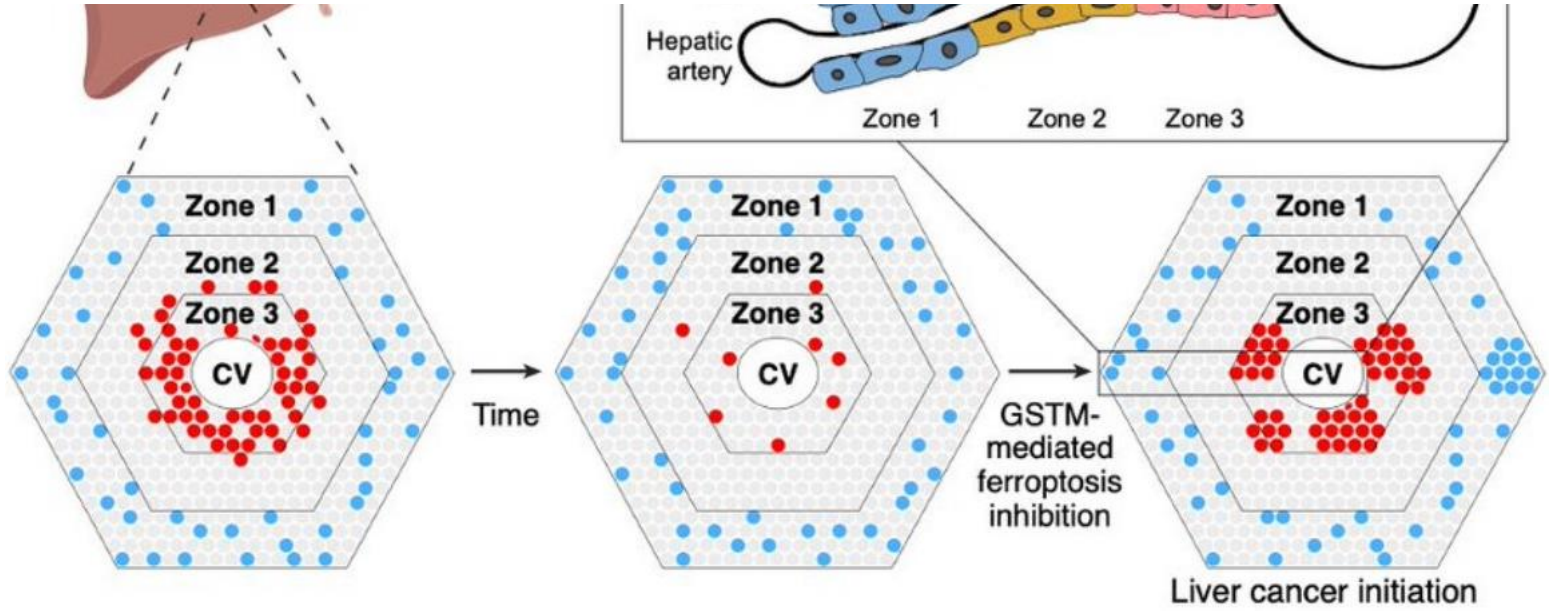
- Hyperglycemia increases glycation of serum proteins and formation of advanced glycation end products
- AGE-collagens forms shorter fibers with lower interconnectivity
- Increased viscoelasticity increases tumor proliferation and metastatic potential through enhanced YAP singnaling

Fan *et al.*, Nature 2024

Metabolic zonation: organizing different liver functions

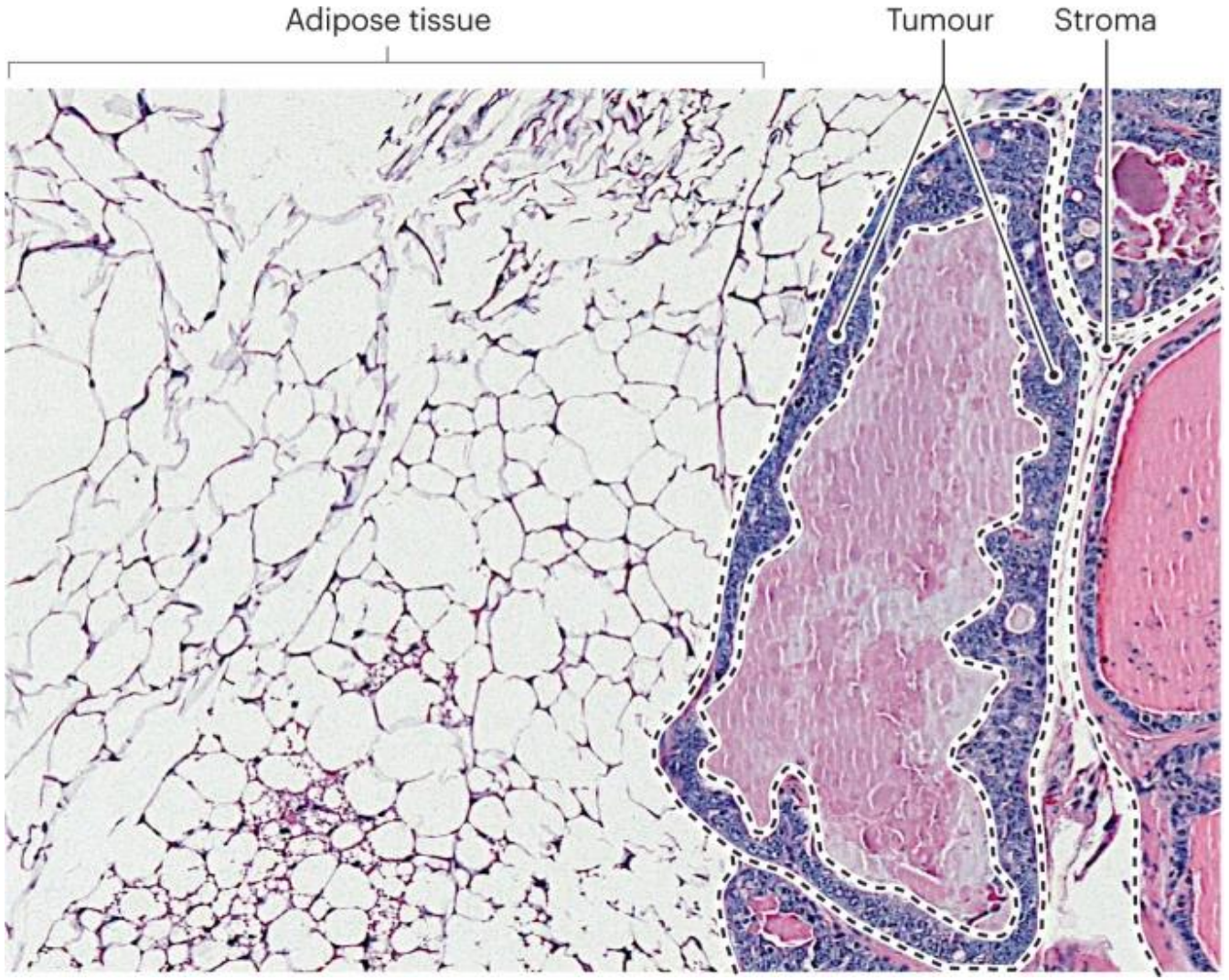


But what about other organs?



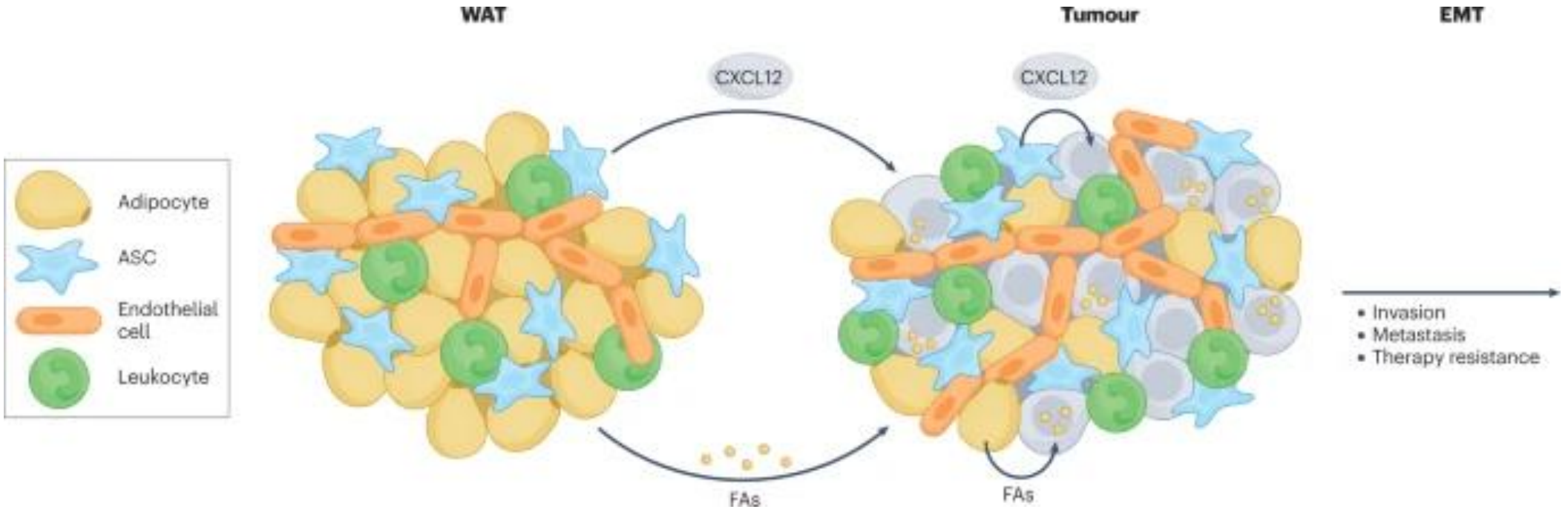
Guo *et al.*, Science, 2025

Obesity establishes a supportive niche for prostate cancer



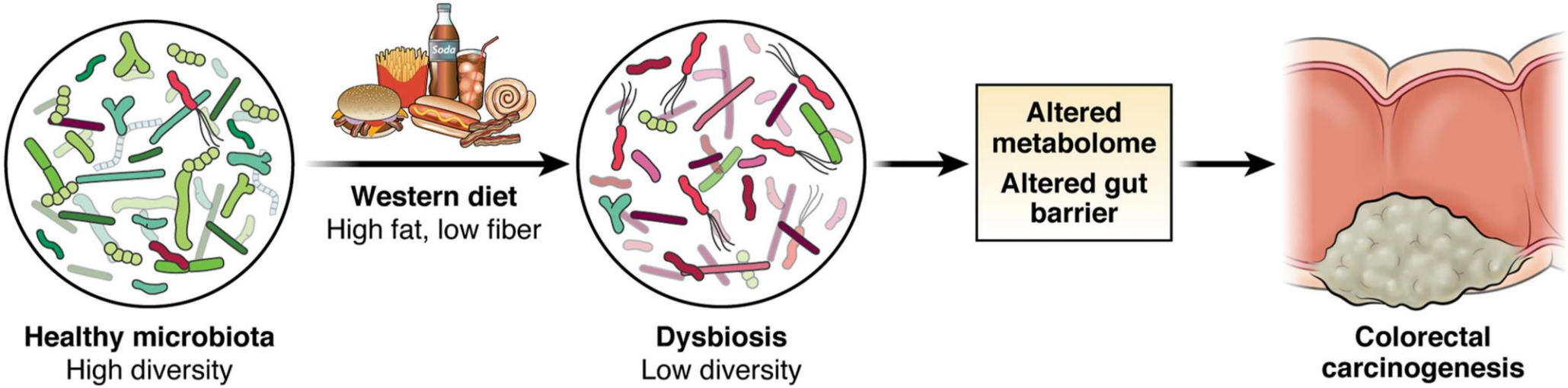
Saha *et al.*, Naure Urology, 2023

Obesity establishes a supportive niche for prostate cancer



Saha *et al.*, Nature Urology, 2023

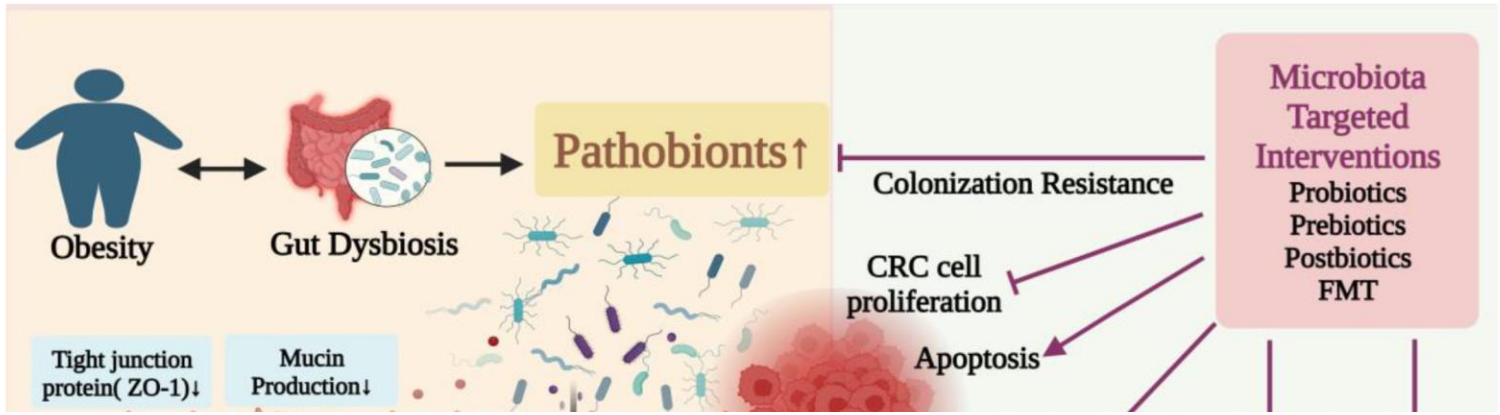
Obesity alters gut microbiome diversity and repertoire



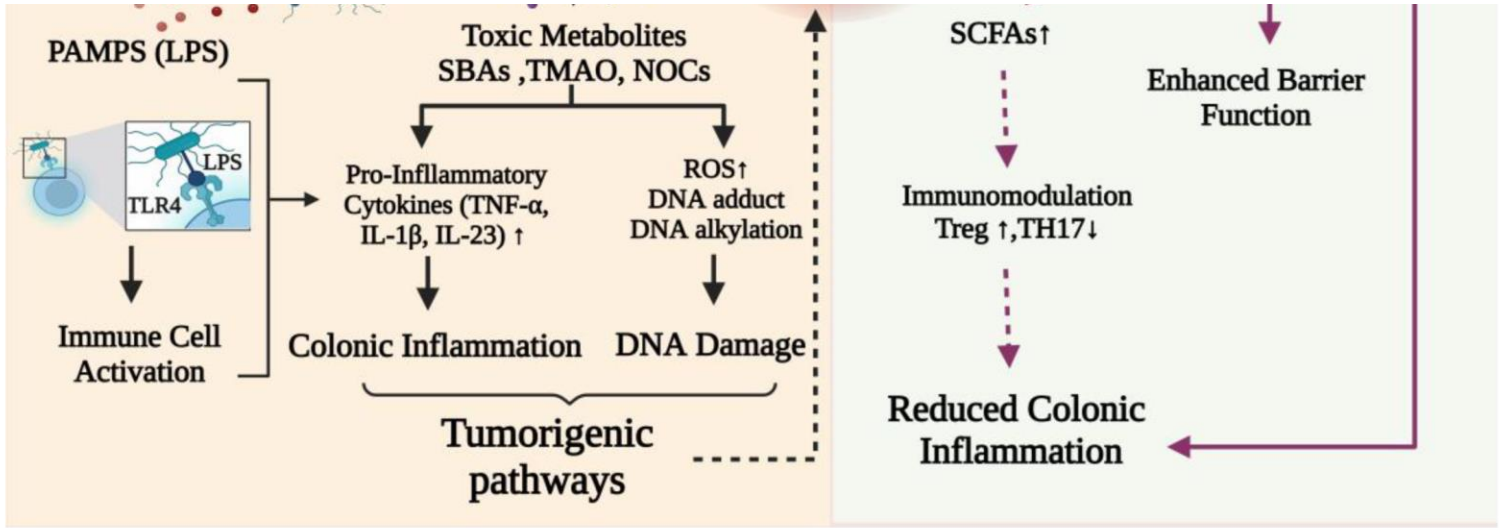
- WD and Obesity reduces gut microbial biodiversity (dysbiosis)
- Decreases health-supporting bacteria and preferentially selects oncometabolite-producing bugs

Viennois *et al.*, Gastroenterology, 2022

Obesity alters gut microbiome diversity and repertoire

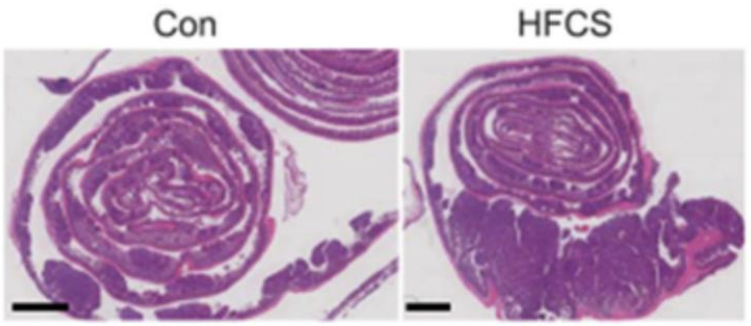


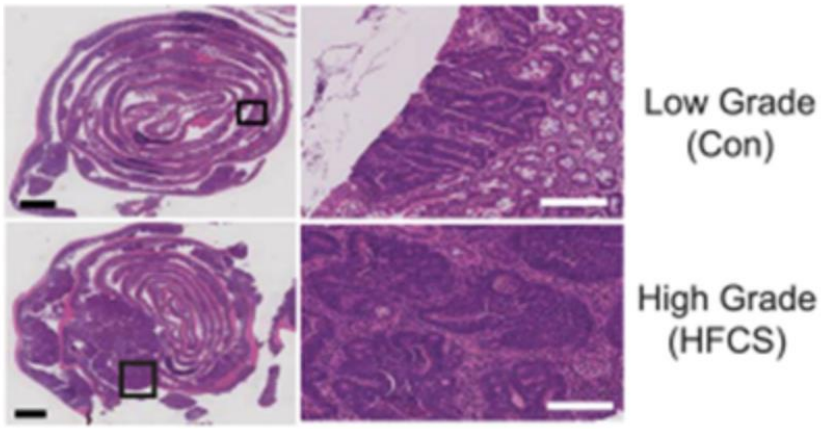
Are all so-called Western diets eqally oncogenic?

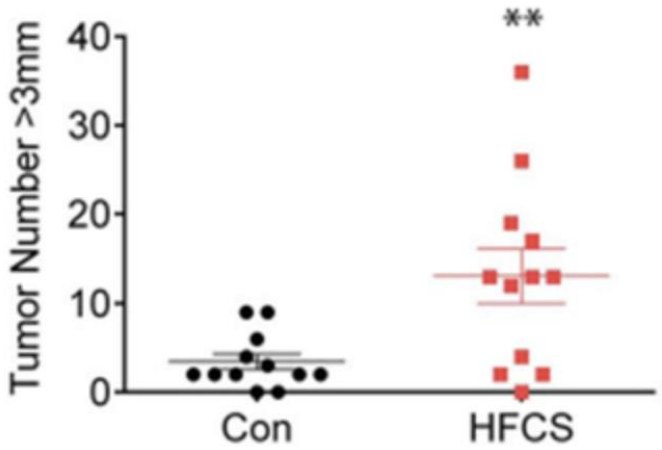


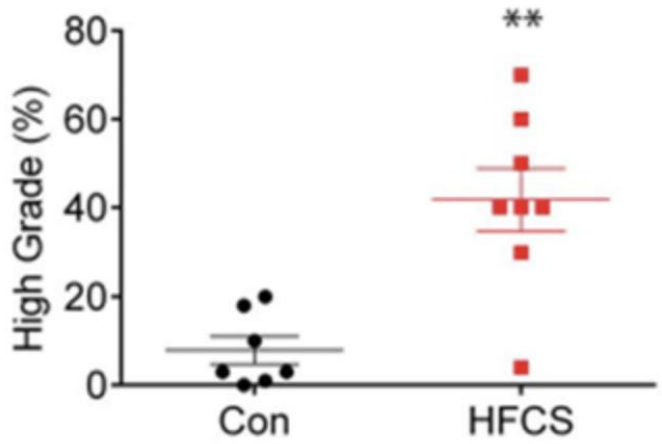
Viennois *et al.*, Gastroenterology, 2022

High fructose corn syrup (HFCS) promotes CRC





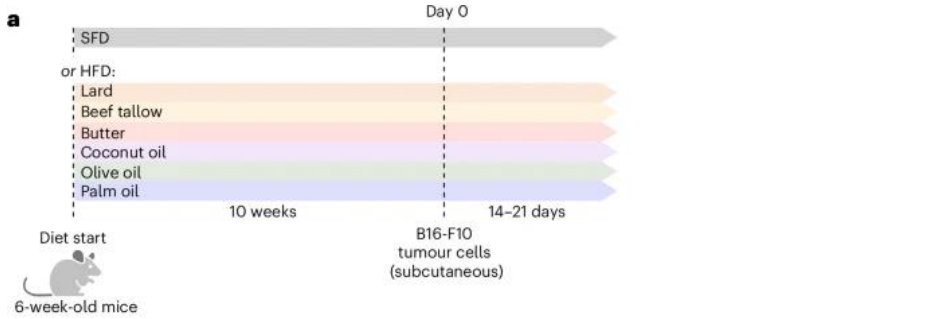


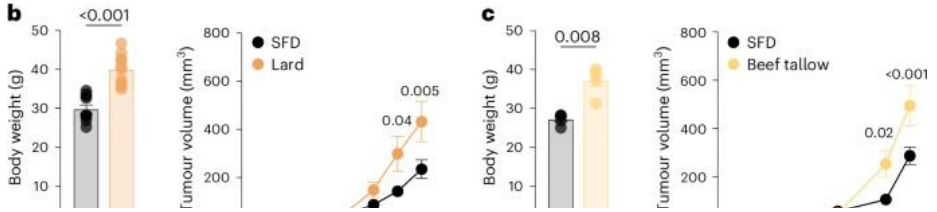


HFCS supplementation feeds into glycolysis and lipogenesis

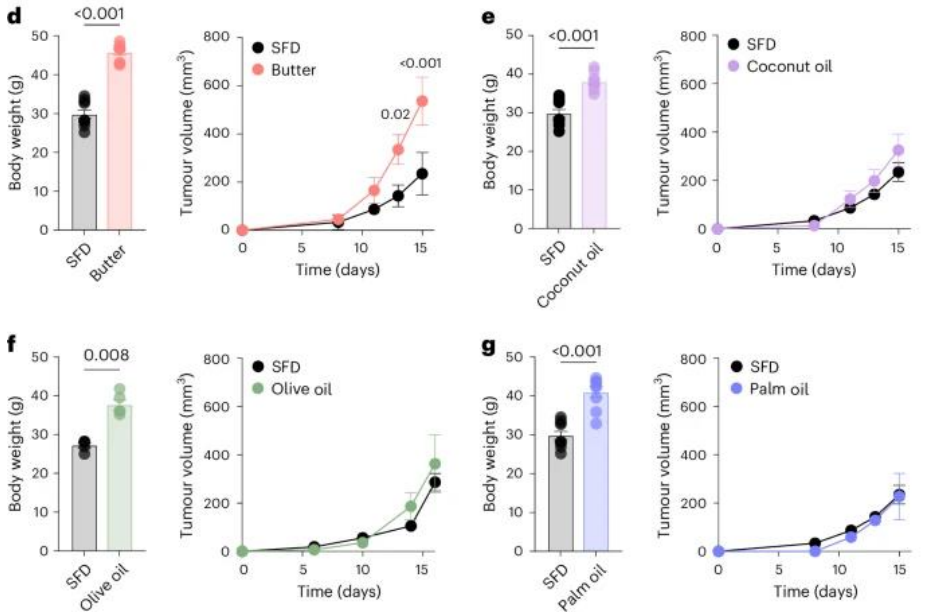
Goncalves *et al.*, Science, 2019

Not all lipids are equally oncogenic



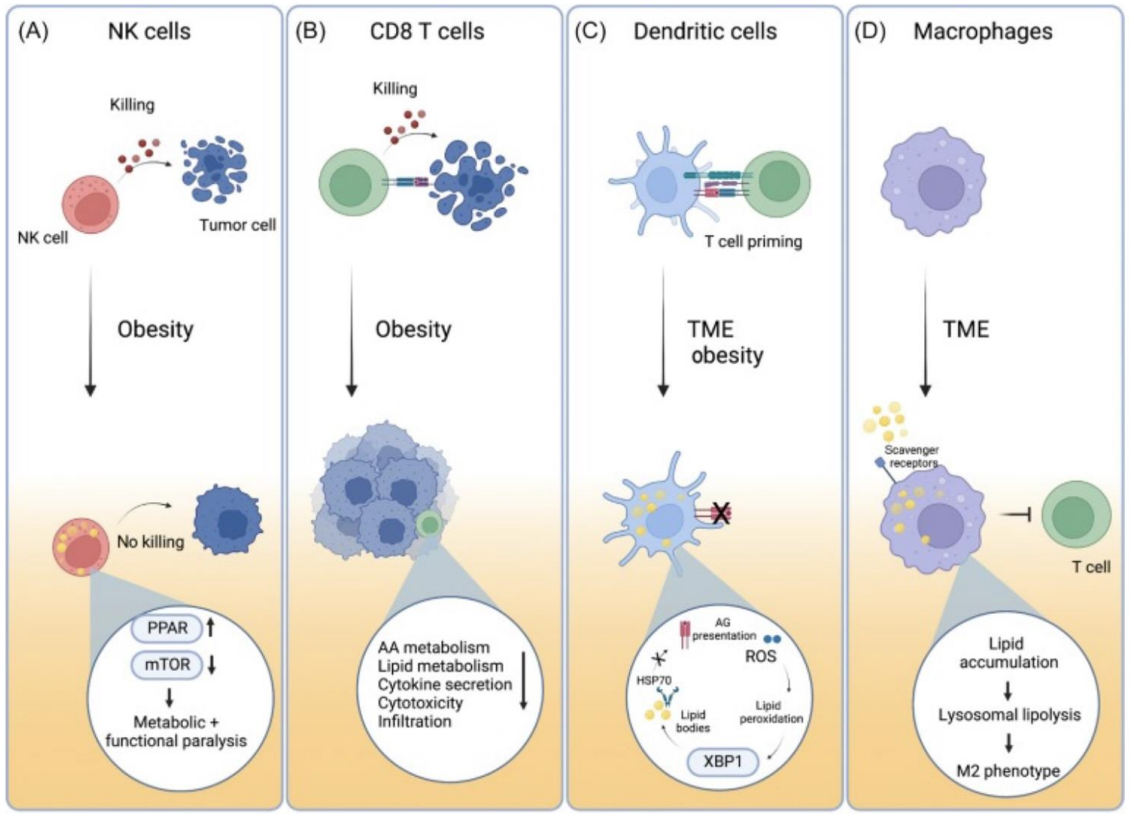


But what about the TME?



Kunkemoeller *et al.*, Nat. metabolism, 2025

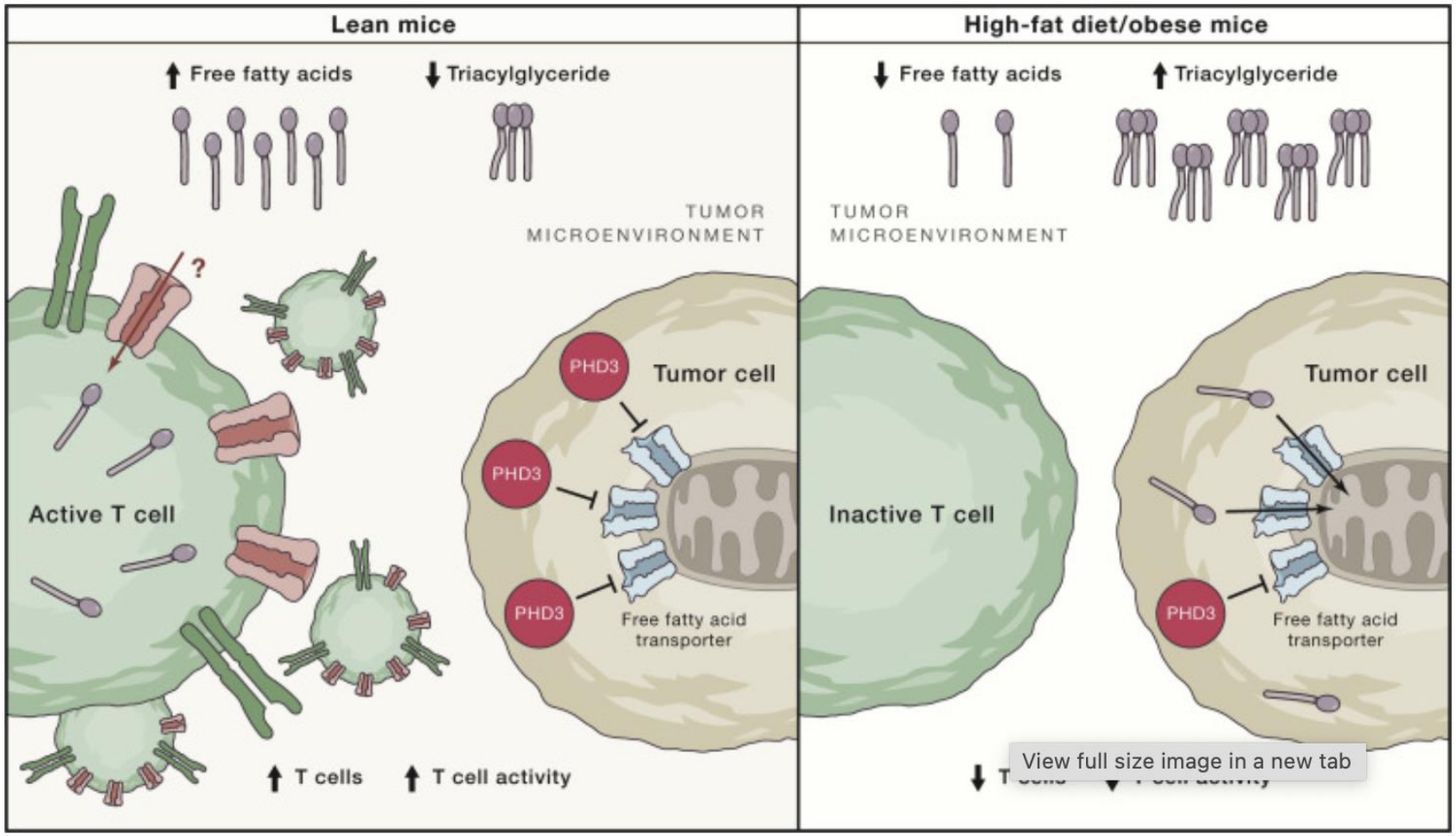
Obesity intersects with multiple immune cells of the TME



Dyck *et al.*, Trends in Molecular Medicine, 2023

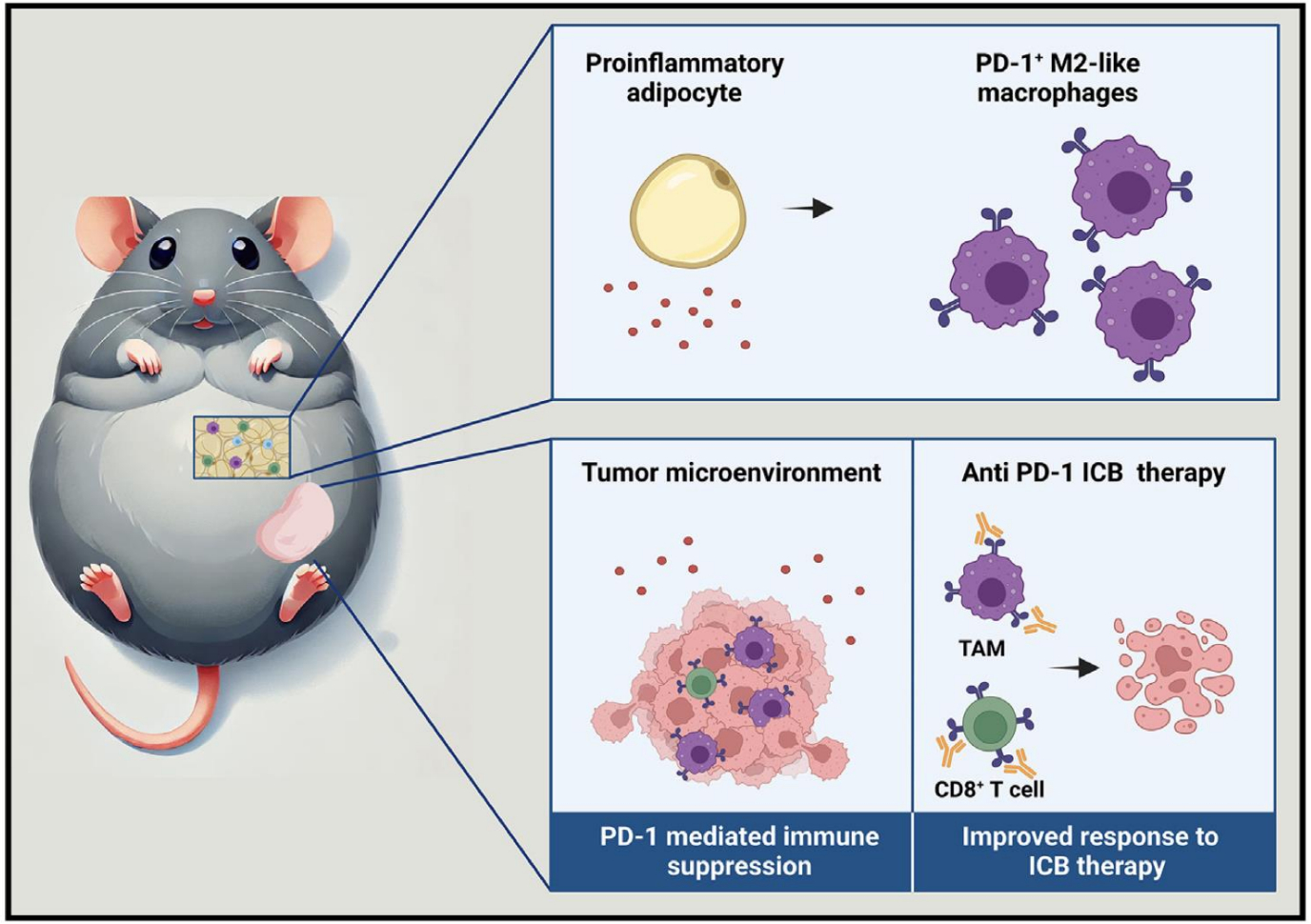
- Tumor-infiltrating T cells are metabolically unfit
  - Competitive nutrient uptake and impaired nutrition partitioning
    - Lipids: preferentially influxed by cancer cells
    - Glucose: largely imported my MDSCs and regulatory T cells
  - Increased expression of checkpoints PD-1 and CTLA4
  - Direct effects of specific nutrients – e.g. different fatty acids
  - Increased leptin have shown to be immunosuppressive
  - T cell suppression is not systemic and depends on the specific TME

Increased lipid uptake and oxidation by “obese” tumor cells



Ringel *et al.*, Cell 2020

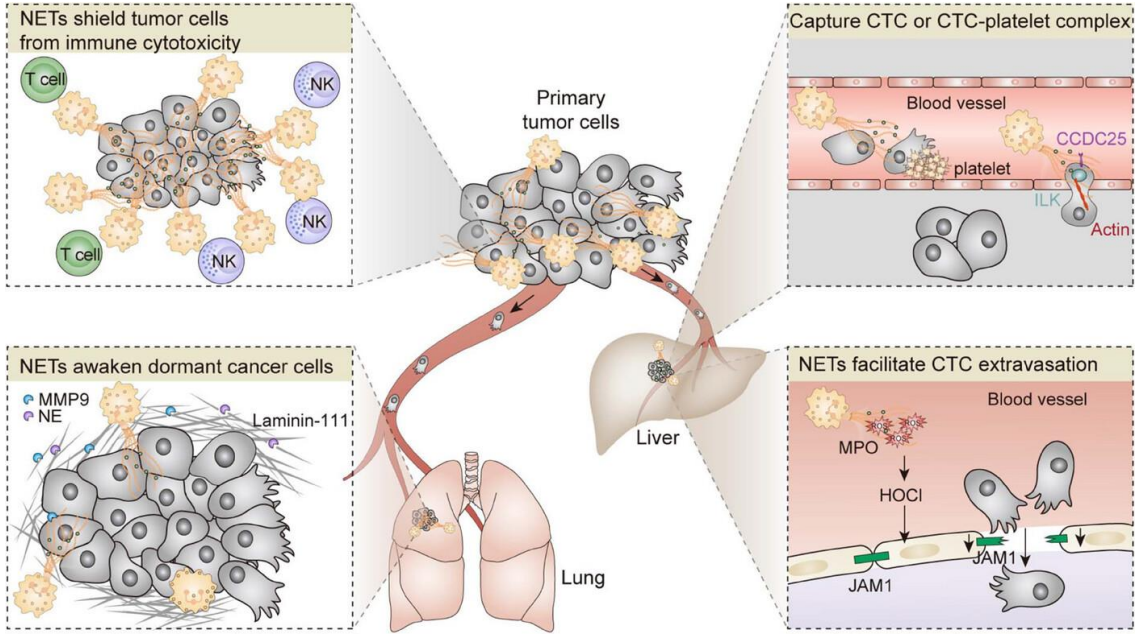
Obesity increases PD-1 expression on macrophages to inhibit T cells



bader *et al.*, Nature 2024

Obesity creates a metastatic niche for improved distant seeding

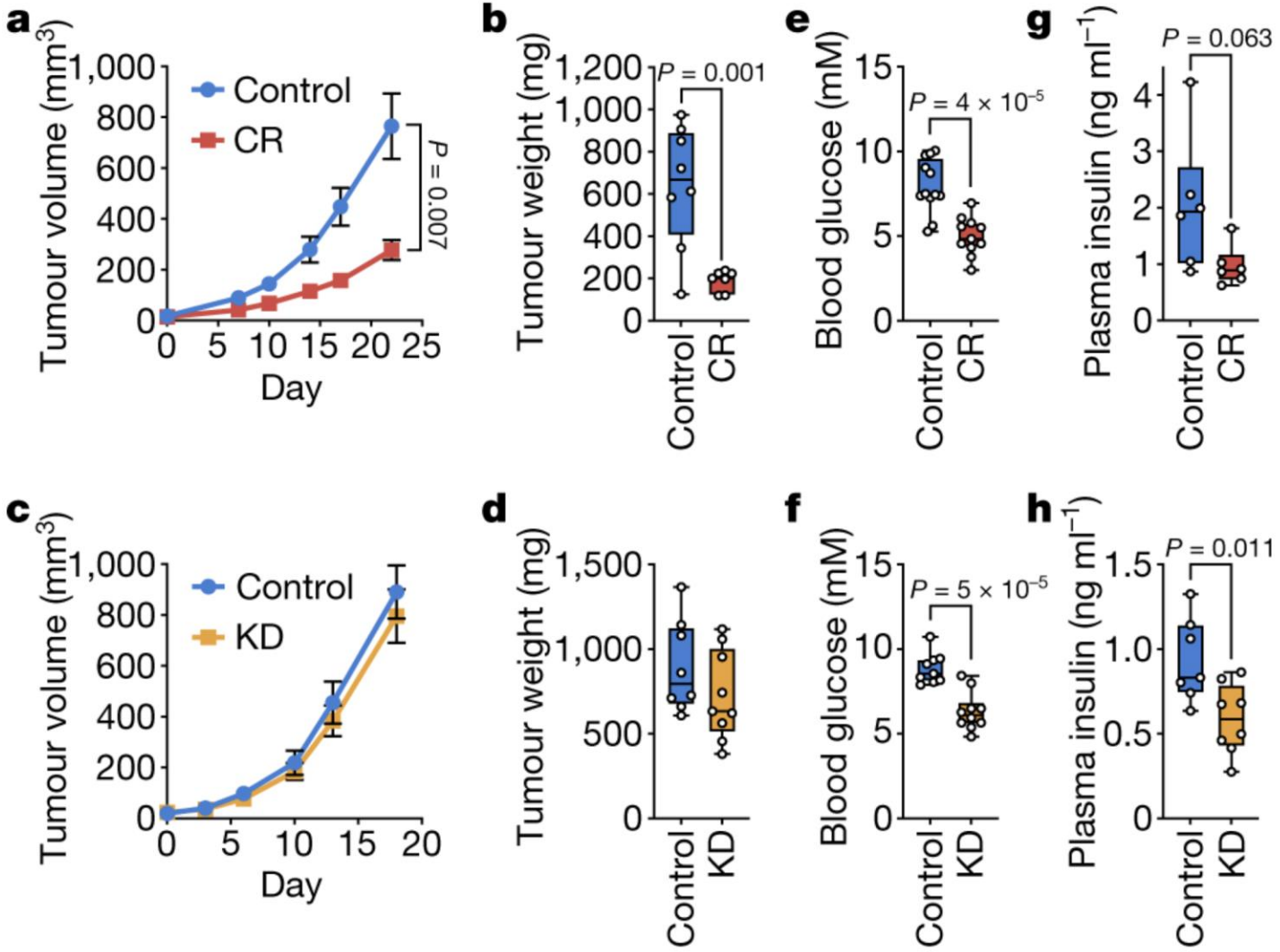
- Obesity – known metastatic promoter
  - Dampening immune responses
  - Providing nutrients during migration and seeding
  - Changing the microbiome
  - Increasing viscoelasticity



Dietary interventions in cancer treatment

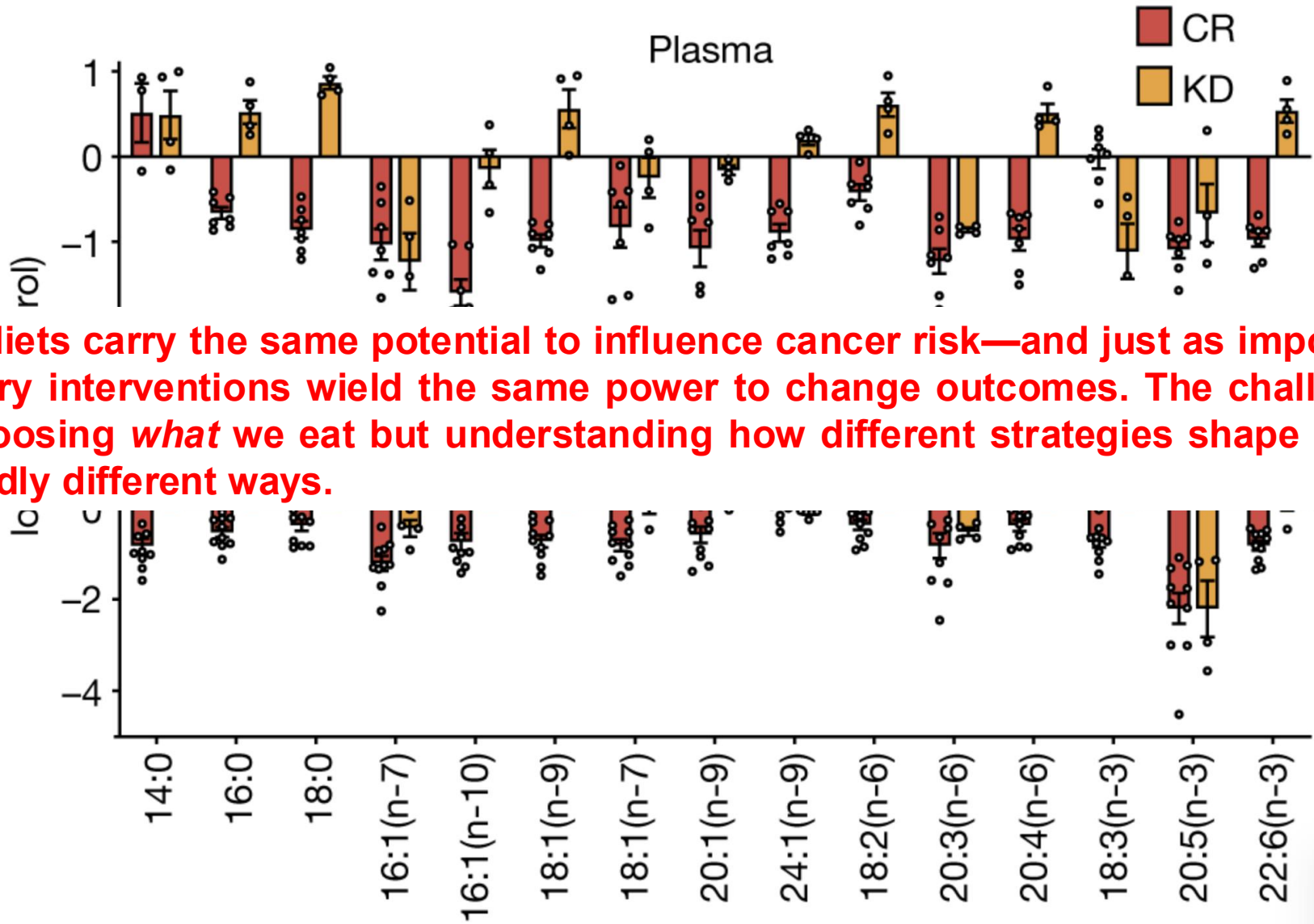
- Caloric restriction decreases tumor growth *in vivo* (Rous, 1914)
- Dietary restriction impede tumor growth in cell autonomous (metabolic flux) and non-cell-autonomous (insulin/IGF-1, TME) manner
- Not one dietary change fits all tumor types: Caloric restriction V ketogenic diets V intermittent fasting V specific formulations
- Depends on anatomical site and mutational drivers (e.g. PI3K-activated tumors less responsive to dietary restrictions)

Tumor suppressive effect of caloric restriction in PDAC



Lien *et al.*, Nature, 2021

Caloric restriction and lipogenesis



Not all diets carry the same potential to influence cancer risk—and just as importantly, not all dietary interventions wield the same power to change outcomes. The challenge is not only choosing *what* we eat but understanding how different strategies shape the body in profoundly different ways.

Lien *et al.*, Nature, 2021

Outstanding questions

How does distinct dietary components (lipids, sugars) drive organismal changes, oncogenesis, and TME remodeling?

What biological pathways link obesity to specific cancer types and which are the most targetable for therapy?

What role do gut microbiome and related metabolic byproducts play in cancer development?

How does obesity promote inflammation in adipose tissue while suppressing antitumor T cell responses?

In which context does obesity affect or even improve the immune response after ICB, and what are the underlying mechanisms?

What are good biomarkers for responsiveness and patient selection for cancer immunotherapy?

Does obesity affect the efficacy of other immunotherapies such as adoptive cell therapies?

Take home message

- Cancer is an extremely rare event that requires several adaptations – cell intrinsic as well as extrinsic
- Cancer is a systemic disease with multiple areas of crosstalk
- Obesity is a major risk factor for cancer development
- Obesity promotes oncogenesis via multiple mechanisms, some with overlapping phenotypes
- These metabolic adaptations have created several “actionable” dependencies and is an active area of investigation

- Leo Loeb (early 1900):
  - Proposed that **tissue growth requires external stimuli**.
  - Demonstrated dependence of transplanted tissues on host environment.
  - Set the conceptual groundwork that **cell proliferation is extrinsically regulated**.
- Alexis Carrel (early 1920-1930):
  - His early (and later controversial) long-term tissue culture experiments suggested cells could proliferate indefinitely **only with the right external nutrients and media**.
  - Influenced the field's thinking on nutrient requirements decades before Eagle formalized them.
- Harry Eagle
  - Systematically identified essential **exogenous nutrients** needed for mammalian cell growth.
  - Created Eagle's Minimum Essential Medium (MEM).
  - Proved that even cancer cells have strict **external metabolic requirements**.
- Stanley Cohen & Rita Levi-Montalcini
  - Discovered **nerve growth factor (NGF)** and **epidermal growth factor (EGF)**.
  - Revealed that **soluble external proteins** could directly stimulate cell division.
- Harold Varmos & J. Michael Bishop
  - Discovered that cancer-causing genes (oncogenes) are normal genes regulating **extrinsic growth-factor signaling pathways**.
  - Showed cancer arises from dysregulation of **external signaling inputs**.