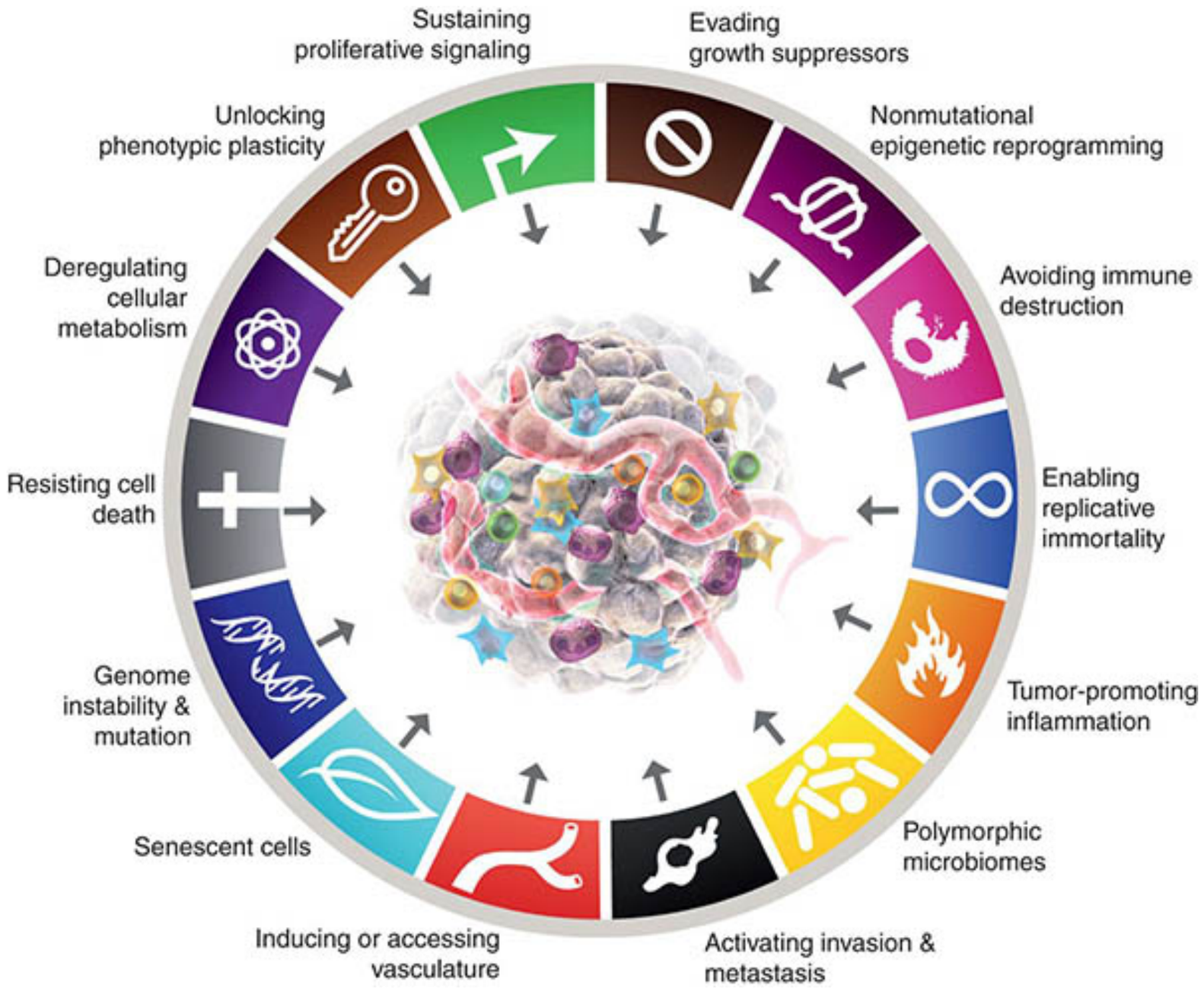
Cancer Metabolism

How cancer reprograms cell's machinery for energy and biomass production

Alessandro Carrer, PhD

Metabolic rewiring is one of the “HALLMARKS OF CANCER”

*Hanahan D & Weinberg RA - **Cell**, 2000 & 2011; **Cancer Discovery** 2022.*



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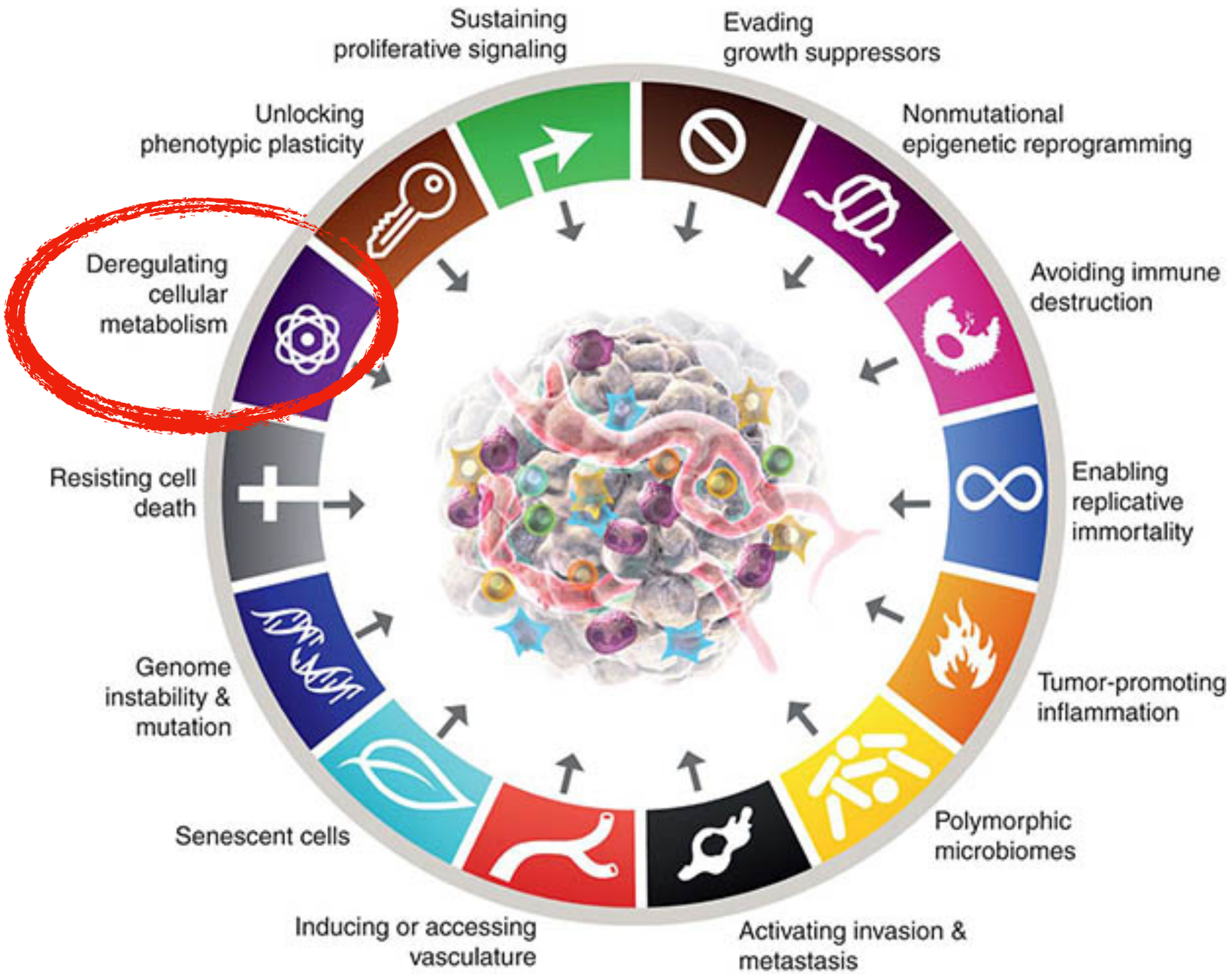

Cancer metabolism

Cancer metabolism is different than normal tissue. First time it was noted in 1920 by biochemist Otto Warburg that when cancer cells are provided with glucose , they generate large amount of lactate regardless of whether oxygen is present or not.

This metabolic difference is referred as **THE WARBURG EFFECT**

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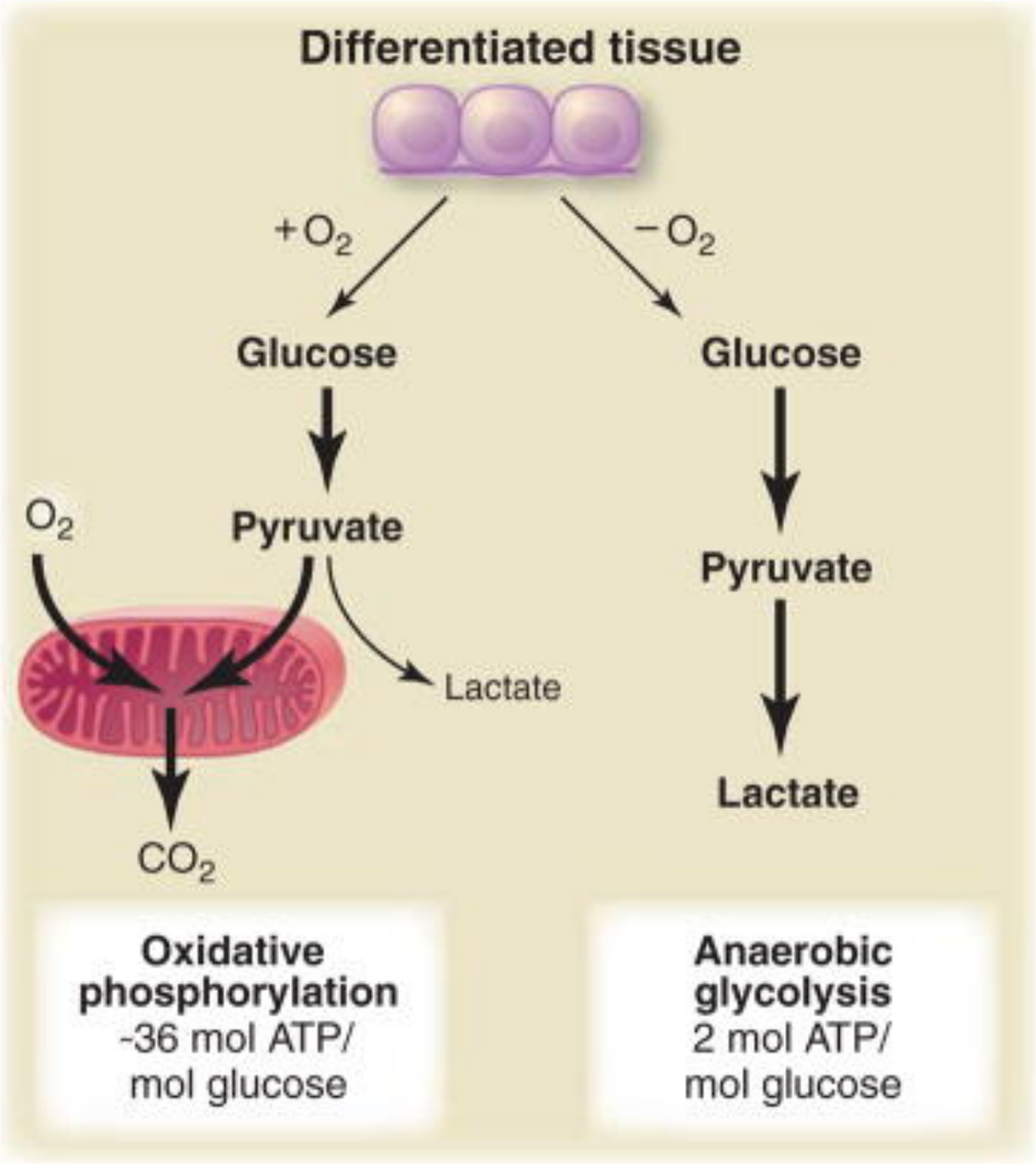
Bundesarchiv, Bild 102-12525
Foto: o.Ang. | Oktober 1931

- Warburg made vital contributions to many areas of biochemistry, including respiration, photosynthesis, and the enzymology of intermediary metabolism (Nobel Prize in 1931).
- In the mid 1920s Warburg and co-workers showed that, under Aerobic conditions, tumor tissues metabolize approximately **tenfold more glucose to lactate** in a given time than normal tissues. This phenomenon later came to be known as “Warburg Effect”.
- Warburg purified and crystallized seven of the enzymes of glycolysis. He used a tool called as “ Warburg Manometer” which measured directly the consumption of oxygen by monitoring changes in gas volume.

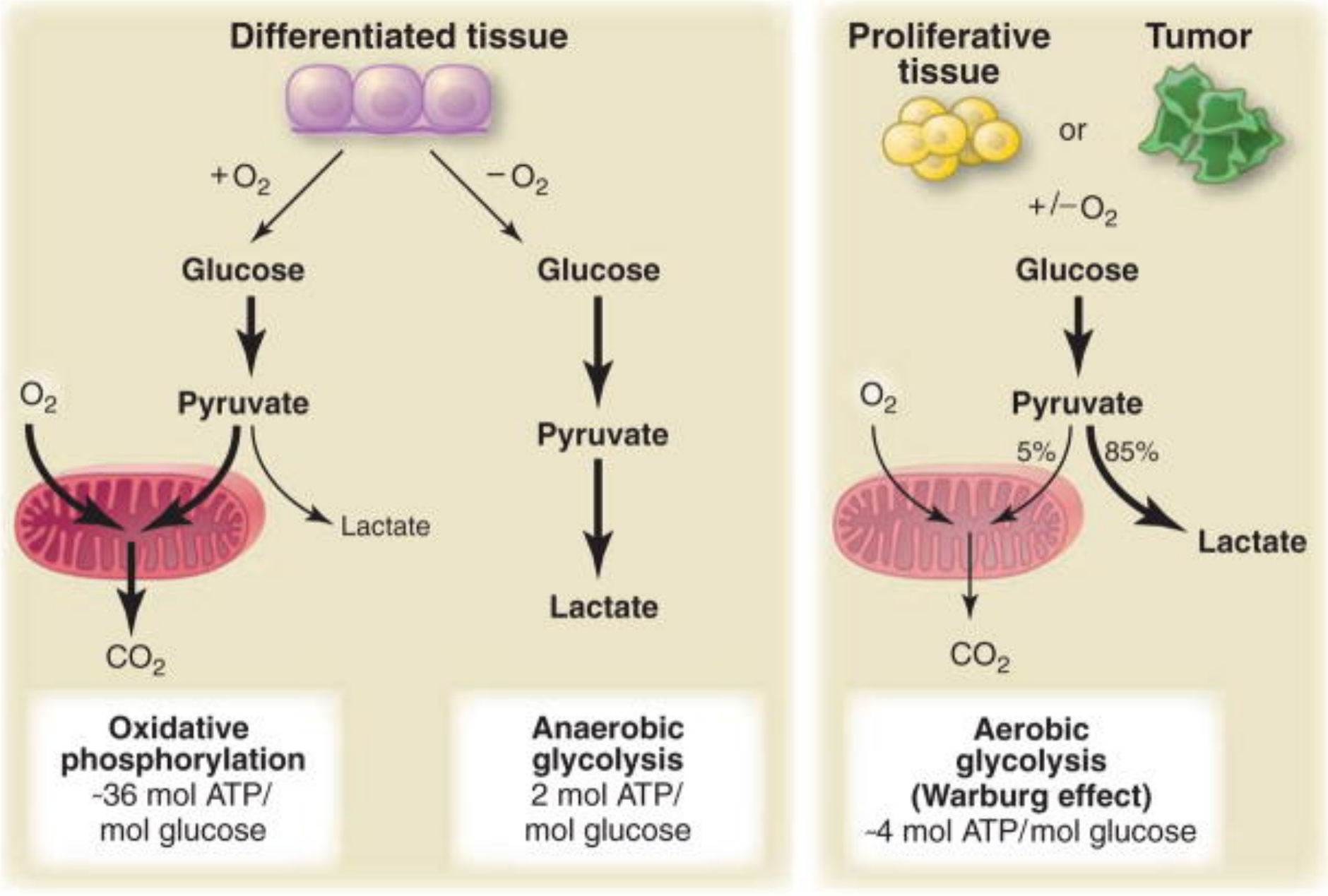
Catabolic reactions generate energy-carrying molecules



In presence of O_2, most tissues rely on oxidative phosphorylation (cellular respiration) to produce ATP

*Vander Heiden M, Cantley LC, Thompson CB, **Science**, 2009*

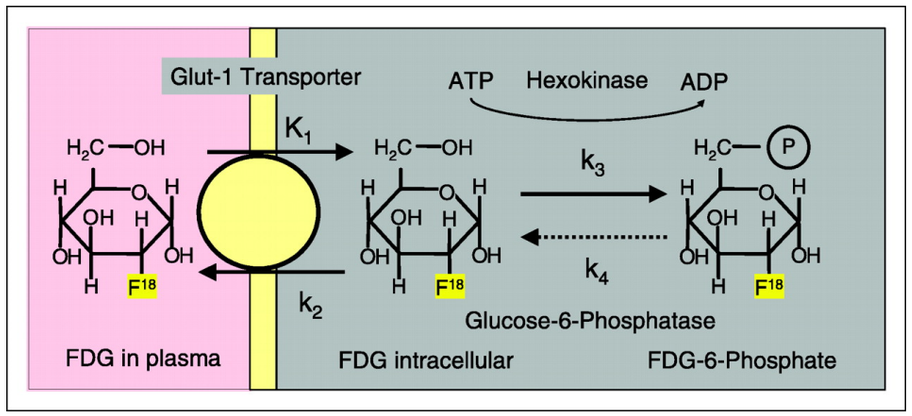
The Warburg Effect, aka Aerobic Glycolysis



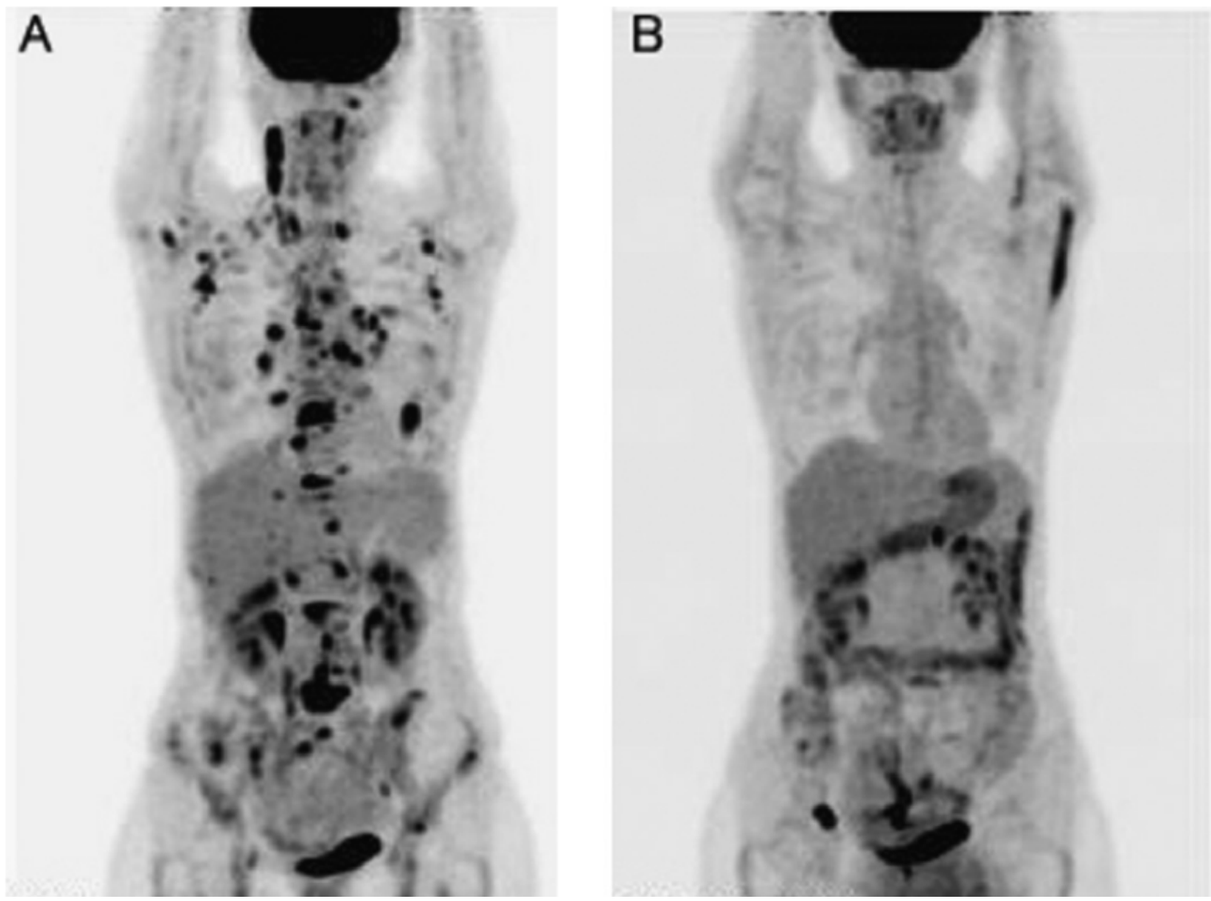
Vander Heiden M, Cantley LC, Thompson CB, ***Science****, 2009*

Augmented glucose uptake is useful (!!) in the clinic

FDG-PET of 18F-glucose is widely used in diagnosis, staging, monitoring of a variety of tumors



Fluoro(18F)-deoxyGlucose



Kimura H et al, ***Lung Cancer****, 2012*

Causes of the Warburg Effect

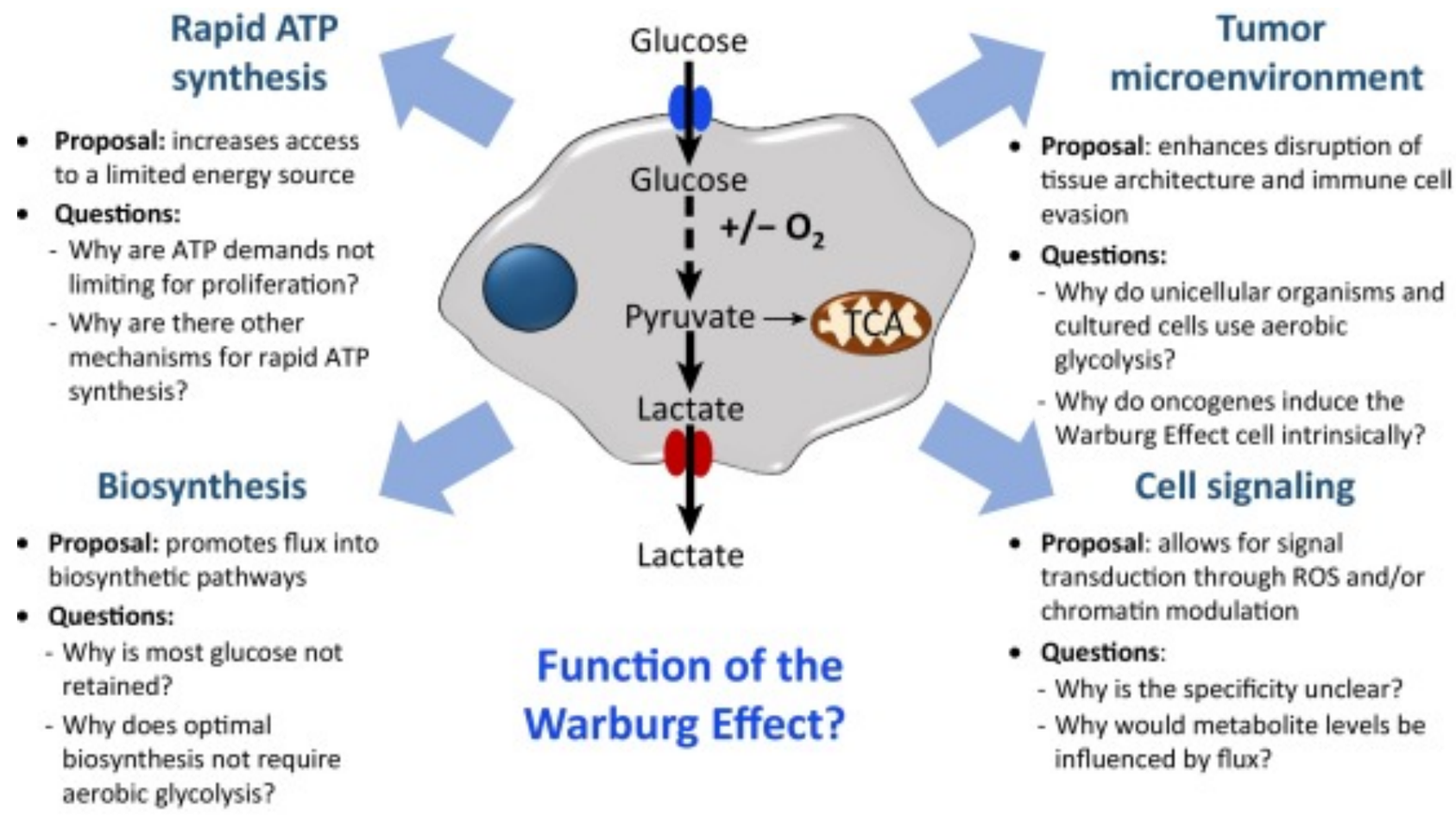
What Warburg though:

- *Mitochondrial Defects:* organelles are damaged and malfunctioning. In fact, cancer originates because of injuries to mitochondria and can be attacked with anti-acidic treatments.

What modern science thinks:

- *Mitochondrial Defects:* mtDNA mutations lead to malfunction in respiration and oxidative phosphorylation.
- *Hypoxia:* Possible adaptation owing to lack of Oxygen availability in the Environment.
- *Oncogenic Signals:* Point Mutations in genes such as Ras family can result in proliferation of cells and signal initiation.
- *Altered Metabolic Enzymes:* Overproduction and mimicking of metabolic enzymes such as Hexokinase-II result in increased Glycolytic activity.

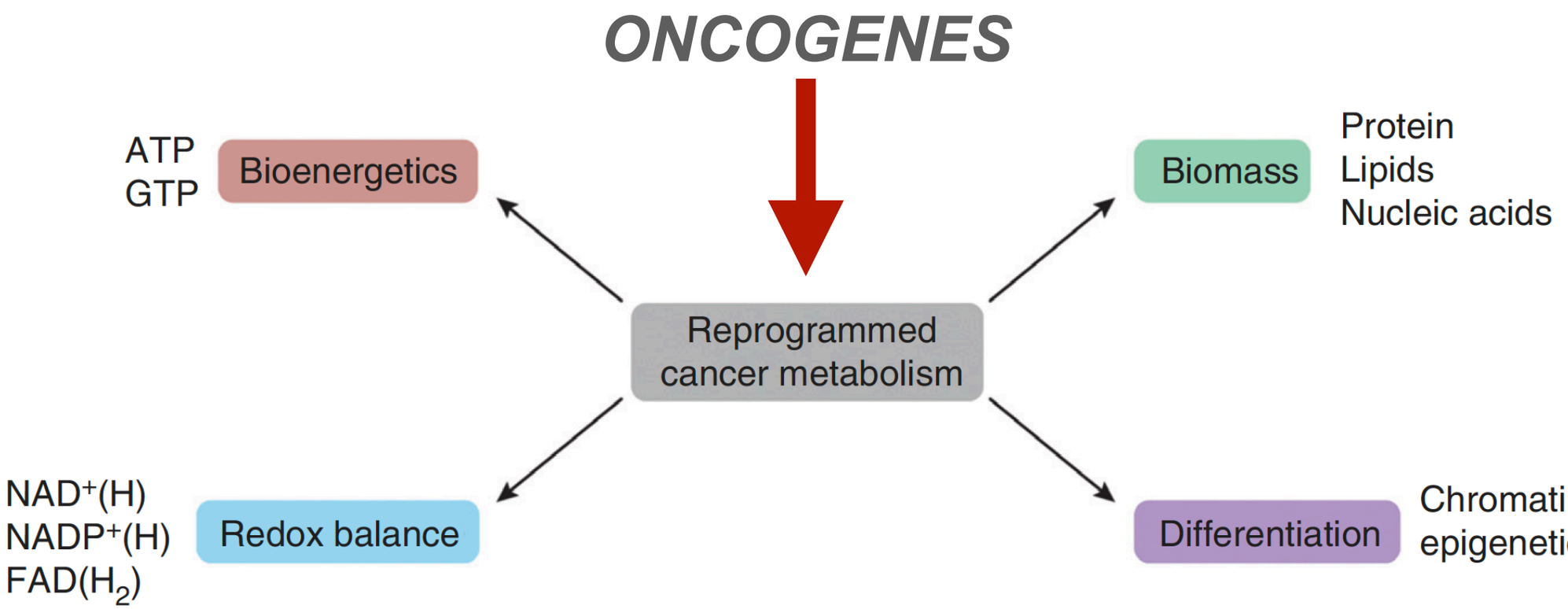
Why the Warburg Effect? We still don't get it….



Liberti M, Locasale JW, ***Trends Biochem Sci****, 2016*
DeBerardinis RJ, Chandel NS, ***Nat Metab****, 2020*

Cancer cells reprogram their metabolism:

anabolic and catabolic pathways are rewired to tackle different needs



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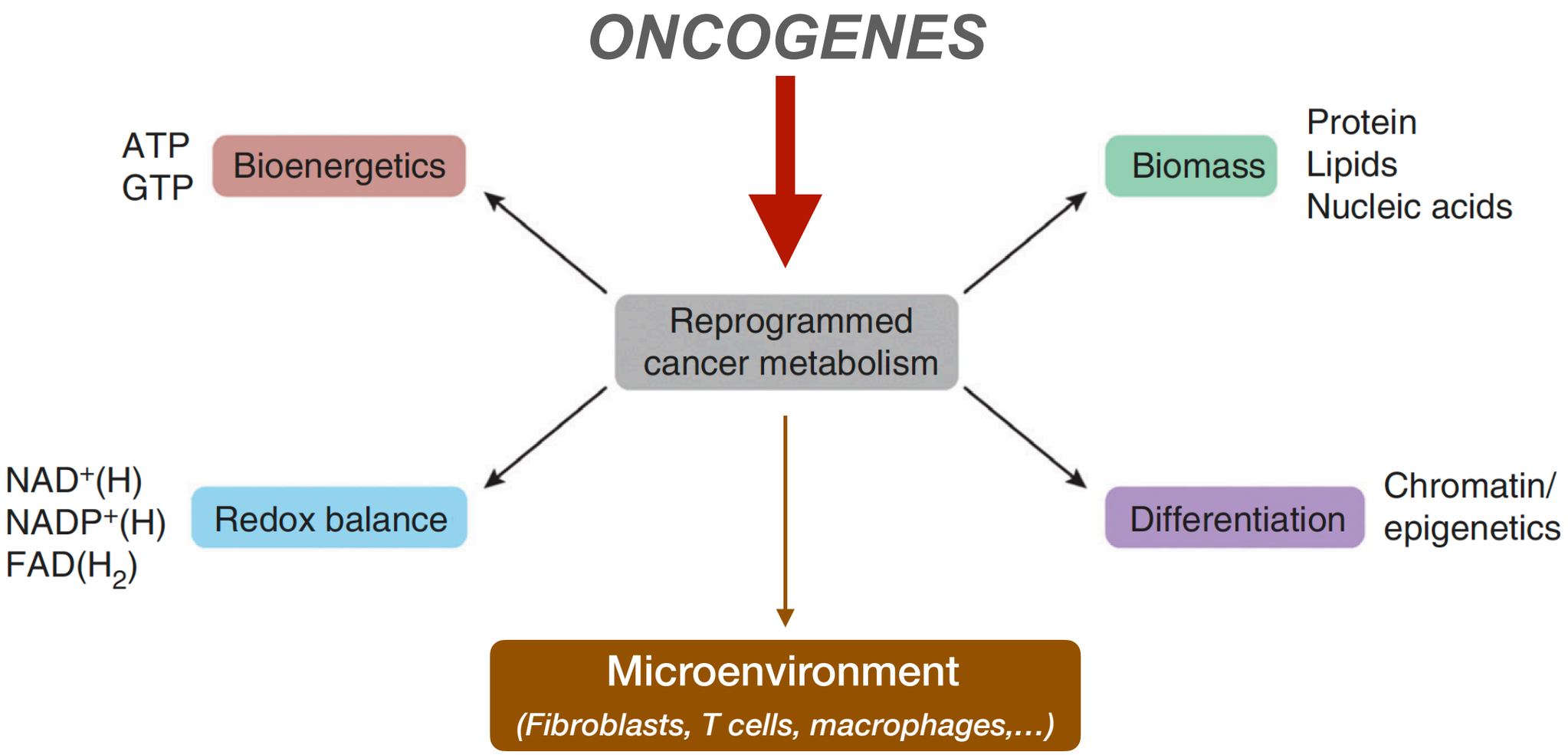


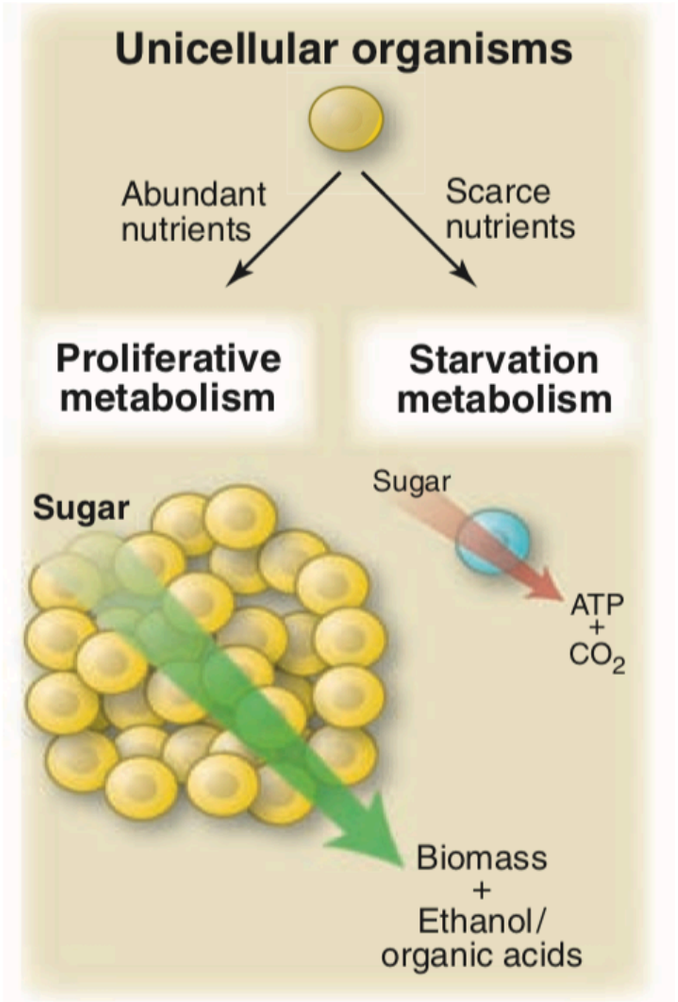
Tumor cells need to reprogram their metabolism in order to:

- **Produce more biomass (accelerated cell division)**
- **Produce more nucleotides (accelerated cell division)**
- **Cope with oxidative stress (replication and nutrient stress)**
- **Adapt to different environments (dissemination, 3D growth)**
- **Secrete immunomodulatory molecules (evade immune response)**
- **Adjust availability of “signaling metabolites” (support growth signals)**

Several reviews from: Thompson, CB; Chandel, NS; DeBerardinis, RJ; Locasale, JW; Wellen, KE; Sabatini, DM; Lyssiotis, C; others

1

Metabolism is reprogrammed to support proliferation



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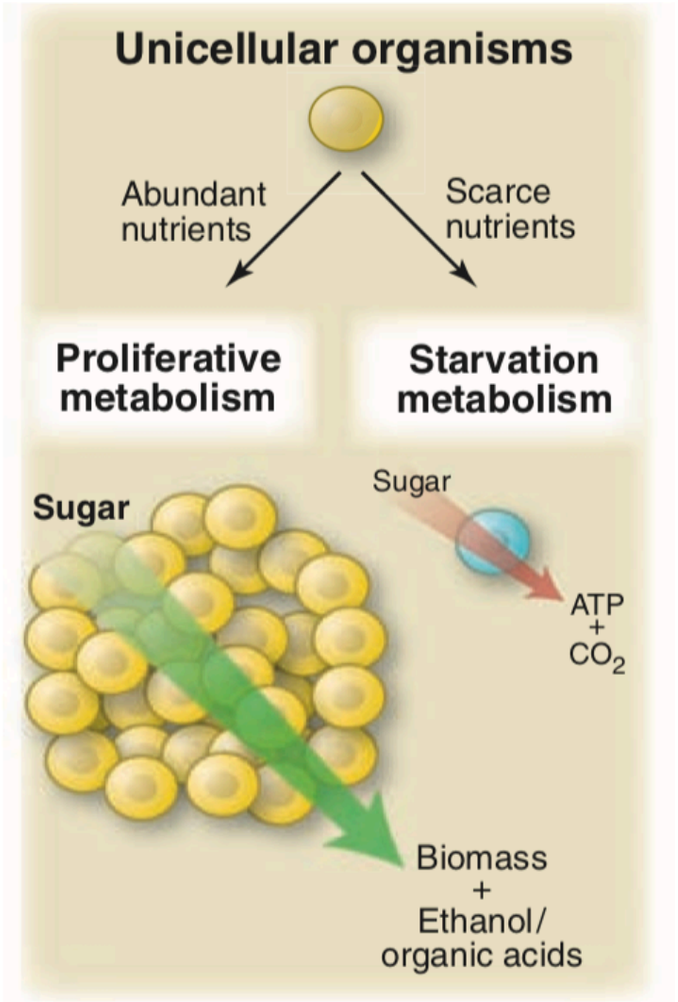

Nutrient sensing regulates growth in unicellular organisms
Growth factor signals induce proliferation in multicellular organisms

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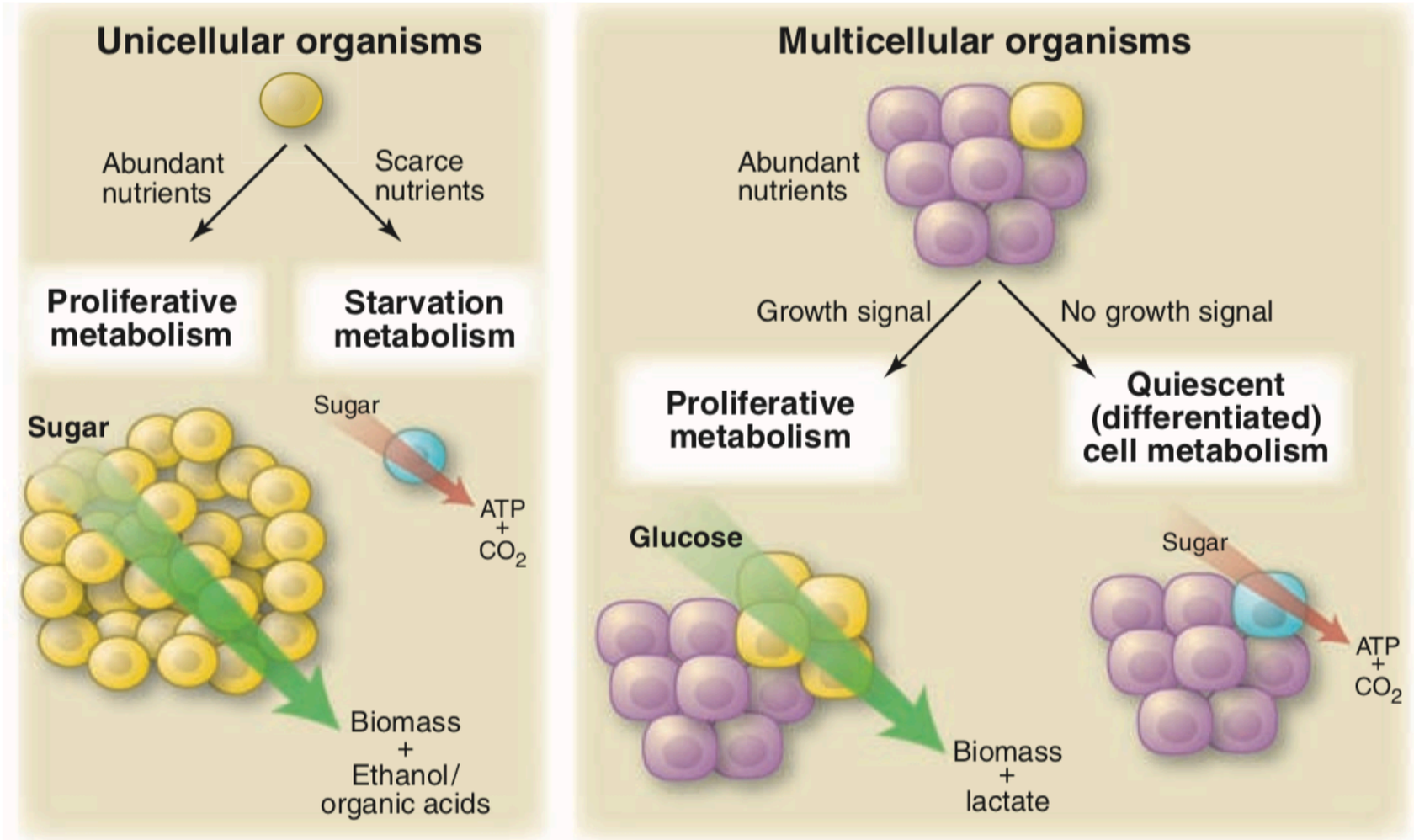

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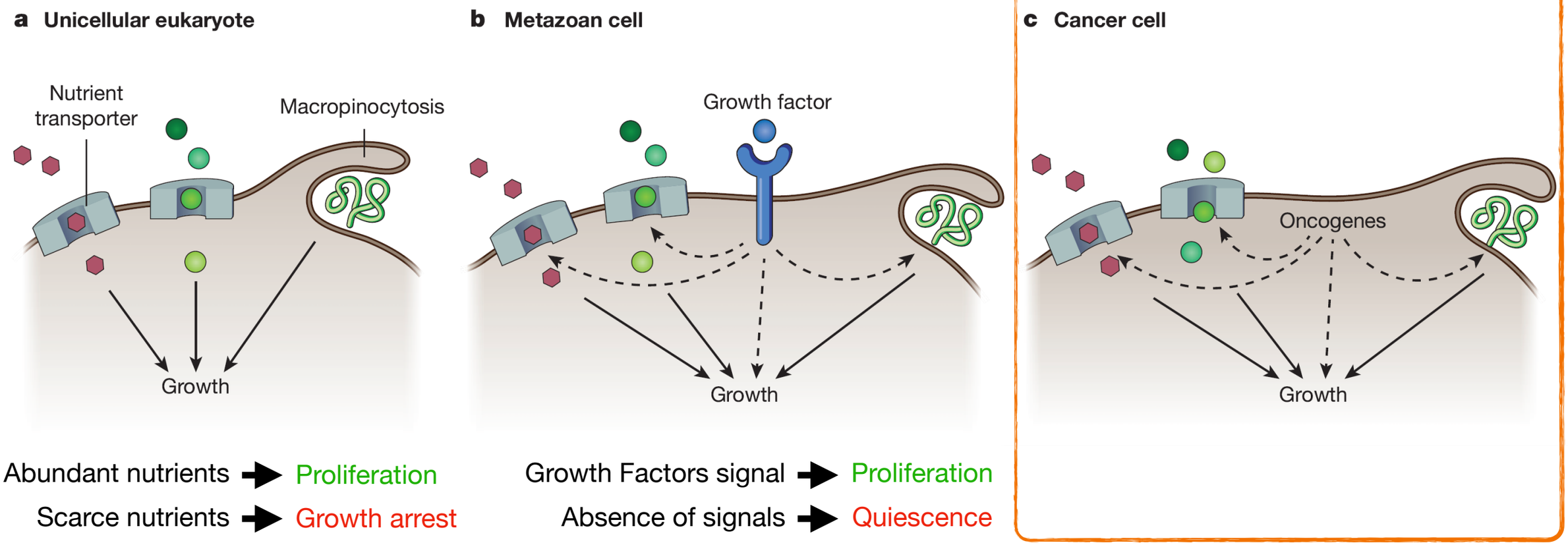
Oncogenes hijack cell ability to sense nutrients



Abundant nutrients → Proliferation

Scarce nutrients → Growth arrest

Growth Factors signal → Proliferation

Absence of signals → Quiescence

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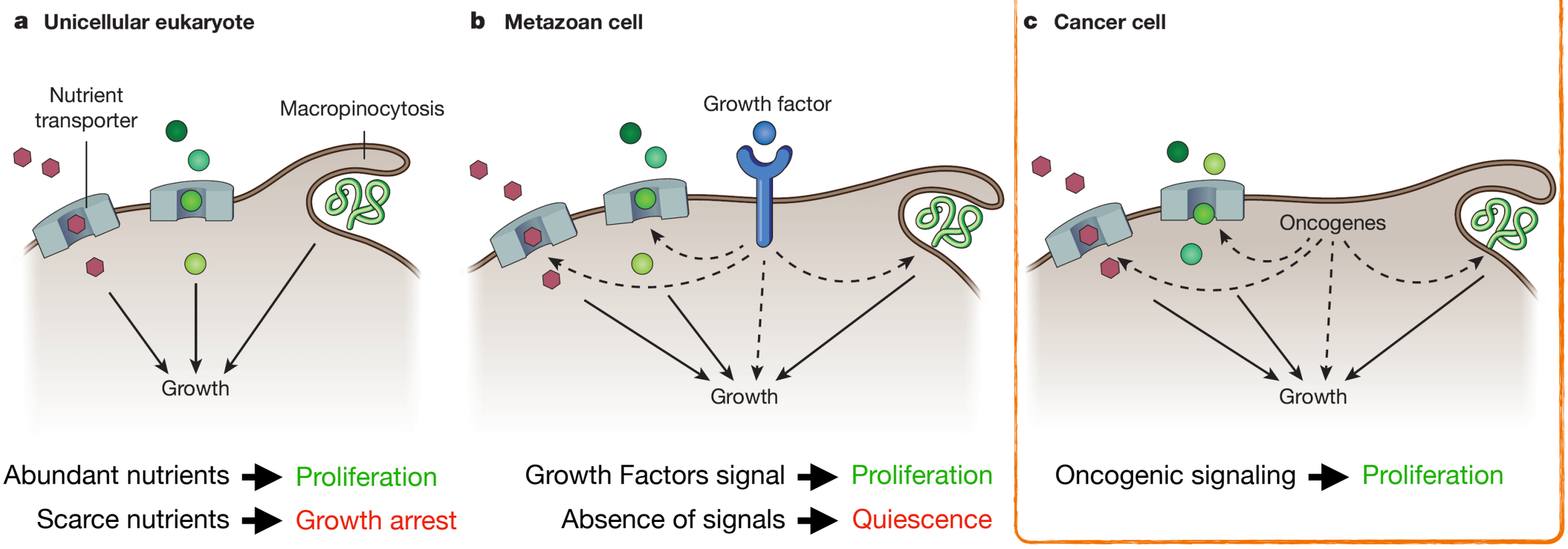

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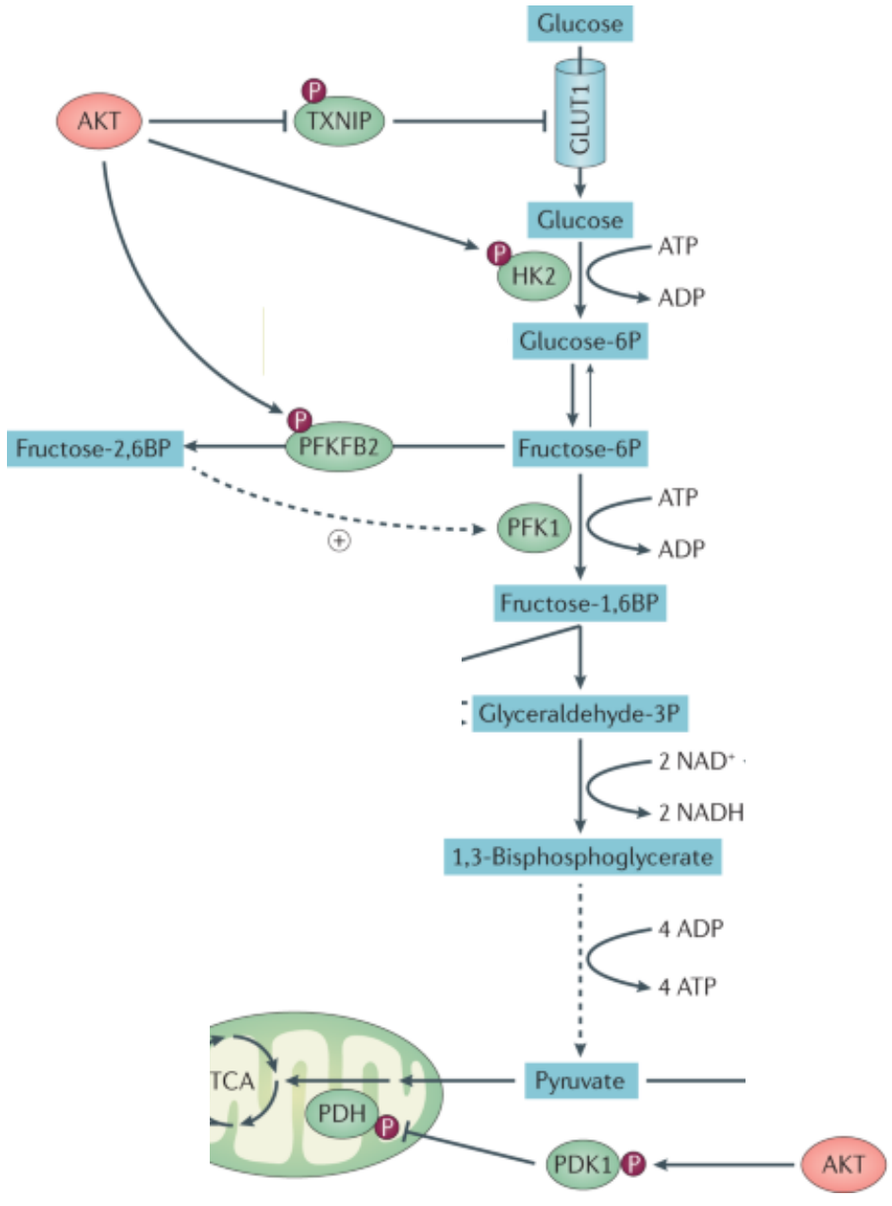
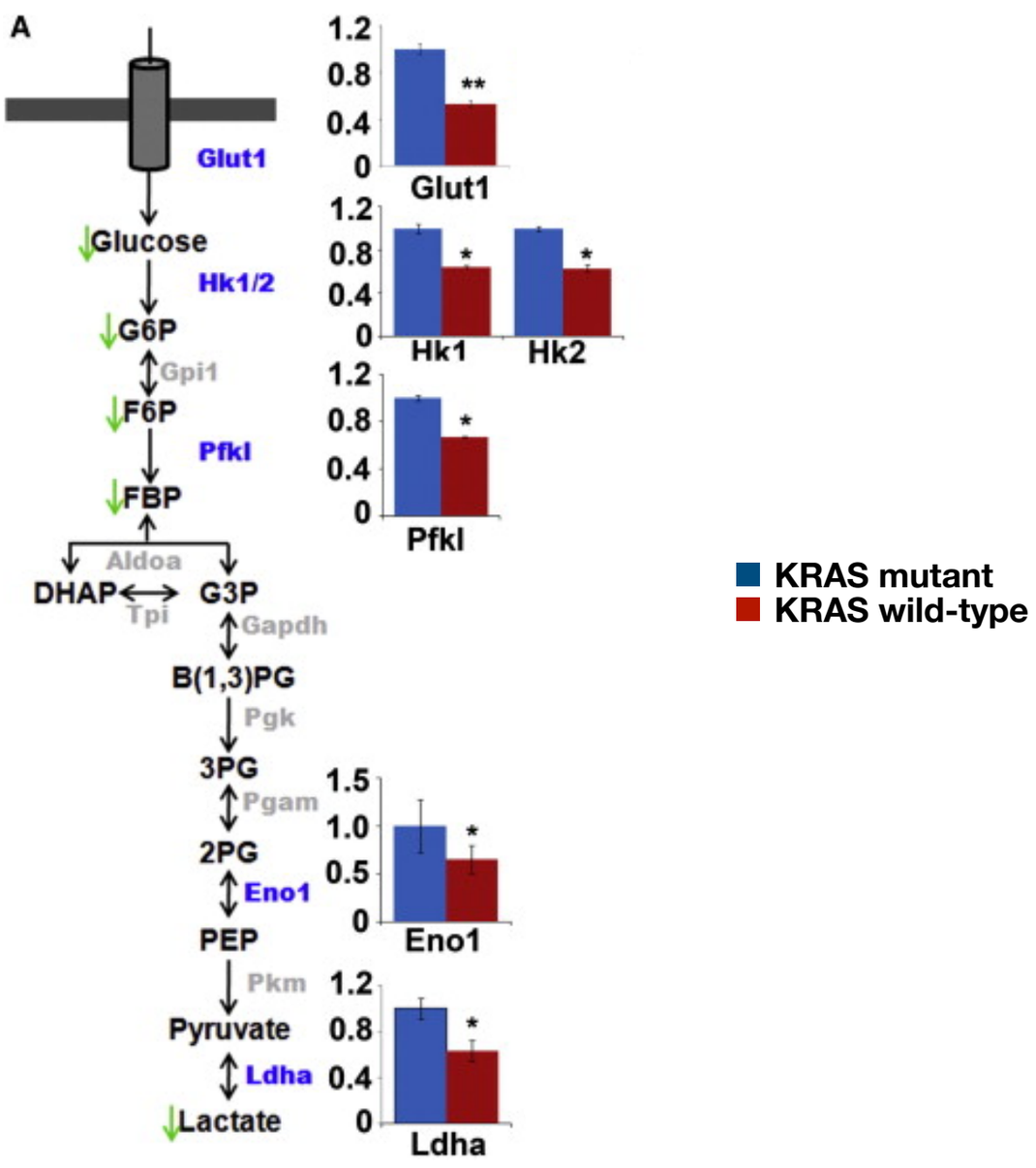
Commonly activated oncogenes enhance glycolysis

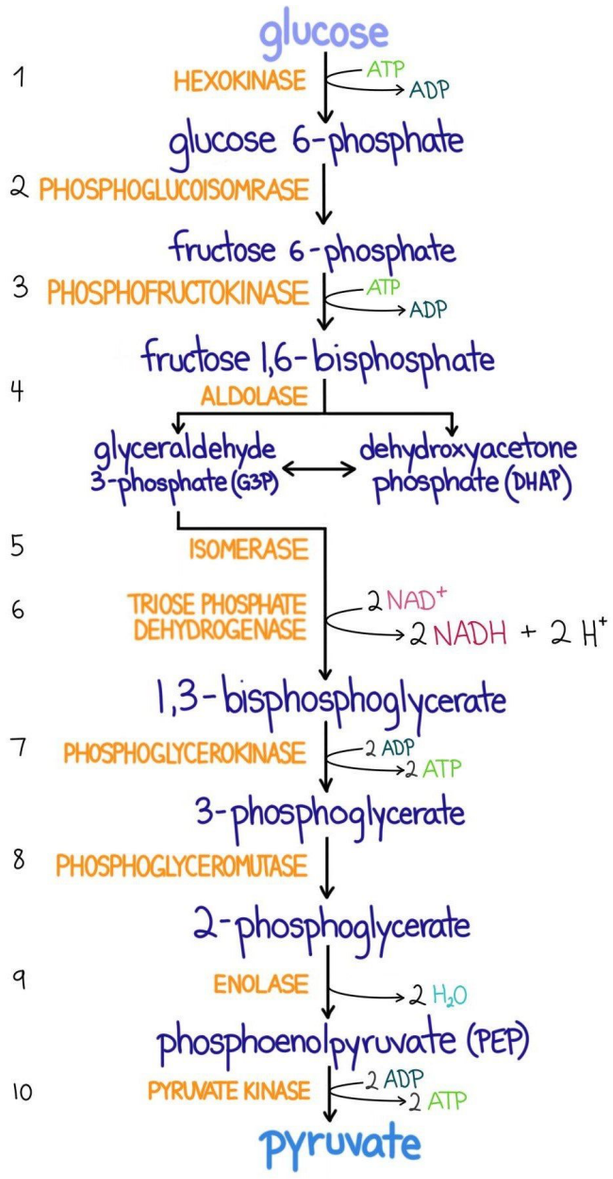


Hoxhaj G & Manning BD, ***Nat Rev Cancer****, 2019*



Ying H et al, ***Cell****, 2012*

Glycolytic flux is regulated and provides substrates for biosynthetic pathways



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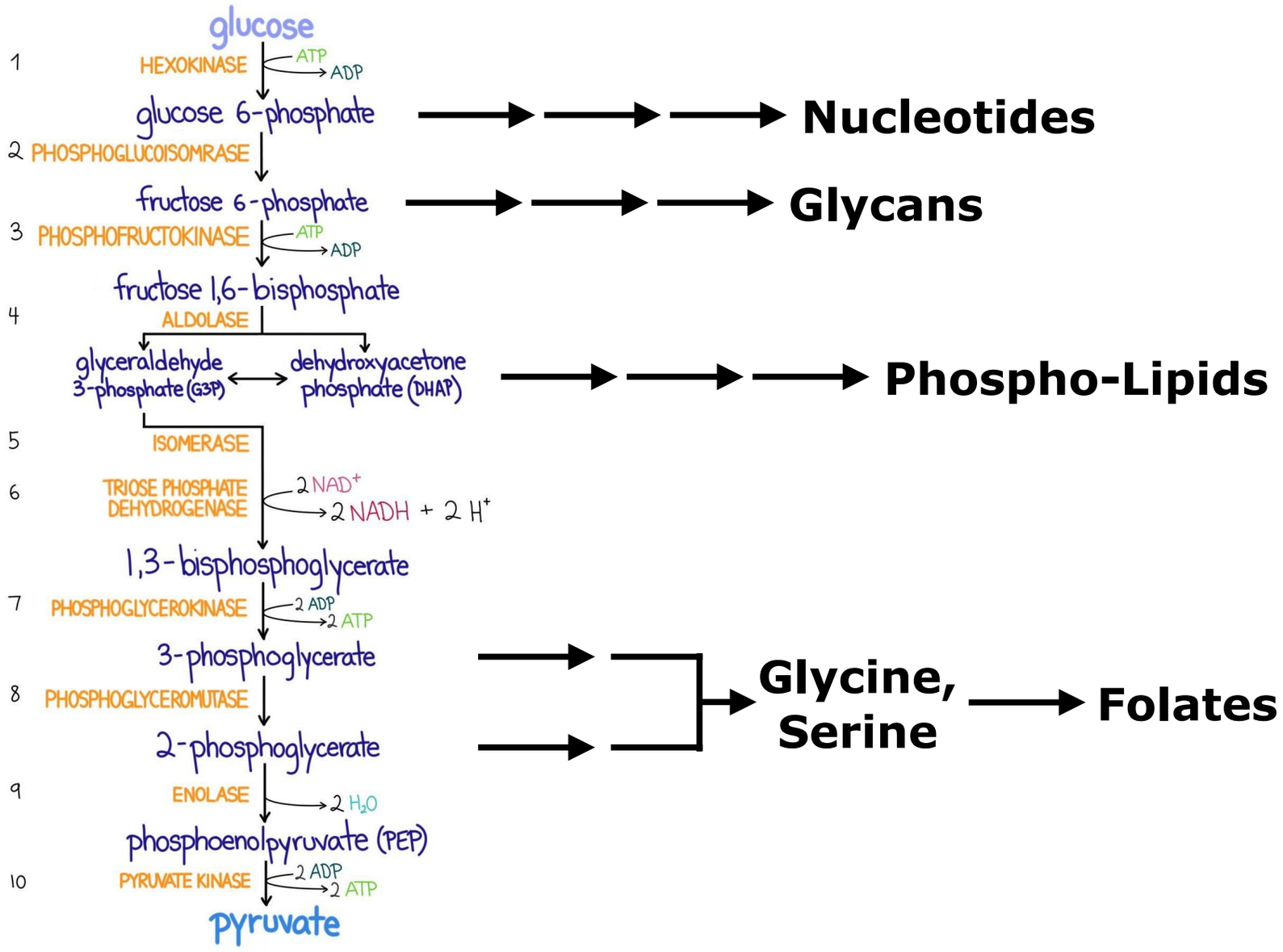

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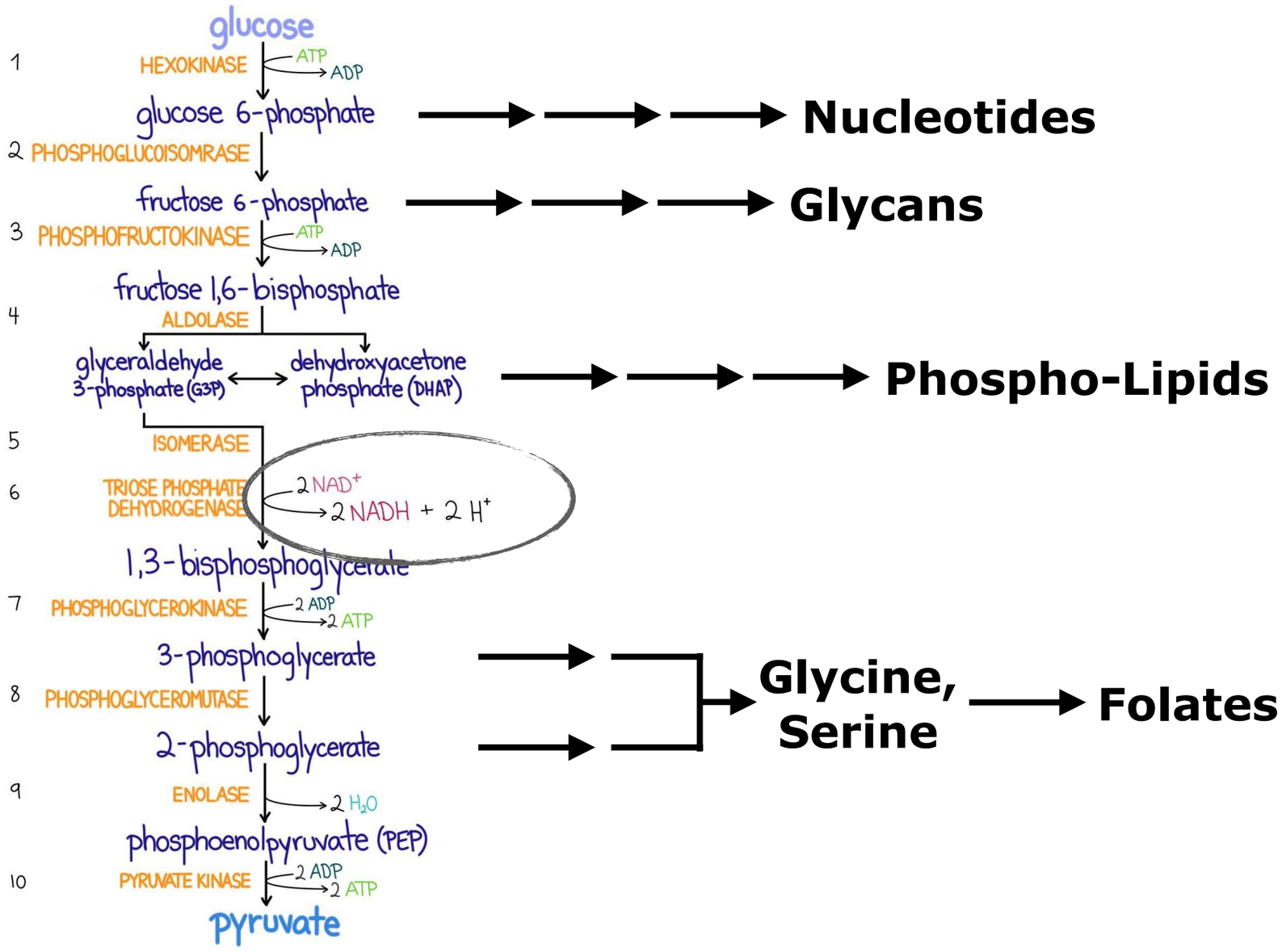

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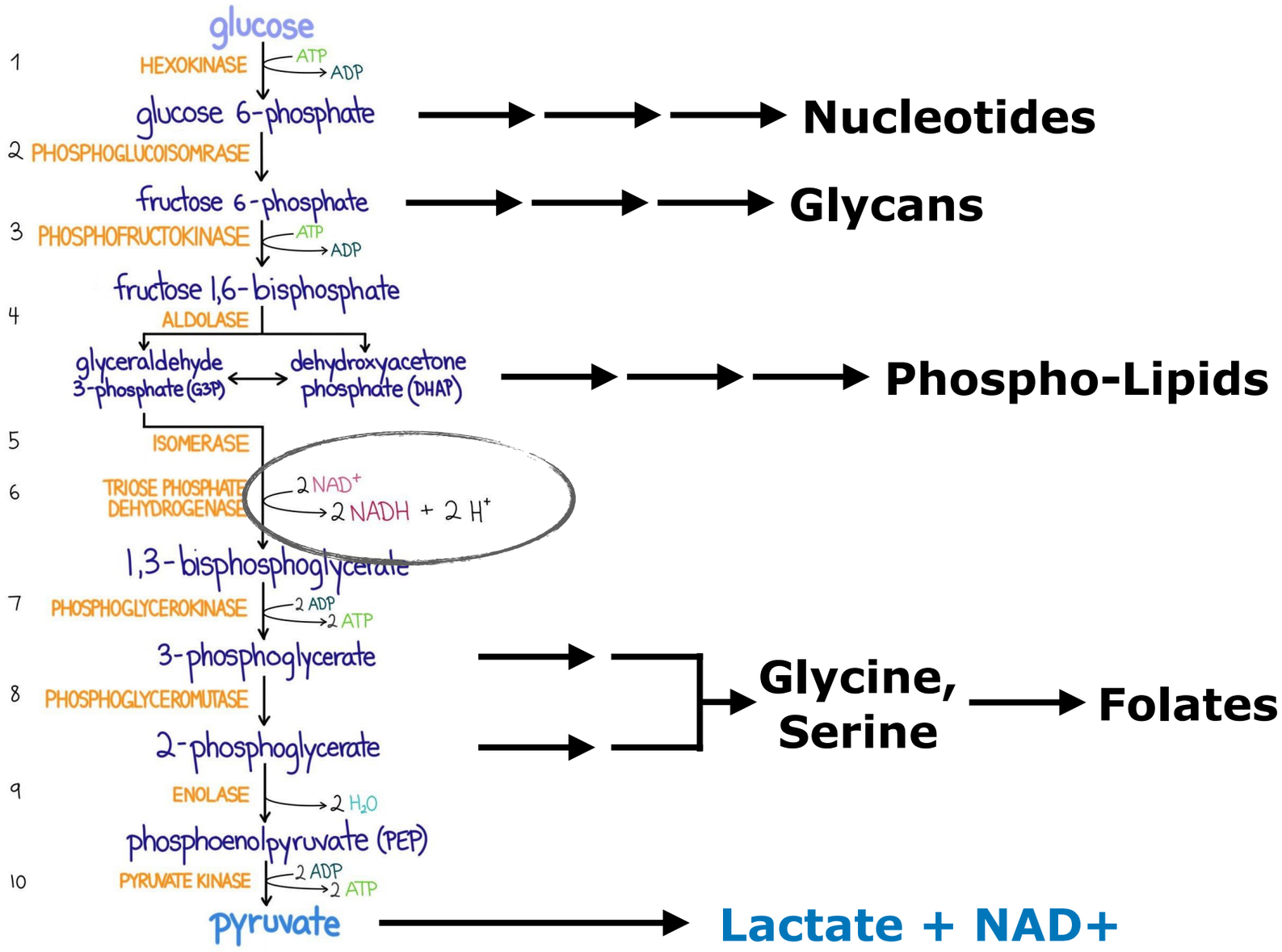
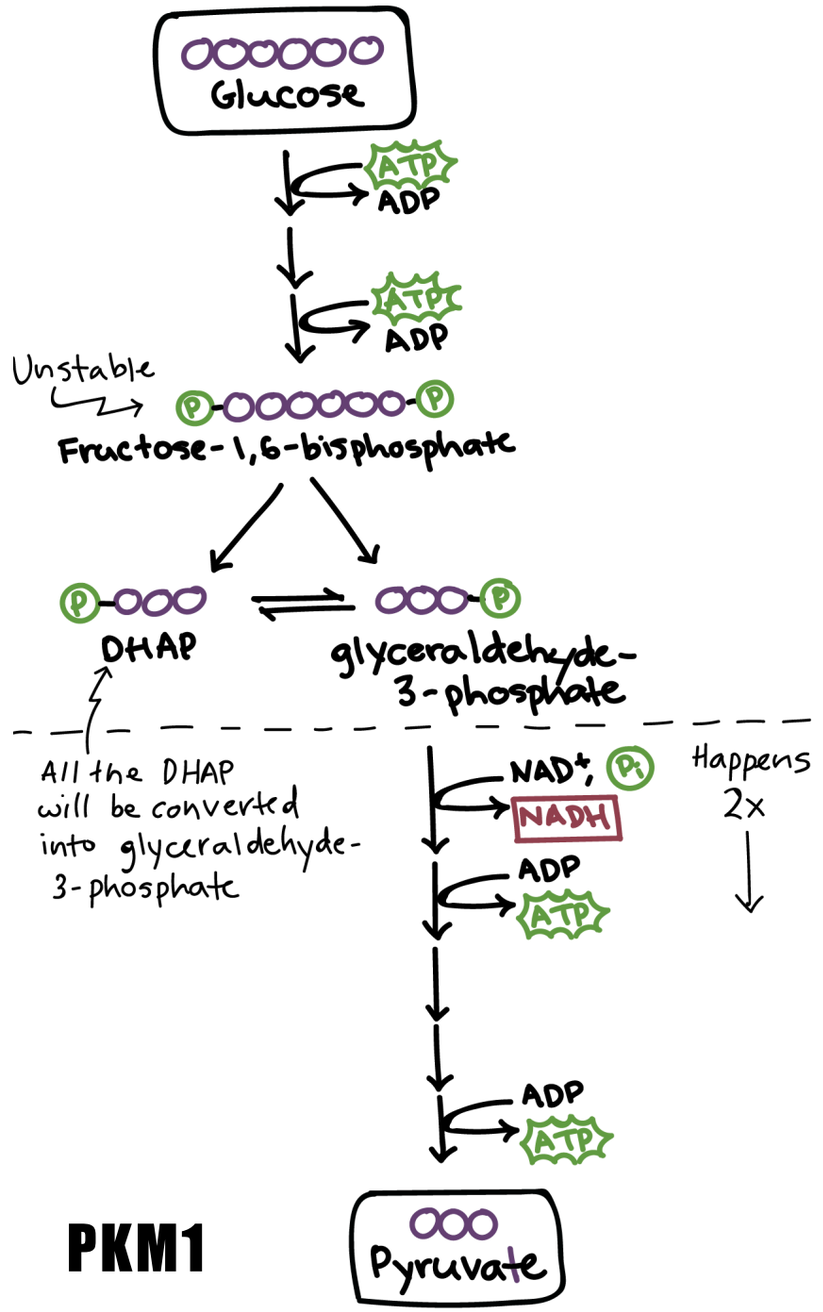


Fast proliferating cells express an alternative form of Pyruvate Kinase



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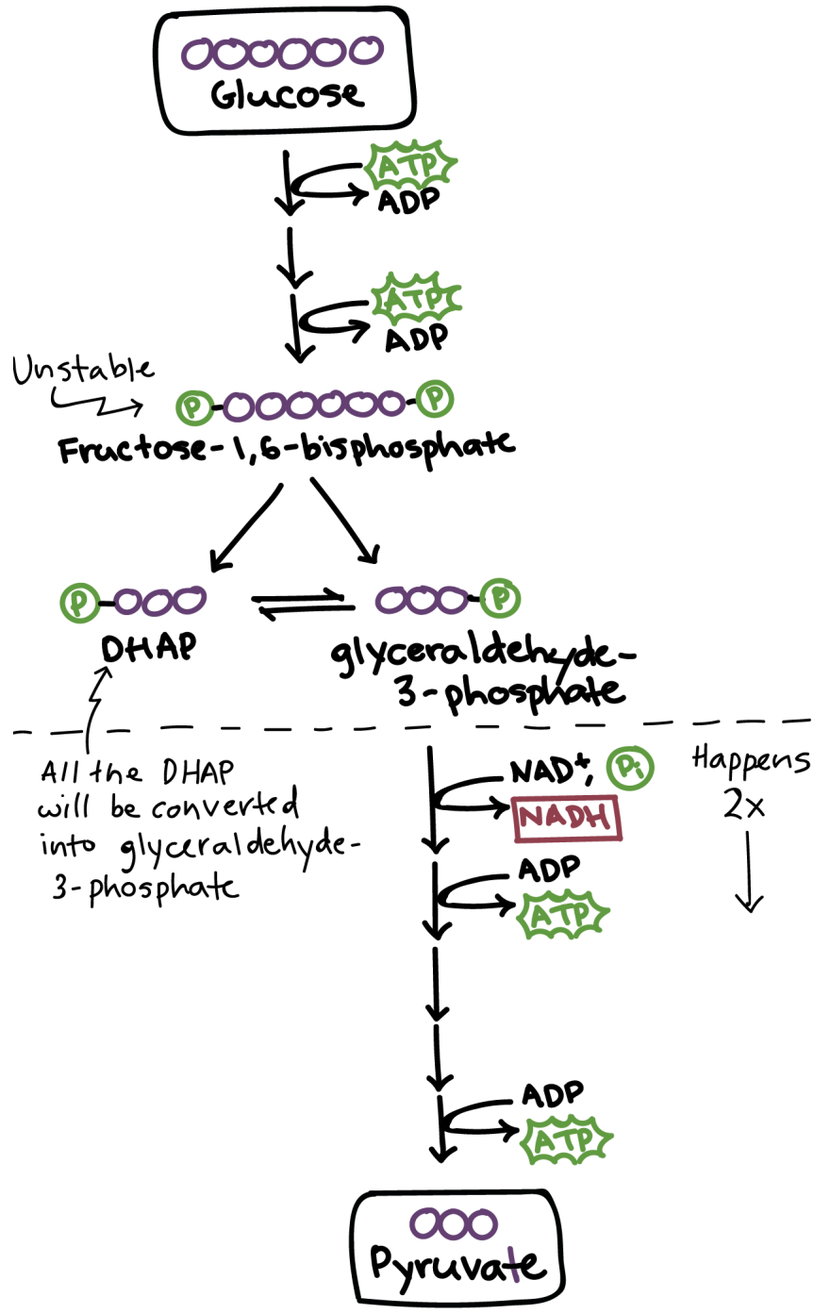

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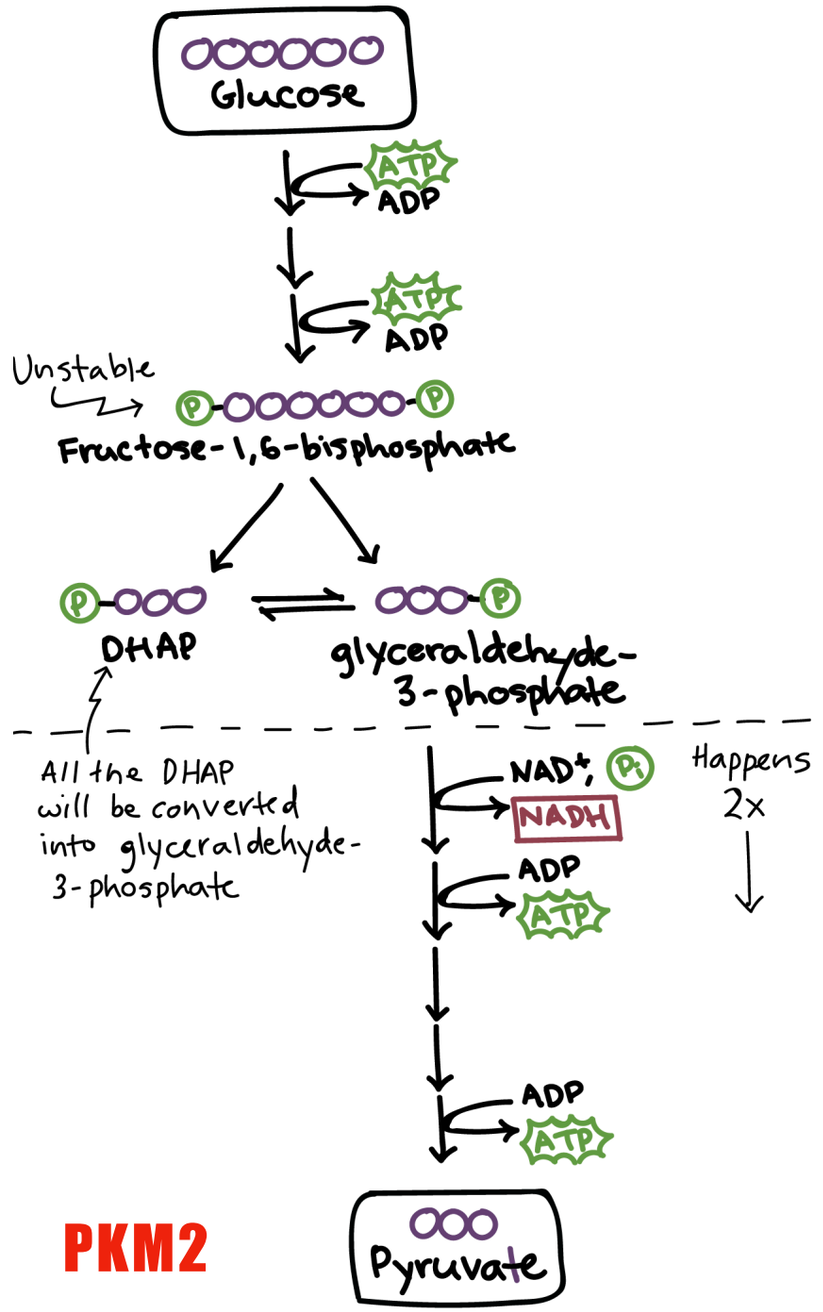

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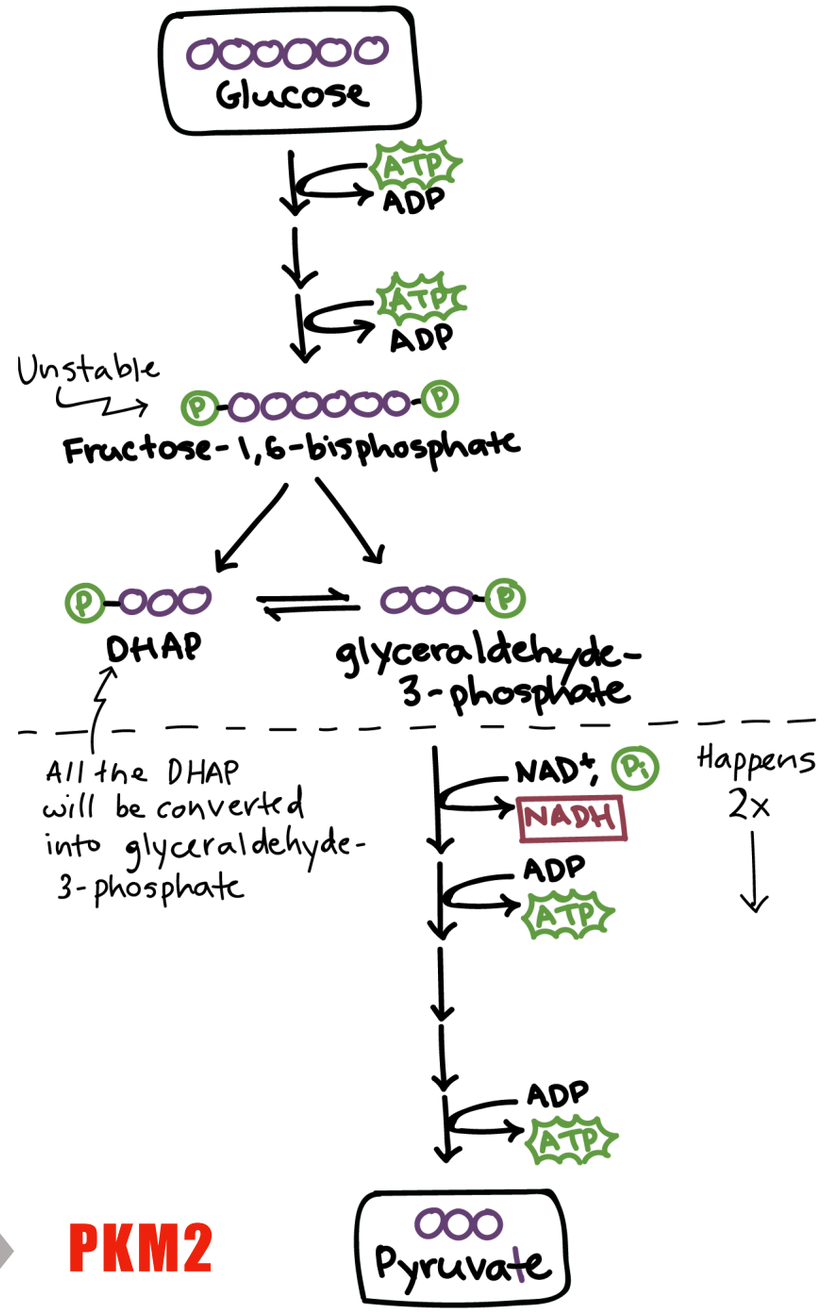
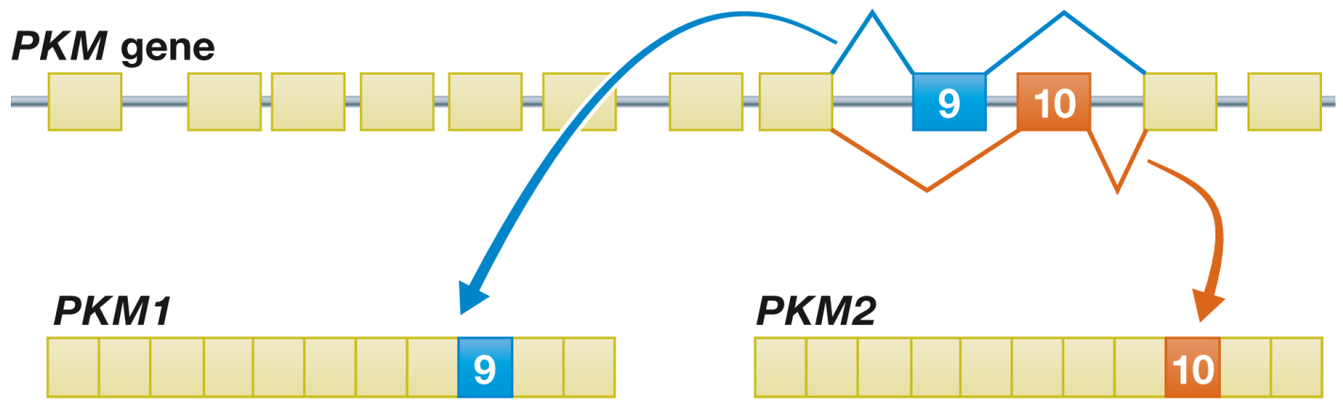


1. Allosteric/metabolic
2. Transcription (Growth Factor Signaling)
3. Phosphorylation

PKM2

Tumors (and proliferating tissues) express PKM2



Expressed in

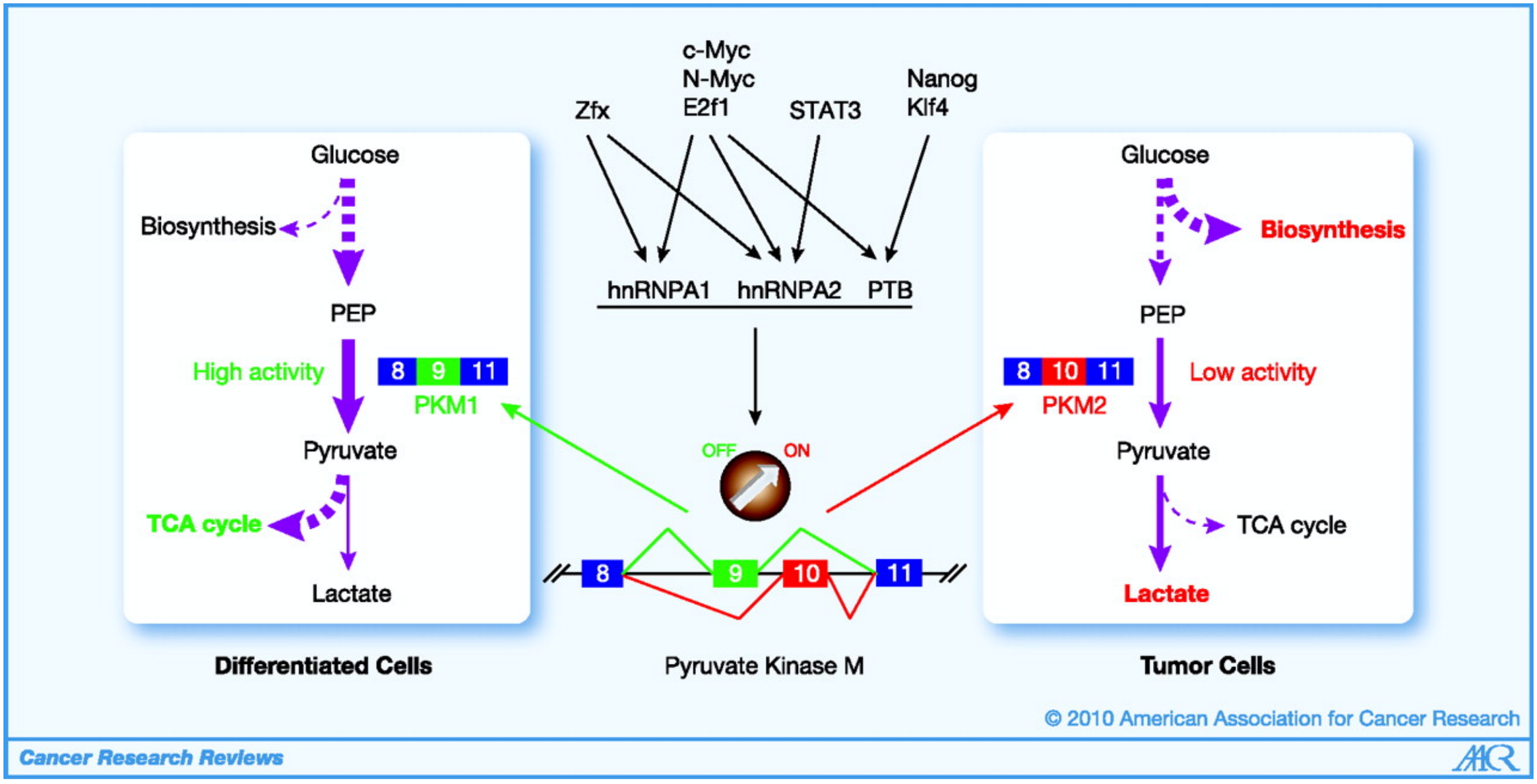
- Heart
- Skeletal muscle
- Smooth muscle
- Brain
- Adrenal medulla
- Mature sperm

Expressed in

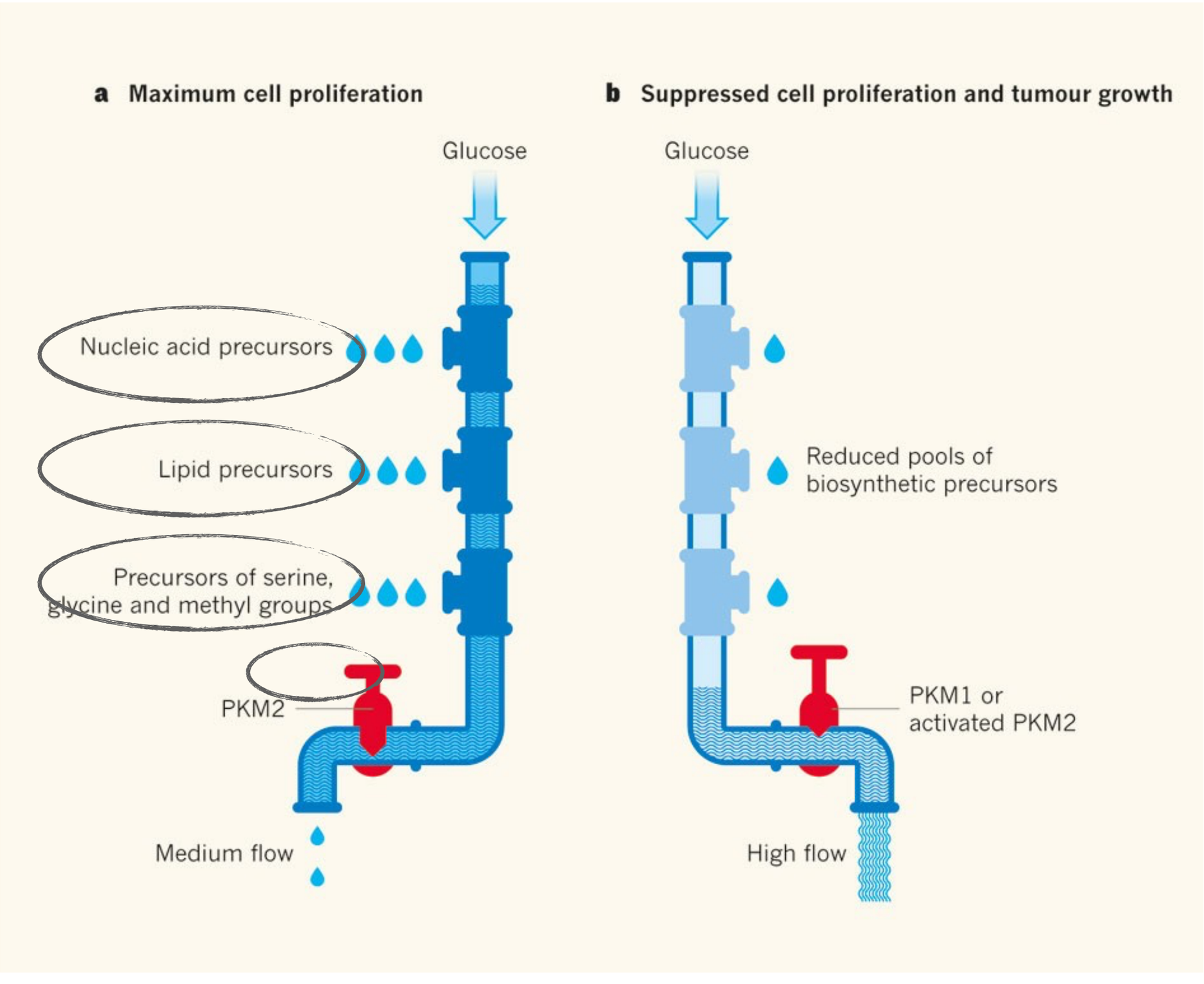
- Most tumour cells
- Embryonic tissue
- Leucocytes
- Kidney distal tubule cells
- Parenchymal lung
- Intestine (most cells)
- Thymus
- Pancreatic islet cells
- White fat
- Spleen
- Ovaries
- Adrenal cortex
- Testis

Dayton et al, ***EMBO Rep****, 2016*

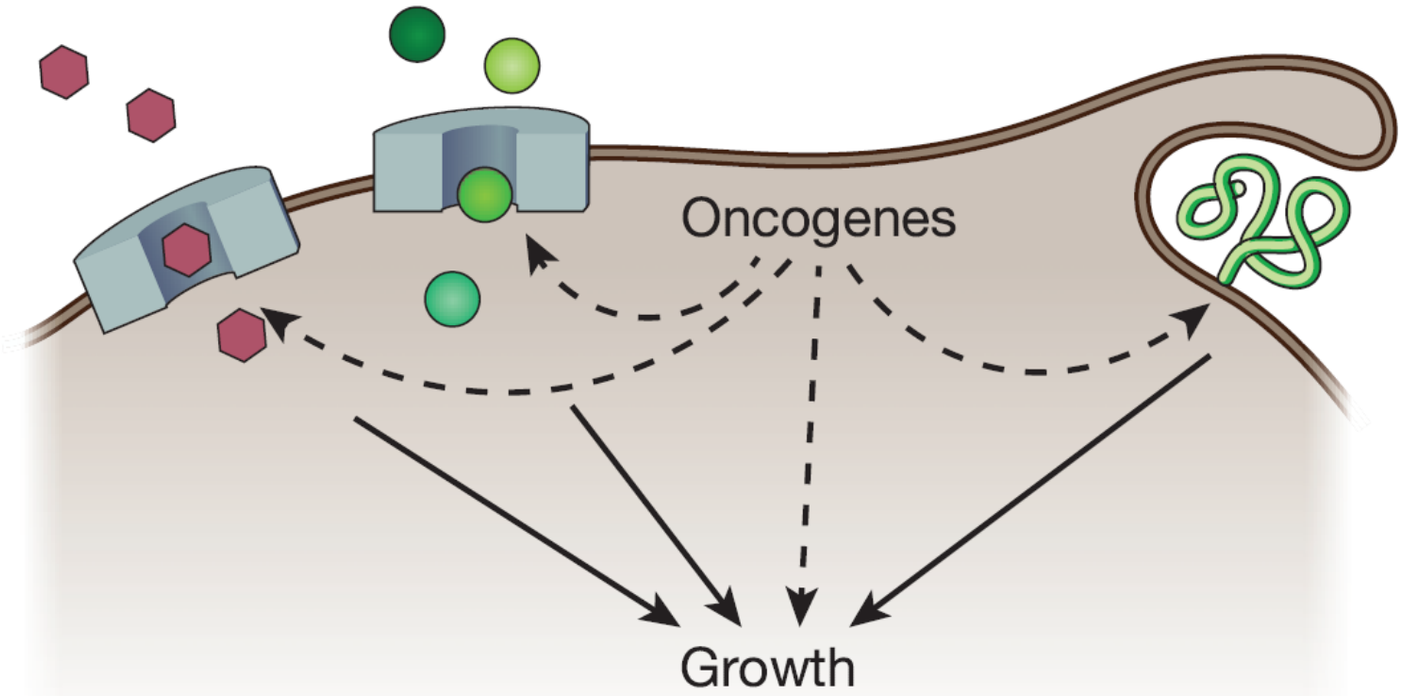
PKM2 has LOWER activity



Lower PKM activity leads to accumulation of glycolytic intermediates



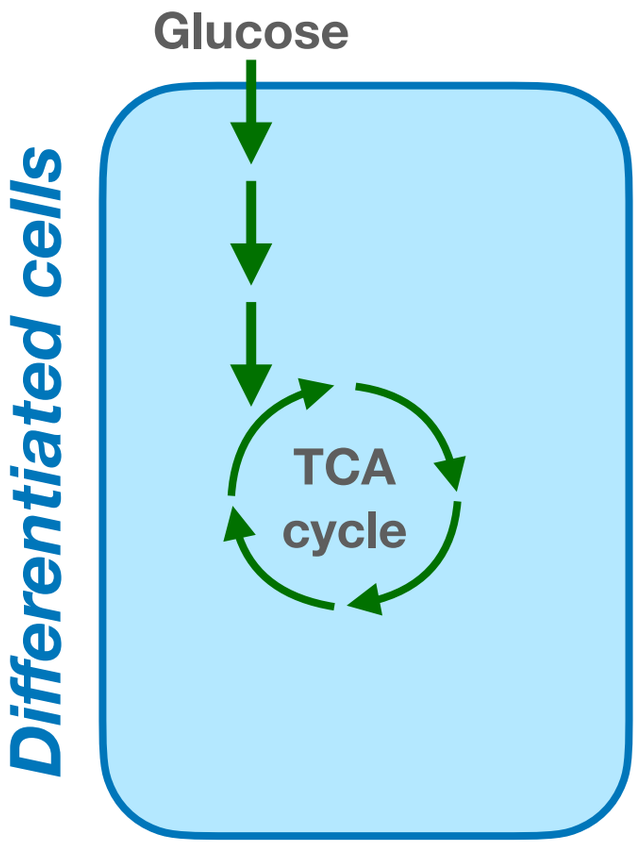
Oncogenes hijack cell ability to uptake nutrients



Enhanced uptake of glucose, glutamine AND alternative carbon sources

Cancer cells thrive in harsh environments:

they can pick up ALL sorts of nutrients



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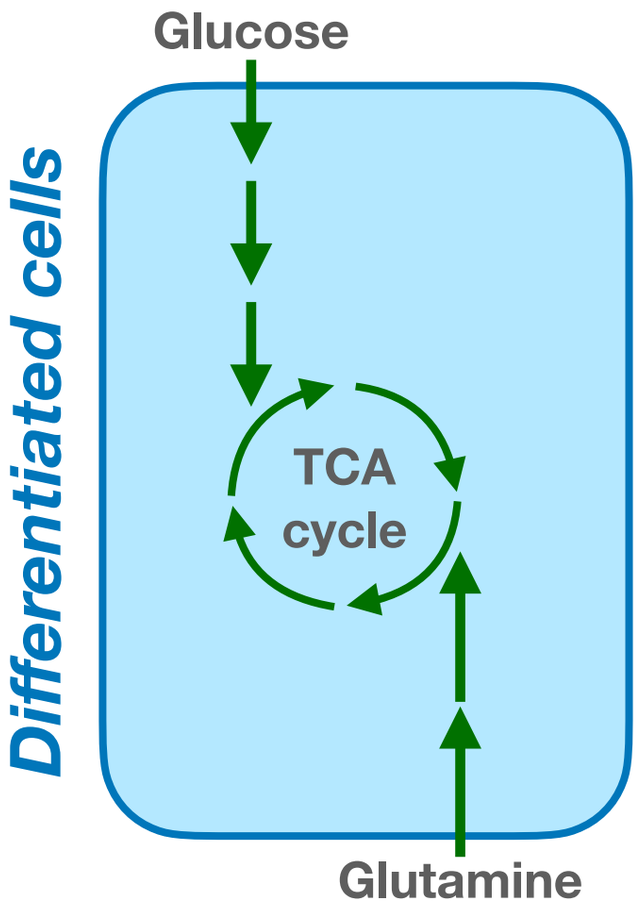

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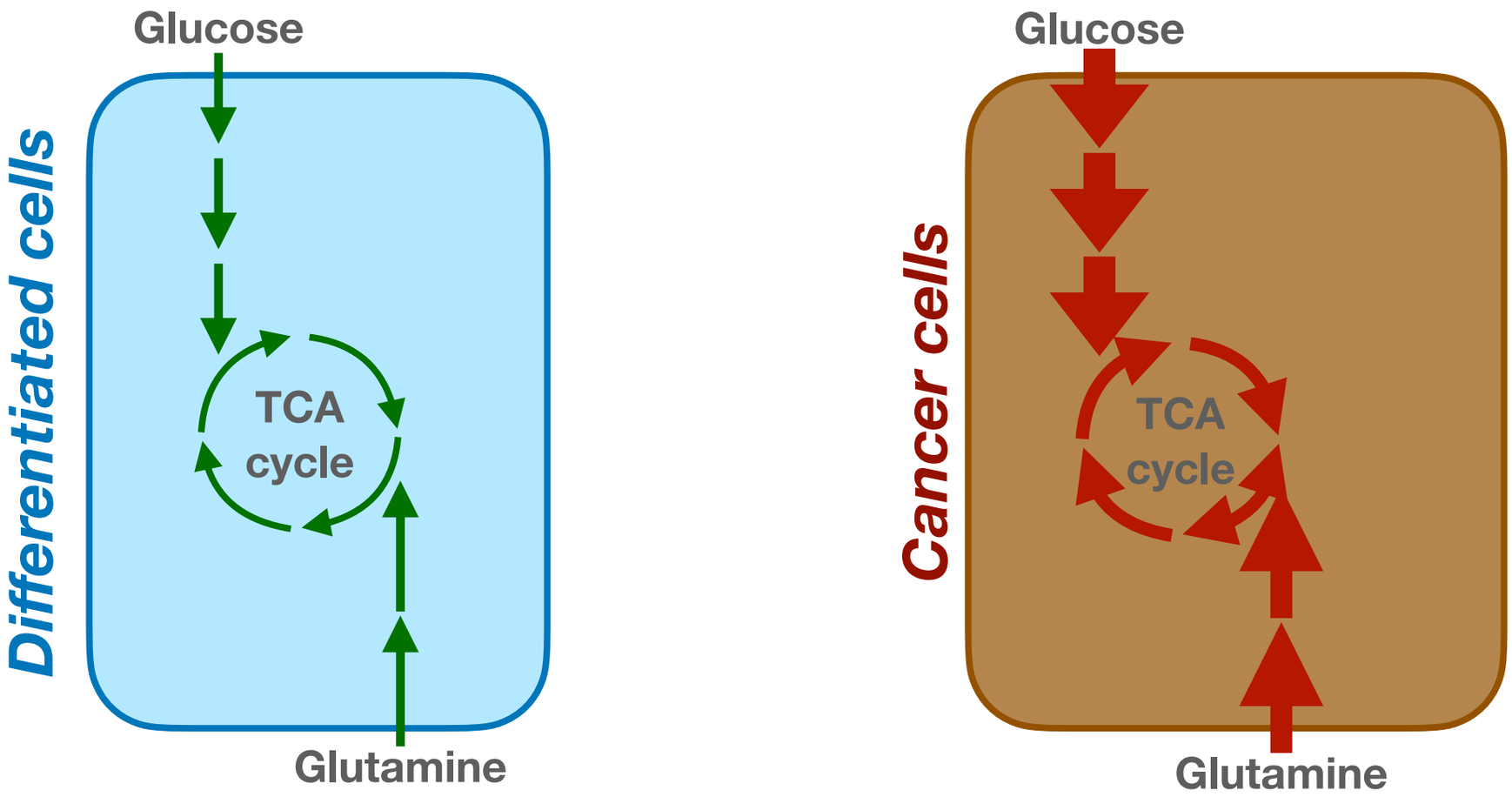

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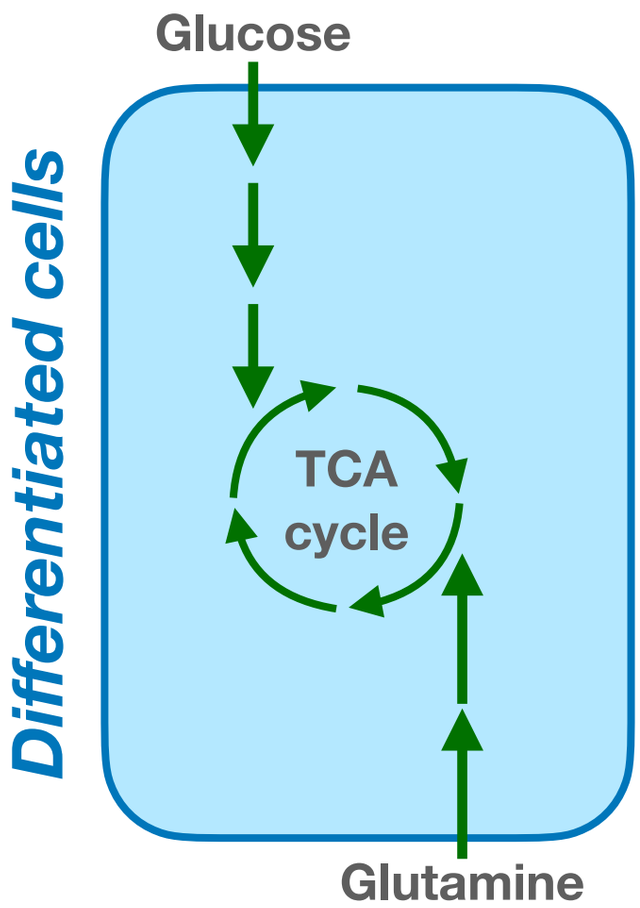

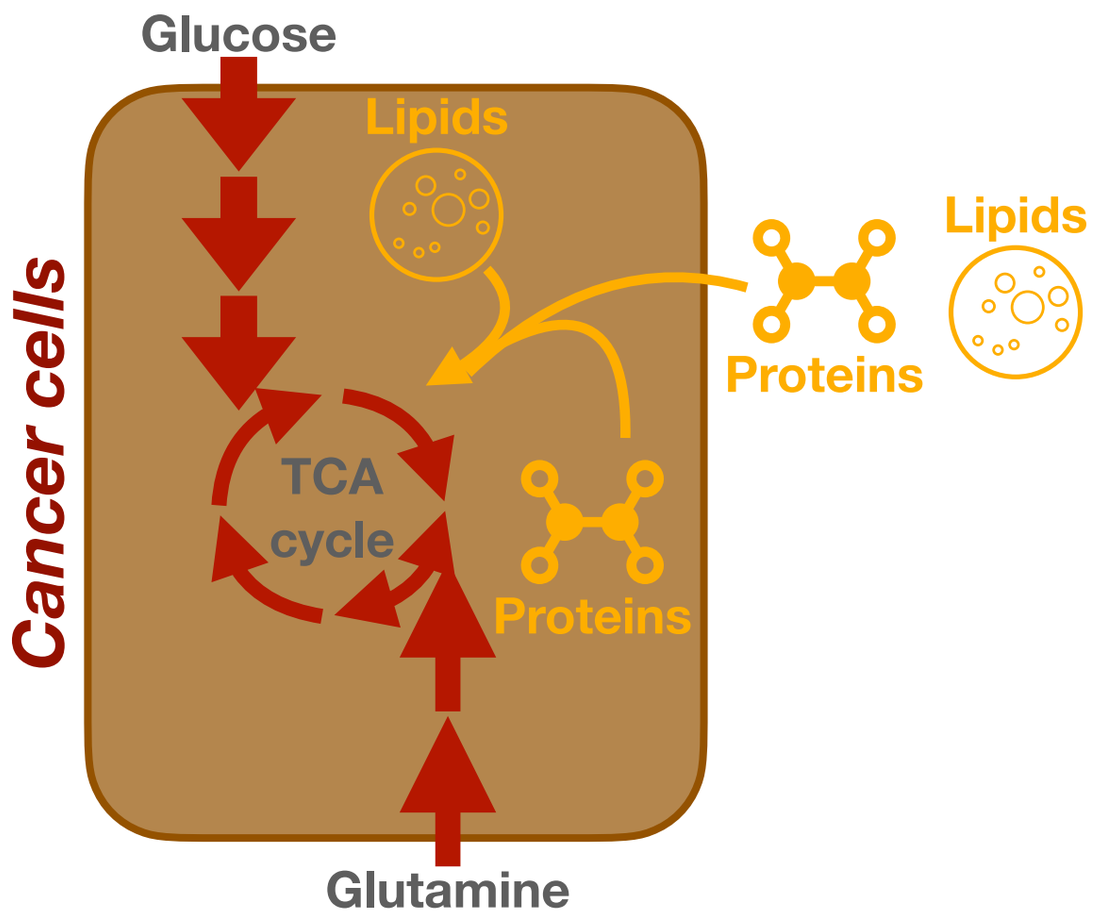

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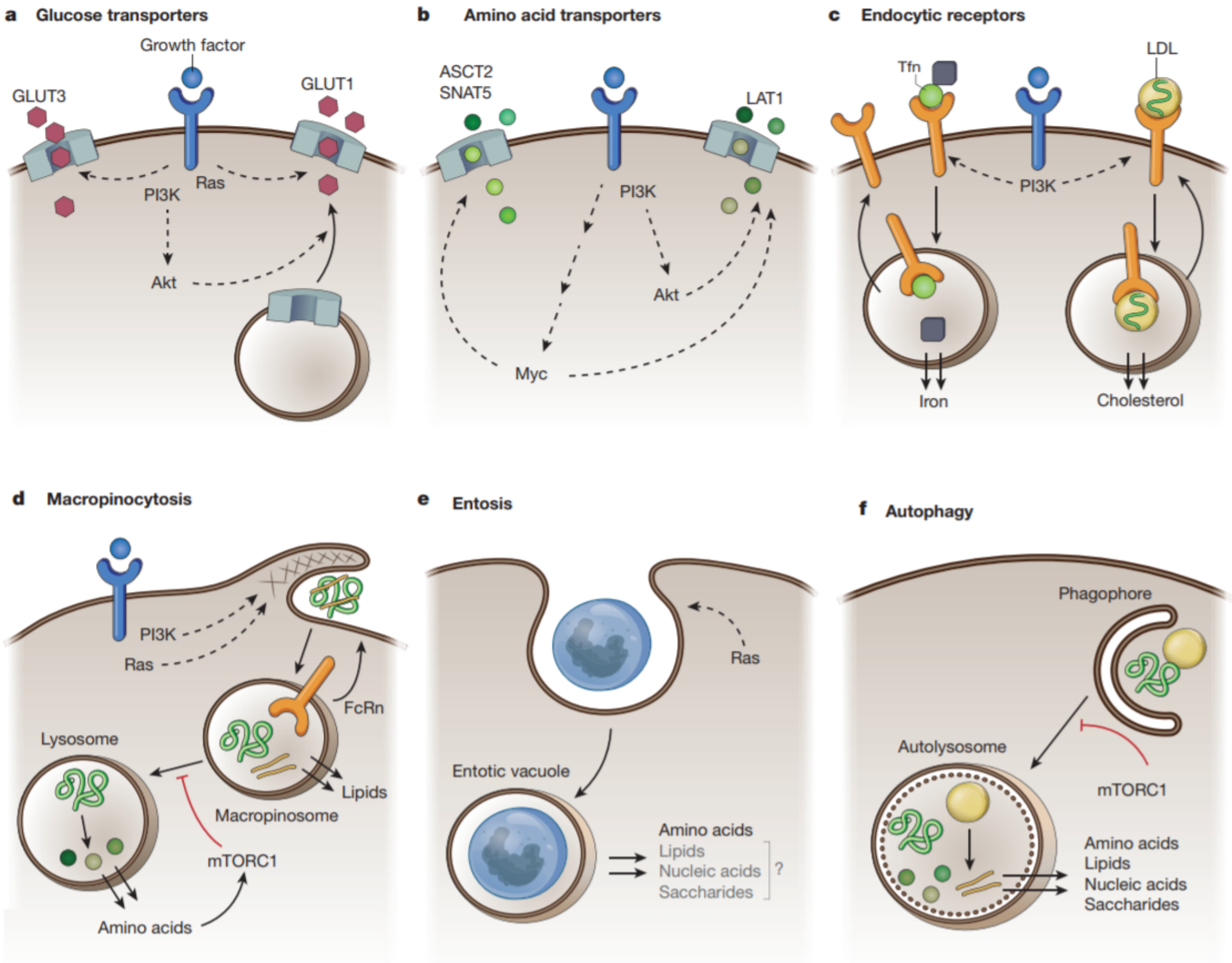
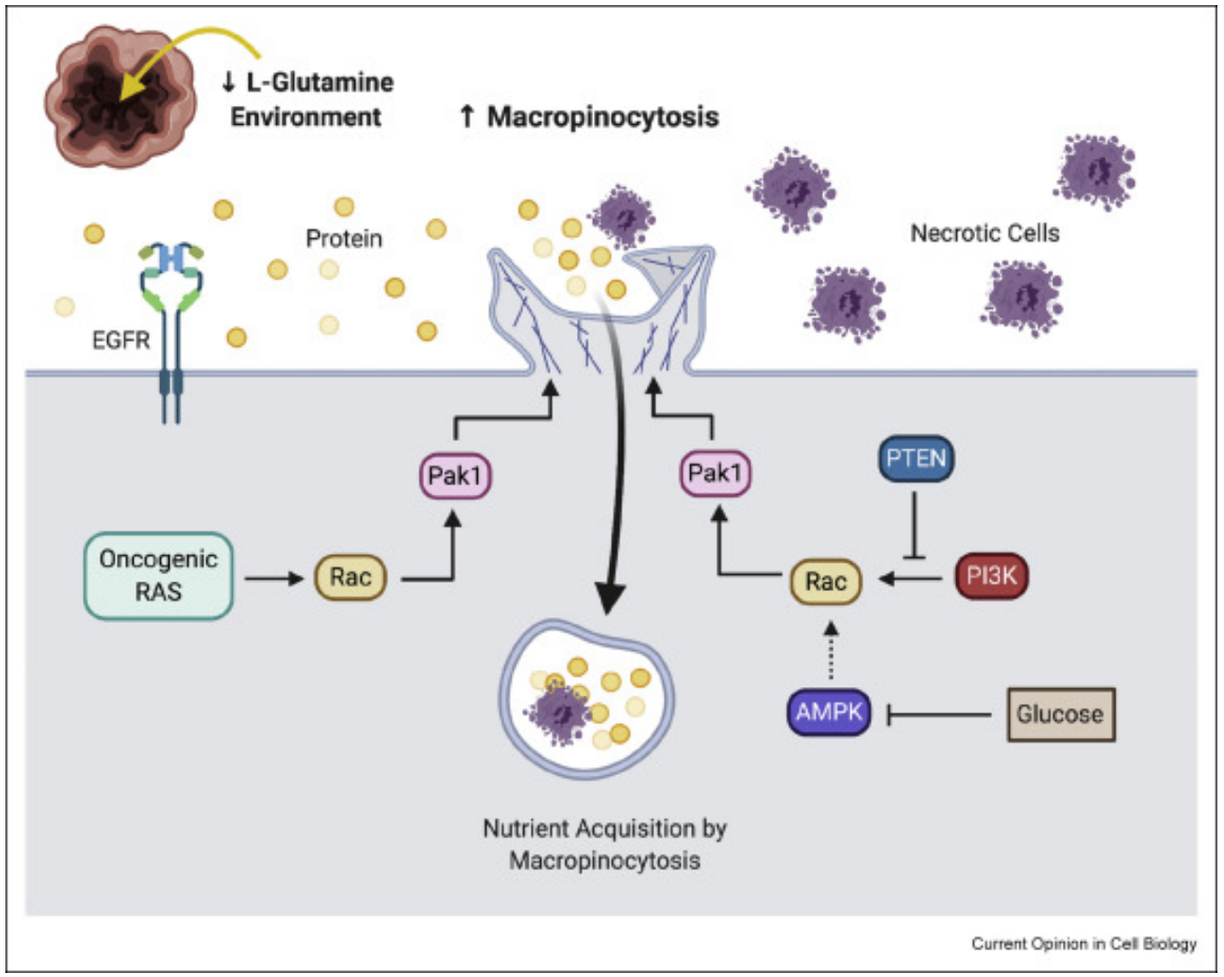
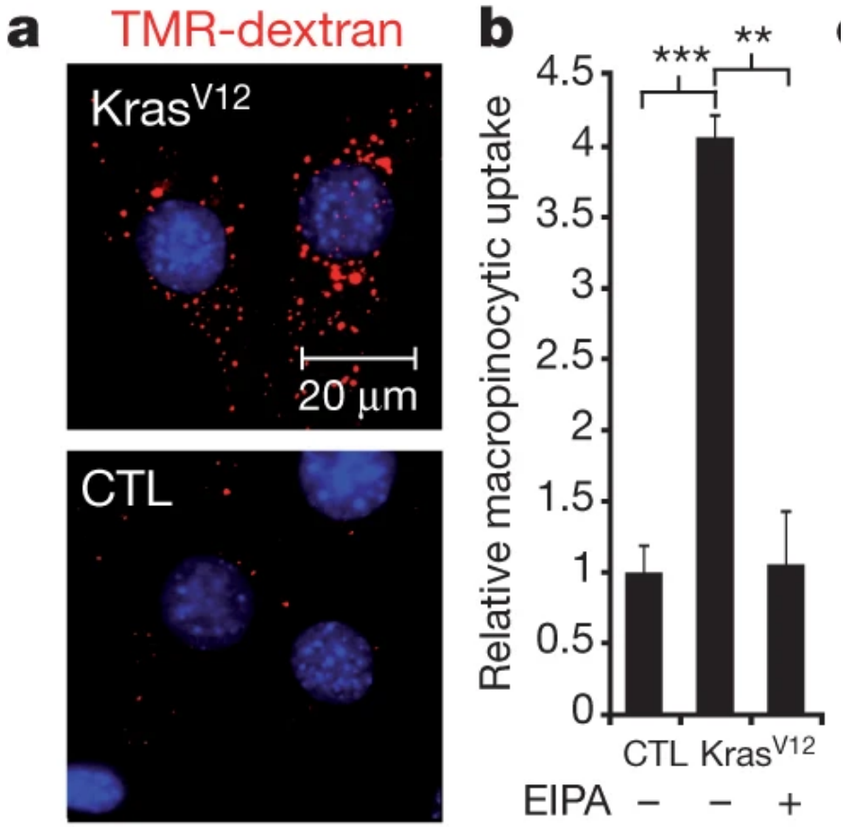
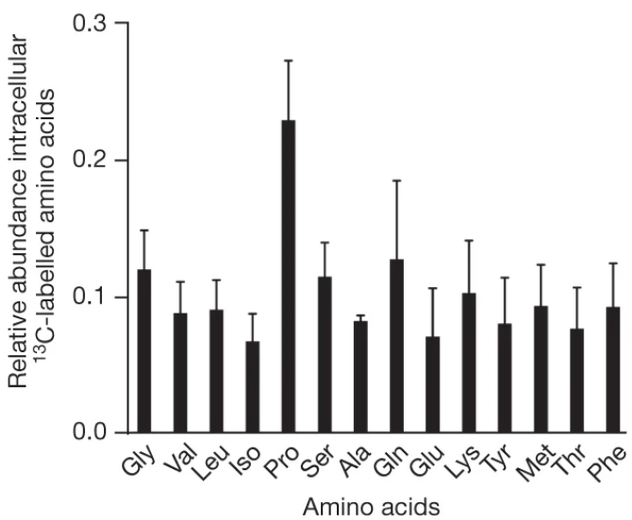


Oncogenic *Kras* induces macropinocytosis for nutrient scavenging



Stow & Wall, ***Curr Opin Cell Biol****, 2020*





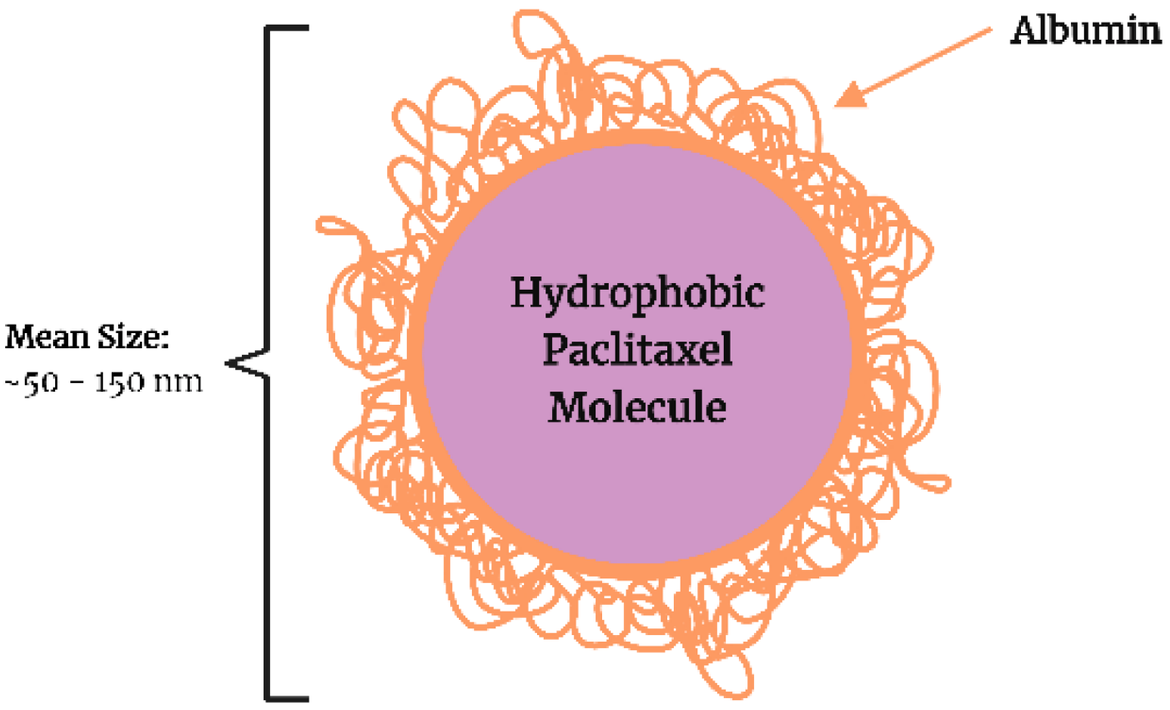
Uniformly ^{13}C-labelled intracellular amino acid pools were detected in NIH 3T3 Kras^{V12} cells supplemented with 2% ^{13}C-labelled yeast protein. Protein-derived alanine enters central carbon metabolism upon transamination to pyruvate, and pyruvate can be directly converted to lactate.

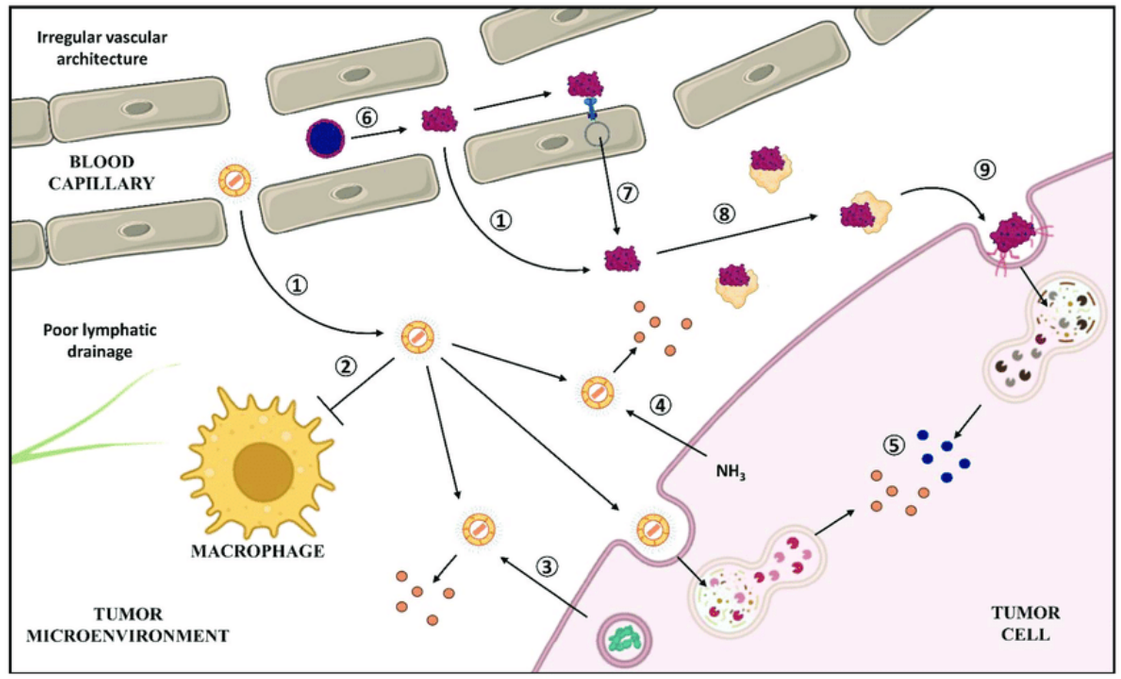
Commisso et al, ***Nature****, 2013*

Exploiting metabolic reprogramming of cancer cells:

Nab-paclitaxel (Abraxane®)

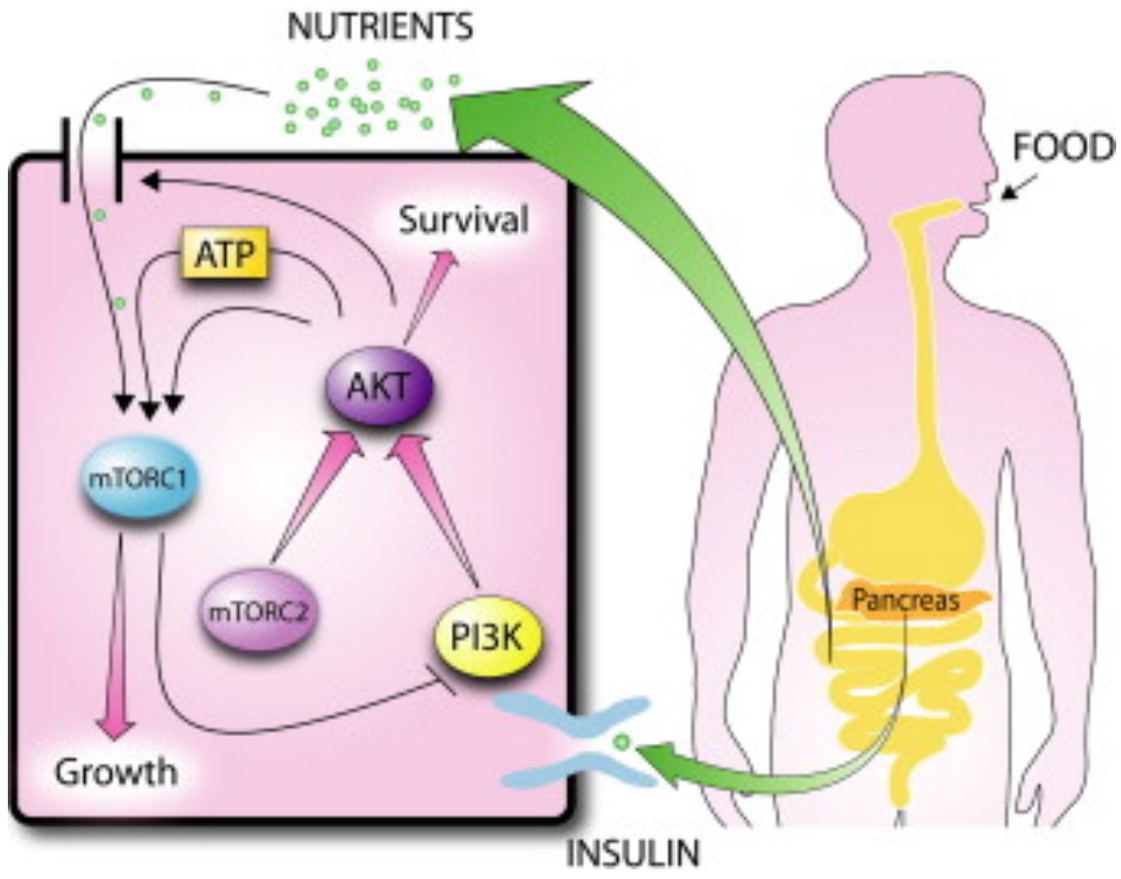
Molecular structure of nab-paclitaxel





ABRAXANE® is a prescription medicine used to treat advanced pancreatic cancer, when used in combination with gemcitabine, as the first medicine you receive for advanced pancreatic cancer.

mTOR is hyper activated in cancer to sustain growth

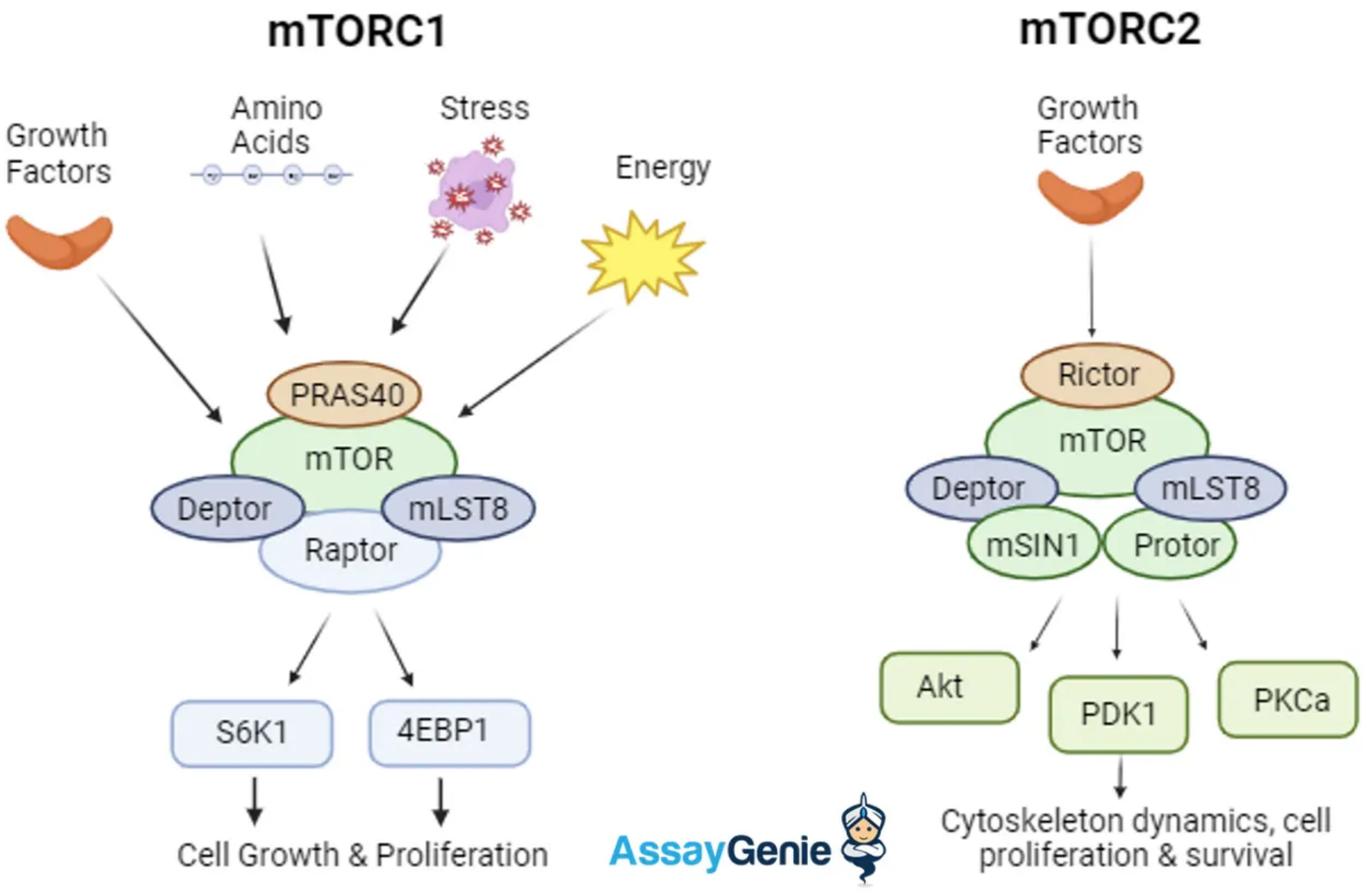


mTORC1 is an ancient regulator of cell growth that is activated by intracellular nutrients. The ancient function of mTORC2 is unclear, but it may have evolved to indirectly sense nutrients by way of insulin signaling. Circulating glucose triggers the release of insulin into the bloodstream. In peripheral tissues harboring growth factor responsive cells, insulin activates the PI3K-mTORC2-AKT pathway. In individual cells, activation of AKT promotes survival, nutrient influx, and energy (ATP) generation. Signals from intracellular nutrients, energy, and from AKT itself subsequently activate mTORC1, which drives protein synthesis and promotes cell growth.

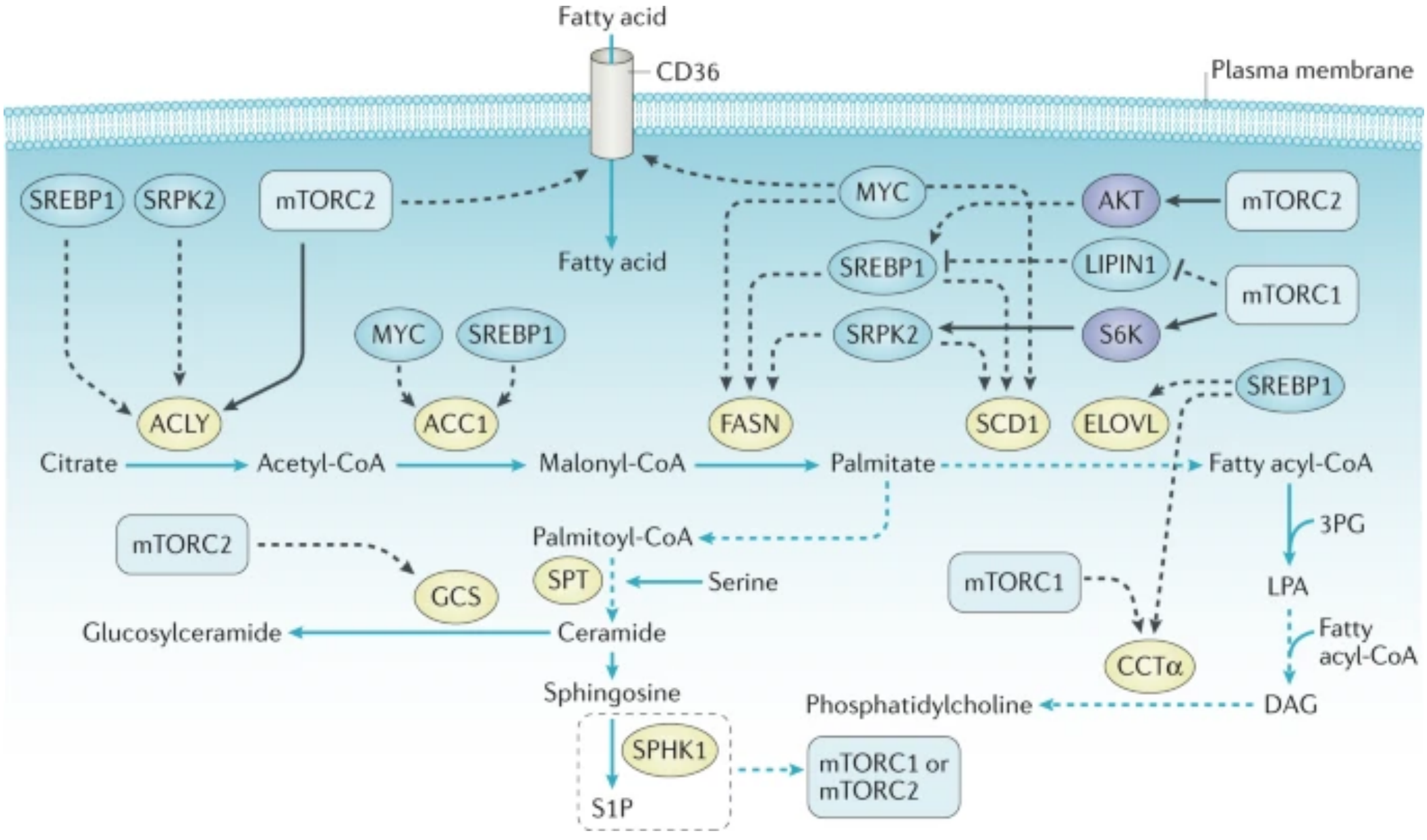
Guertin & Sabatini, ***Cancer Cell****, 2007*

mTOR is hyper activated in cancer to sustain growth

Mutations, over nutrition, obesity, aging

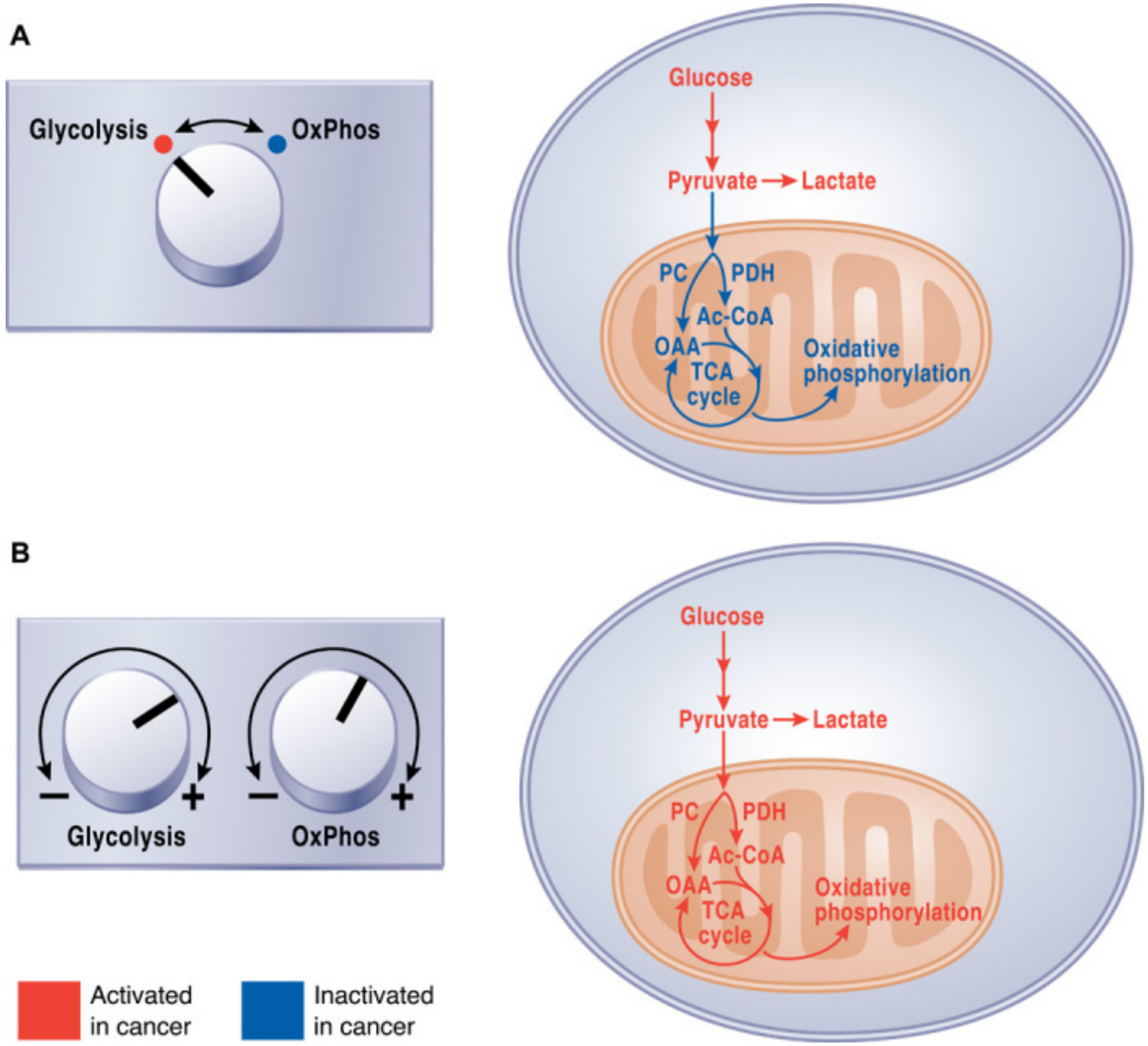


mTOR sustains growth:
lipid synthesis



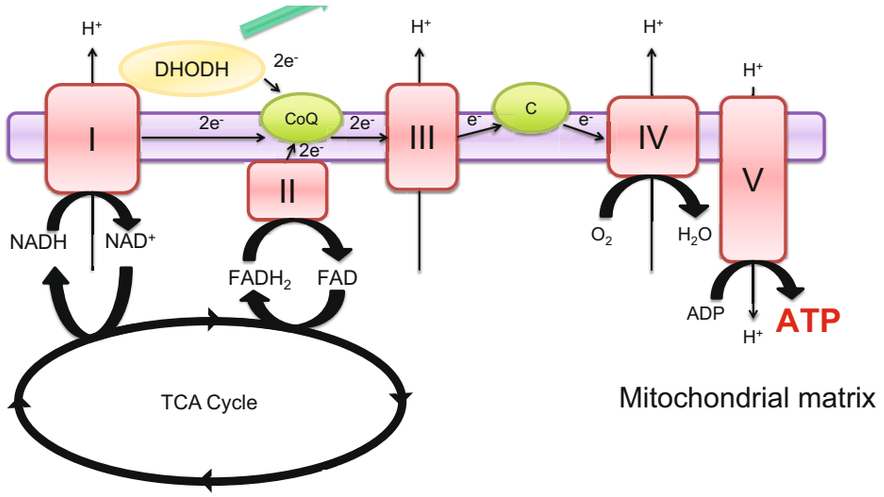
Mossman et al, ***Nat Rev Cancer****, 2018*

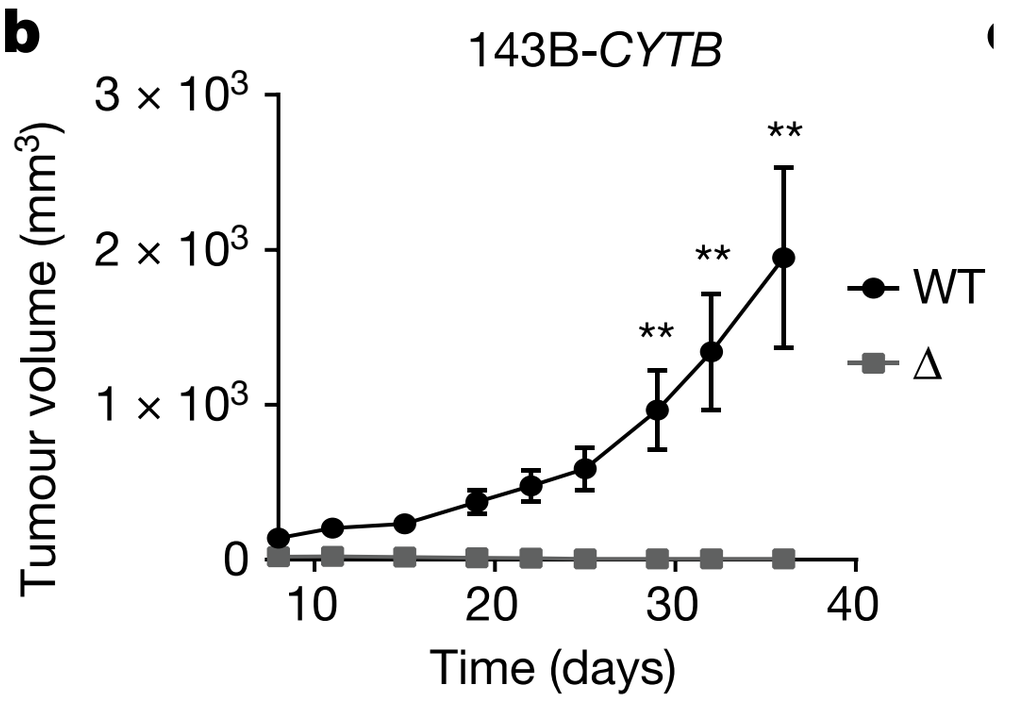
Cells can turn a “glycolytic switch”



DeBerardinis RJ, Chandel N, ***Science Signal****, 2016*

Targeting mitochondrial genes impairs tumor growth



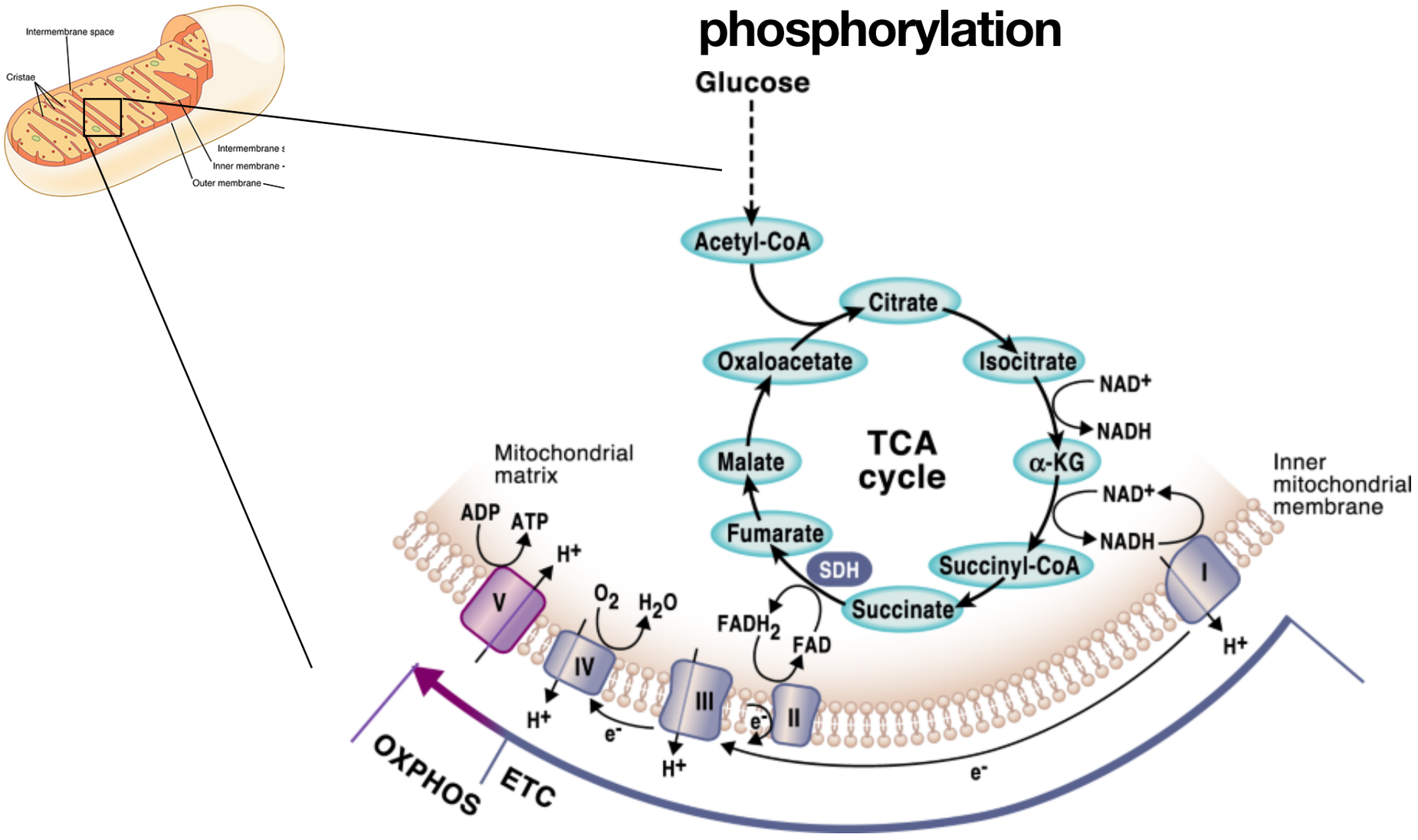


Martinez-Reyes et al, ***Nature****, 2020*

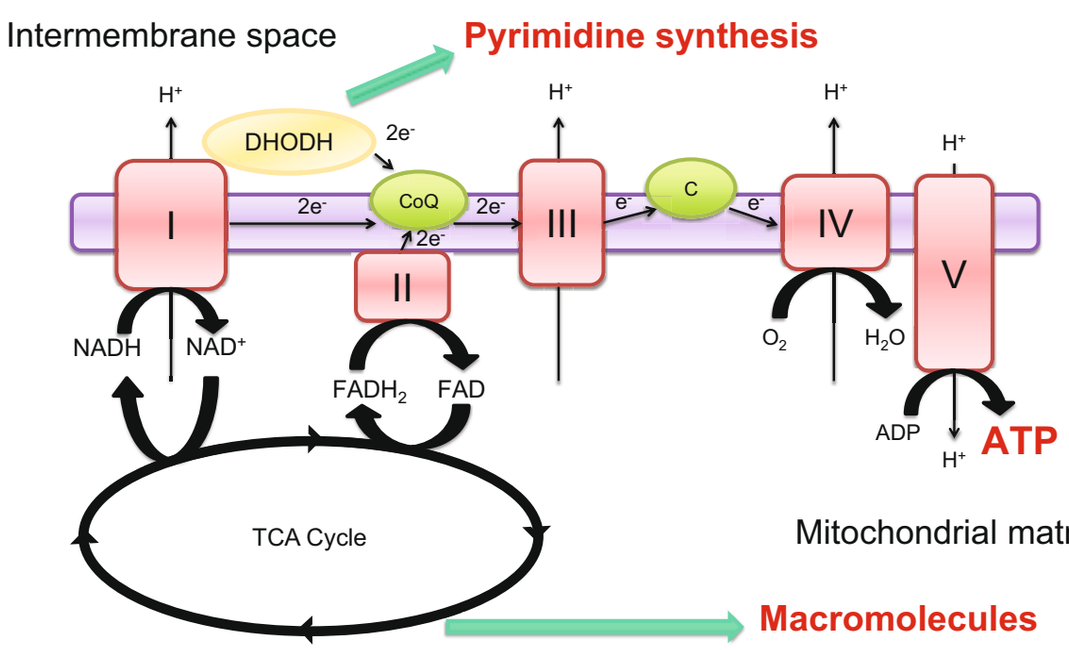
Mitochondria have been proposed as targets for cancer therapy

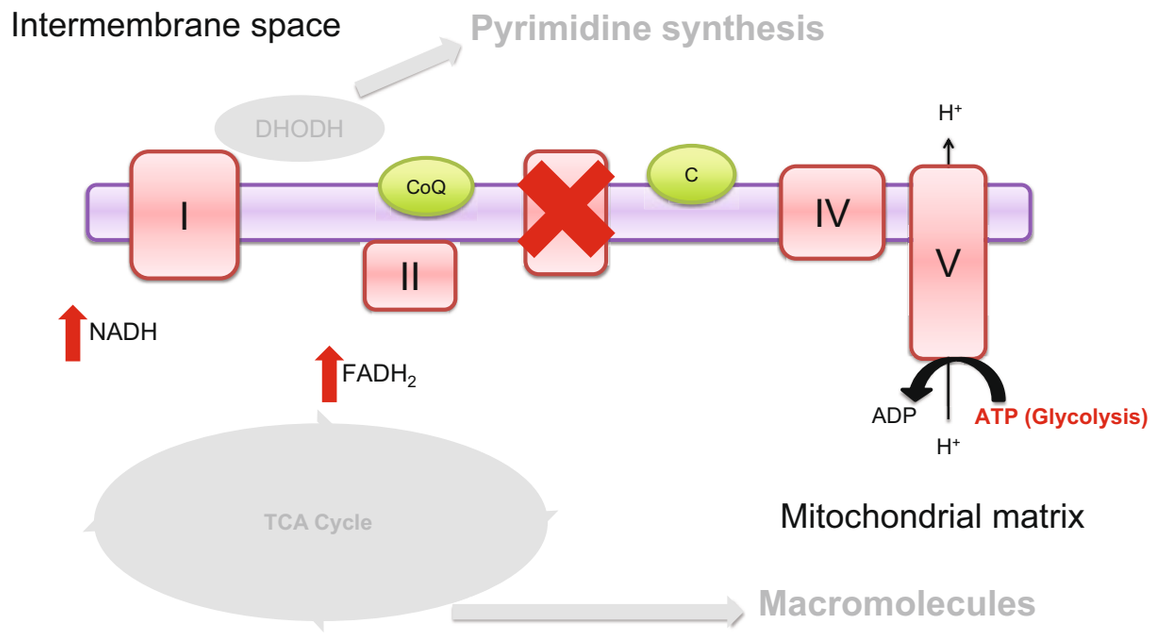
Bachman et al, ***Int J Mol Sci****, 2018*
Vasan et al, ***Cell Metab****, 2020*
Fulda et al, ***Nat Rev Drug Discov****, 2010*

Mitochondria couple pyruvate oxidation, electron transport and oxidative phosphorylation



Mitochondrial ATP production is NOT essential for tumor growth



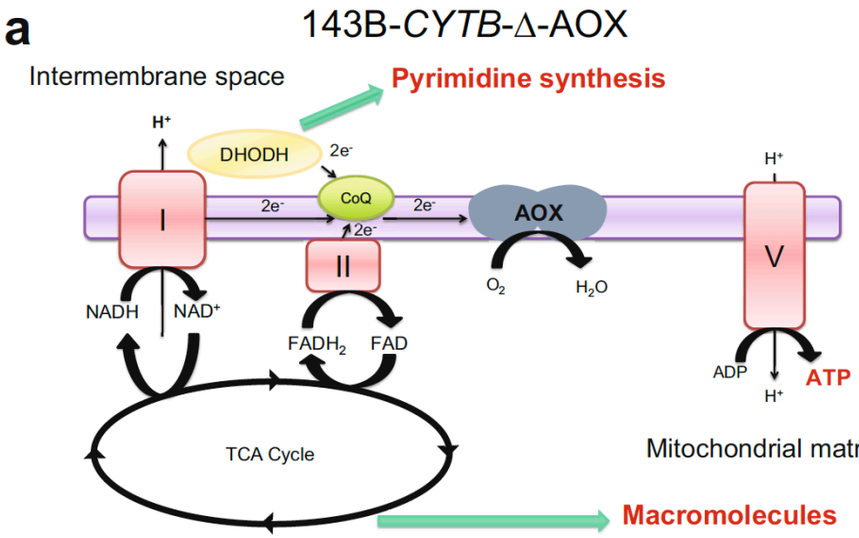


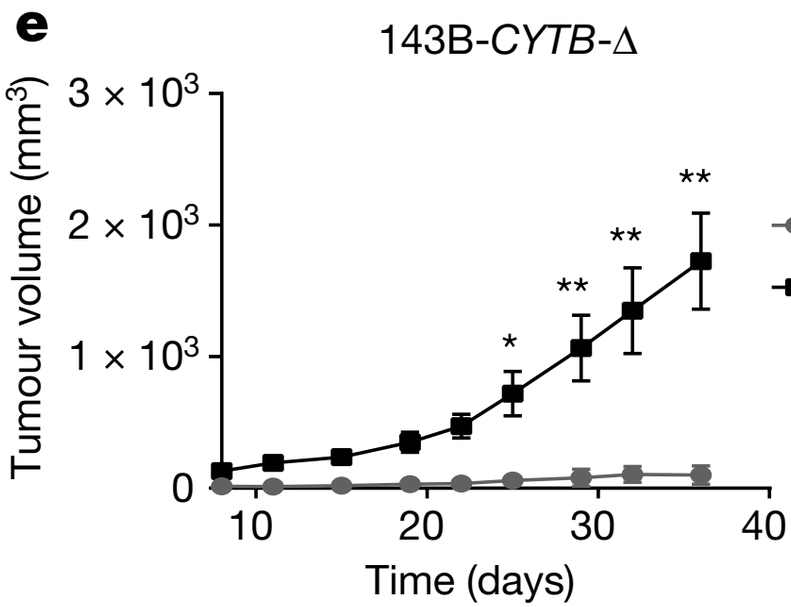
Complex III deficiency suppresses:

- *ATP synthesis*
- *Proton pumping*
- *Electron transport*
- *TCA cycle*
- *CoQ oxidation (necessary for DHODH activity in pyrimidine biosynthesis)*

Martinez-Reyes et al, ***Nature****, 2020*

Mitochondrial ATP production is NOT essential for tumor growth





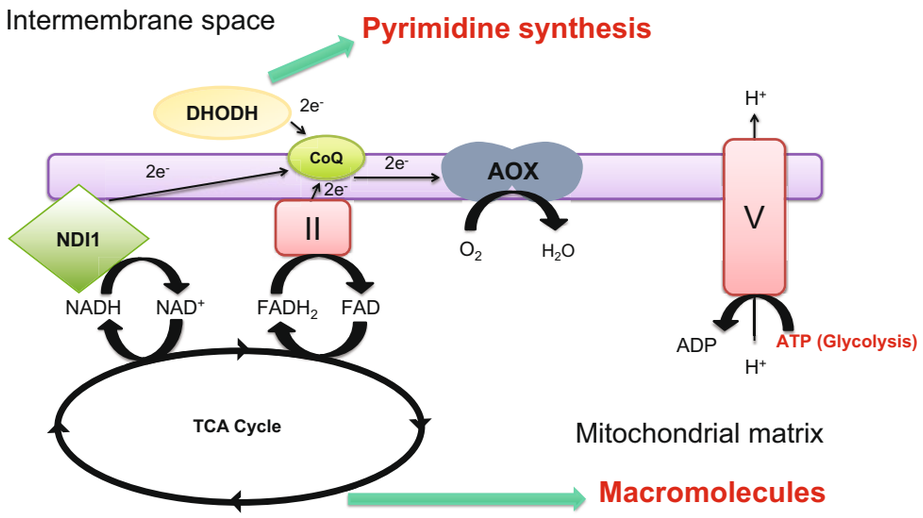
AOX expression (in C3-KO tumors) re-establish fully functional C1-C2 activity, only modestly rescues proton pumping, ATP synthesis

Martinez-Reyes et al, ***Nature****, 2020*

Mitochondrial ATP production is NOT essential for tumor growth

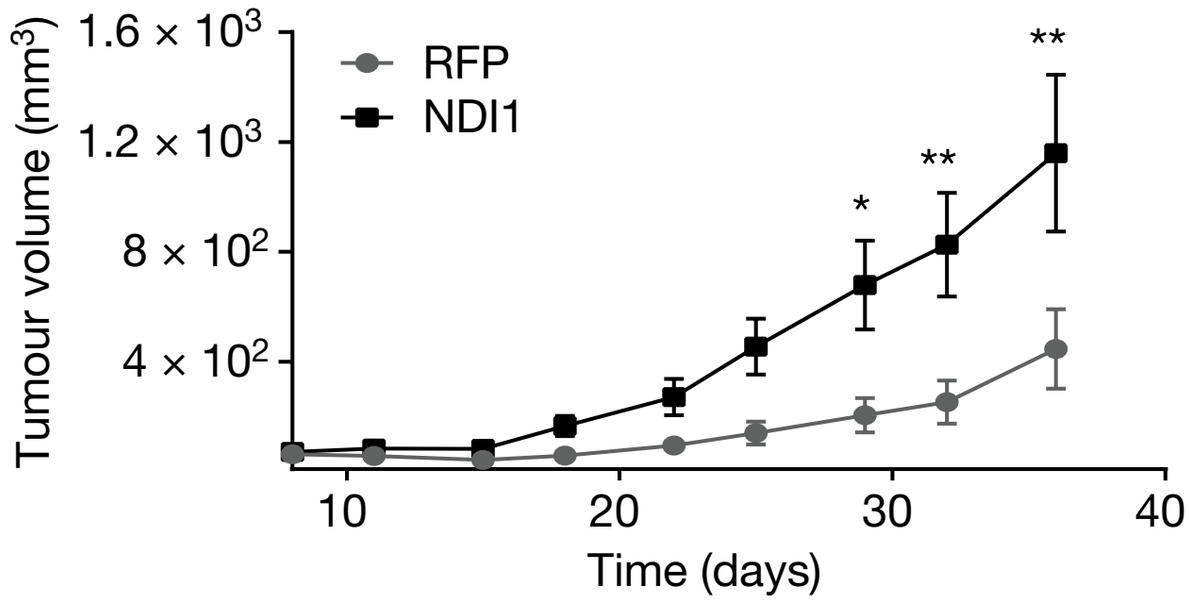
a

143B-*CYTB*-Δ–NDUFS2_KO-AOX-NDI1



f

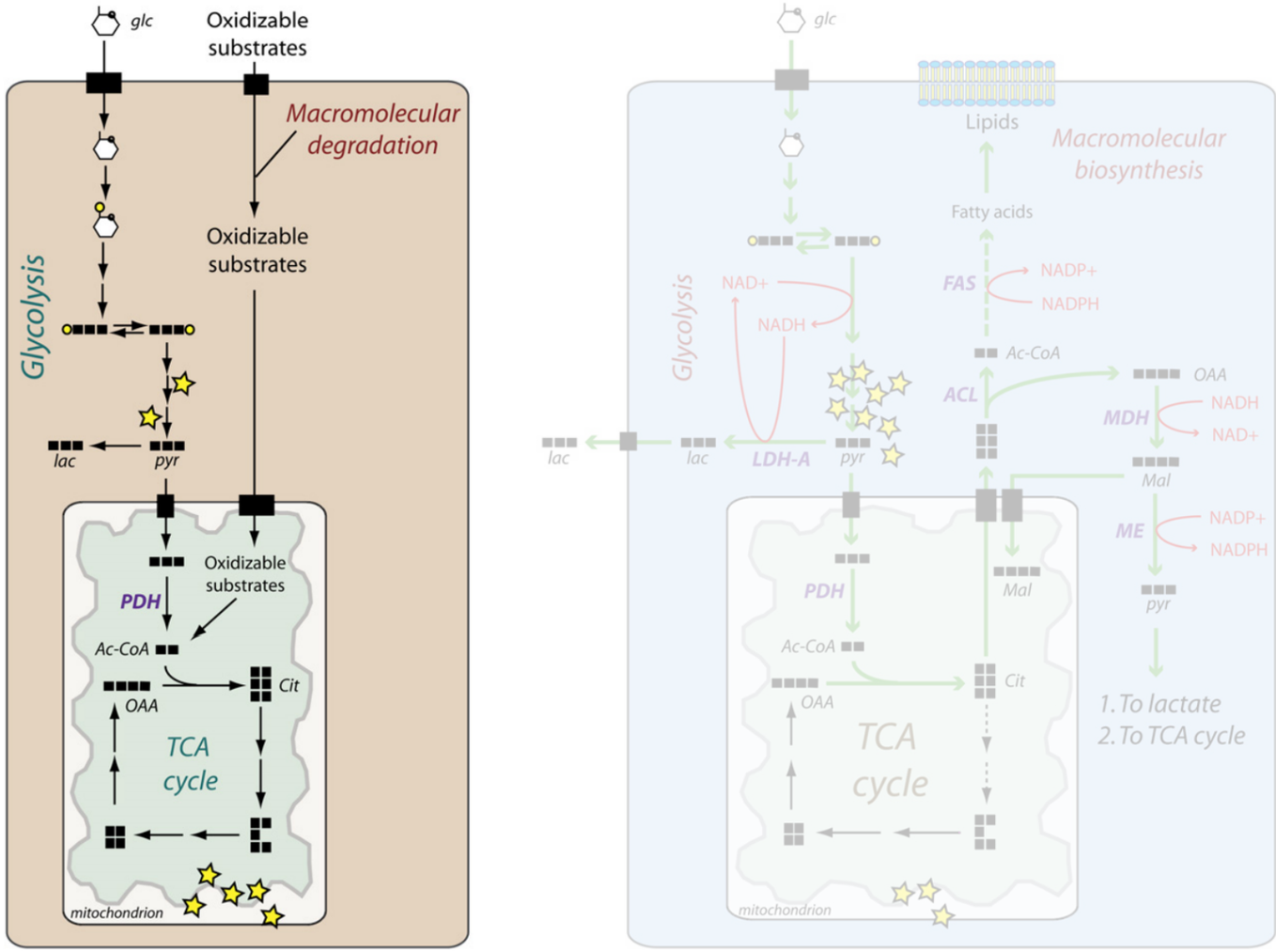
143B-*CYTB*-Δ-NDUFS2_KO1-AOX



CoQ oxidation and TCA cycle are most important for tumor growth

Martinez-Reyes et al, ***Nature****, 2020*

Mitochondria are major metabolic hubs



DeBerardinis RJ, Thompson CB, ***Cell Metab****, 2008*

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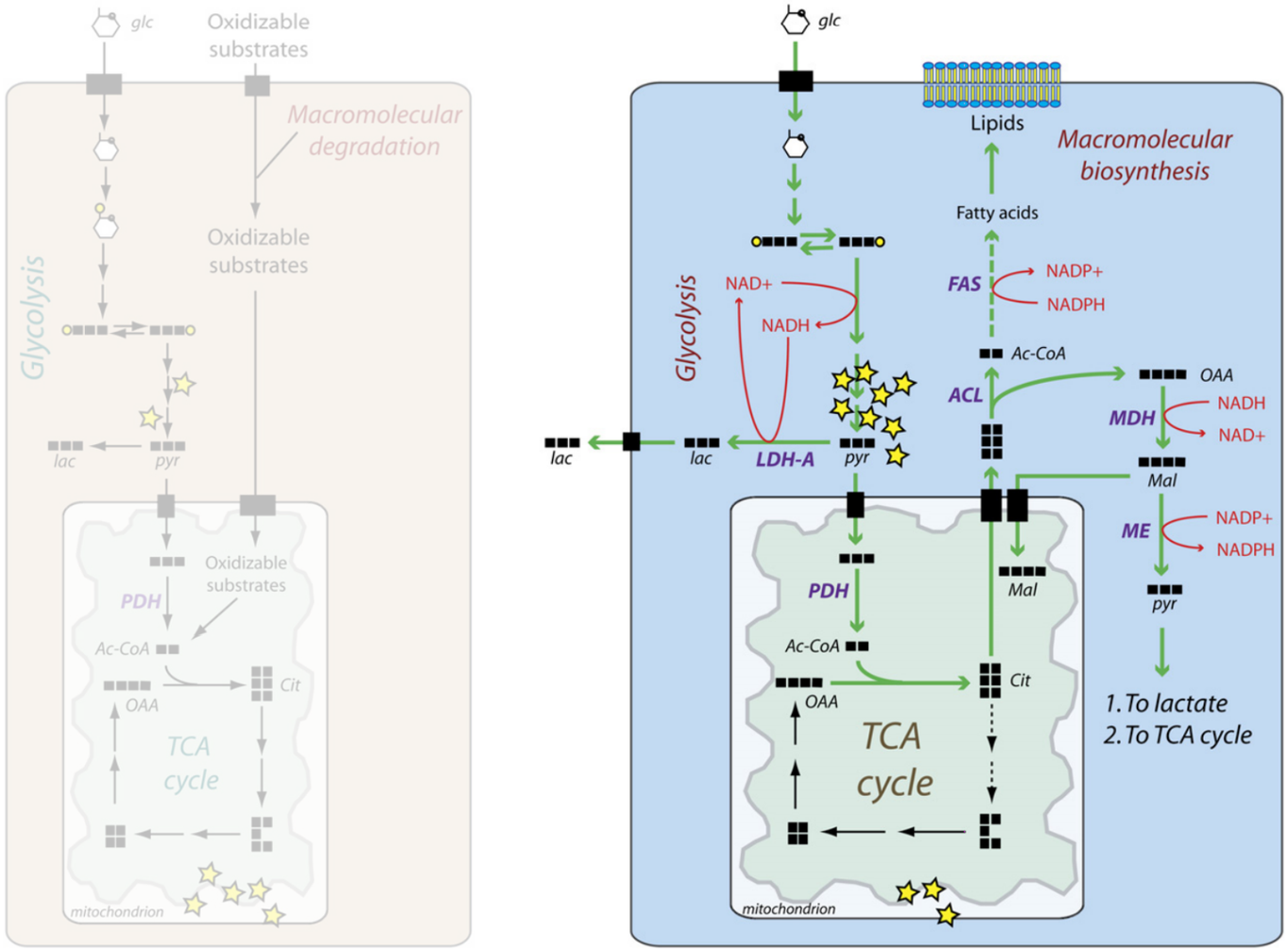
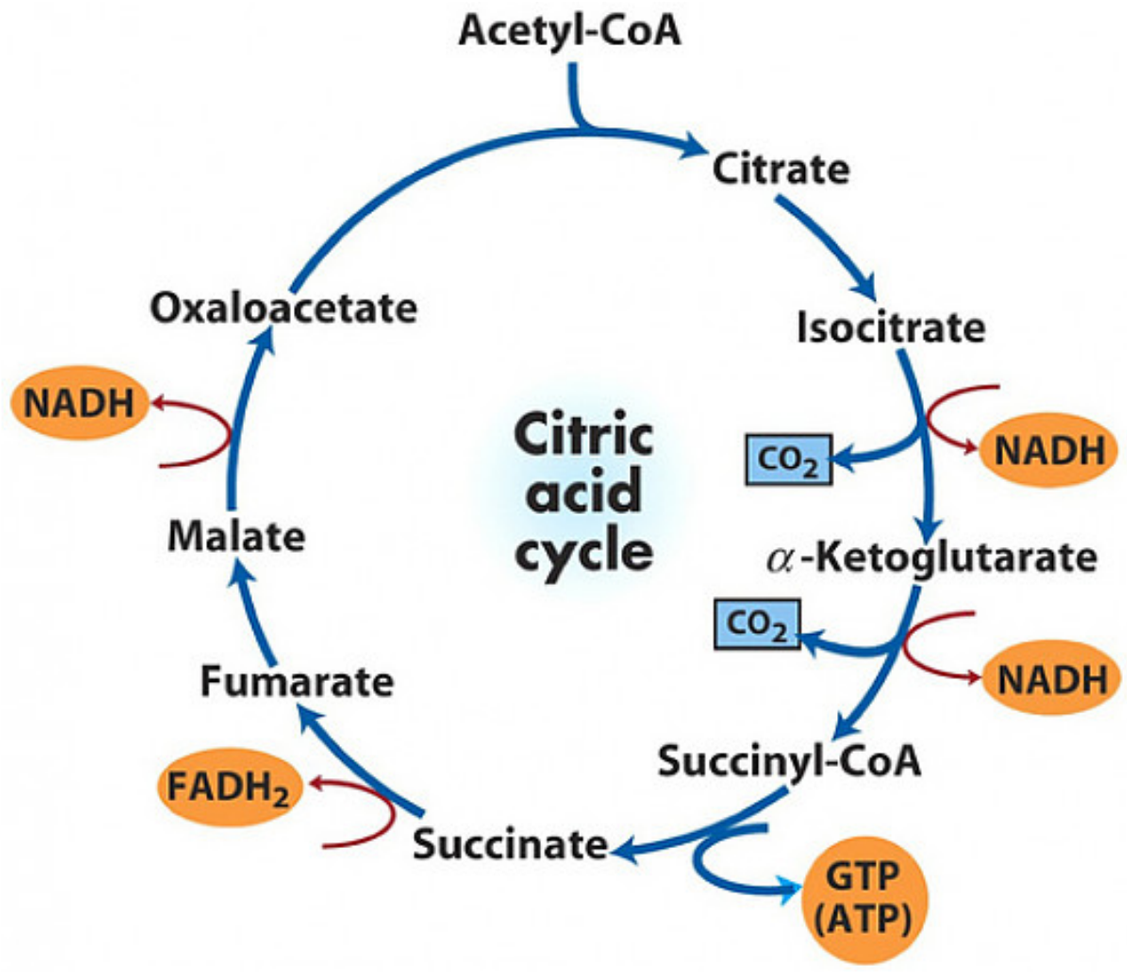


DeBerardinis RJ, Thompson CB, ***Cell Metab****, 2008*

The TCA cycle at the crossroad of catabolism and anabolism



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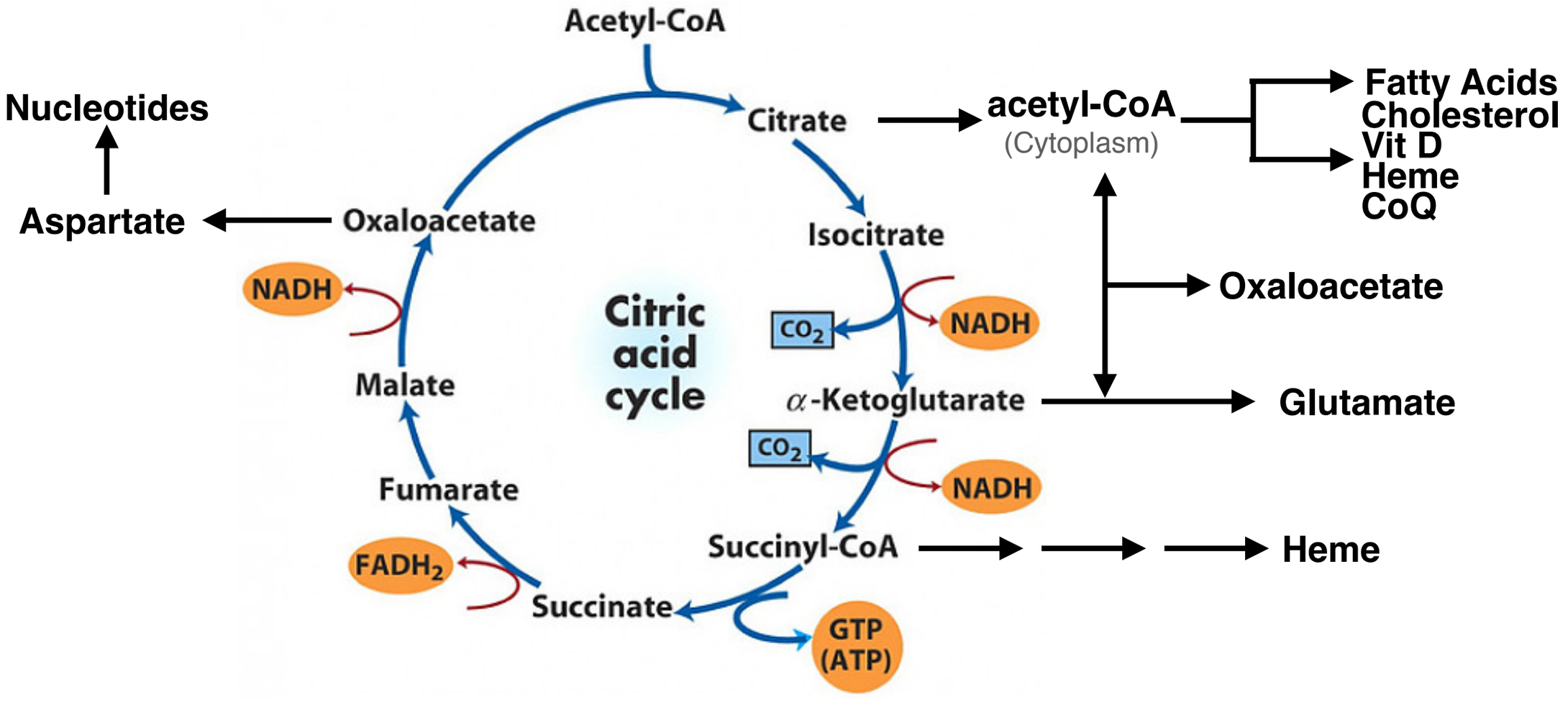

Cancer cells need TCA metabolites for:

- **Fatty acids:** proliferating cells need to rapidly double their membranes.
- **Cholesterol:** essential component of plasma and mitochondrial membranes. Regulates tran membrane signaling.
- **Heme:** buffer redox stress.
- **CoQ:** essential for electron transport in the mitochondria. Limiting co-factor of nucleotide biosynthesis.
- **Nucleotides:** proliferating cells need to rapidly double their DNA.
- **Glutamate:** signaling molecule. Also involved in nitrogen metabolism.

DeBerardinis RJ, Chandel NS, ***Nat Metab****, 2020*
DeBerardinis RJ, Thompson CB, ***Cell Metab****, 2008*
Libert M, Locasale JW, ***Trends Biochem Sci****, 2016*
Cantor JR, Sabatini DM, ***Cancer Discov****, 2012*

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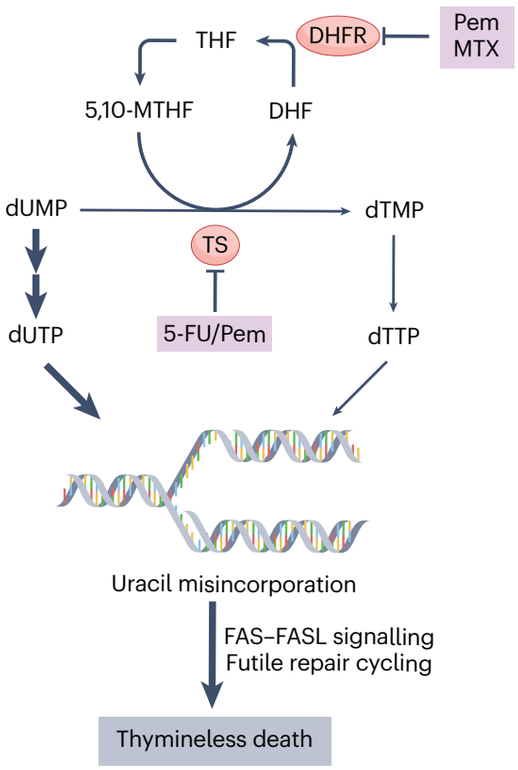
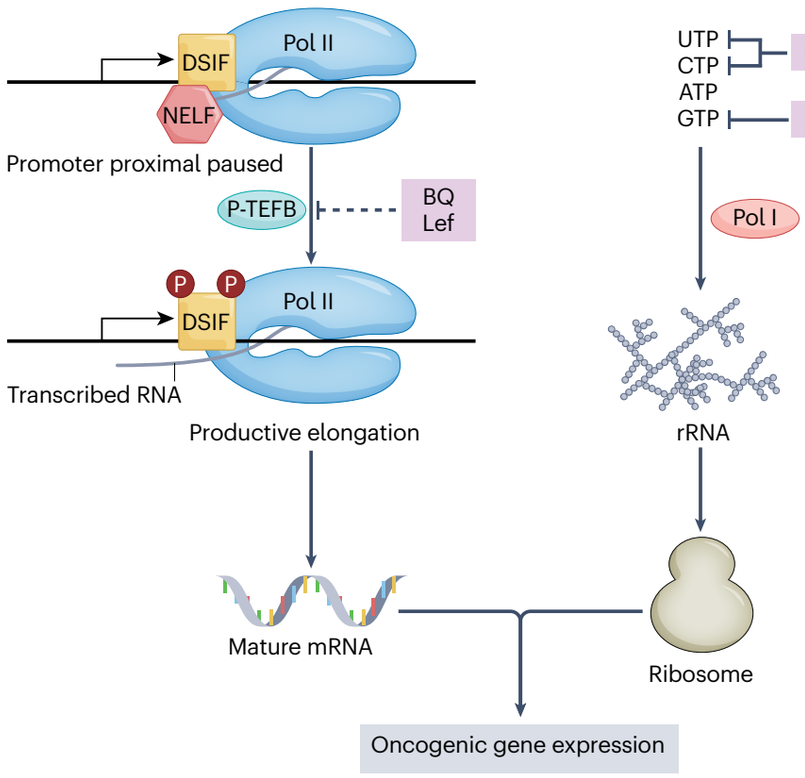
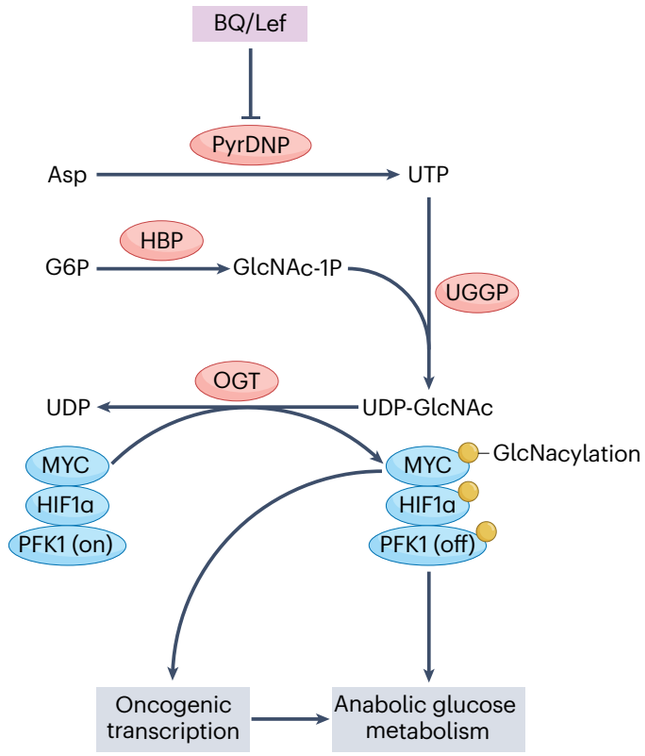
2

Metabolism is reprogrammed to produce nucleotides



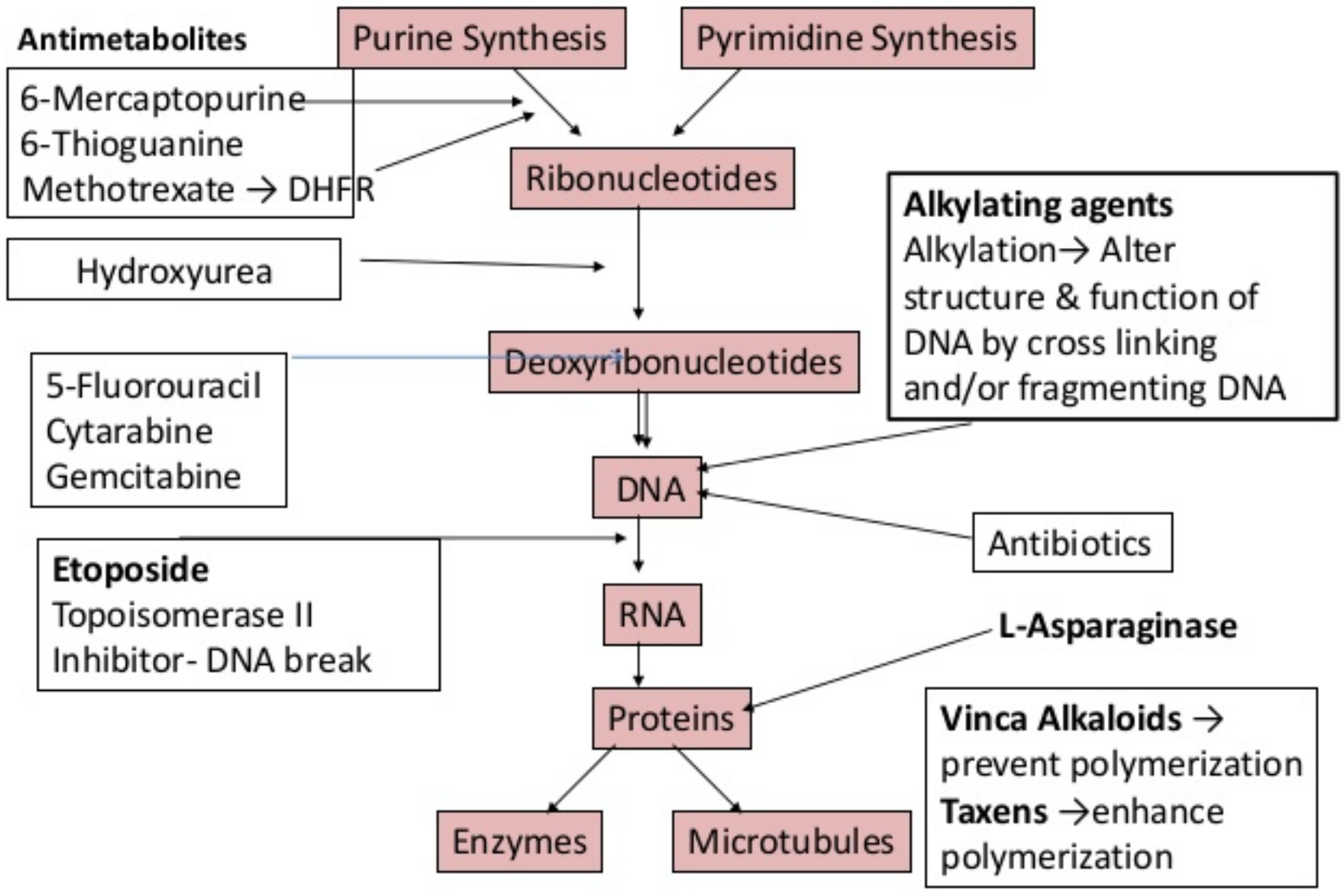




Nucleotides fuels cancer cell growth and proliferation:

- DNA synthesis
- DNS repair
- rRNA synthesis and proteostasis
- glycosylation

Nucleotide metabolism is a common anti-cancer target



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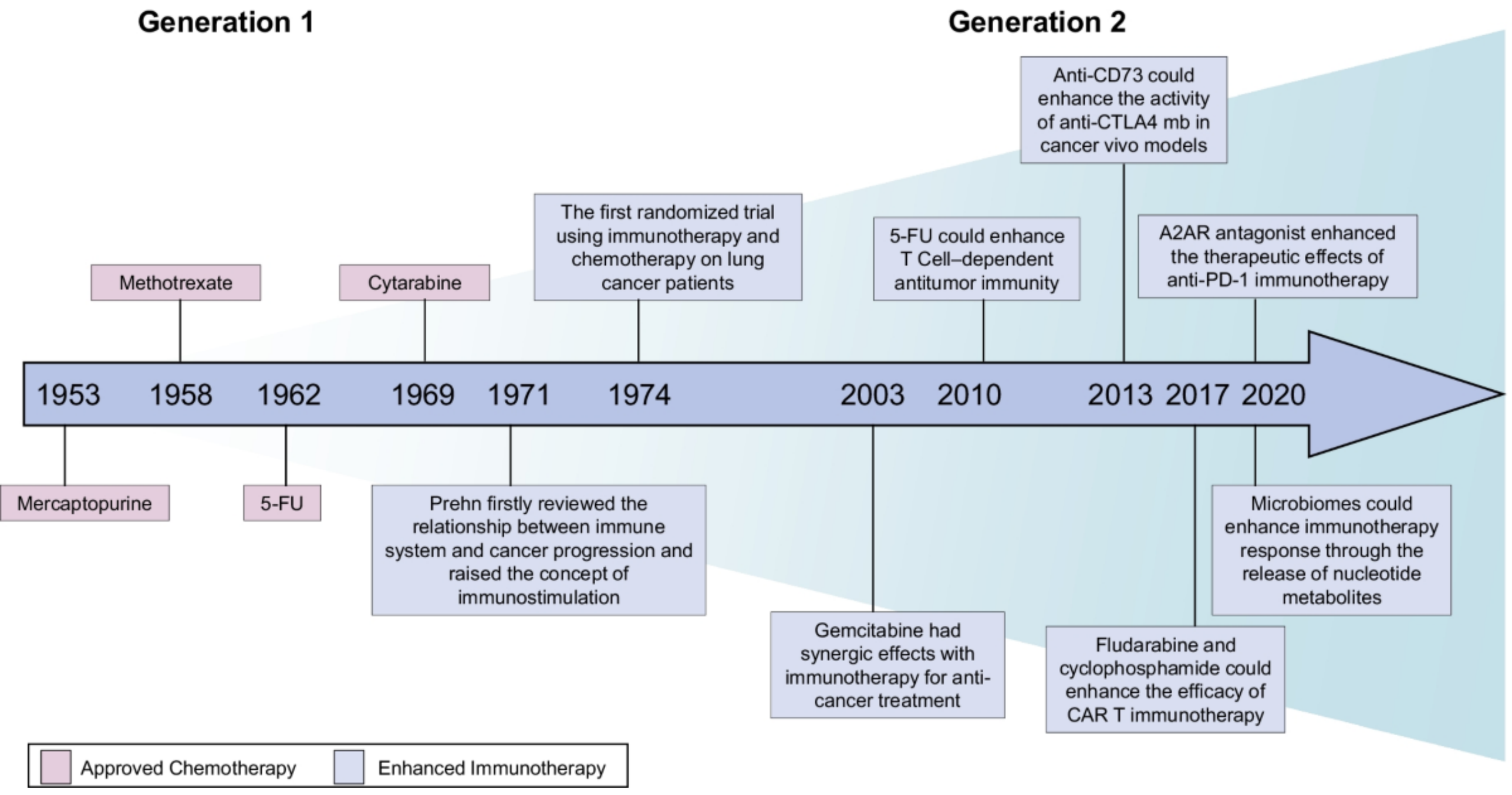
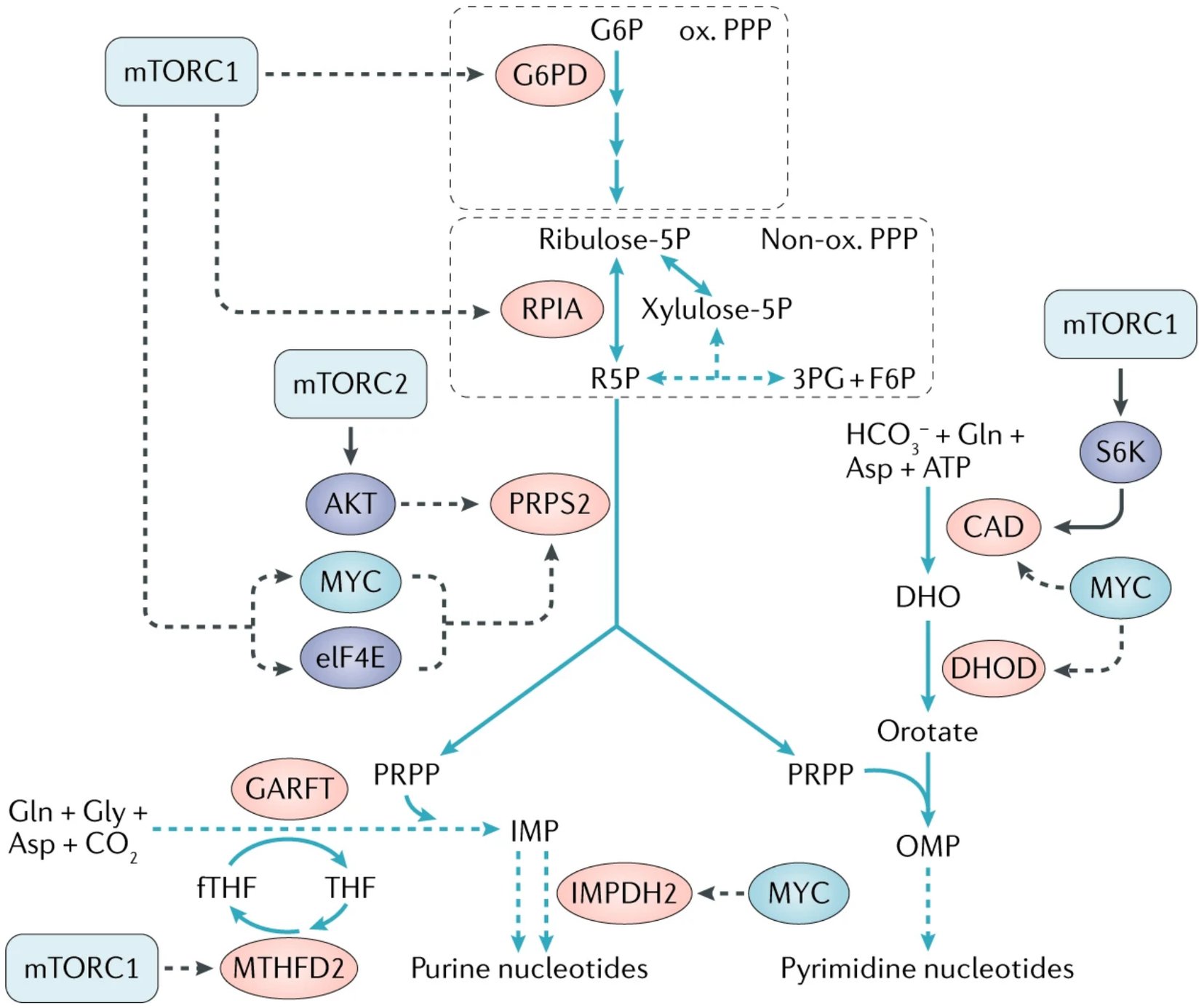


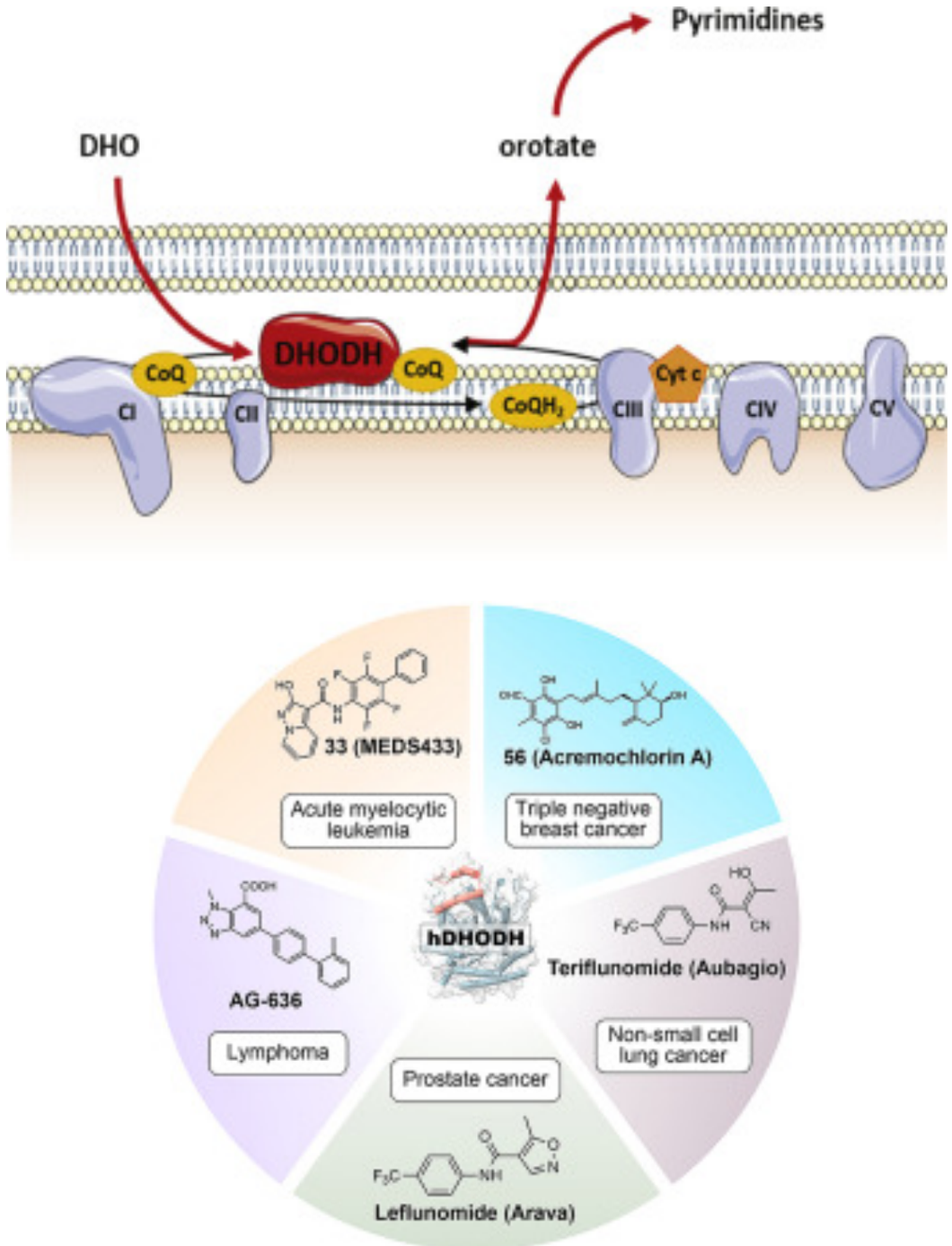
Wu et al, ***J Hematol Oncol****, 2022*

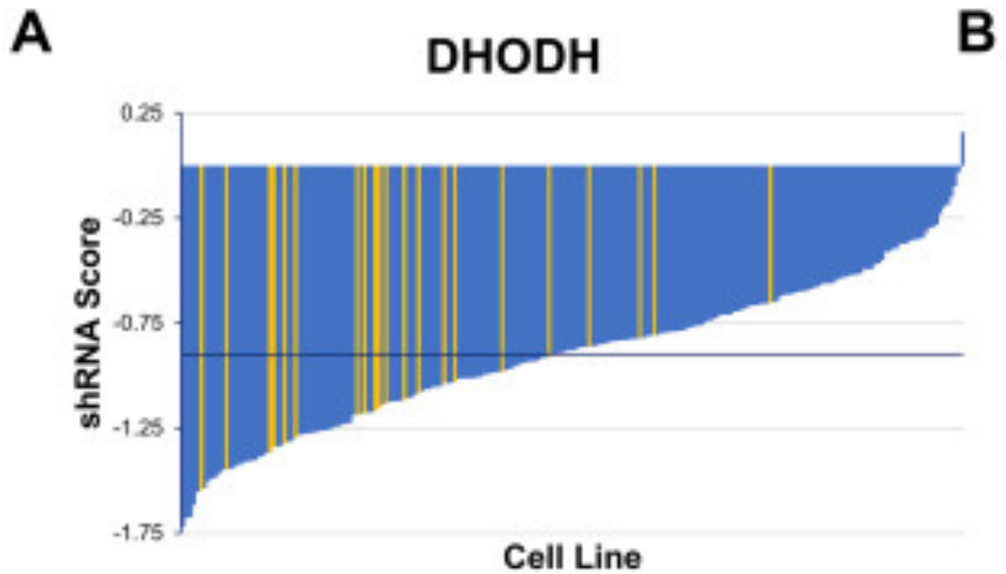
mTOR signaling enhances nucleotide metabolism

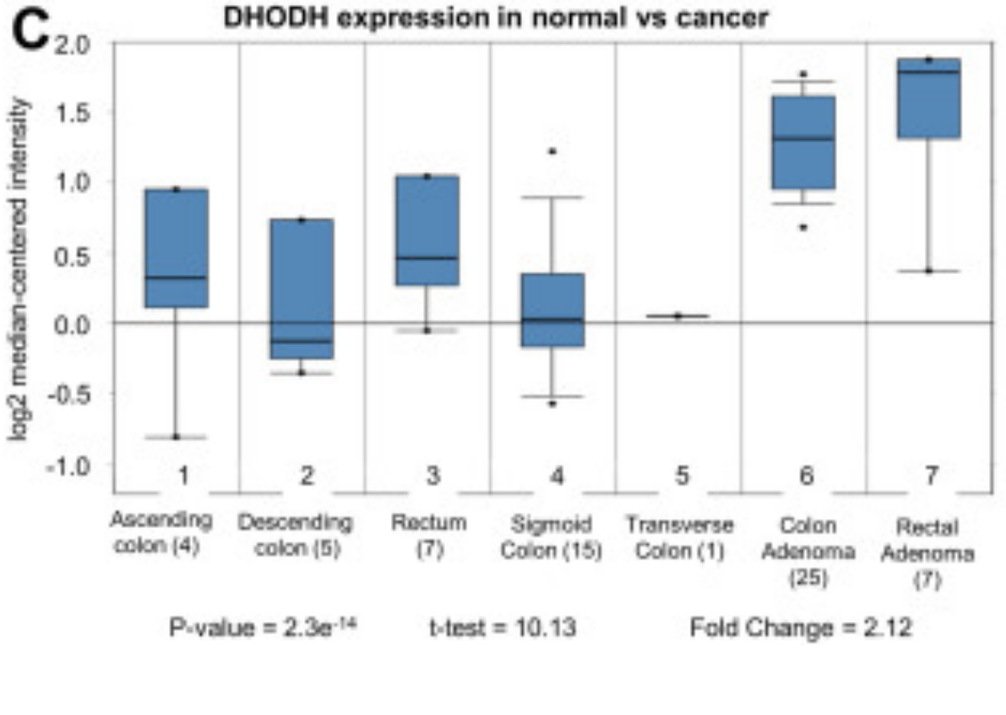


Mossman et al, ***Nat Rev Cancer****, 2018*

DHODH is a pan-cancer metabolic vulnerability







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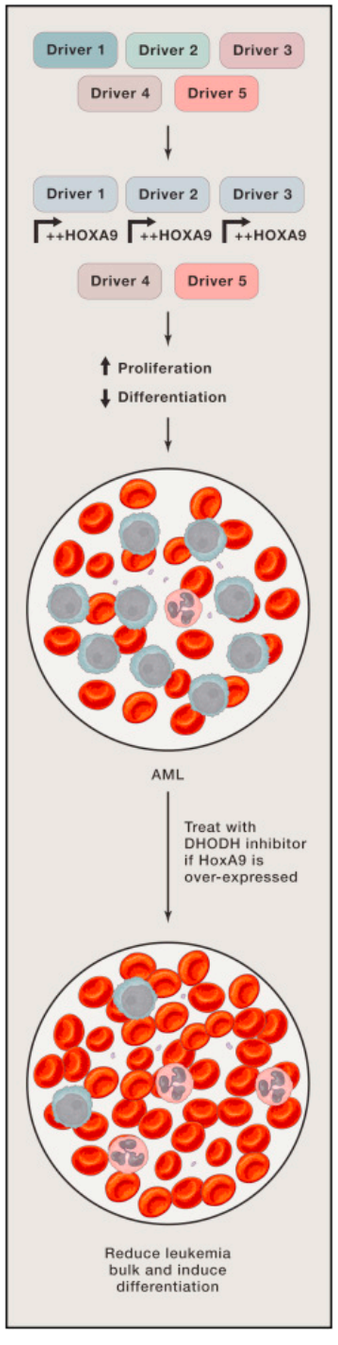
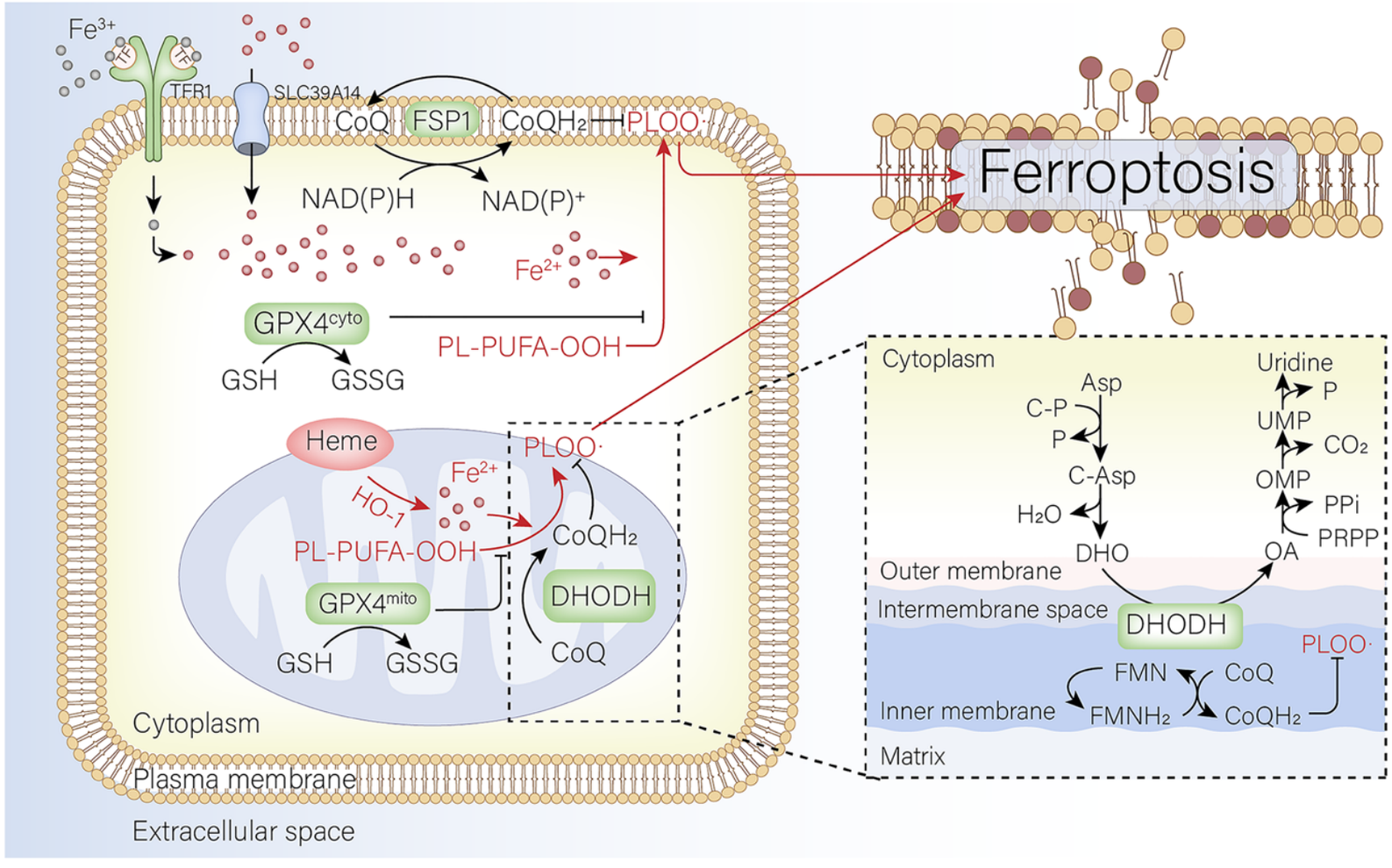




DHODH inhibition is a hot topic in cancer research:

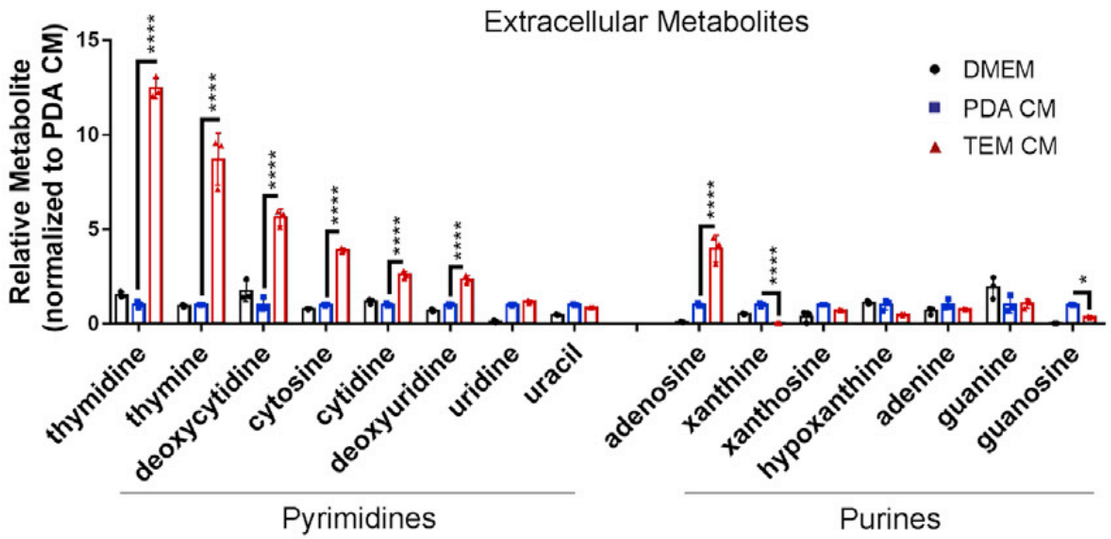
- Can suppress pyrimidine synthesis, impair DNA replication
- Can promote cell differentiation (*Sykes et al, **Cell**, 2016*)
- Can sensitize to ferroptosis (*Mao et al, **Nature**, 2021*)

Nucleotide metabolism can also be reprogrammed for:

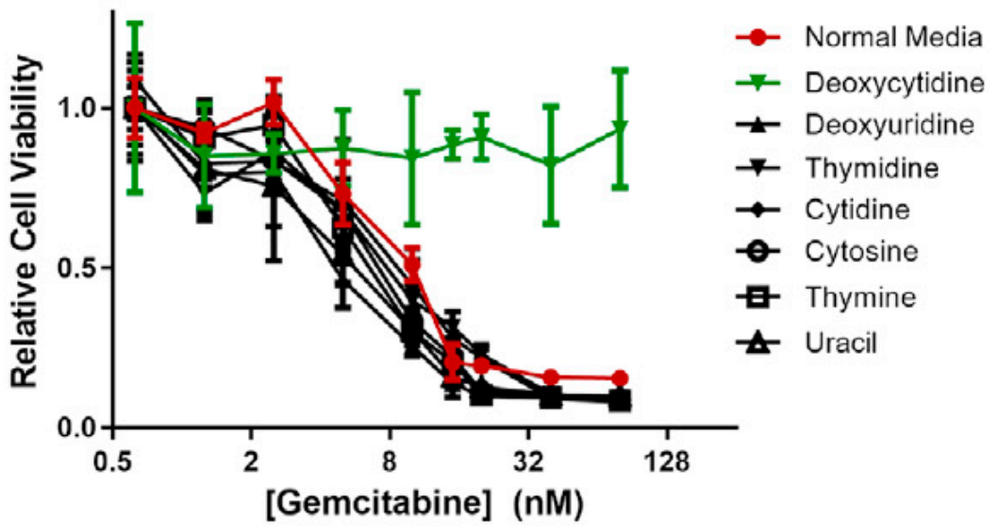
- **Regulation of ROS homeostasis (NADPH saving)**
- **Immune evasion (purinergic signaling, cytosolic acidification, …)**
- **Metastatic spread (RHO-GTPases activity)**
- **Cell de-differentiation (DHODH activity - mechanism??)**
- **Therapy resistance (competition with nucleoside analogues)**
- **Protection from ferroptosis (CoQ reduction)**

For complete review: Mullen & Singh, ***Nat Rev Cancer****, 2023*

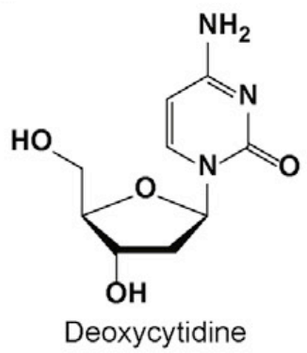
Macrophage-Released Pyrimidines Inhibit Gemcitabine Therapy in Pancreatic Cancer

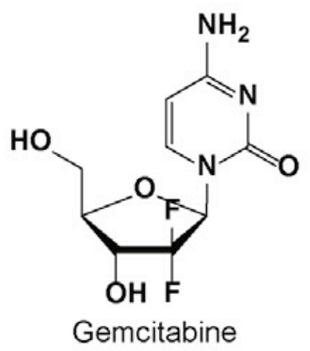


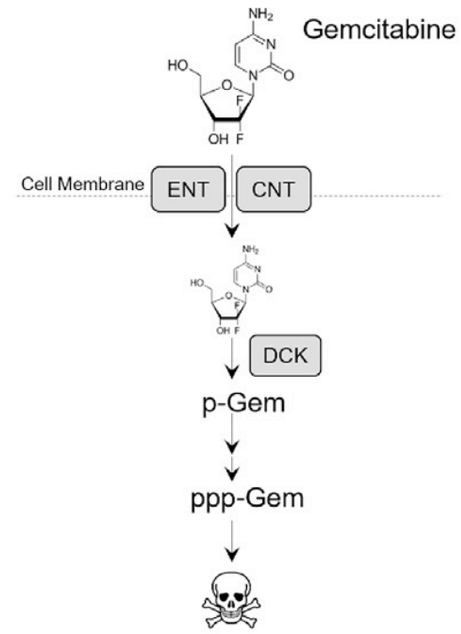
Tumor-educated macrophages produce and secrete nucleotides

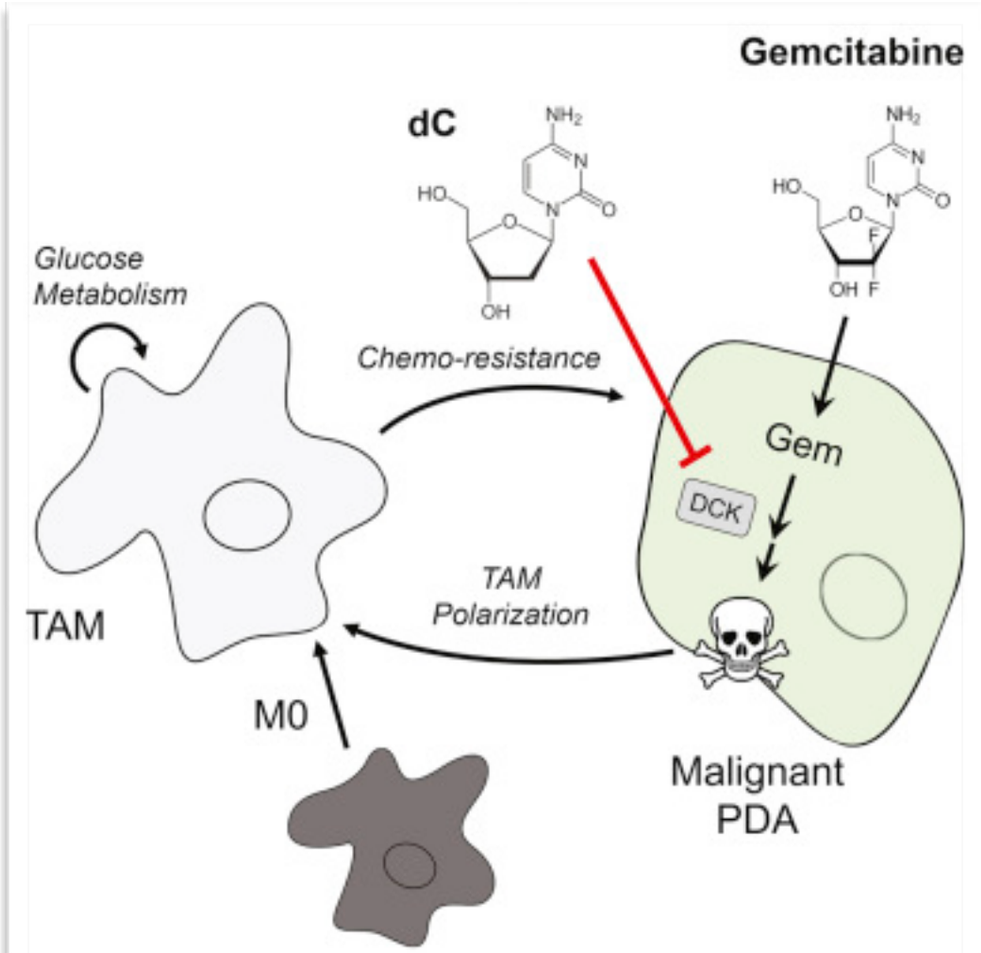


dC confers resistance to gemcitabine









Halbrook et al, ***Cell Metab****, 2019*

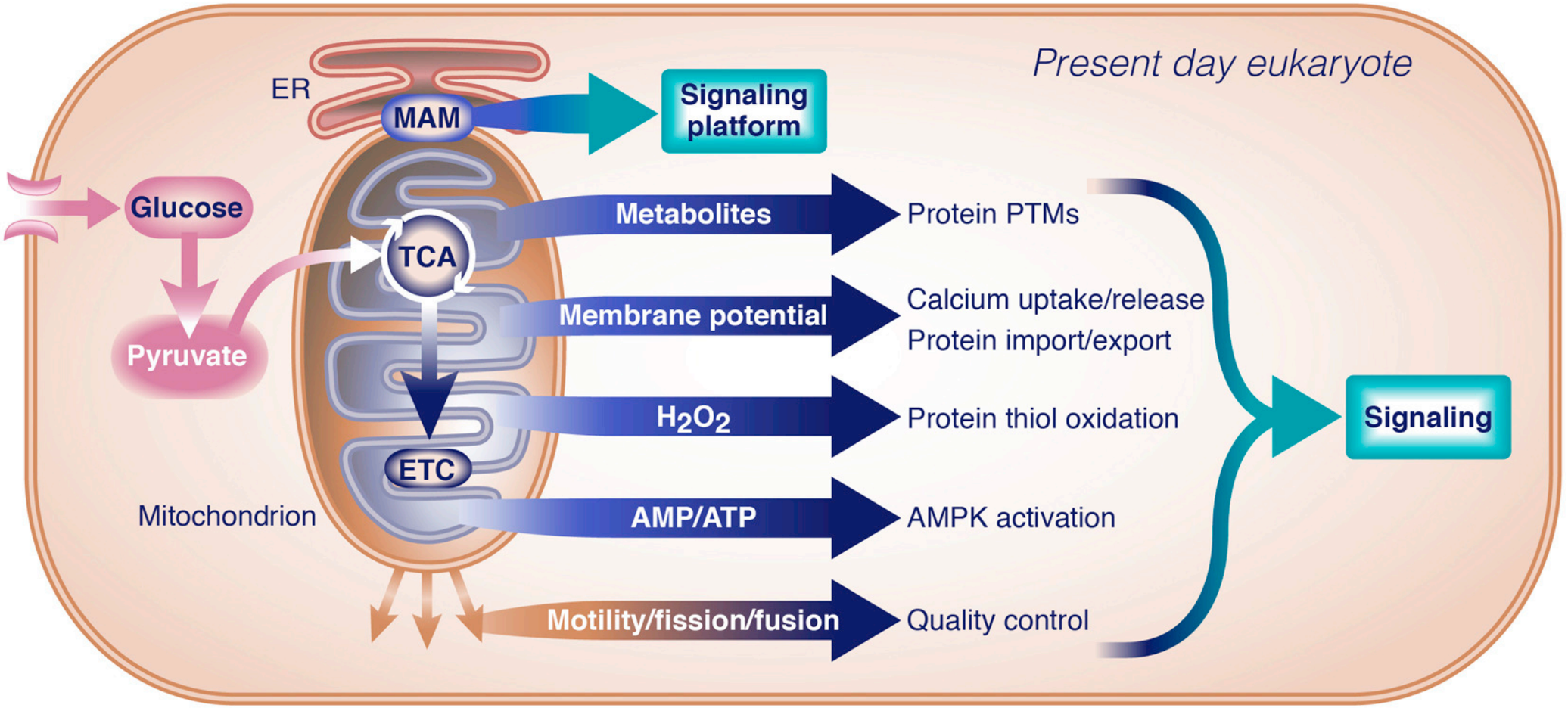
3

Metabolism is reprogrammed to cope with oxidative stress

3

Metabolism is reprogrammed to cope with oxidative stress

Enhanced mitochondrial activity has redox implications

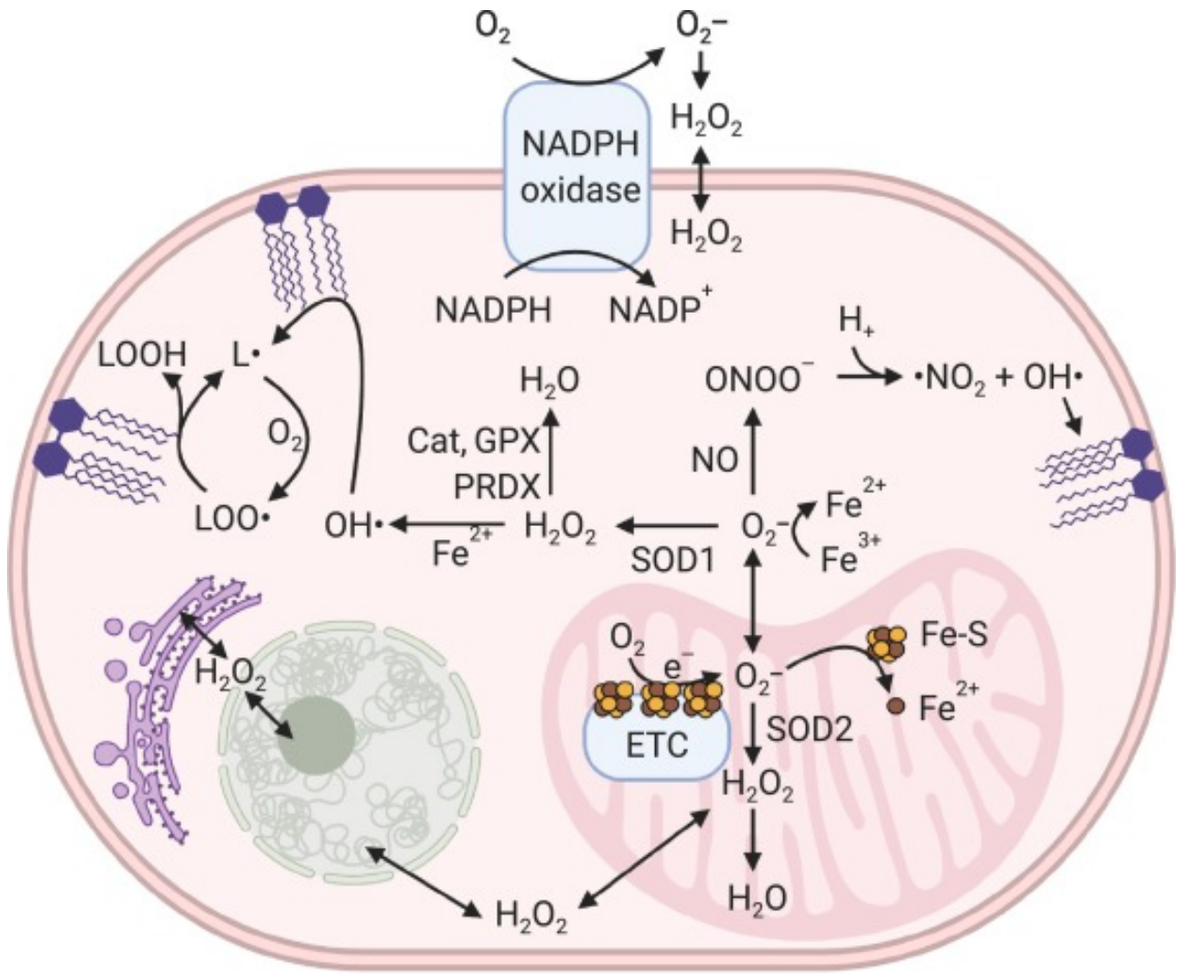


Chandel NV, ***Cell Metab****, 2015*

3

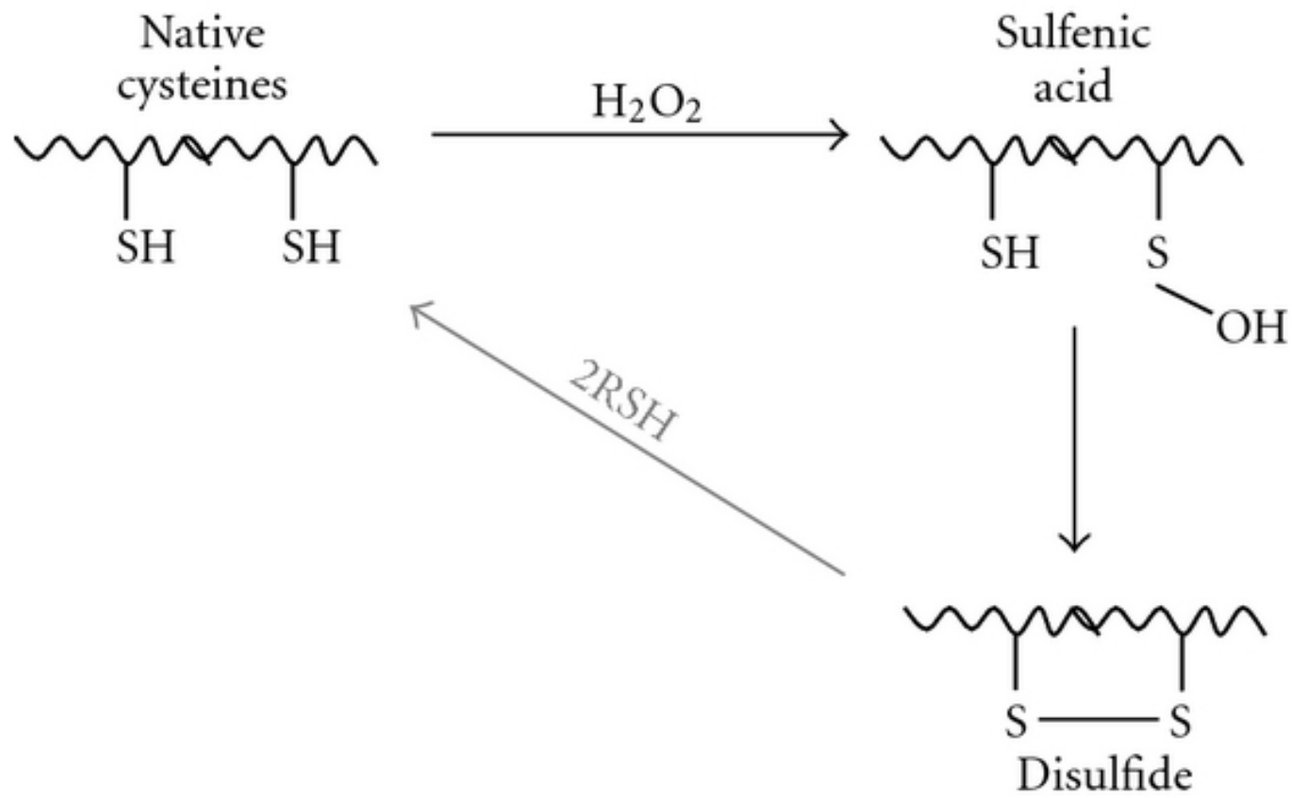
Metabolism is reprogrammed to cope with oxidative stress

Mitochondria are major sources of ROS



Trends in Cell Biology

ROS influence Cysteine state and protein conformation



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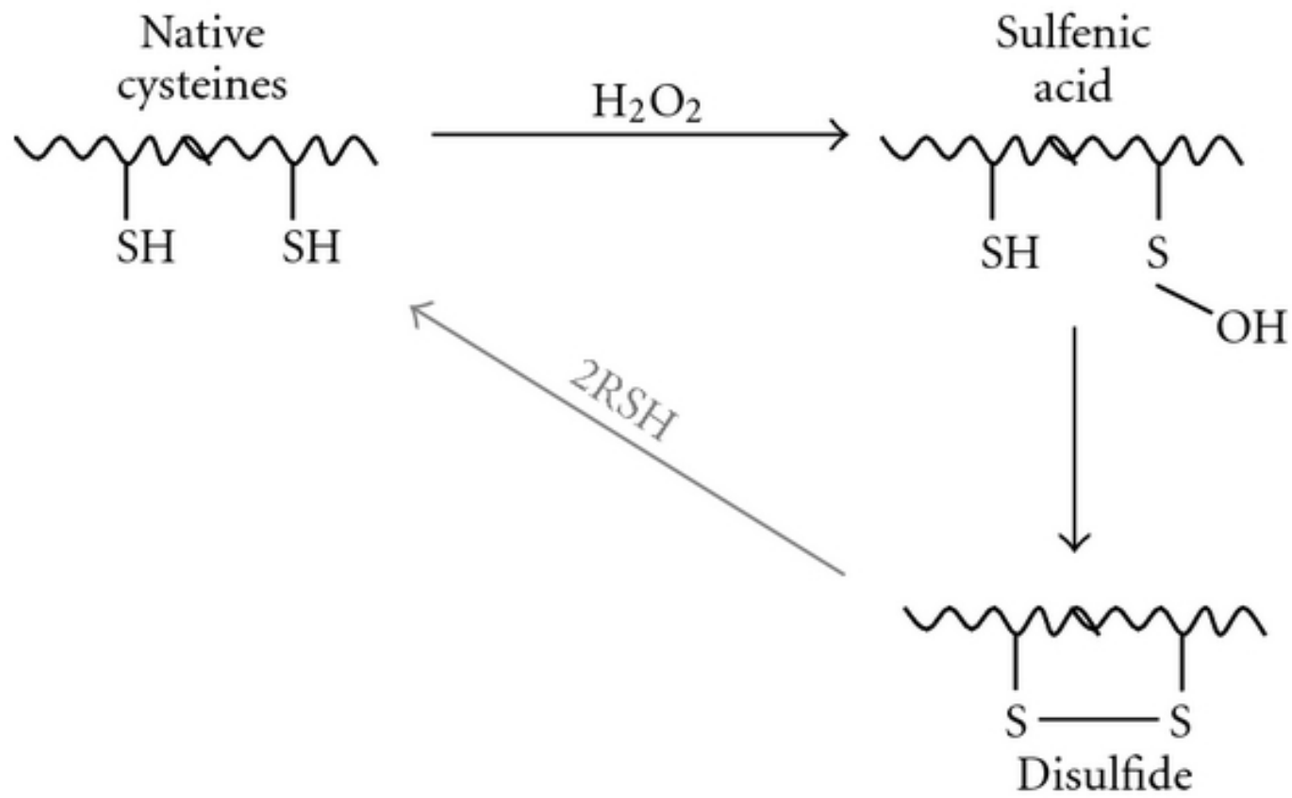
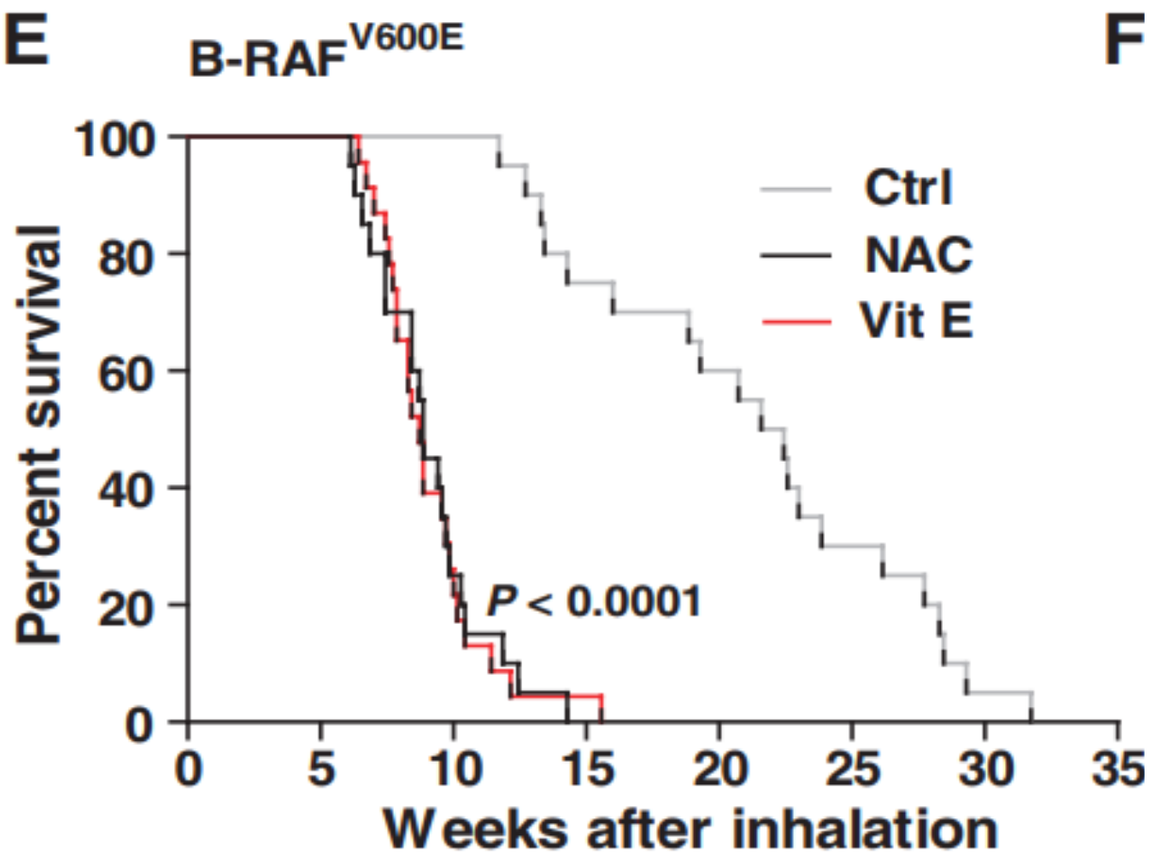


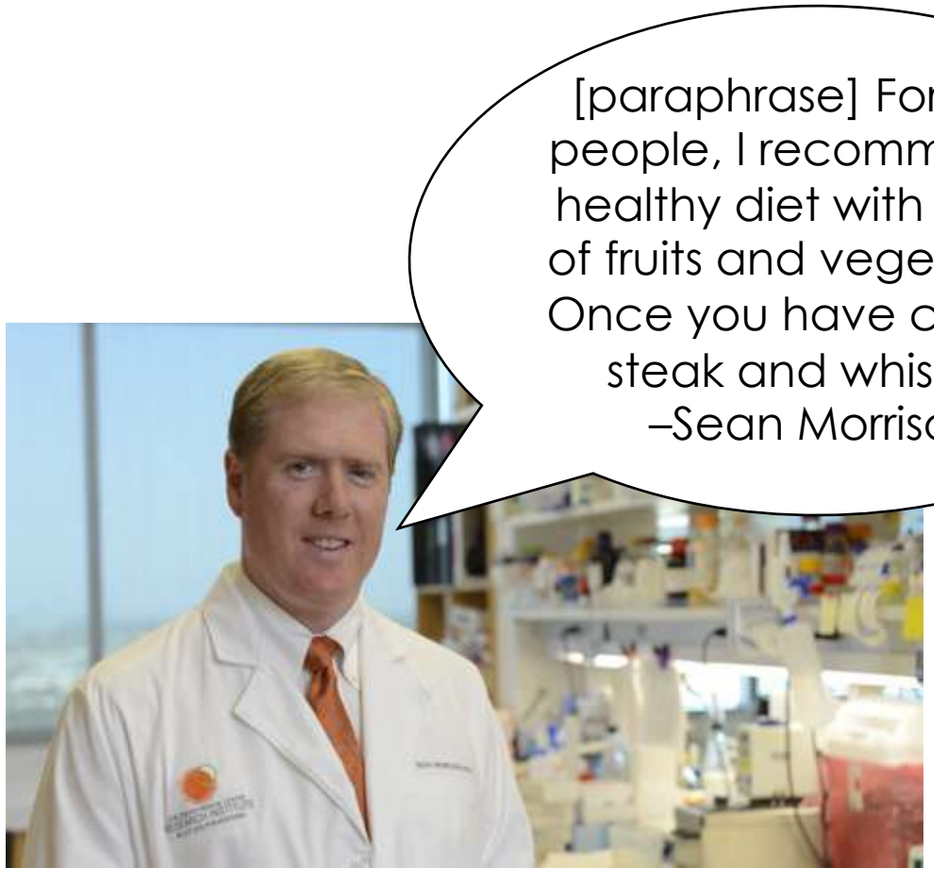
…the presence/absence of disulfide bonds influence protein conformation and activity (i.e.: HIF, mTOR, PTEN, others)

Anti-Oxidants make cancer WORSE



Sayin et al, ***Sci Transl Med****, 2014*

Anti-Oxidants promote cancer progression and metastasis



Sayin et al, ***Sci Transl Med****, 2014*

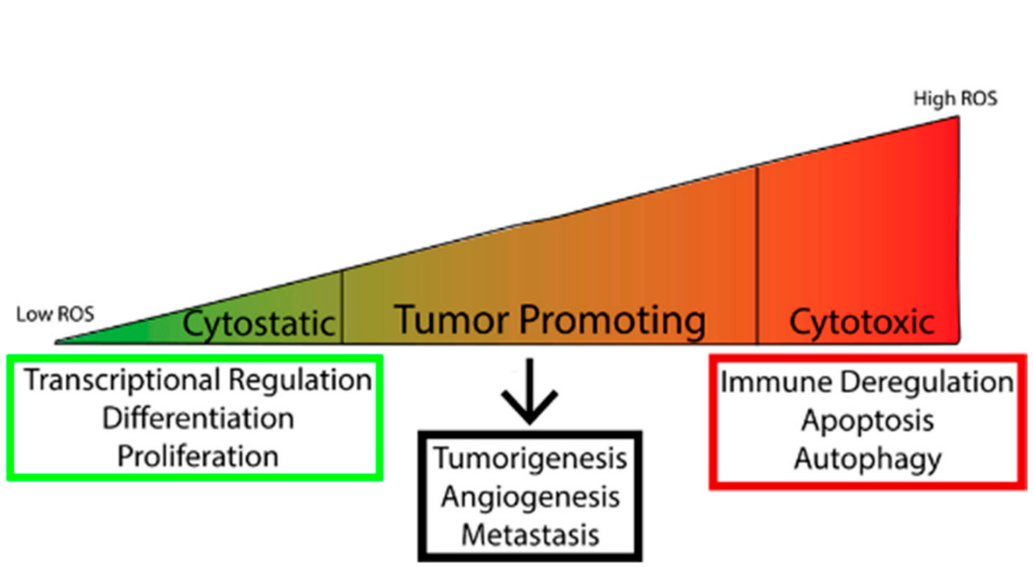
DeNicola GM et al, ***Nature****, 2011*

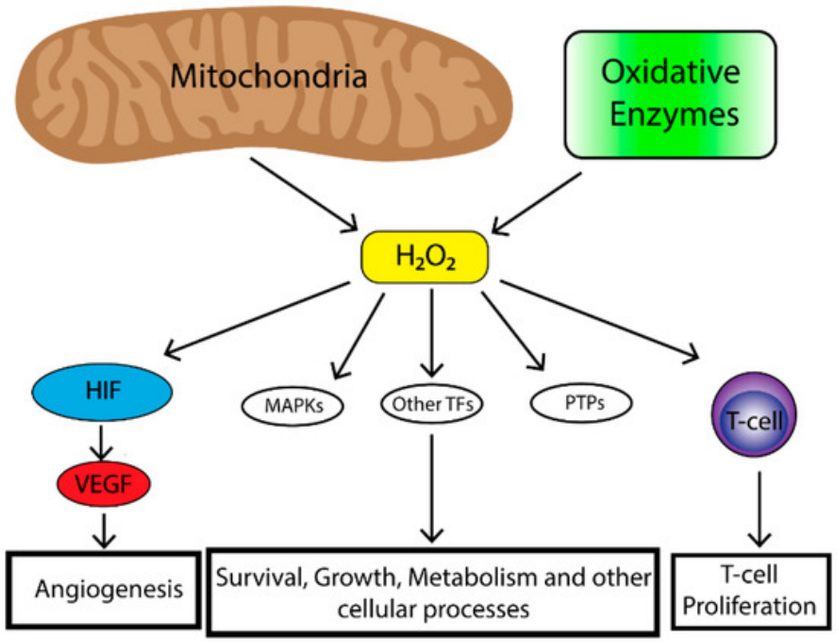
Al-Mehdi et al, ***Sci Signal****, 2012*

Tasdogan et al, ***Nature****, 2020*

Lignitto et al, ***Cell****, 2019*

ROS exert signaling functions

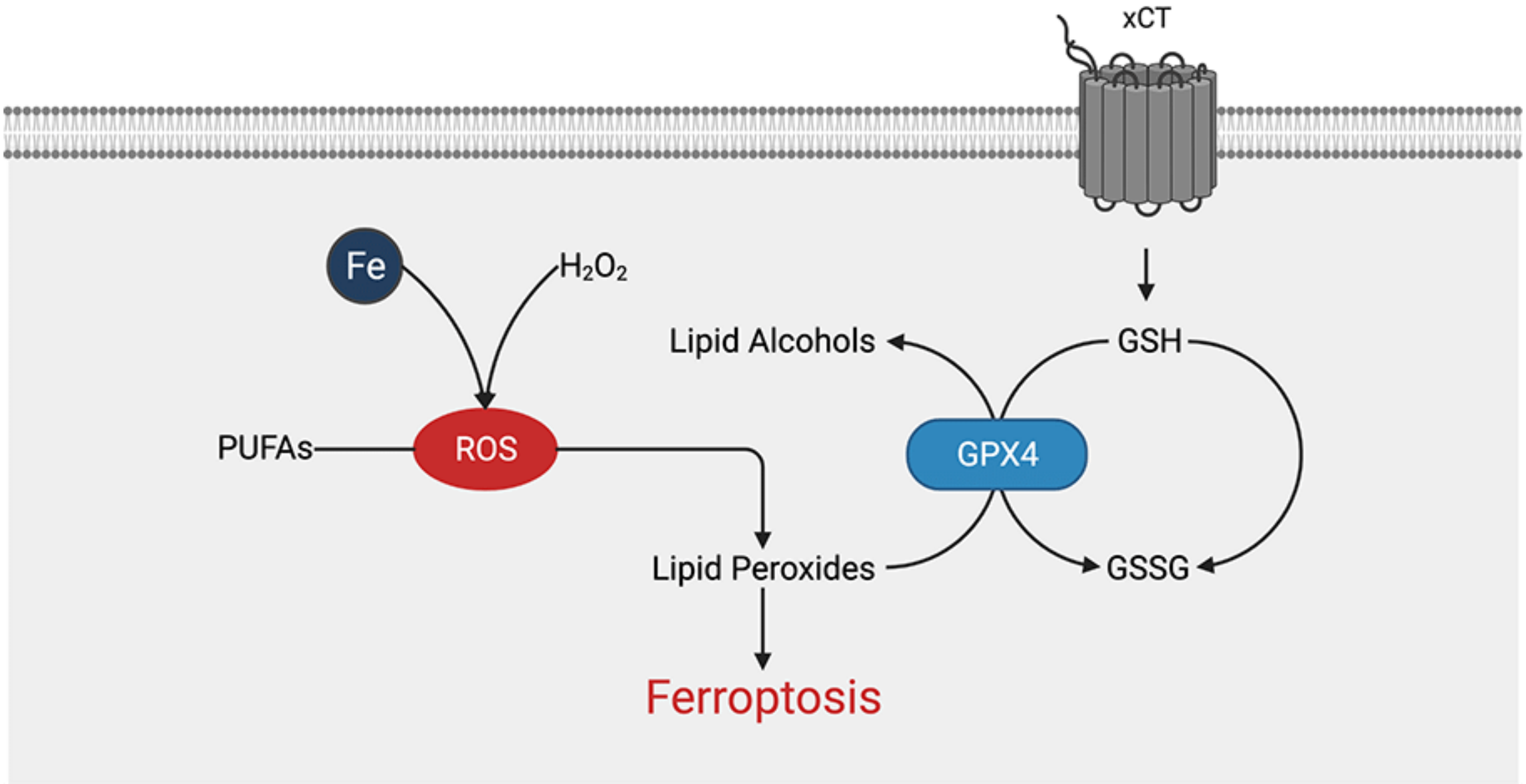




Cancer cells need to carefully watch and control ROS levels to avoid negative consequences

Weinberg F et al, ***Cancers****, 2019*

Excessive ROS levels cause ferroptosis

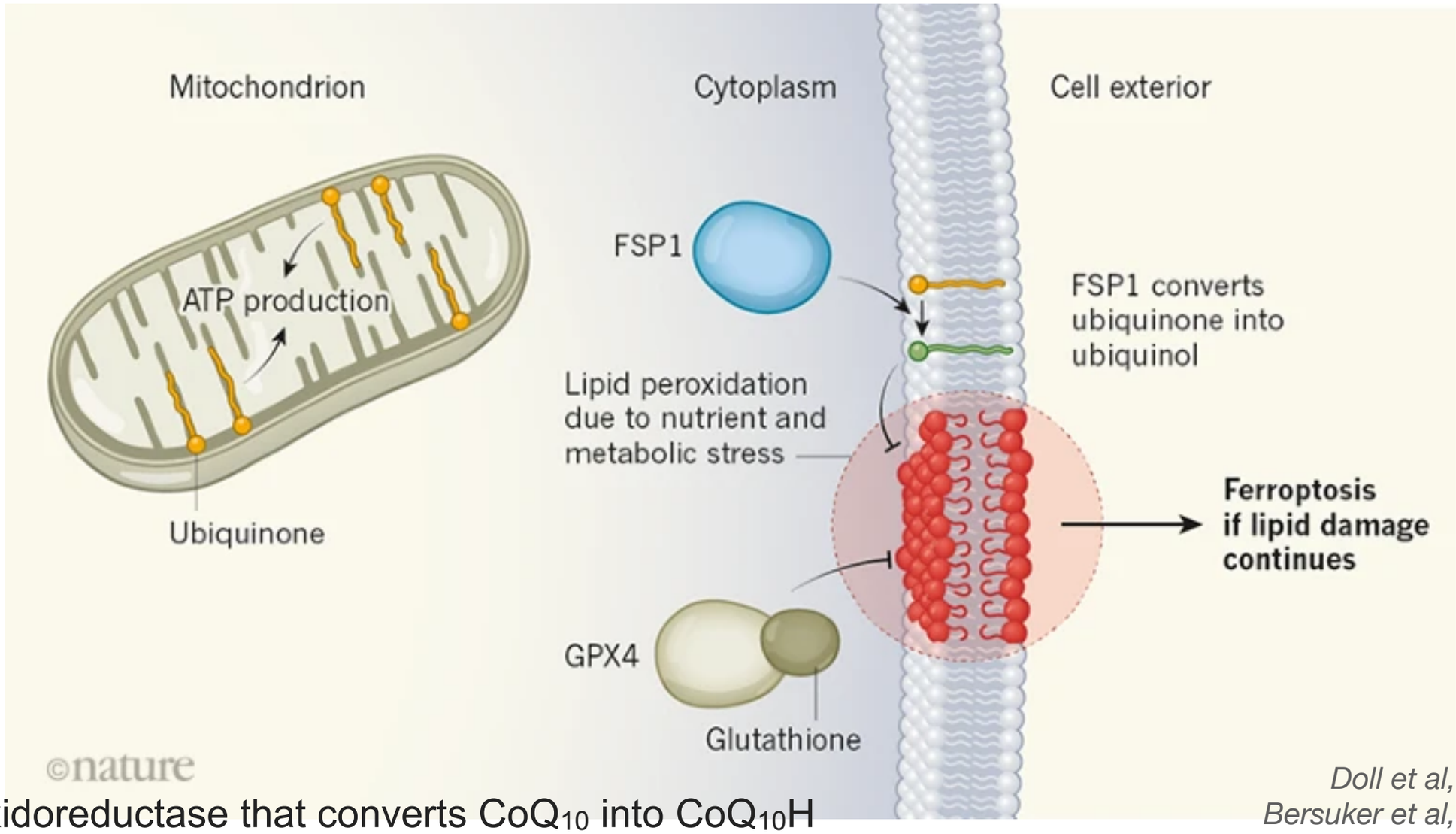


Sensitivity to ferroptosis is dictated by cell metabolism

Cancer cell reprogram their metabolism to be protected from ferroptotis stress and death

Reduced CoQ (ubiquinol) suppresses ferroptosis

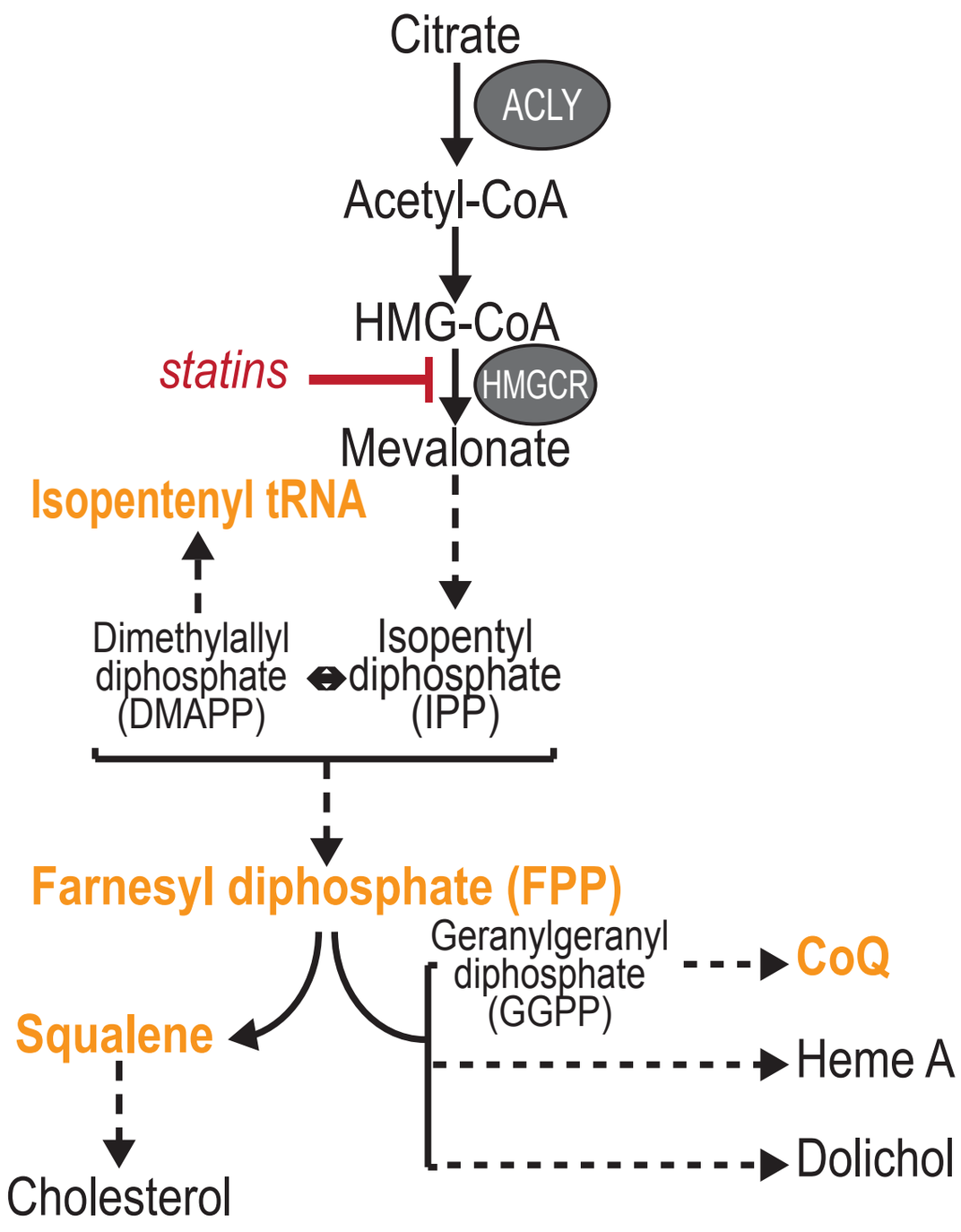
Doll *et al*. and Bersuker *et al*. hypothesized that cells have a way of protecting themselves against ferroptosis even in the absence of GPX4. This was a heretical idea given that, during the short history of ferroptosis research, the dogma that GPX4 is essential to guard against ferroptosis in all contexts had already been established. Nevertheless, these two teams searched for other such protective mechanisms. Both groups analysed human cells grown *in vitro* to test whether any components block ferroptosis when GPX4 is not present, and they independently identified a gene encoding a protein that they name ferroptosis suppressor protein 1 (FSP1), which was previously called AIFM2.



FSP1: oxidoreductase that converts CoQ_{10} into $CoQ_{10}H$

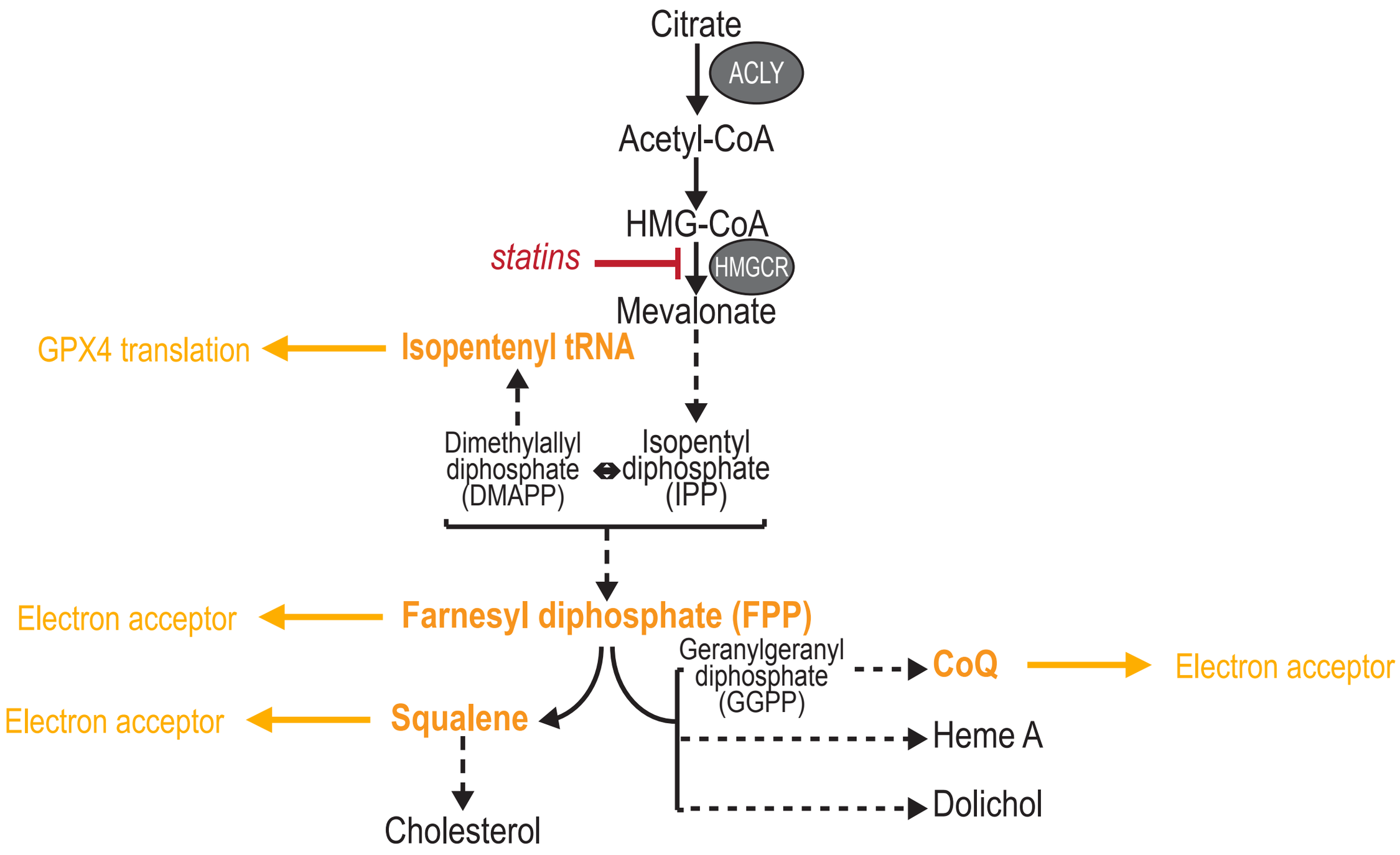
Doll et al, ***Nature****, 2019*
Bersuker et al, ***Nature****, 2019*
Stokwell, ***Nature****, 2019*

Mevalonate pathway desensitizes from ferroptosis



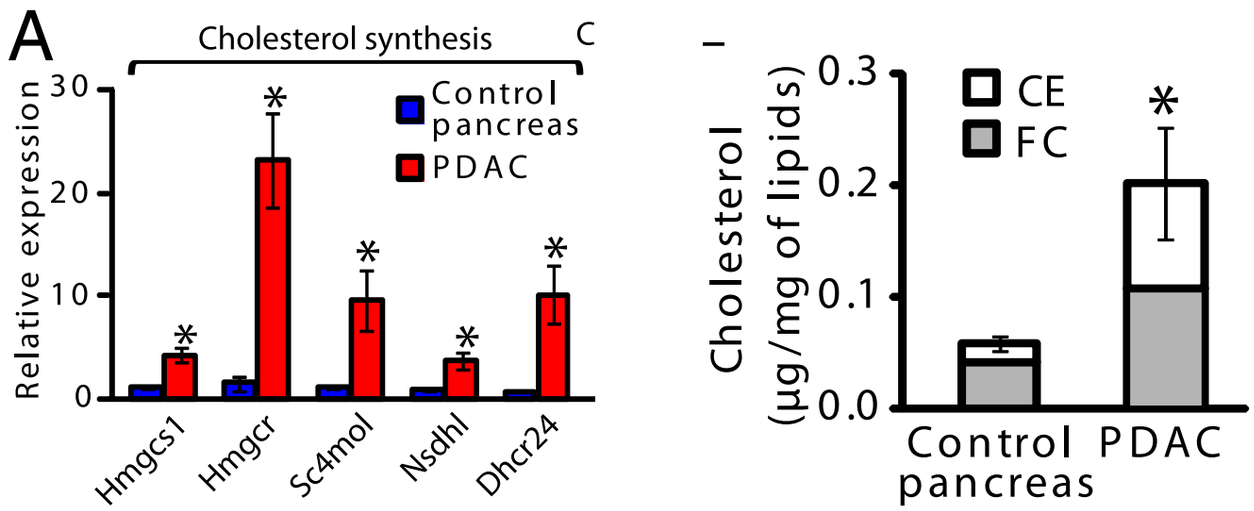
Noè et al, ***Redox Biol****, 2023*

Mevalonate pathway desensitizes from ferroptosis

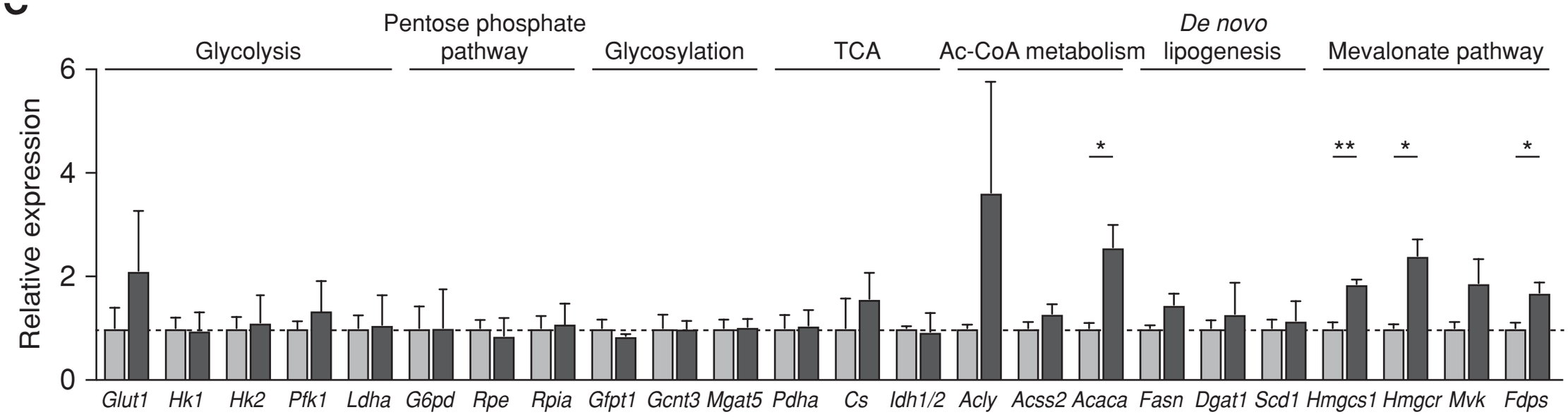


Noè et al, ***Redox Biol****, 2023*

Mevalonate pathway is often upregulated in cancer

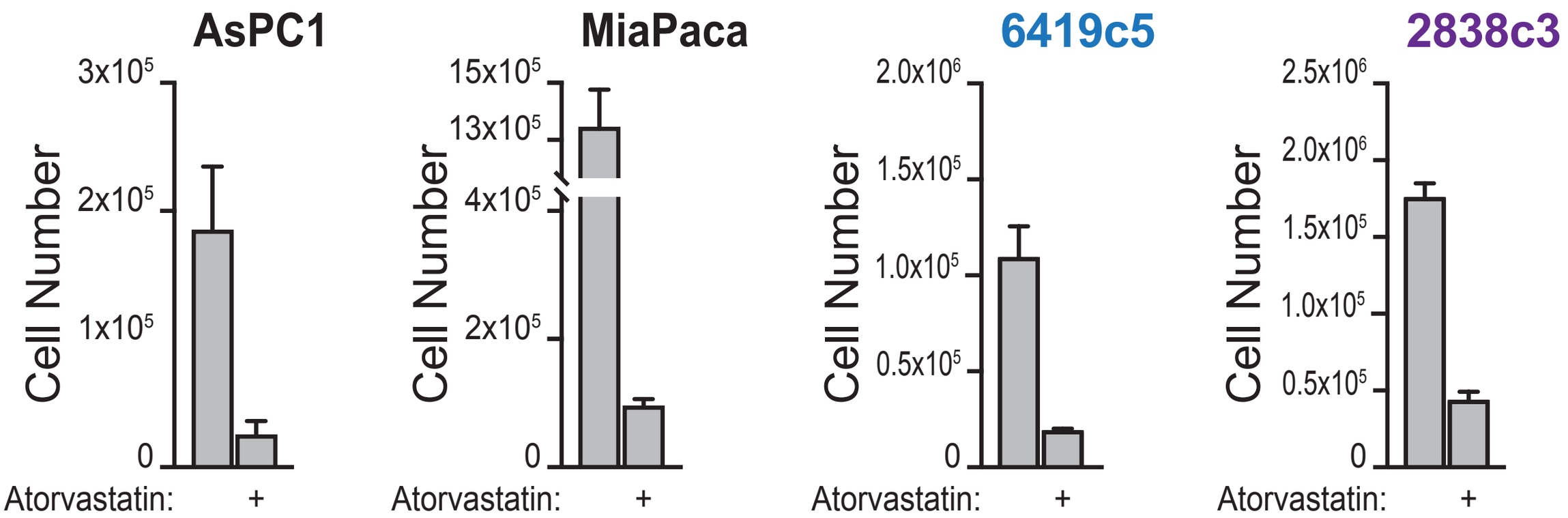


Guillaumond et al, ***PNAS****, 2013*



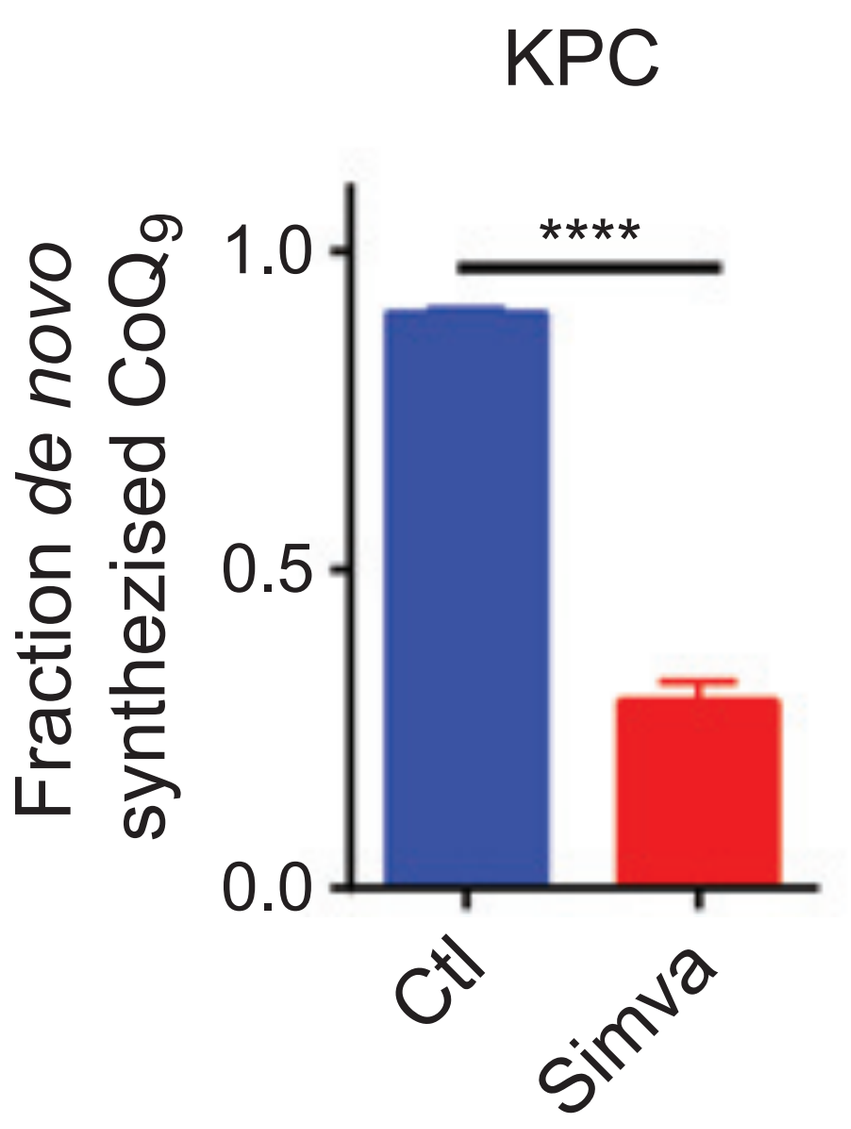
Carrer et al, ***Cancer Discov****, 2019*

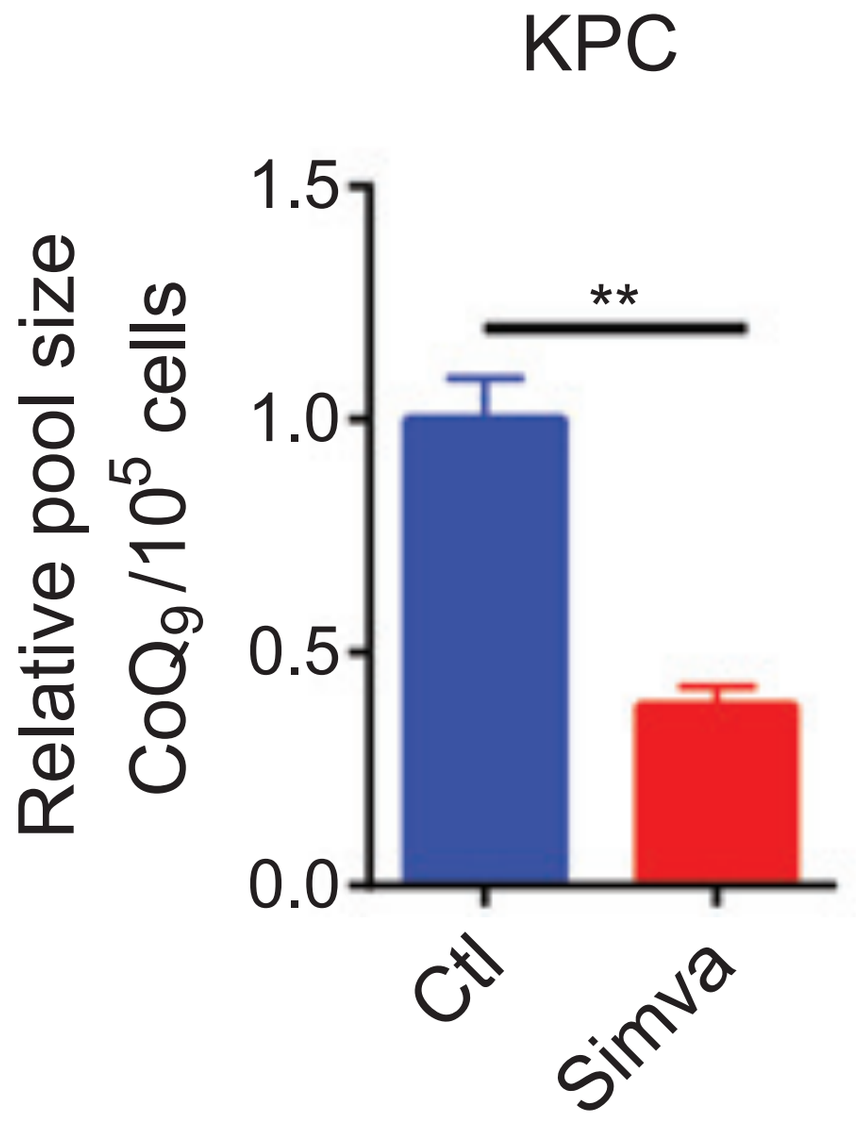
Statin treatment suppresses PDA growth in vitro



Adapted from: *Carrer et al,* ***Cancer Discov****, 2019*

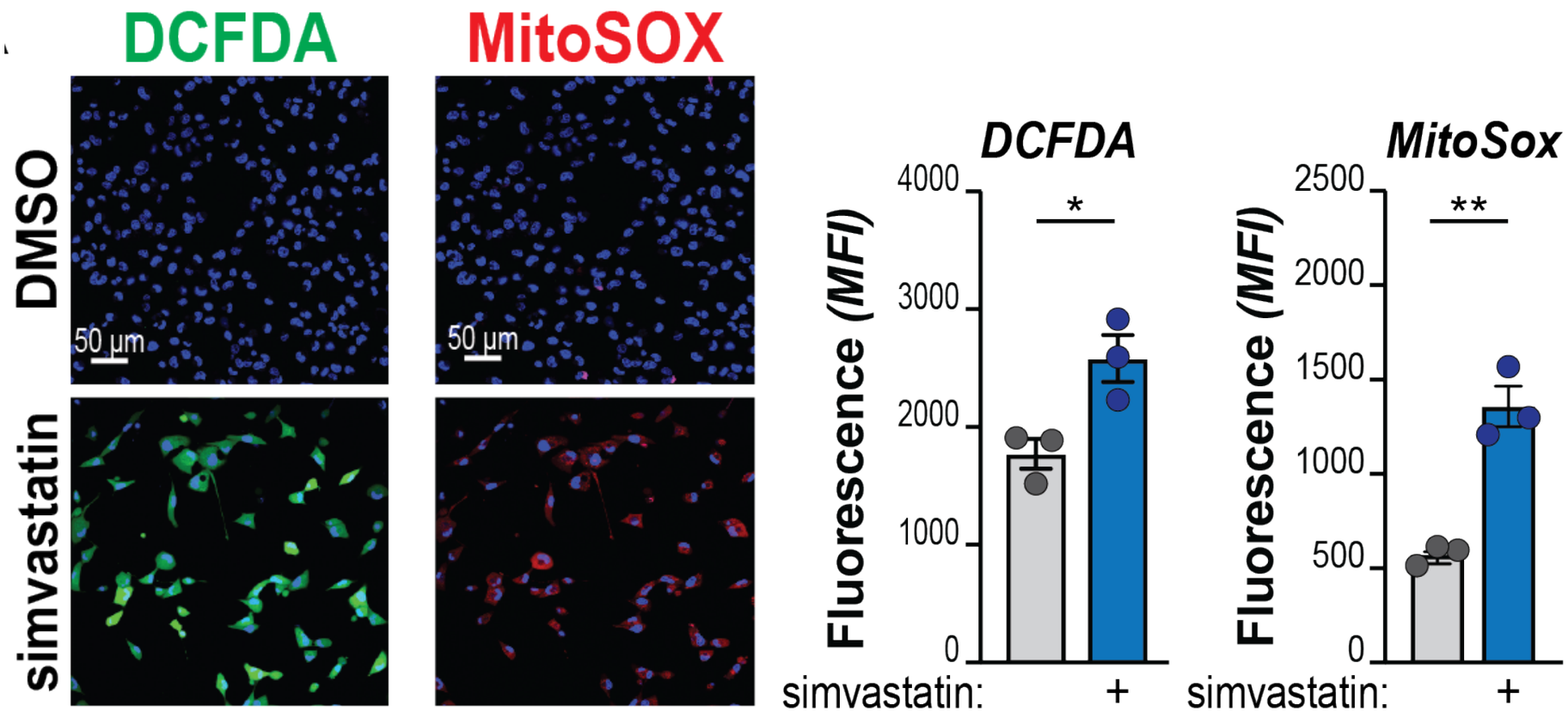
Statin treatment inhibits CoQ synthesis





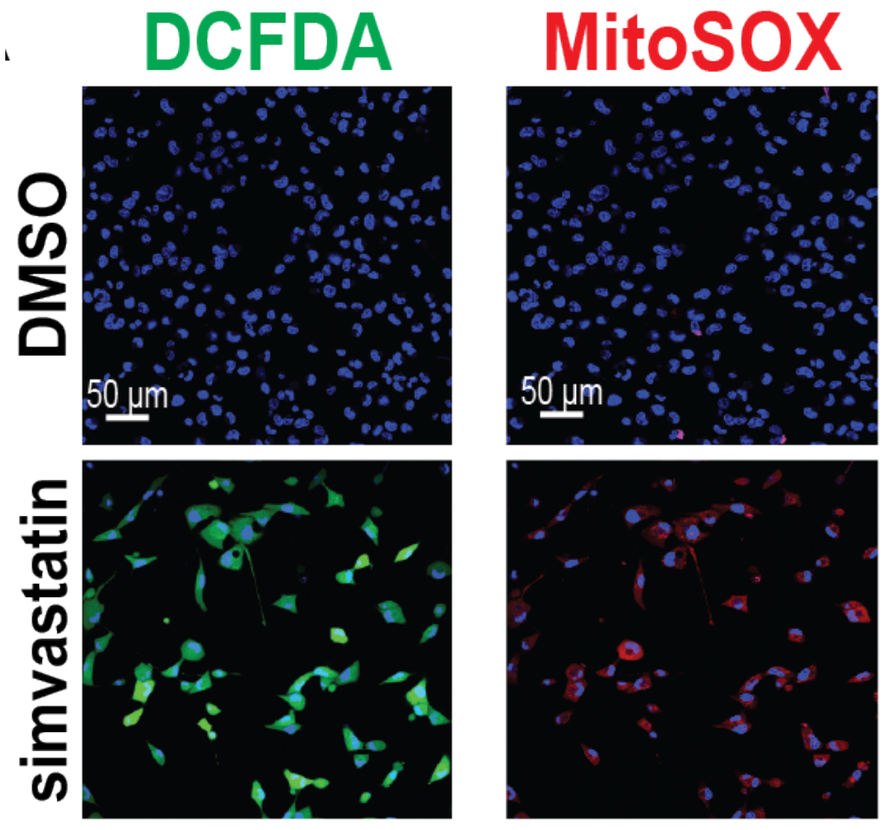
McGregor et al, ***Cancer Res****, 2020*

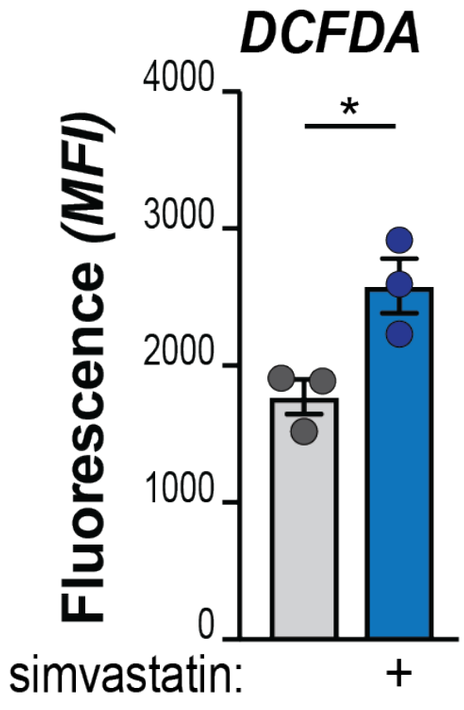
Statin treatment elicits ROS stress

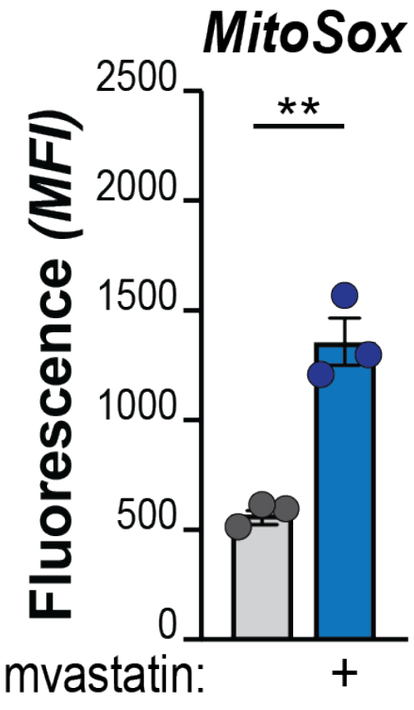


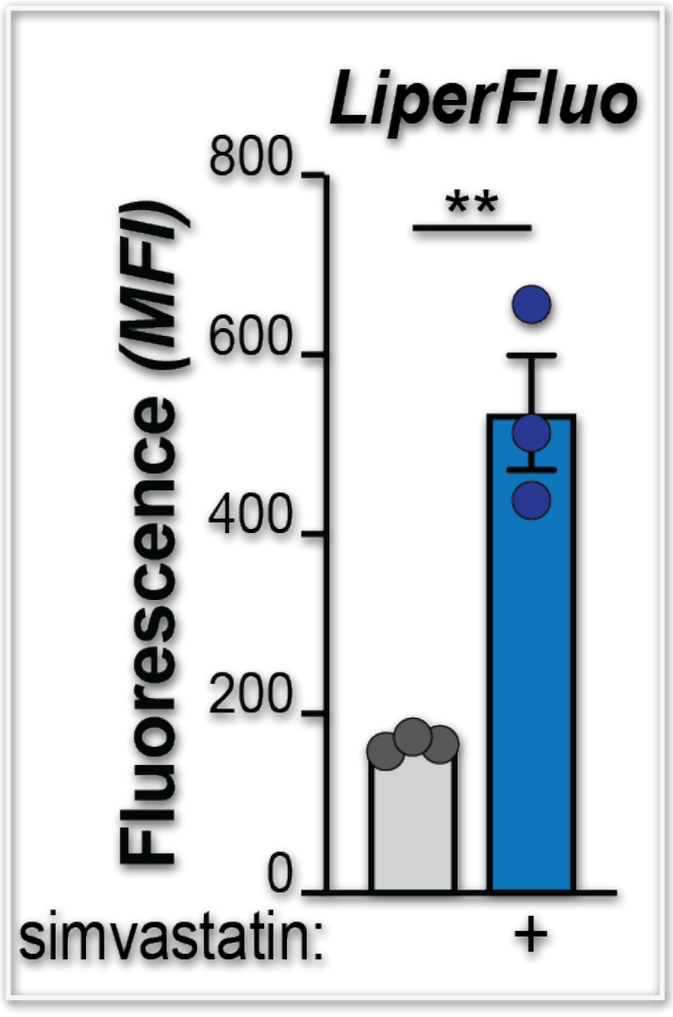
Noè et al, ***Redox Biol****, 2023*

Statin treatment elicits ROS stress



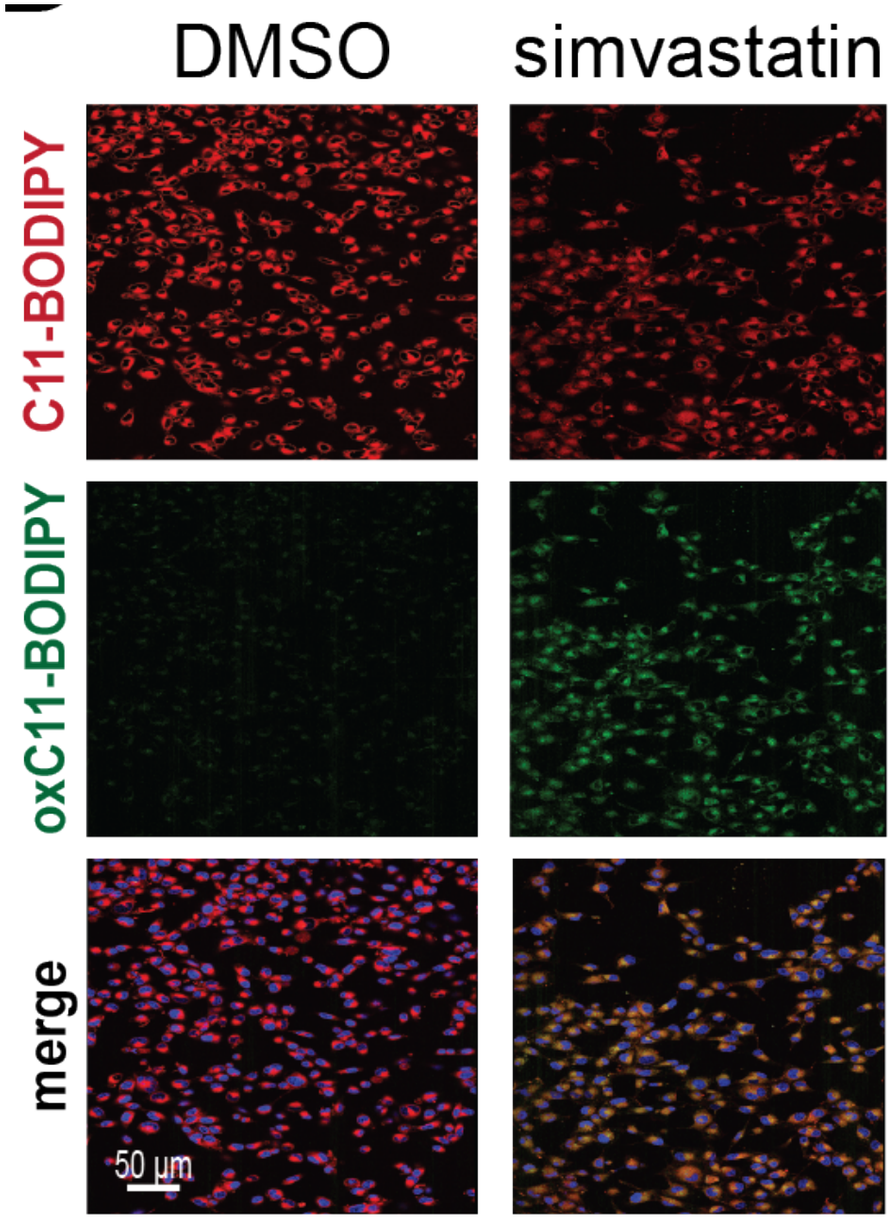


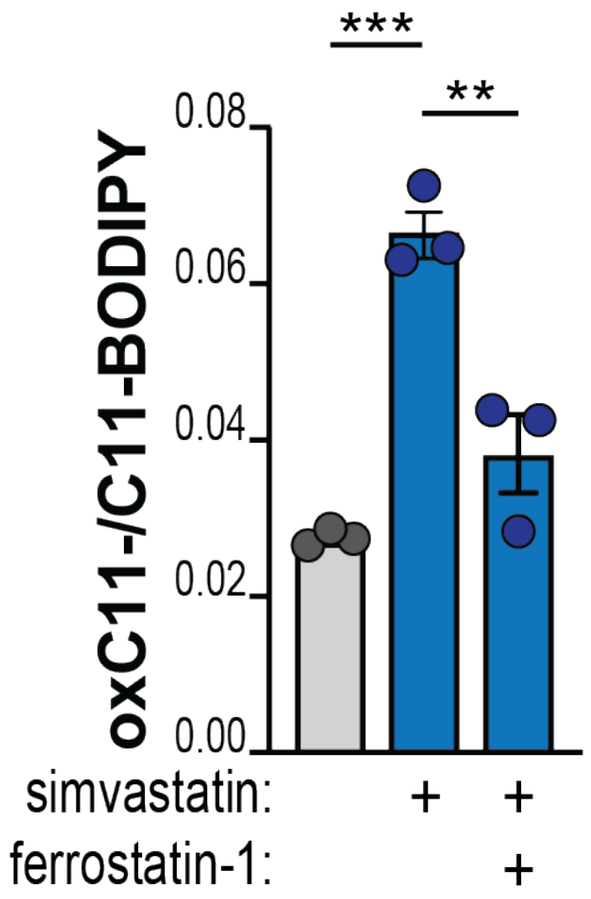


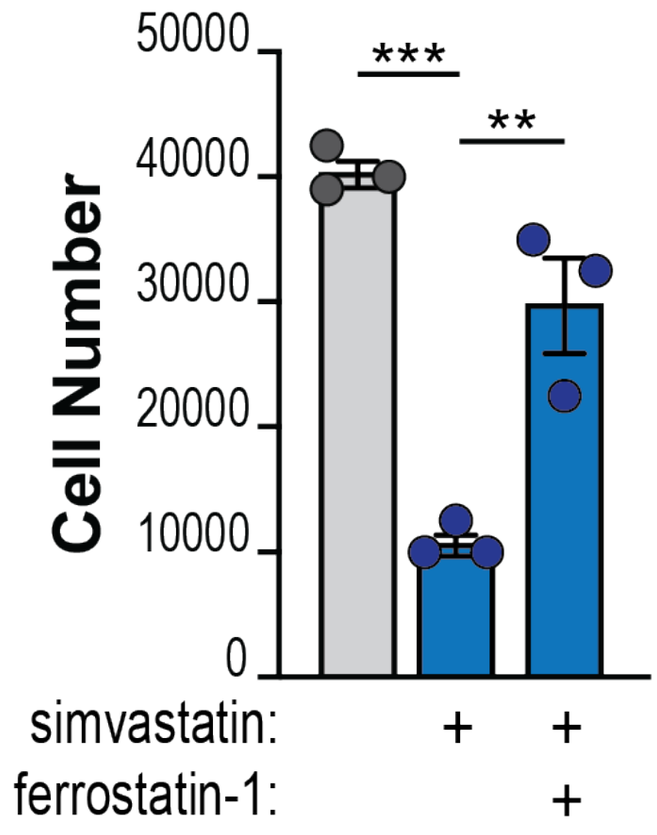


Noè et al, ***Redox Biol****, 2023*

Statin treatment elicits ferroptosis

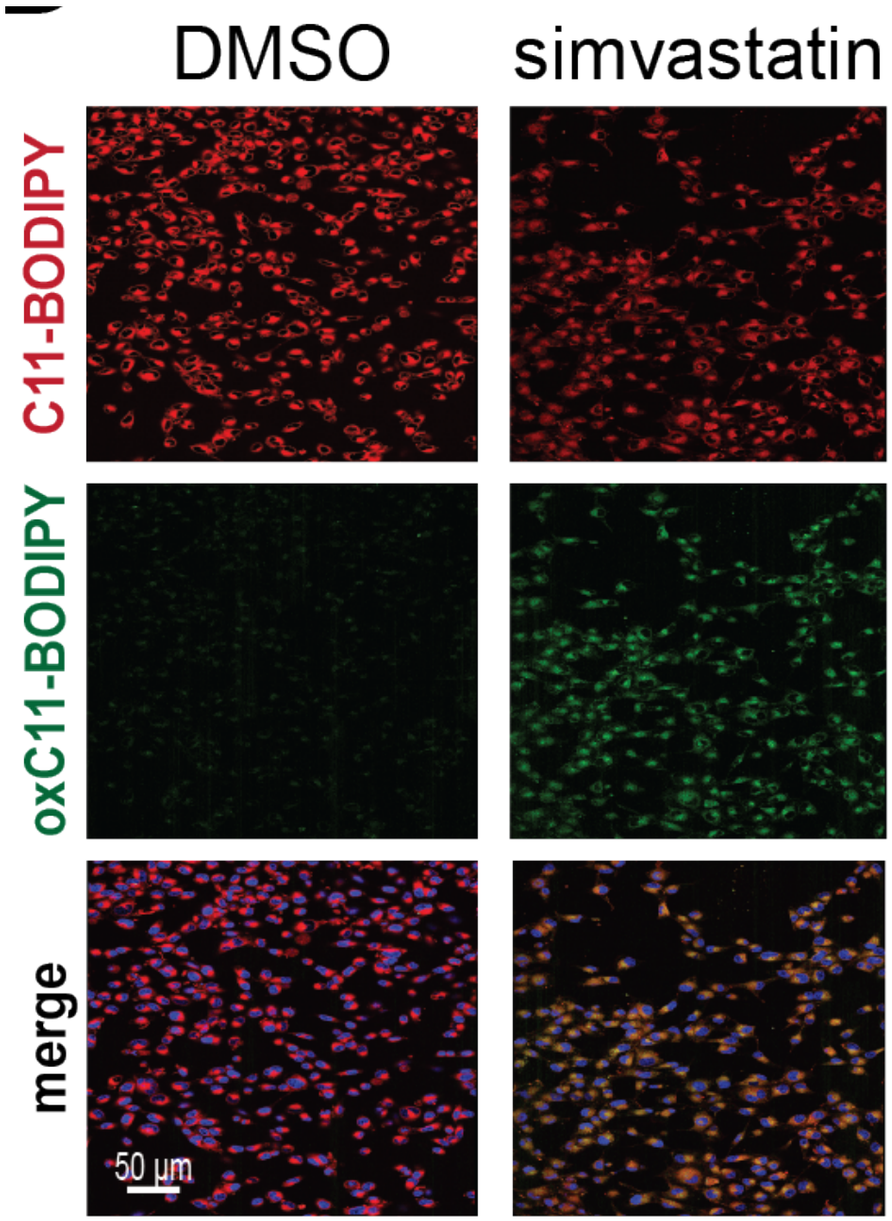


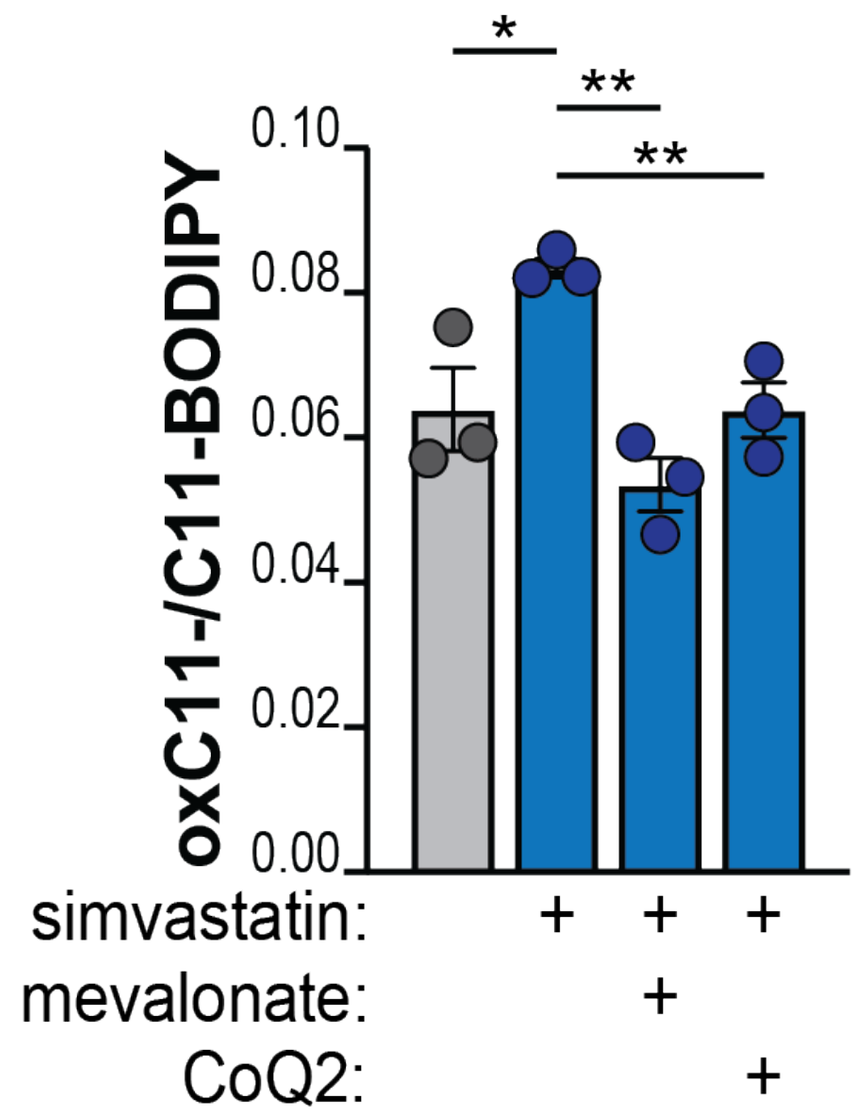




Noè et al, ***Redox Biol****, 2023*

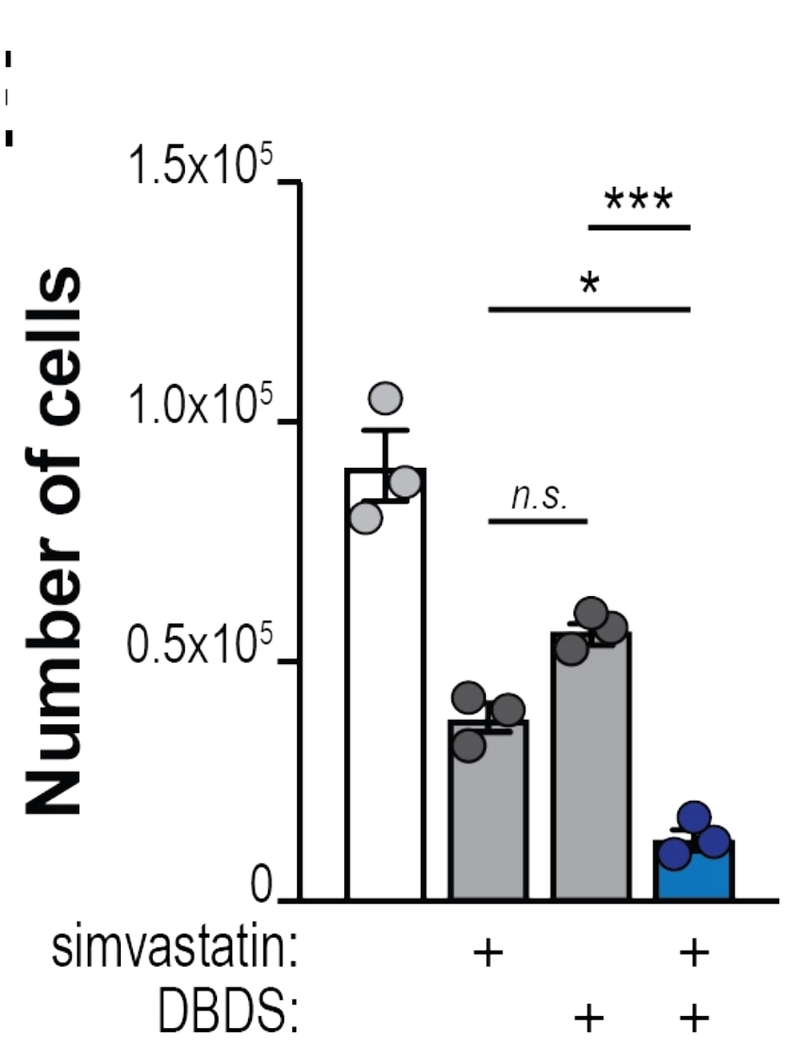
Mevalonate and CoQ supplementation protects from ferroptosis

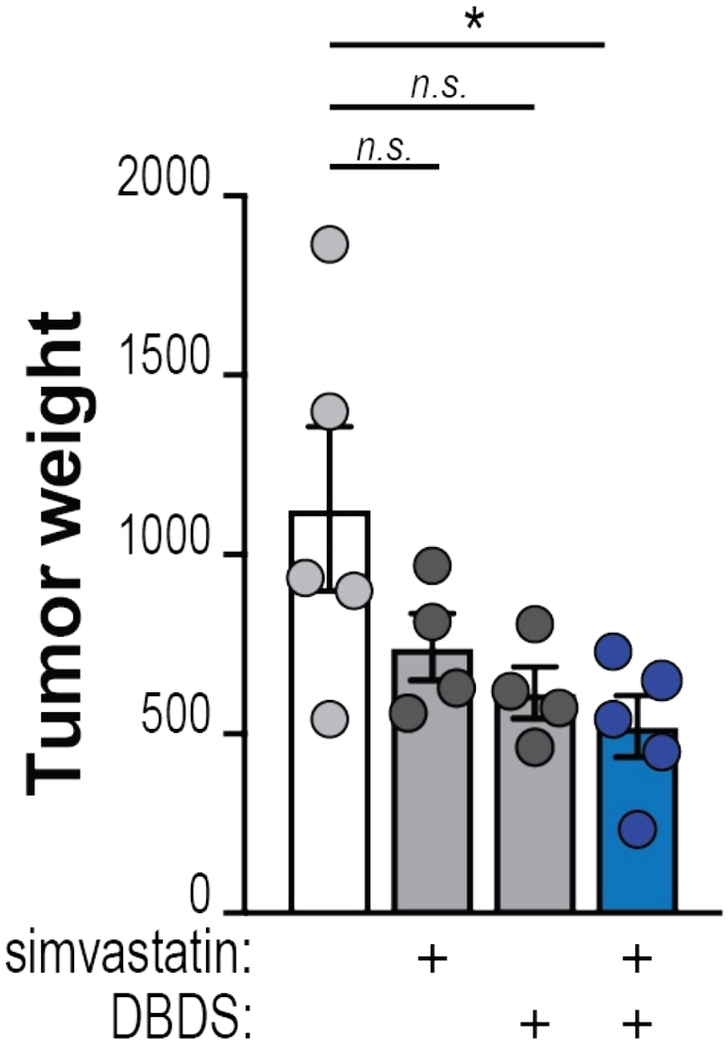




Noè et al, ***Redox Biol****, 2023*

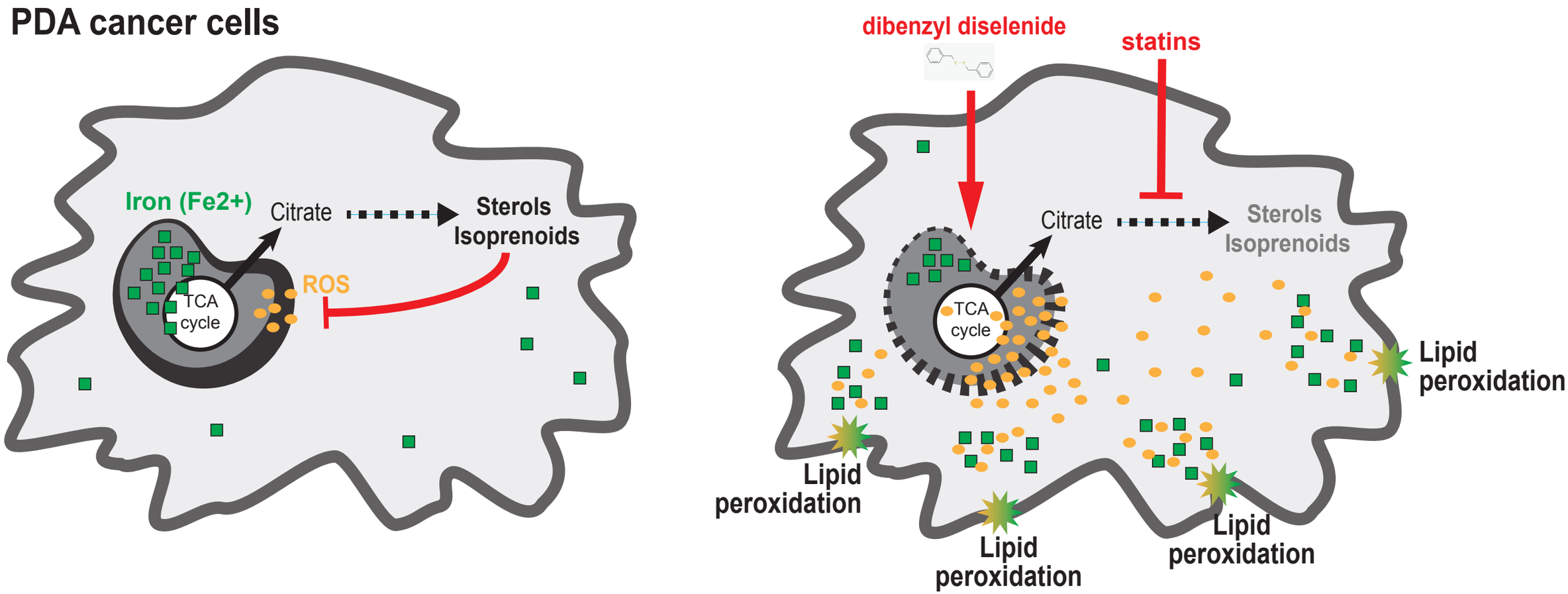
Stain-promoted ferroptosis can be exploited for cancer therapy





Noè et al, ***Redox Biol****, 2023*

Metabolism is reprogrammed to cope with oxidative stress



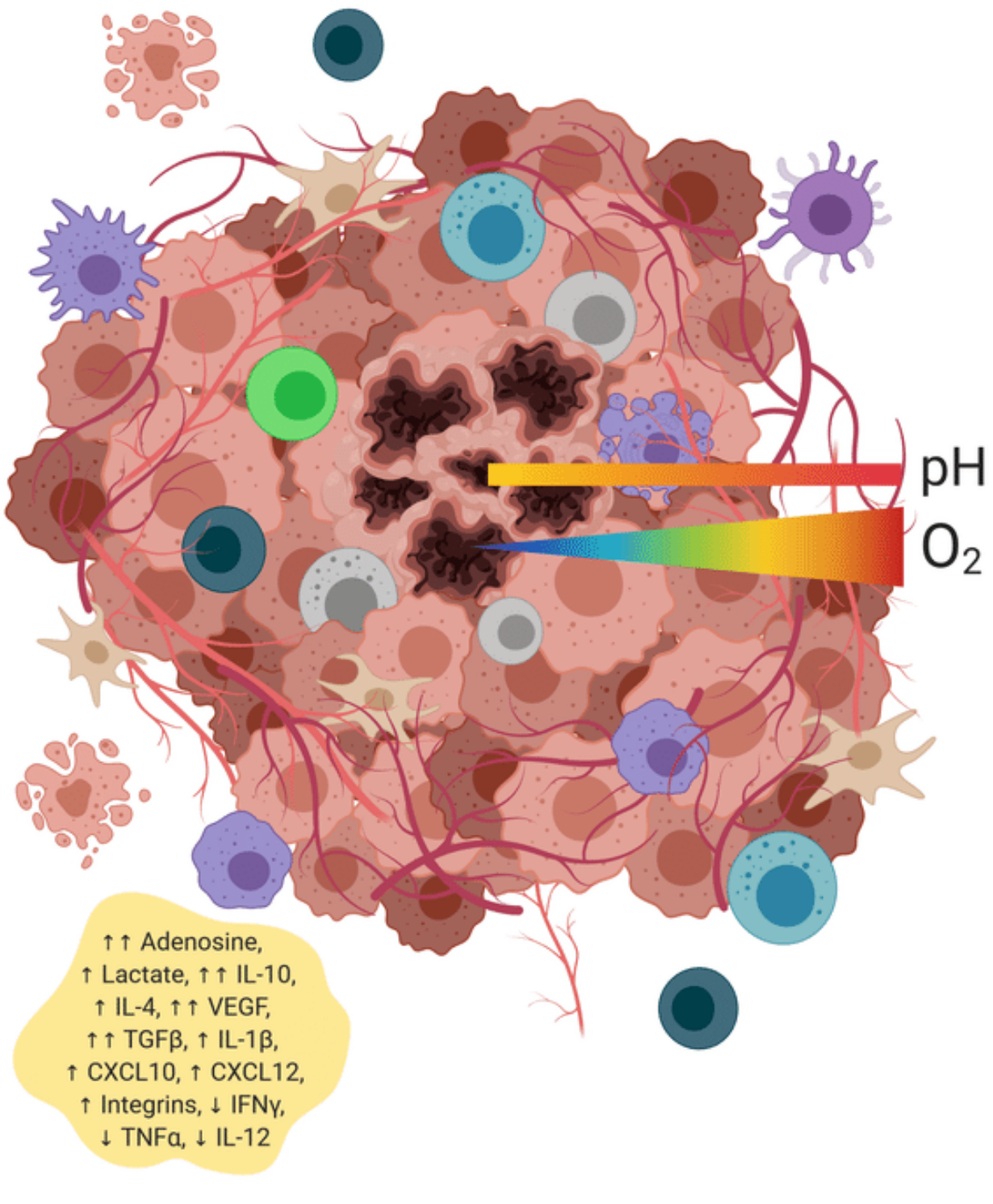
Cancer cells gain benefits from enhanced redox stress, but potentially toxic species need to be constantly monitored and held in check.

Multiple mechanisms:

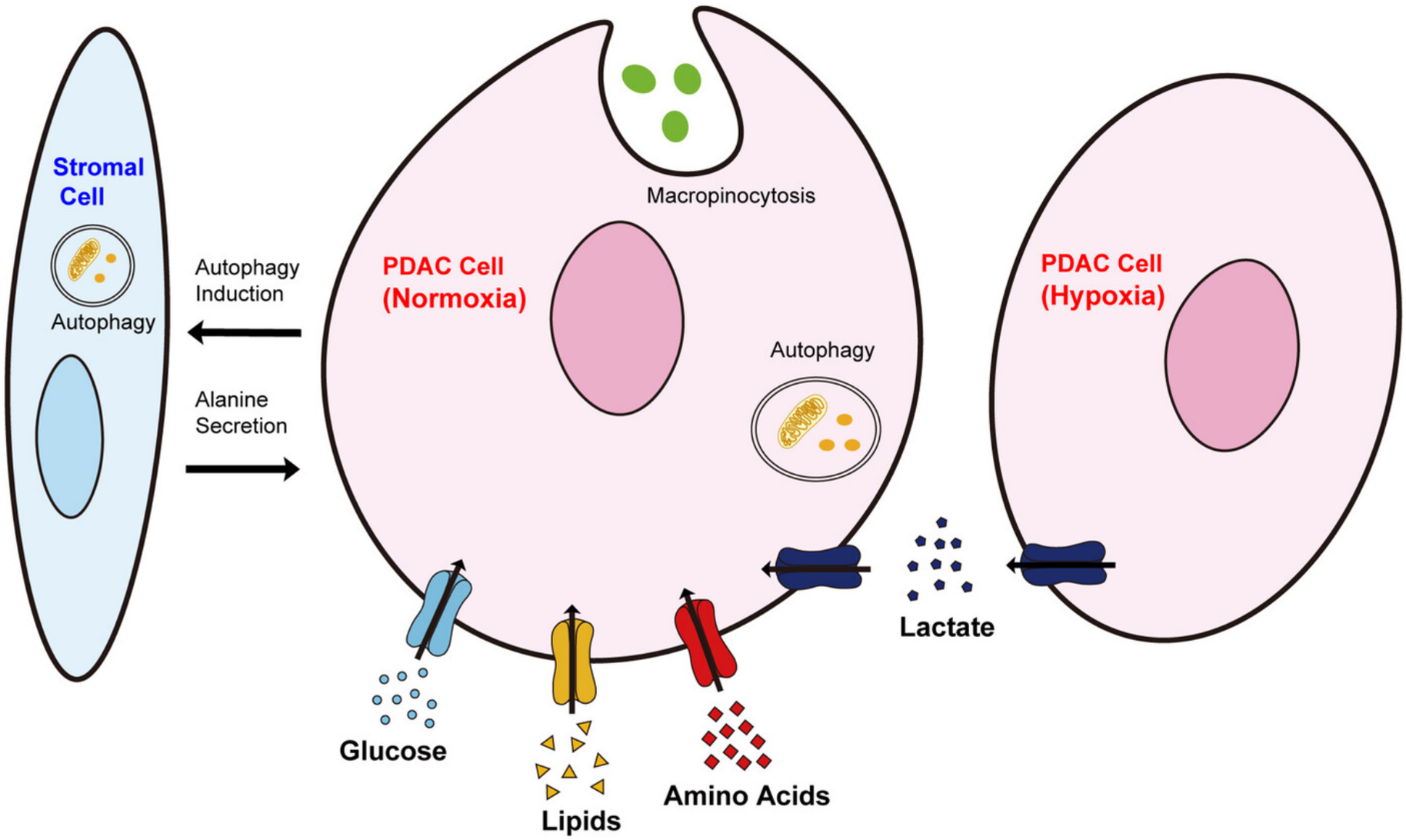
- NRF2 activation
- Feeding of mevalonate pathway
- Accumulation of redox-stabilizing metabolites
- Metabolic rewiring for NADPH saving (i.e.: altered utilization of glutamine and malate)

4

Metabolism is reprogrammed to thrive in harsh TME



Pancreatic TME is avascular and nutrient scarce



Cancer cells employ several strategies to overcome nutrient/oxygen limitations:

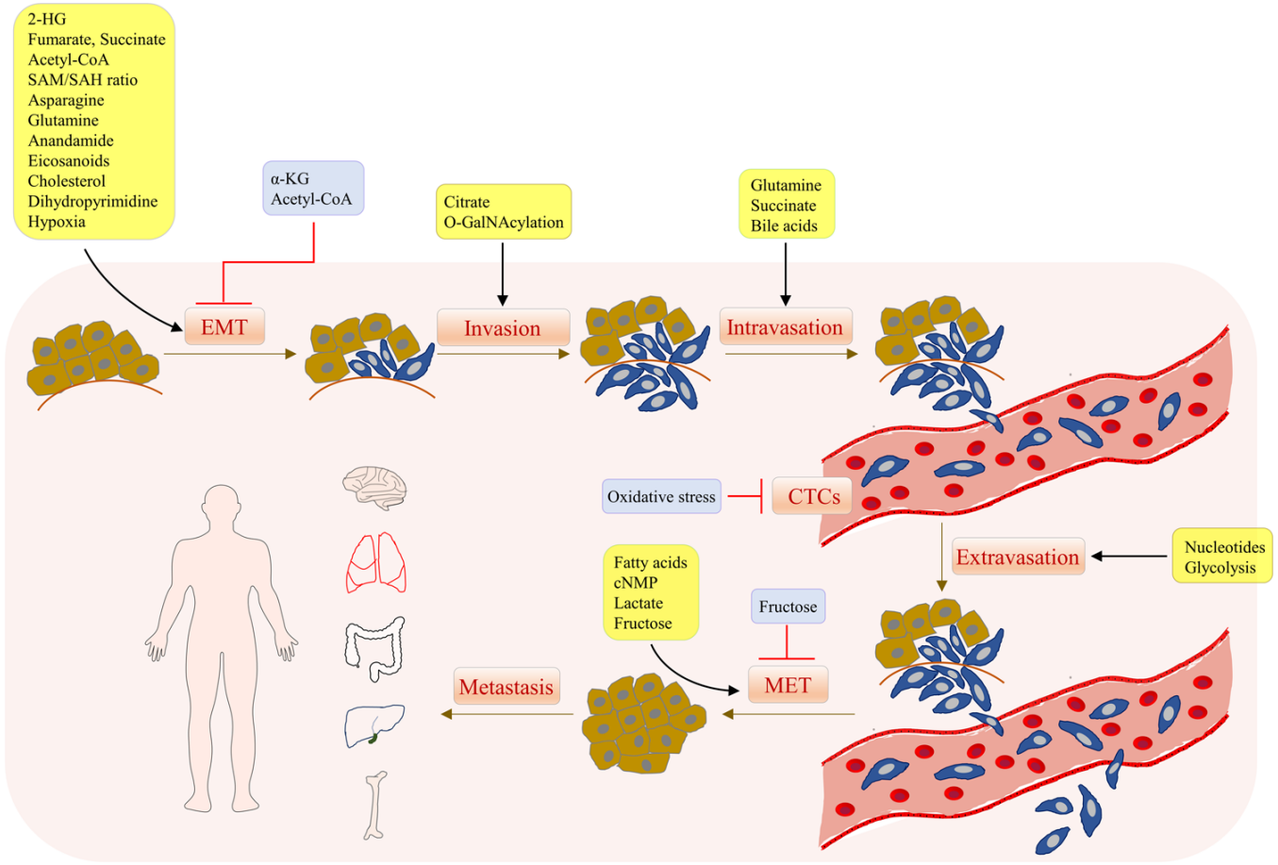
- Macropinocytosis (scavenging of free floating proteins)
- Digestion of ECM and uptake of AAs
- Symbiosis with CAFs (alanine, lipids)
- Symbiosis among metabolically heterogeneous cancer cells
- Metabolic waste (lactate, urea, others??) recycling

Suzuki et al, ***MedComm****, 2020*

4

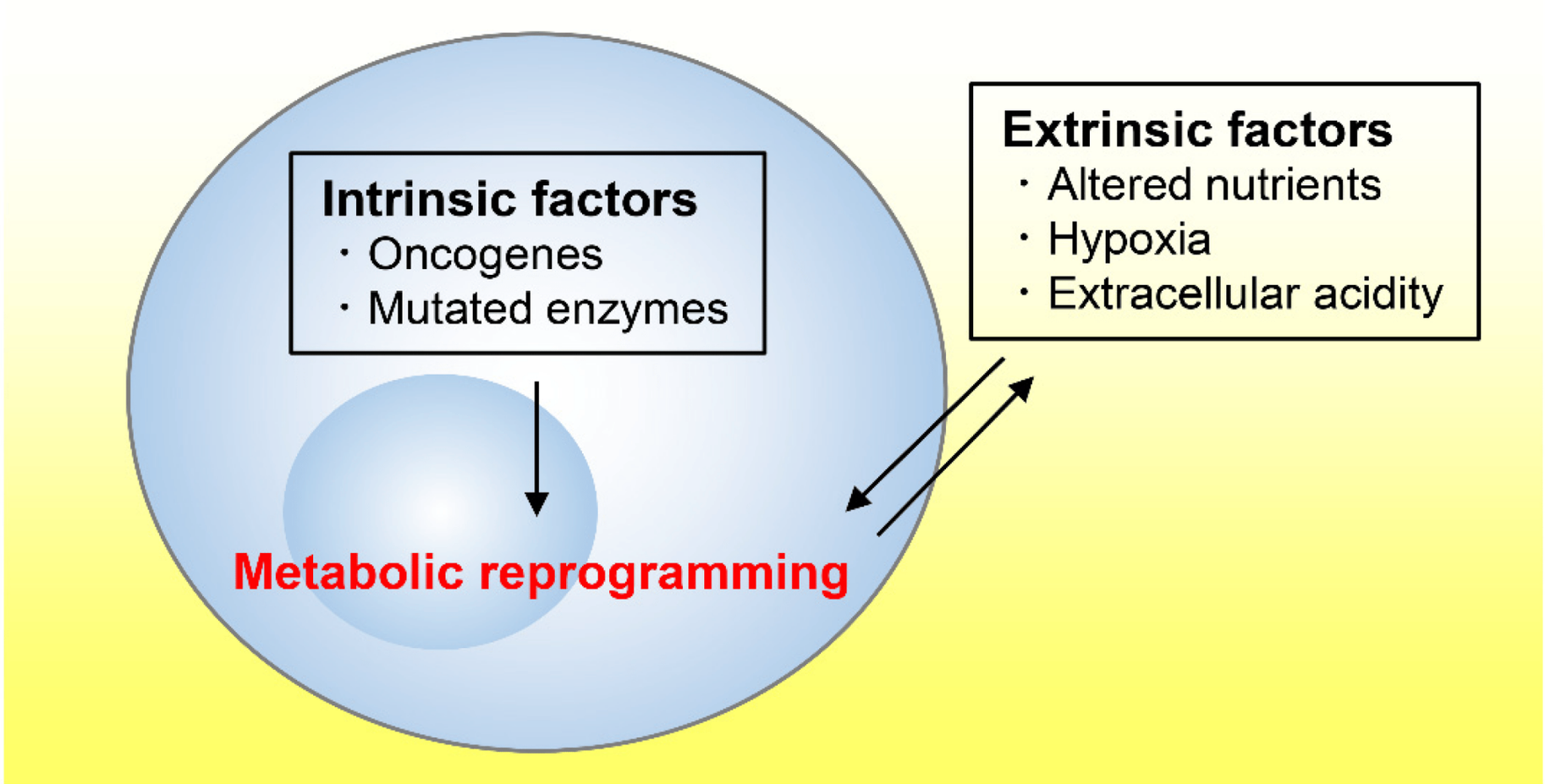
Metabolism is reprogrammed to support spreading

Metastasis formation is a multistep process that requires cancer cells to dynamically change their phenotype. The early metastatic steps include invasion into the surrounding tissue and dissemination via the blood and lymphatic circulation to distant organs. Once the cancer cells have settled outside the primary tumor, they have to colonize and outgrow in the new organ. In recent years, it has emerged that alterations in metabolism are a prerequisite for the early and later steps of metastasis formation because metabolism responds to but also enables the plasticity and heterogeneity of metastasizing cancer cells.

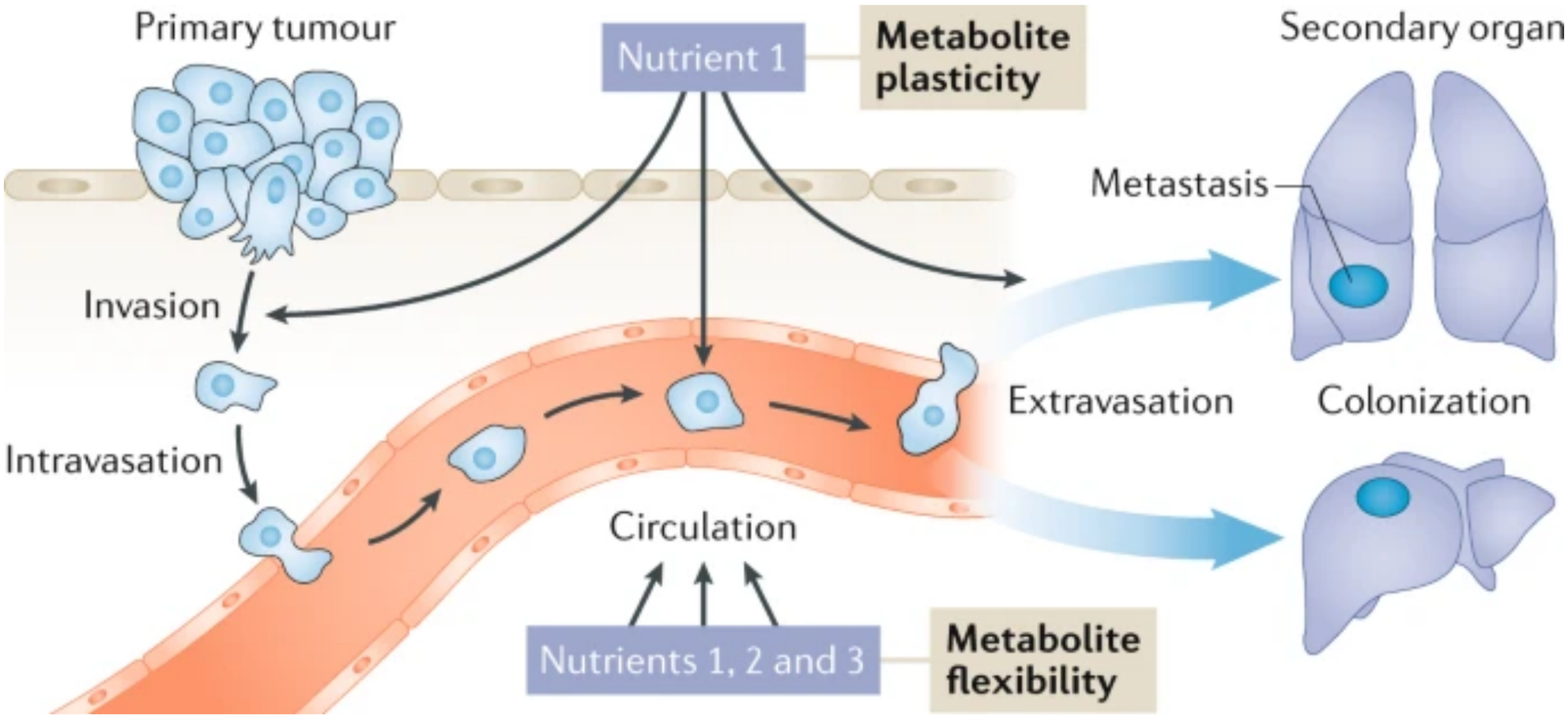


Wei et al, ***Oncogene****, 2020*

Both mutated oncogenes and changing environments force cells to acquire new metabolic features, which influence cell behavior.



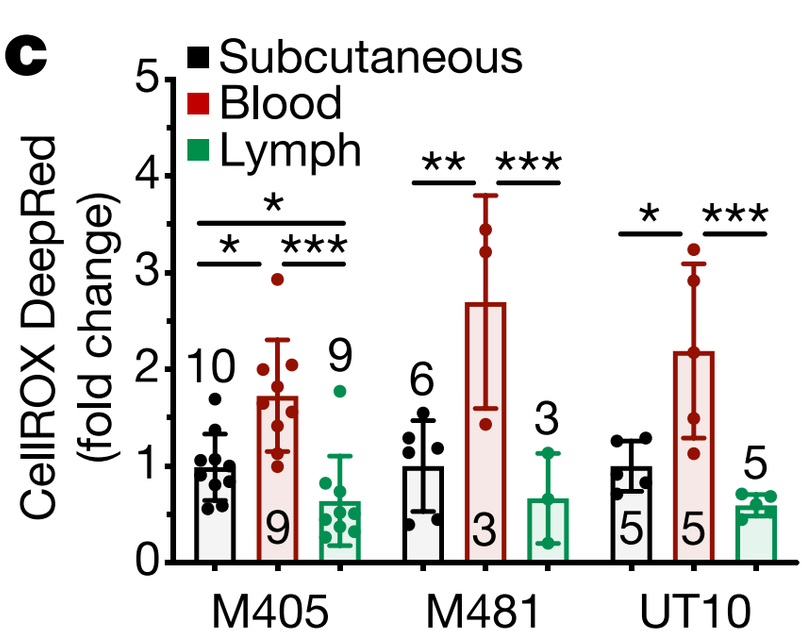
Oshima & Morii, ***Metabolites****, 2021*

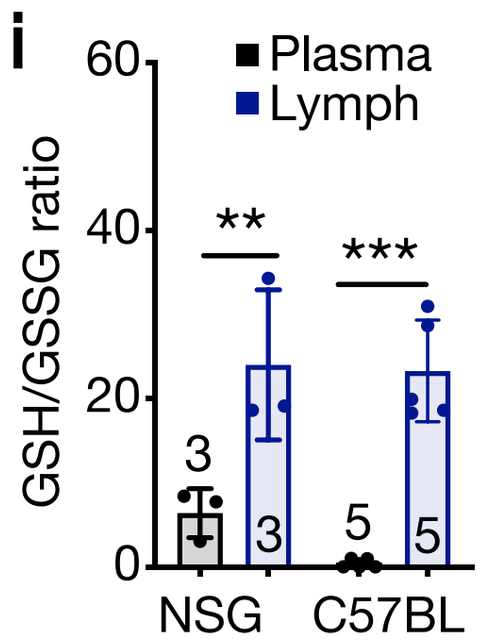


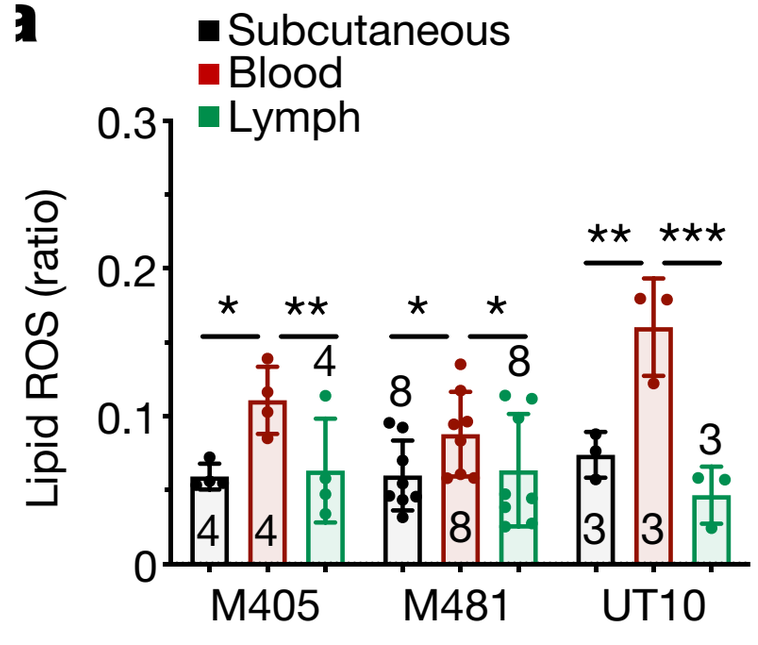
Metastasizing cells undergo dynamic metabolic changes to adjust to the differing microenvironments while traveling to distant organs. Thereby, metastasizing cells can exhibit metabolic plasticity in which they use one metabolite to fuel the various metabolic requirements of the different steps in the metastatic cascade. Alternatively, they can display nutrient flexibility by using multiple metabolites to meet the same metabolic requirement imposed by a specific step of the metastatic cascade. In cancer cells, both phenomena, metabolic plasticity and metabolic flexibility, contribute to metastasis formation and may be targeted for therapy.

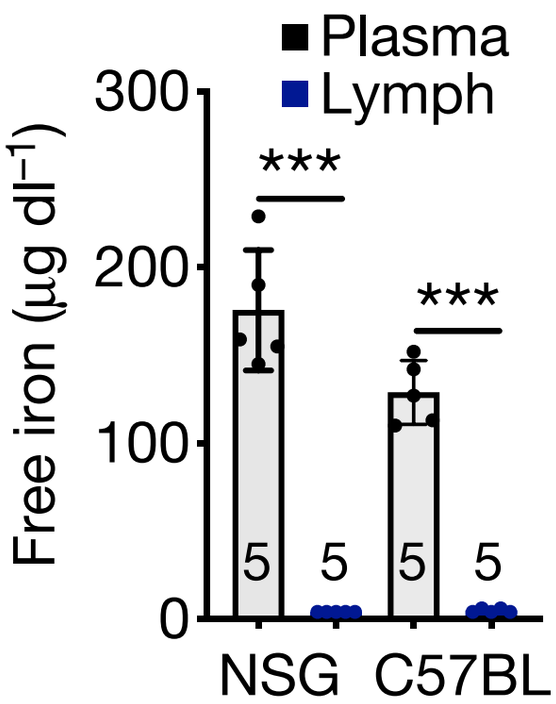
Bergers & Fendt, ***Nat Rev Cancer****, 2021*

Lymph protects metastasizing melanoma cells from ferroptosis









Ubellacker et al, ***Nature****, 2020*

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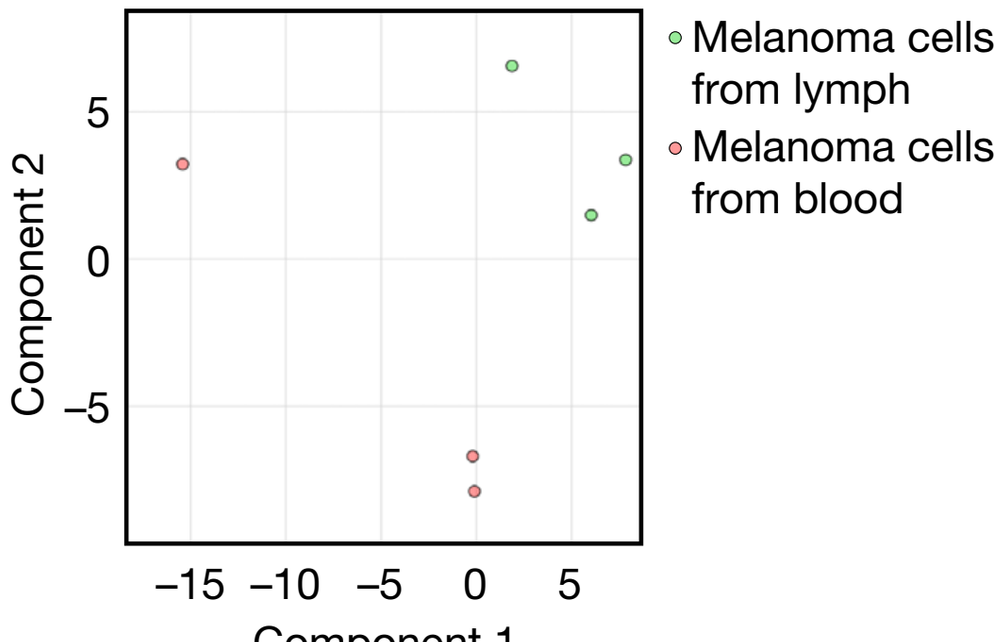

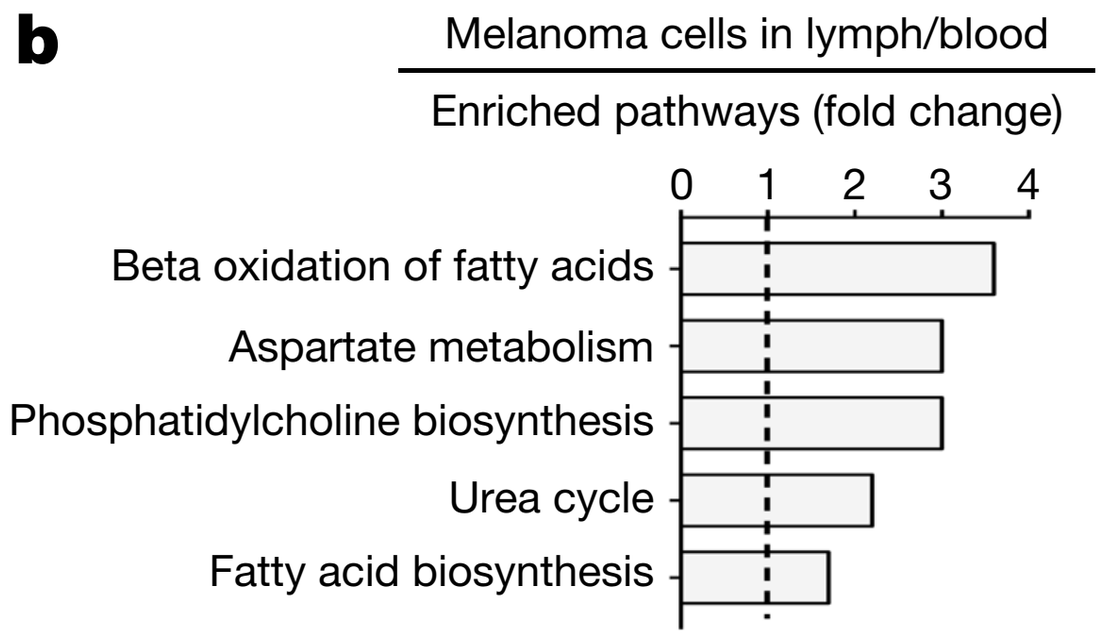

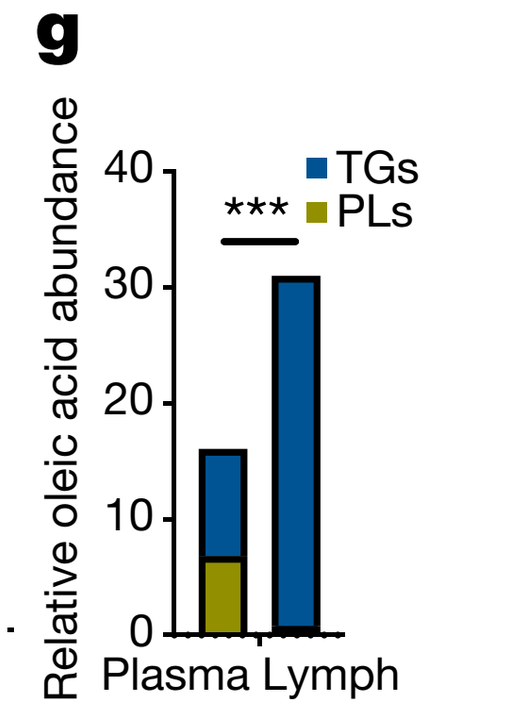

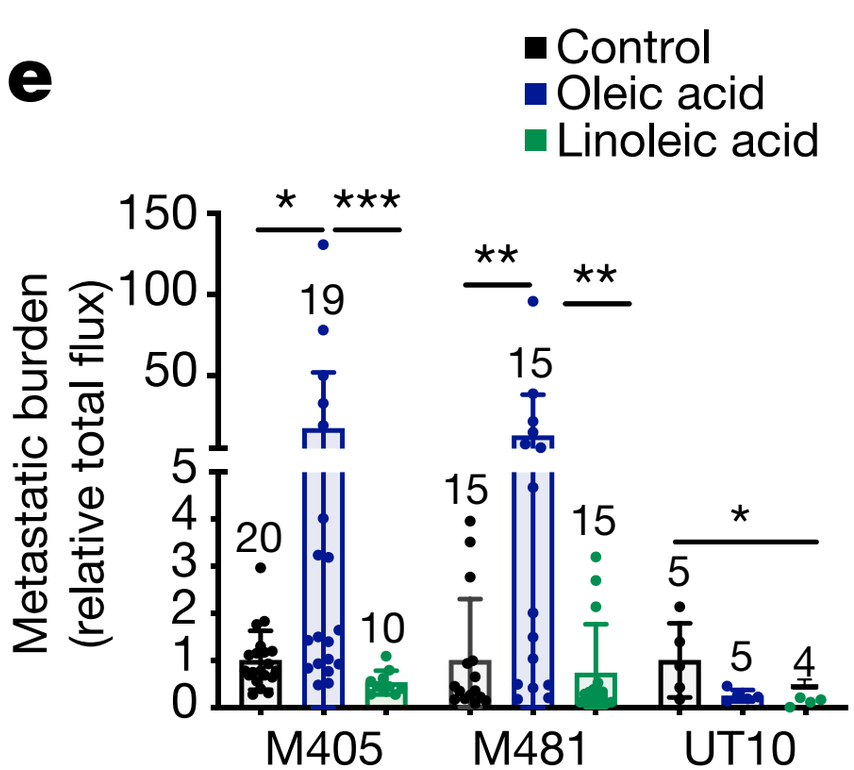

Ubellacker et al, ***Nature****, 2020*

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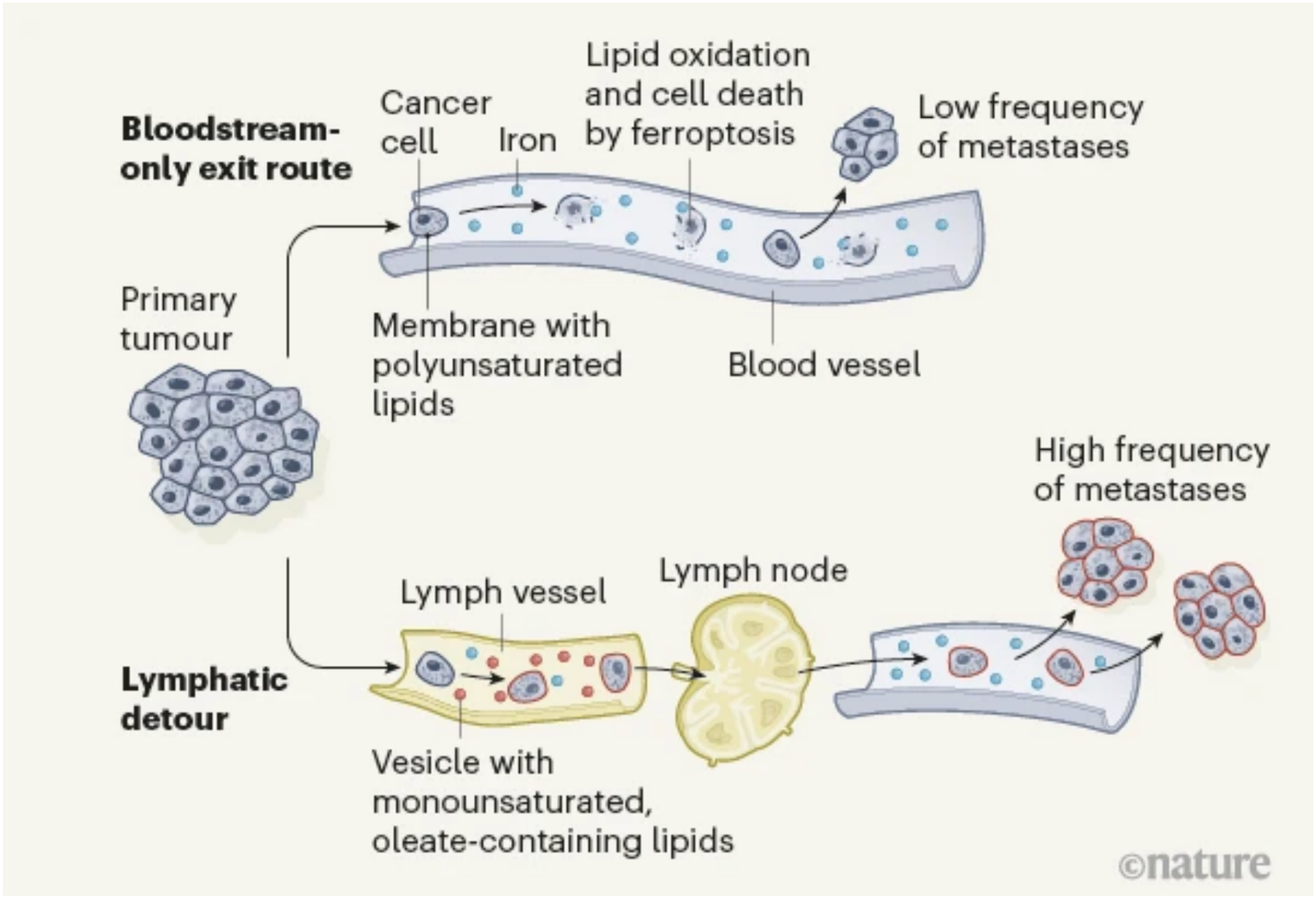
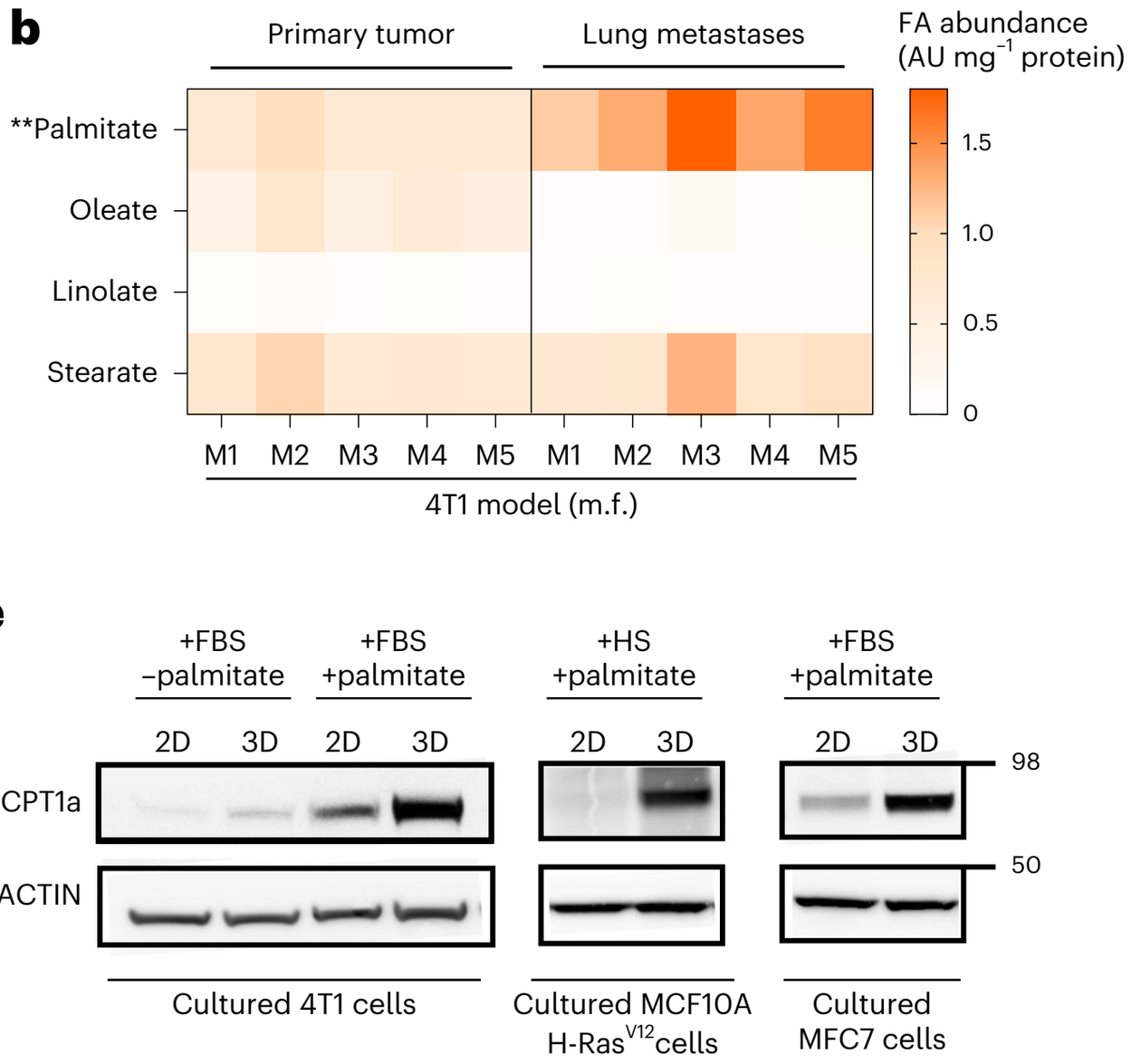


Gruner & Fendt, ***Nature****, 2020*
Ubellacker et al, ***Nature****, 2020*

Article https://doi.org/10.1038/s43018-023-00513-2

A palmitate-rich metastatic niche enables metastasis growth via p65 acetylation resulting in pro-metastatic NF-κB signaling



Altea-Manzano et al, ***Nat Cancer****, 2023*

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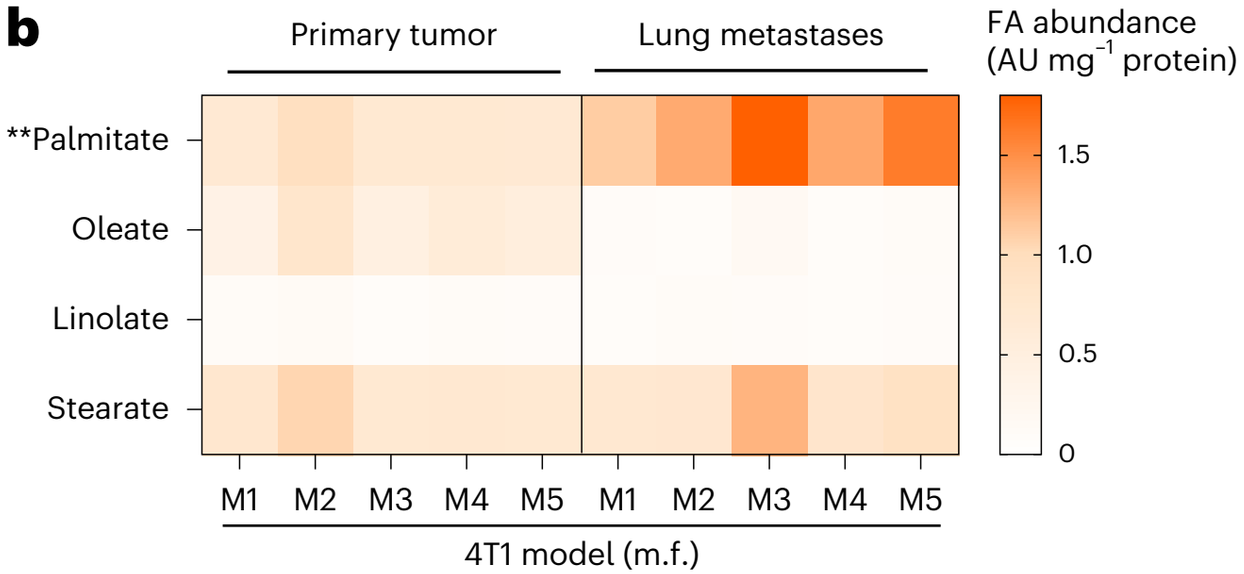

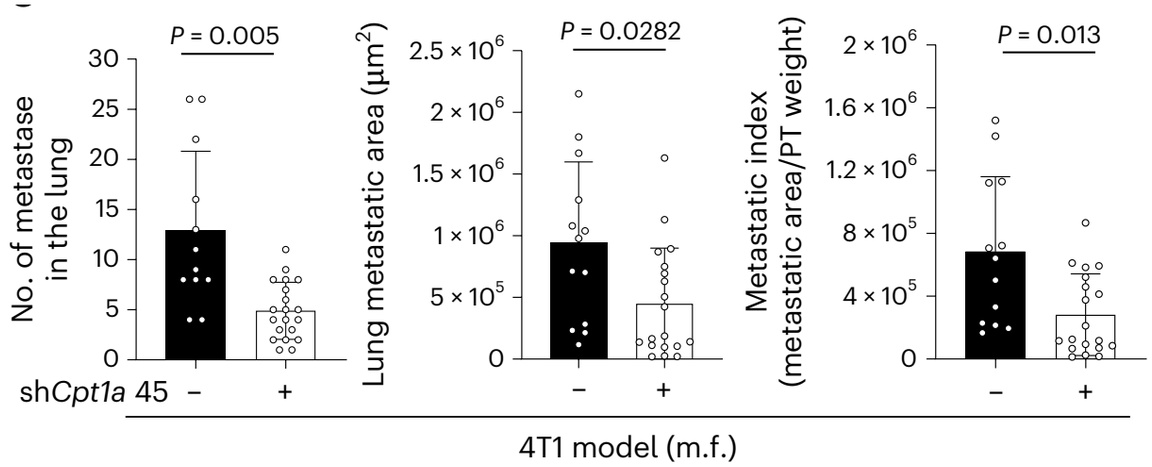

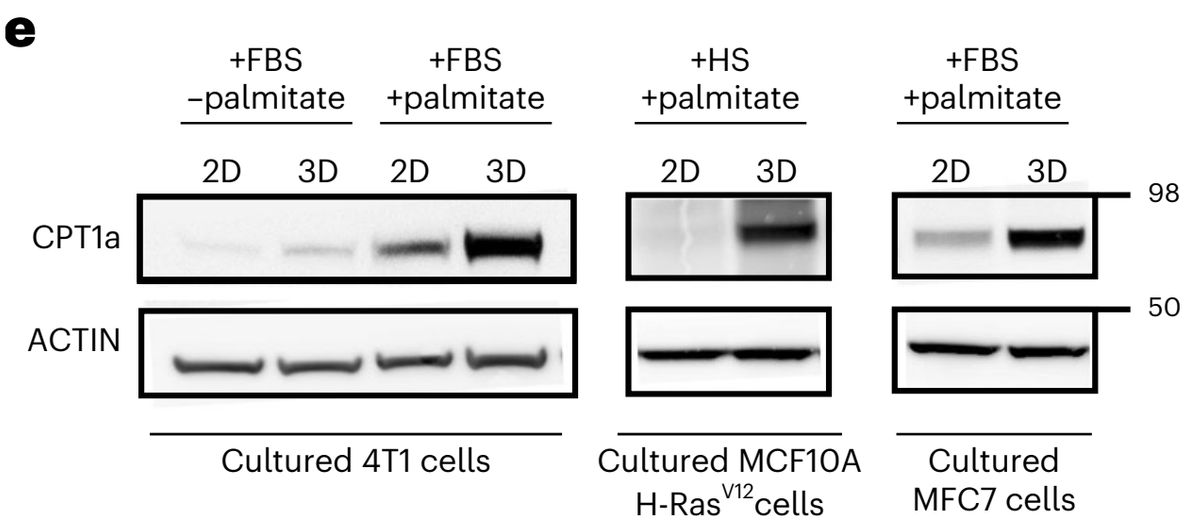

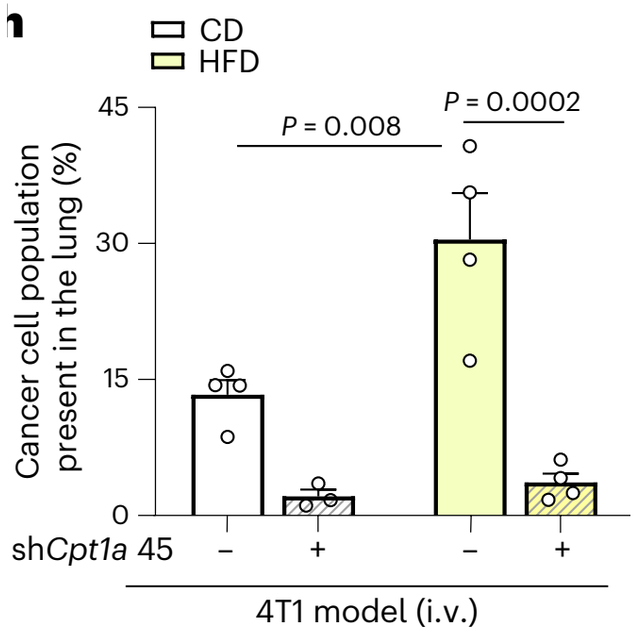

Altea-Manzano et al, ***Nat Cancer****, 2023*

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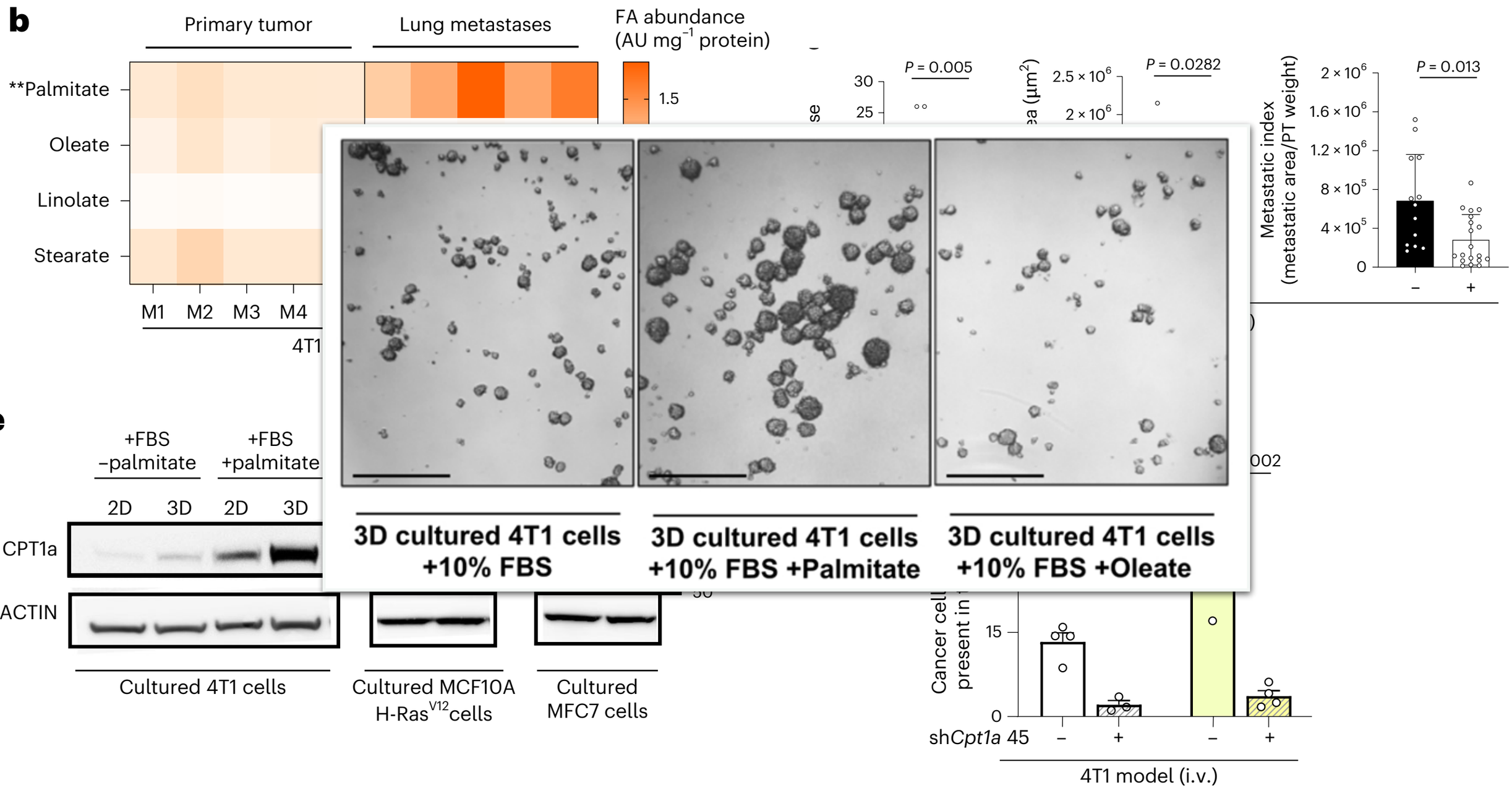

Altea-Manzano et al, ***Nat Cancer****, 2023*

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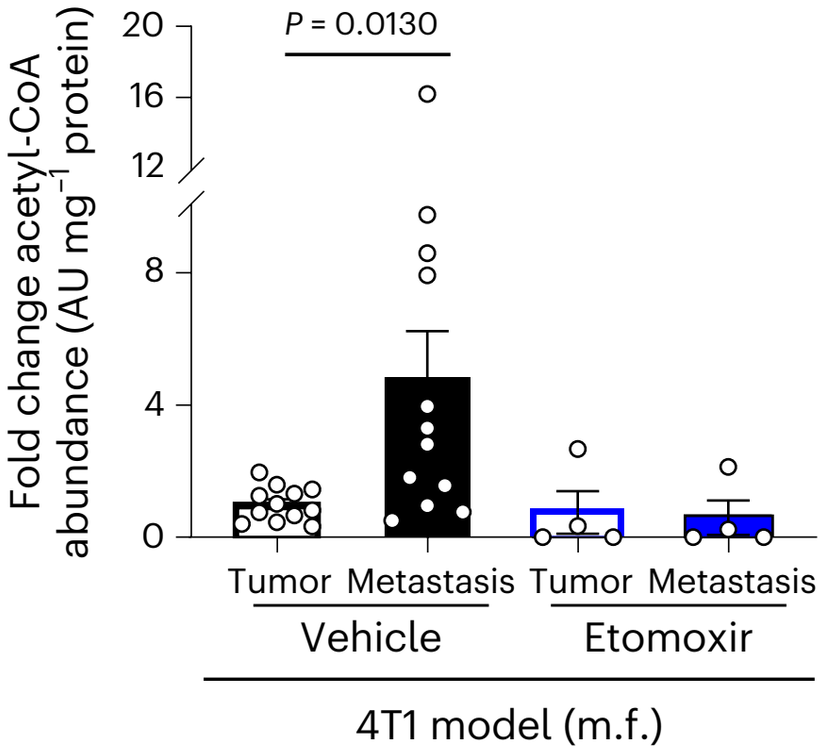
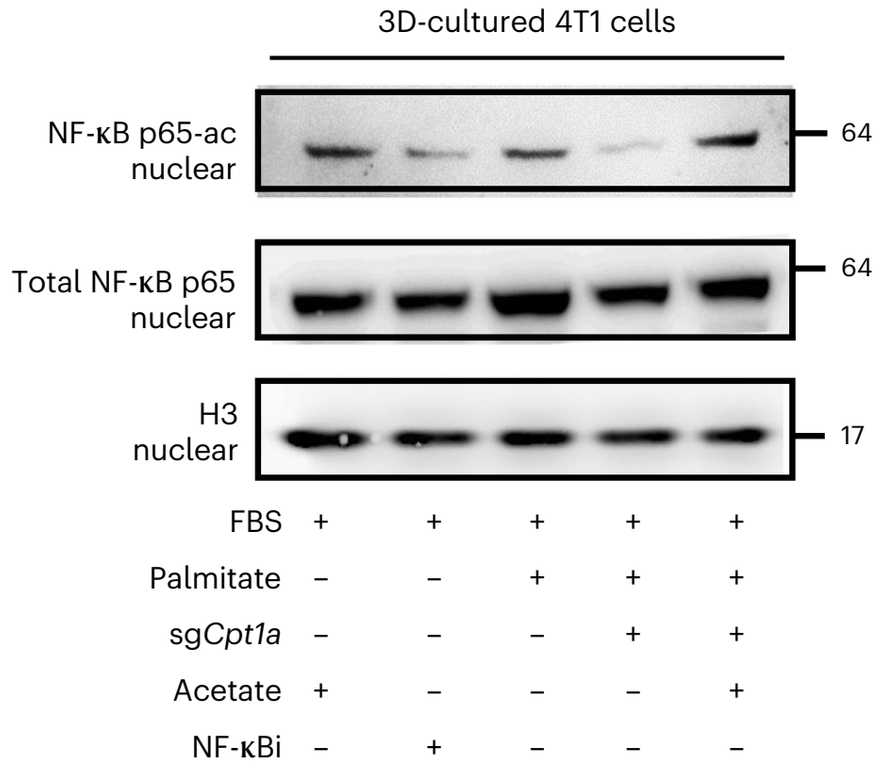
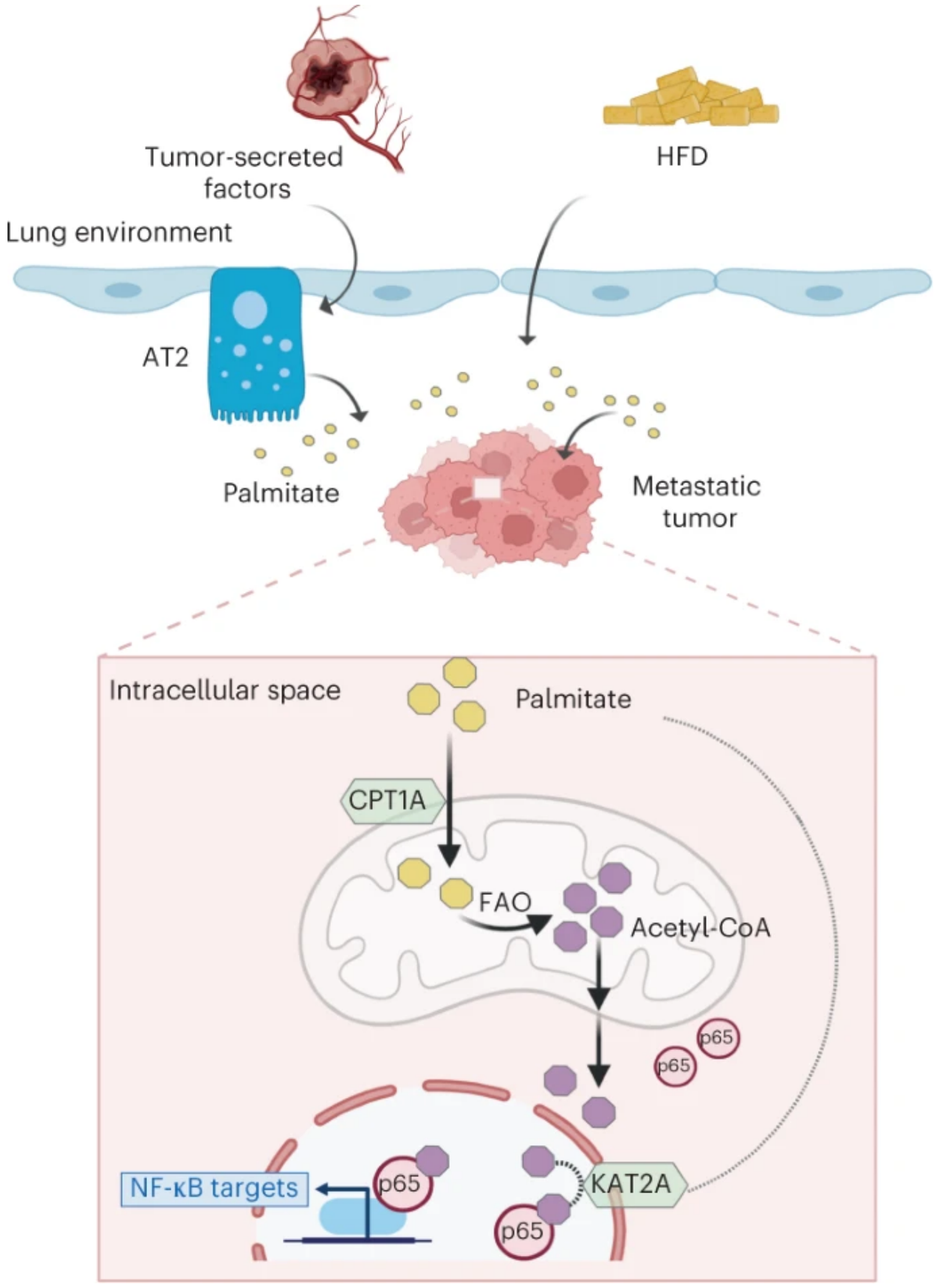




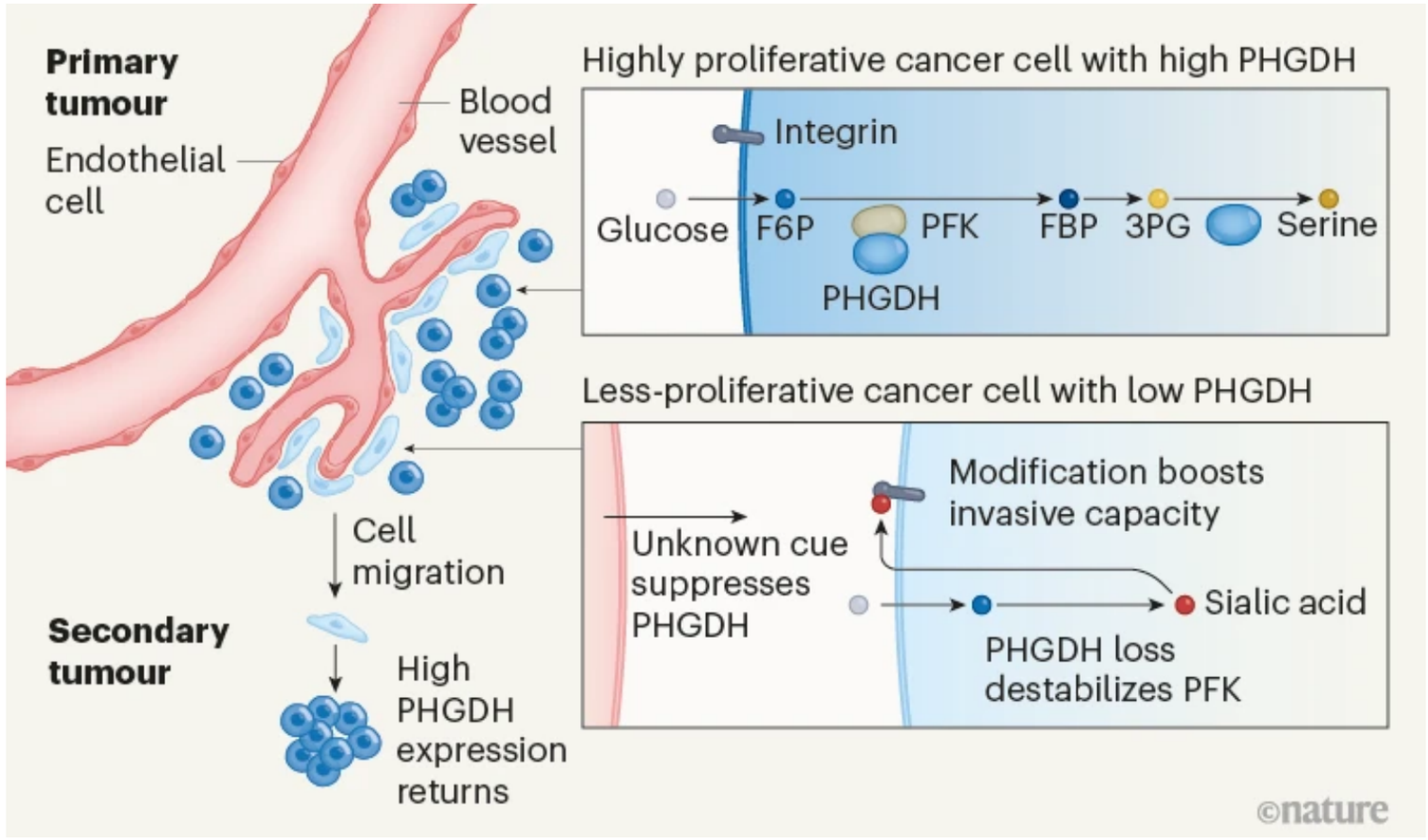
Altea-Manzano et al, ***Nat Cancer****, 2023*



Altea-Manzano et al, ***Nat Cancer****, 2023*

Article

PHGDH heterogeneity potentiates cancer cell dissemination and metastasis

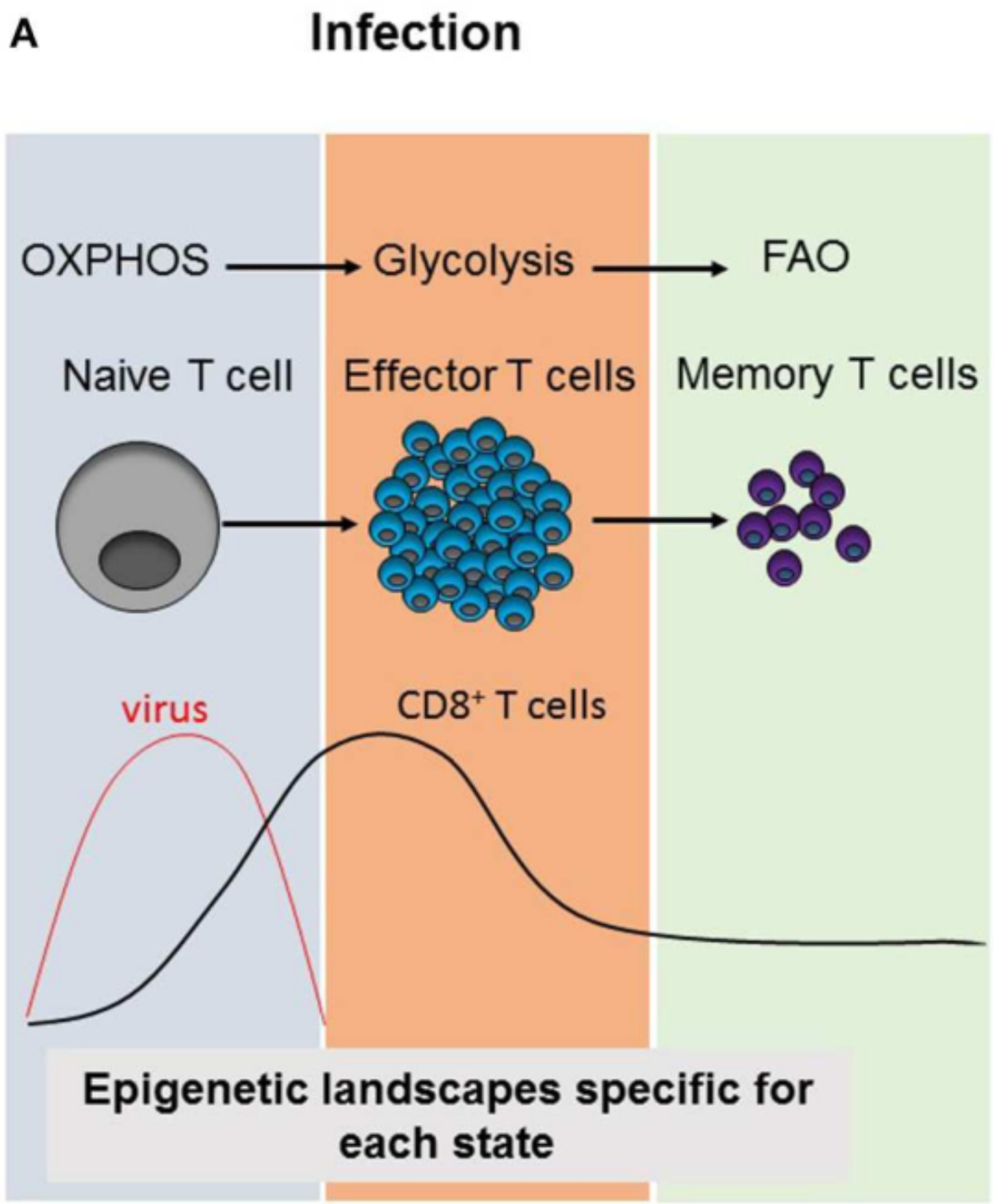


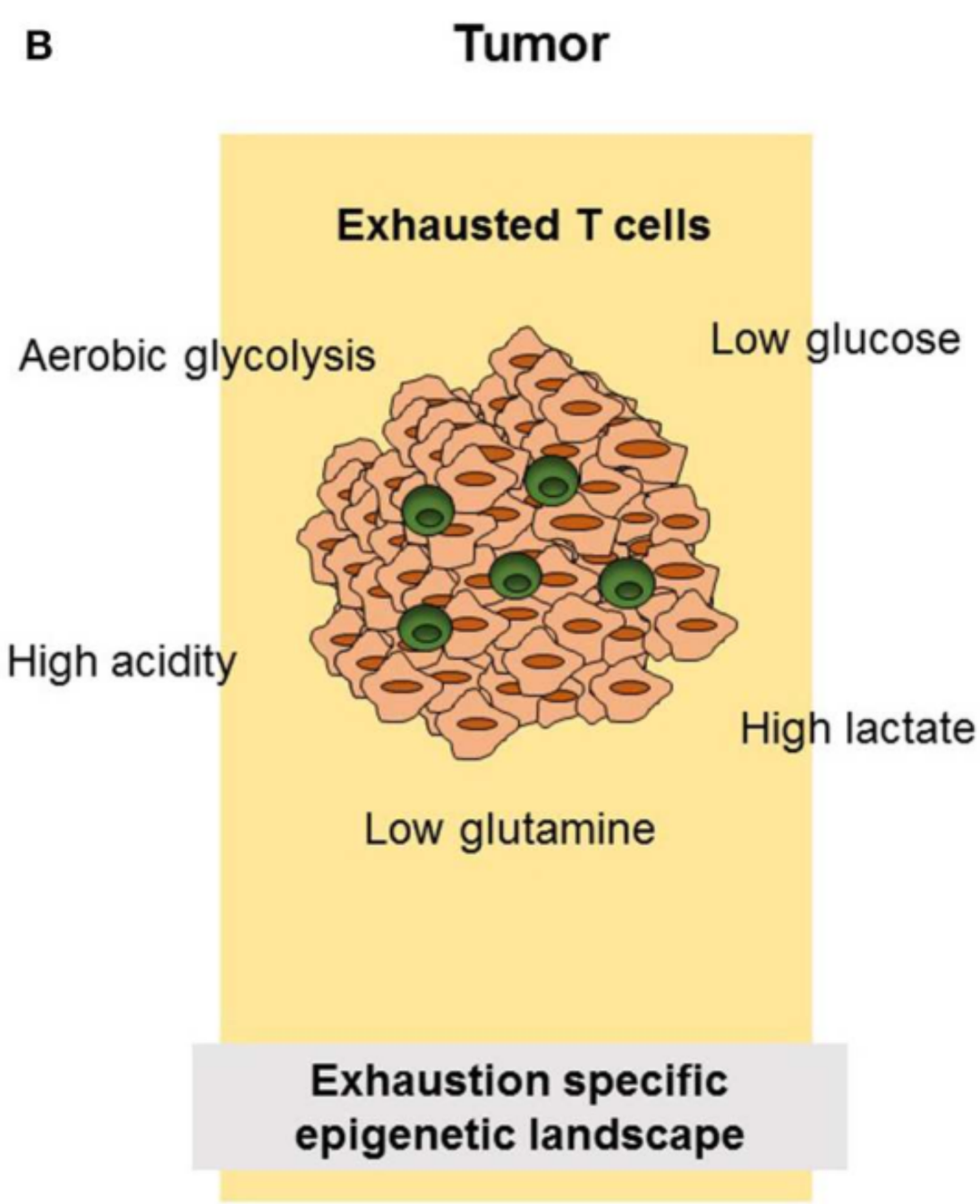
- Primary tumors upregulate Ser/Gly synthesis pathway to support growth/proliferation
- Endothelial cells suppress PHGDH (rate limiting enzyme).
- $PHGDH^{low}$ clones spread
- Lower Ser/Gly synthesis promotes extravasation by increasing *integrin* sialylation
- Metastasis re-activate Ser/Gly synthesis pathway to support metastatization (non-catalytical roles)

Rossi et al, ***Nature****, 2022*

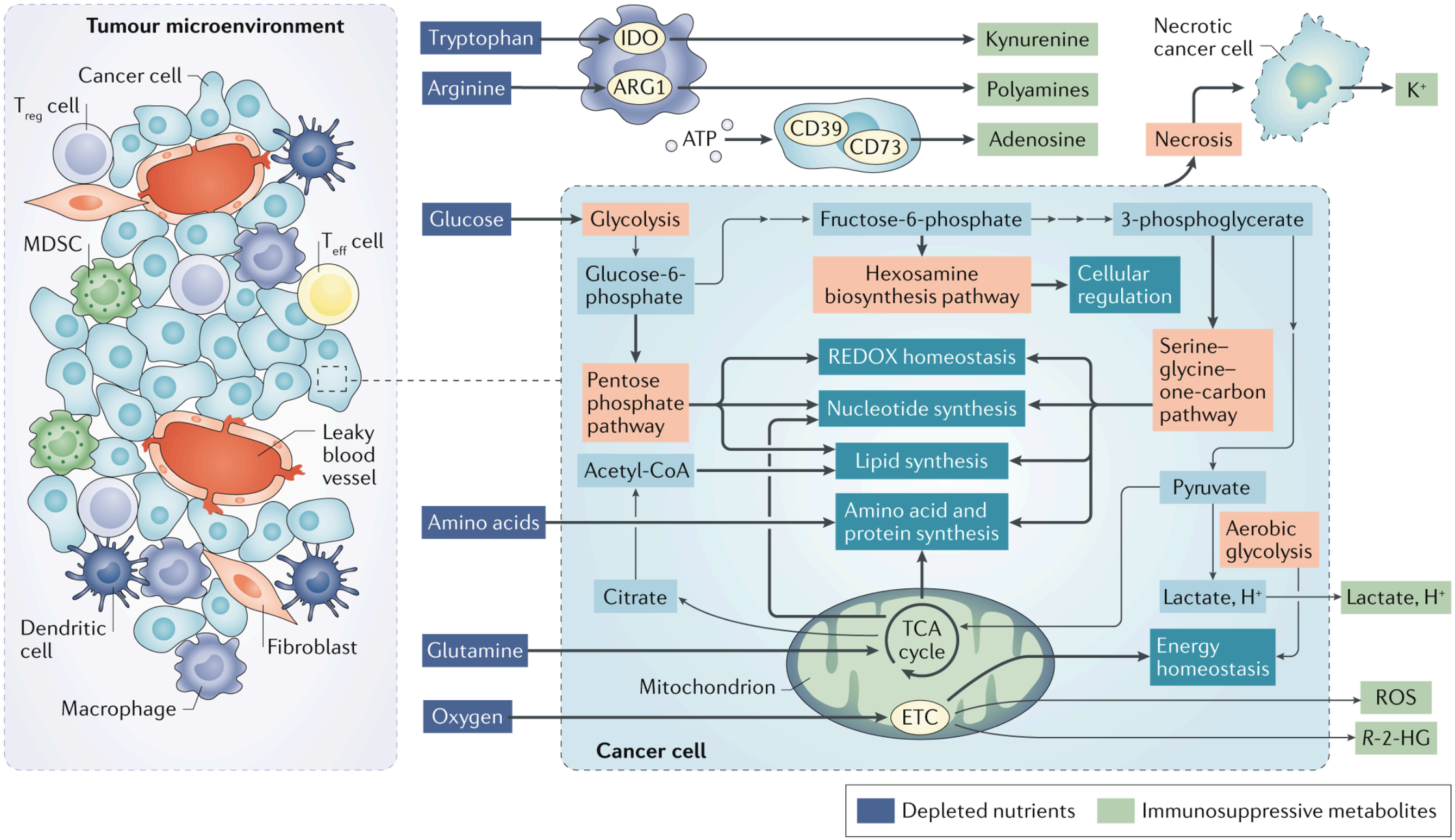
5

Metabolism is reprogrammed to support immune evasion



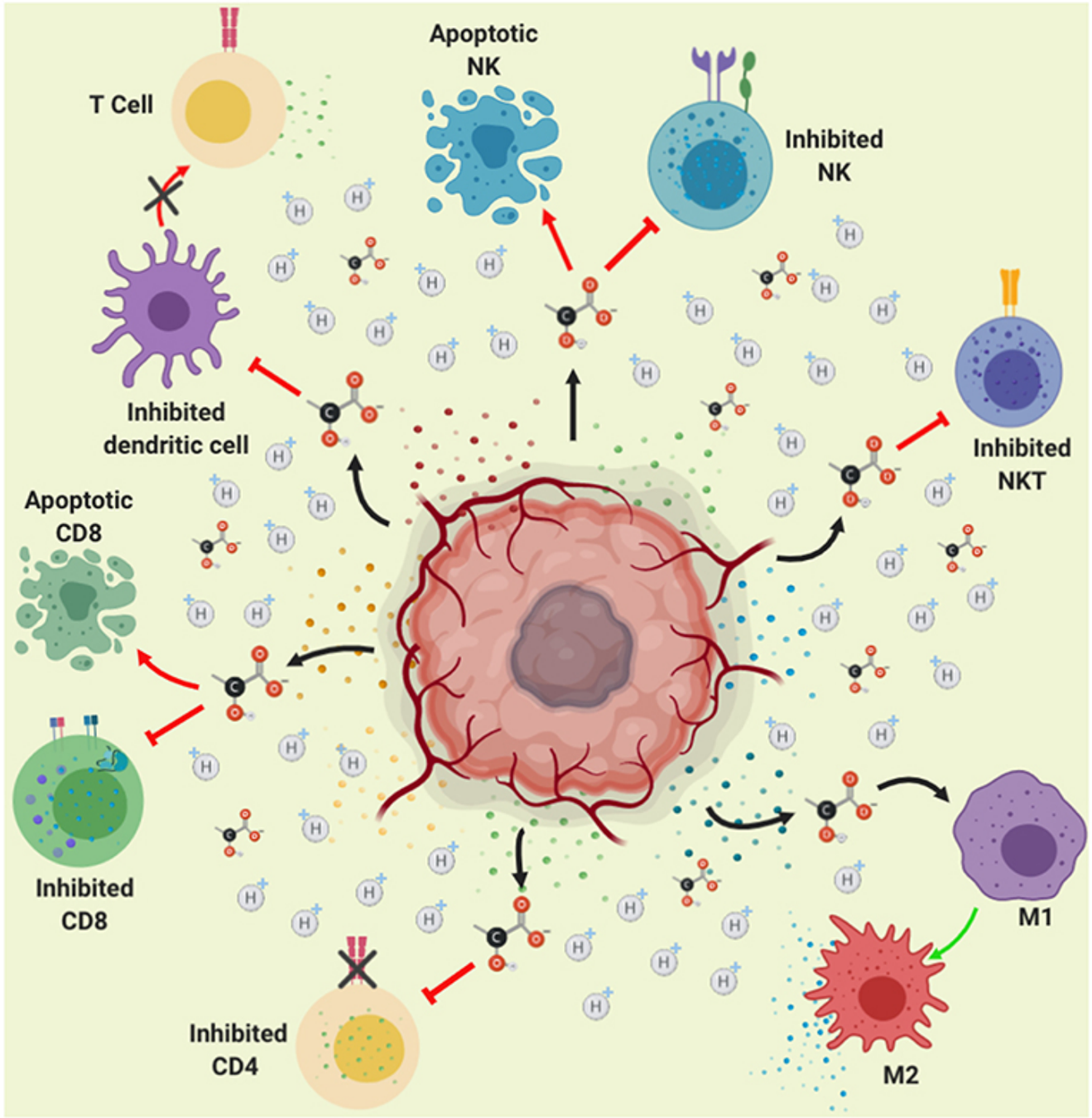


Tumor cells dictate a immunosuppressive TME



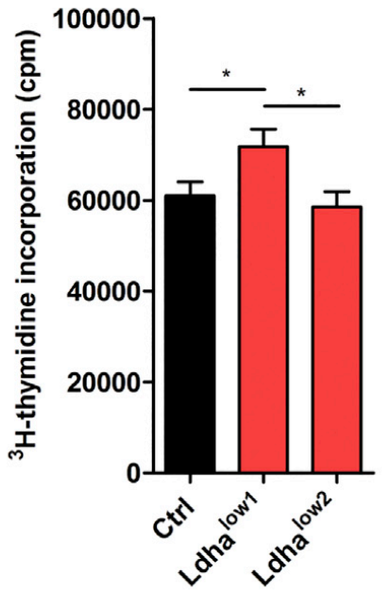
Leone & Powell, ***Nat Rev Cancer****, 2020*

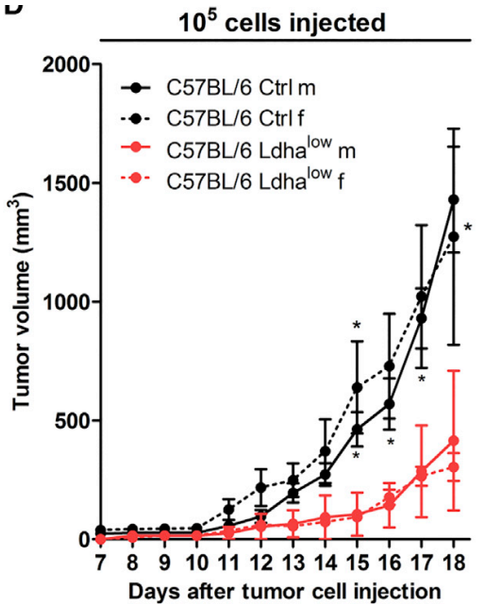
Lactate creates a immunosuppressive tumor microenvironment

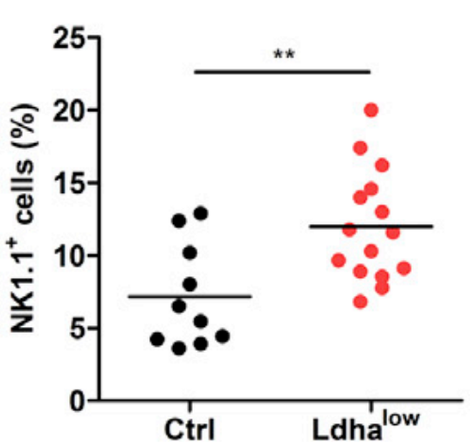


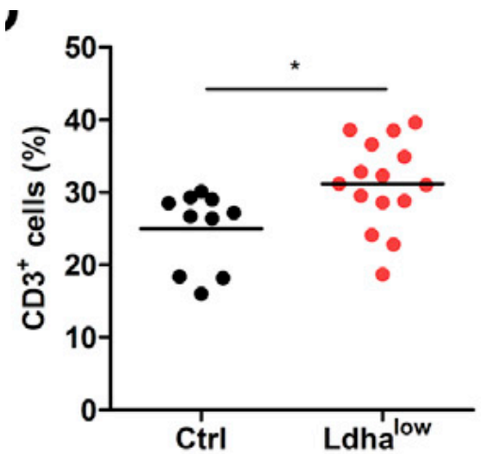
LDHA-Associated Lactic Acid Production Blunts Tumor Immunosurveillance by T and NK Cells

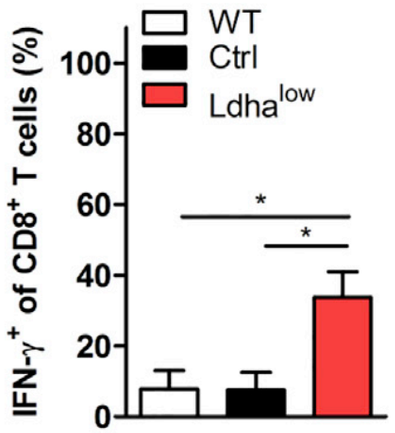
Almut Brand,[1] Katrin Singer,[1] Gudrun E. Koehl,[2] Marlene Kolitzus,[1] Gabriele Schoenhammer,[1] Annette Thiel,[1] Carina Matos,[1] Christina Bruss,[1] Sebastian Klobuch,[1] Katrin Peter,[1,3] Michael Kastenberger,[1] Christian Bogdan,[4] Ulrike Schleicher,[4] Andreas Mackensen,[5] Evelyn Ullrich,[5,6] Stefan Fichtner-Feigl,[2,3] Rebecca Kesselring,[2] Matthias Mack,[3,7] Uwe Ritter,[8] Maximilian Schmid,[1,8] Christian Blank,[9] Katja Dettmer,[10] Peter J. Oefner,[10] Petra Hoffmann,[1,3] Stefan Walenta,[11] Edward K. Geissler,[2] Jacques Pouyssegur,[12,13] Andreas Villunger,[14,15] André Steven,[16] Barbara Seliger,[16] Stephan Schreml,[17] Sebastian Haferkamp,[17] Elisabeth Kohl,[17] Sigrid Karrer,[17] Mark Berneburg,[17] Wolfgang Herr,[1] Wolfgang Mueller-Klieser,[11] Kathrin Renner,[1,3] and Marina Kreutz[1,3,18,*]

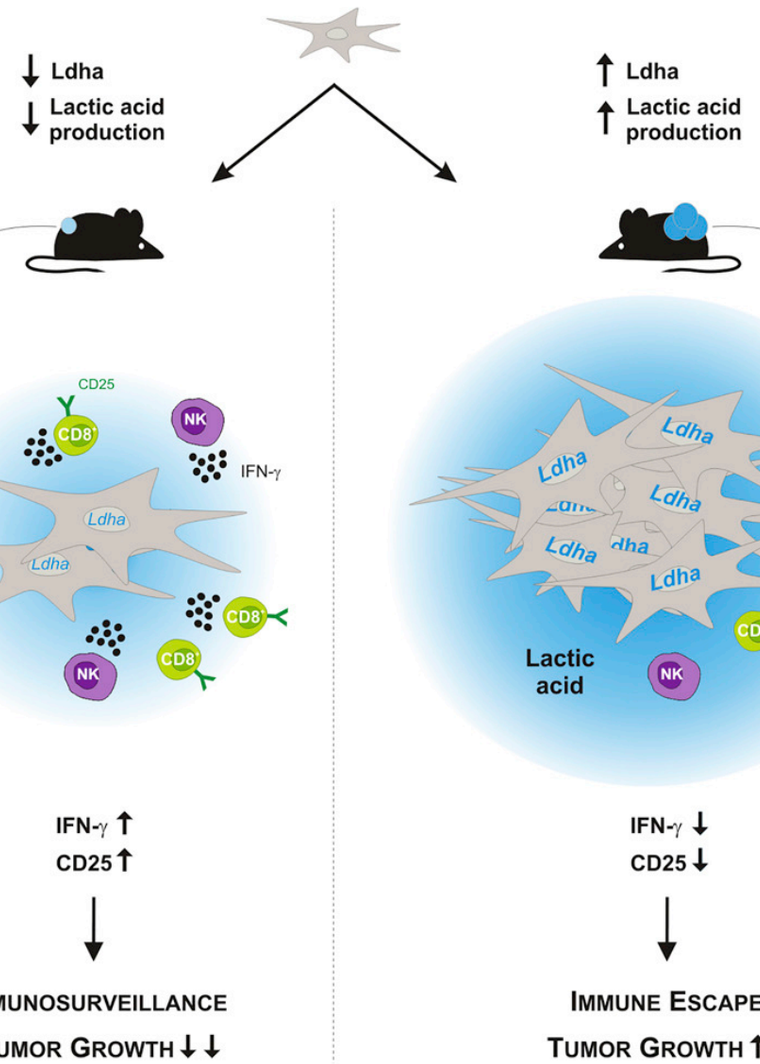






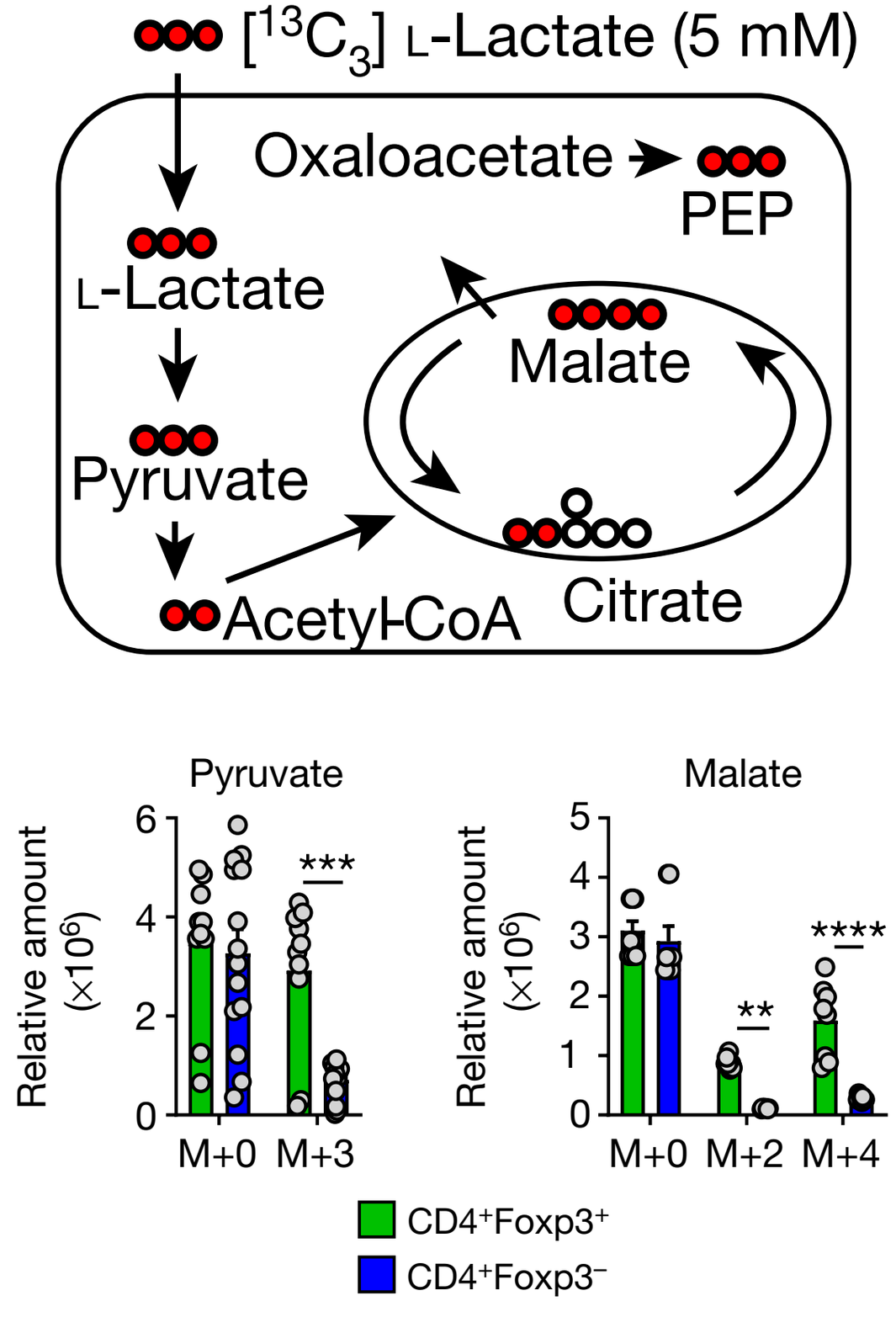




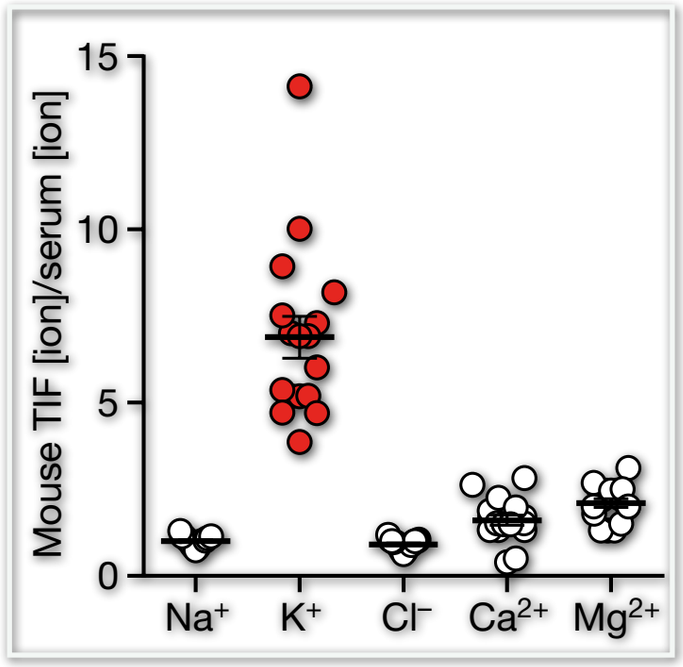


*Brand et al, **Cell Metab**, 2016*

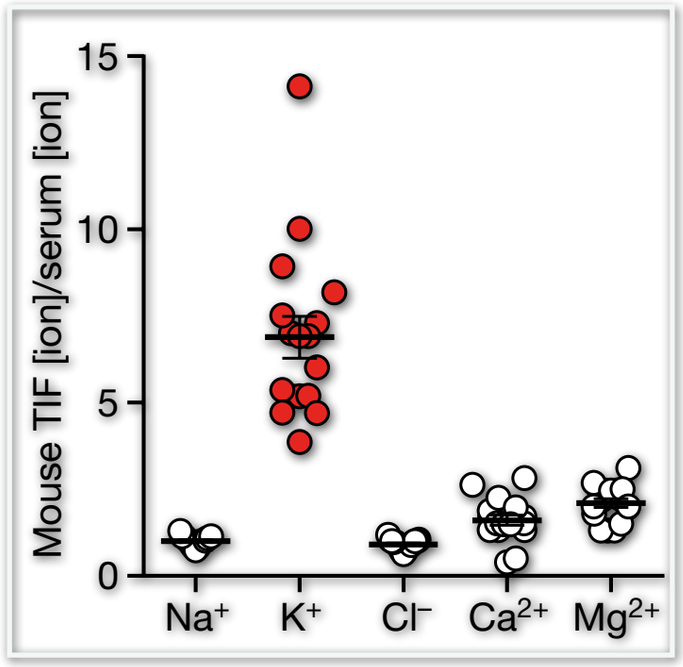
Lactate is actively metabolized by immune cells (T lympho)

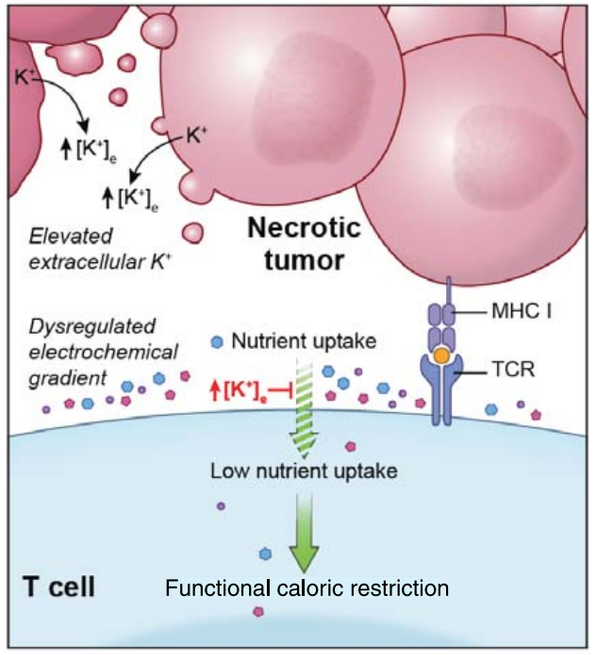


Angelin et al, ***Cell Metab****, 2017*
Watson et al, ***Nature****, 2020*
Feng et al, ***Nat Comm****, 2022*

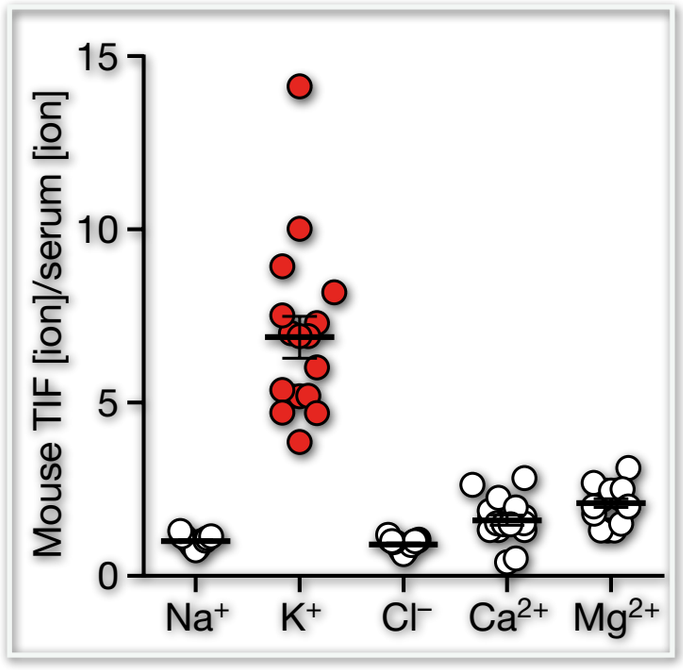


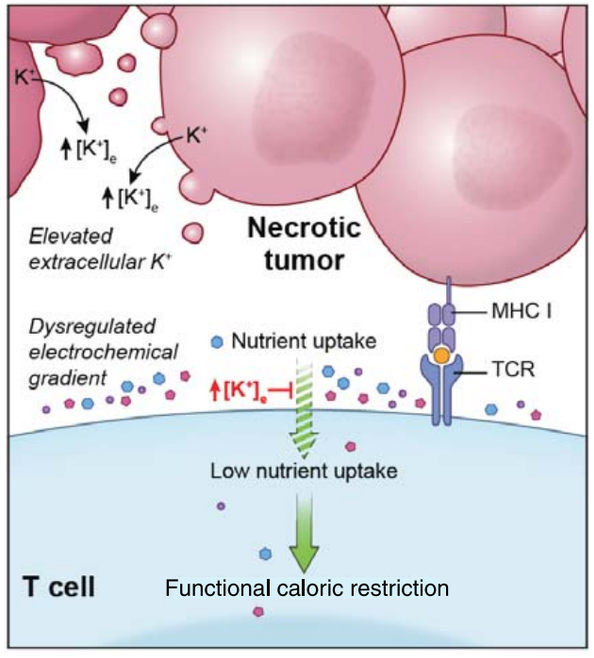
Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*

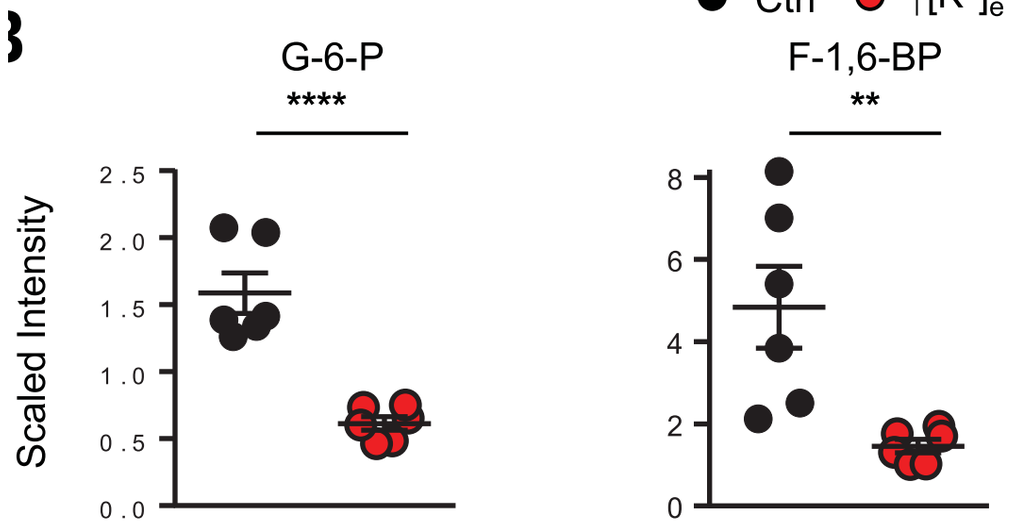




Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*







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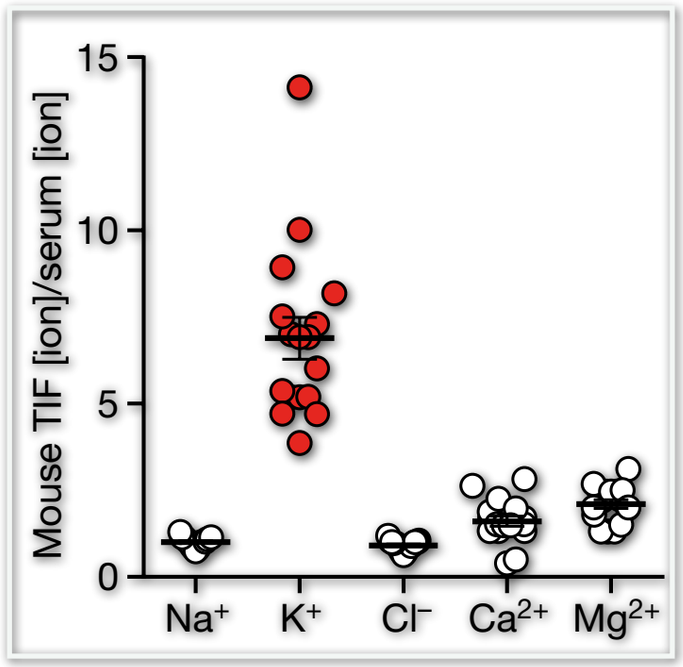

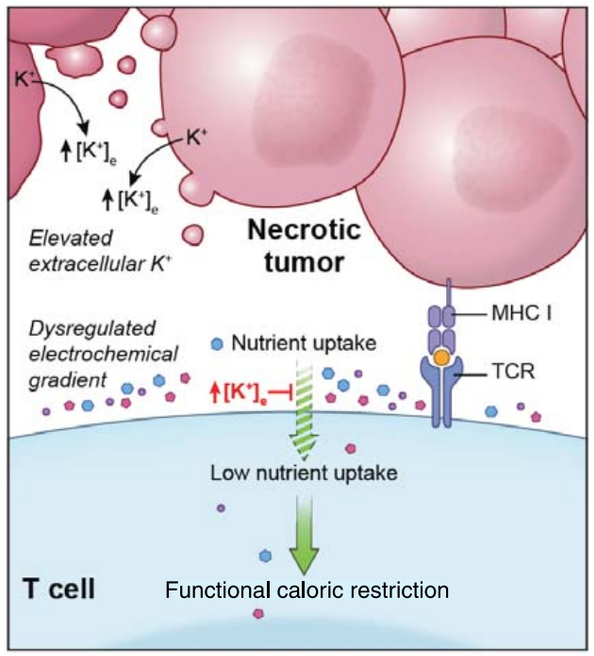

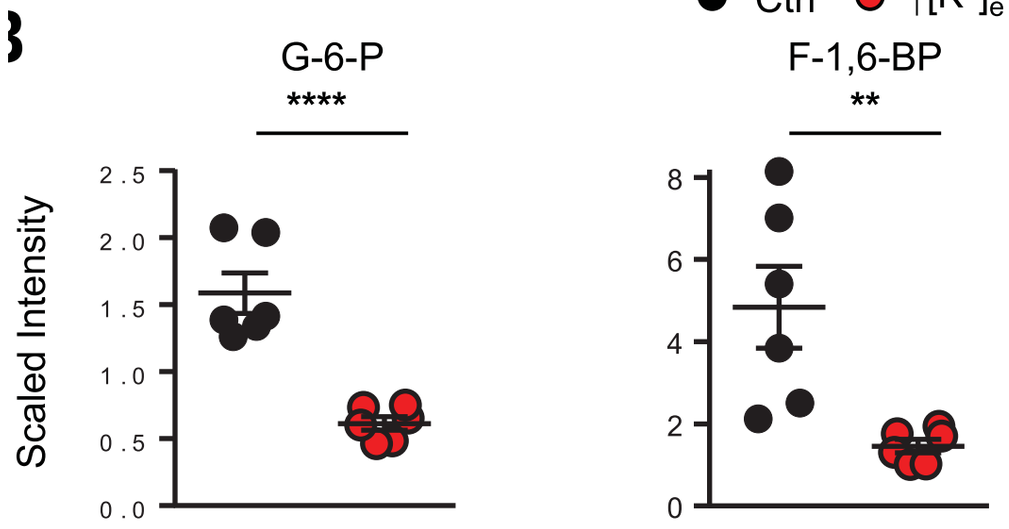

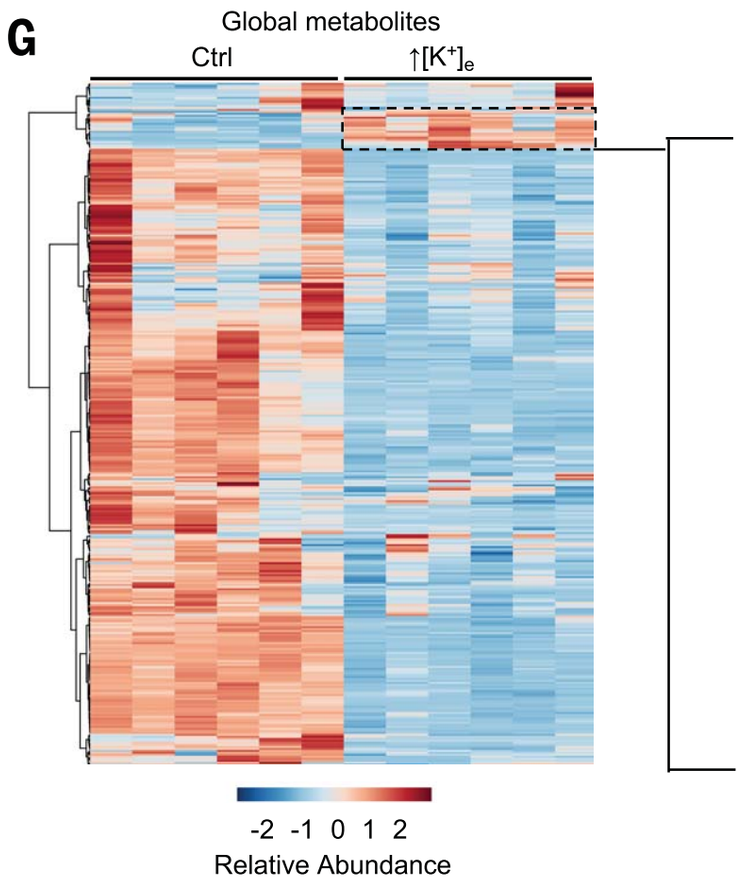

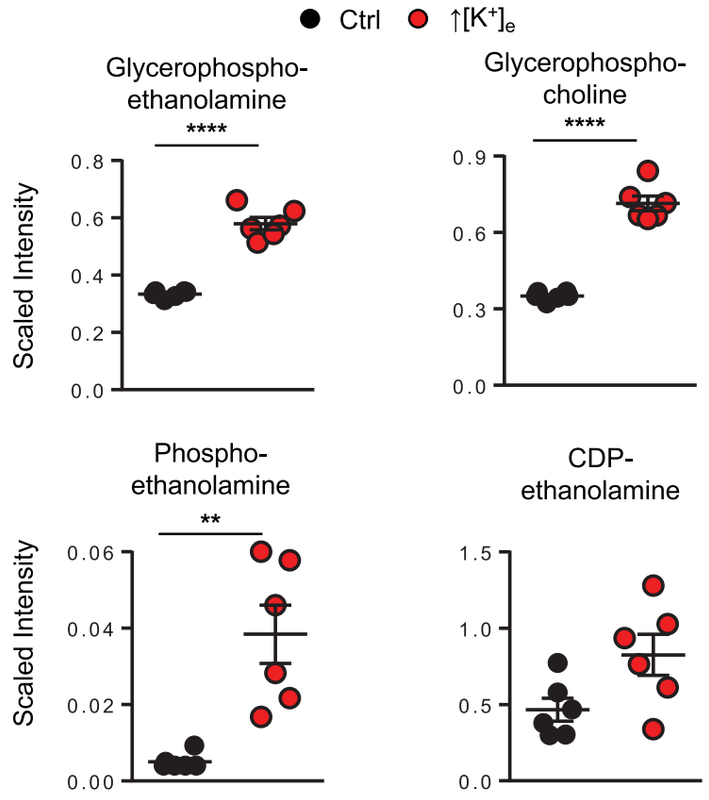

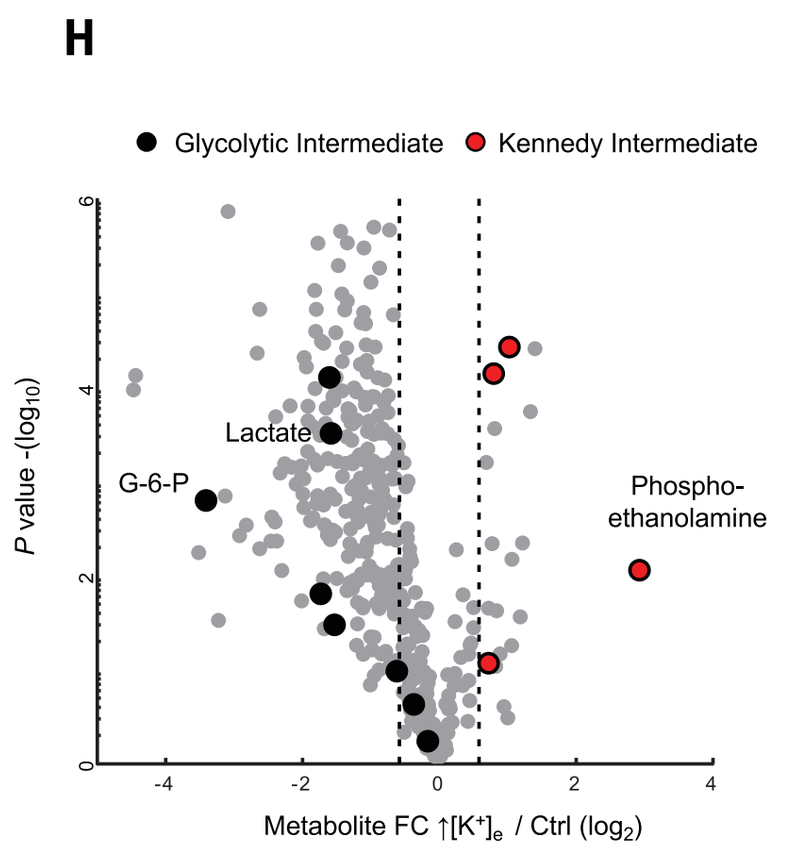

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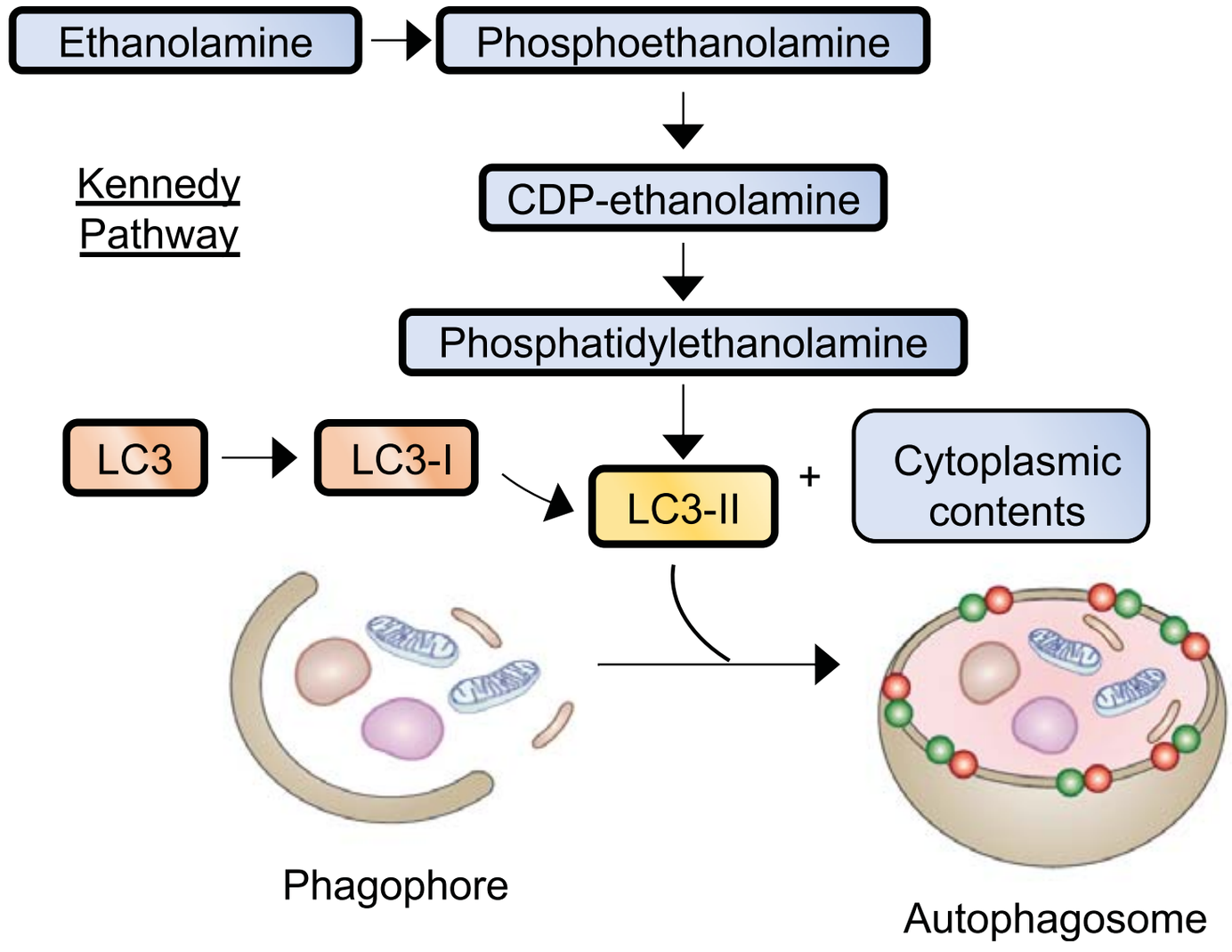

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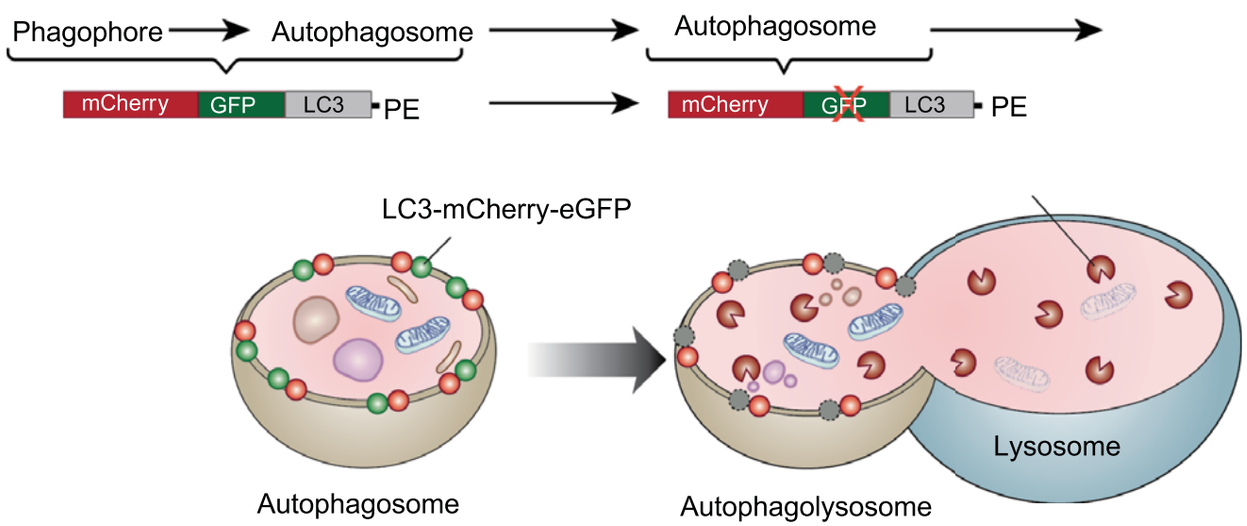
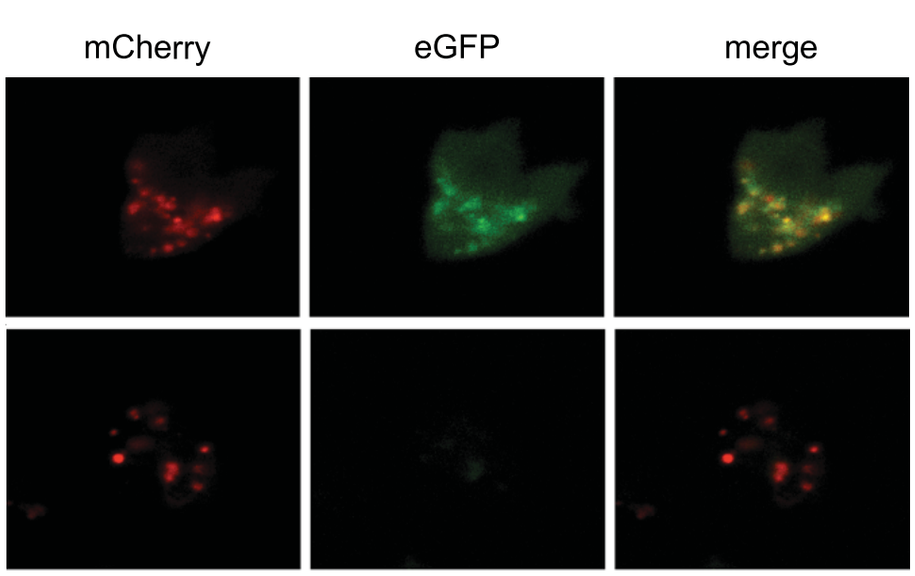
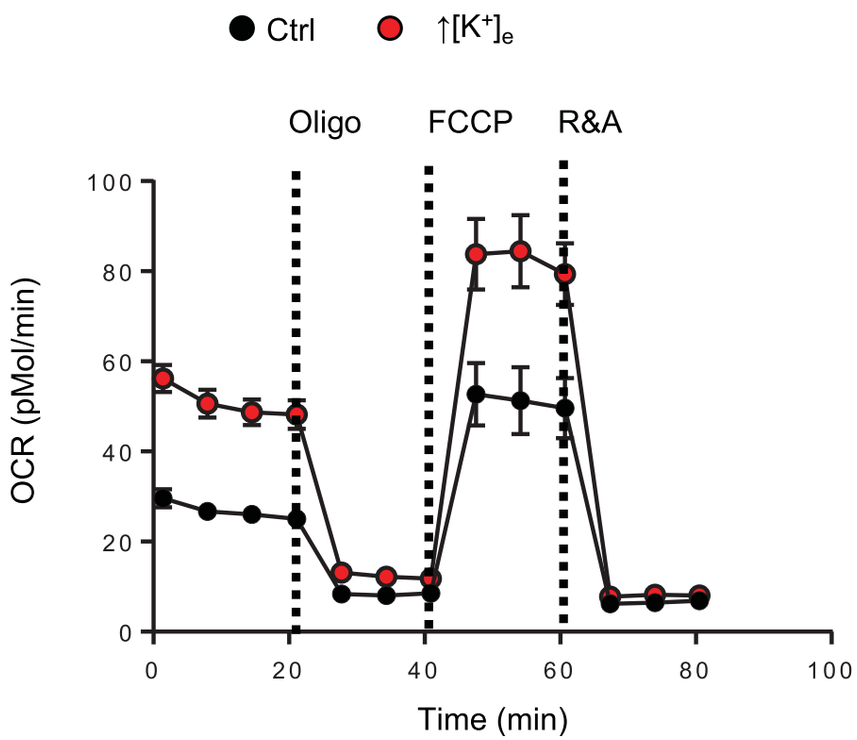
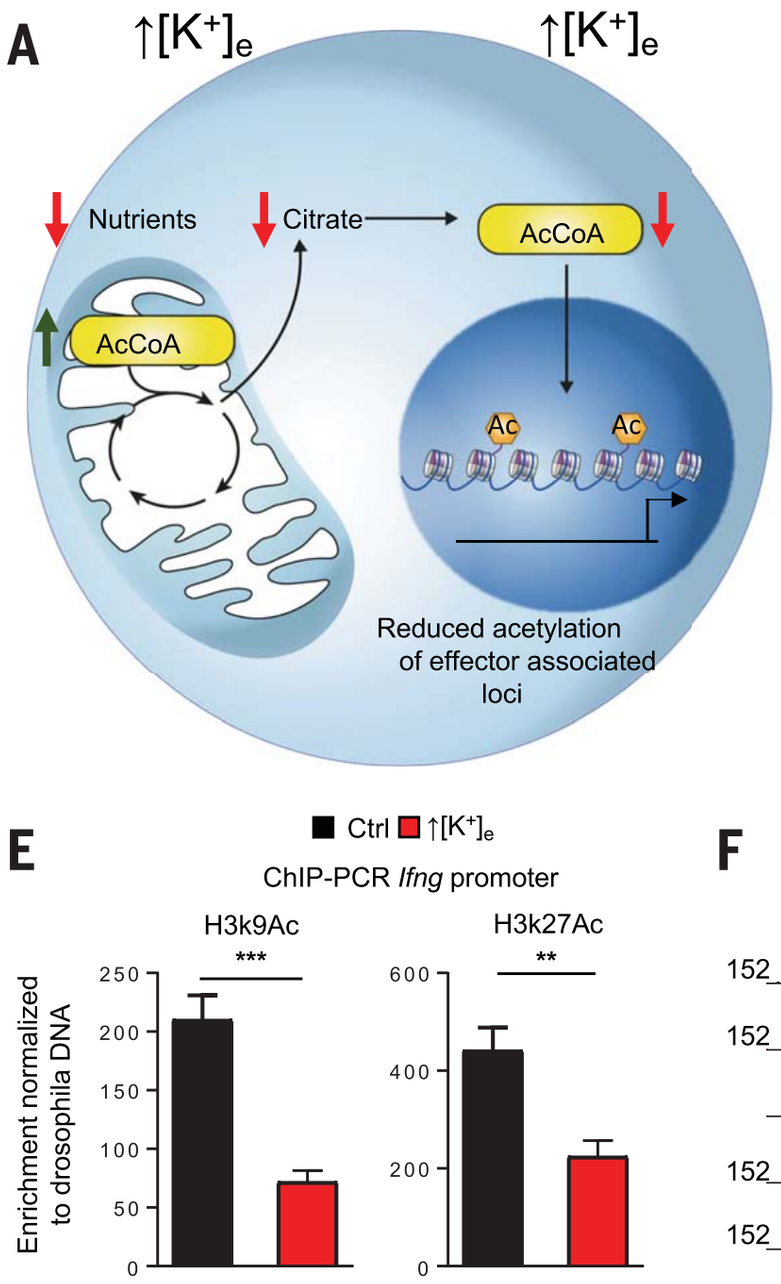


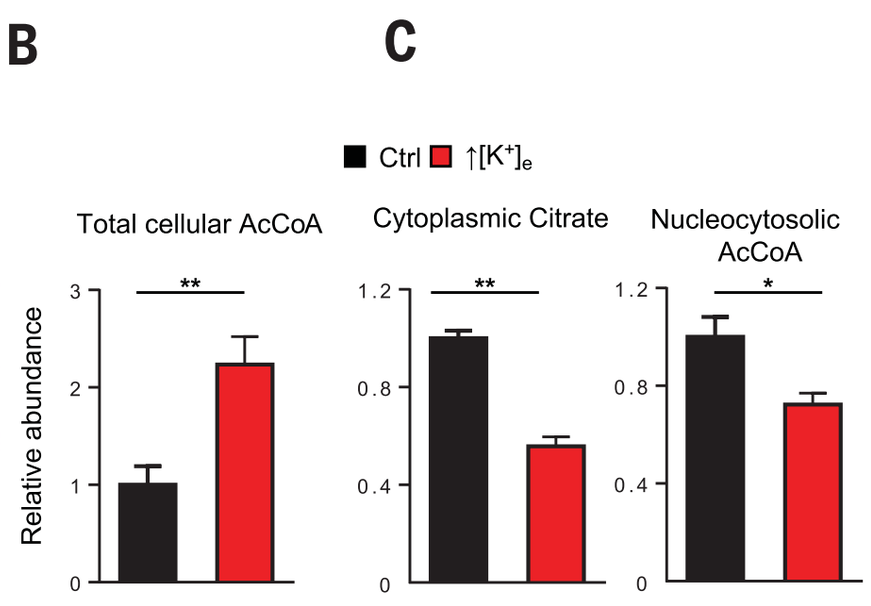


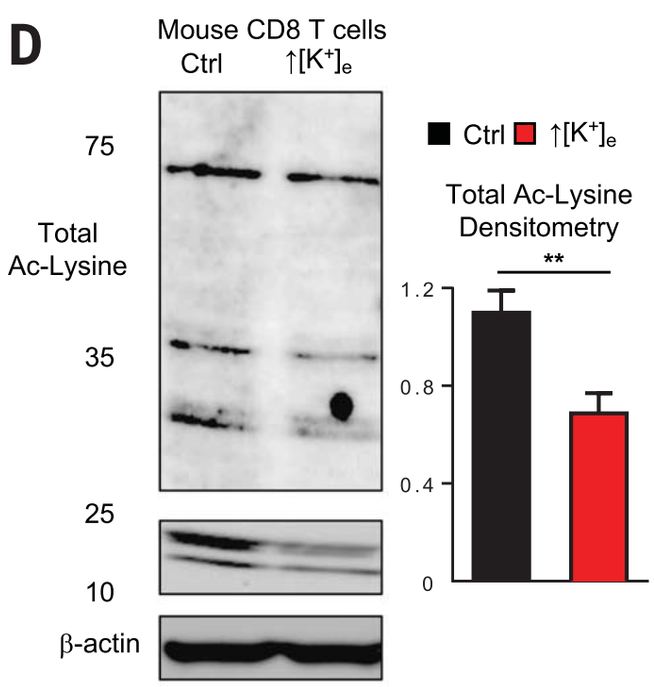


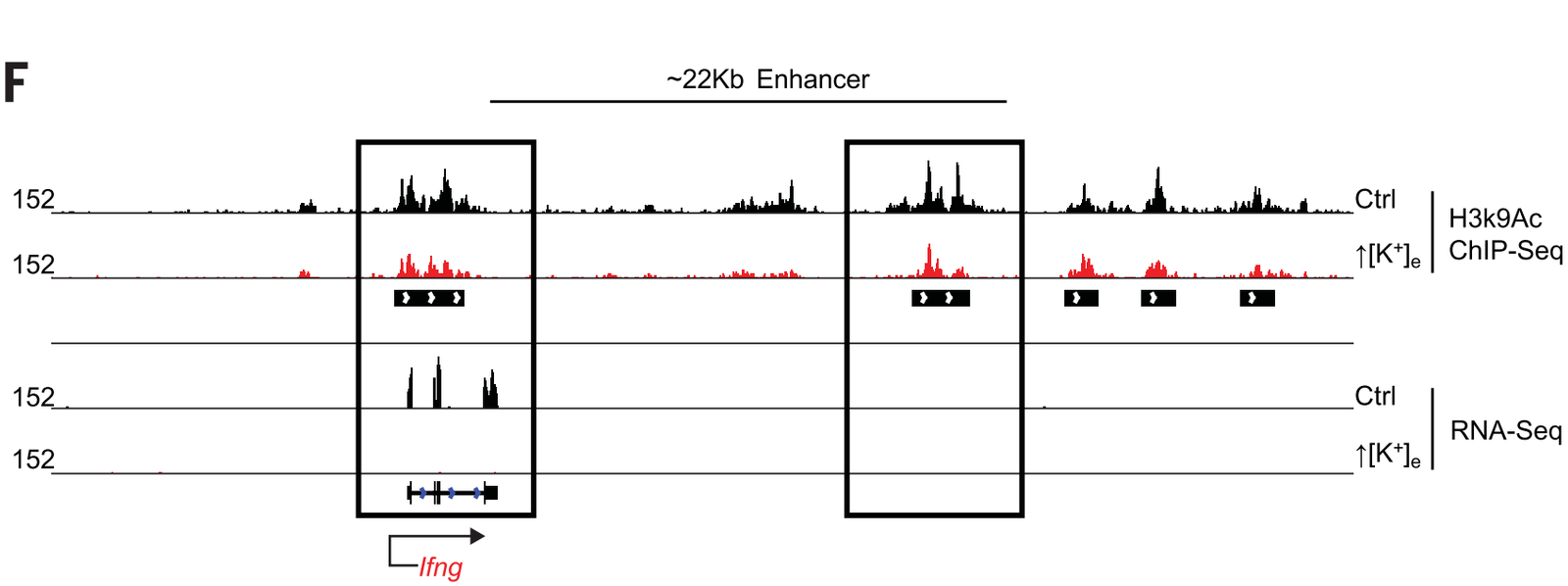
T cells exposed to increased $[K^+]_e$ recycle nutrients via autophagy during functional caloric restriction.

Eil et al, ***Nature****, 2016*
Vodnala et al, ***Science****, 2019*









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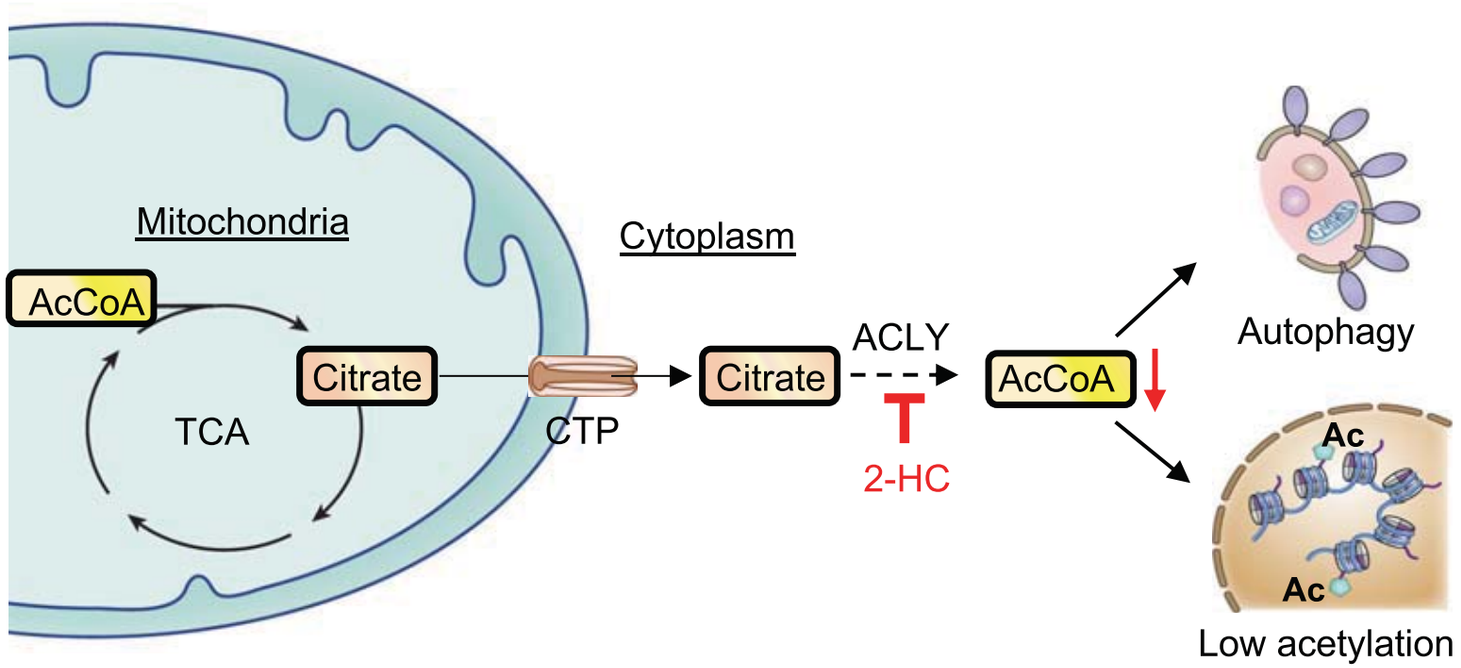

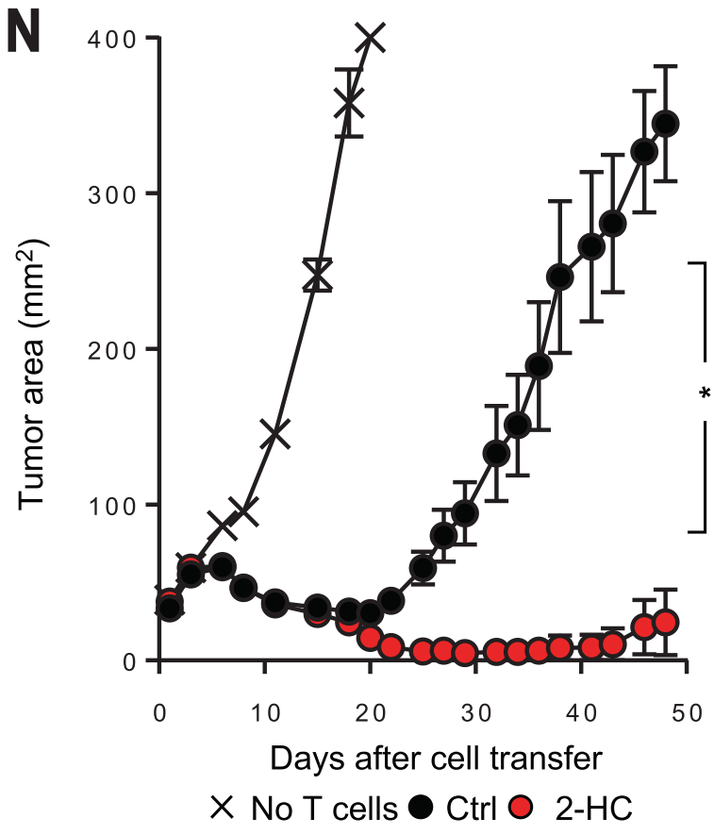

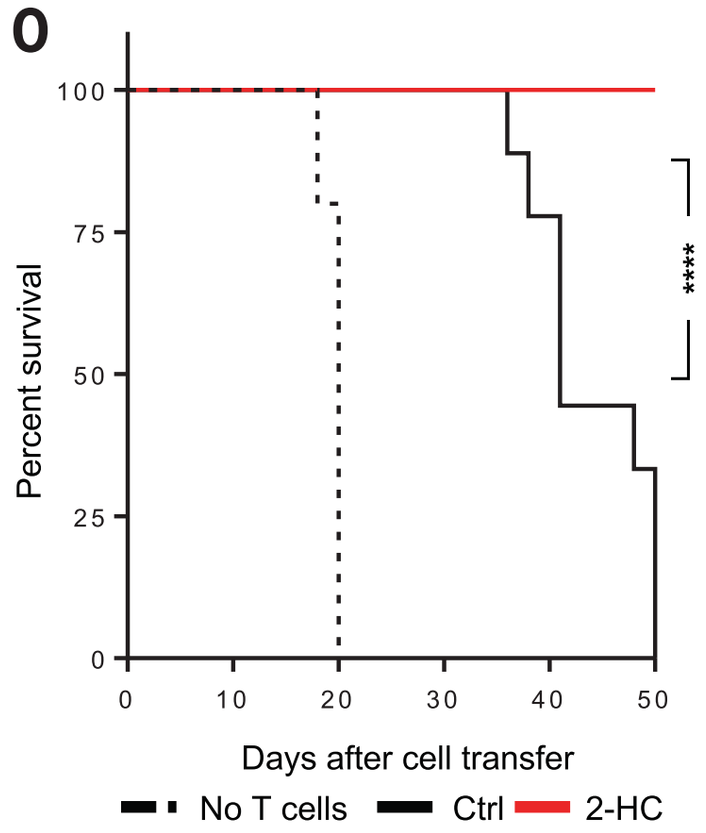

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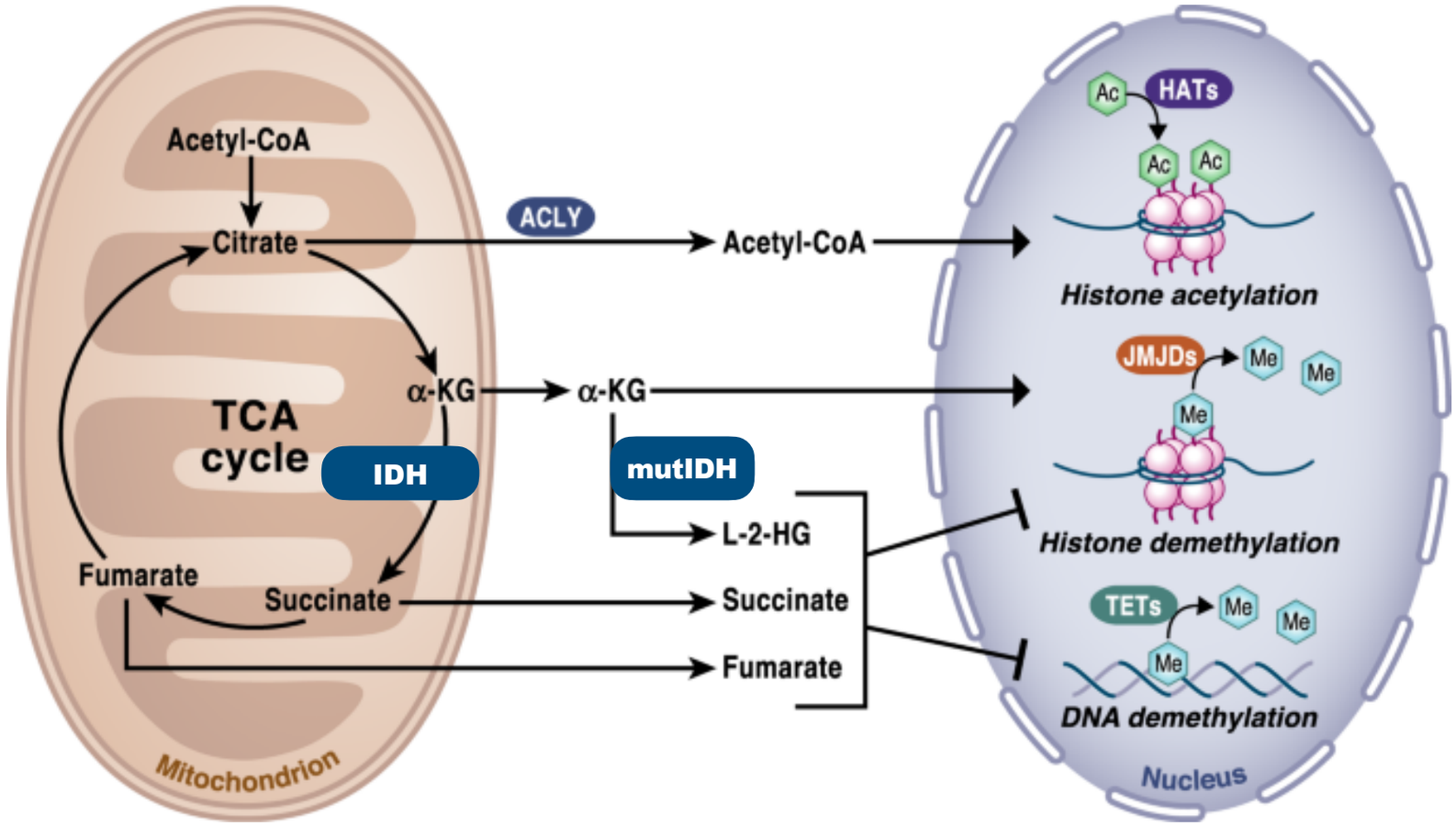
Vodnala et al, ***Science****, 2019*

6

Metabolic reprogramming cooperates with signaling

Mitochondria-derived metabolites impact the epigenome



Reyes & Chandel, ***Nat Comm****, 2020*

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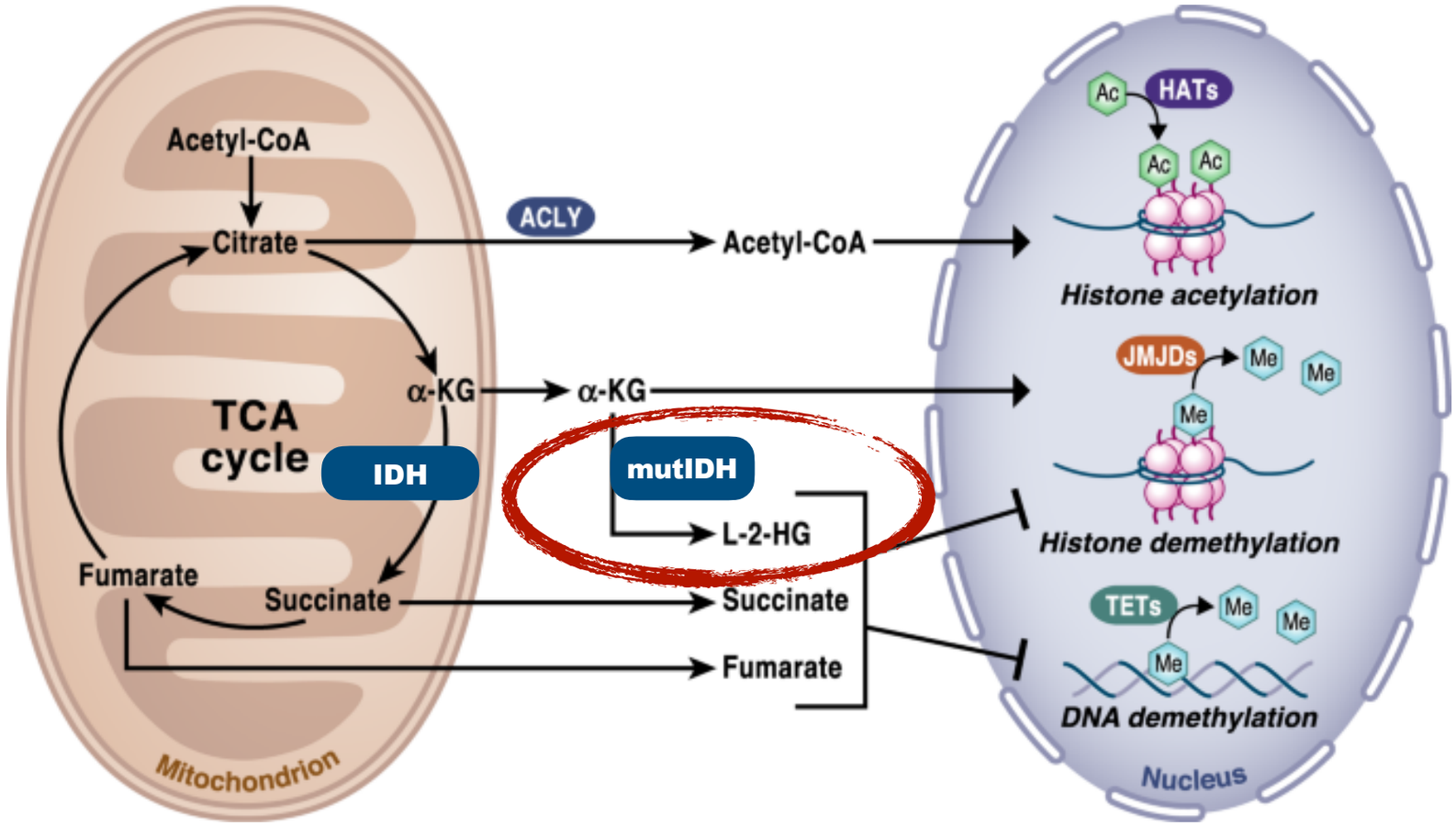

Reyes & Chandel, ***Nat Comm****, 2020*

α-KG is a mitochondrial and cytosolic cofactor

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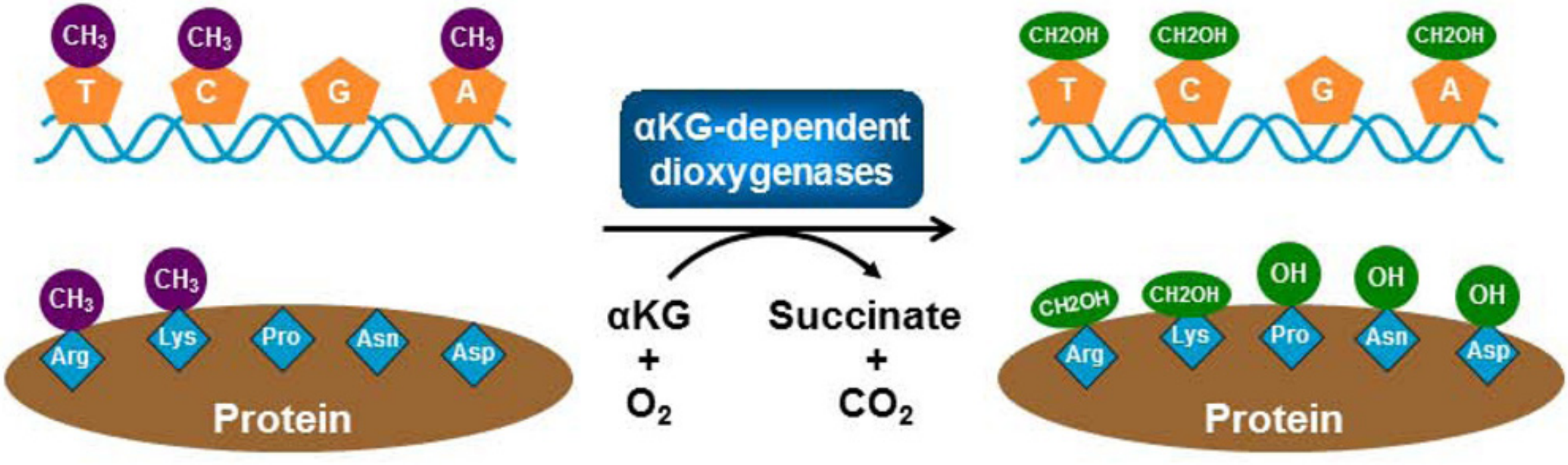
TCA cycle intermediates are sensed through alpha-ketoglutarate (aKG)-dependent dioxygenases, a versatile group of iron-containing enzymes that includes key players in epigenetic regulation, oxygen sensing, lipid metabolism, and other critical processes.

These enzymes couple the decarboxylation of aKG with the oxidation of the substrate, and in many cases the predicted K_M of those enzymes to aKG overlaps with its physiological levels, suggesting that their activity may dynamically respond to intracellular aKG levels.



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Particularly useful when metabolite/co-factor synthesis and availability is highly compartmentalized

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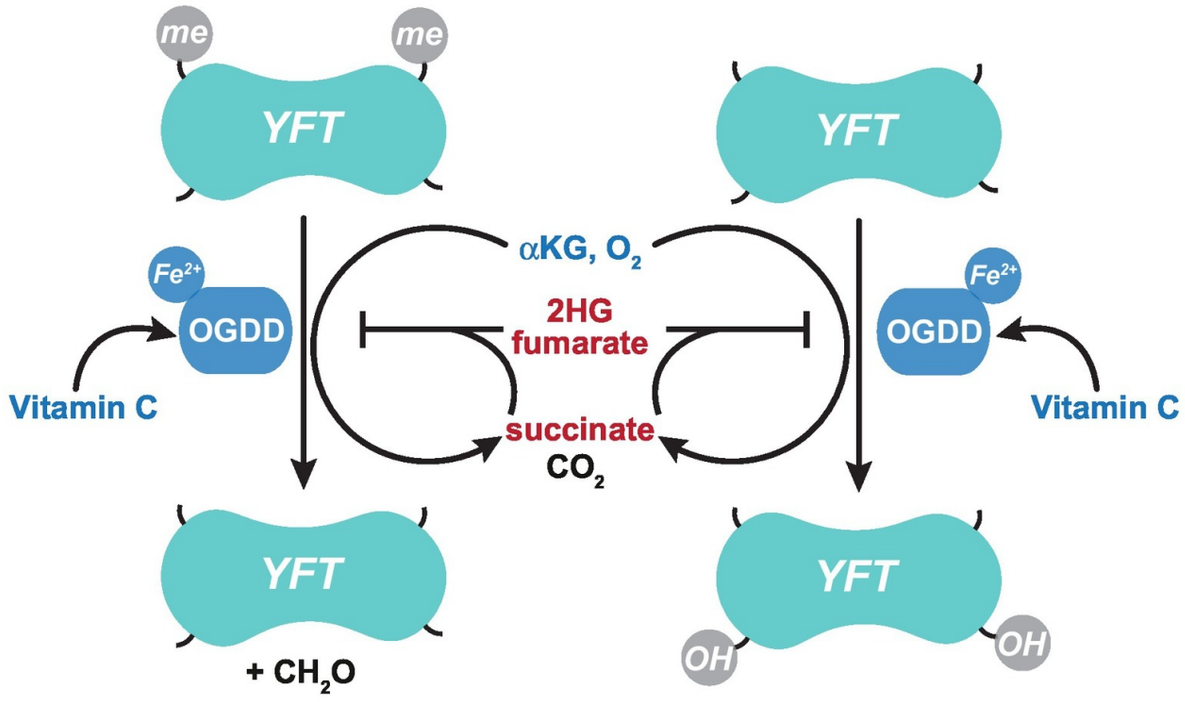
(B)



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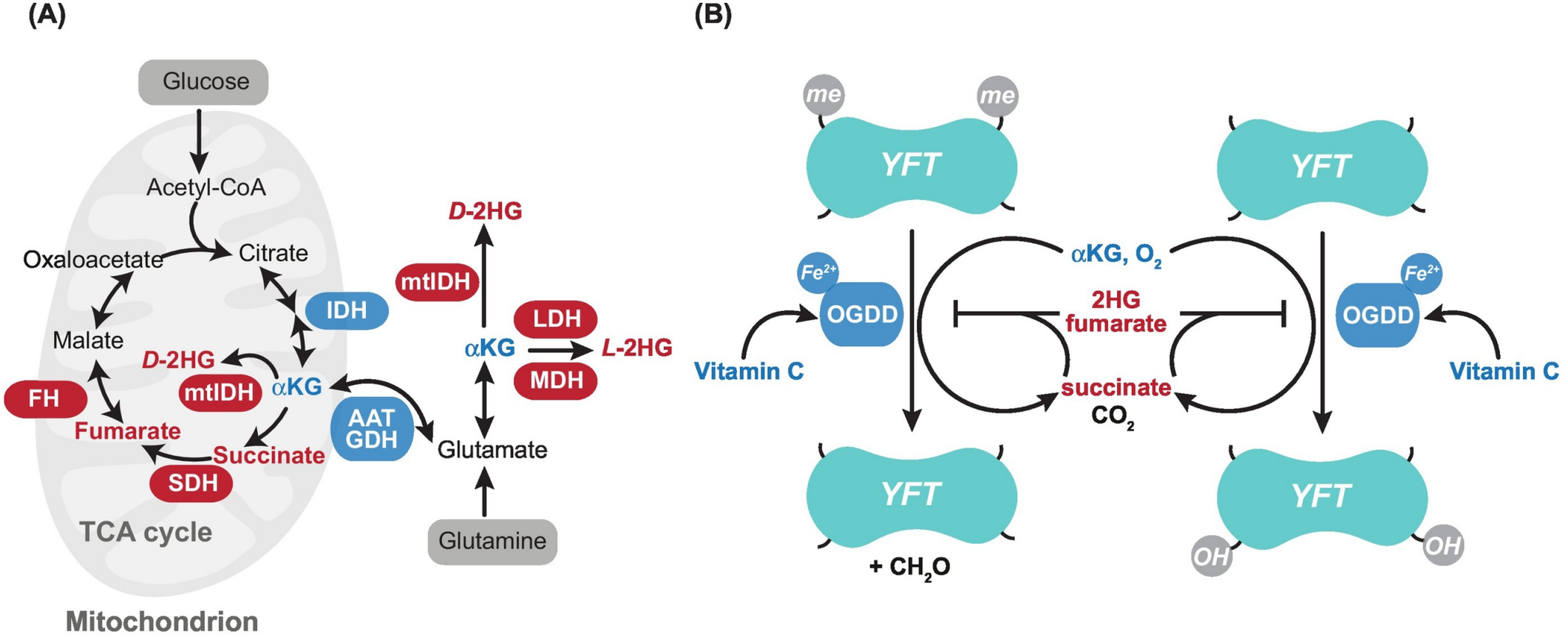
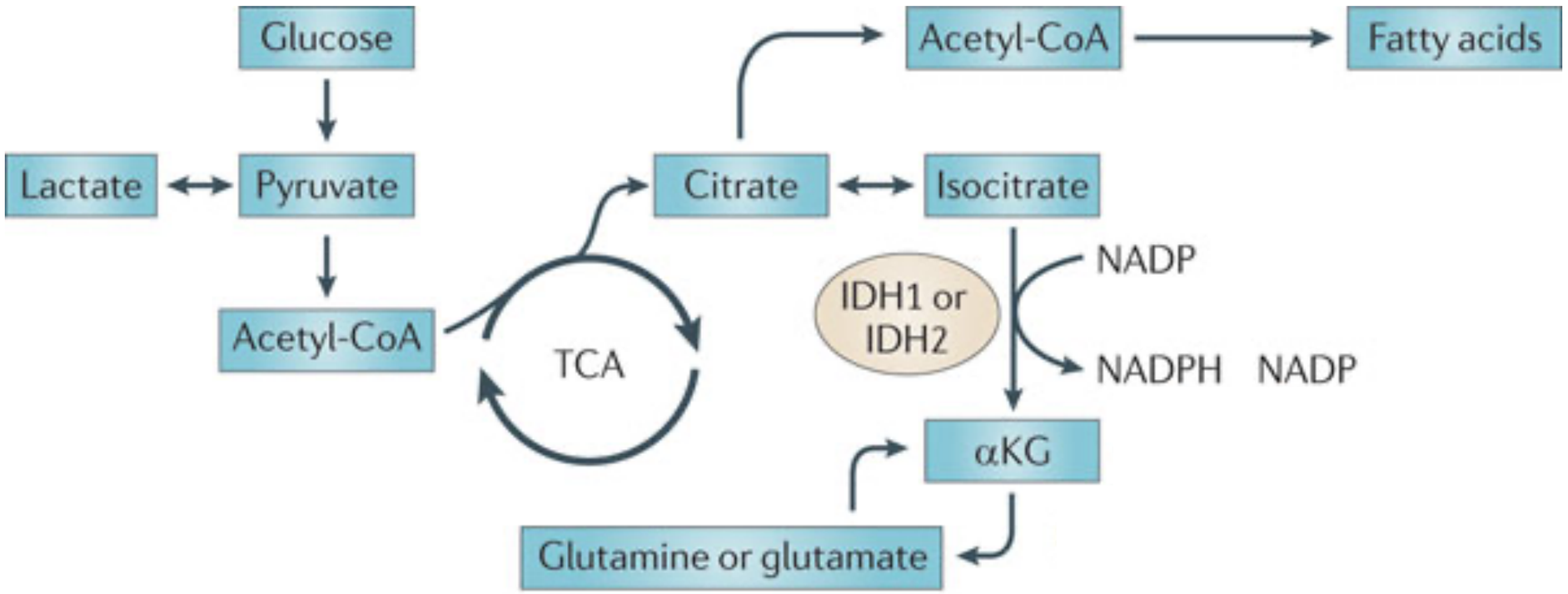
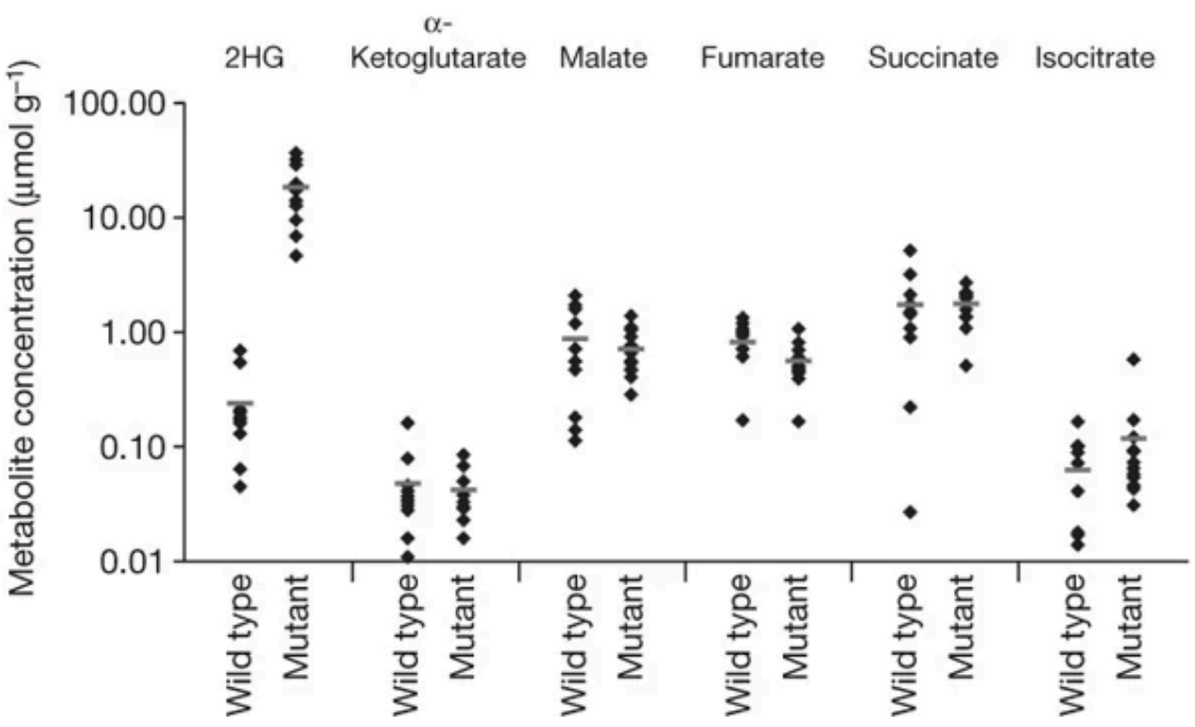


α-KG is generated by IDH enzymes





Cairns et al, ***Nat Rev Cancer****, 2011*

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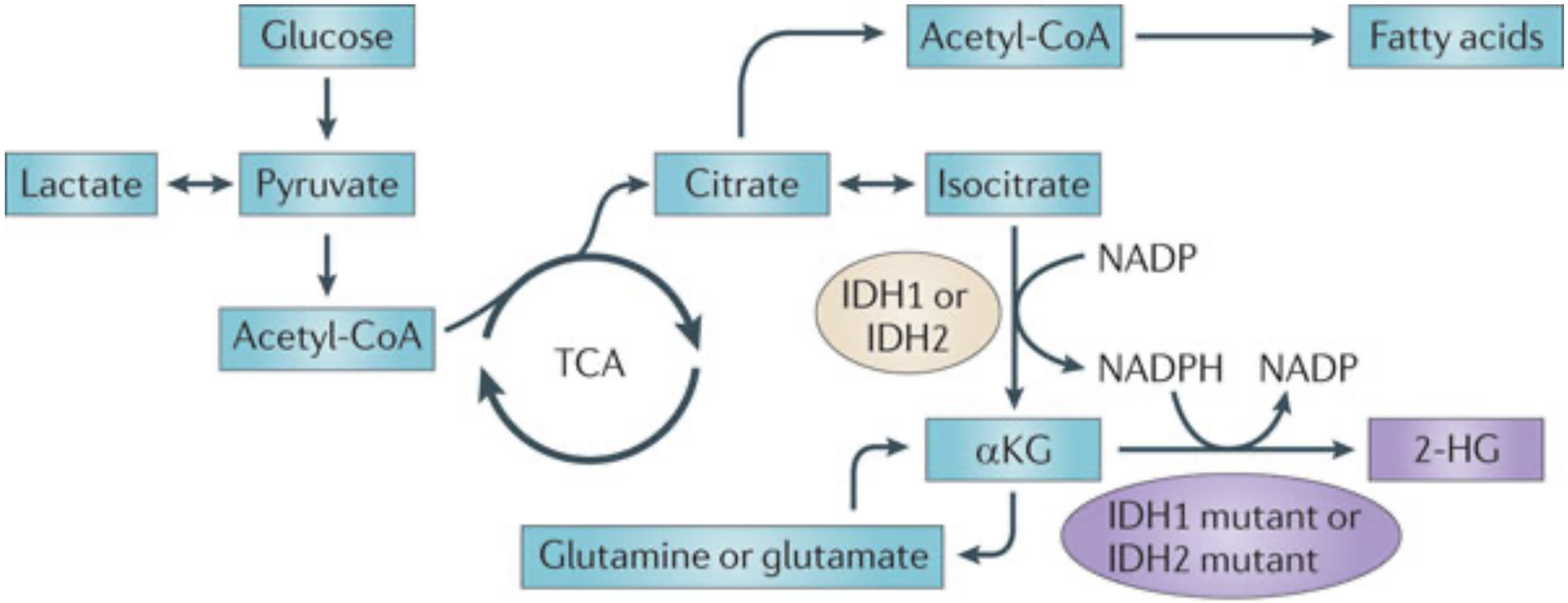
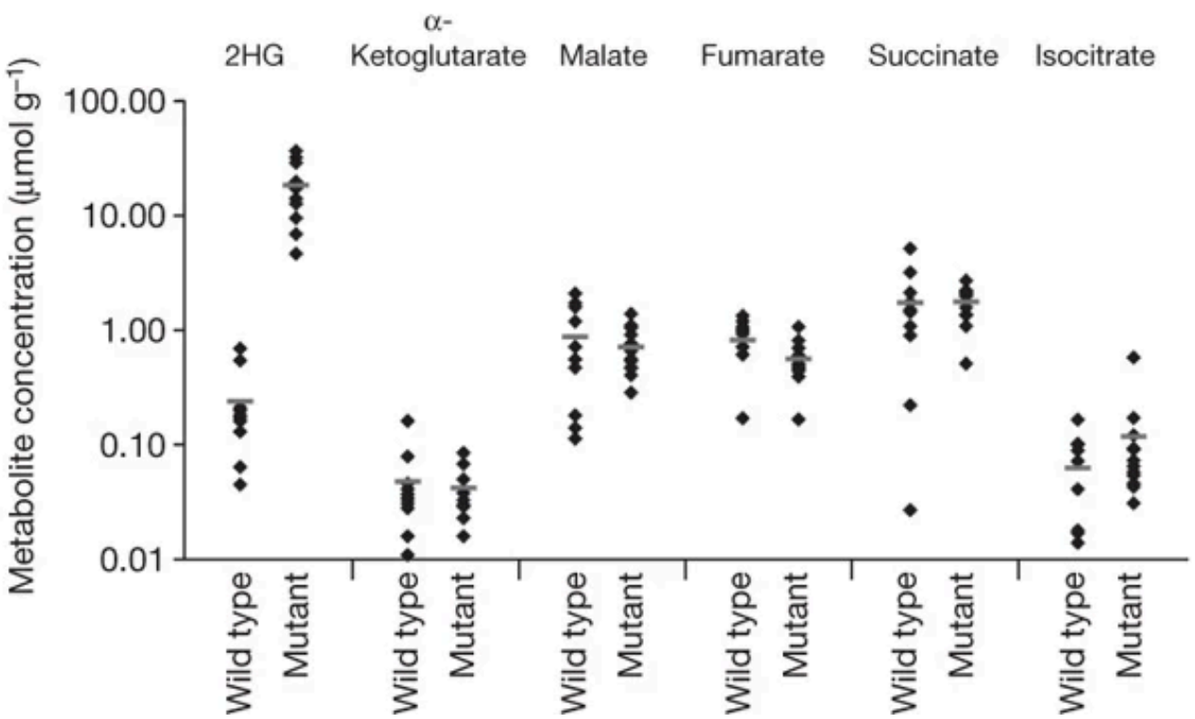
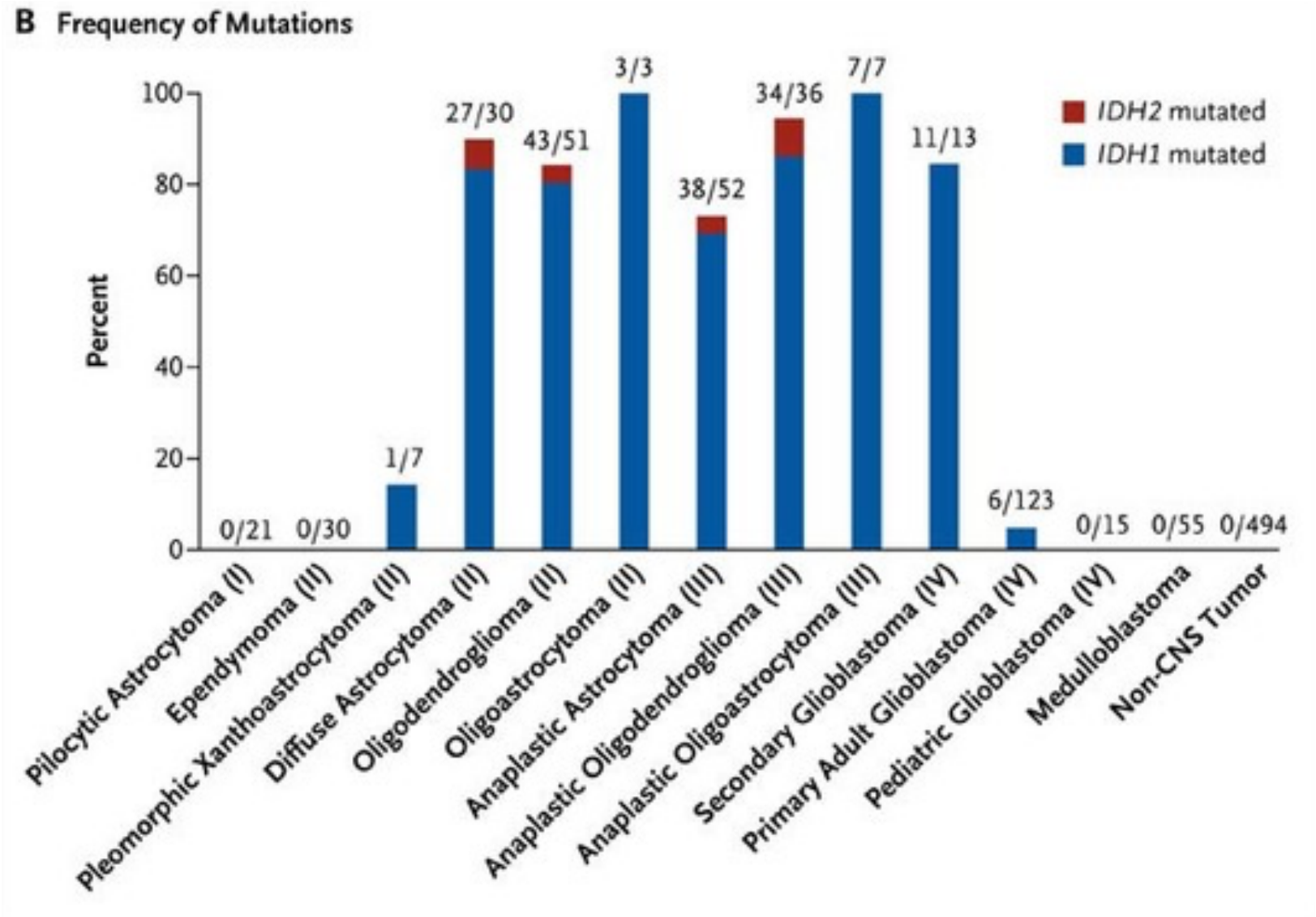


Nature Reviews | Cancer

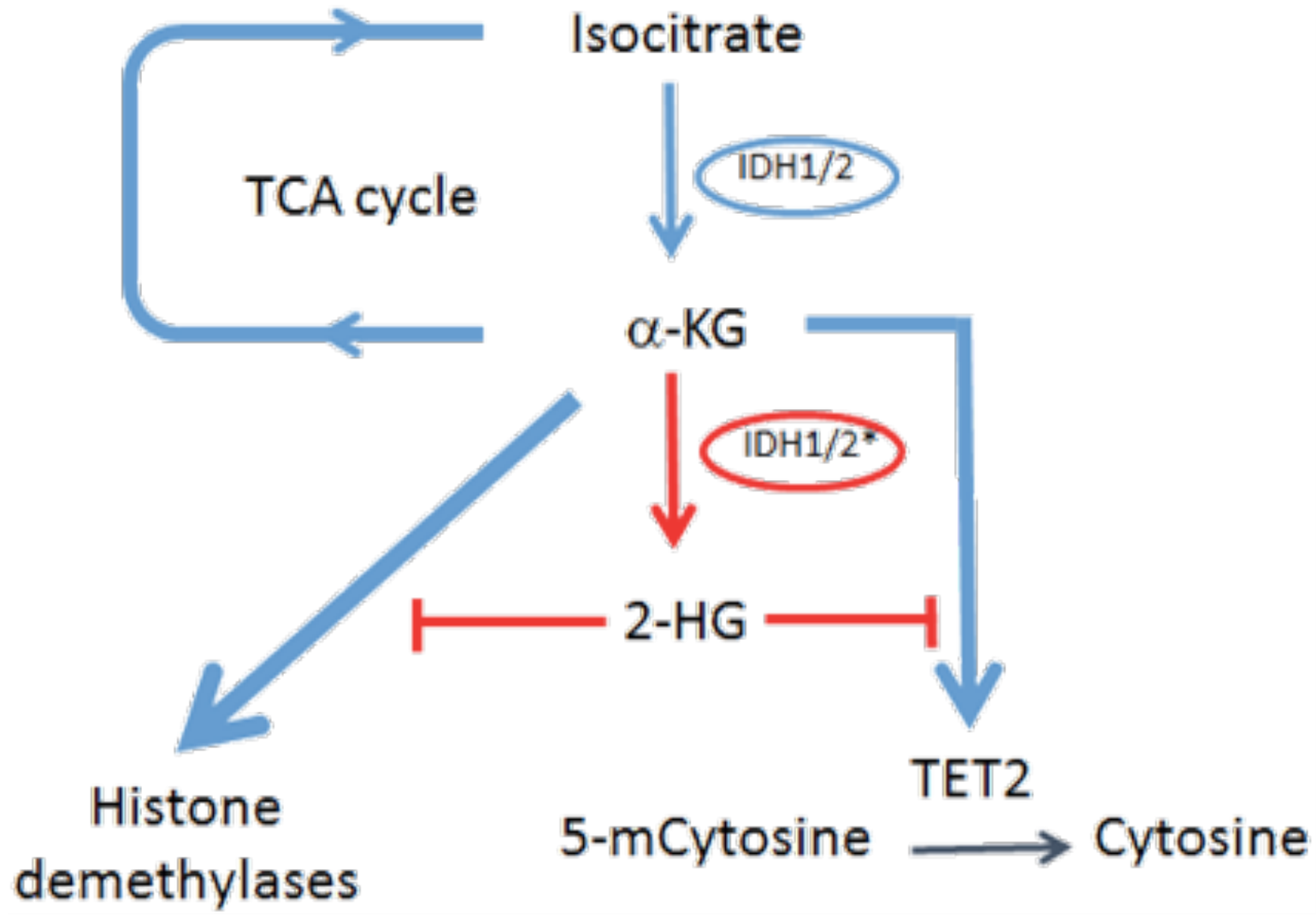


Cairns et al, ***Nat Rev Cancer****, 2011*

IDH1/2 are frequently mutated in gliomas



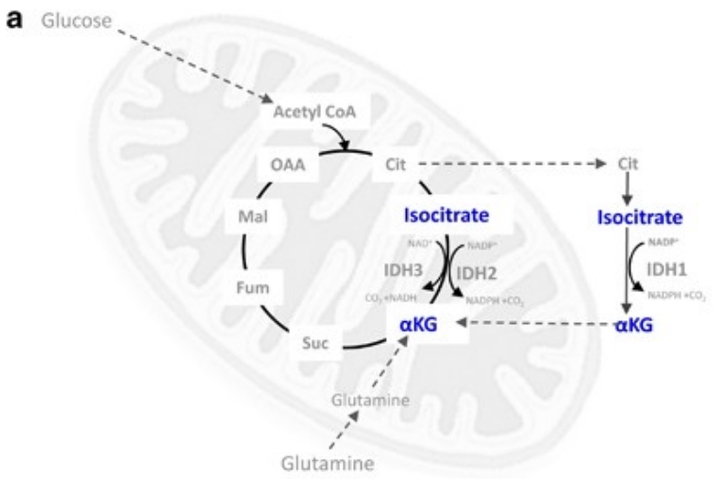
Mutant IDH are neomorphic

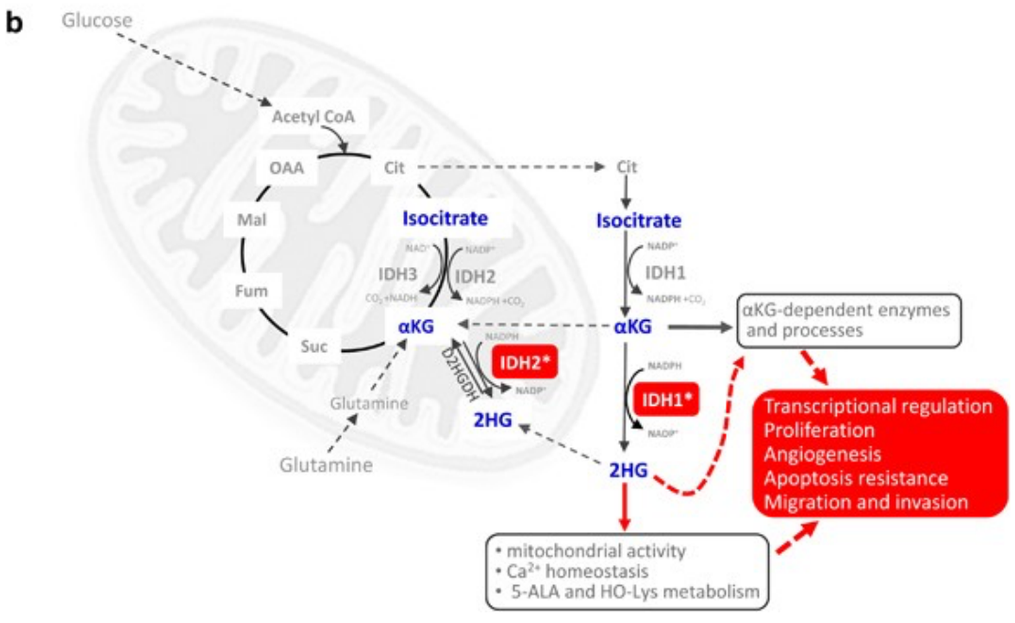


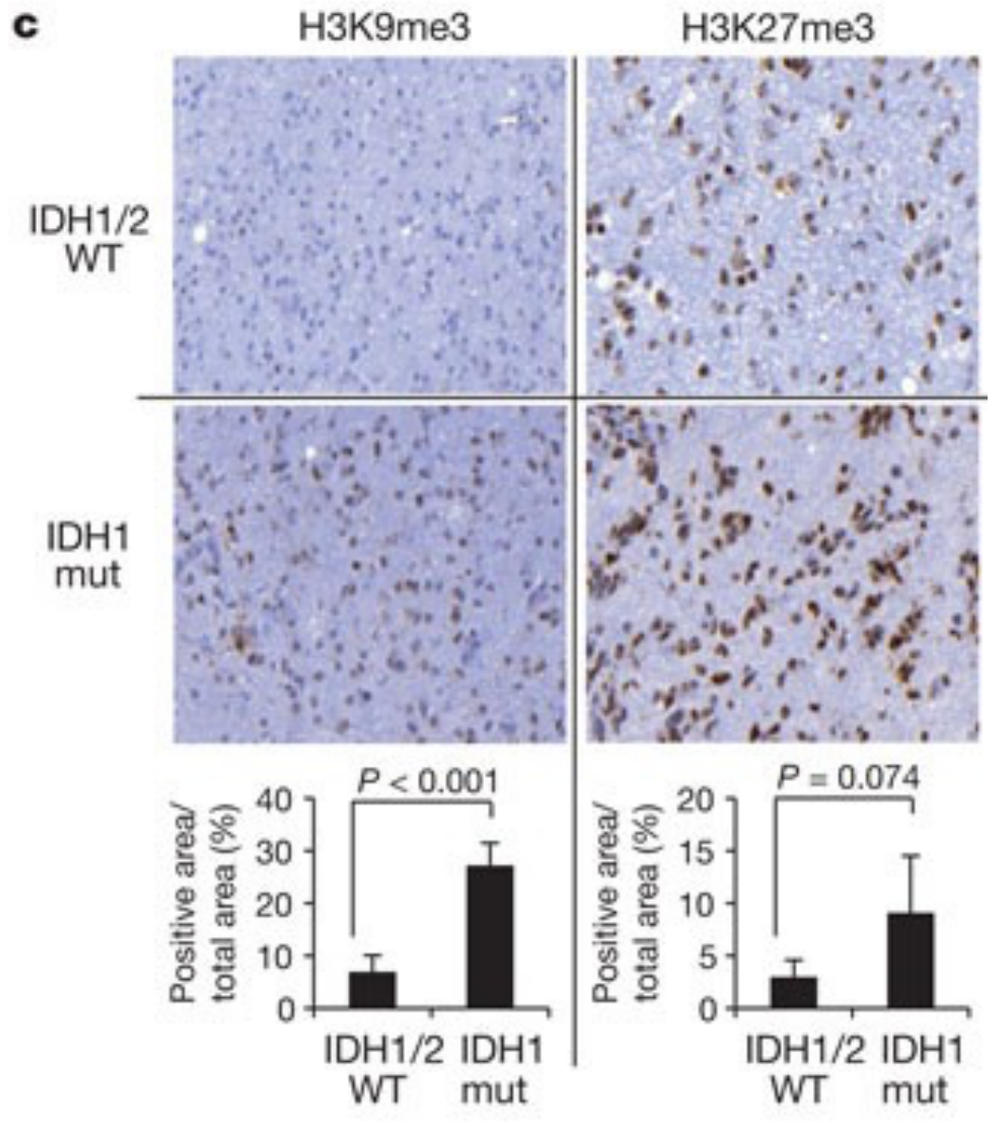
Mutant IDH enzymes generate a new metabolite (“oncometabolite”) that works as a competitive inhibitor for physiological a-KG

2-HG is an ONCOMETABOLITE

It drives gliomagenesis through rewiring of both the epigenome and cellular metabolism

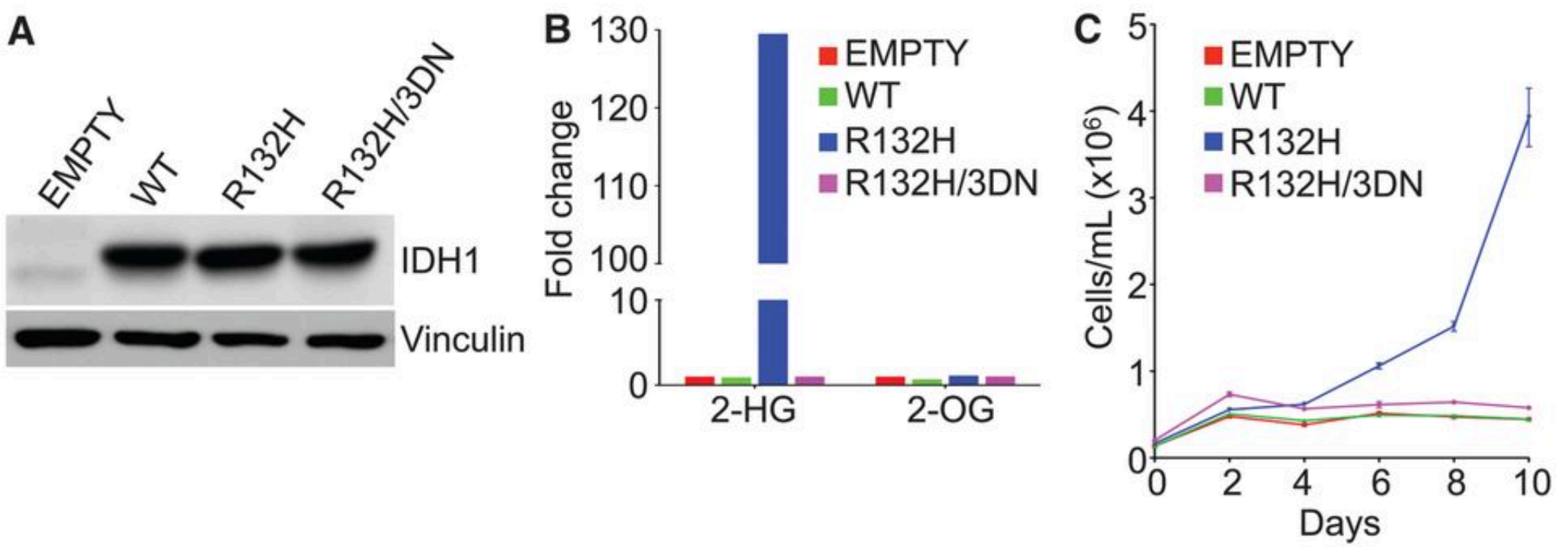






Lu et al, ***Nature****, 2012*

2-HG induces reversible leukemogenesis



Losman et al, ***Science****, 2013*

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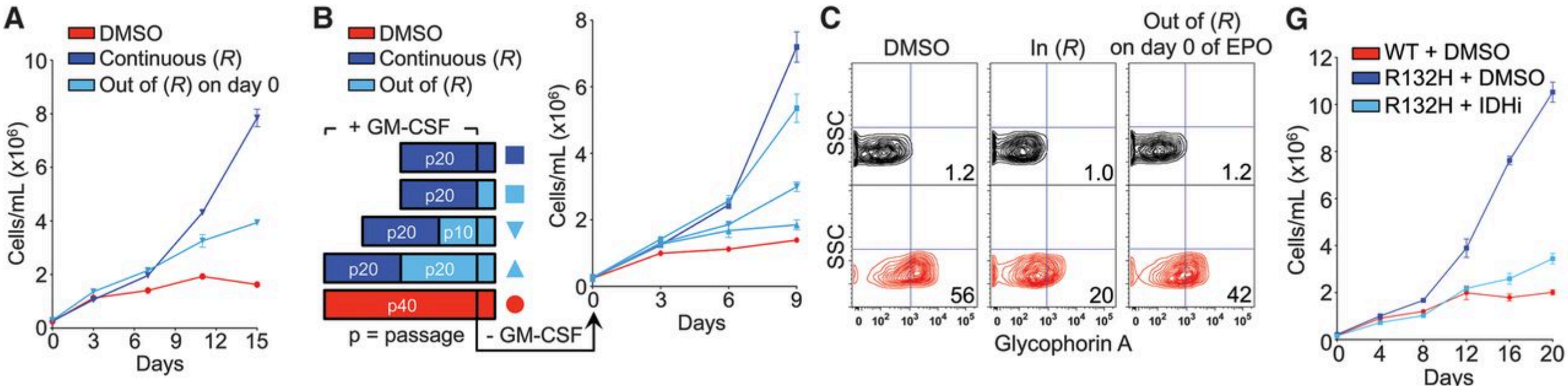
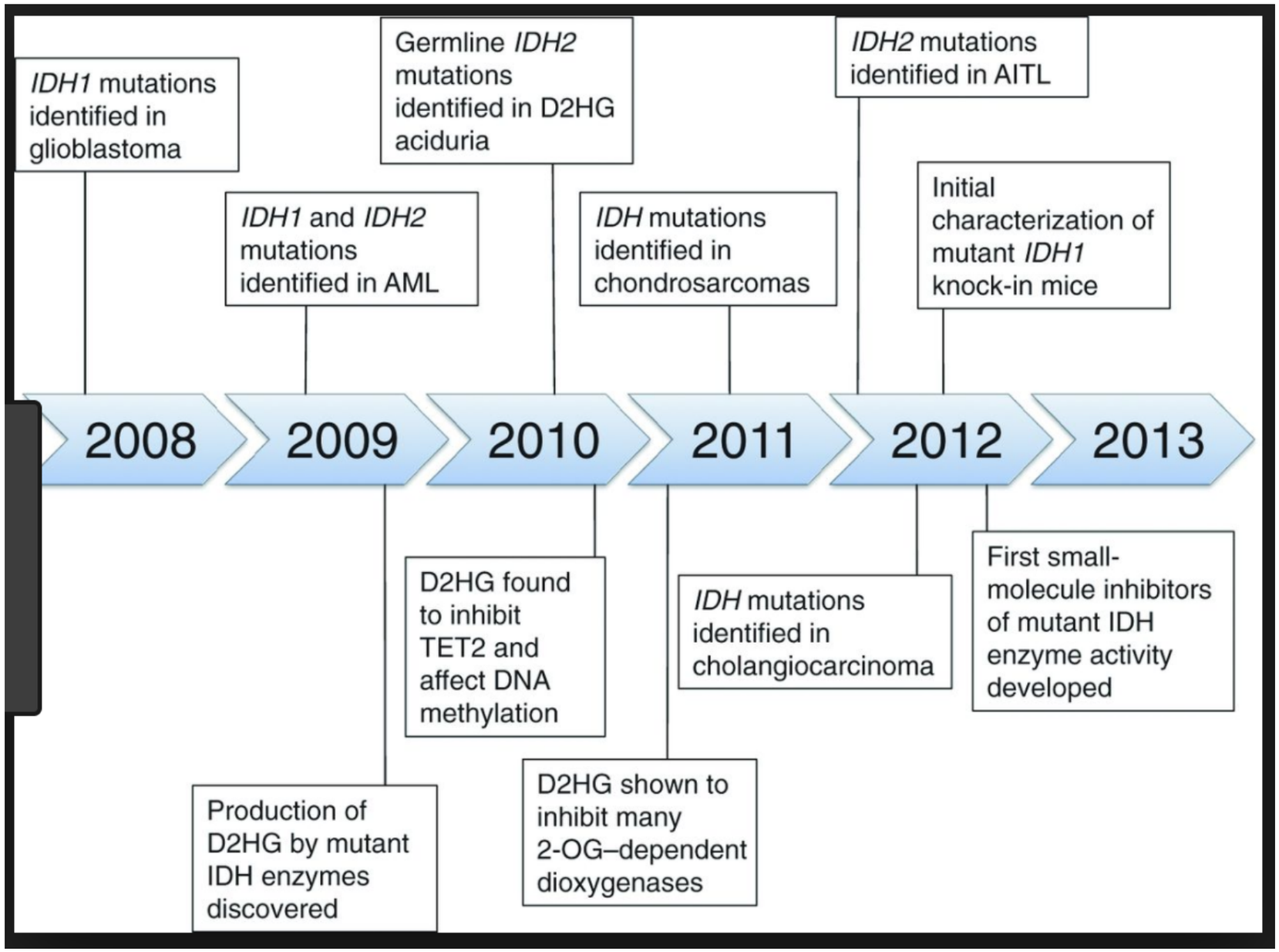
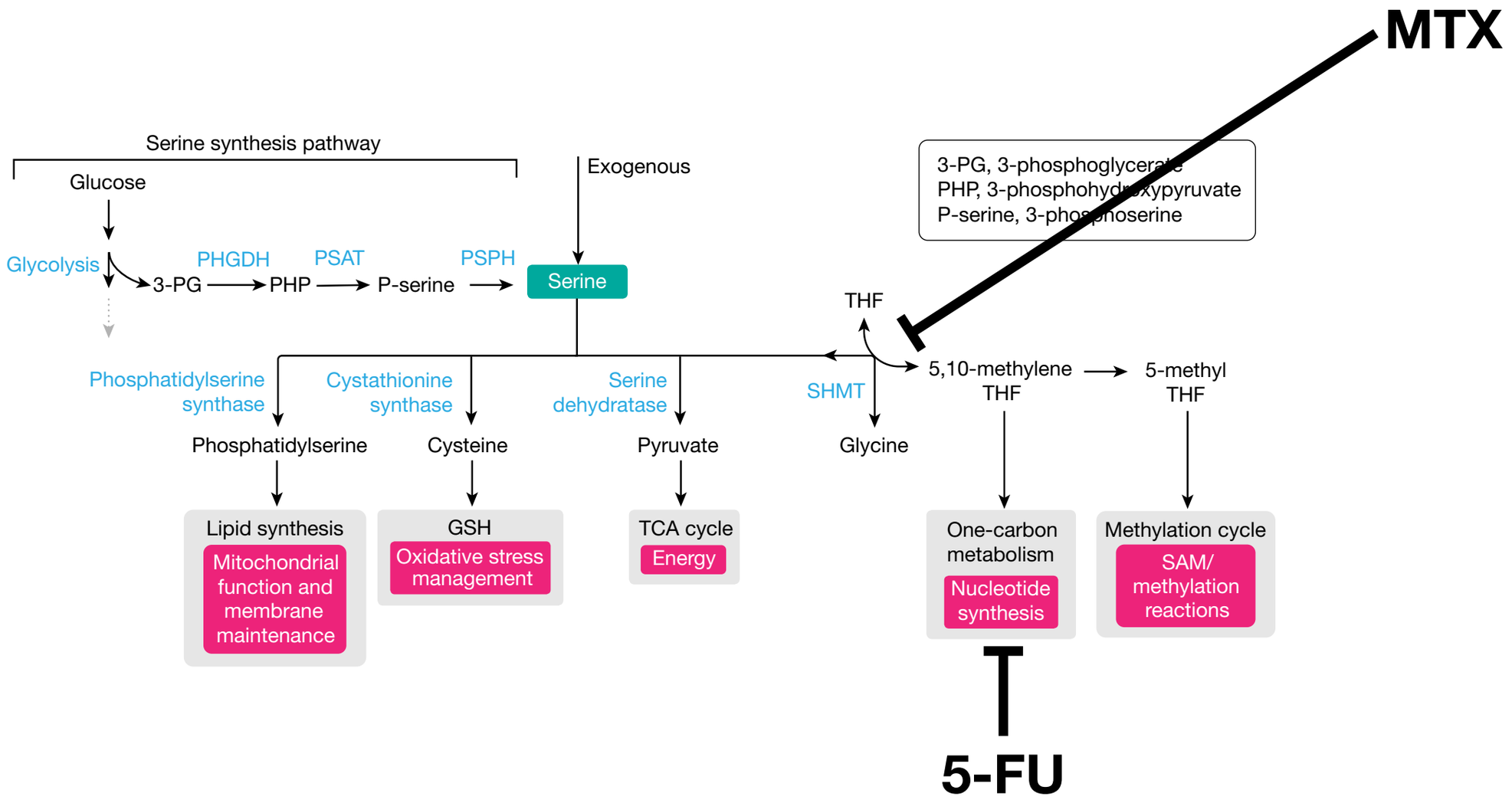


Losman et al, ***Science****, 2013*

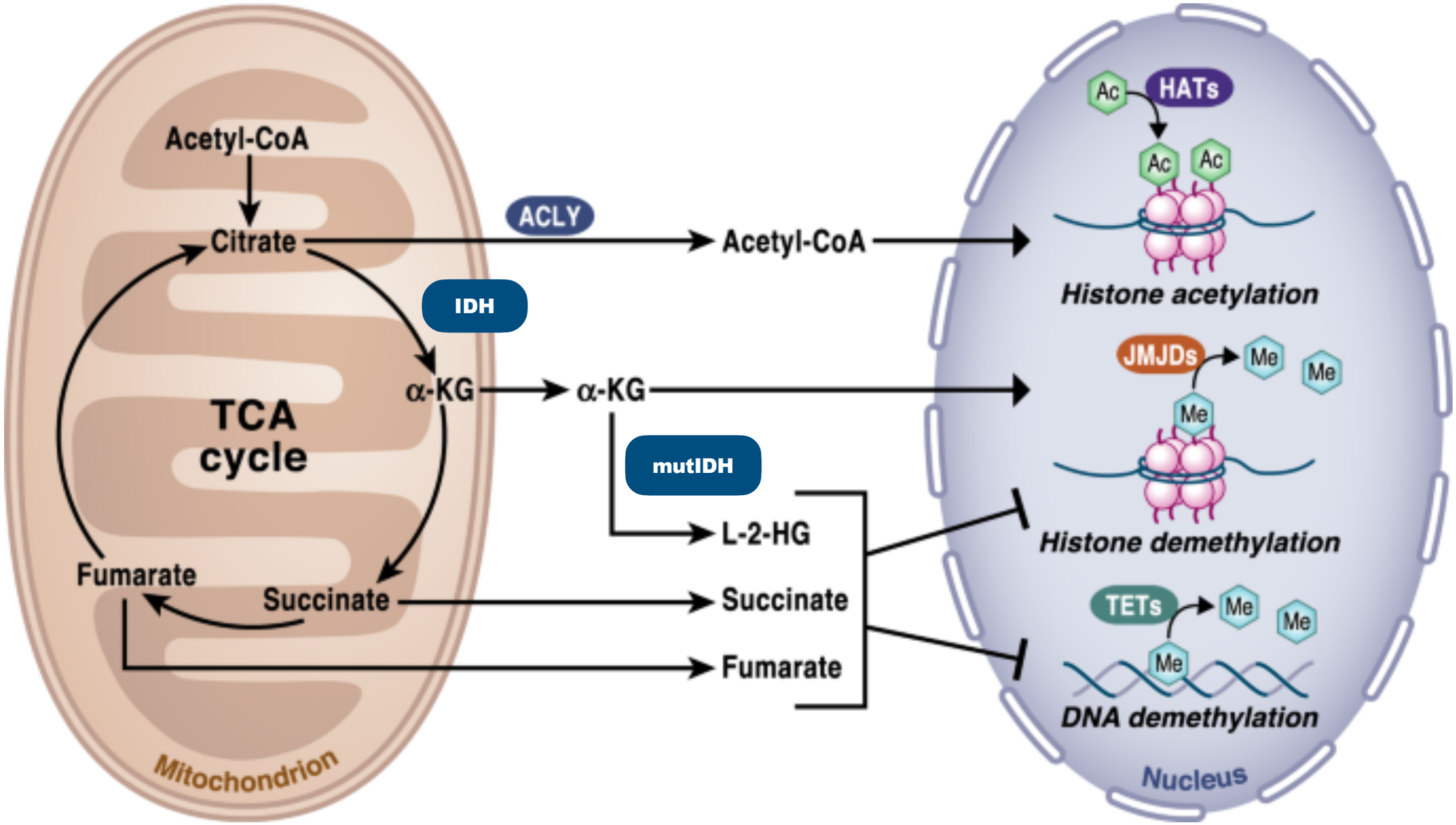
2-HG blockade can reverse tumorigenesis



i.e.: antifolates are “METABOLIC drugs”



Mitochondria-derived metabolites impact the epigenome



Reyes & Chandel, ***Nat Comm****, 2020*

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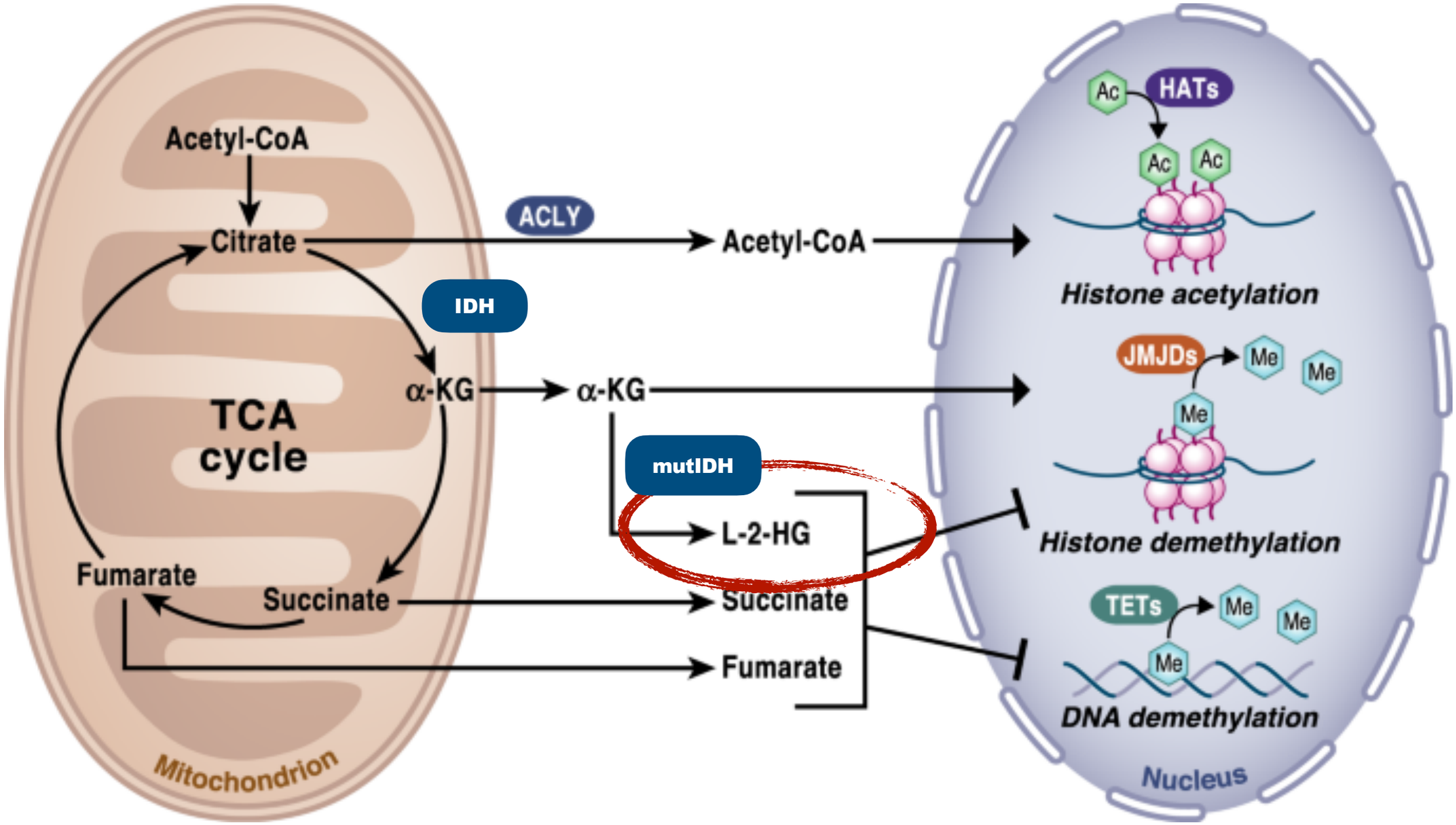

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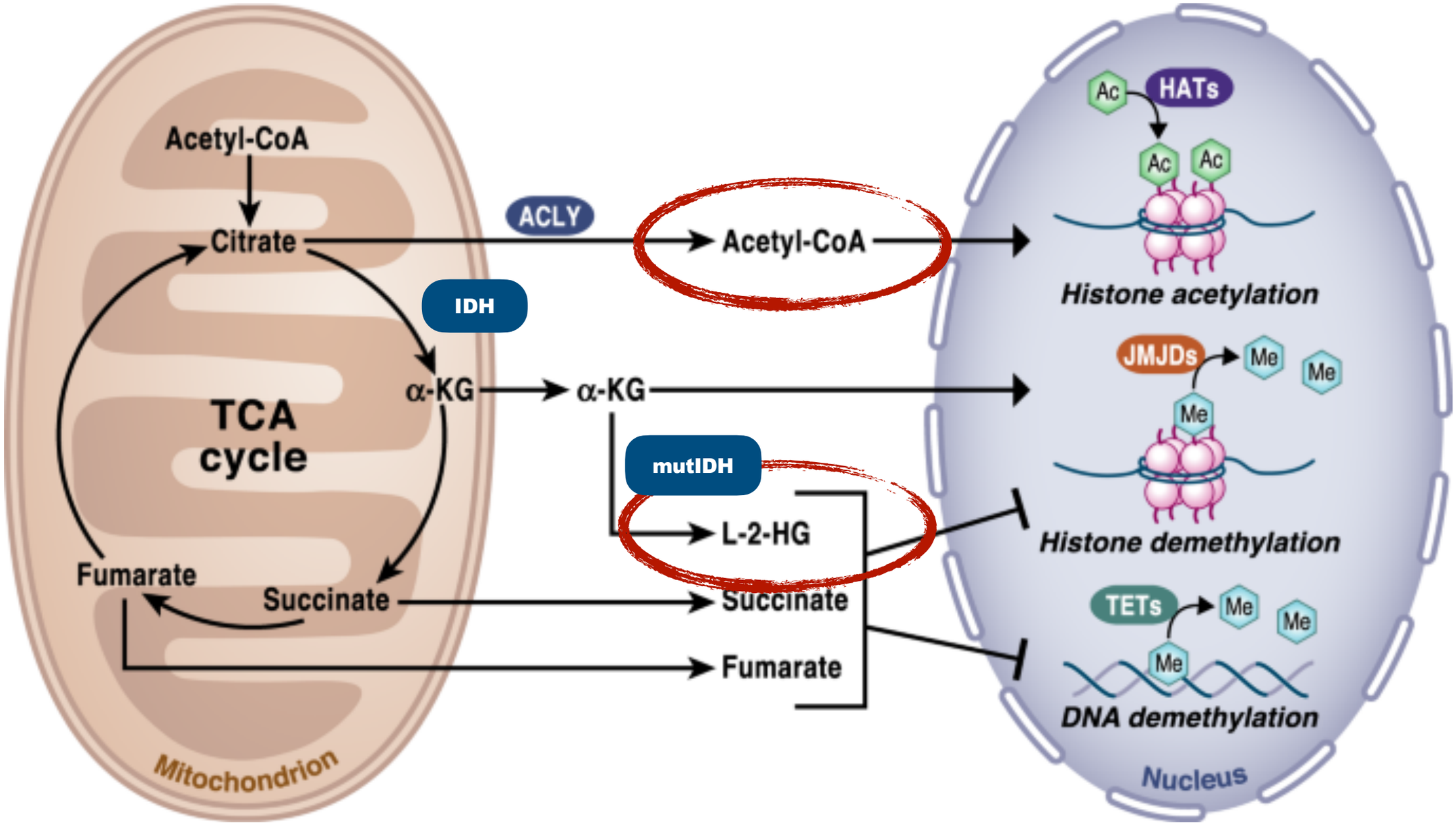
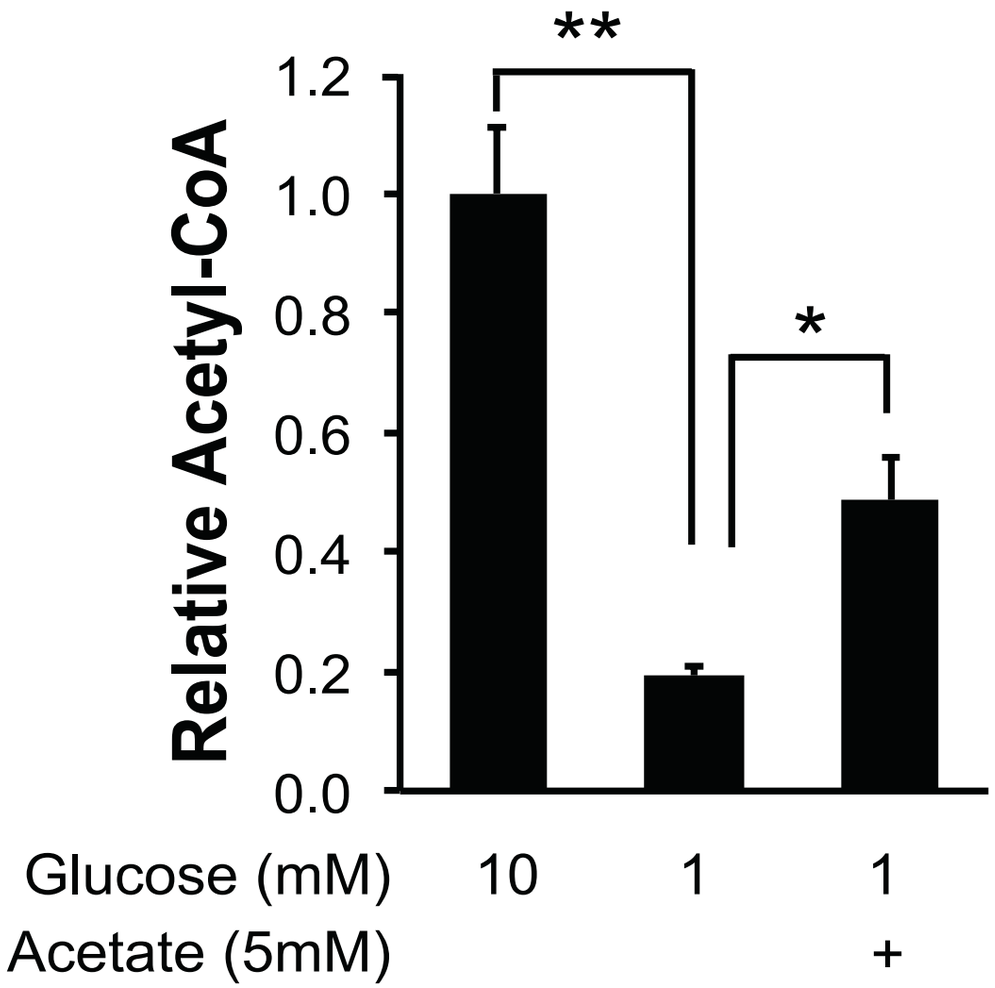


Reyes & Chandel, ***Nat Comm****, 2020*

Acetyl-CoA levels fluctuate in response to nutrient availability



Lee, Carrer, Shah et al, Cell Metabol, 2014

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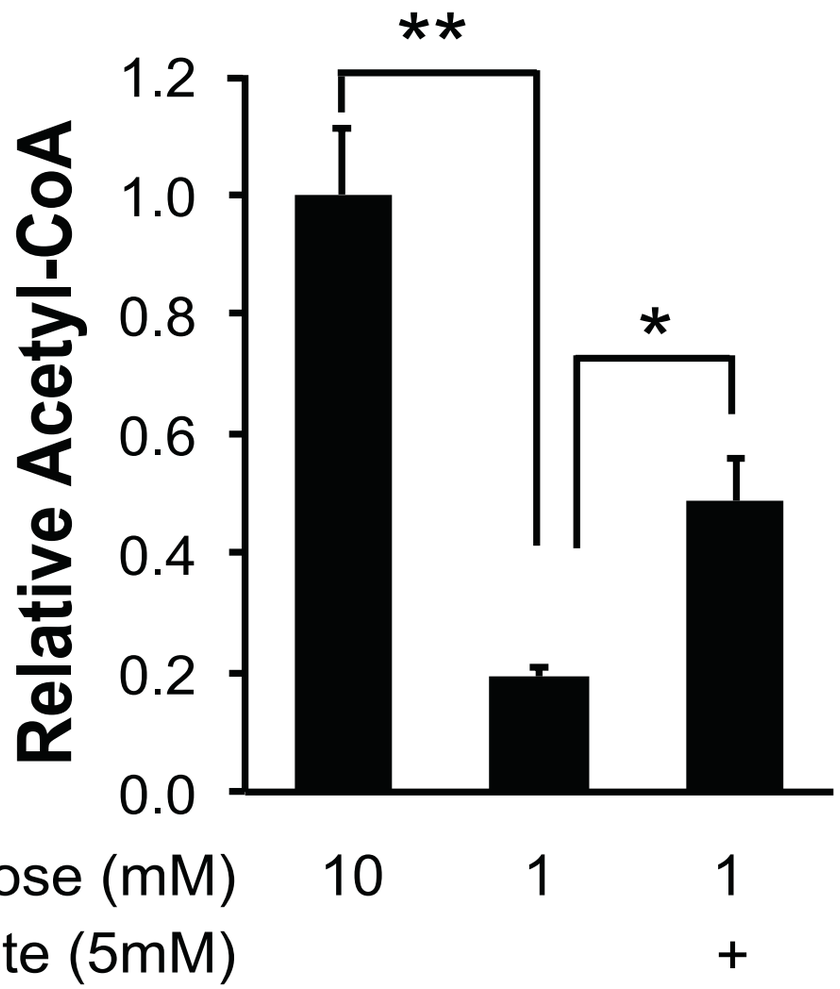

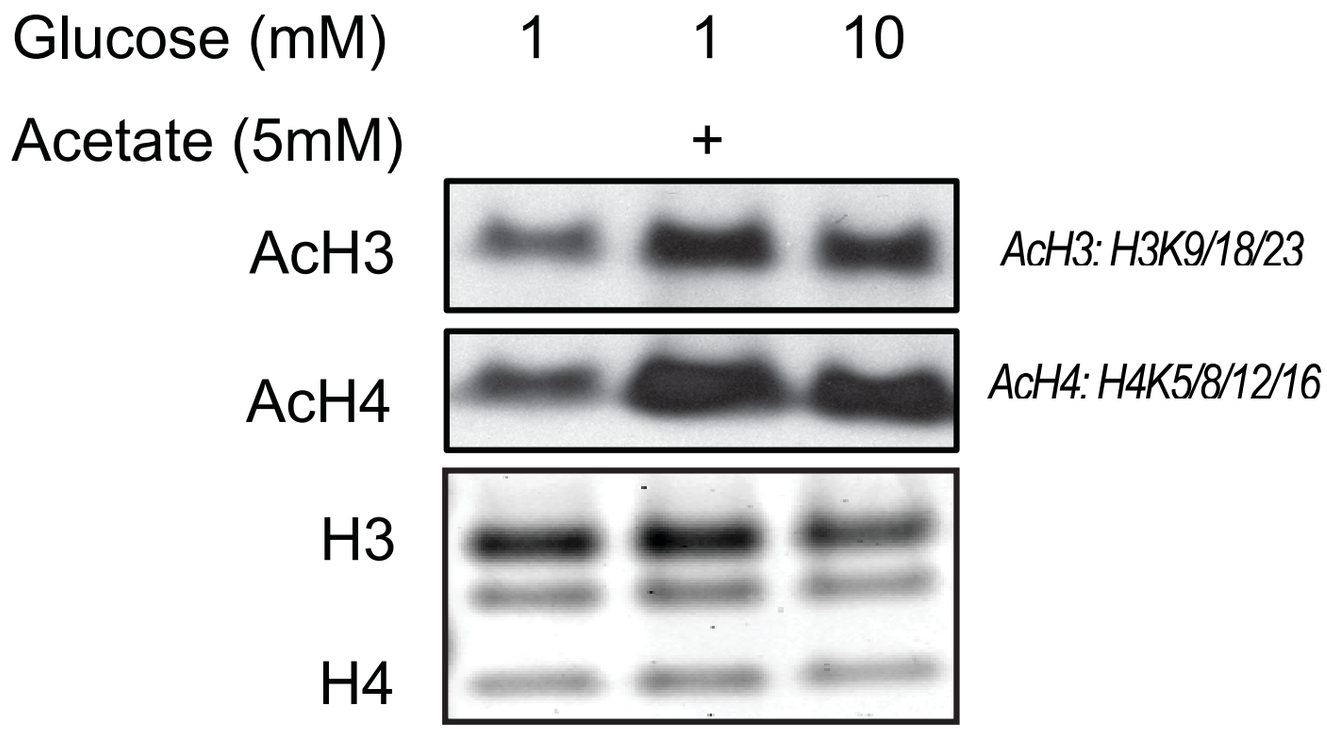

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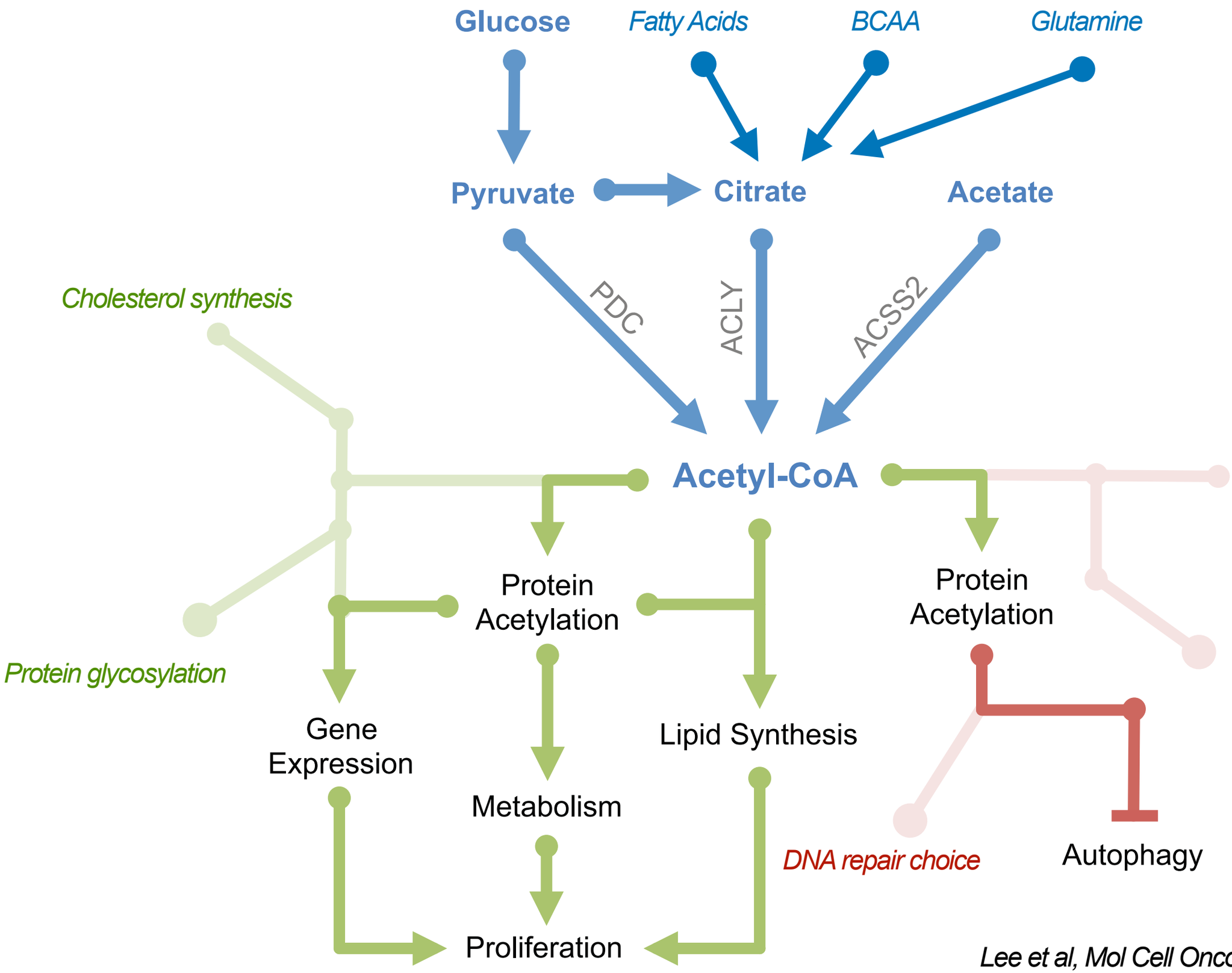
Acetyl-CoA gauges extra-cellular conditions and influences cell behavior



Lee et al, Mol Cell Oncol, 2014 (modified)

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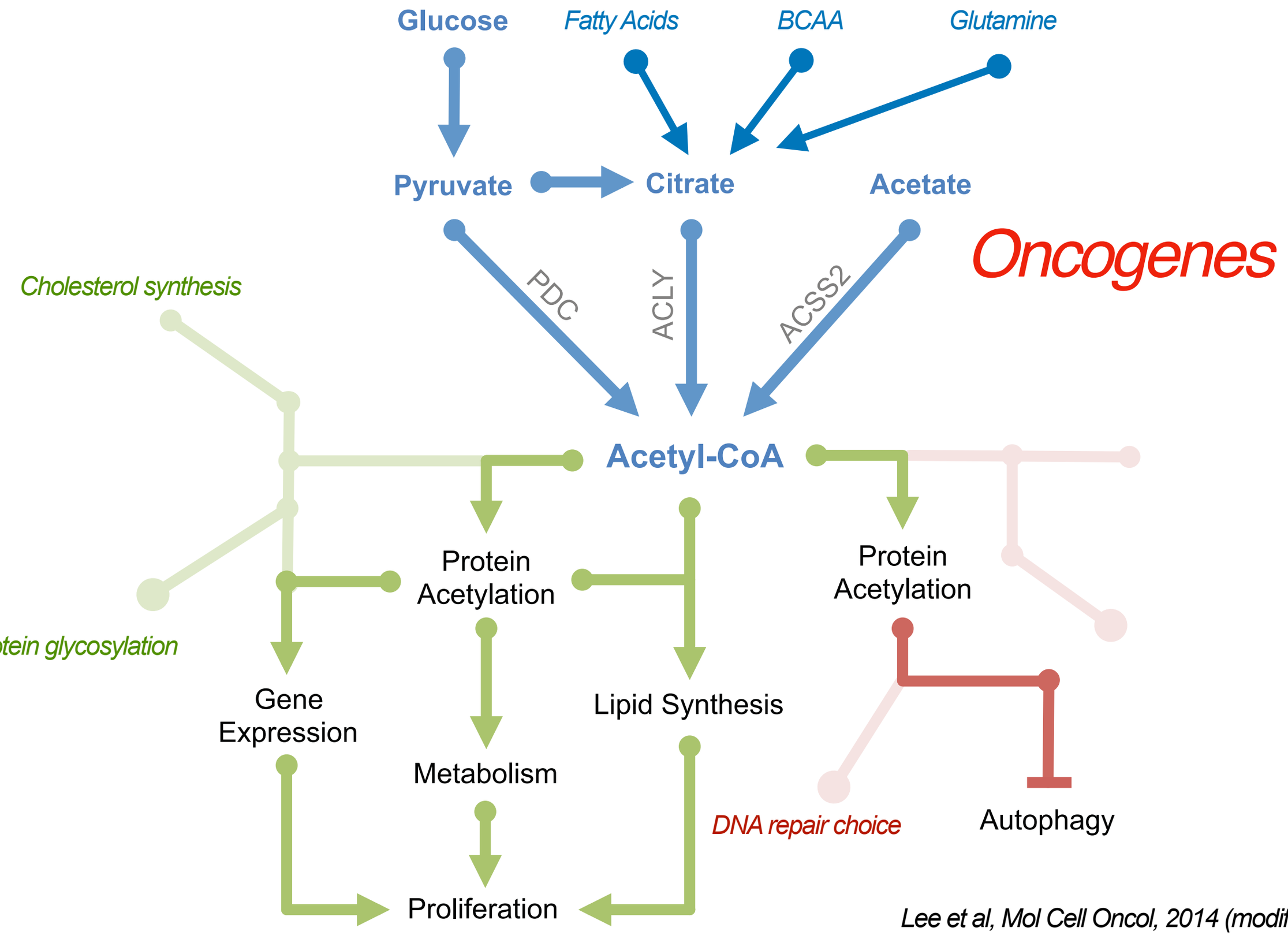

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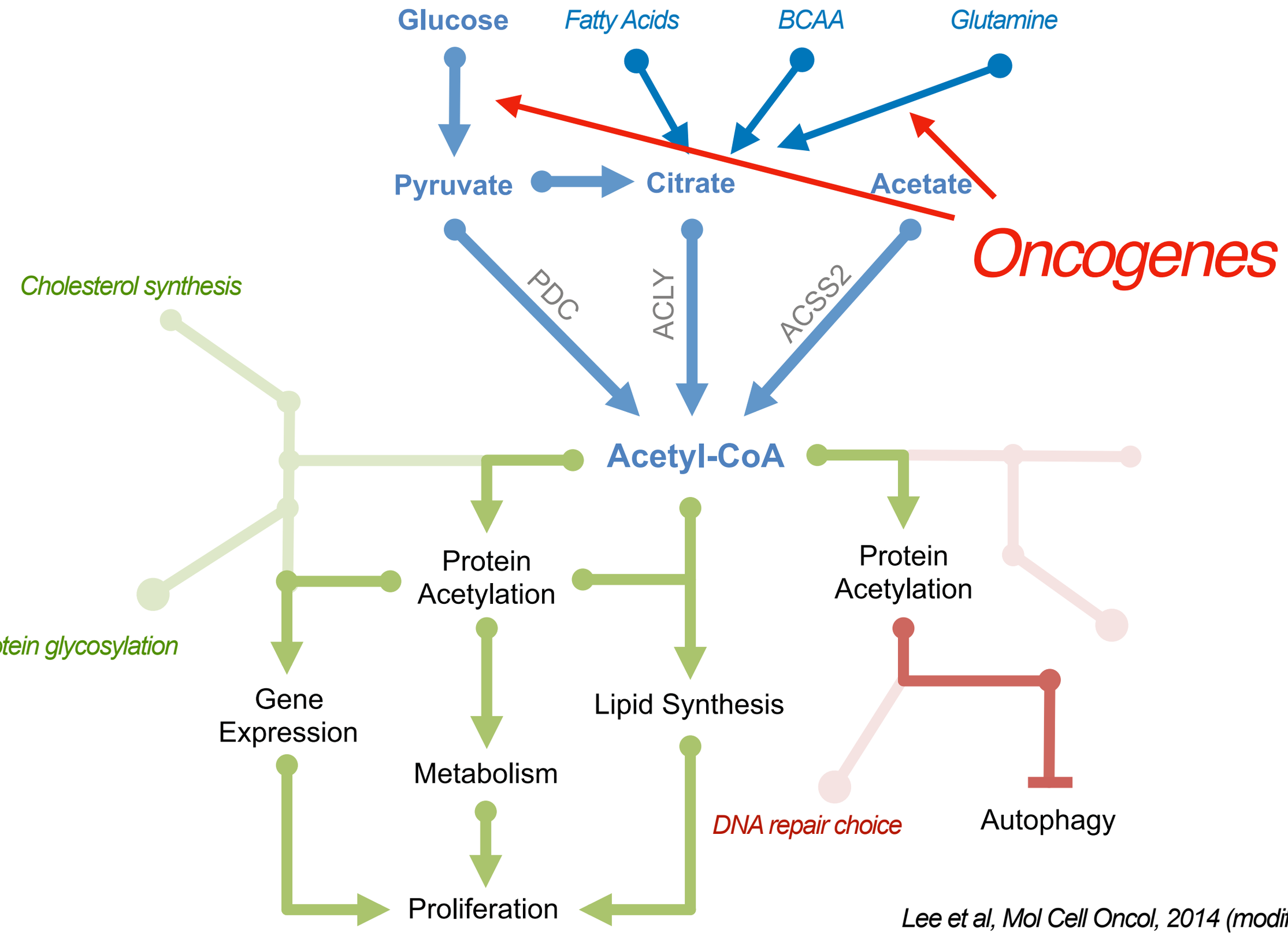

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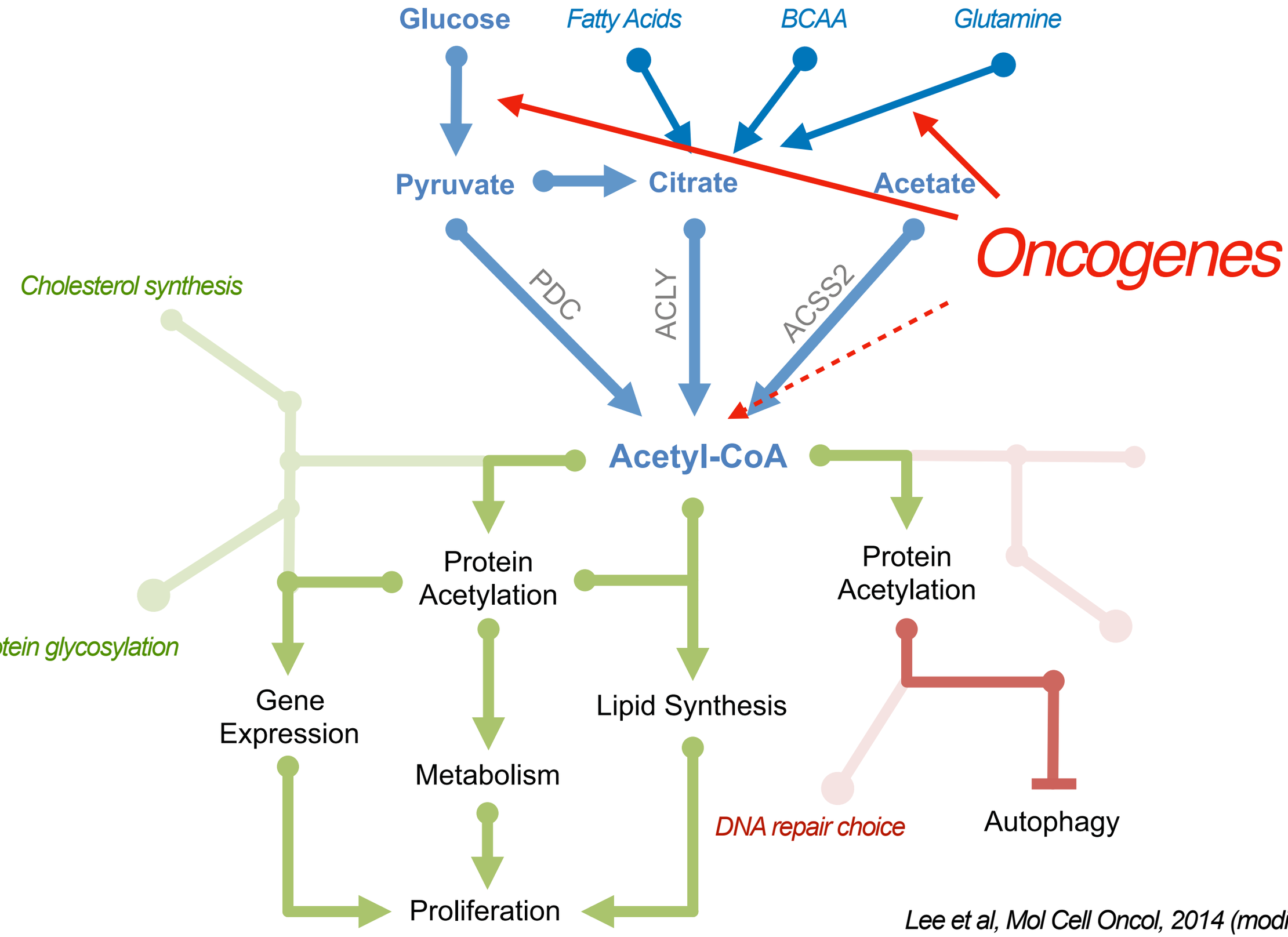

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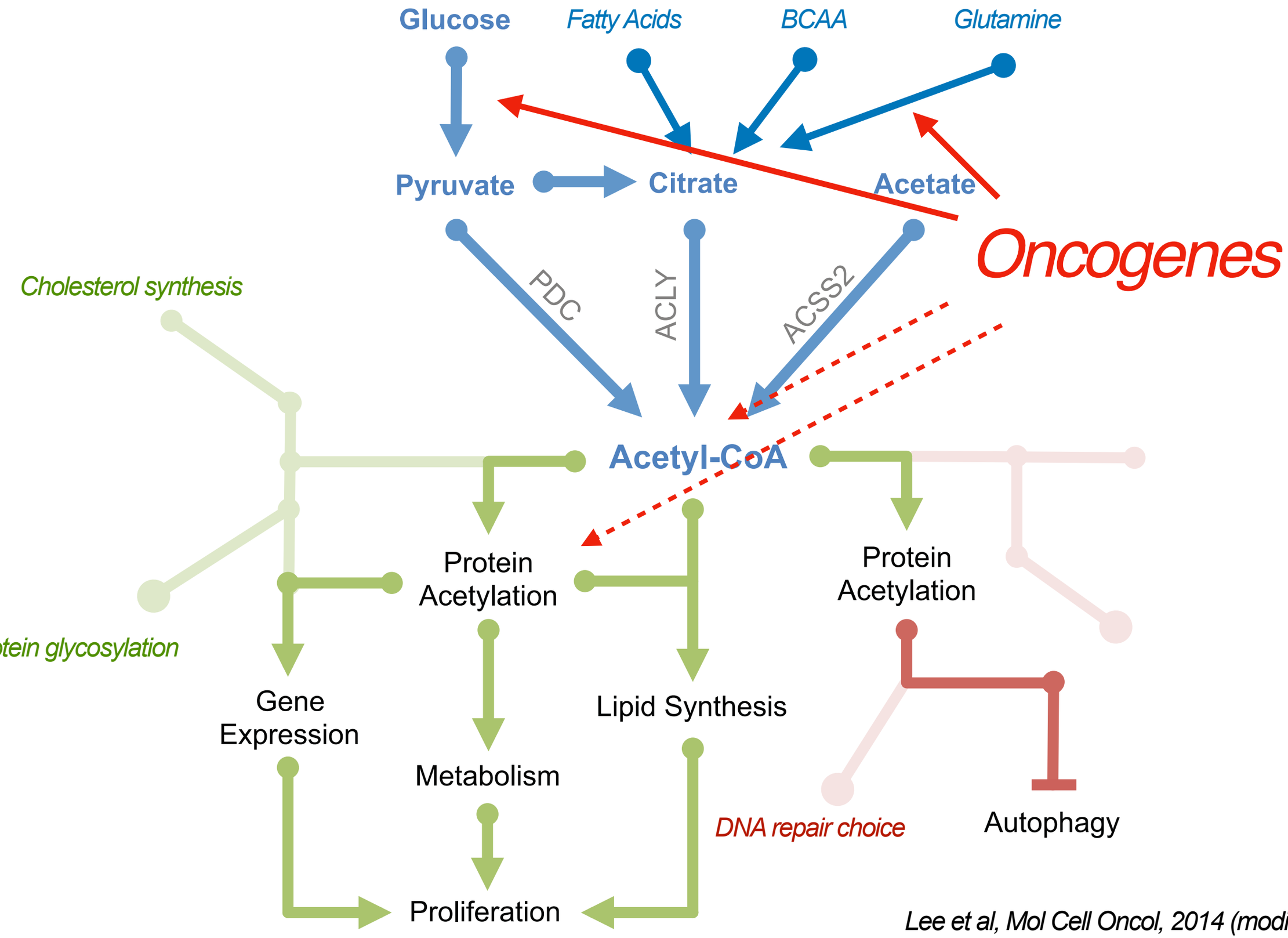
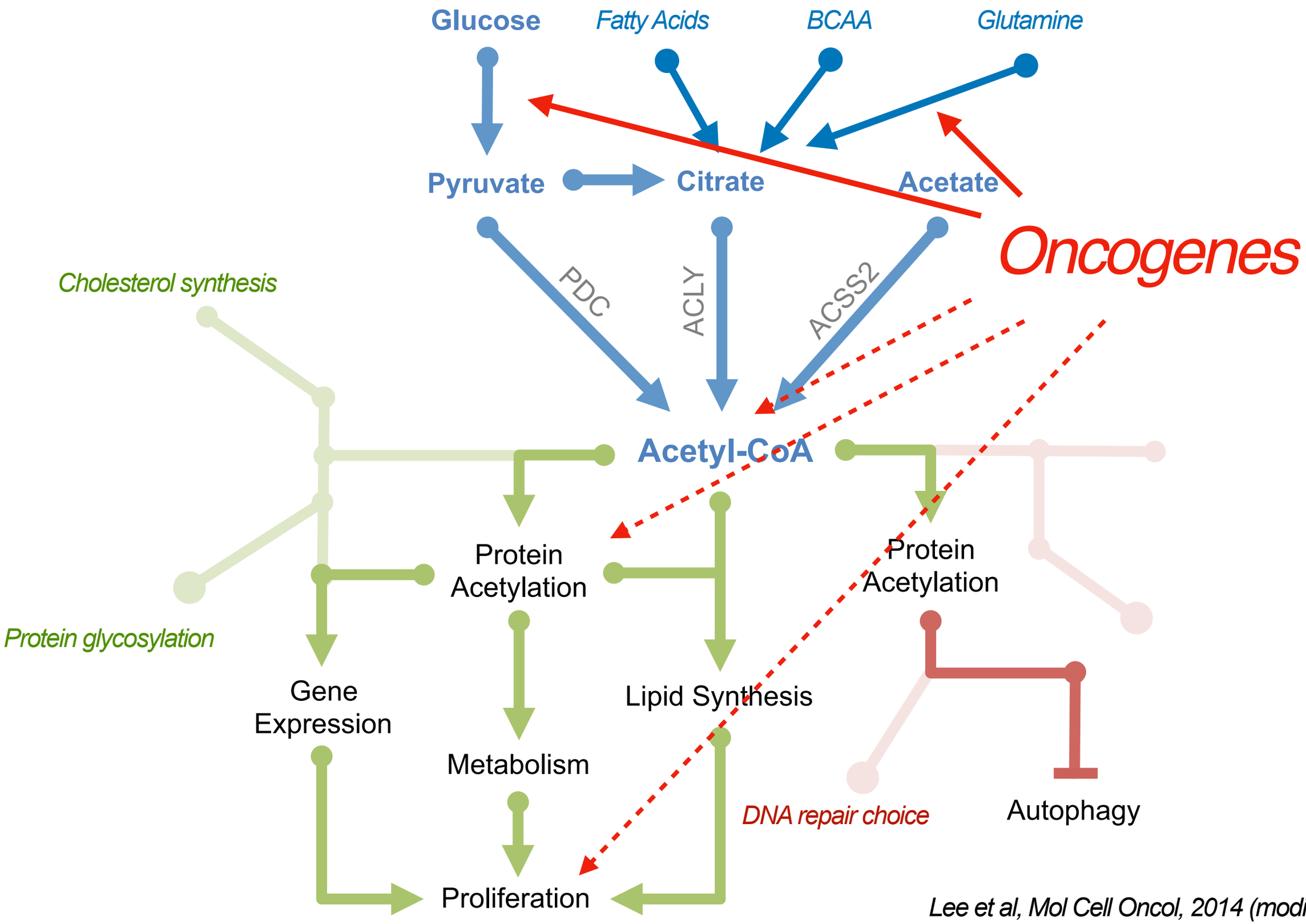


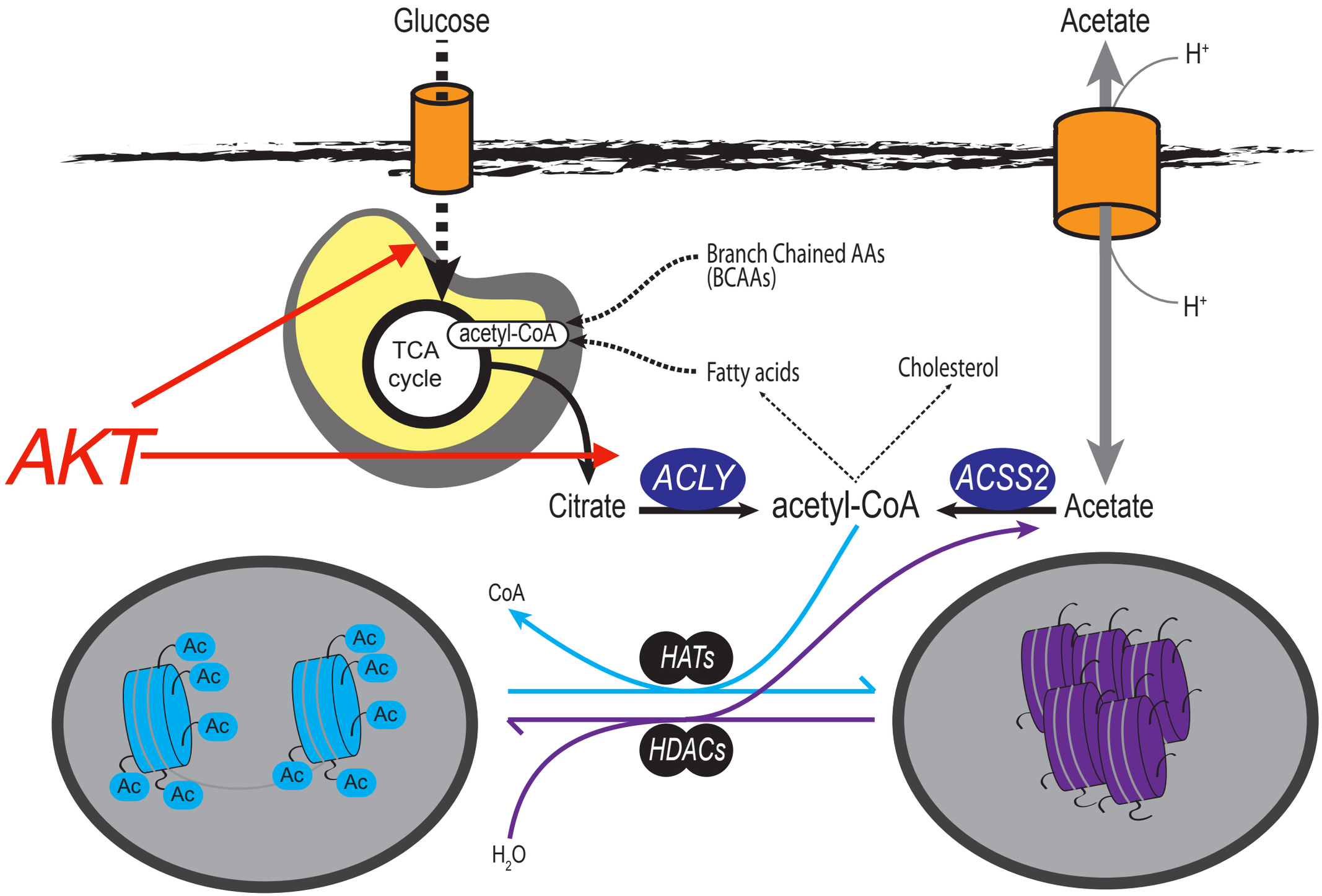
Lee et al, Mol Cell Oncol, 2014 (modified)

Acetyl-CoA gauges extra-cellular conditions and influences cell behavior



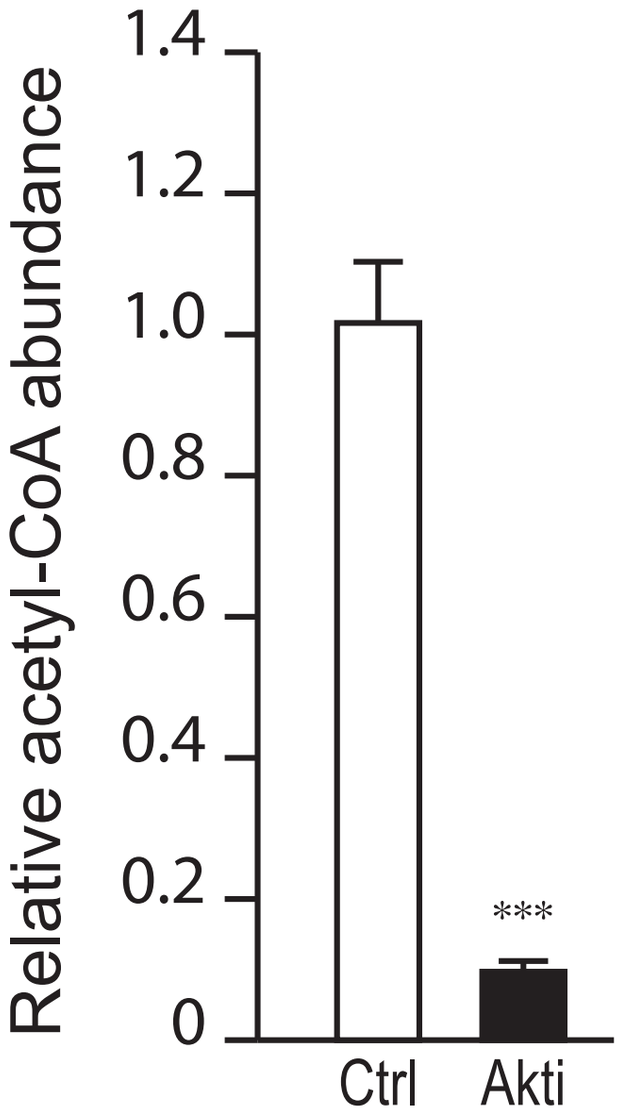
Lee et al, Mol Cell Oncol, 2014 (modified)

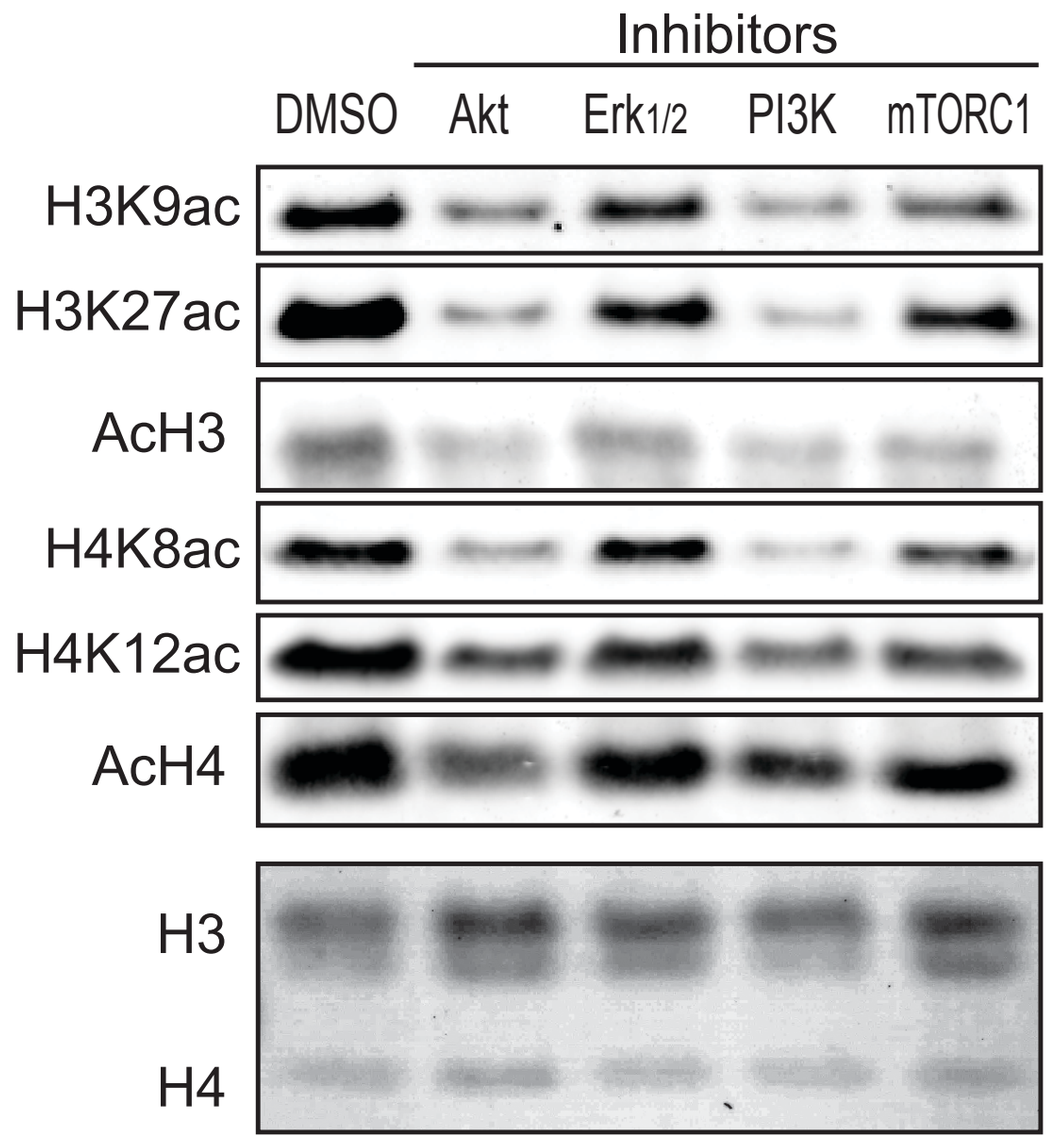
AKT promotes acetyl-CoA production



Carrer & Wellen, Curr Opin Biotechnol, 2015

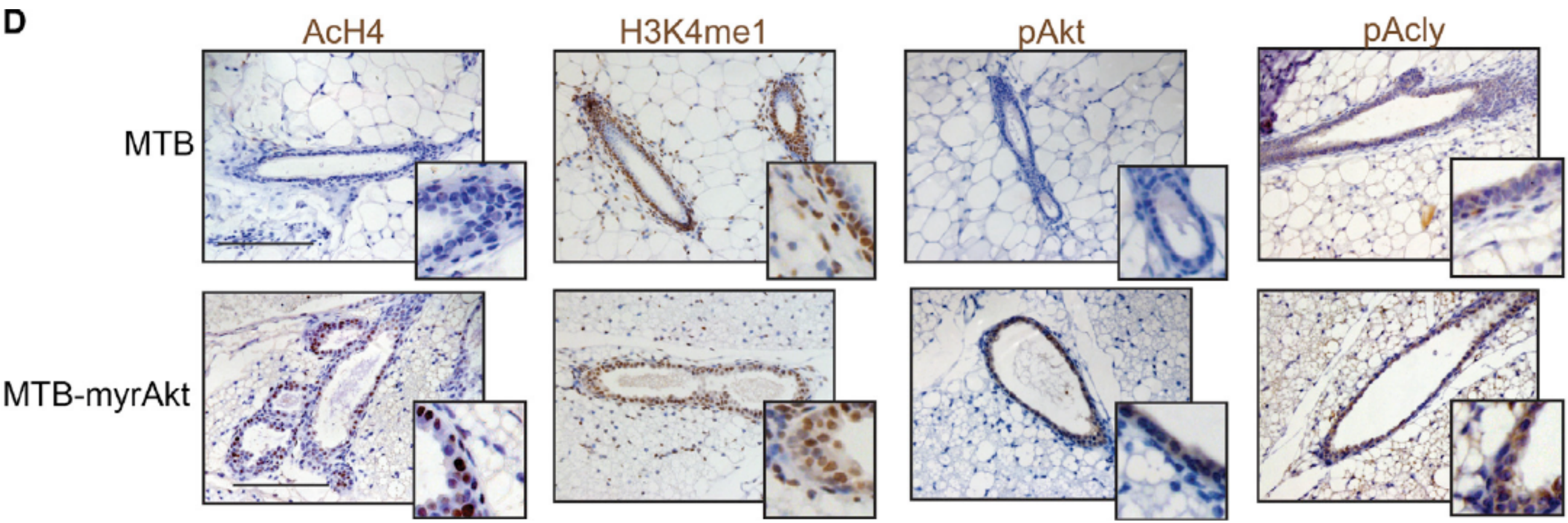
Akt-dependent regulation of histone acetylation





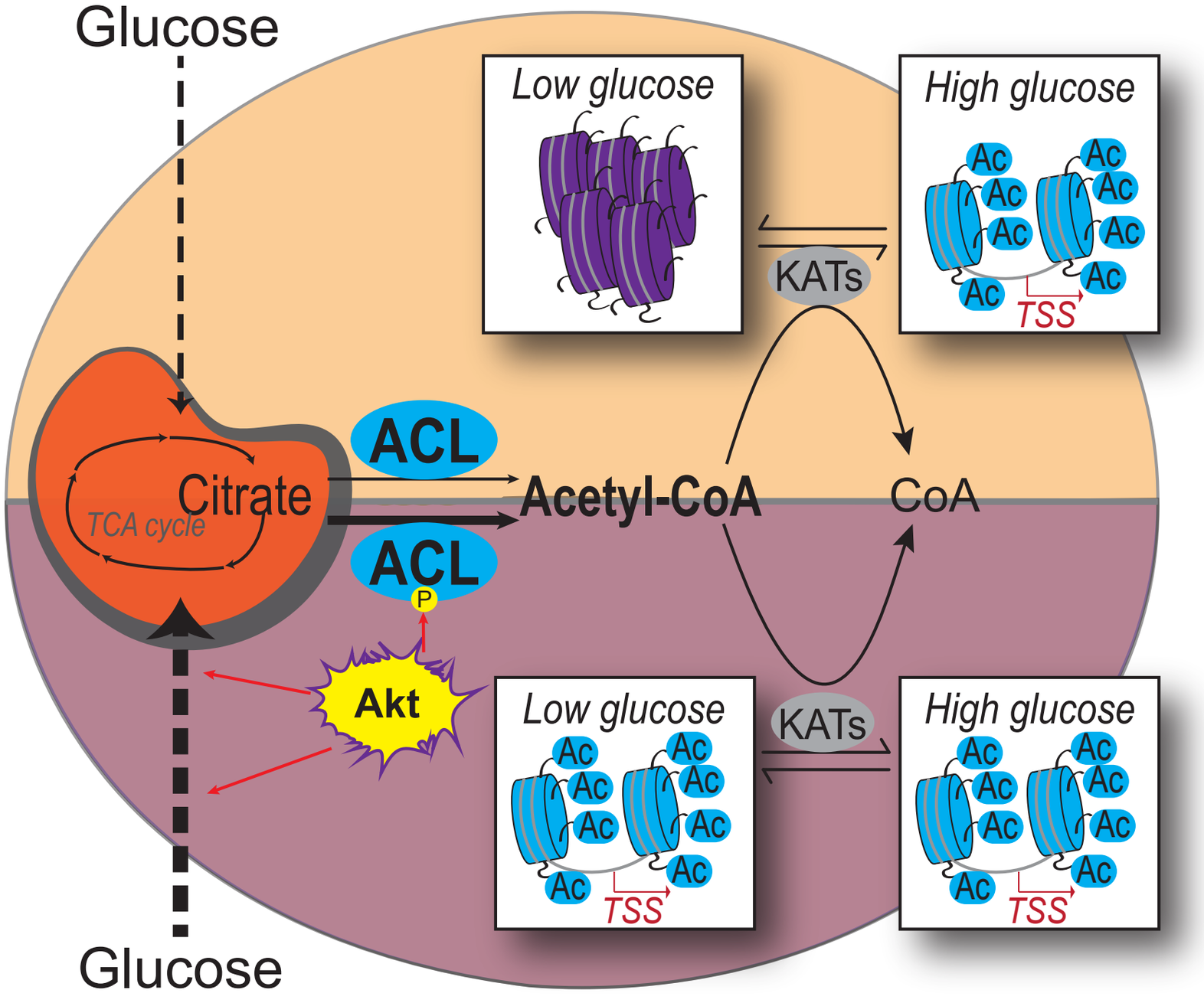
Lee, Carrer, Shah et al, Cell Metabol, 2014

AKT induces histone acetylation through a AKT-ACLY axis



Lee, Carrer, Shah et al, Cell Metabol, 2014

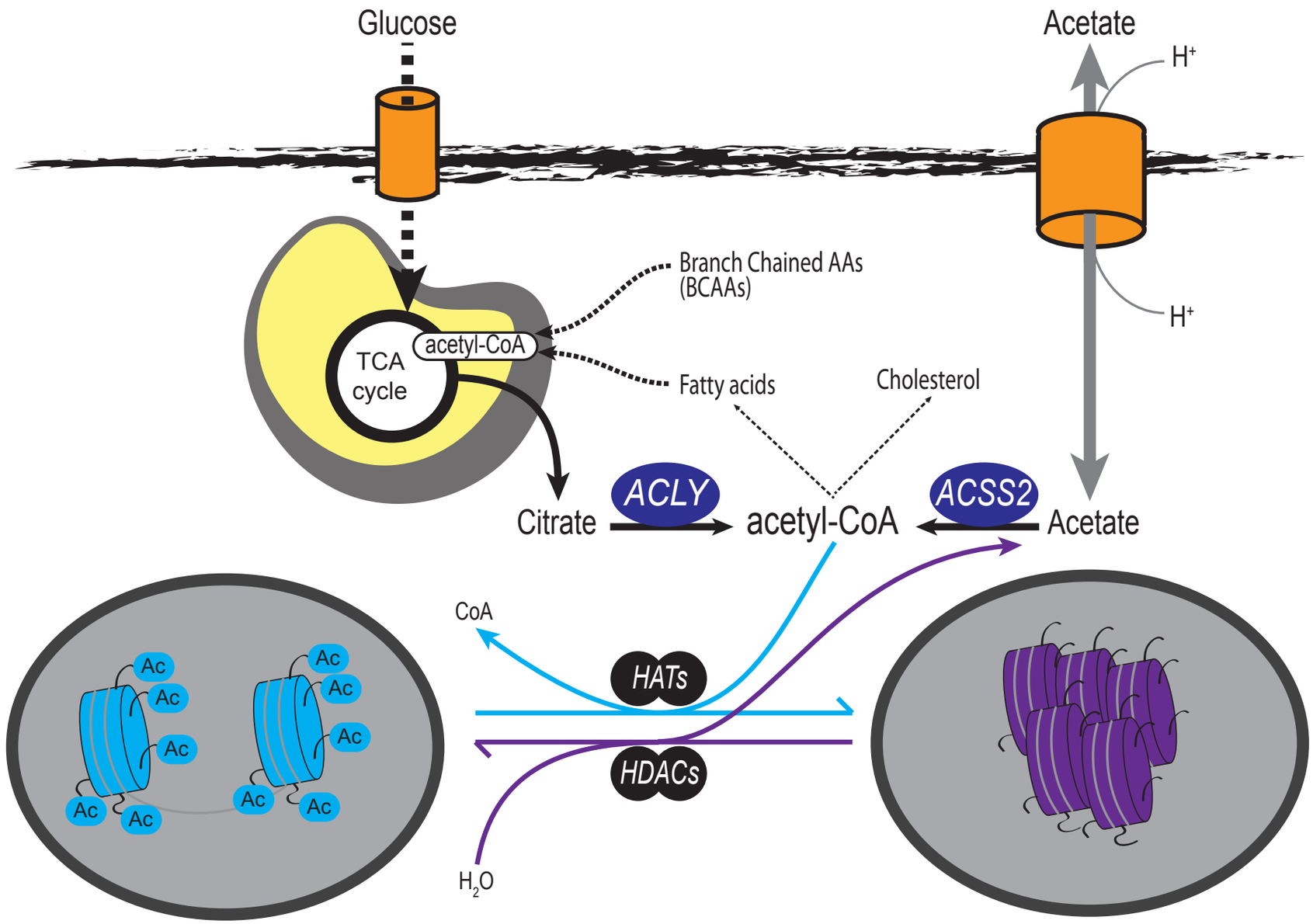
Akt activity low



Akt activity high

Lee, Carrer, Shah et al, Cell Metabol, 2014

acetyl-CoA at the interface of metabolism and epigenome



Carrer & Wellen, Curr Opin Biotechnol, 2015

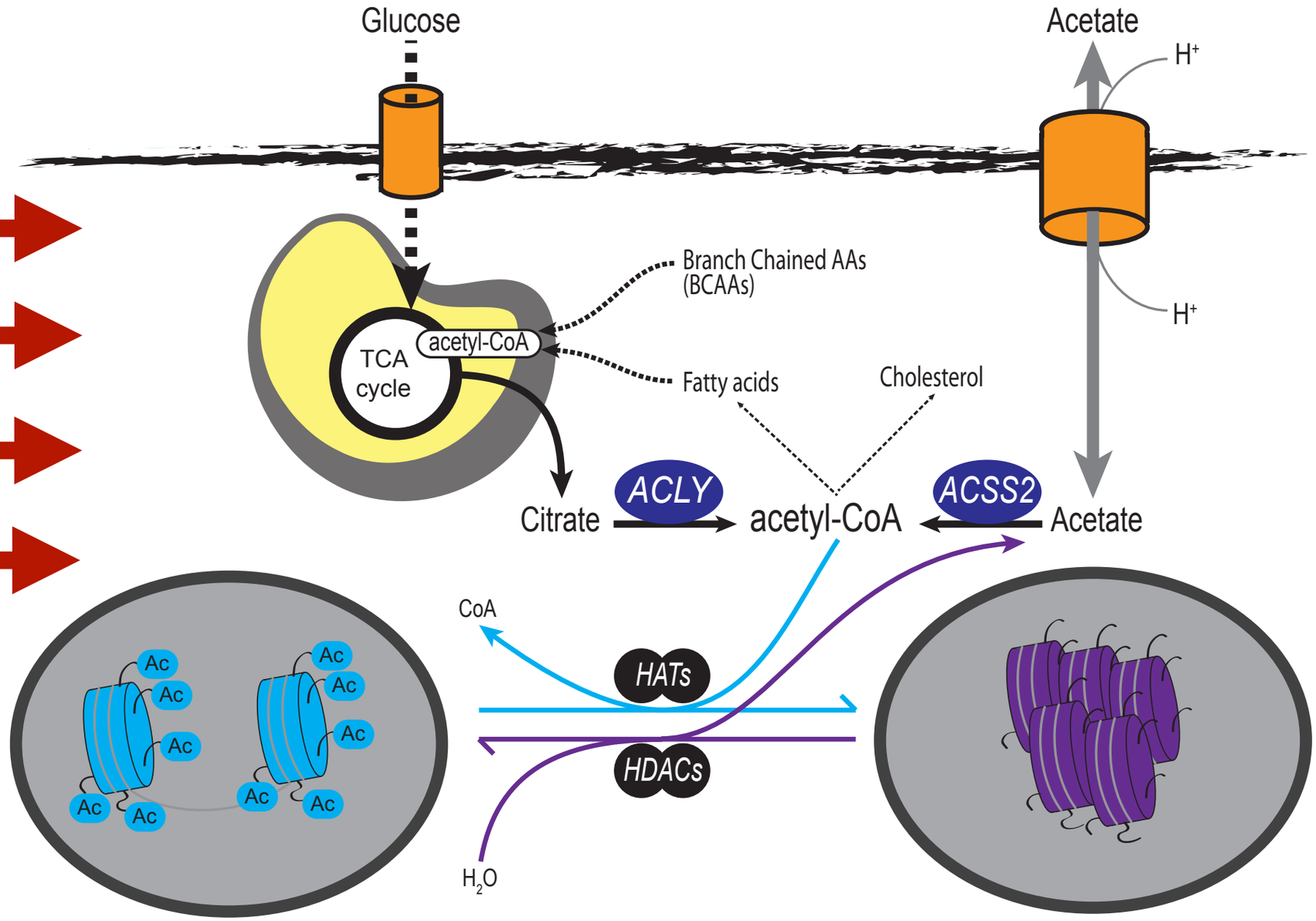
acetyl-CoA at the interface of metabolism and epigenome

Oncogenes

Diet

Microenvironment

Circadian oscillations



Wellen et al, Science, 2010
Lee, Carrer et al, Cell Metabol, 2014
Carrer et al, JBC, 2017
Zhao et al, Cell Reports, 2016
Donohoe et al, Cancer Discov, 2016
Schug et al, Cancer Cell, 2015
Sahar et al, JBC, 2014
Das et al, Cell Reports, 2017
Moussaieff et al, Cell Metabol, 2015
Karner et al, JBC, 2016
Peng et al, Science, 2016

Carrer & Wellen, Curr Opin Biotechnol, 2015

acetyl-CoA at the interface of metabolism and epigenome

Oncogenes

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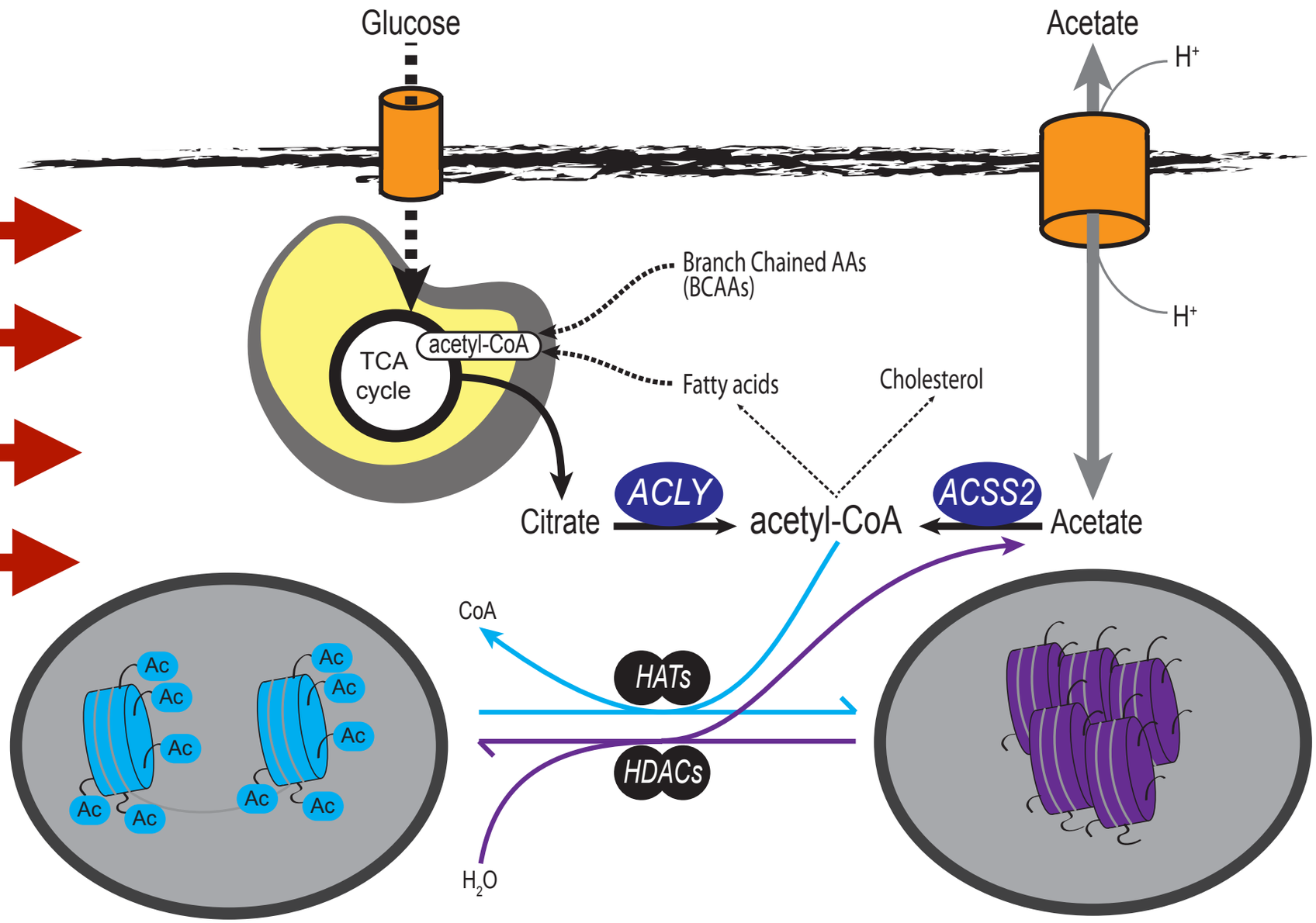


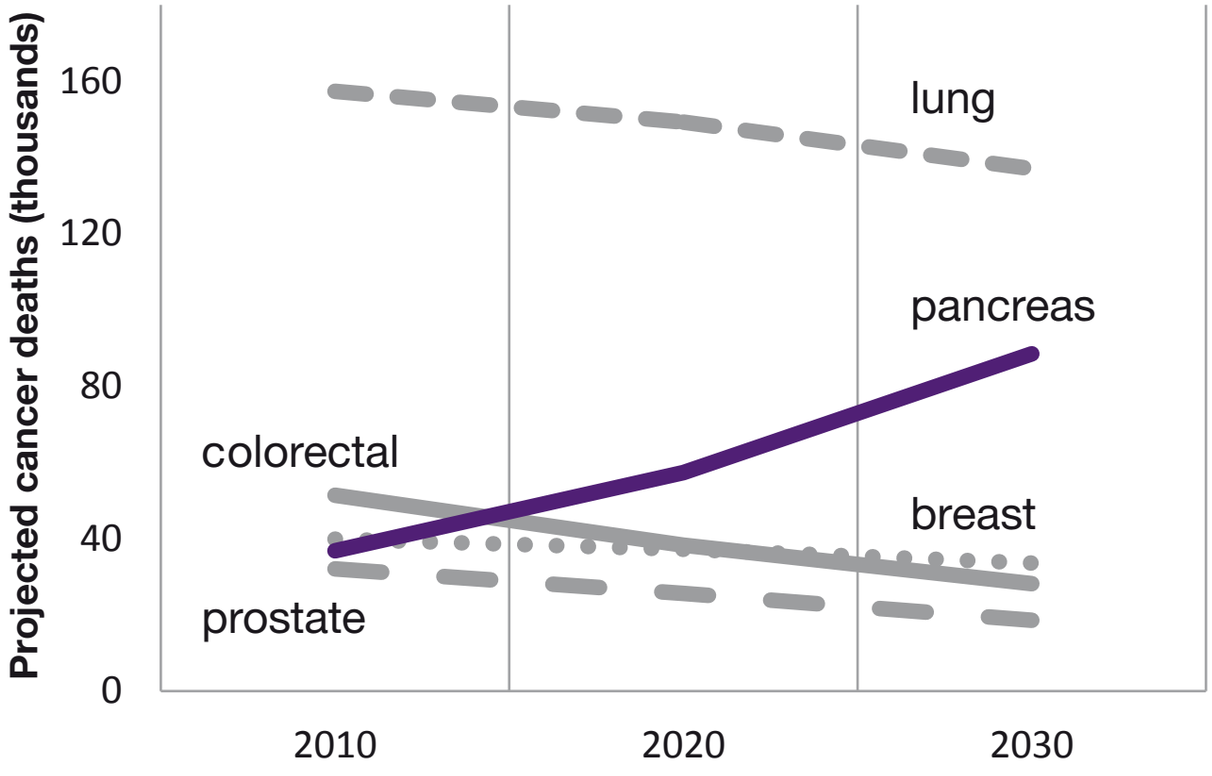
Wellen et al, Science, 2010
Lee, Carrer et al, Cell Metabol, 2014
Carrer et al, JBC, 2017
Zhao et al, Cell Reports, 2016
Donohoe et al, Cancer Discov, 2016
Schug et al, Cancer Cell, 2015
Sahar et al, JBC, 2014
Das et al, Cell Reports, 2017
Moussaieff et al, Cell Metabol, 2015
Karner et al, JBC, 2016
Peng et al, Science, 2016

Tumor development and progression

Carrer & Wellen, Curr Opin Biotechnol, 2015

Pancreatic Ductal AdenoCarcinoma (PDAC)

PROJECTED CANCER DEATHS

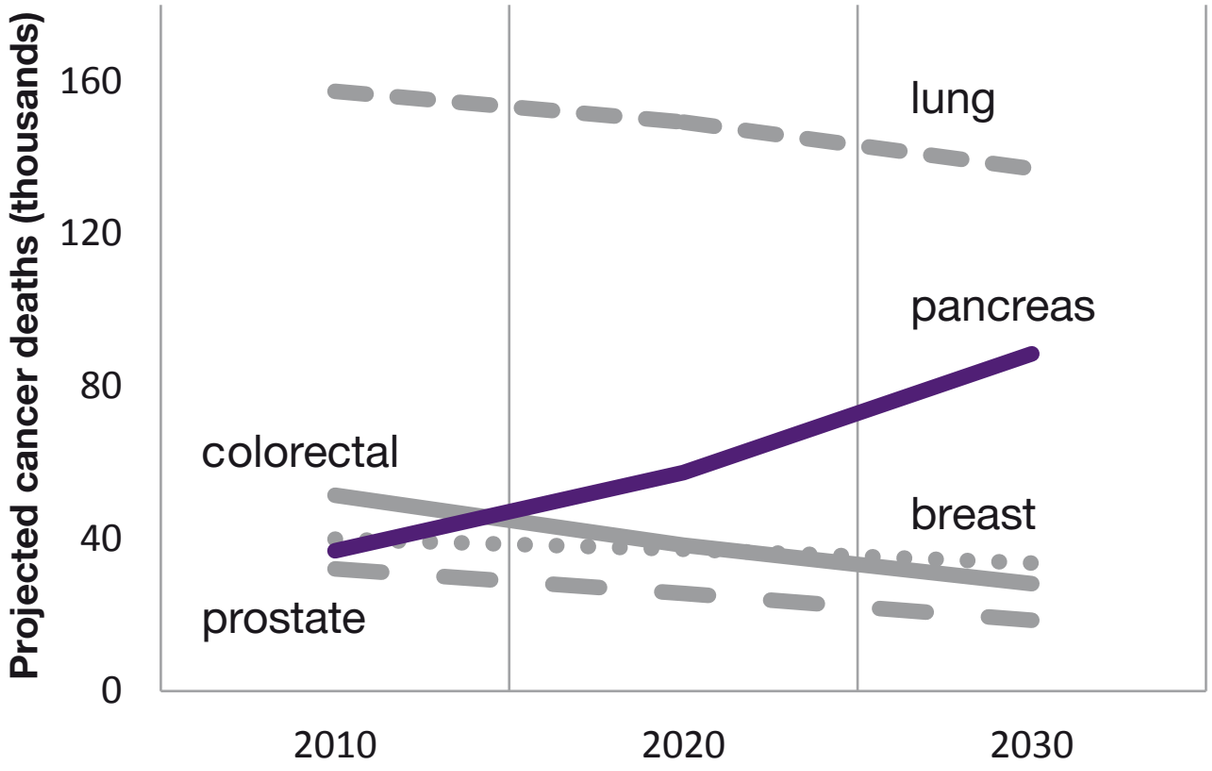


PanCan Action Network Report, 2015

Rahib et al, Cancer Res, 2014

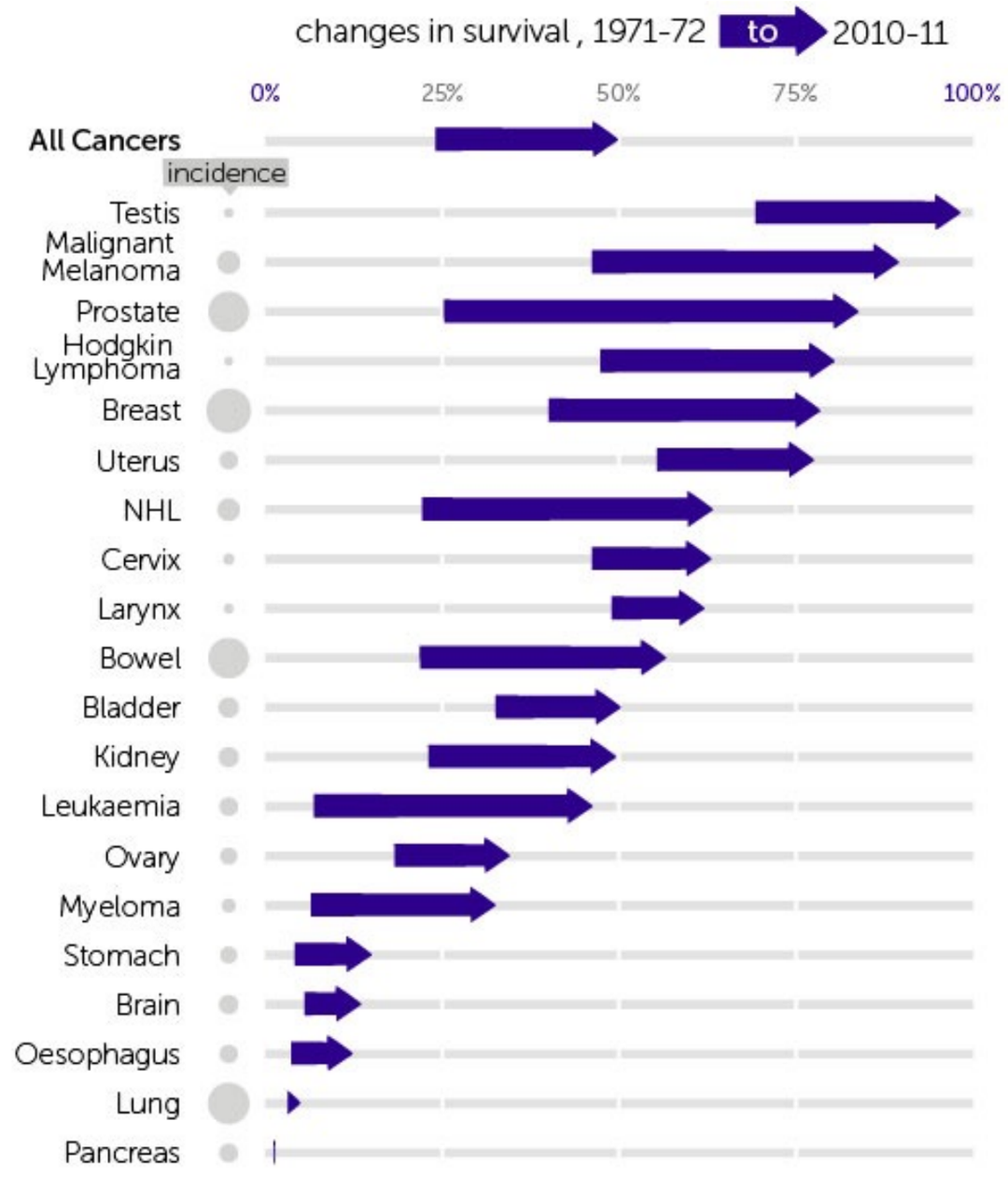
Pancreatic Ductal AdenoCarcinoma (PDAC)

PROJECTED CANCER DEATHS



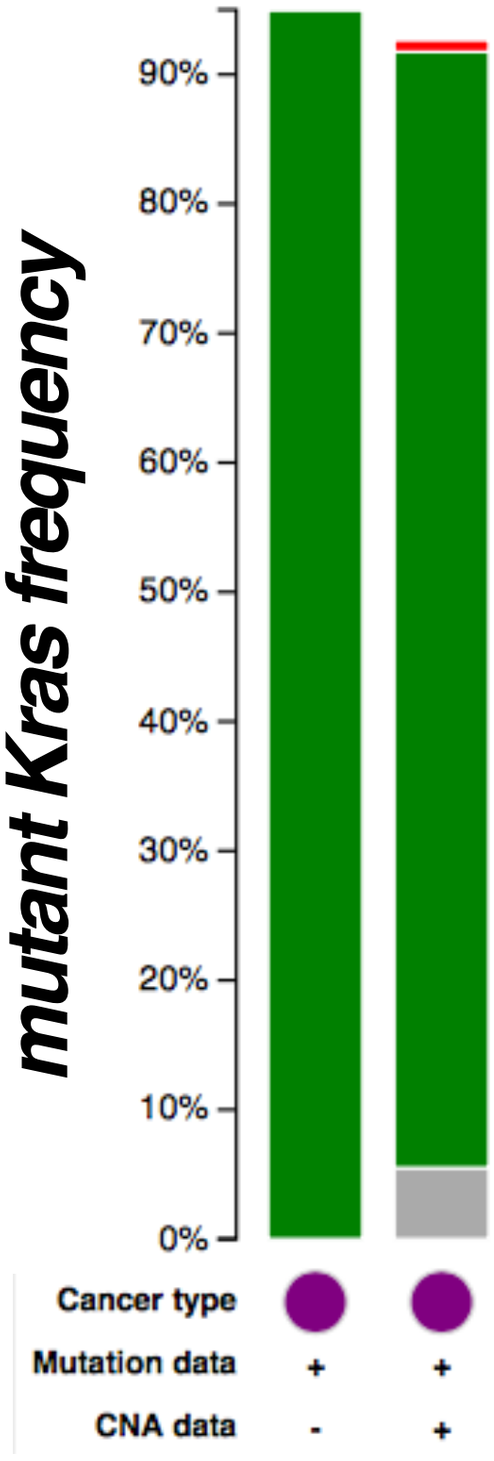
PanCan Action Network Report, 2015

Rahib et al, Cancer Res, 2014



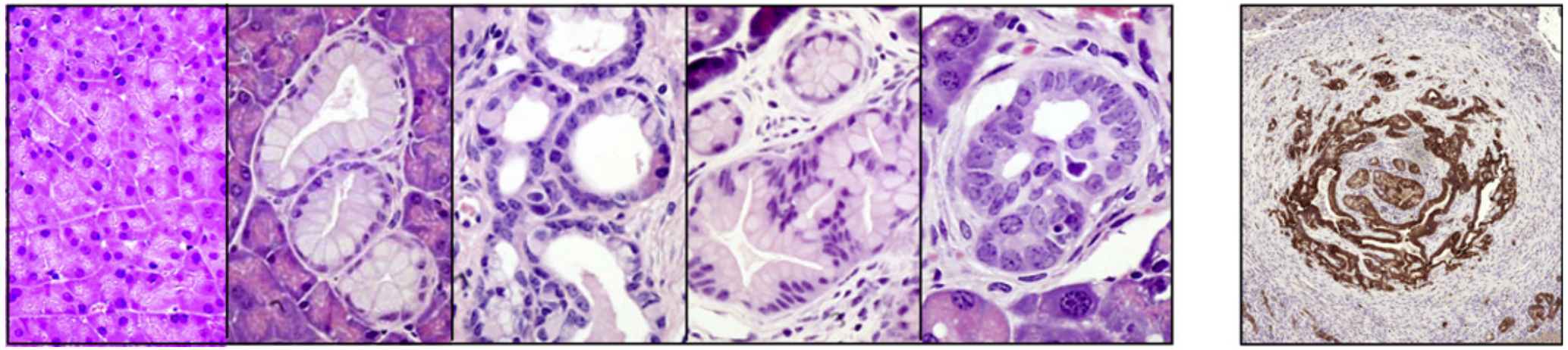
Cancer Research UK

Pancreatic Ductal AdenoCarcinoma (PDA)

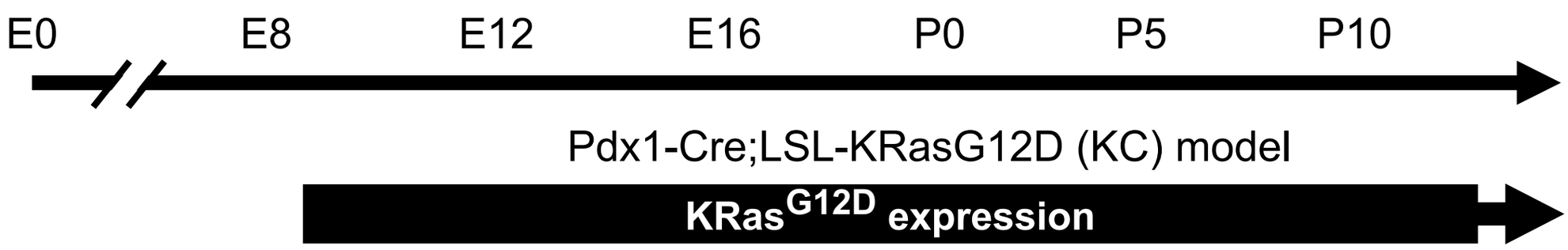


TCGA

PDA mouse models: KC and KPC mice



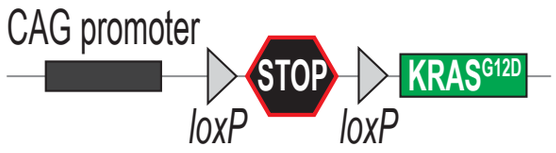
KRas Oncogene-driven Prenatal Models



KC: mutant *Kras* - Cre-mediated gene activation
KPC: mutant *Kras*; *p53* haplodeficiency; - Cre-mediated gene activation

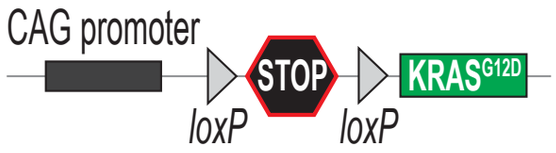
Guerra & Barbacid, Mol Oncol, 2013

The CRE-LoxP system for mouse transgenics

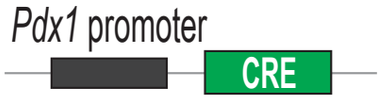


KRAS WT

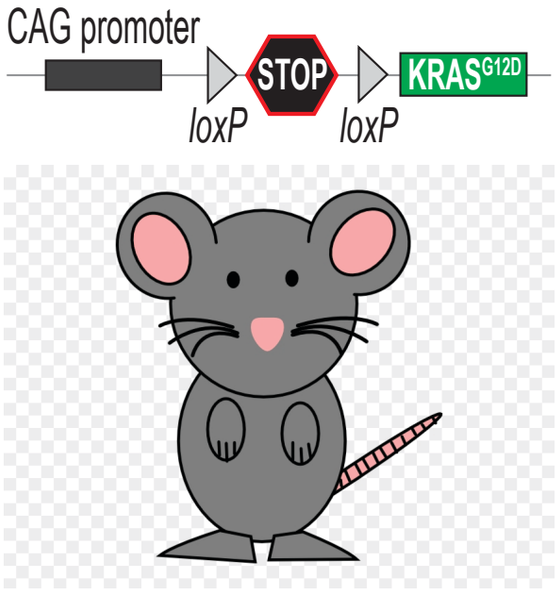
The CRE-LoxP system for mouse transgenics



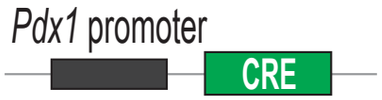
KRAS WT

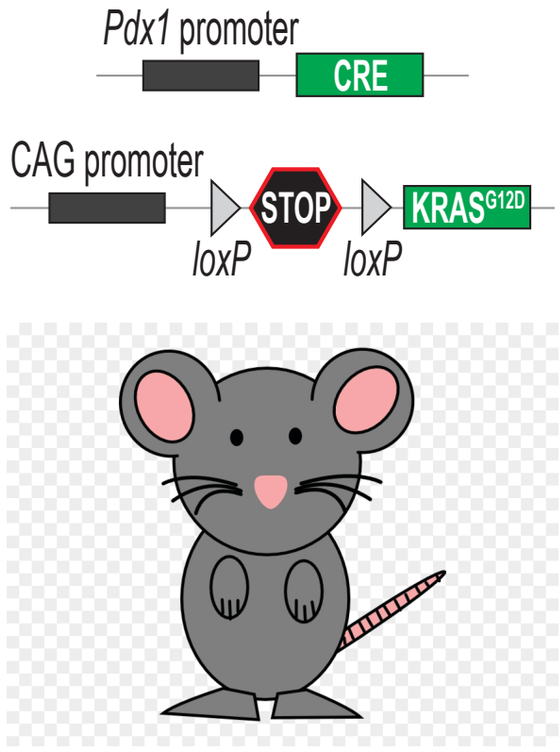


The CRE-LoxP system for mouse transgenics

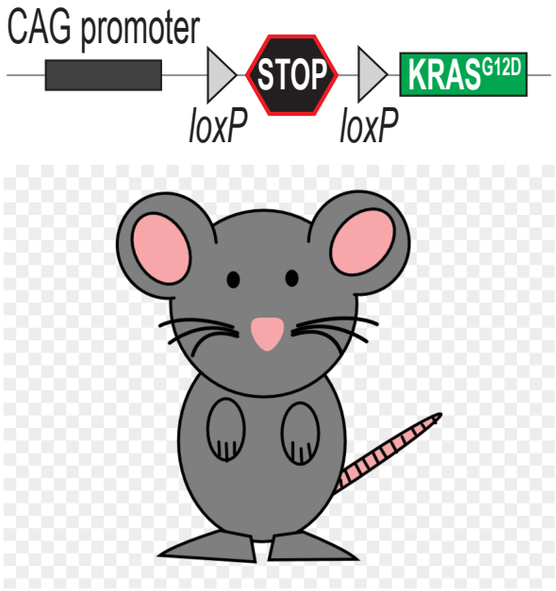


KRAS WT

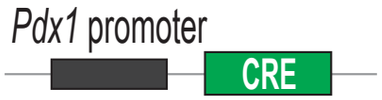


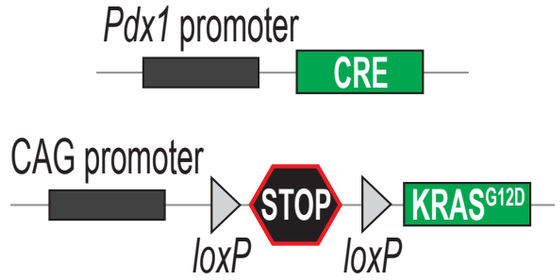


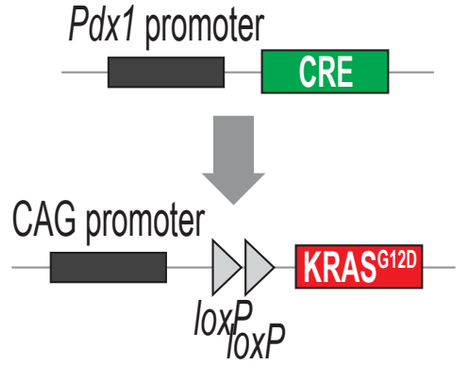
The CRE-LoxP system for mouse transgenics



KRAS WT





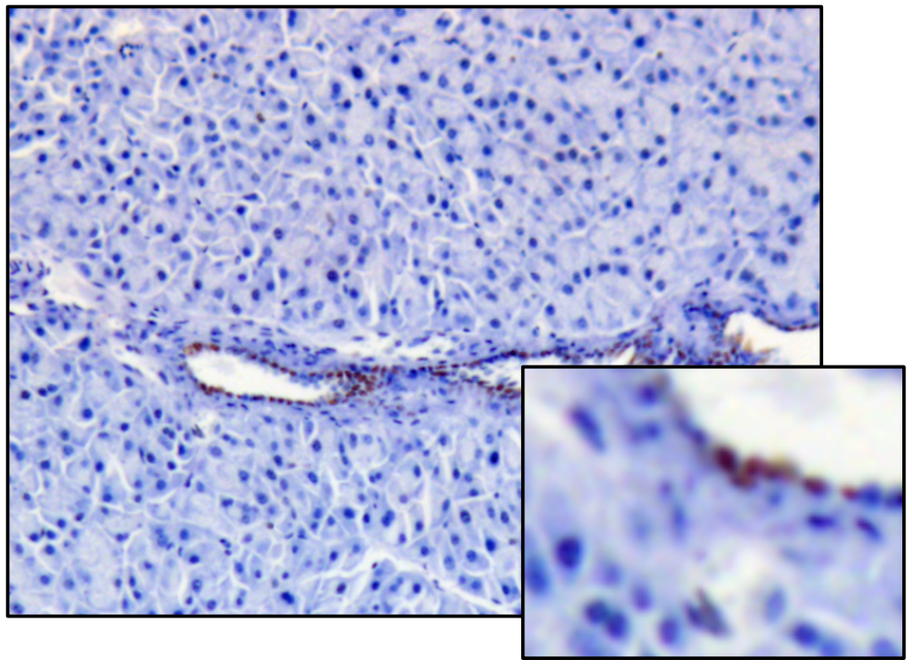


mutant KRAS
(Pancreas ONLY)

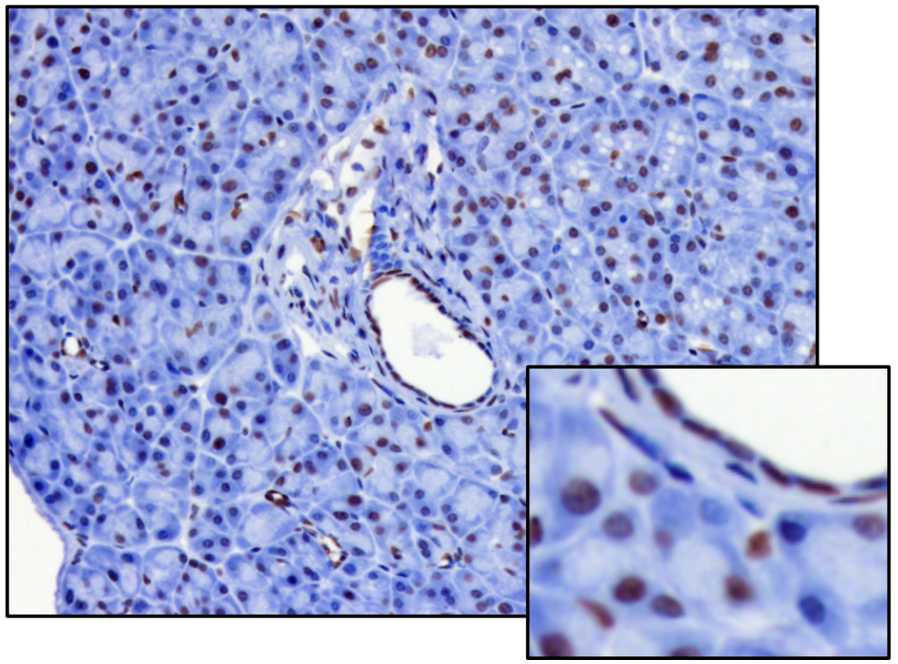
Histone acetylation is elevated in PDA

AcH4 (K5/8/12/16ac)

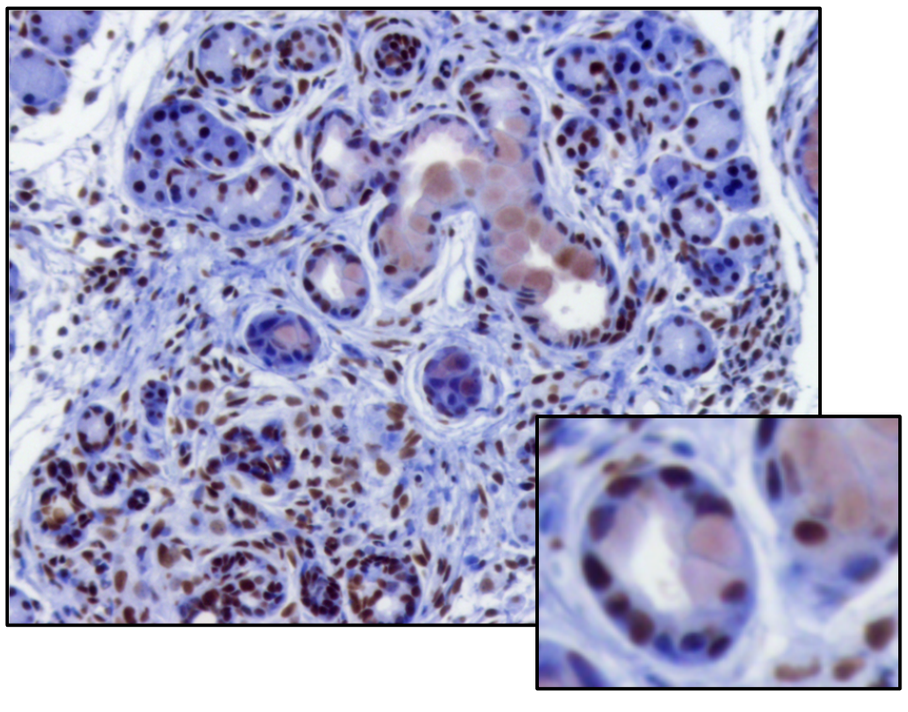
Kras WT



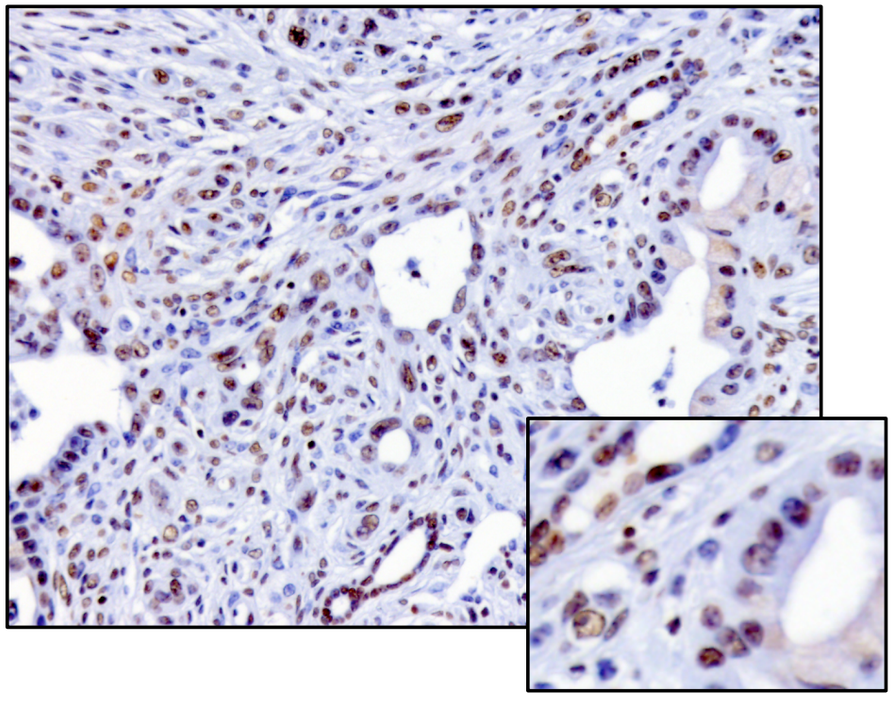
KrasG12D - Normal area



KrasG12D - PanIN

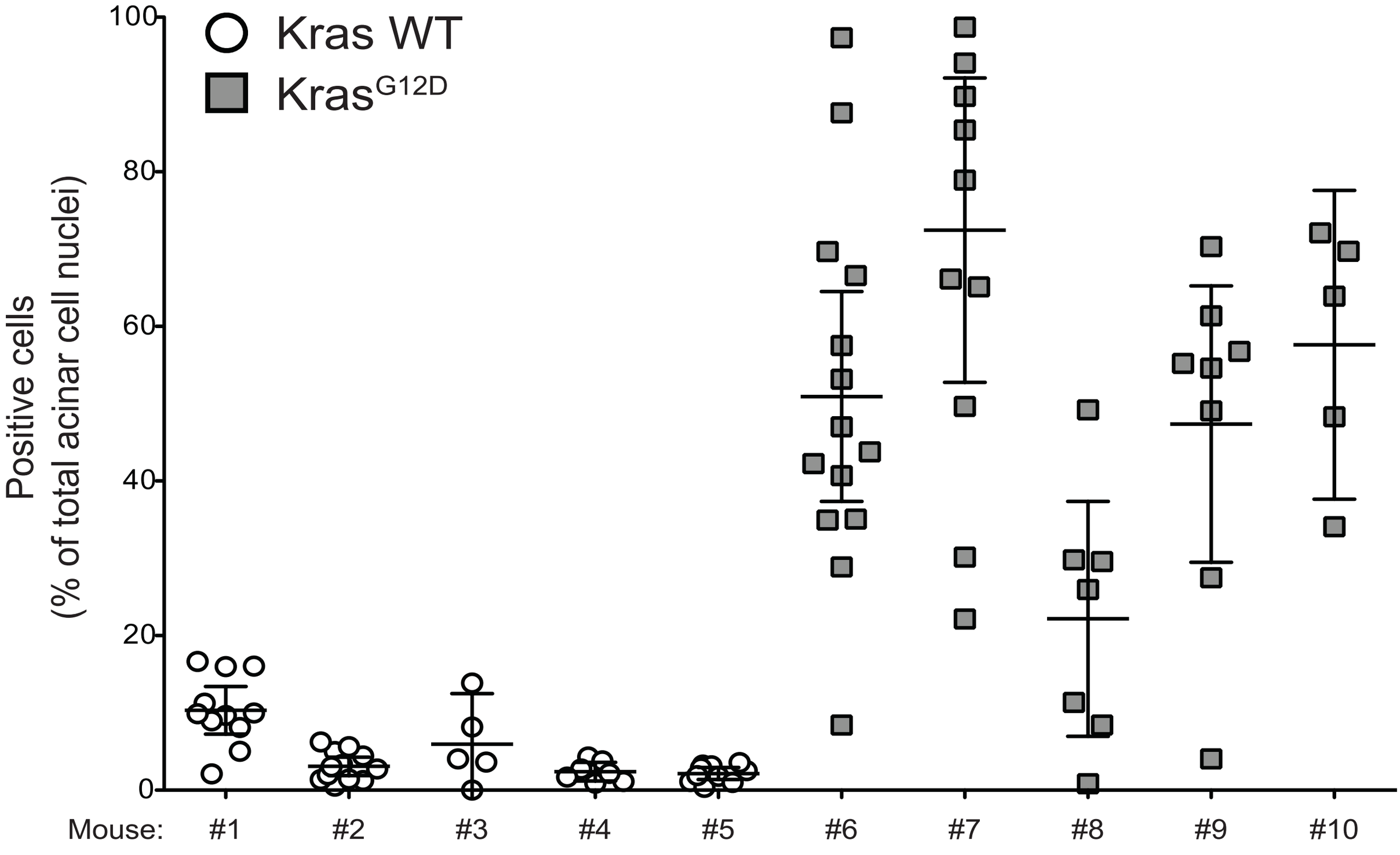


KrasG12D - Tumor

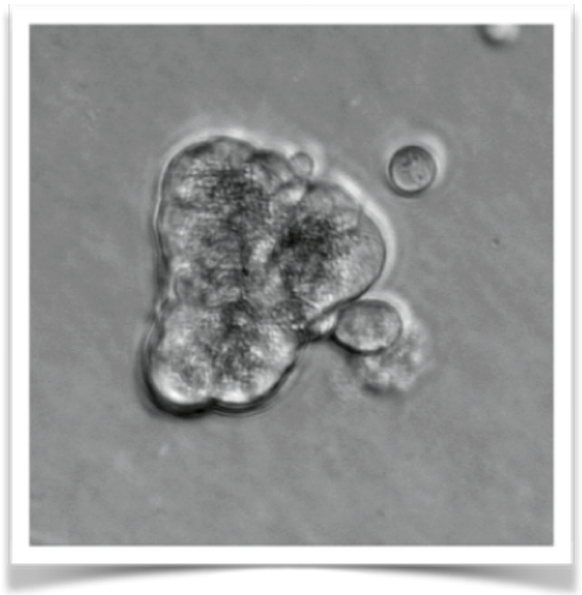


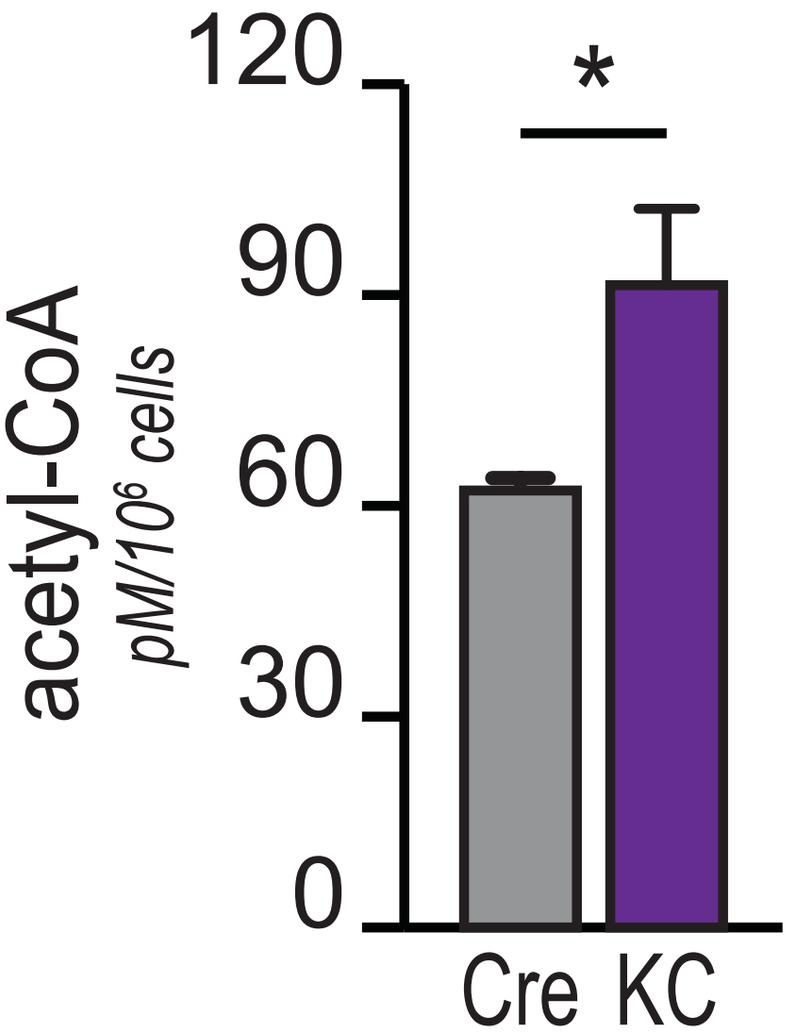
KPC: mutant Kras; P53 haplodeficiency

Histone acetylation is elevated in acinar cells



Oncogenic KRAS elevates acetyl-CoA availability in premalignant acinar cells

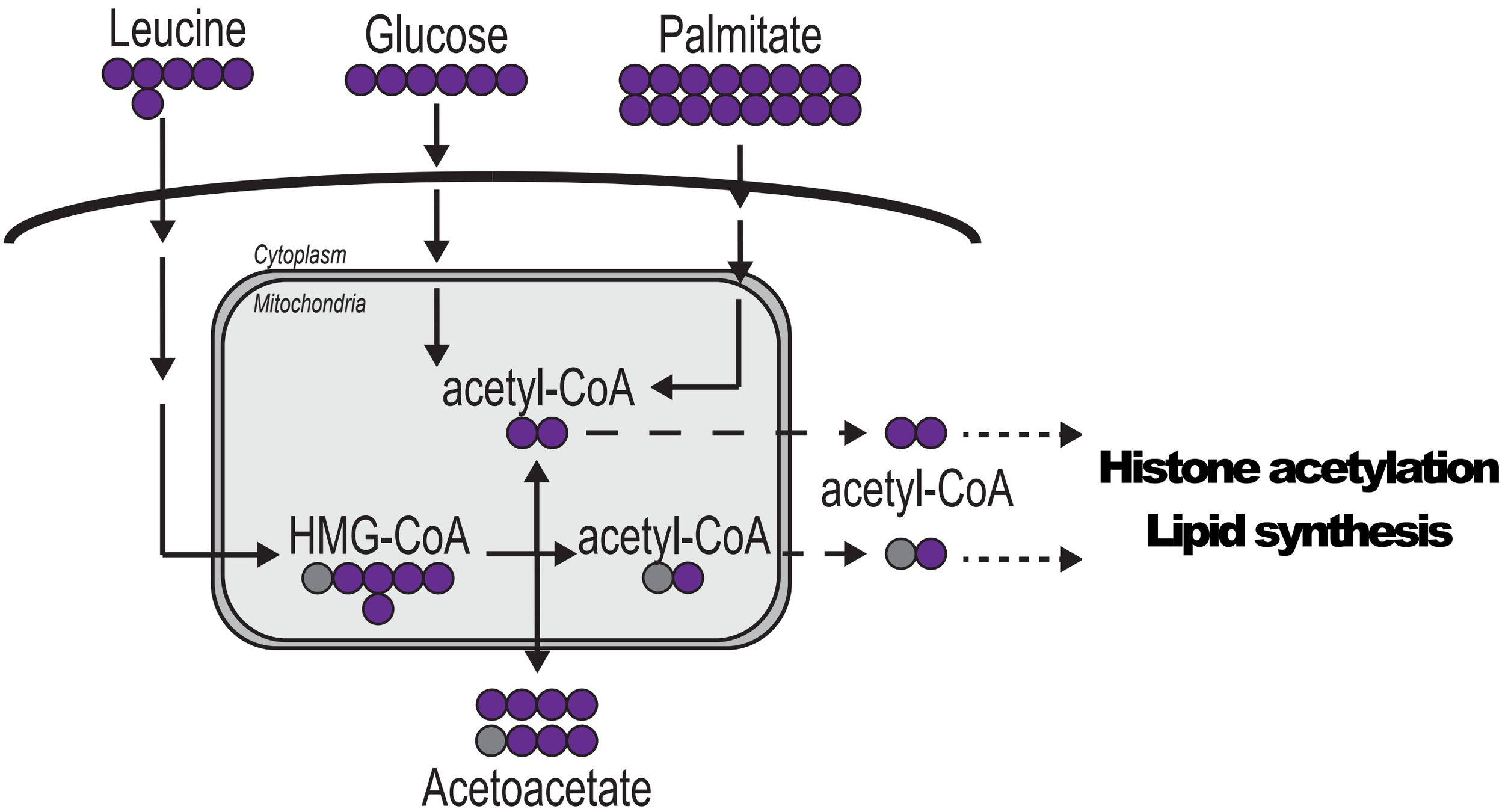




Isolated acinar cells

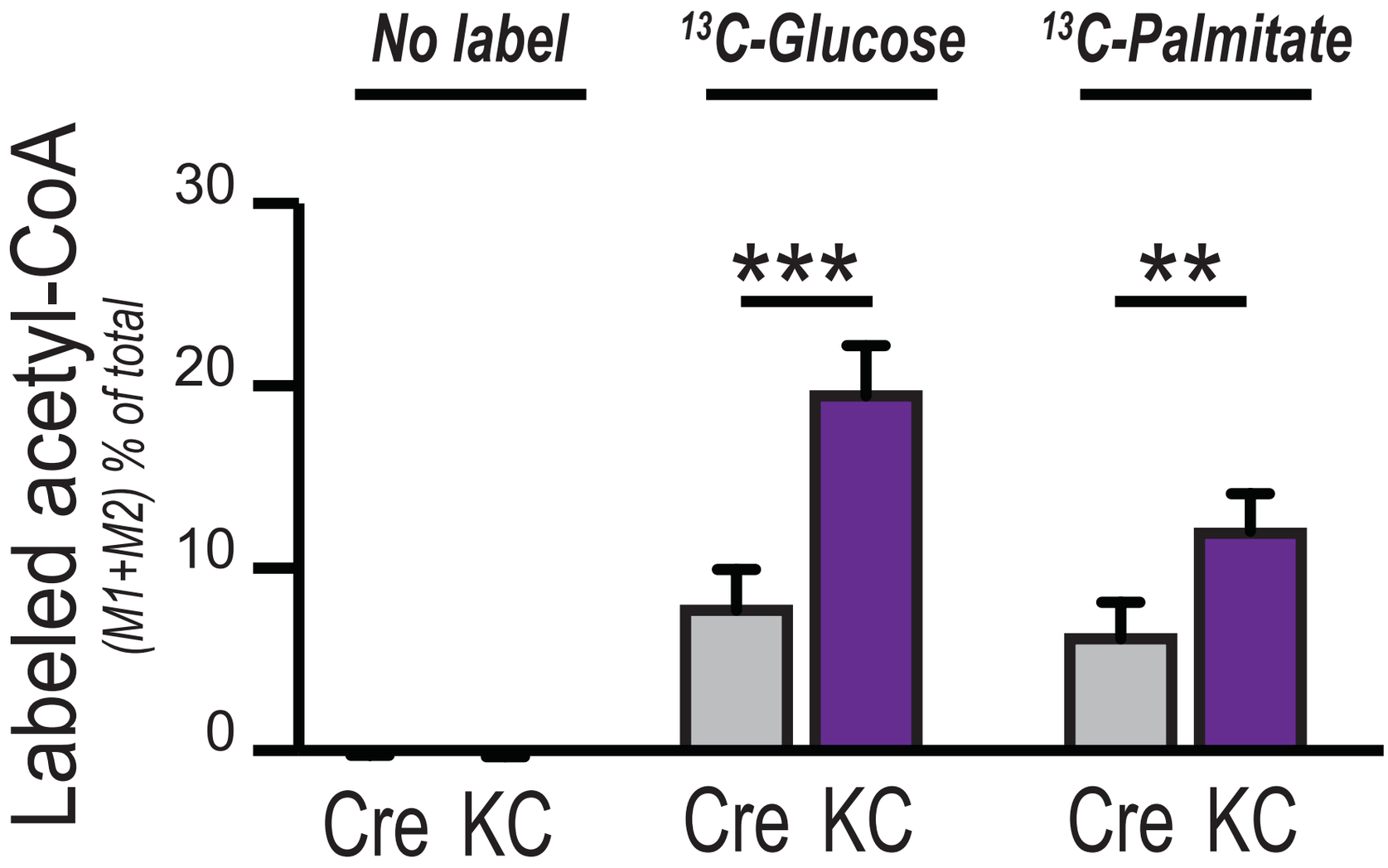
Carrer et al, Cancer Discov., 2019

Nutrients are catabolized into acetyl-CoA



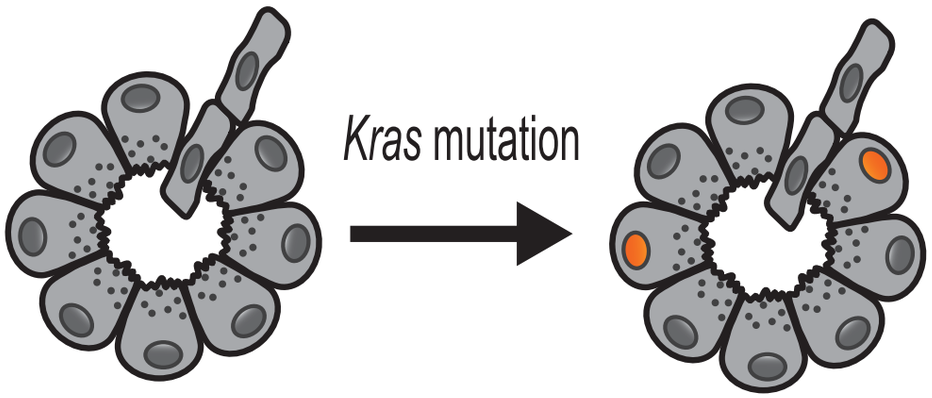
Isolated acinar cells ex vivo

Oncogenic KRAS increases contribution of Glucose and Palmitate to the acetyl-CoA pool



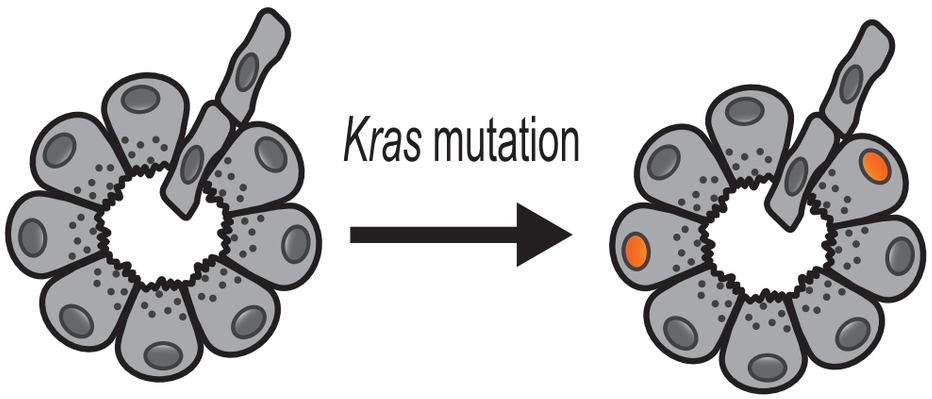
Isolated acinar cells

Carrer et al, Cancer Discov., 2019



Oncogenic KRAS augments acetyl-CoA availability

- increased contribution from glucose and palmitate in $KRAS^{G12D}$-expressing acinar cells



Oncogenic KRAS augments acetyl-CoA availability

- increased contribution from glucose and palmitate in $KRAS^{G12D}$-expressing acinar cells

Impact for tumorigenesis?

AKT inhibition delays Acinar-to-Ductal Metaplasia in vitro

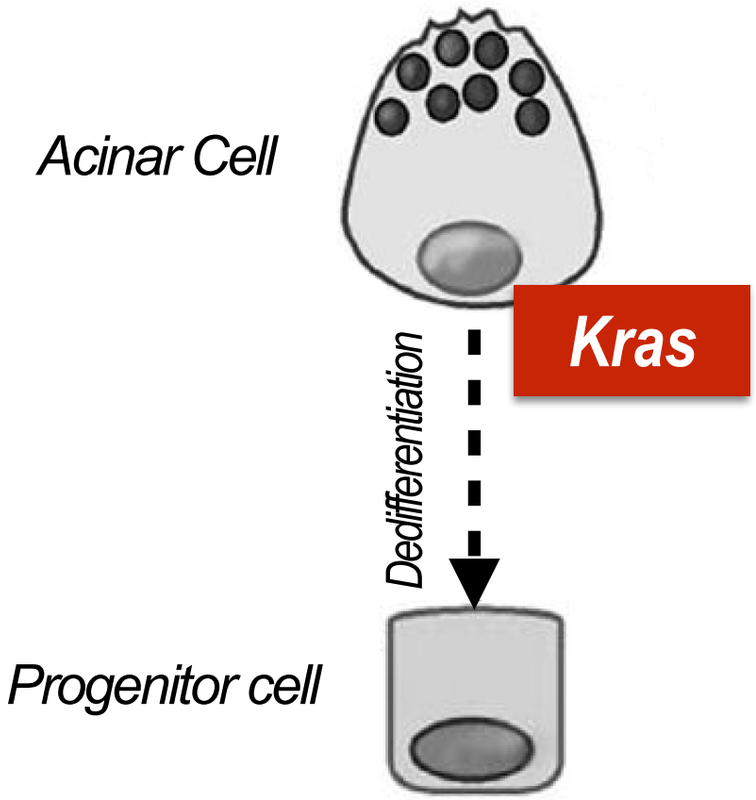
Acinar Cell

AKT inhibition delays Acinar-to-Ductal Metaplasia in vitro

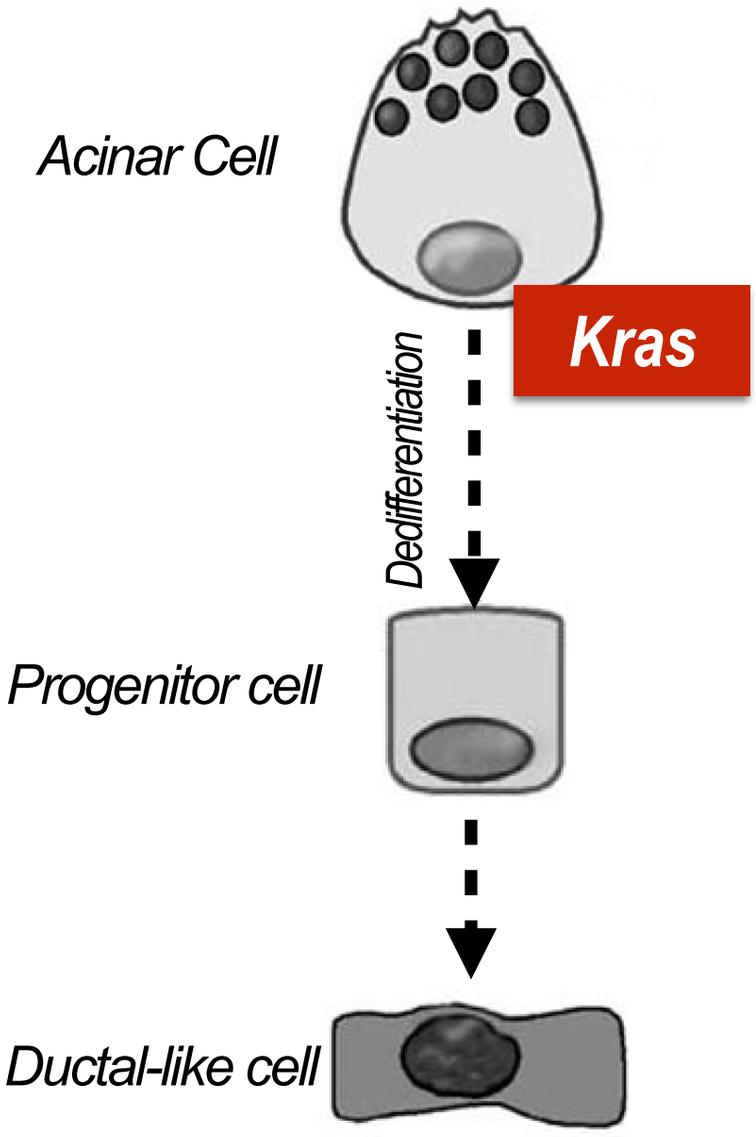
Acinar Cell

Kras

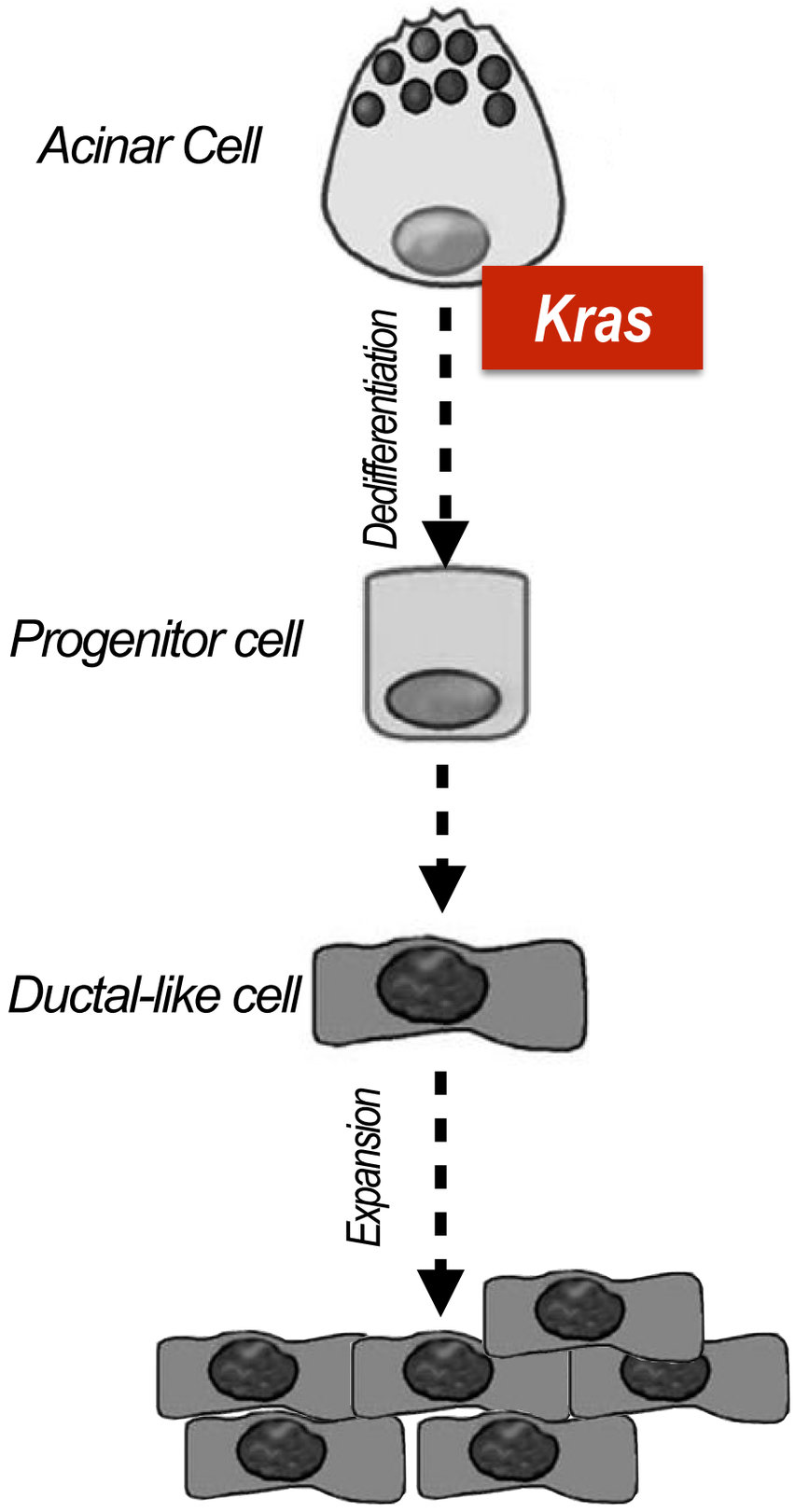
AKT inhibition delays Acinar-to-Ductal Metaplasia in vitro



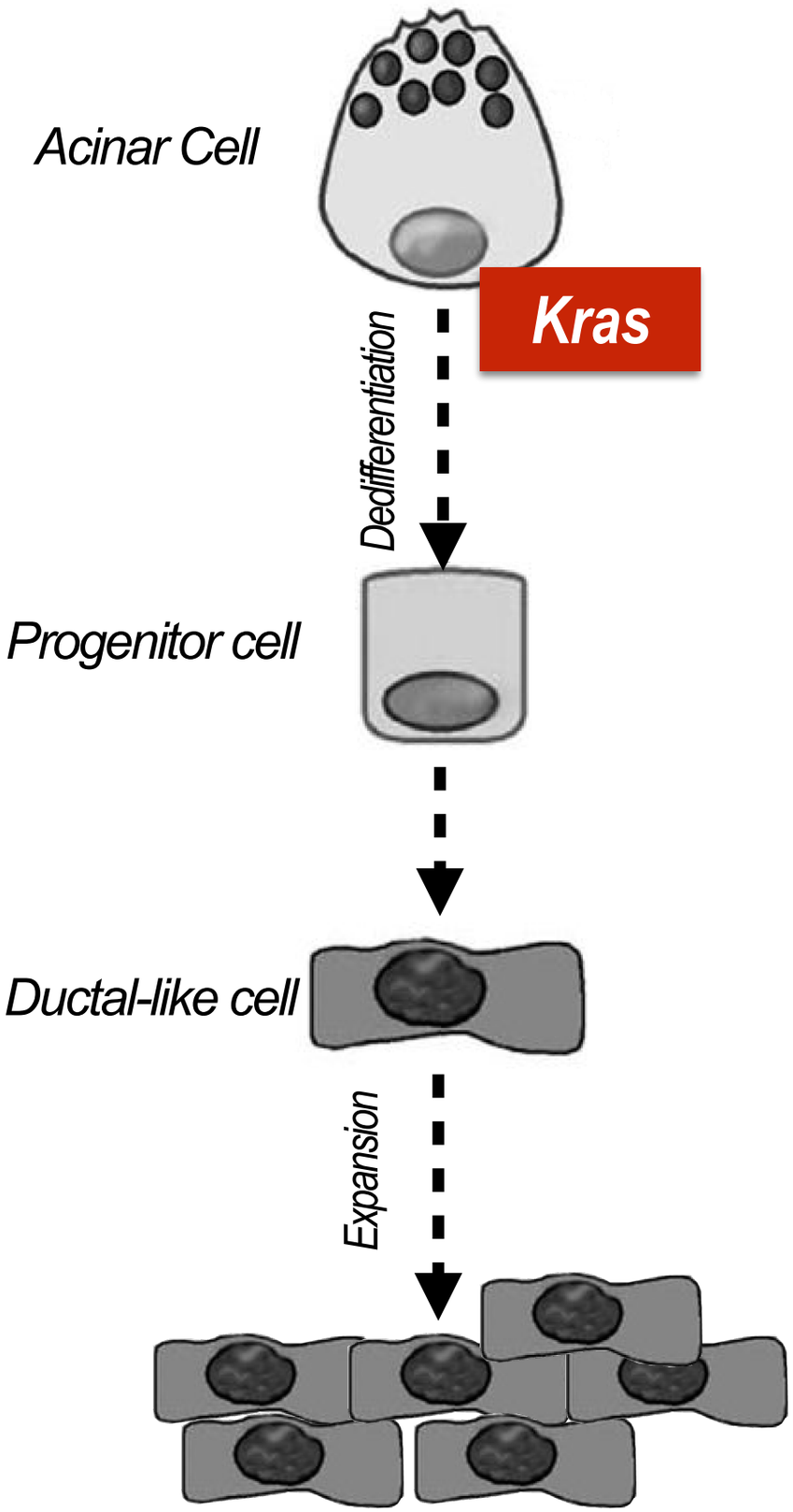
AKT inhibition delays Acinar-to-Ductal Metaplasia in vitro



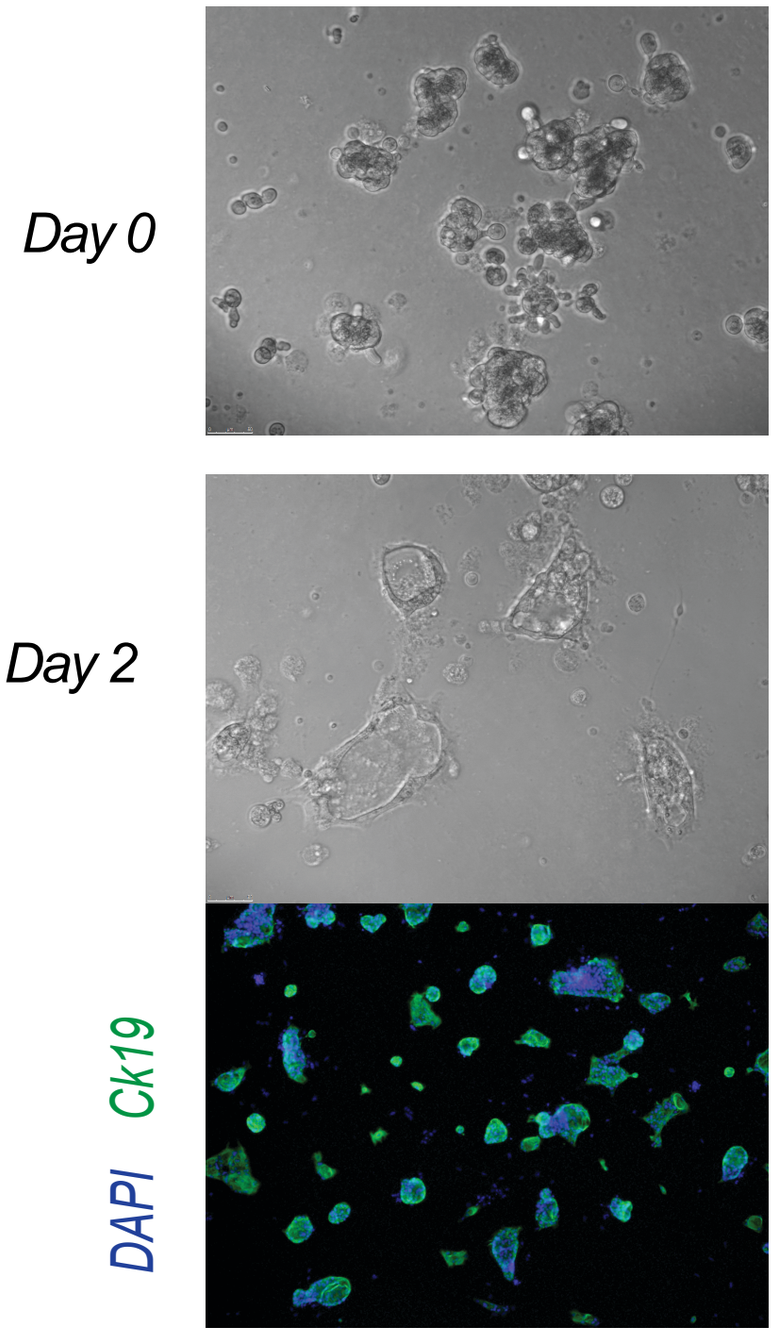
AKT inhibition delays Acinar-to-Ductal Metaplasia in vitro



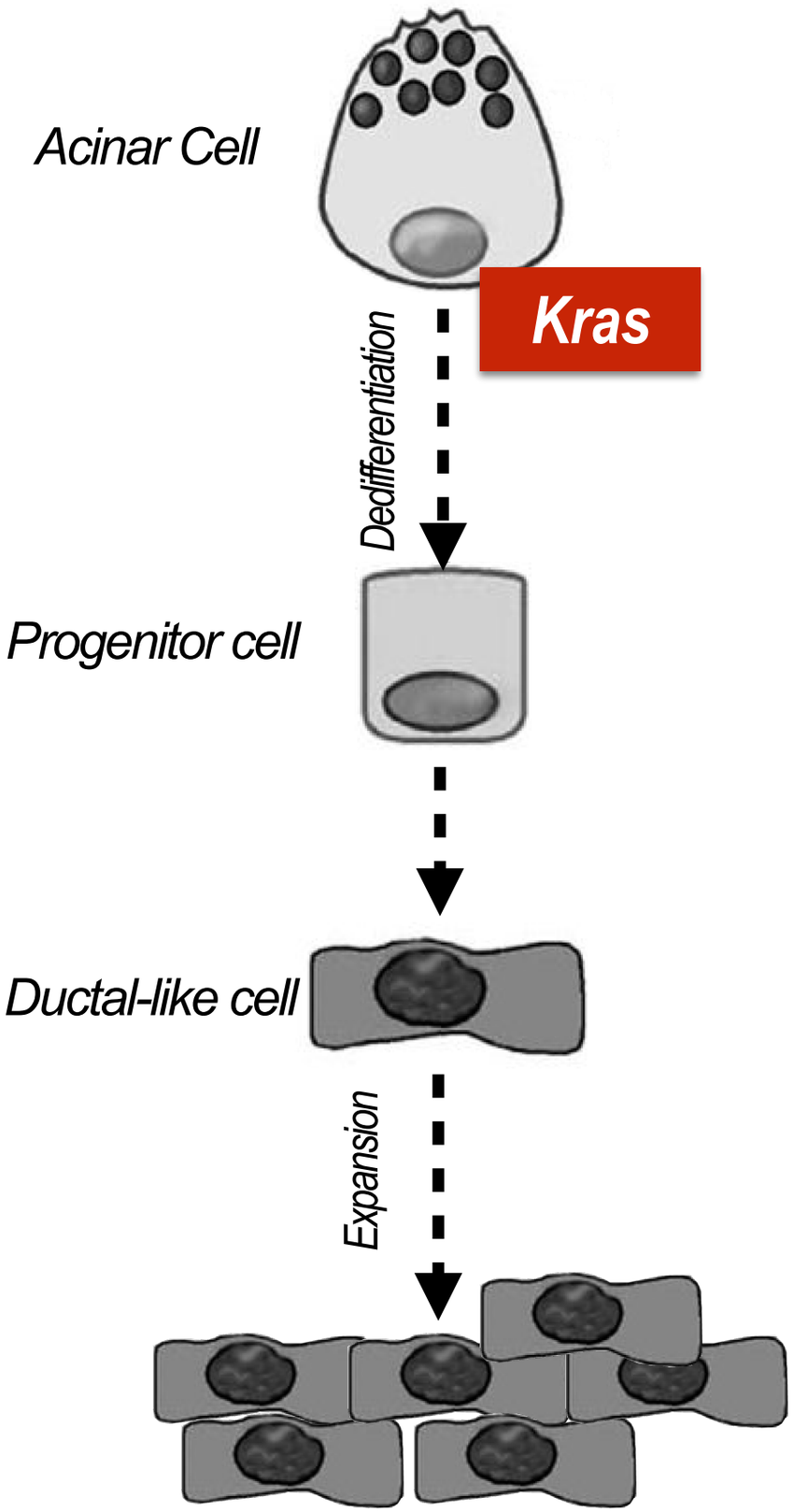
AKT inhibition delays Acinar-to-Ductal Metaplasia in vitro

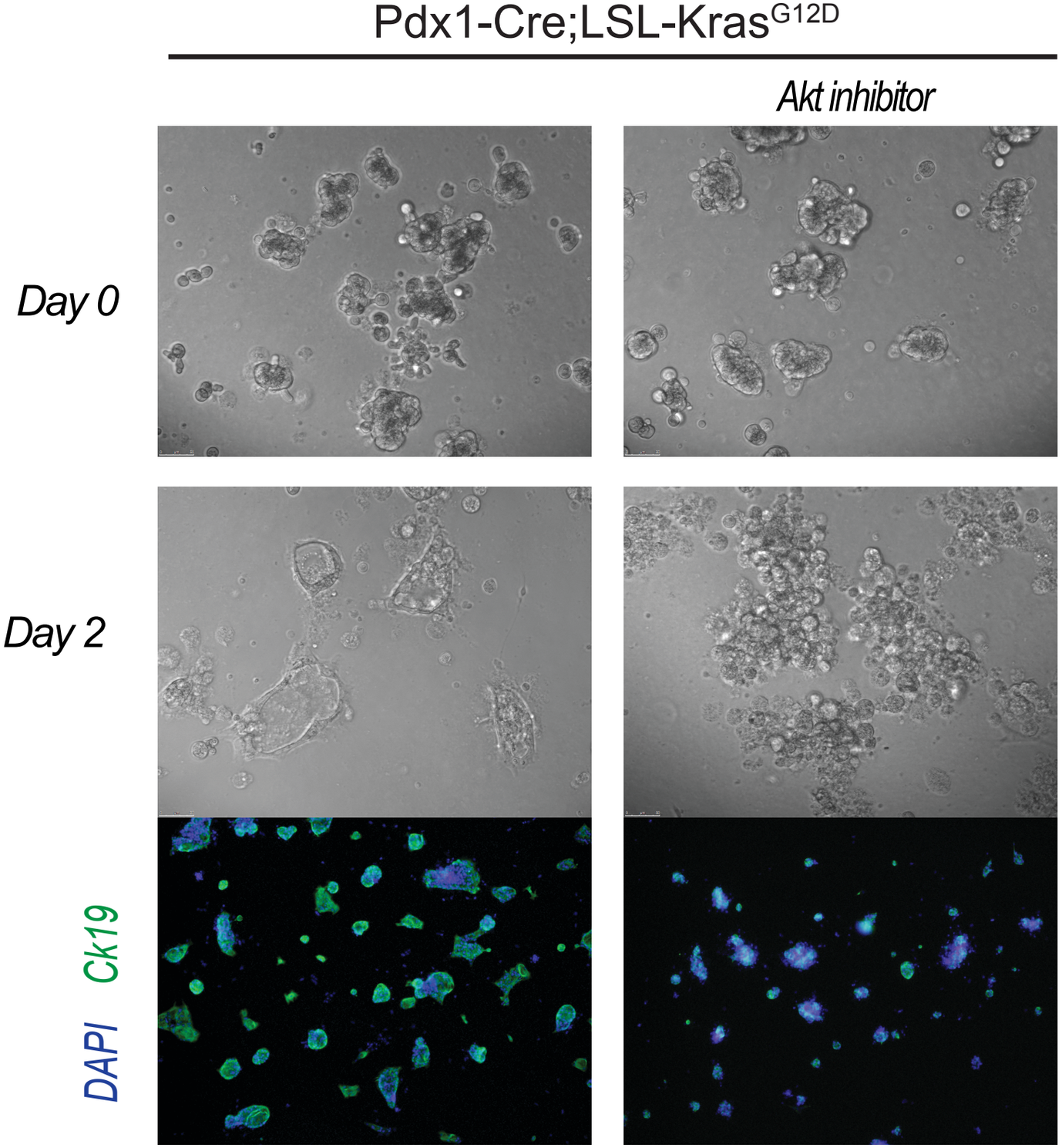


Pdx1-Cre;LSL-Kras^{G12D}

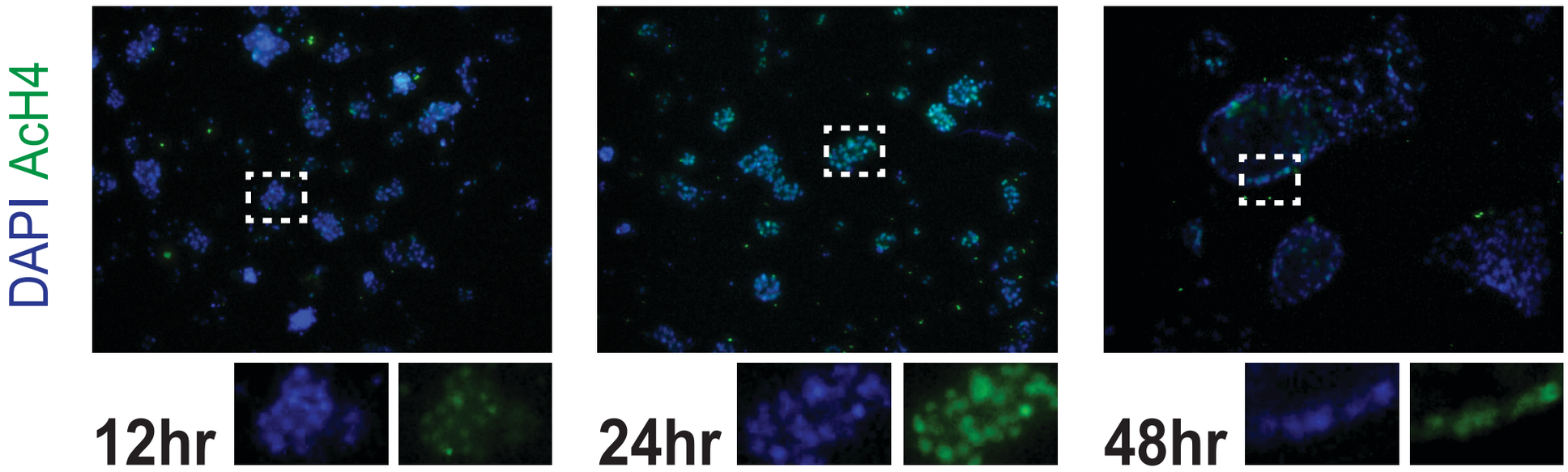


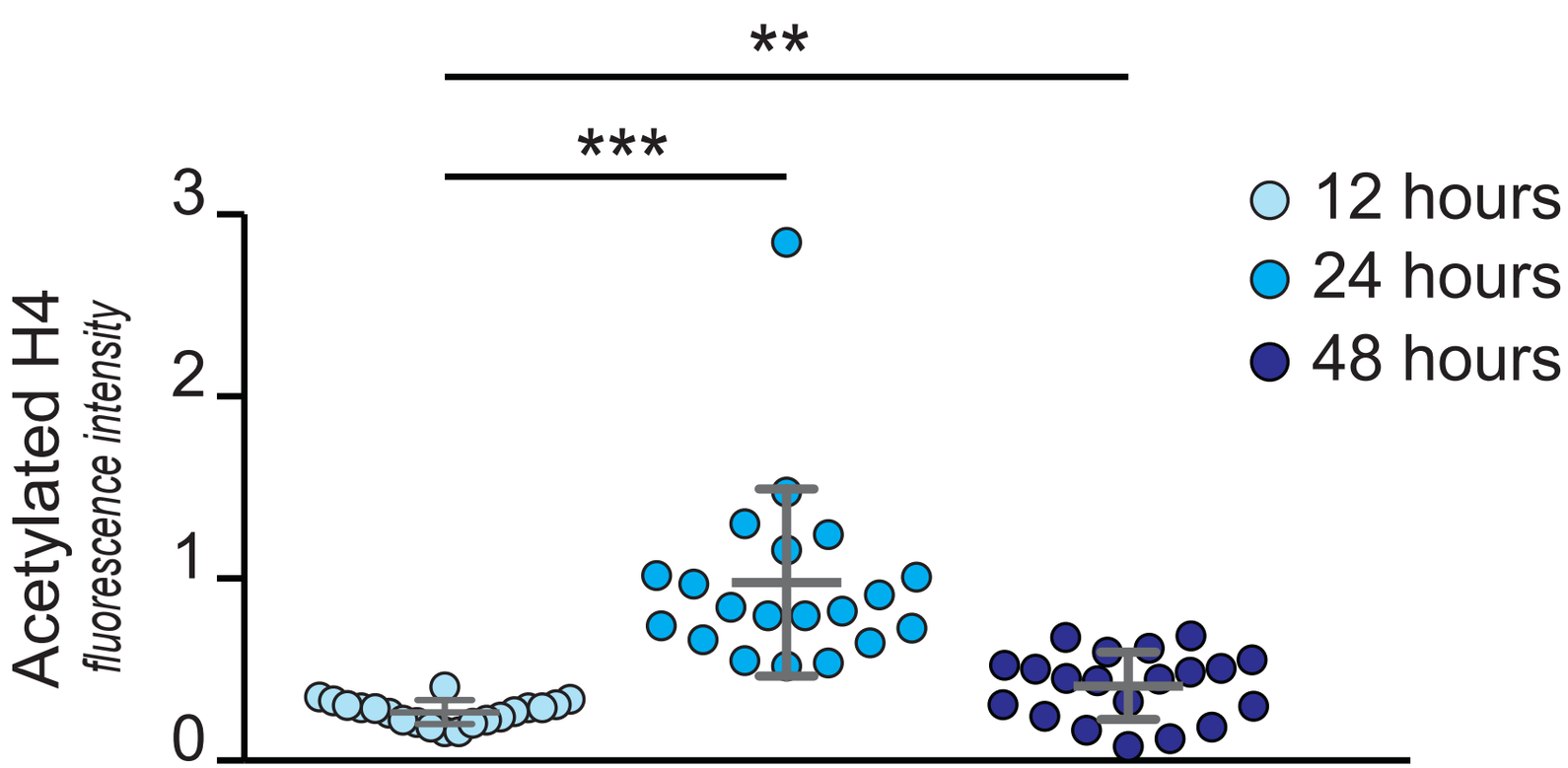
AKT inhibition delays Acinar-to-Ductal Metaplasia in vitro

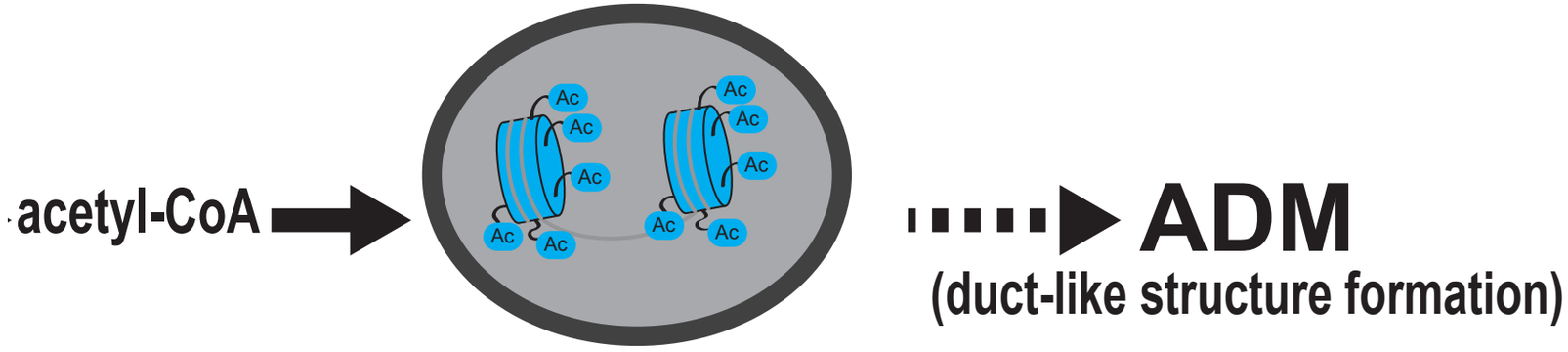




Histone acetylation increases during ADM






acetyl-CoA
Ac
Ac
Ac
Ac
Ac
Ac
Ac
Ac
Ac
ADM
(duct-like structure formation)

JQ1

acetyl-CoA

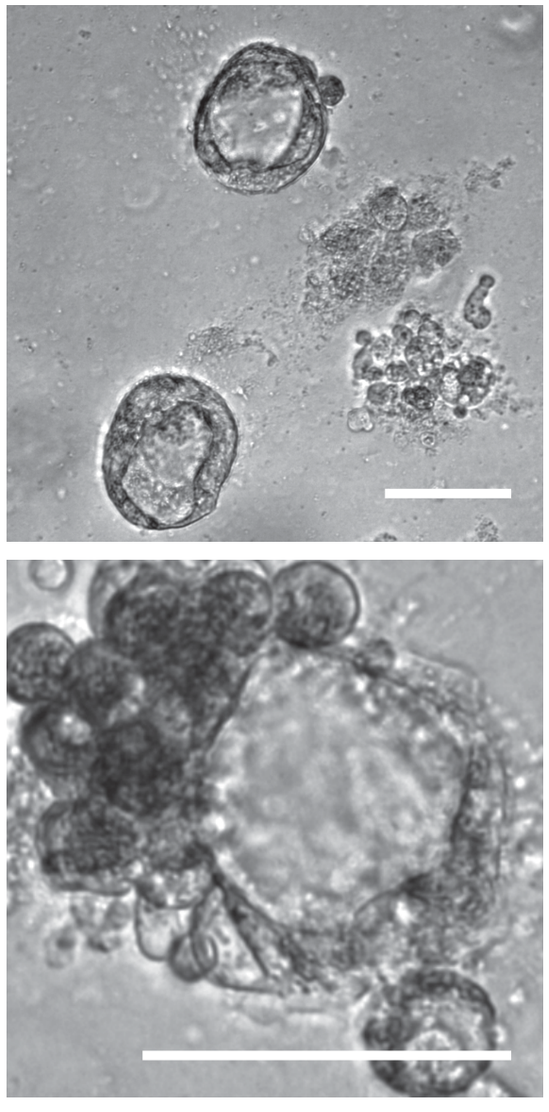
Ac

ADM

(duct-like structure formation)

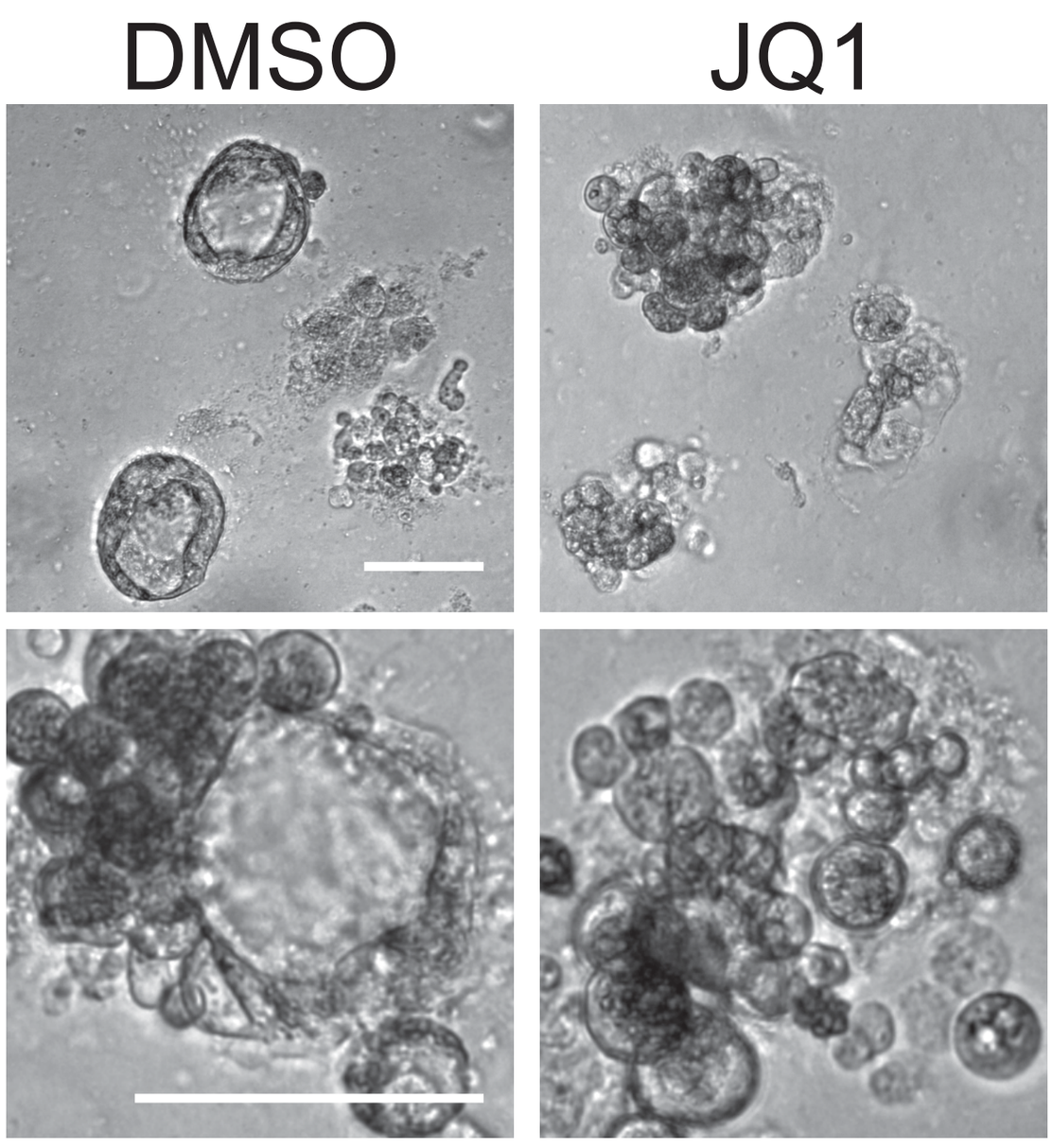
Mitochondrial-dependent histone acetylation promotes ADM

DMSO



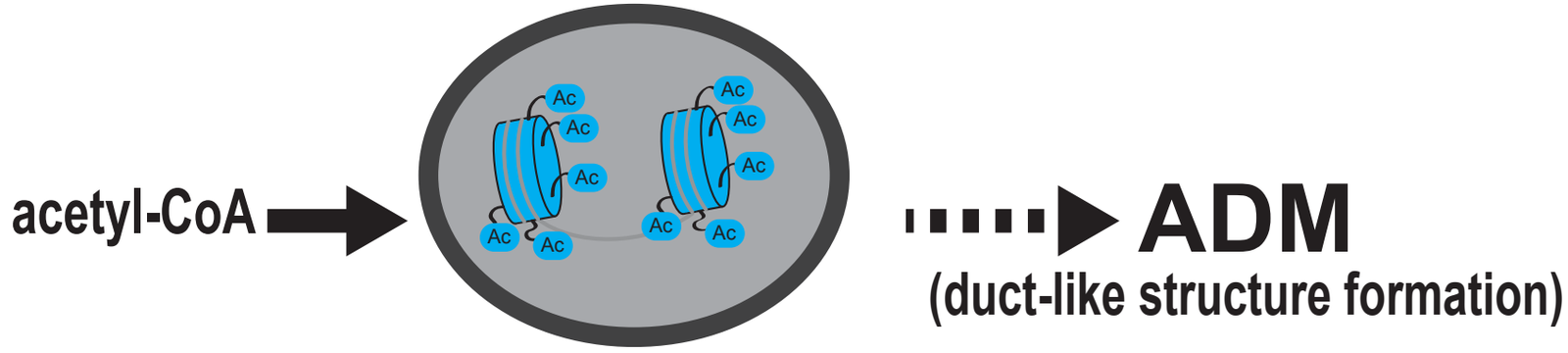
Carrer et al, Cancer Discov., 2019

Mitochondrial-dependent histone acetylation promotes ADM

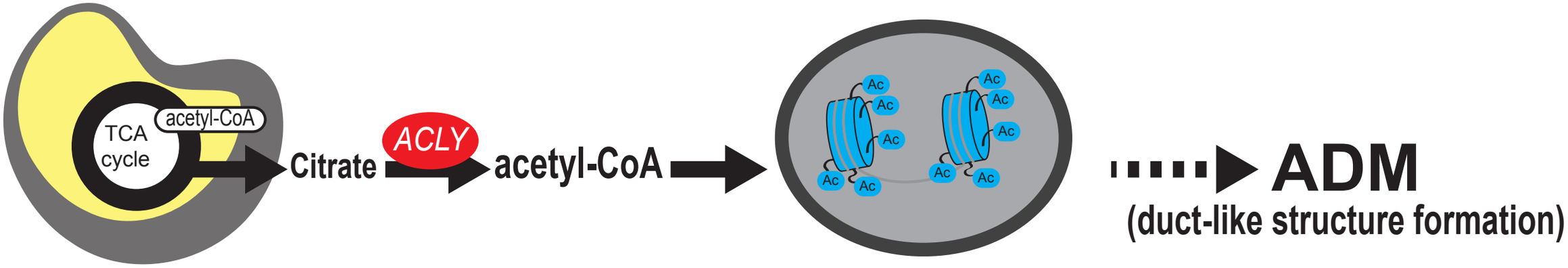


Inhibits reading of acetyl lysines

Carrer et al, Cancer Discov., 2019


acetyl-CoA
Ac
Ac
Ac
Ac
Ac
Ac
Ac
Ac
Ac
ADM
(duct-like structure formation)

KRAS mutant


TCA
cycle
acetyl-CoA
Citrate
ACLY
acetyl-CoA
Ac
ADM
(duct-like structure formation)

BTA

KRAS mutant

TCA cycle

acetyl-CoA

Citrate

ACLY

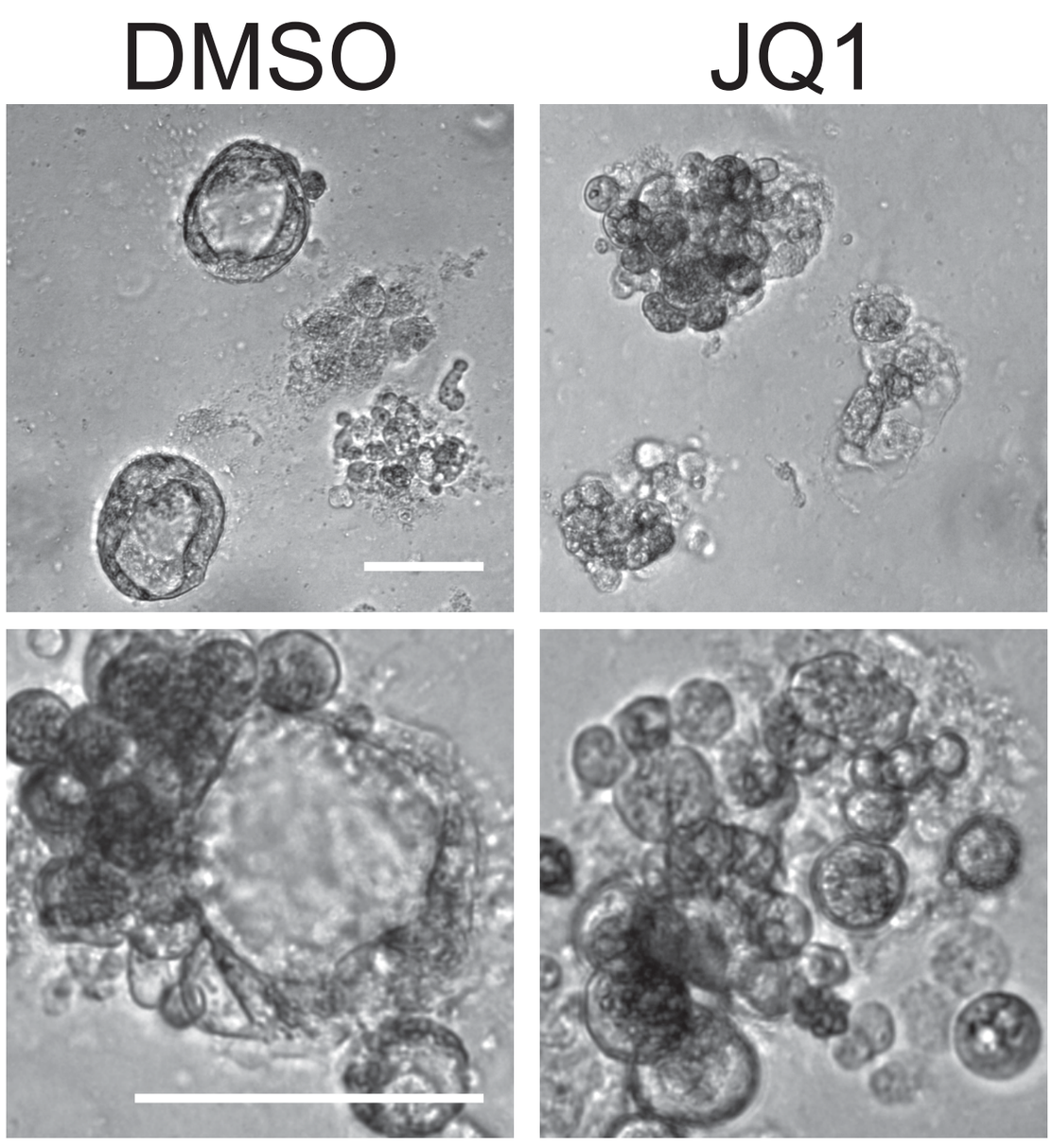
acetyl-CoA

Ac

ADM

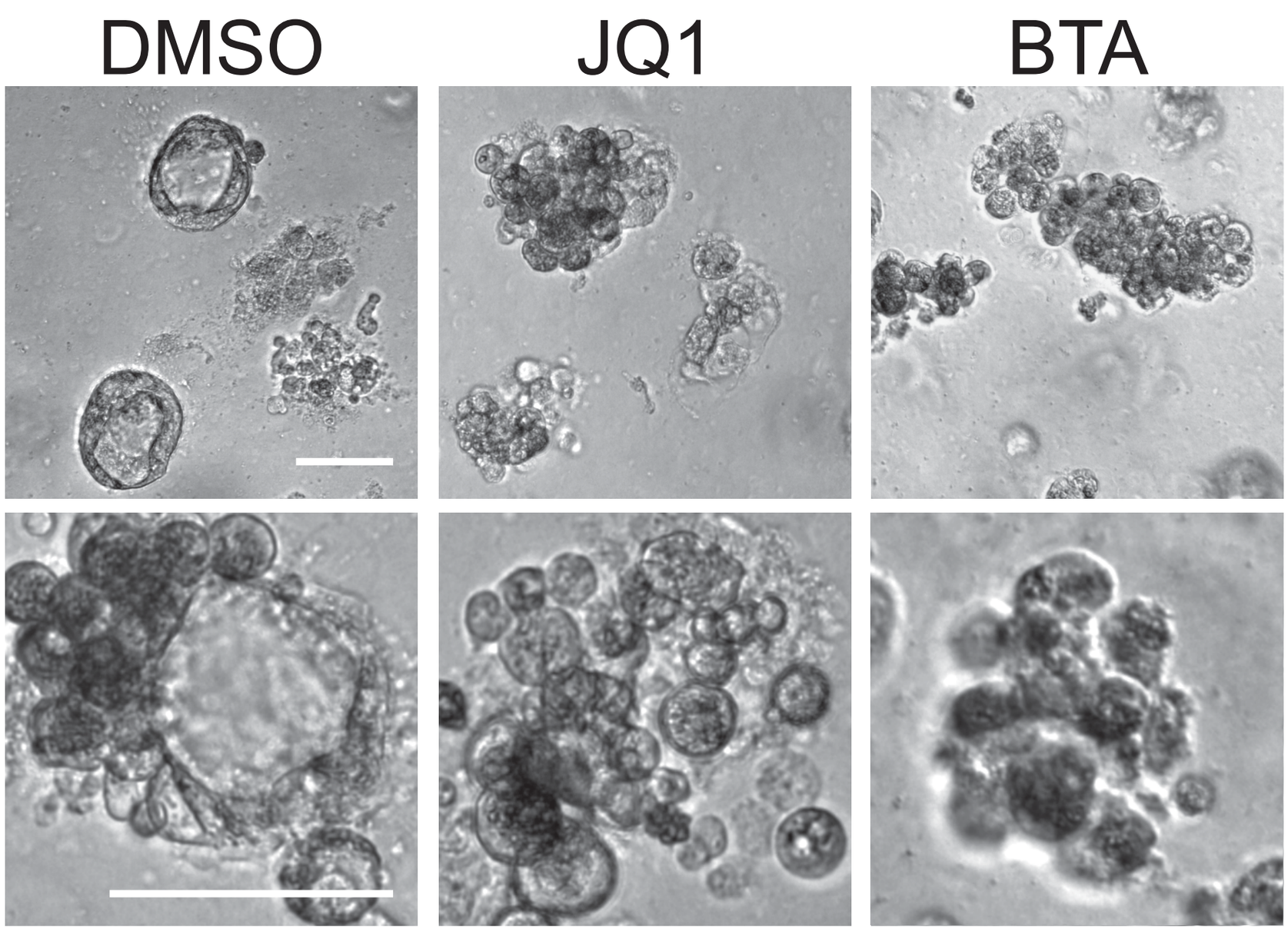
(duct-like structure formation)

Mitochondrial-dependent histone acetylation promotes ADM



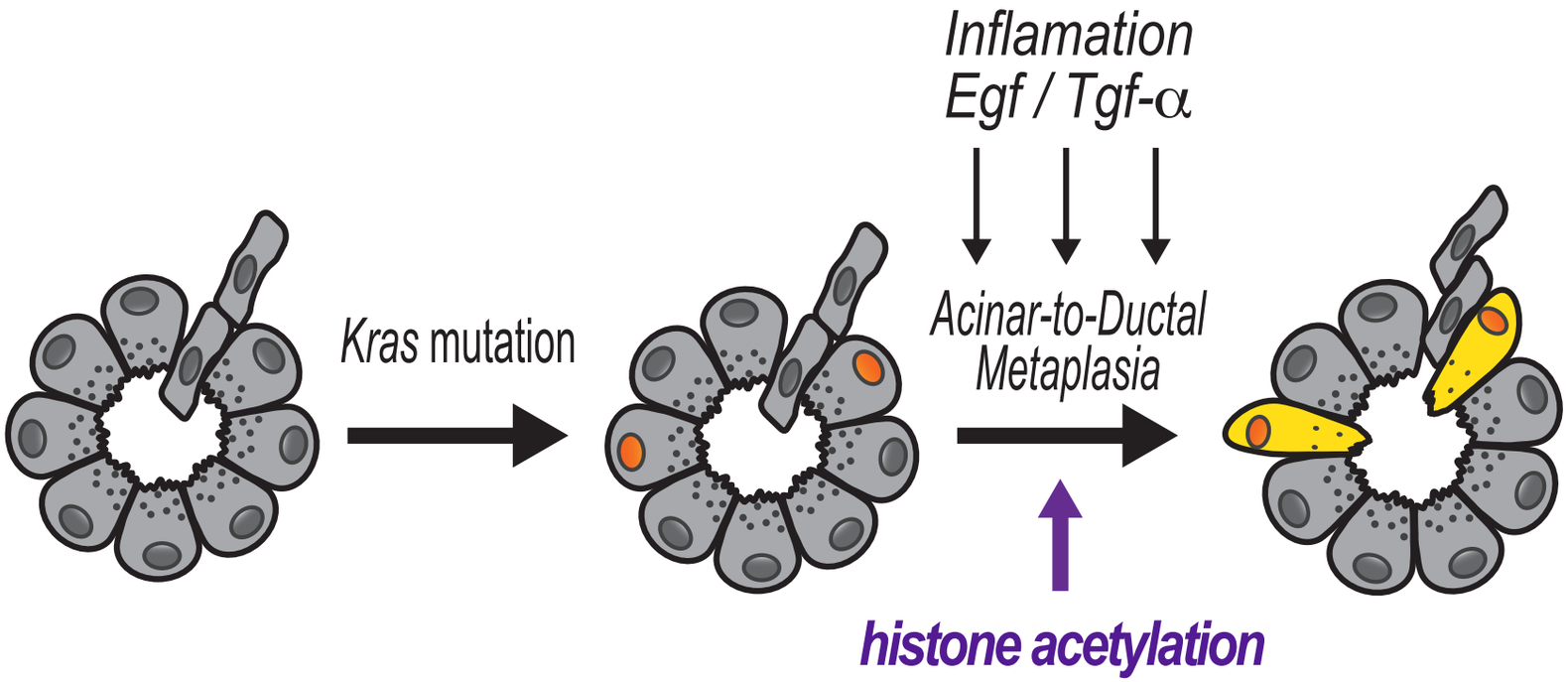
Inhibits reading
of acetyl lysines

Mitochondrial-dependent histone acetylation promotes ADM



Inhibits reading of acetyl lysines

Inhibits CiC -citrate export-

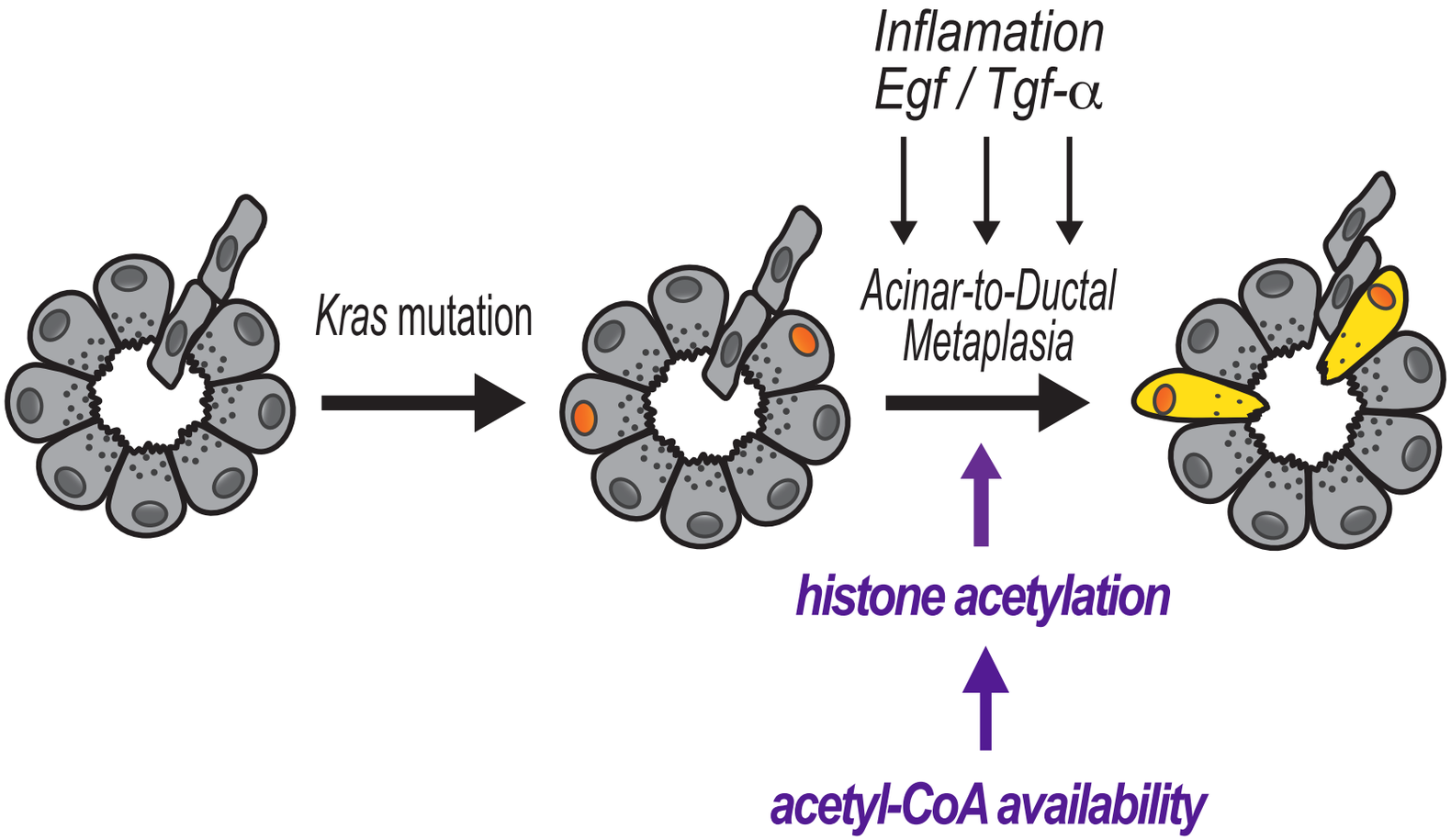


Oncogenic KRAS augments acetyl-CoA availability

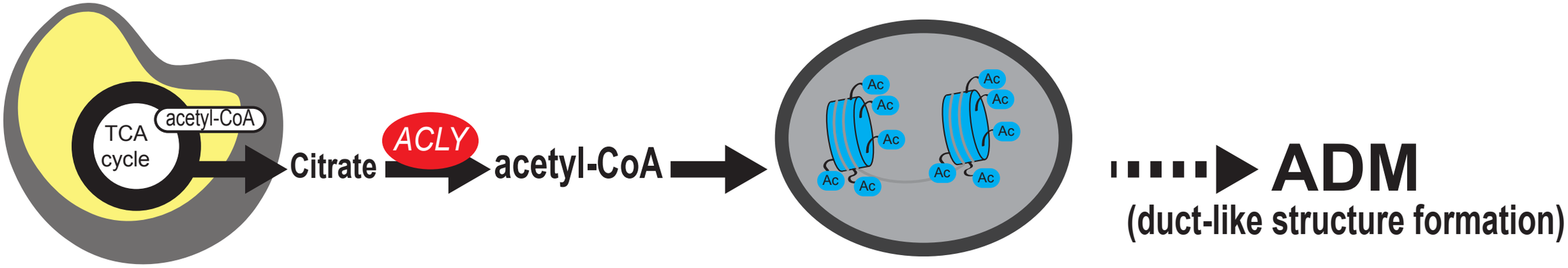
- increased contribution from glucose and palmitate in KRAS-expressing acinar cells

Elevated acetyl-CoA availability promotes ADM

- histone hyper-acetylation


Inflamation
Egf / Tgf-α
Kras mutation
Acinar-to-Ductal
Metaplasia
histone acetylation
acetyl-CoA availability

KRAS mutant


TCA
cycle
acetyl-CoA
Citrate
ACLY
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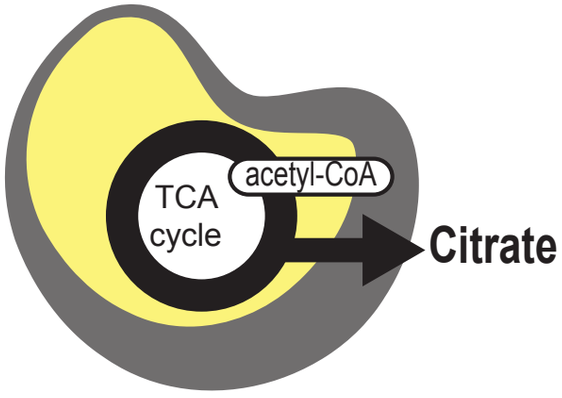
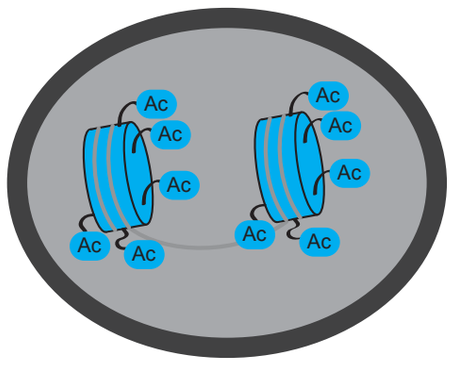
ADM
(duct-like structure formation)

KRAS mutant

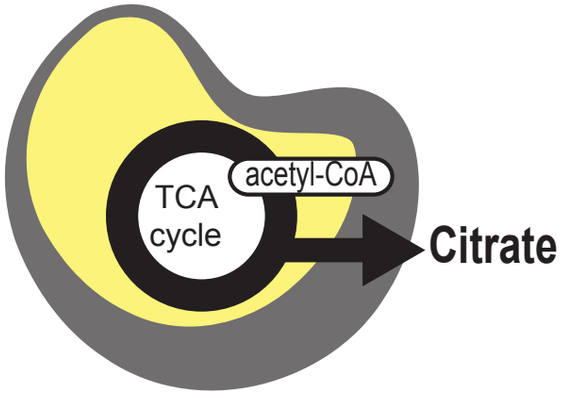


acetyl-CoA

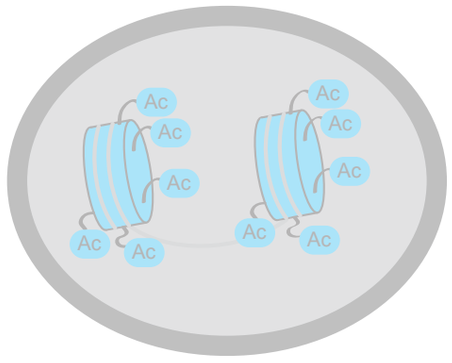


ADM
(duct-like structure formation)

KRAS mutant



acetyl-CoA



ADM

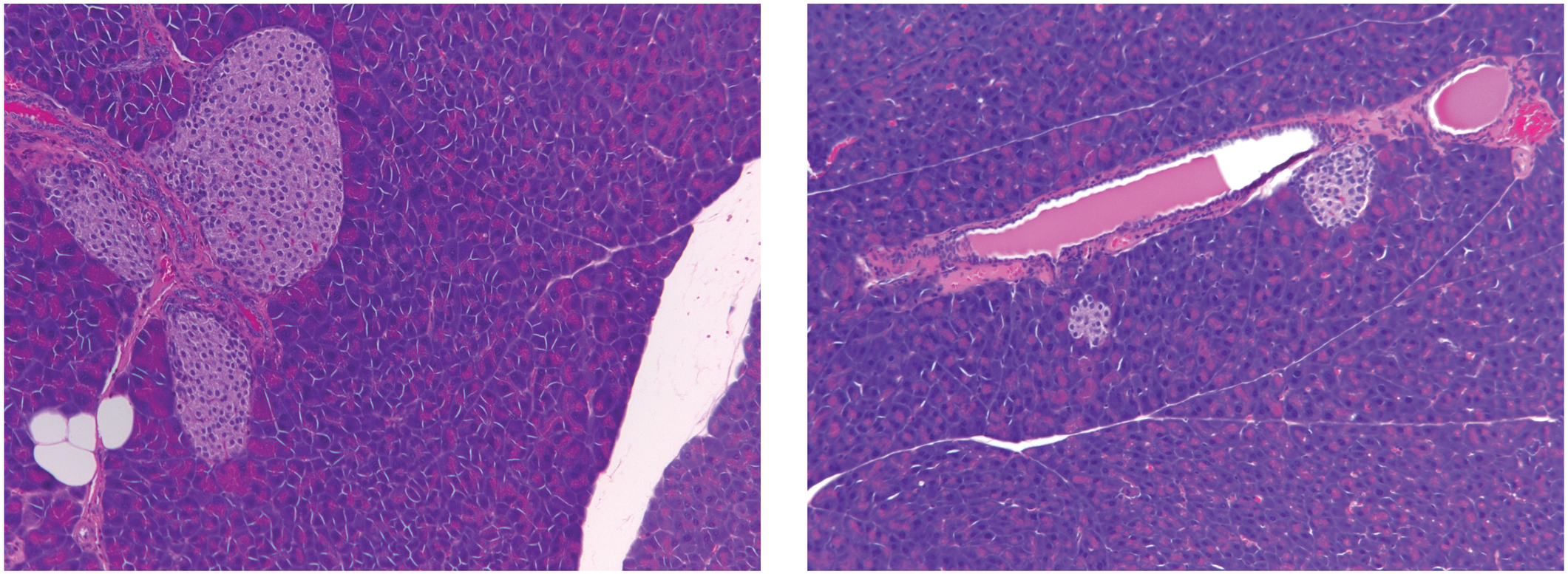
(duct-like structure formation)

Acly deficiency in the pancreas does not induce overt abnormalities

Pdx1Cre

Pdx1Cre;ACLY$^{fl/fl}$ (*Acly*^{PanKO})

H&E

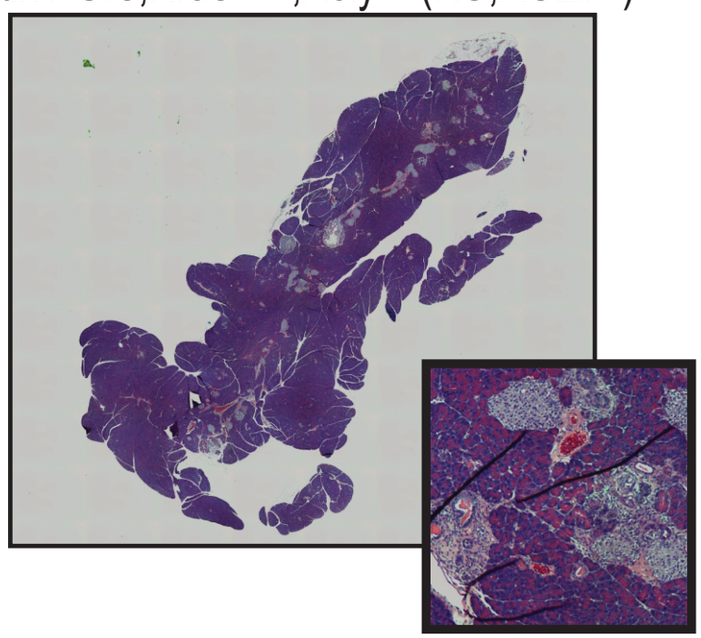


ACLY$^{fl/fl}$ mice are available at VIMM

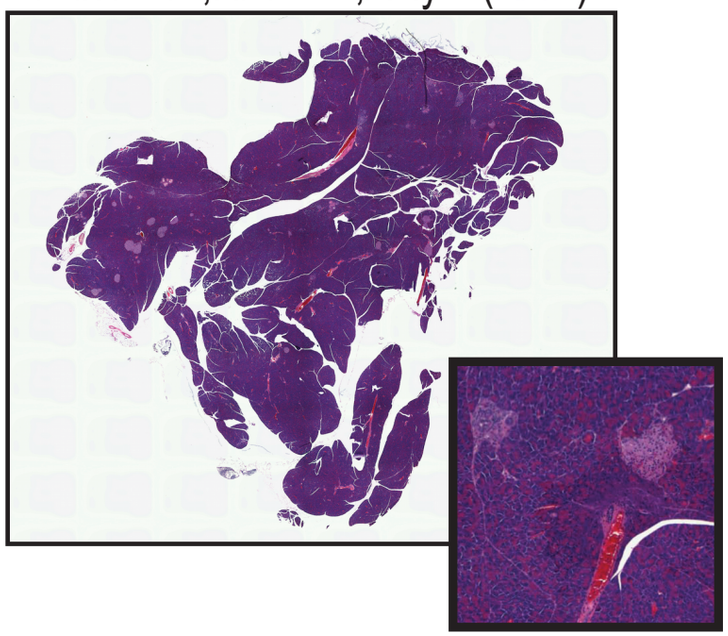
Carrer et al, Cancer Discovery, 2019

Acly deletion inhibits pancreatic tumorigenesis

Pdx1-Cre;Kras^{G12D};Acly$^{fl/+}$ (KC;ACLf/+)



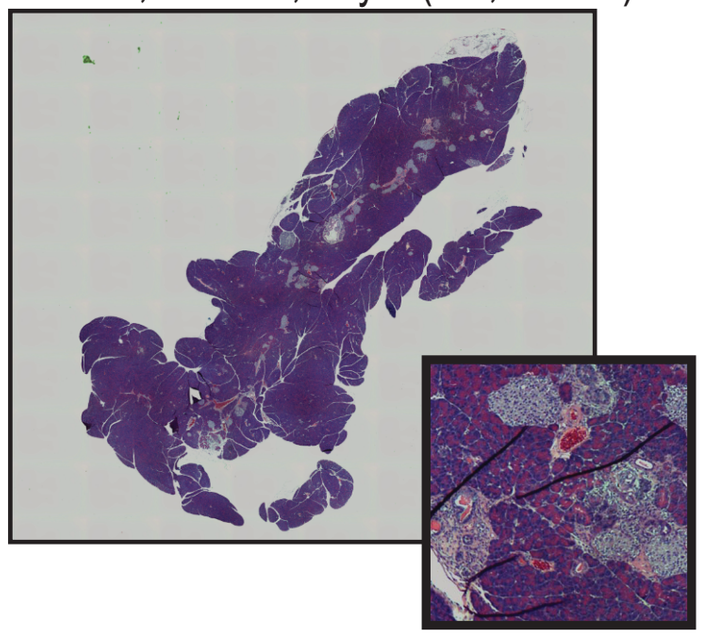
Pdx1-Cre;Kras^{G12D};Acly$^{fl/fl}$ (KAC)



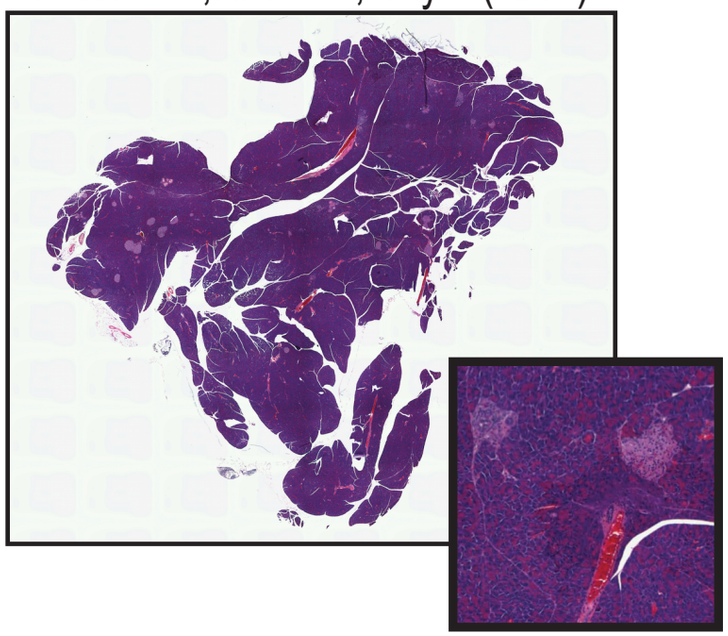
Carrer et al, Cancer Discovery, 2019

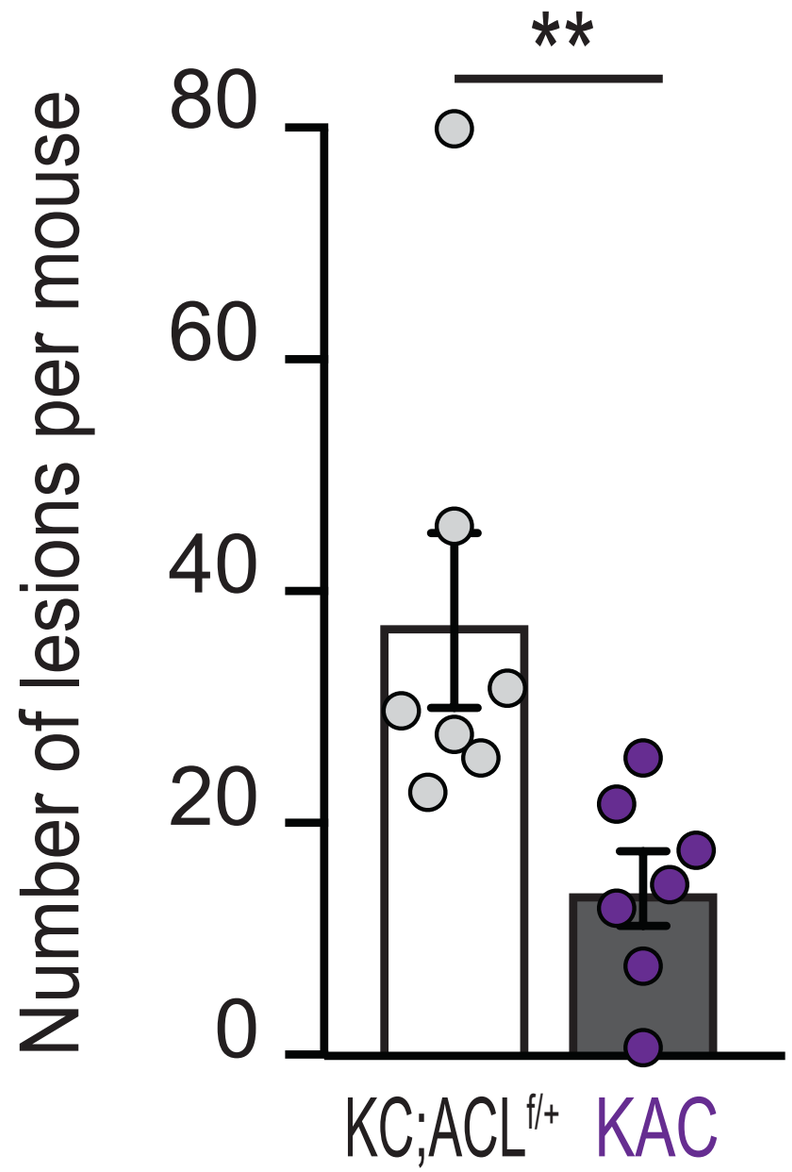
Acly deletion inhibits pancreatic tumorigenesis

Pdx1-Cre;Kras^{G12D};Acly$^{fl/+}$ (KC;ACLf/+)



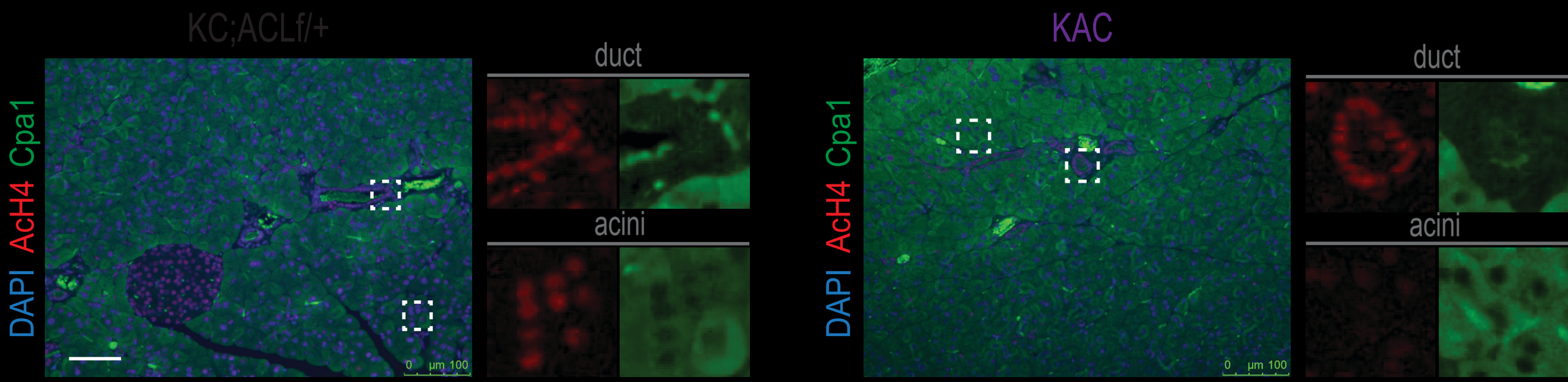
Pdx1-Cre;Kras^{G12D};Acly$^{fl/fl}$ (KAC)



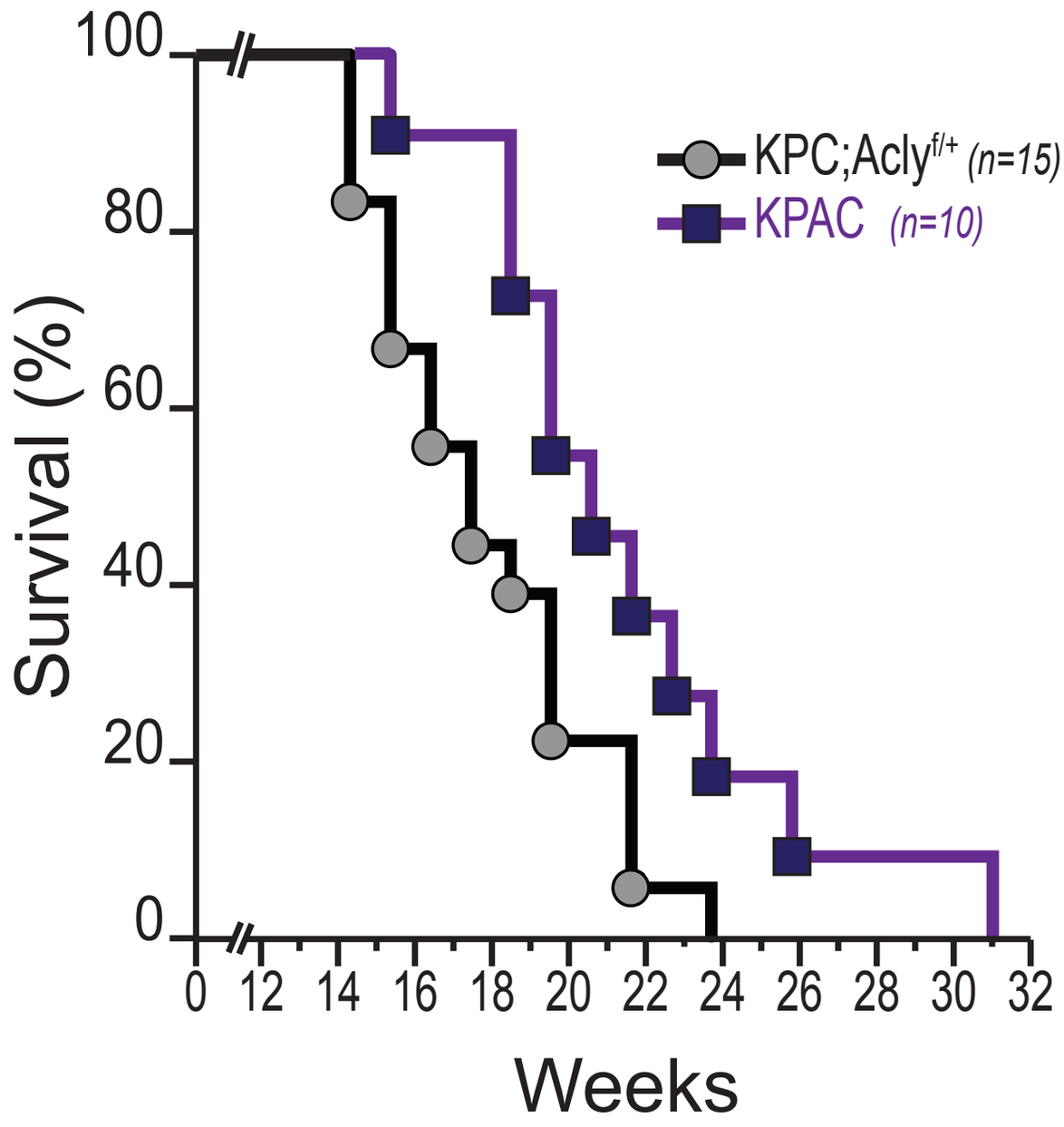


Carrer et al, Cancer Discovery, 2019

Acly deletion reduces histone acetylation in acinar cells



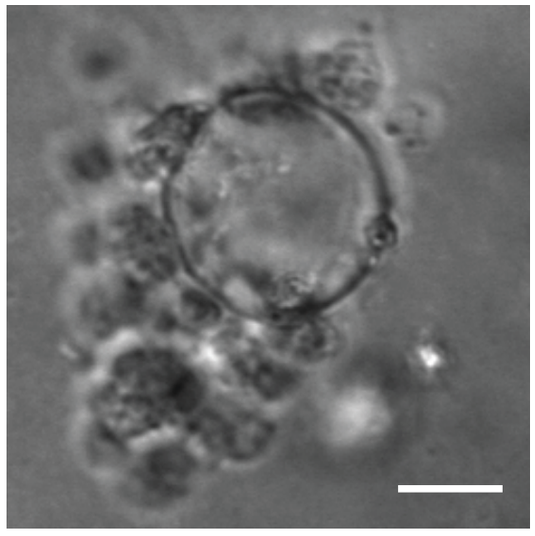
Acly deletion extends survival in a model of pancreatic tumorigenesis



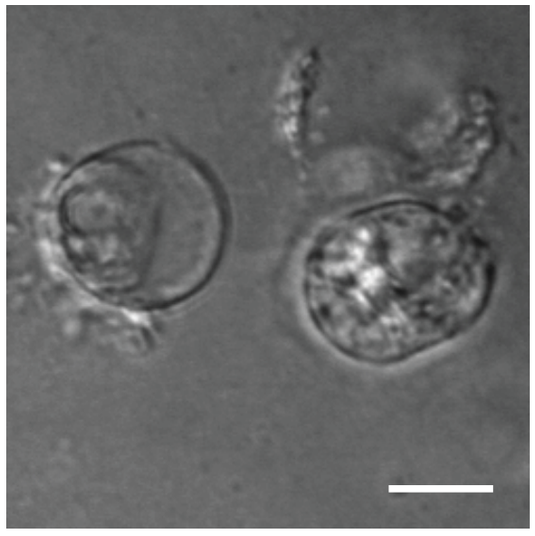
Carrer et al, Cancer Discovery, 2019

Acly deletion suppresses *Kras*-induced acinar cell plasticity

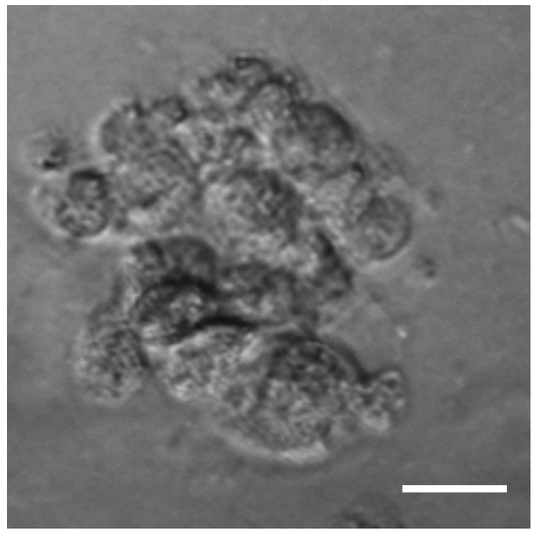
Cre



KC



KAC



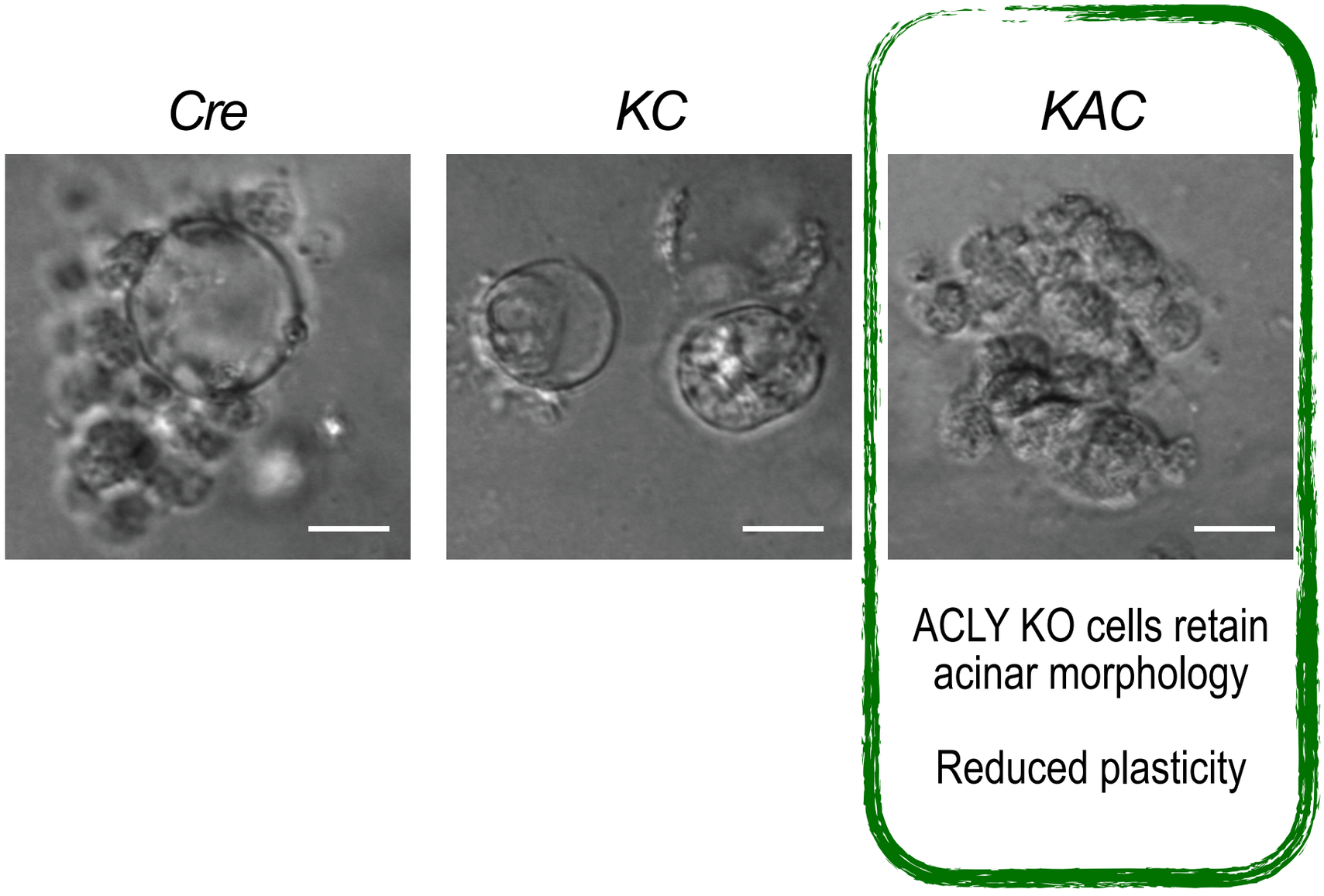
ACLY KO cells retain acinar morphology

Reduced plasticity

$Acly^{fl/fl}$ mice bred with Pdx1-Cre;LSL-$Kras^{G12D}$ (KC) mice

Carrer et al, Cancer Discovery, 2019

Acly deletion suppresses *Kras*-induced acinar cell plasticity



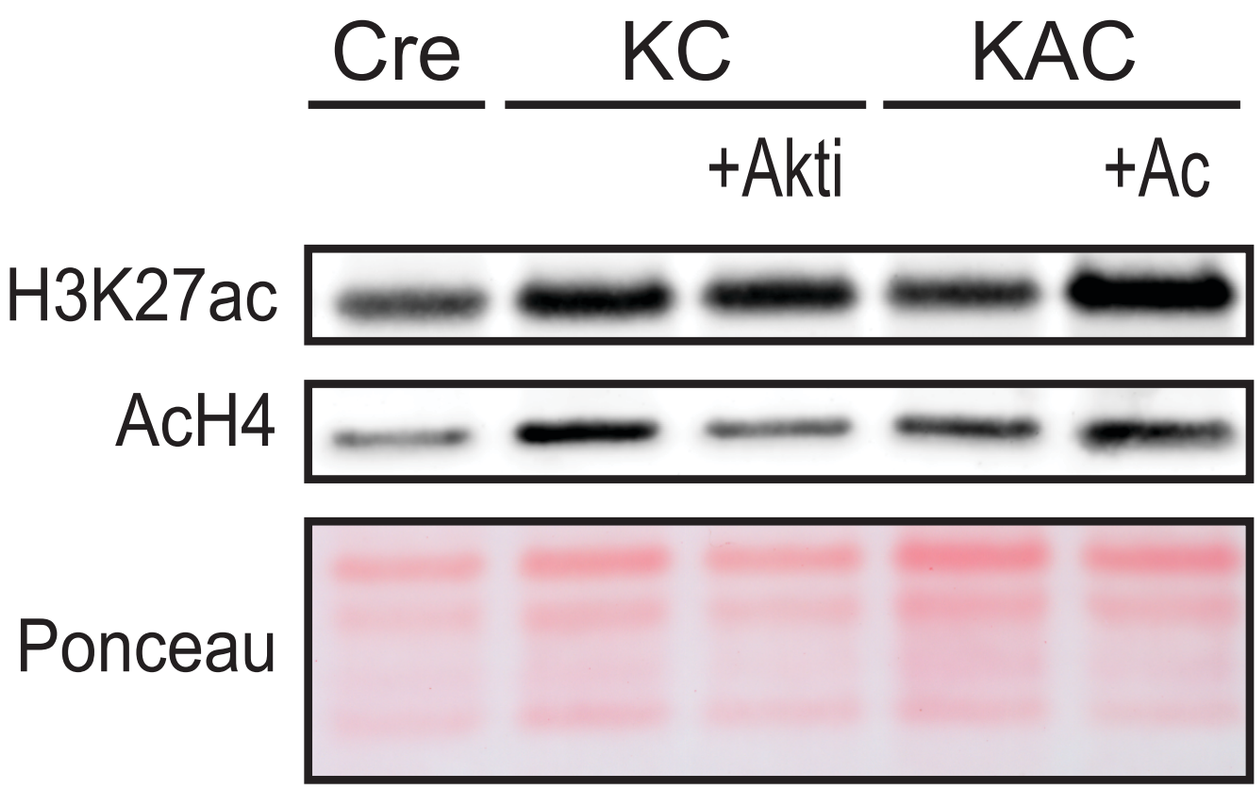
Acly$^{fl/fl}$ mice bred with Pdx1-Cre;LSL-Kras^{G12D} (KC) mice

Carrer et al, Cancer Discovery, 2019

Acly deletion suppresses *Kras*-induced acinar cell histone hyperacetylation

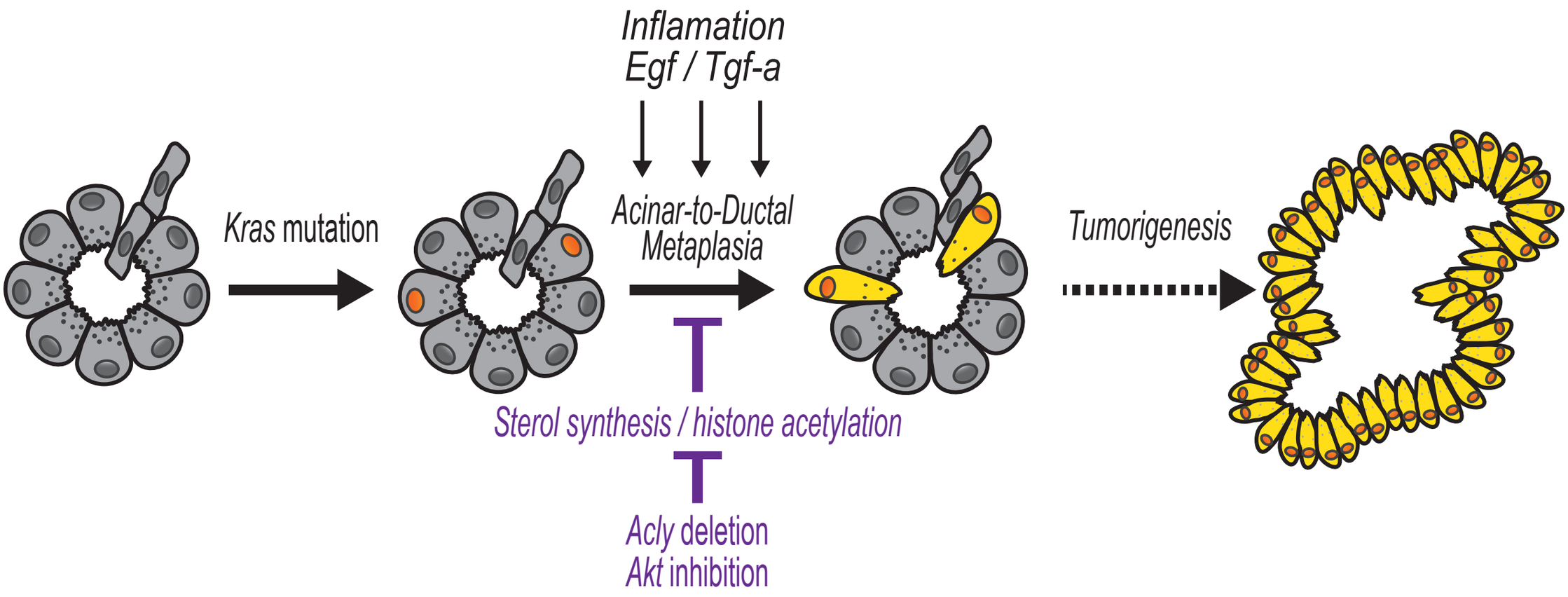
Carrer et al, ***Cancer Discovery****, 2019*

Acly deletion suppresses *Kras*-induced acinar cell histone hyperacetylation



Carrer et al, ***Cancer Discovery****, 2019*

CONCLUSIONS



Oncogenic Kras reprograms acetyl-CoA metabolism in pre-malignant pancreatic epithelial cells

- *effect of Kras on acetyl-CoA availability*
- *effect of oncogene activation in pre-malignant cells*
- *impact of metabolism on signaling in acinar cells*

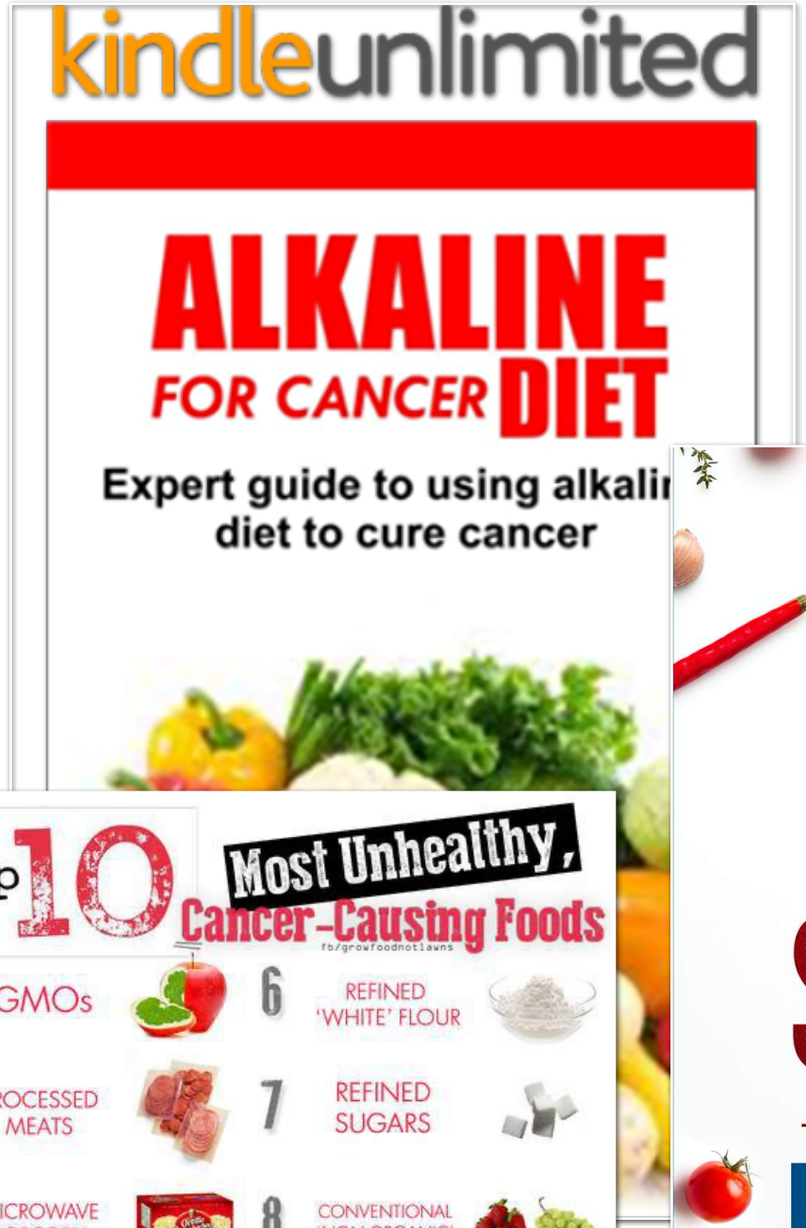
Elevation in acetyl-CoA availability is necessary for ADM

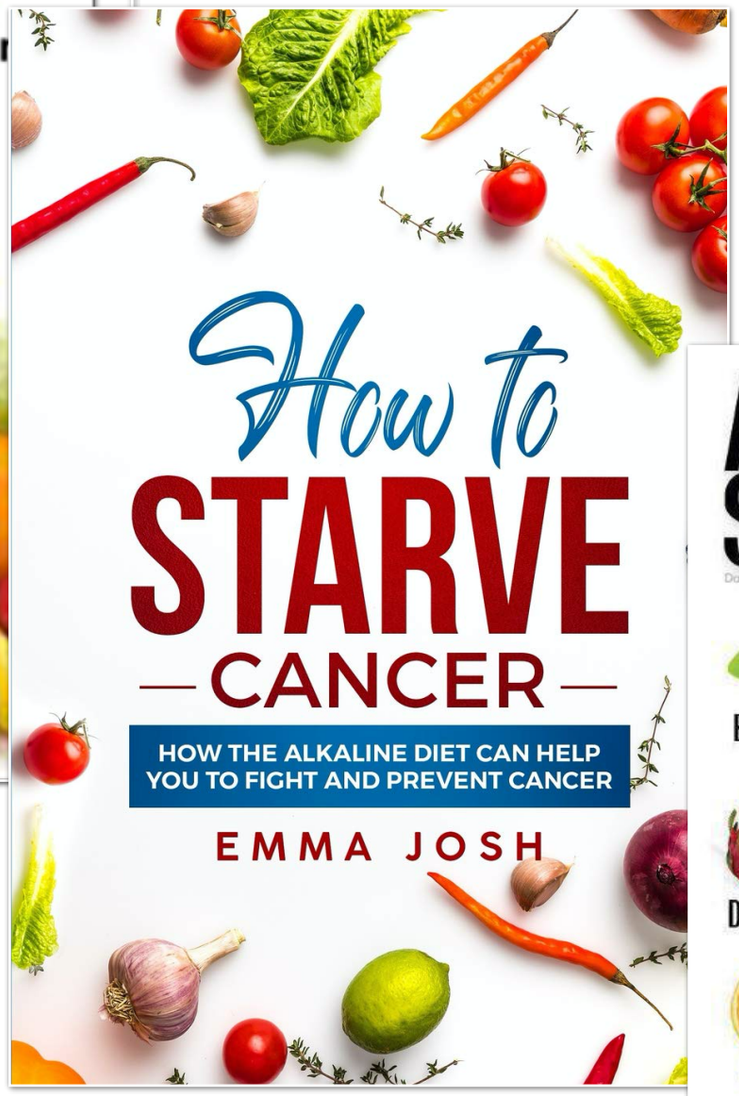
- *deletion on ACLY suppresses tumor formation*
- *metabolites often dictate cell differentiation through epigenetic effect*

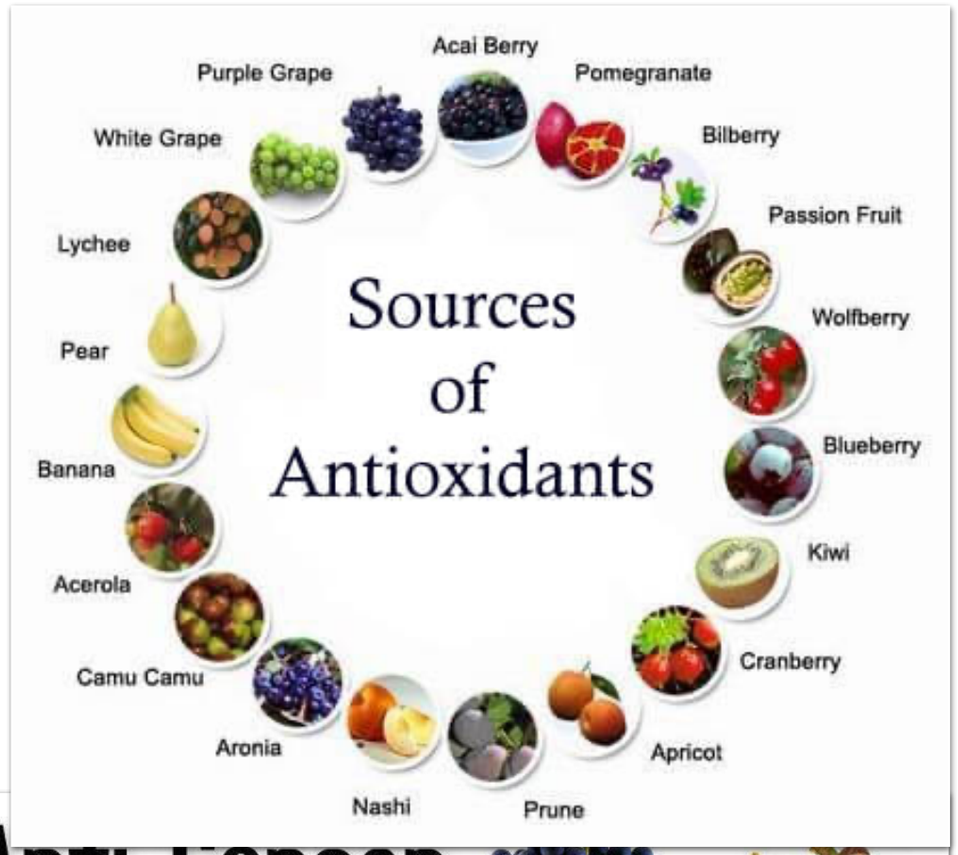
Diet & Cancer Metabolism

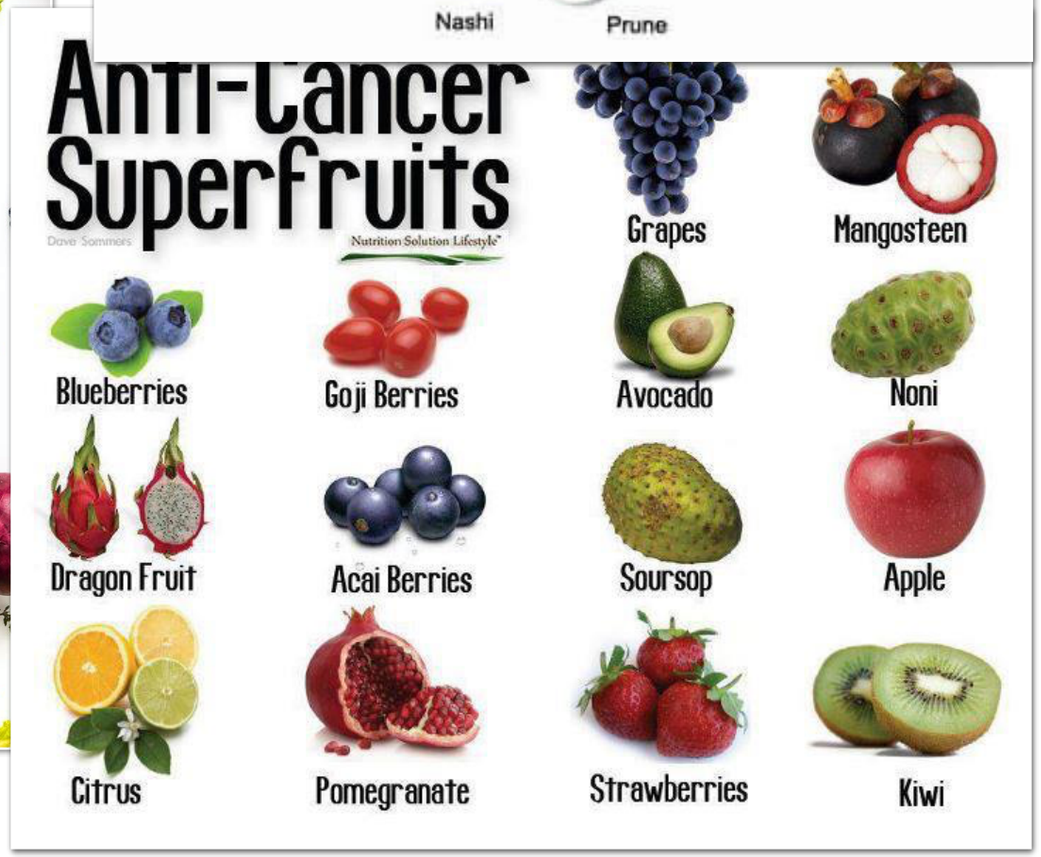
Diet & Cancer:

how to survive strides of misinformation

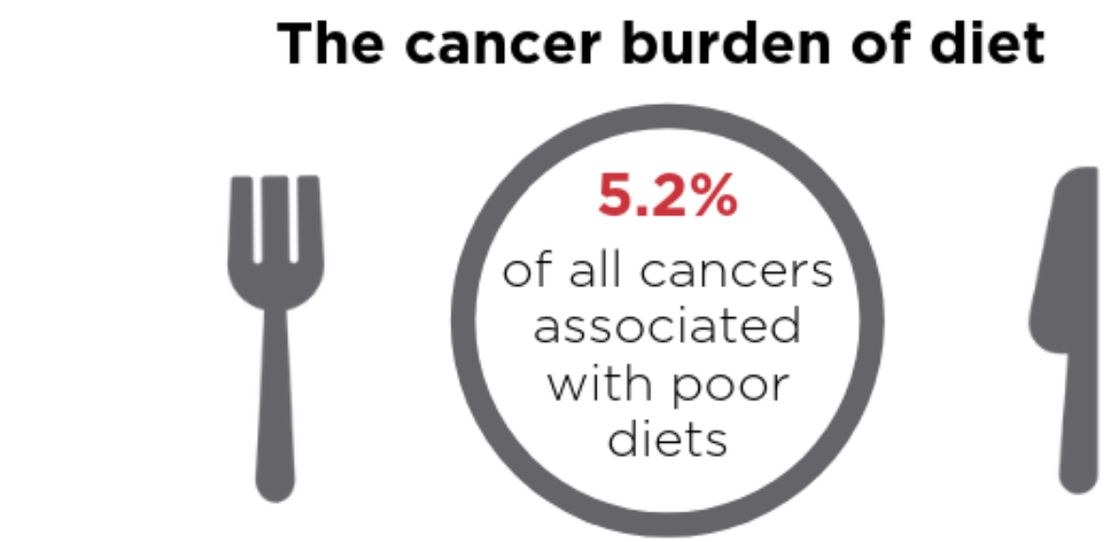






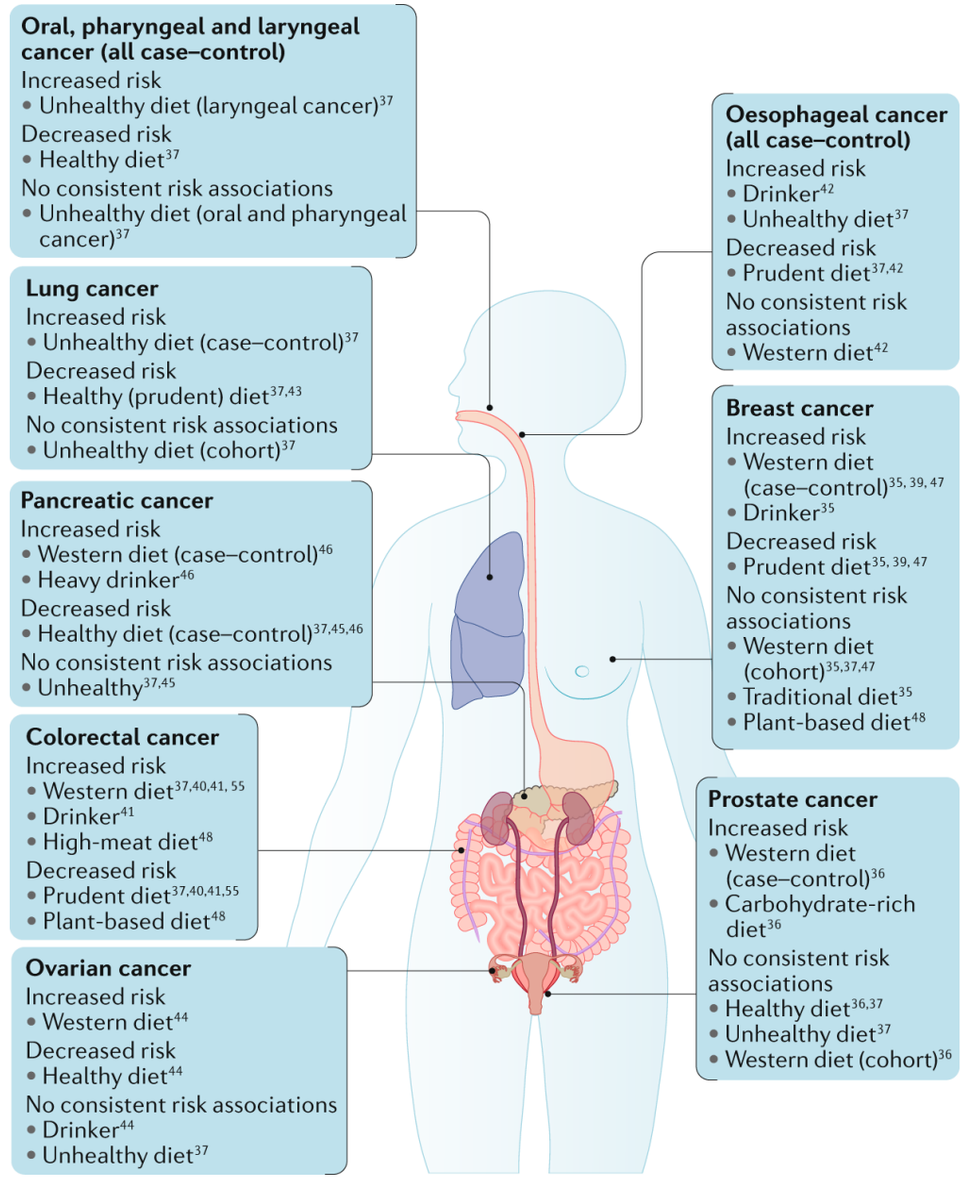


Diet & Cancer: “western diet” is associated with elevated cancer risk



Zhang, F. F., et al. Preventable cancer burden associated with dietary intake in the United States. JNCI Cancer Spectrum (2019). http://doi.org/10.1093/jnci/djz079

Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy at Tufts University

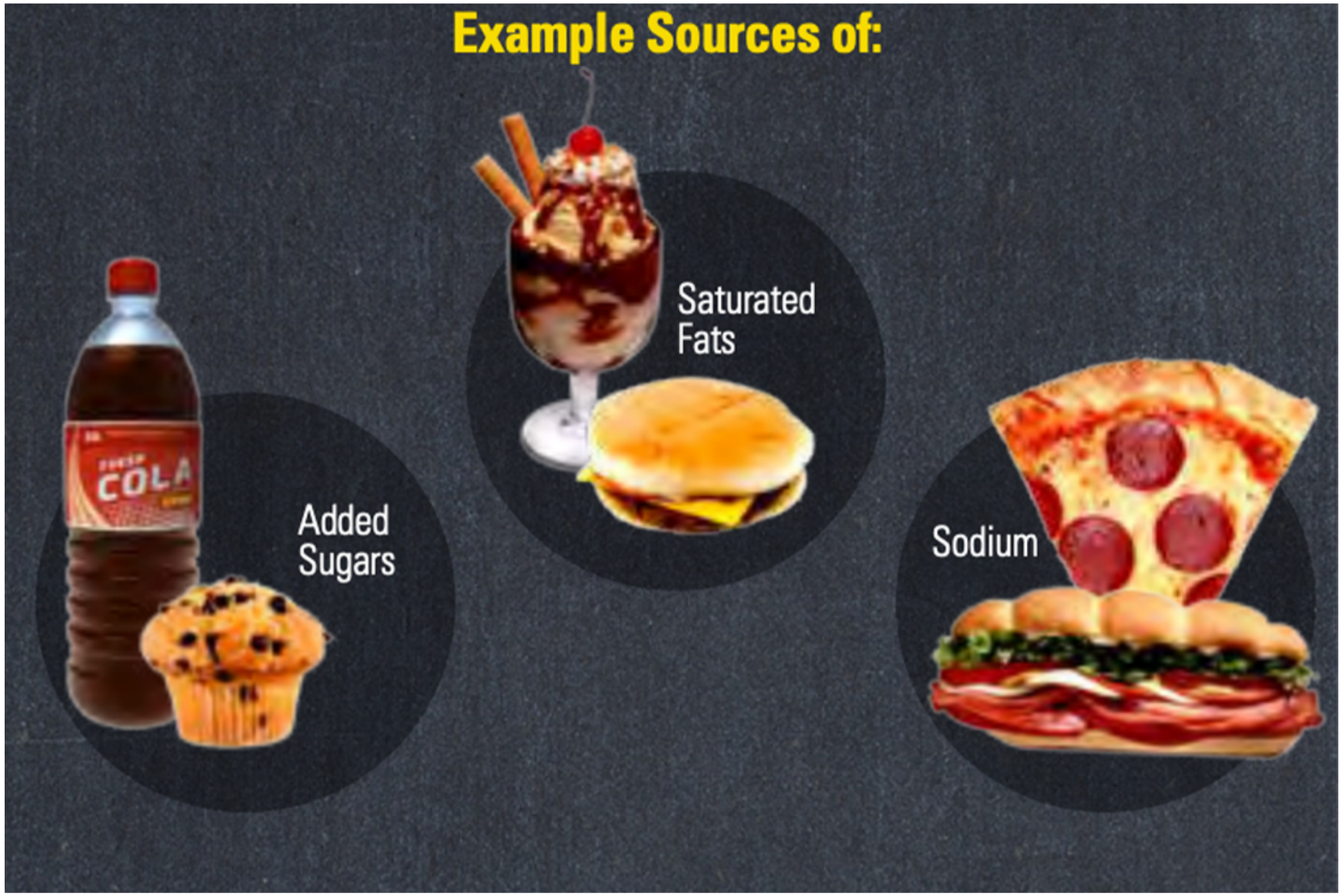


Steck & Murphy, ***Nat Rev Cancer****, 2019*

Western Diet is characterized by high fat AND high sugar

Does obesity predispose to cancer? How?

Western Diet is characterized by high fat AND high sugar



Does obesity predispose to cancer? How?

Can specific nutrient impact tumor development?

Can specific nutrient impact tumor development?

YES

Can specific nutrient impact tumor development?

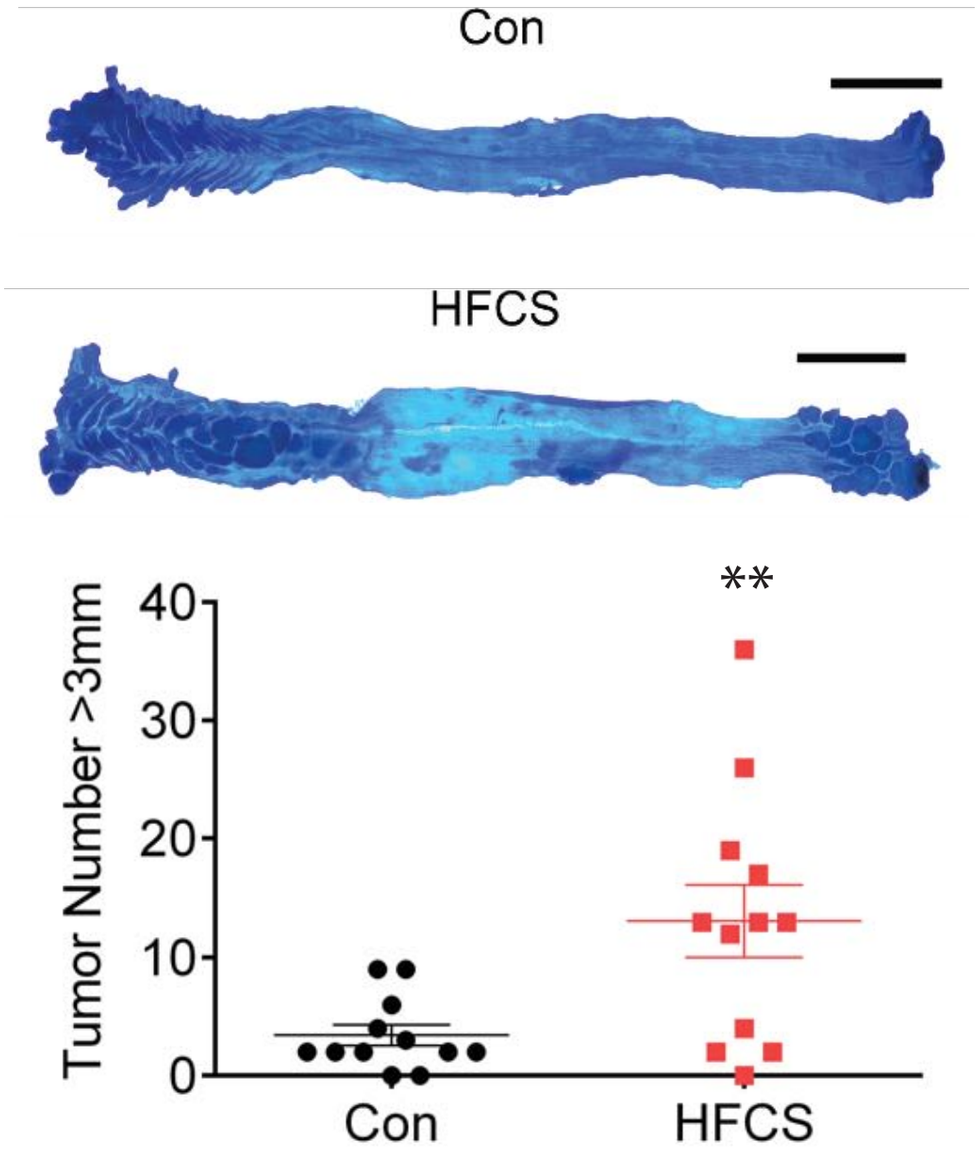
YES

Mechanisms:

Engagement of nutrient sensing pathways
Remodeling of cell metabolism
Competition among cells in the TME

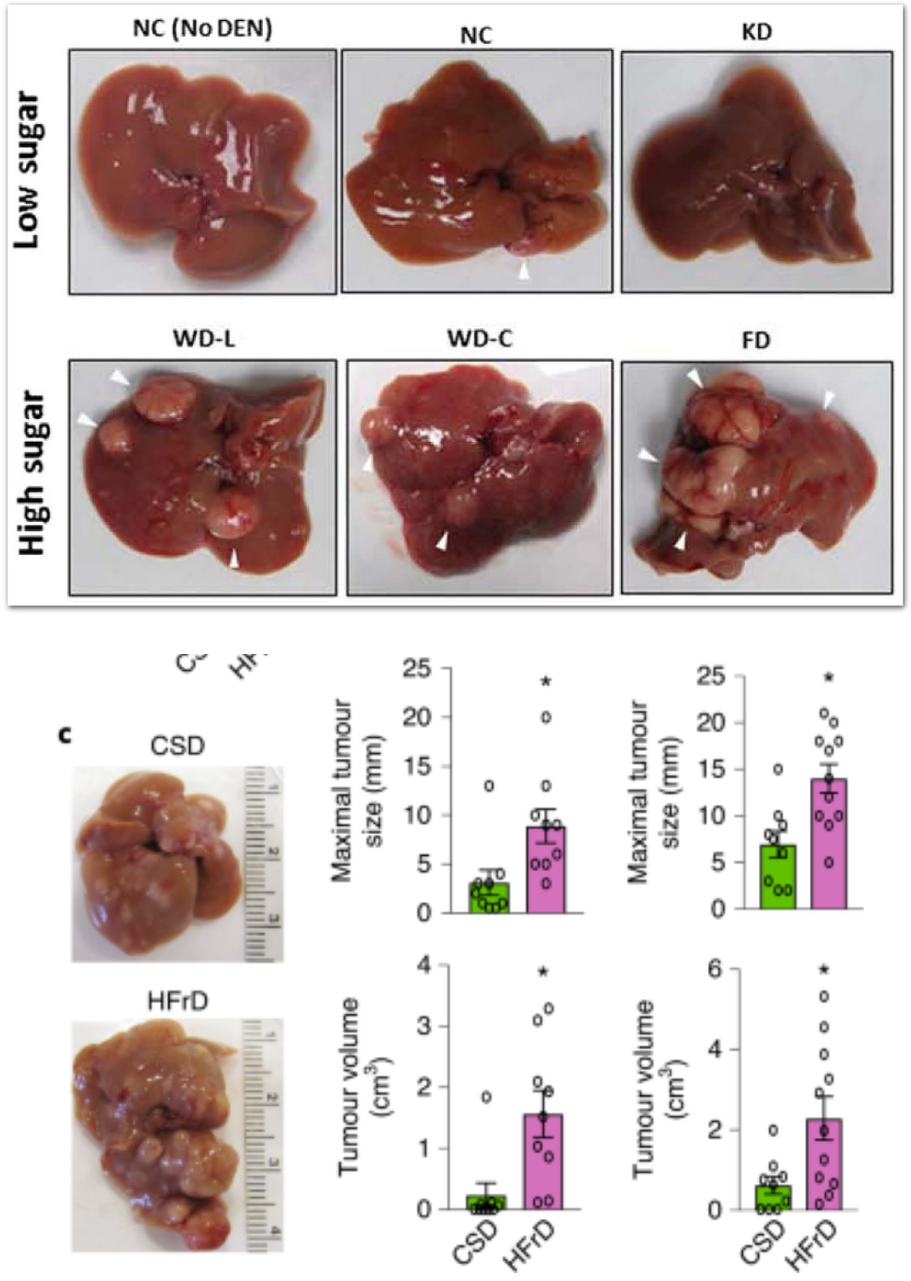
Fructose feeding cause tumorigenesis

Colon-CA



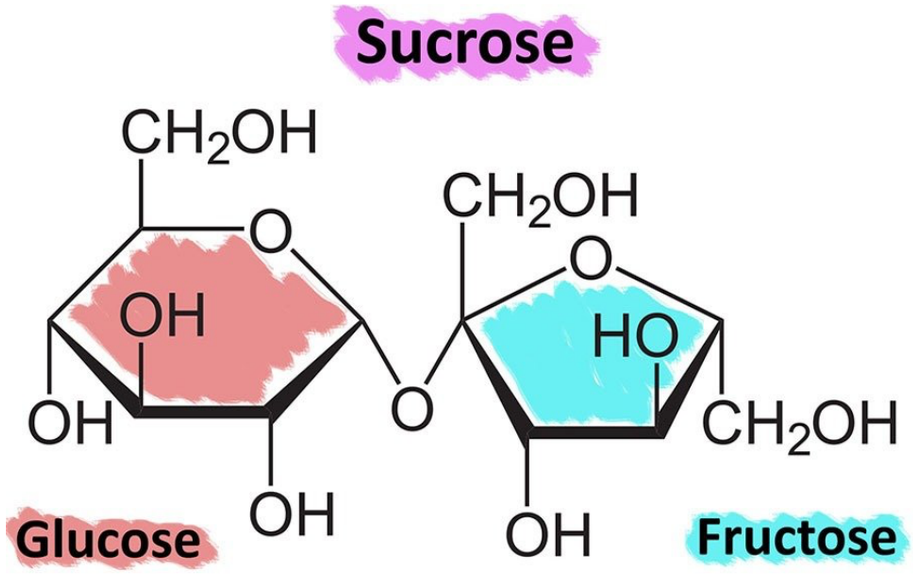
*Goncalves et al, **Science**, 2020*

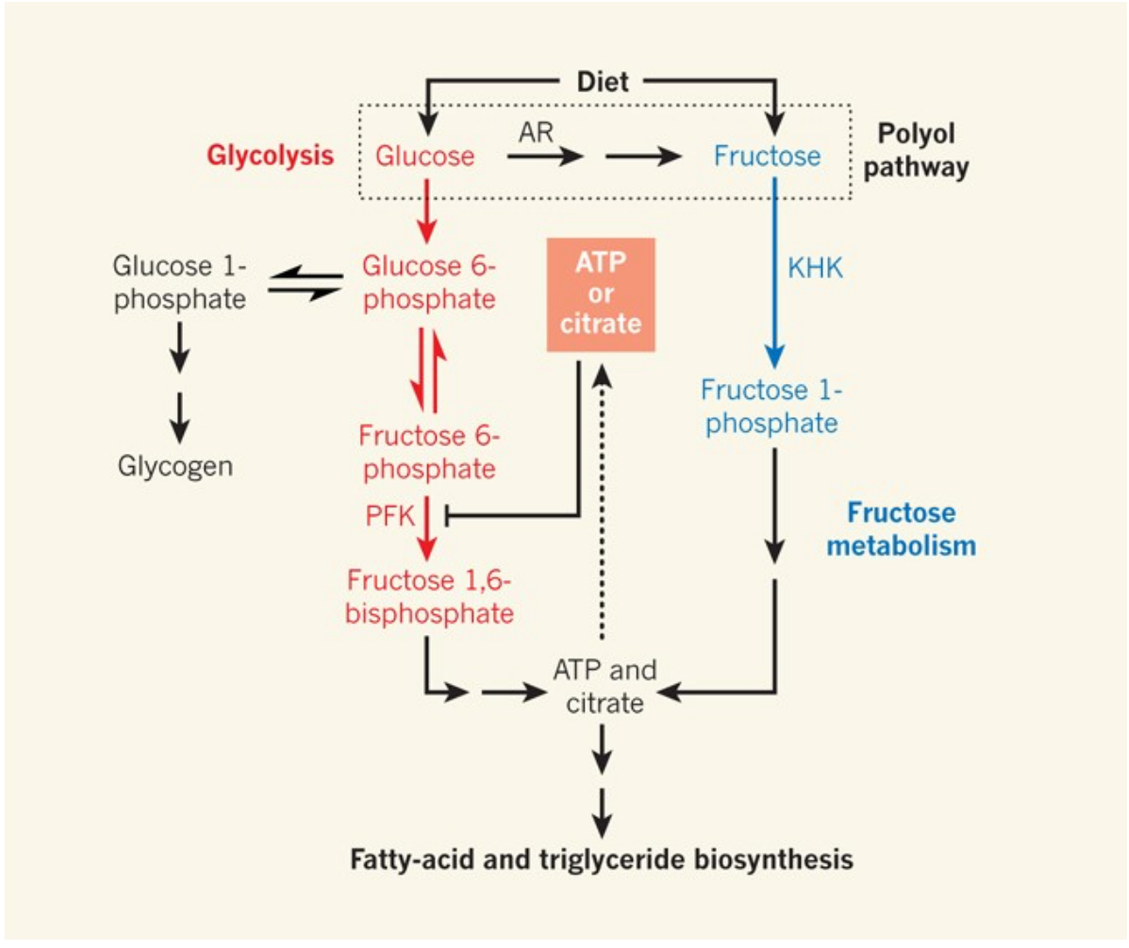
Liver-CA



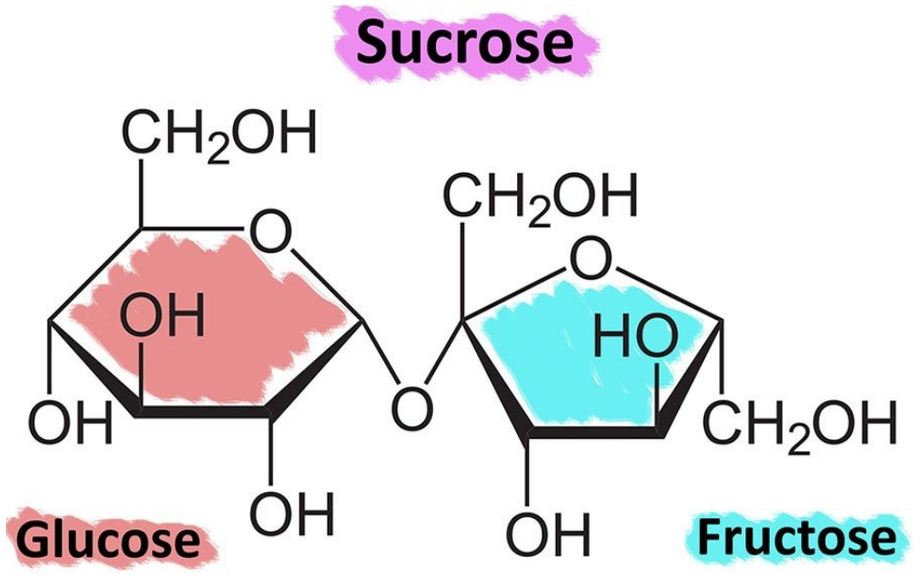
*Healy et al, **Sci Rep**, 2016; Todorovic et al, **Nat Metab**, 2020*

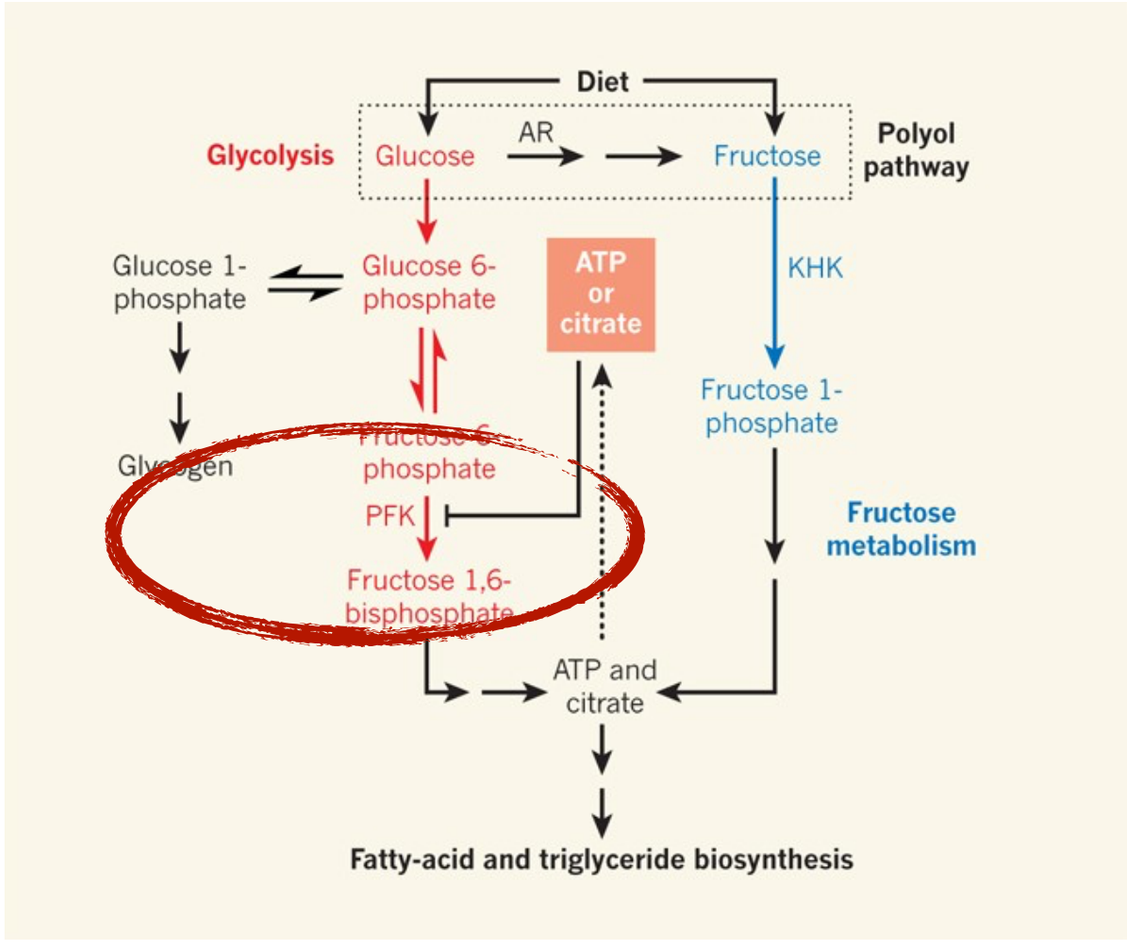
Fructose vs Glucose Metabolism



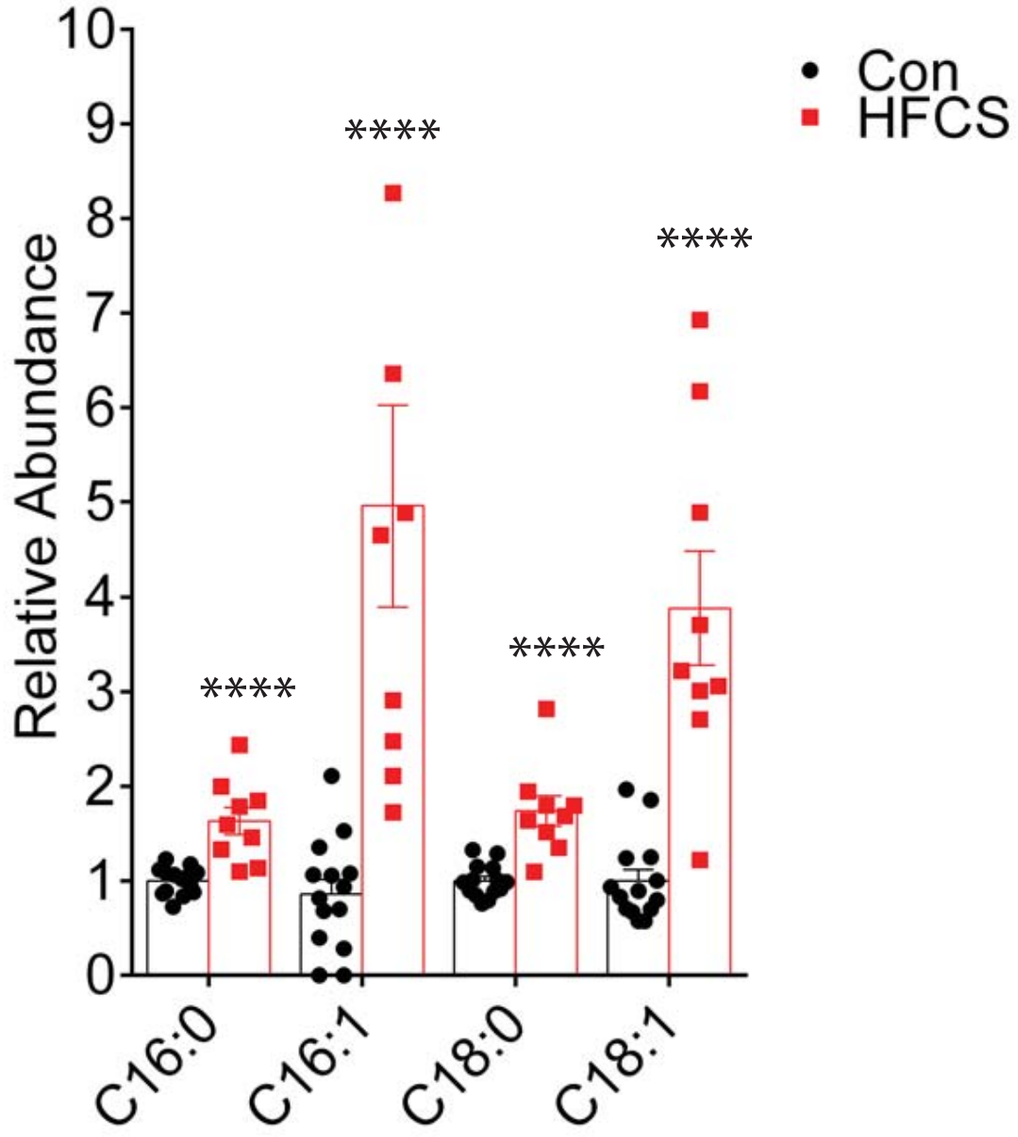


Fructose vs Glucose Metabolism





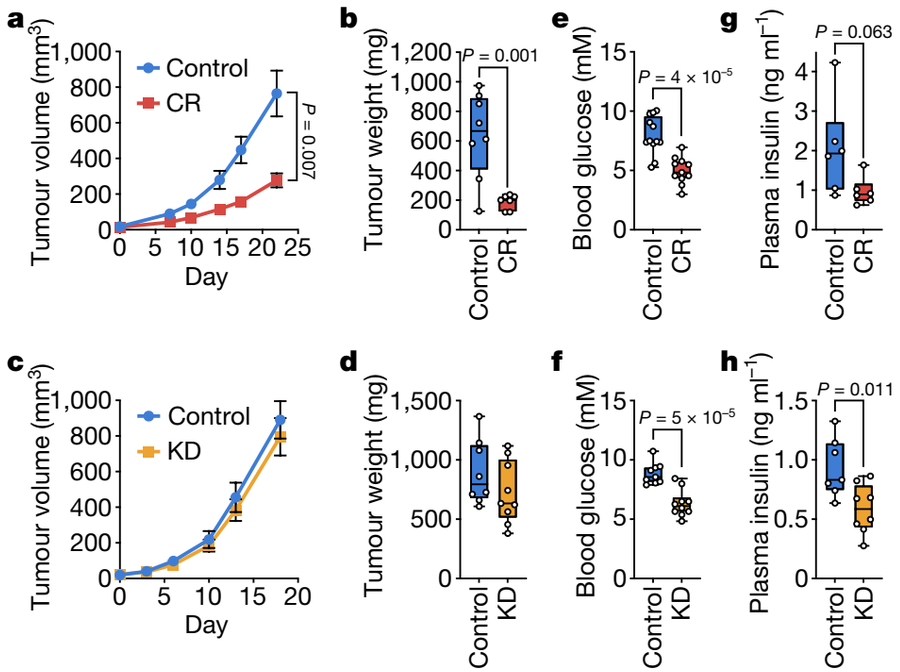
Dietary fructose promotes FAS for tumor growth



Goncalves et al, ***Science****, 2020*

Calorie restriction can impact cancer metabolism per se

Low glycaemic diets alter lipid metabolism to influence tumour growth



Lien et al, ***Nature****, 2021*

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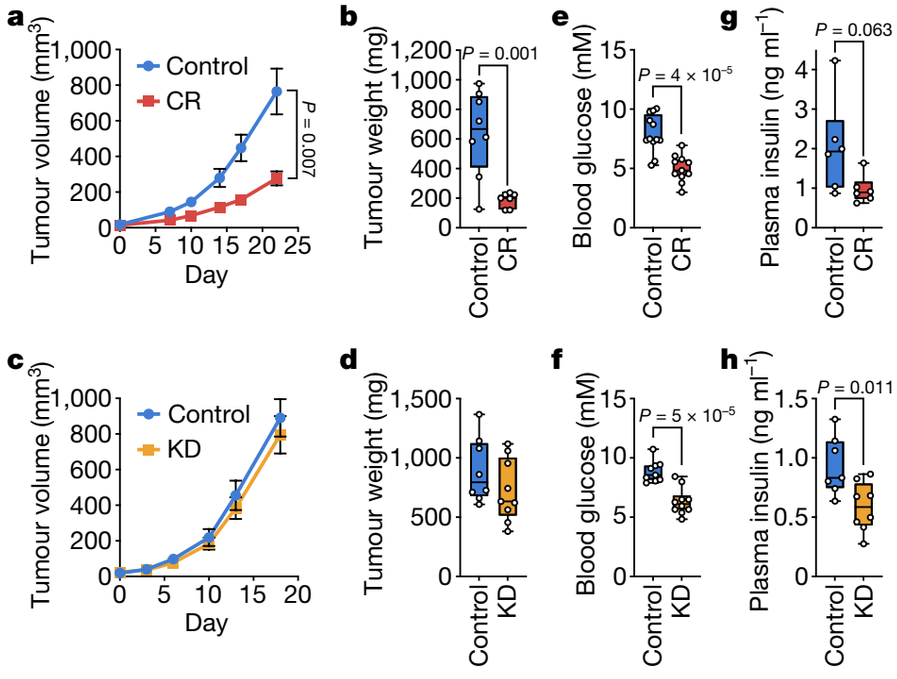
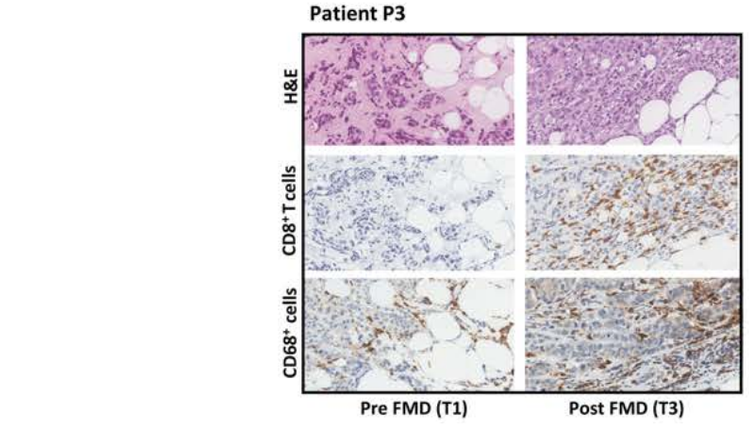
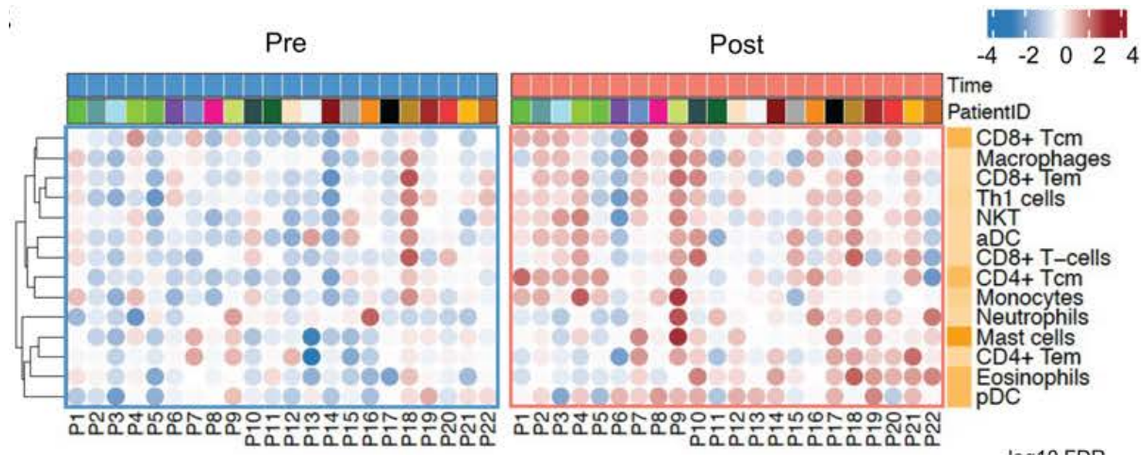


Lien et al, ***Nature****, 2021*

Fasting-mimicking diet is safe and reshapes metabolism and antitumor immunity in cancer patients





Vernieri et al, ***Cancer Discov****, 2021*

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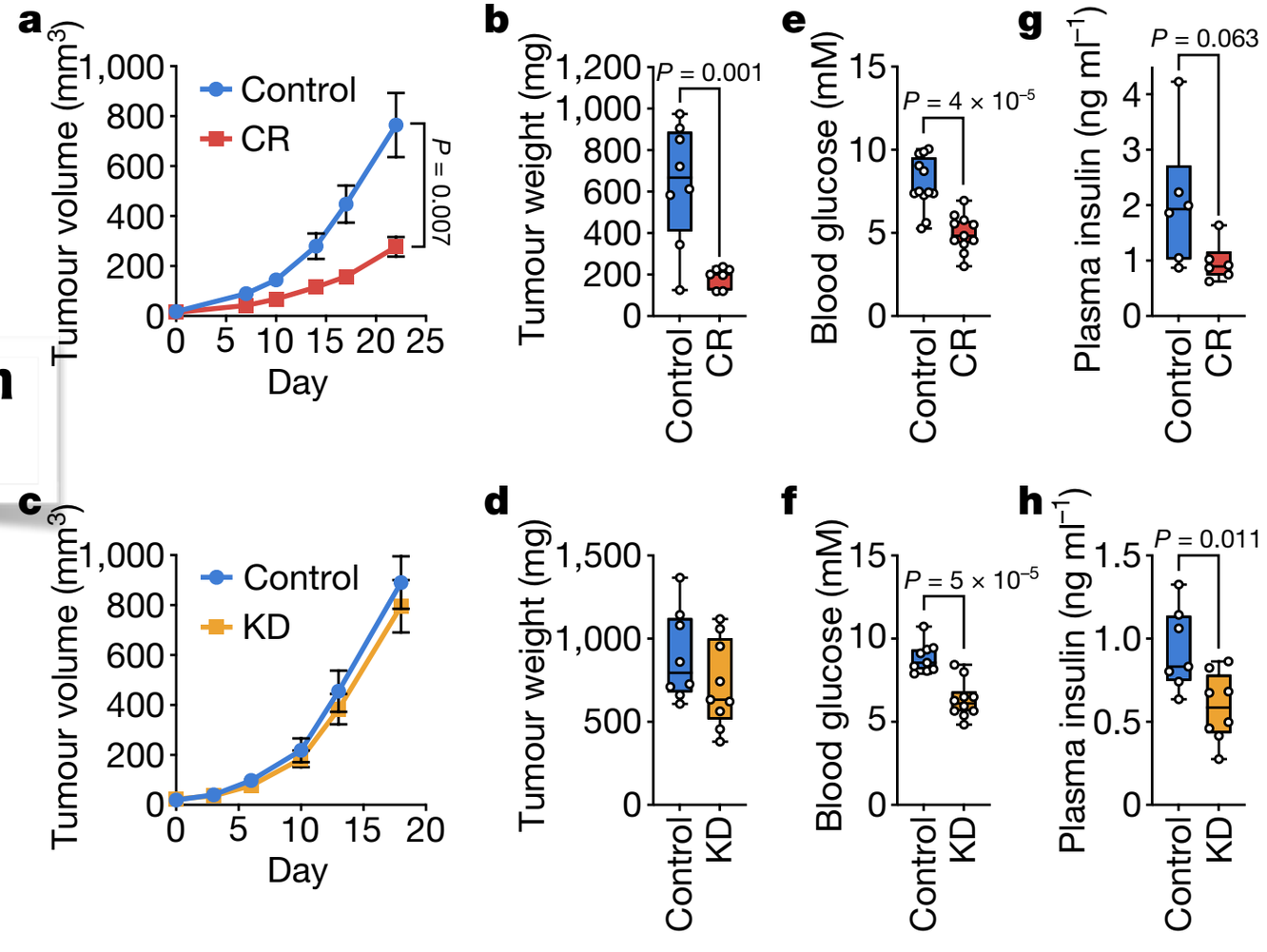
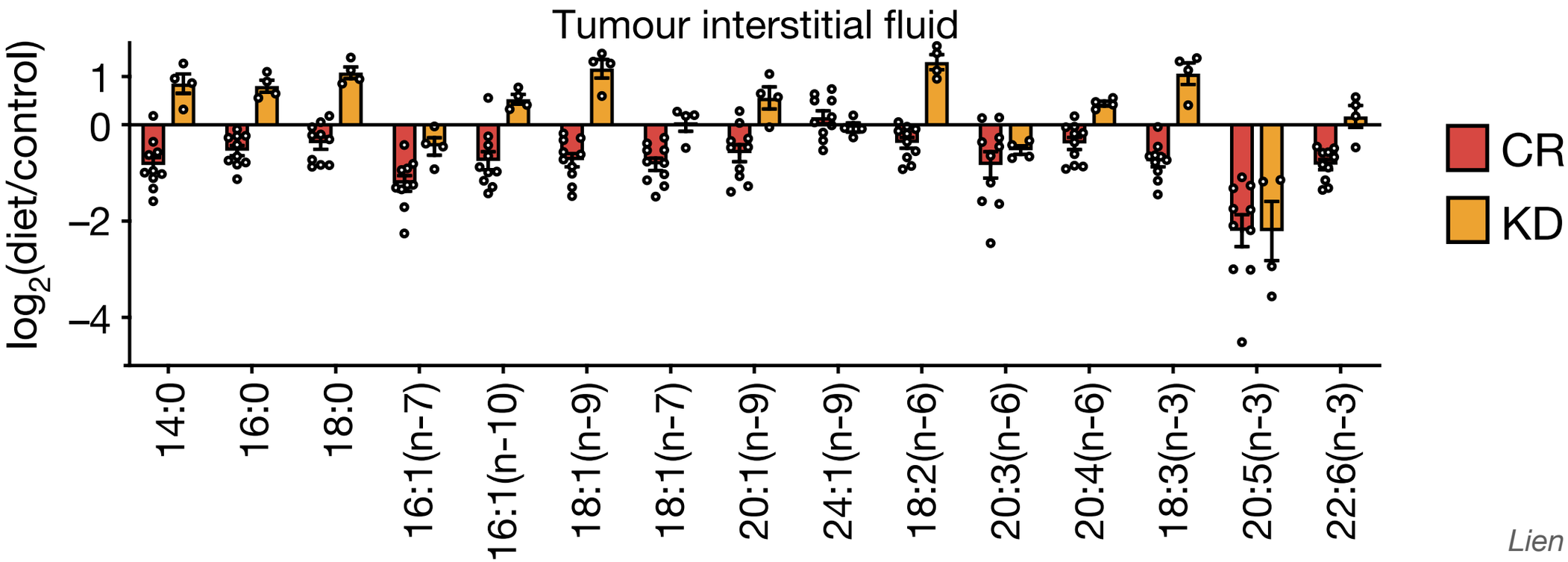
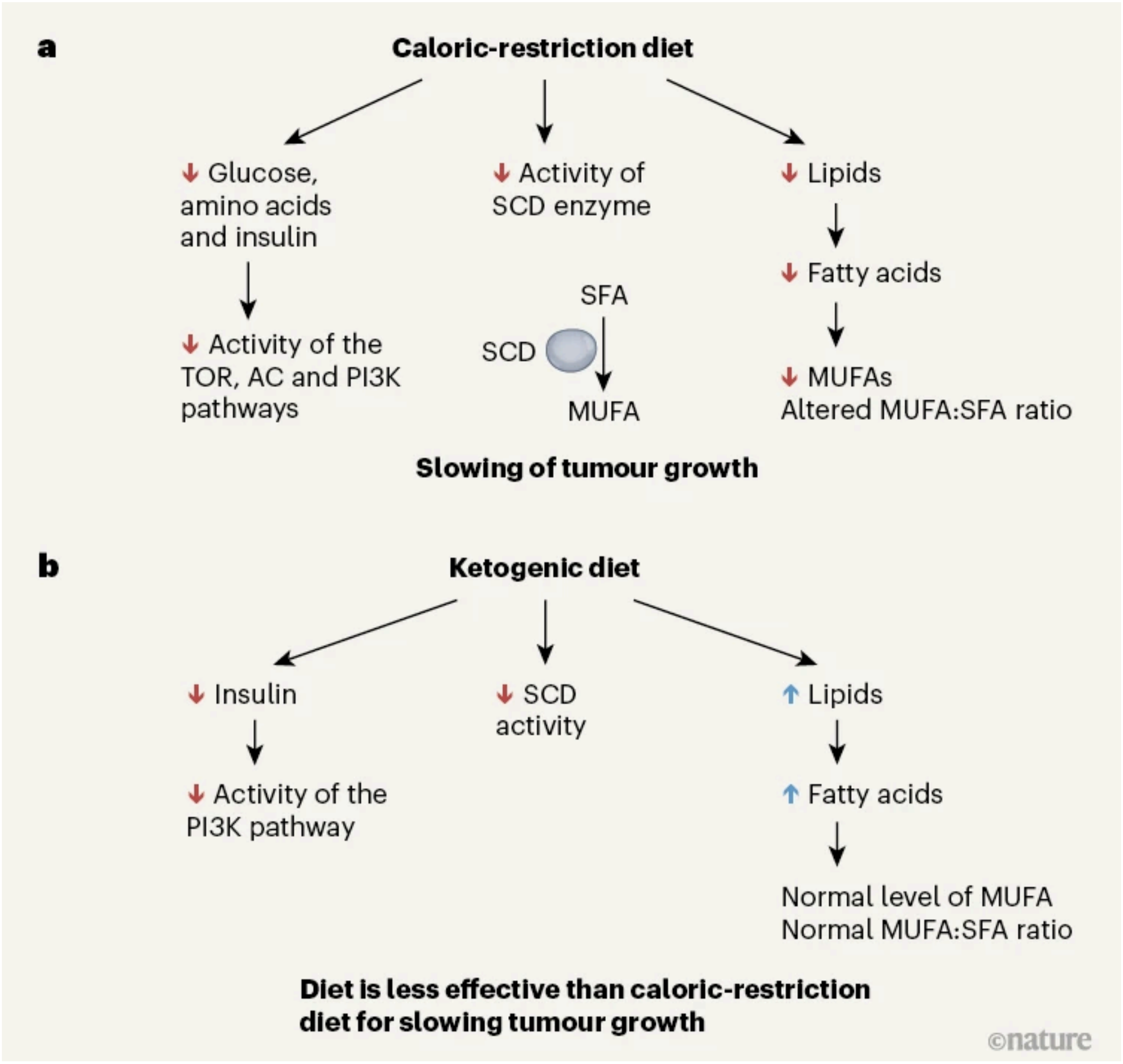




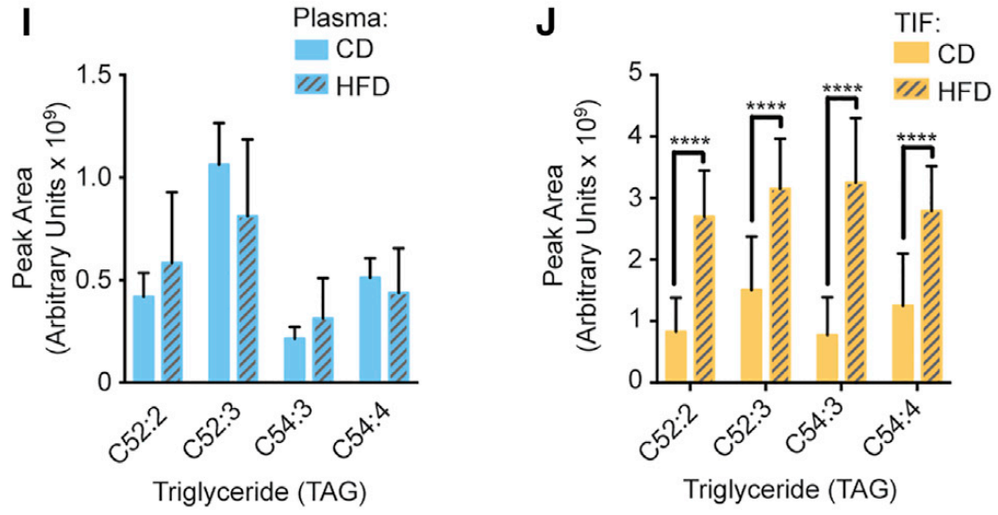
*Lien et al, **Nature**, 2021*


a
Caloric-restriction diet
↓ Glucose, amino acids and insulin
↓ Activity of the TOR, AC and PI3K pathways
↓ Activity of SCD enzyme
SFA
SCD
MUFA
↓ Lipids
↓ Fatty acids
↓ MUFAs
Altered MUFA:SFA ratio
Slowing of tumour growth
b
Ketogenic diet
↓ Insulin
↓ Activity of the PI3K pathway
↓ SCD activity
↑ Lipids
↑ Fatty acids
Normal level of MUFA
Normal MUFA:SFA ratio
Diet is less effective than caloric-restriction diet for slowing tumour growth
©nature

Article

Obesity Shapes Metabolism in the Tumor Microenvironment to Suppress Anti-Tumor Immunity

Alison E. Ringel,[1,13] Jefte M. Drijvers,[1,2,3,8,13] Gregory J. Baker,[4] Alessia Catozzi,[1,5] Juan C. García-Cañaveras,[6,7,9] Brandon M. Gassaway,[1] Brian C. Miller,[2,3] Vikram R. Juneja,[2,3,10] Thao H. Nguyen,[2,3] Shakchhi Joshi,[1] Cong-Hui Yao,[1] Haejin Yoon,[1] Peter T. Sage,[2,3,11] Martin W. LaFleur,[2,3] Justin D. Trombley,[2,3,12] Connor A. Jacobson,[4] Zoltan Maliga,[4] Steven P. Gygi,[1] Peter K. Sorger,[4] Joshua D. Rabinowitz,[6,7] Arlene H. Sharpe,[2,3,*] and Marcia C. Haigis[1,14,*]



Article

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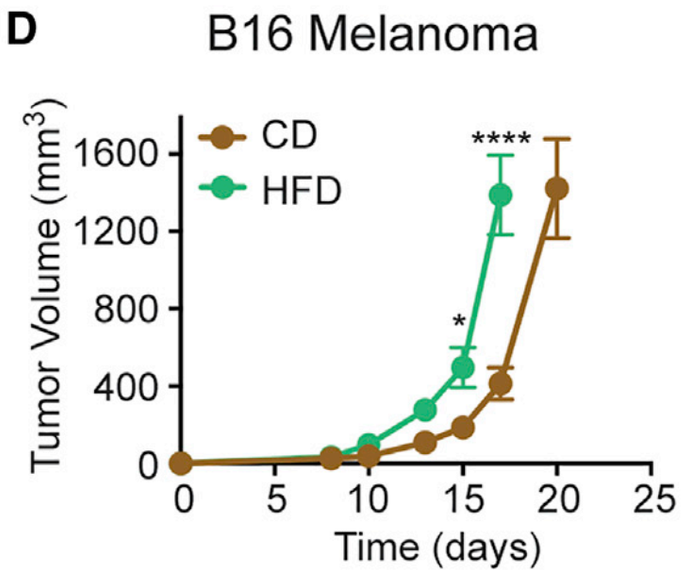

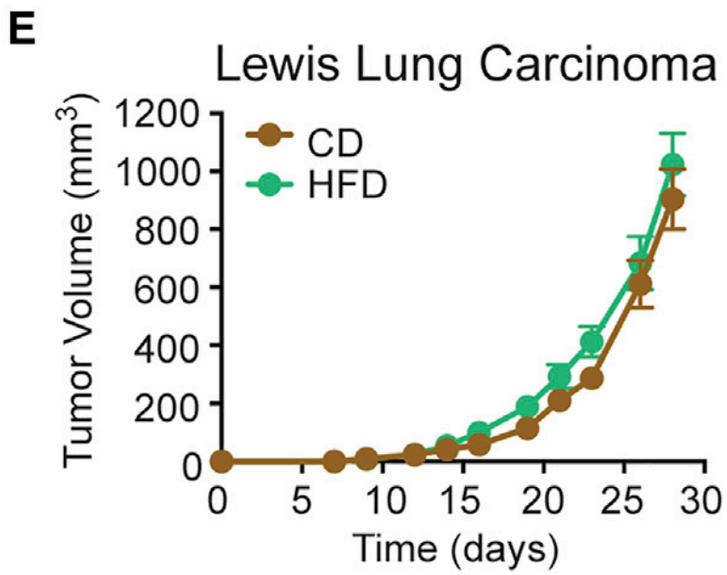

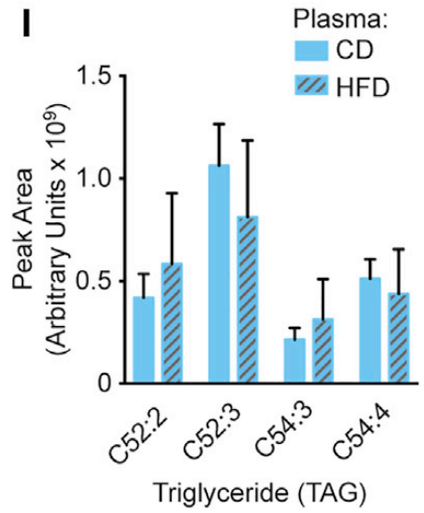

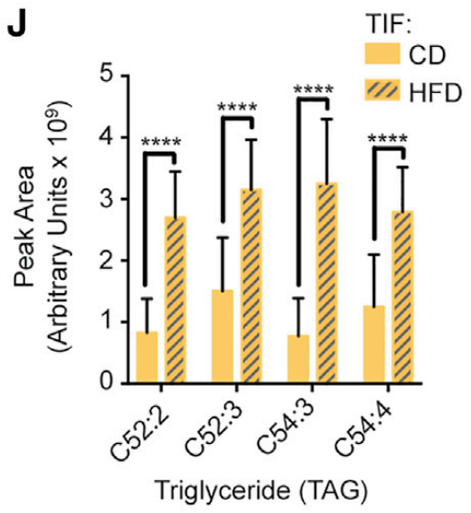

*Ringel et al, **Cell**, 2020*

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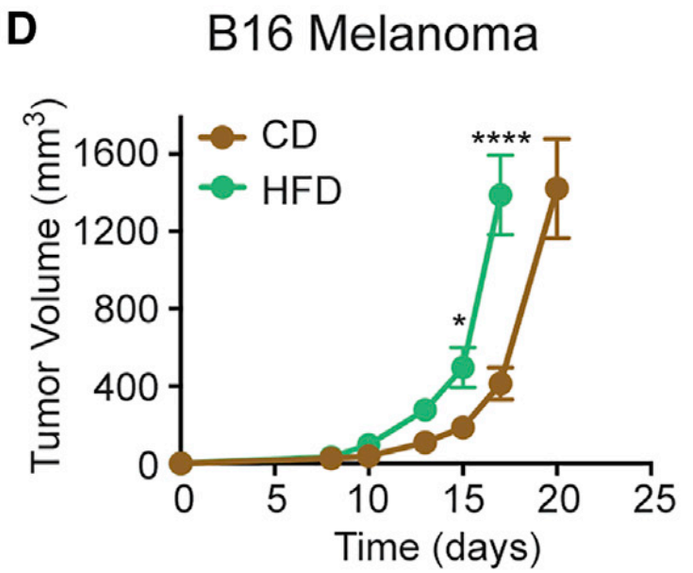

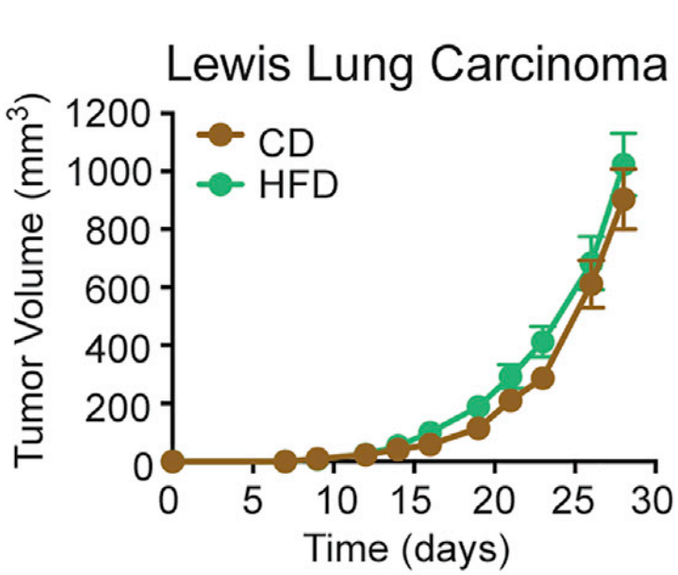

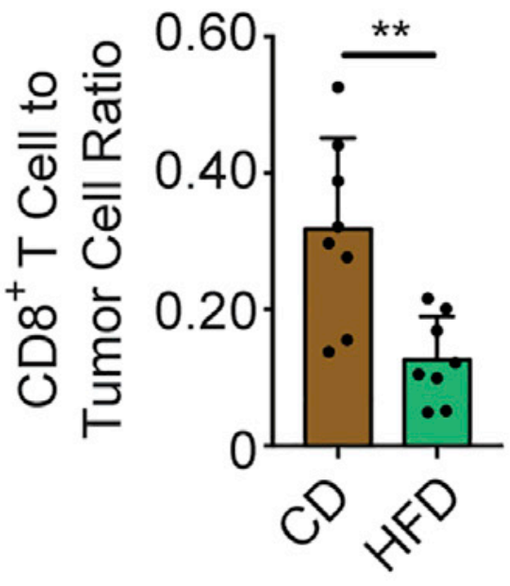

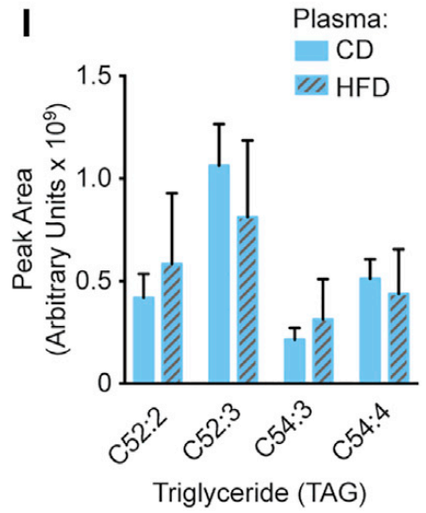

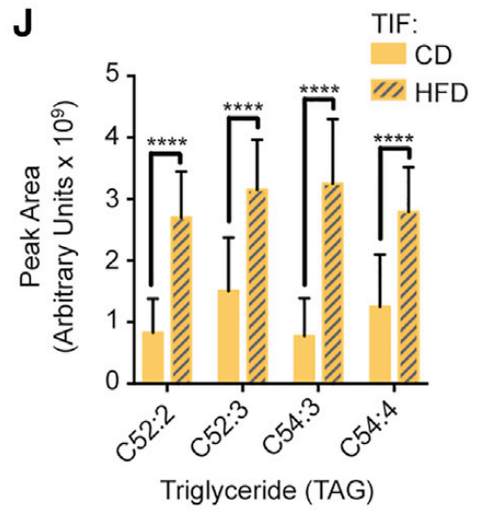

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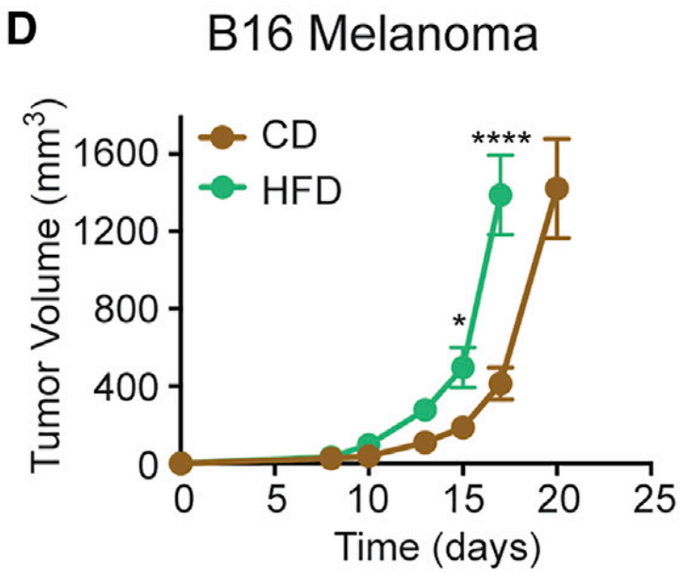

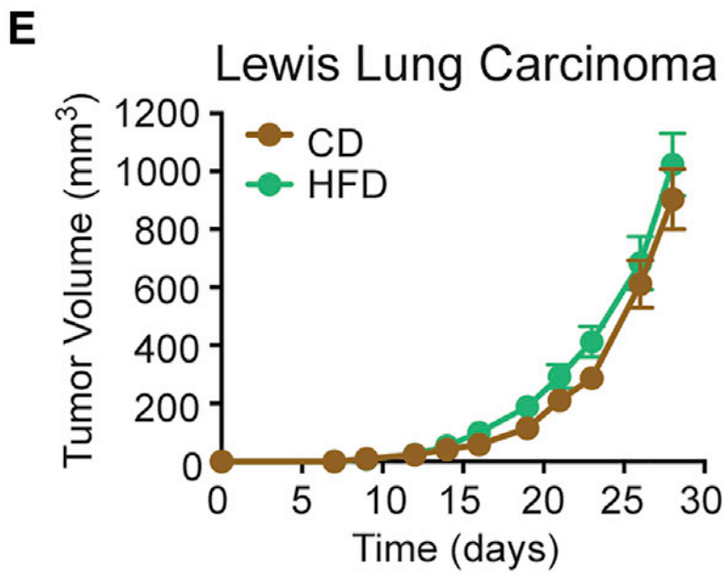

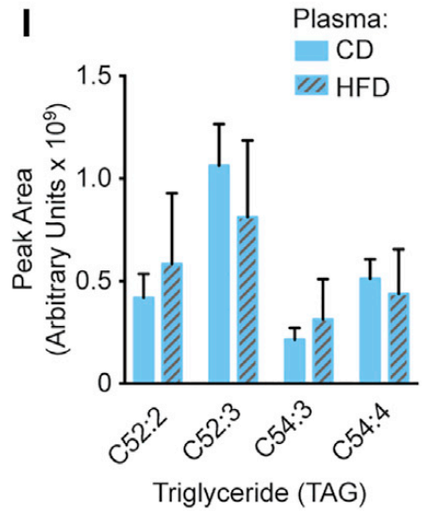

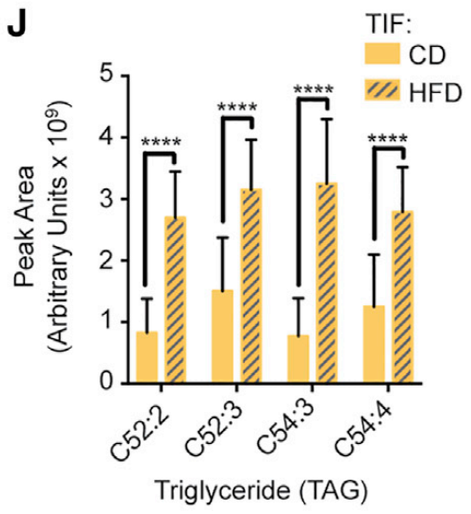

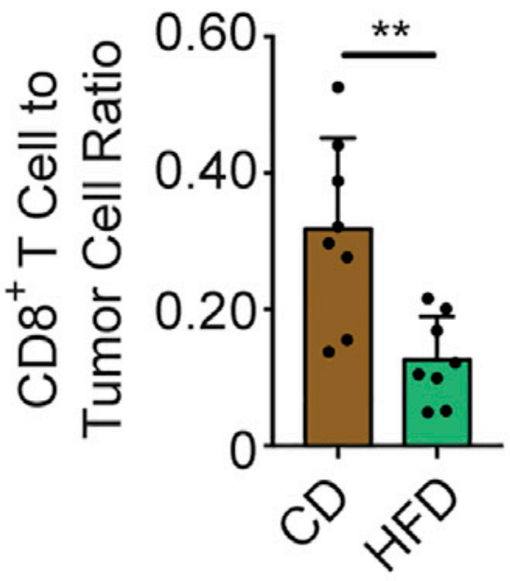

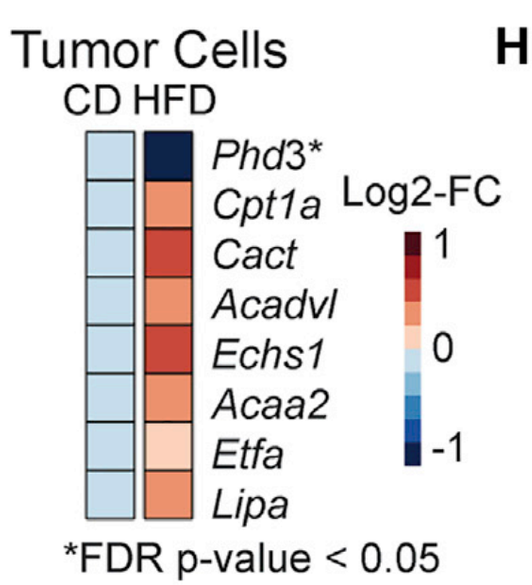

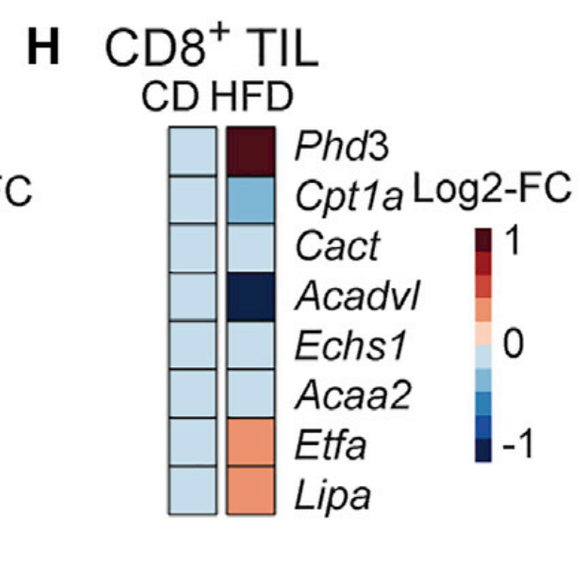

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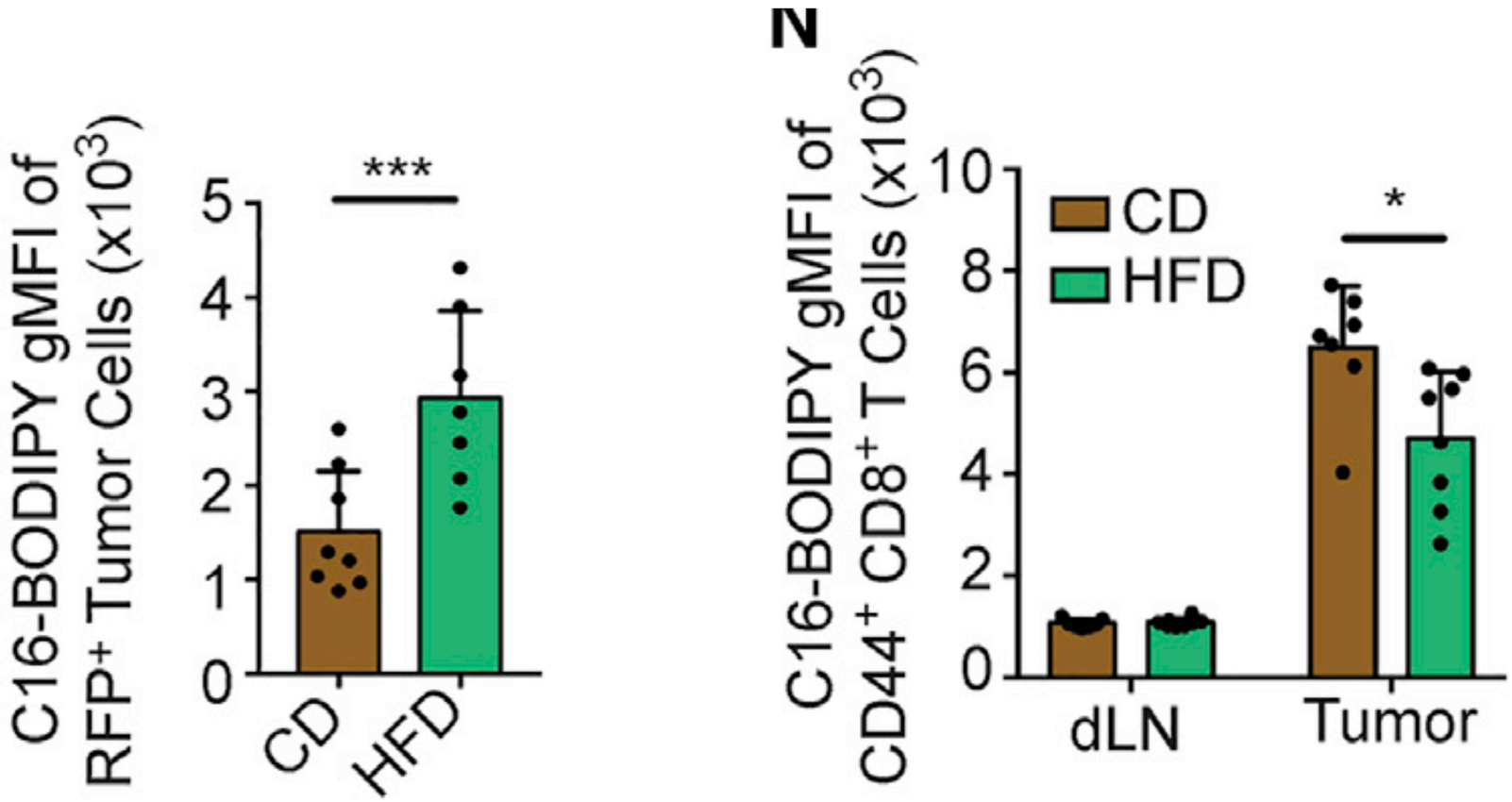
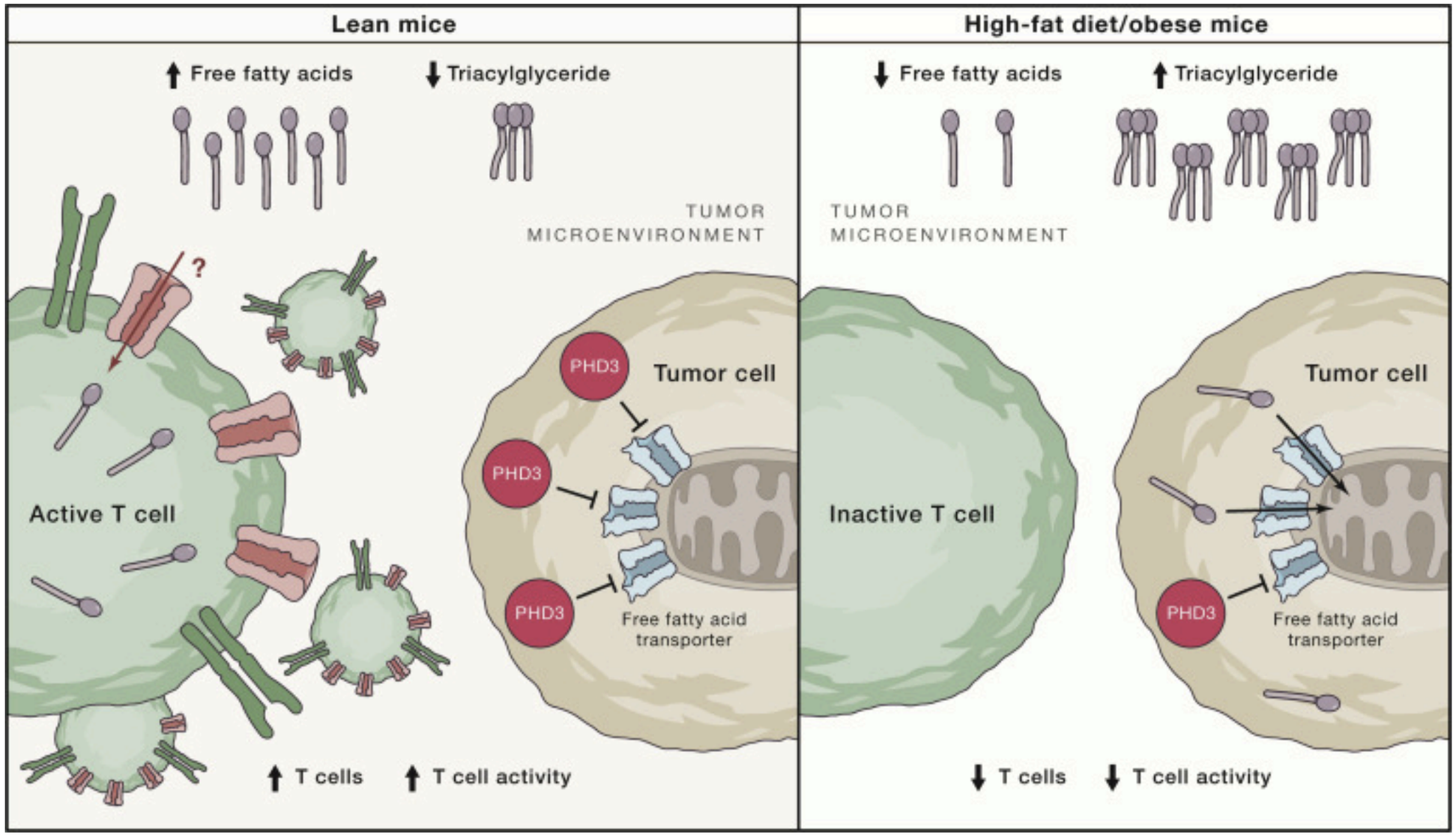




Cancer cells and infiltrating lymphocytes compete for lipids in the TME, with the former being able to outpace the latter for uptake.

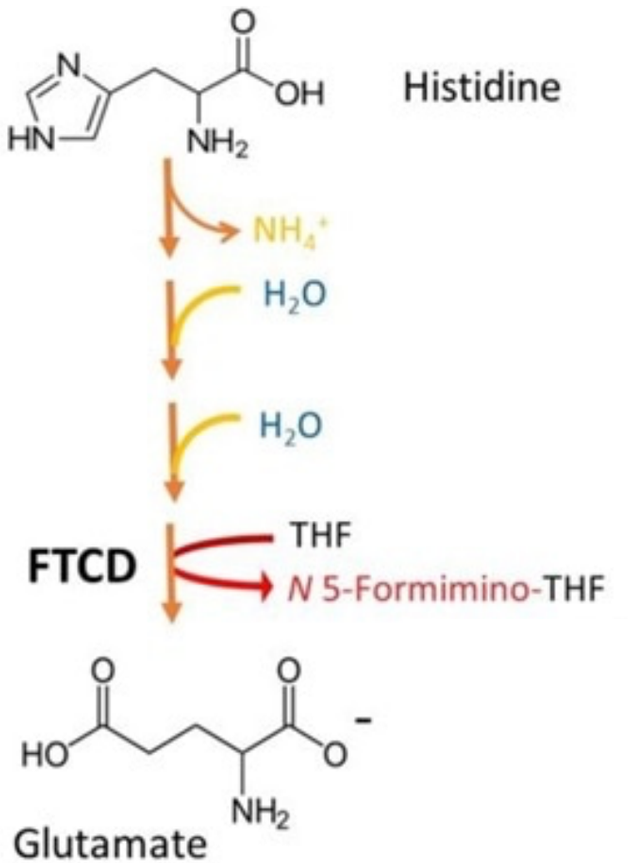
Obesity (HFD) enhances the ability of cancer cells to outcompete T cells

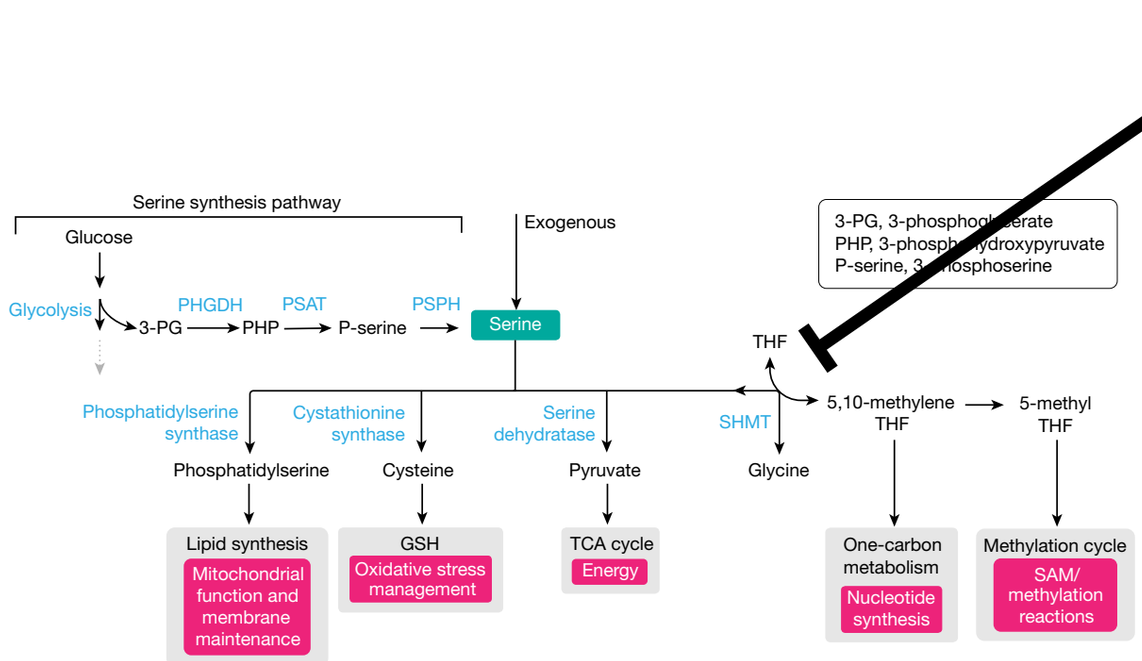
Diet rarely impacts cancer metabolism per se
….but can synergies with treatment!!

- **FASTING:** reduces levels of IGF1, improves response to chemotherapy in models of breast cancer, melanoma, glioma and neuroblastoma
- **METHIONINE RESTRICTION:** reduces levels of SAM, methylation of DNA and mTORC1. Enhances response to therapy in several preclinical models
- **SER/GLY RESTRICTION:** essential nutrient for tumors lacking PHGDH and SHMT amplification. Potentiates effect of biguanidines.
- **HISTIDINE SUPPLEMENTATION:** His catabolism drains THF pool, enhancing the tumor-killing effect of MTX
- **KETOGENIC DIET:** Decrease blood insulin levels. Suppress insulin-driven resistance to anti-PI3K treatment
- **ARGININE DEPRIVATION:** Tumor often silence ASS1 and become auxotrophs for Arg. Arg limitation synergies with inhibition of Arg-degrading enzyme ADI

*For more info: Kanarek et al, **Nature**, 2020*

Histidine catabolism restricts availability of THF





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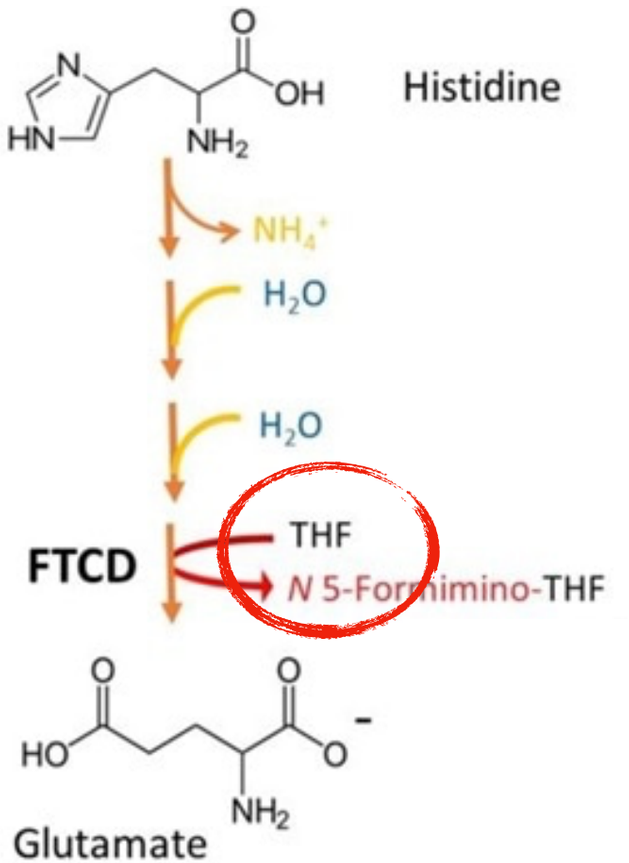
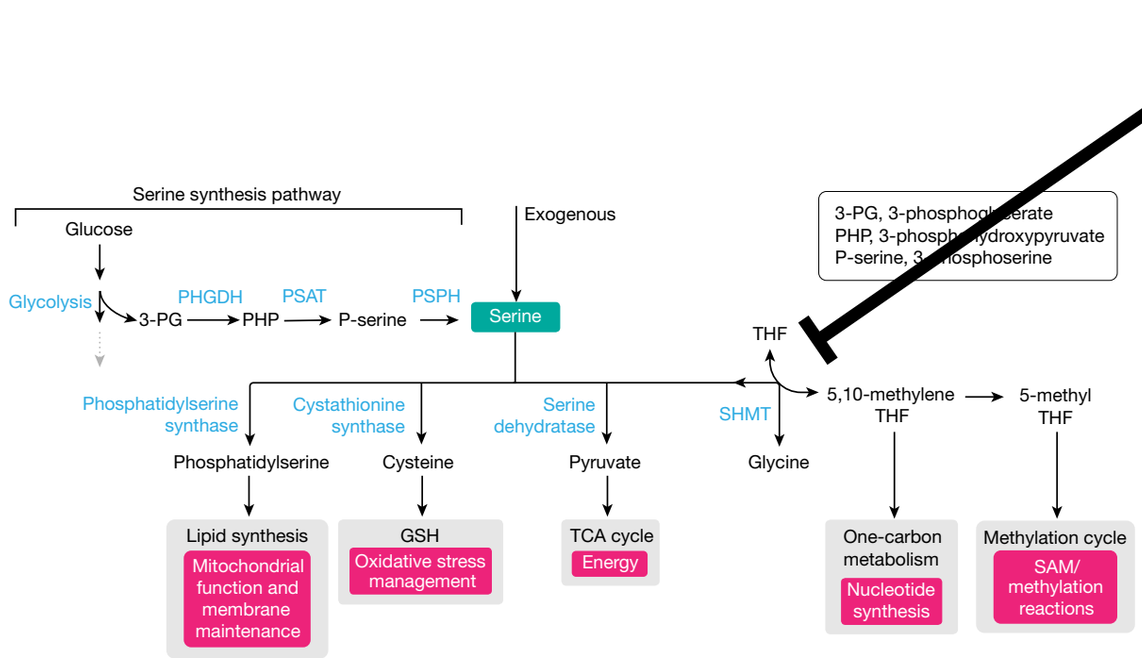
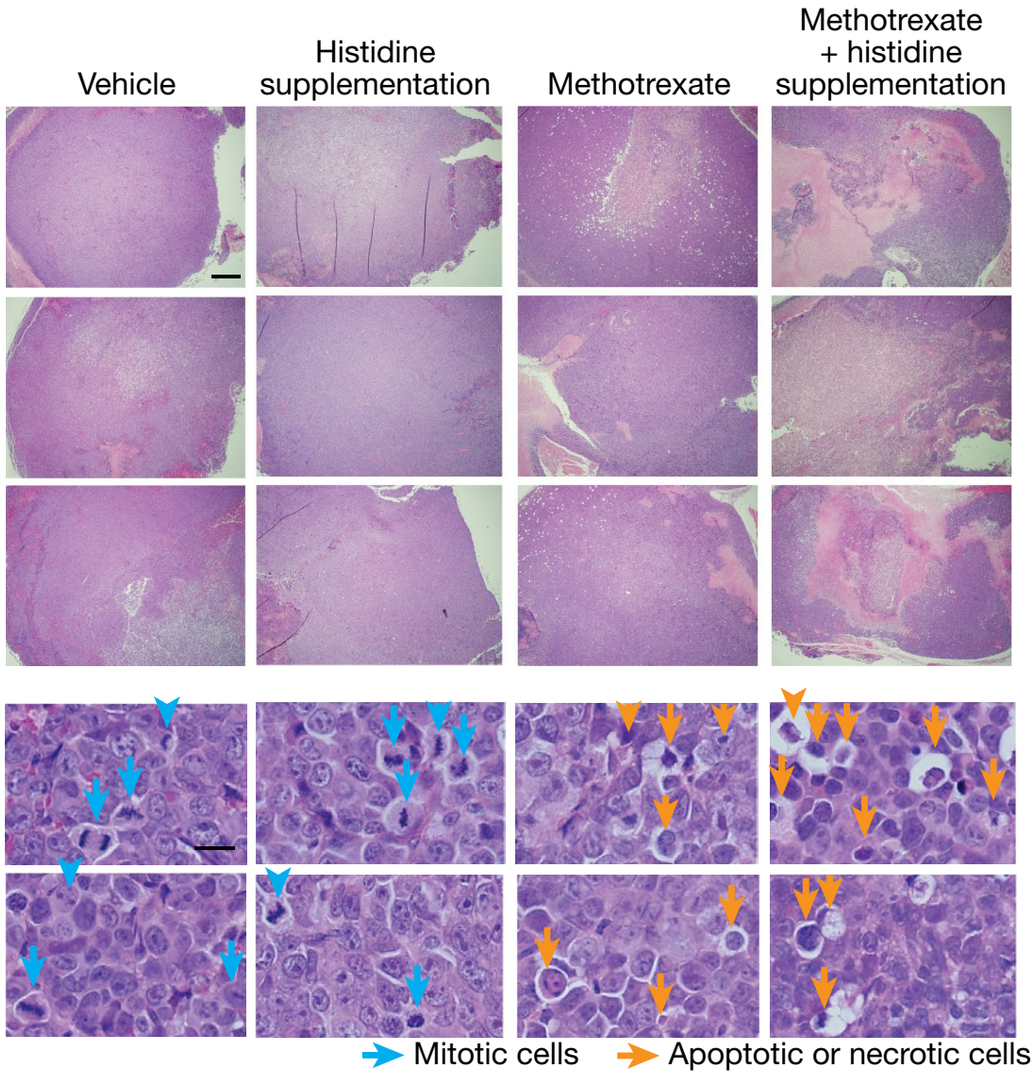
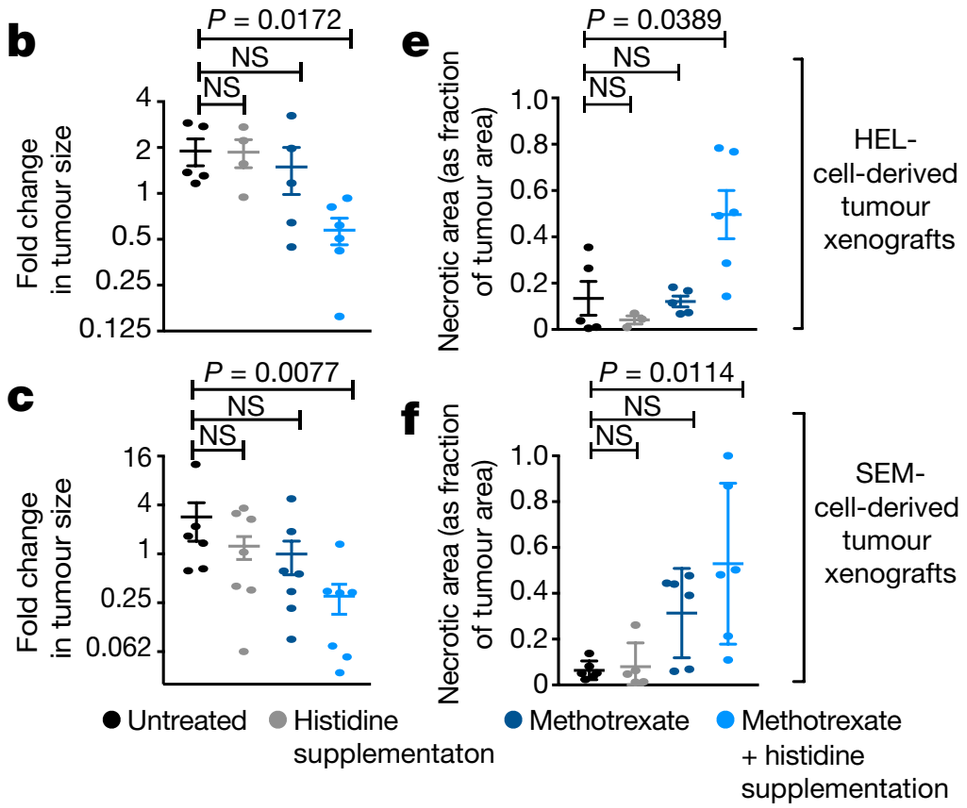




Histidine dietary supplementation potentiates MTX





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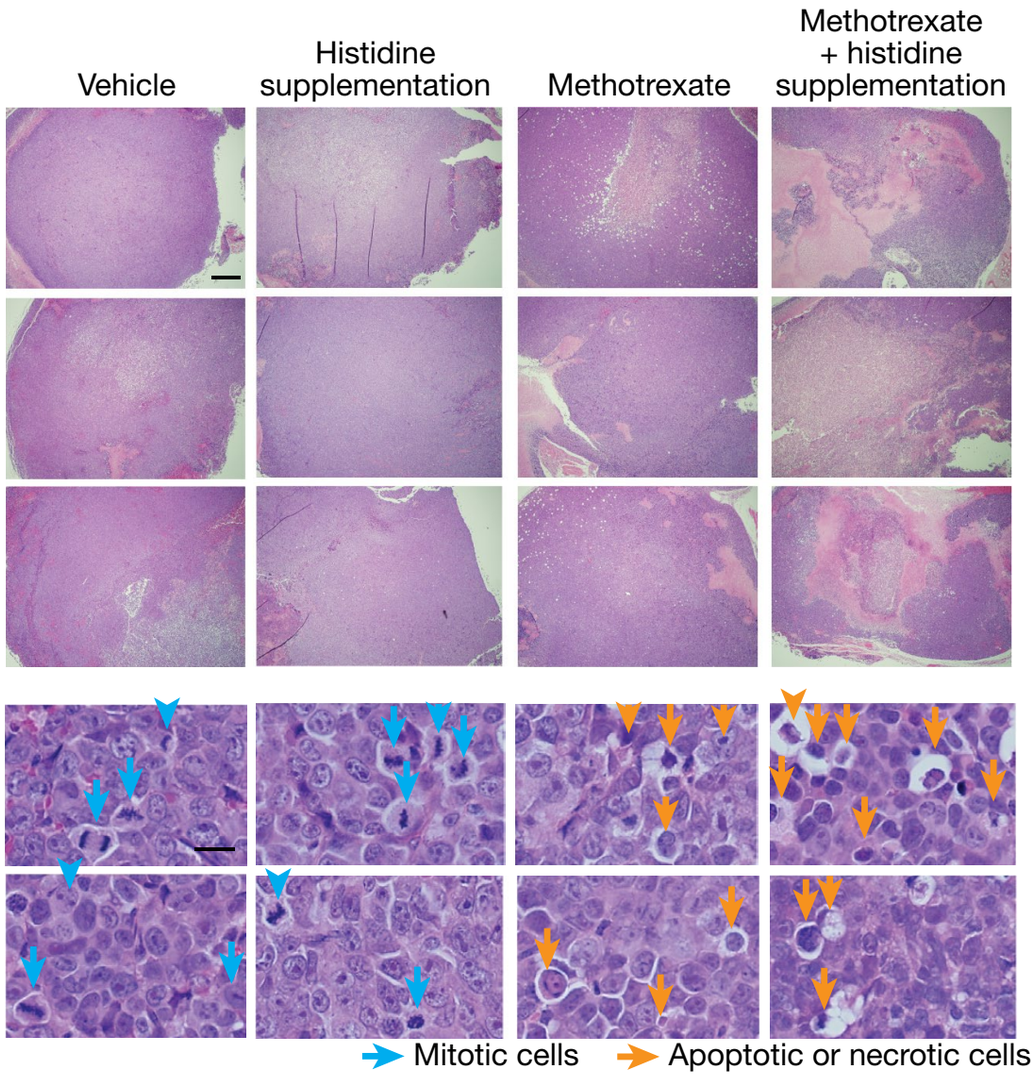
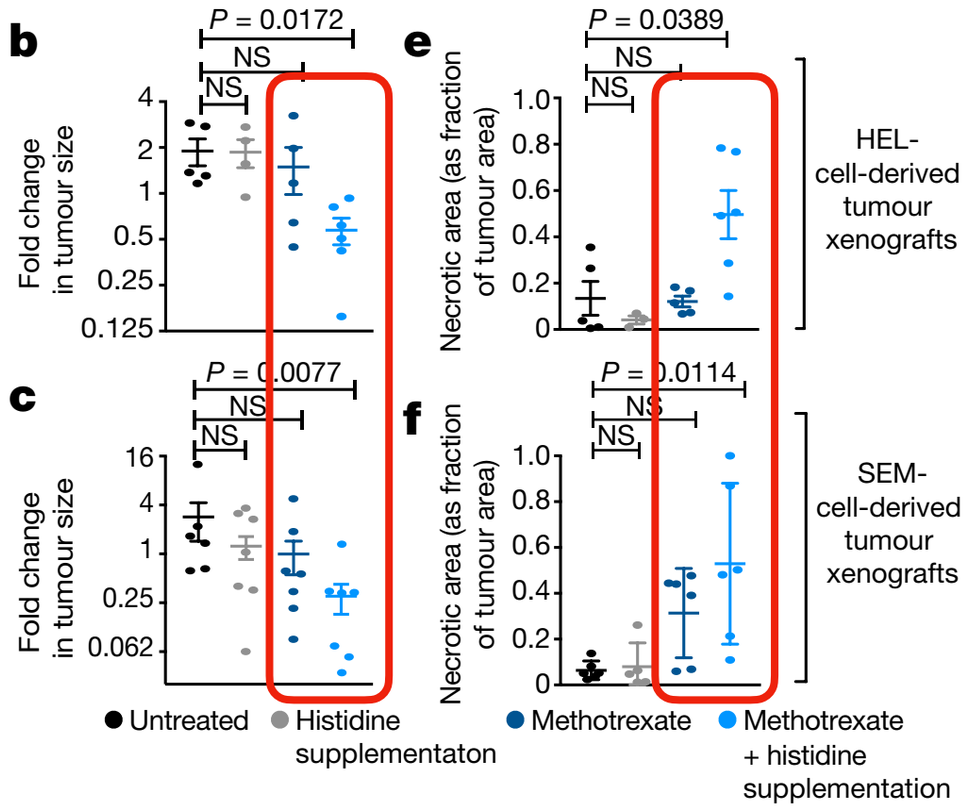
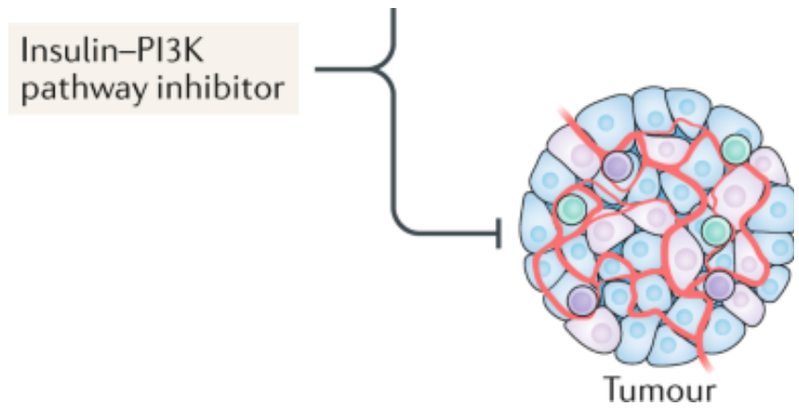




Kanarek et al, ***Nature****, 2019*

PI3K inhibitors suppress tumor growth but activate insulin secretion



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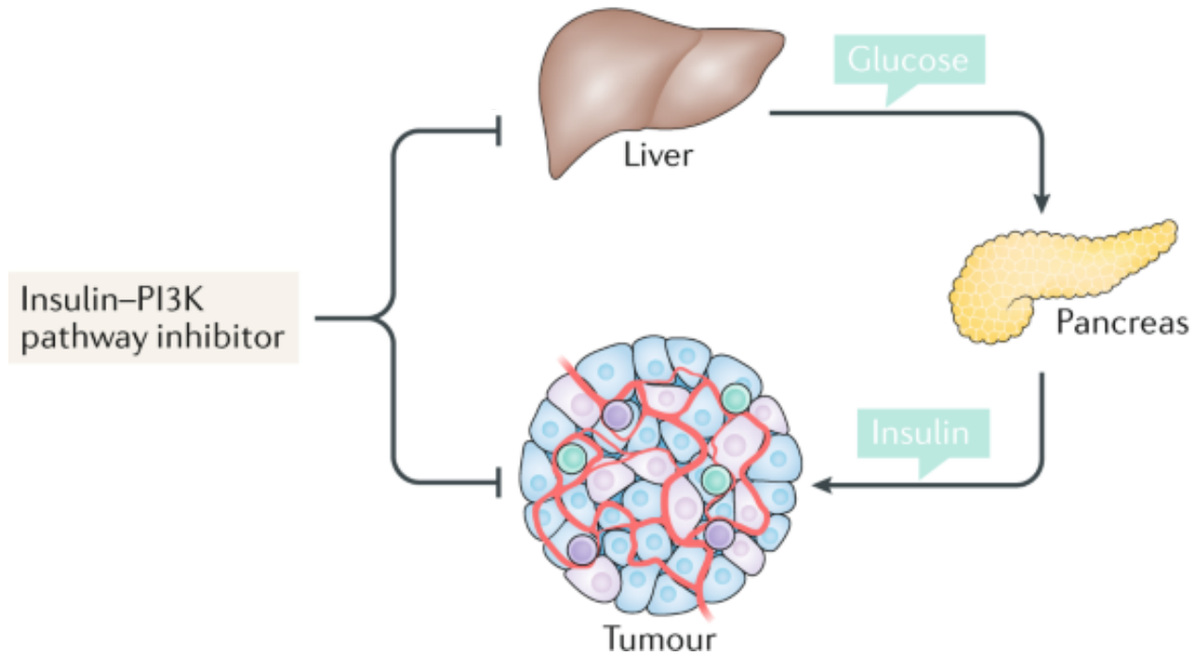

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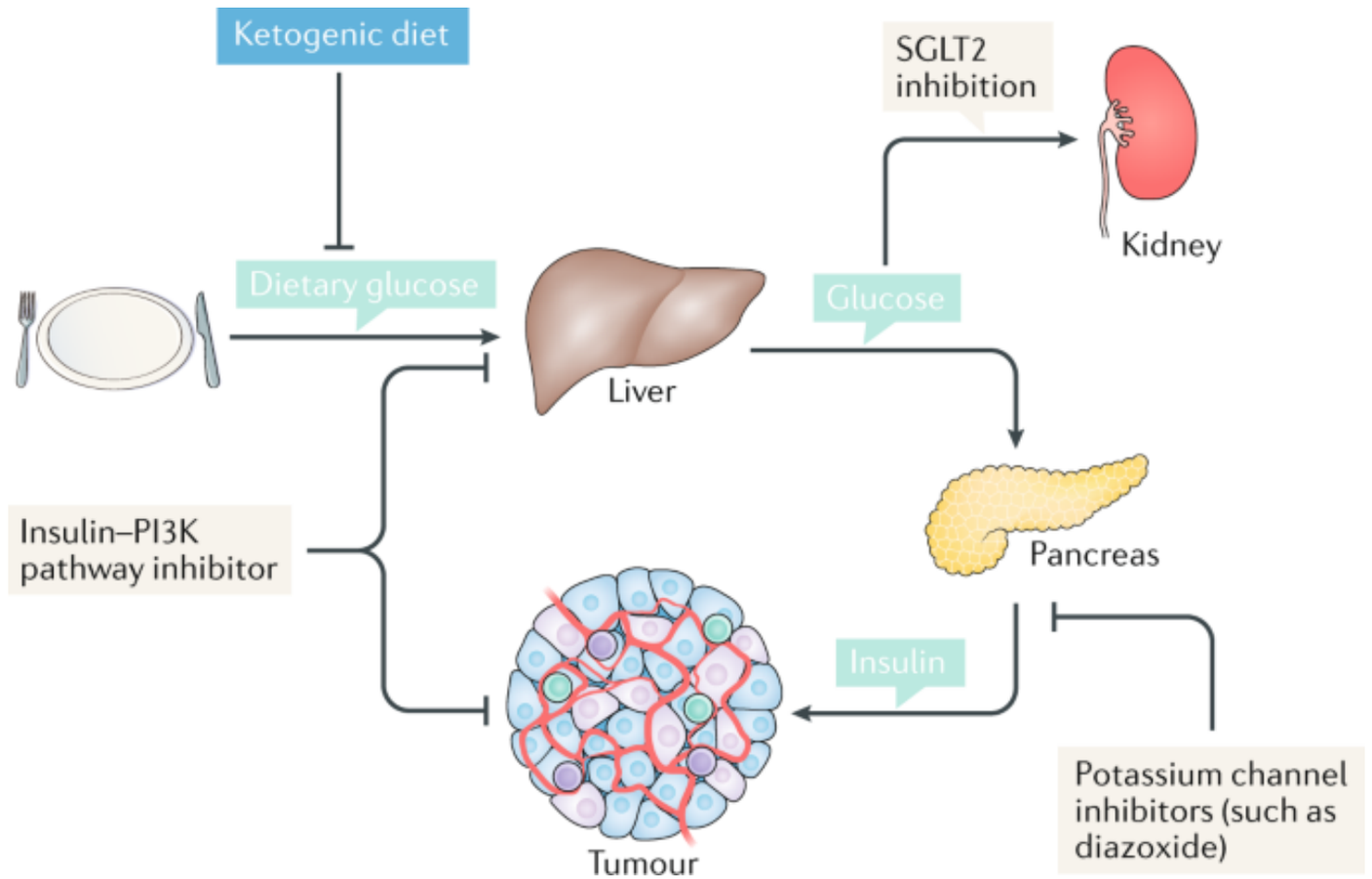
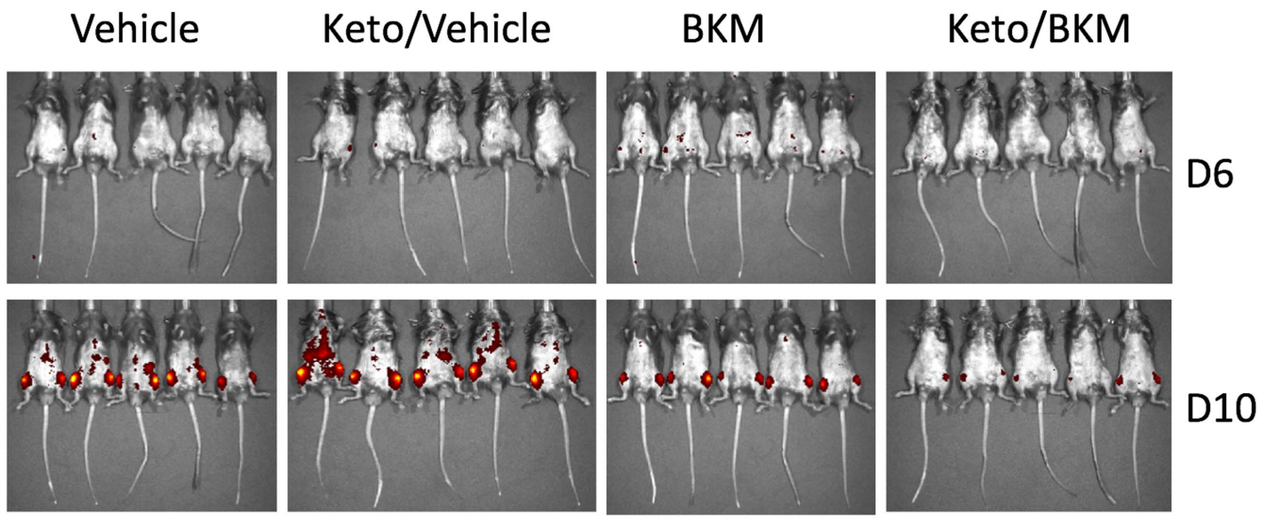
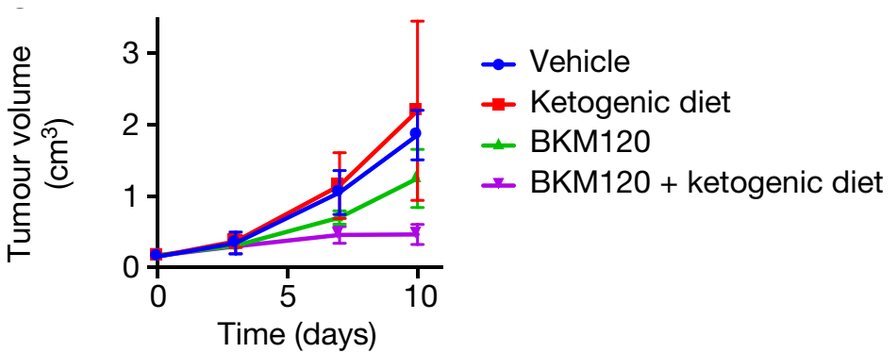


Ketogenic diet impedes insulin-driven resistance





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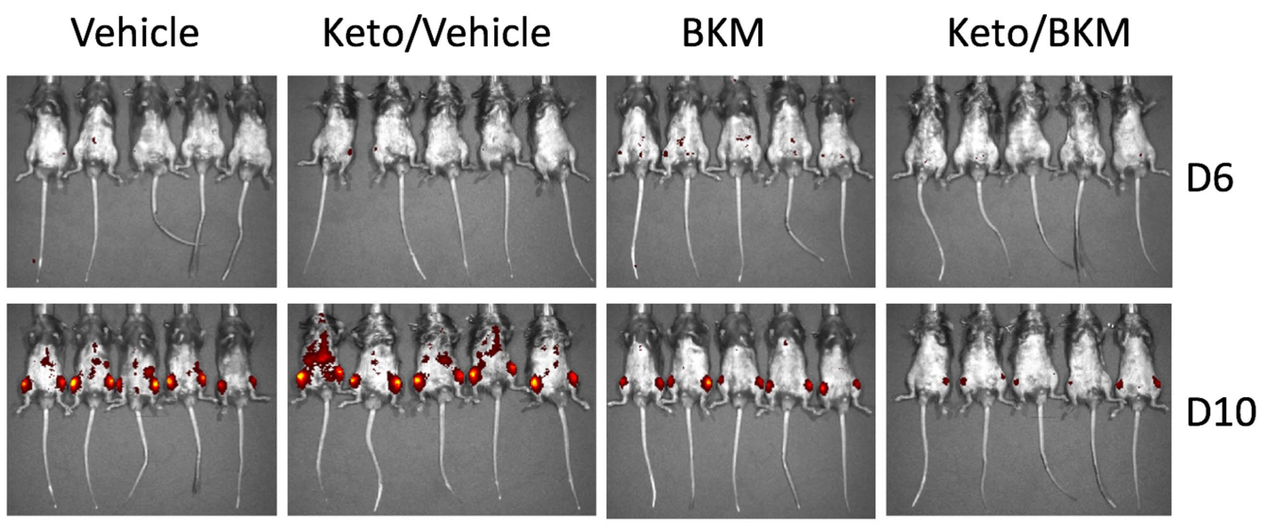

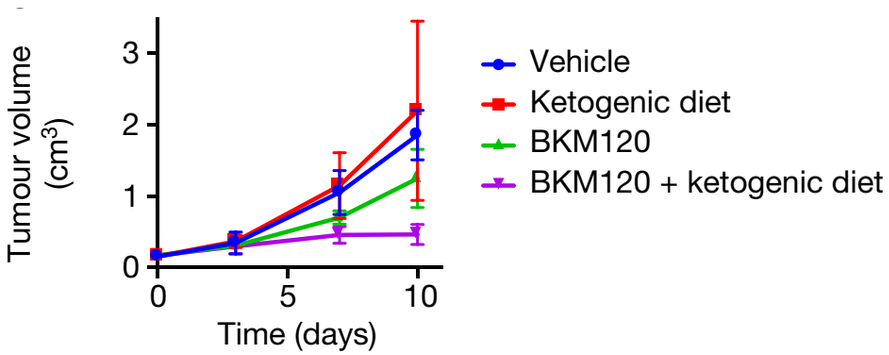

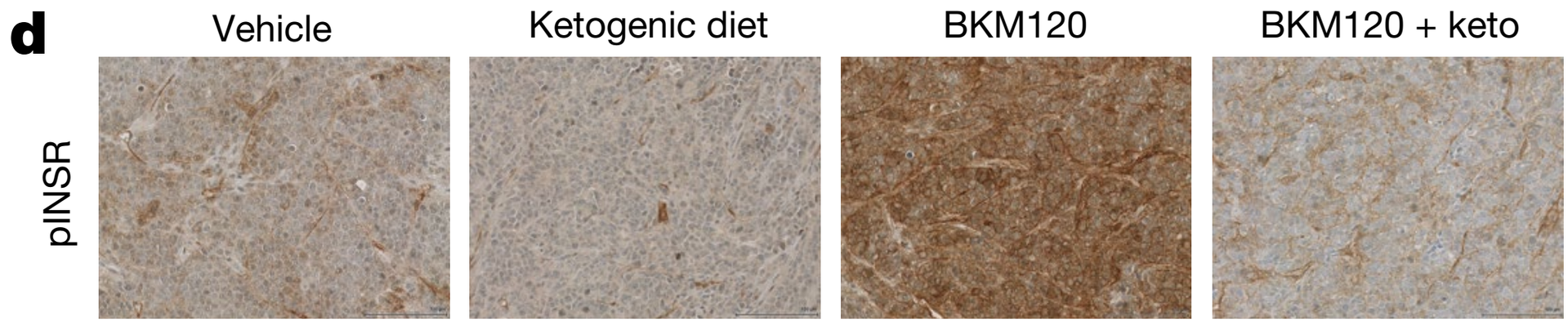

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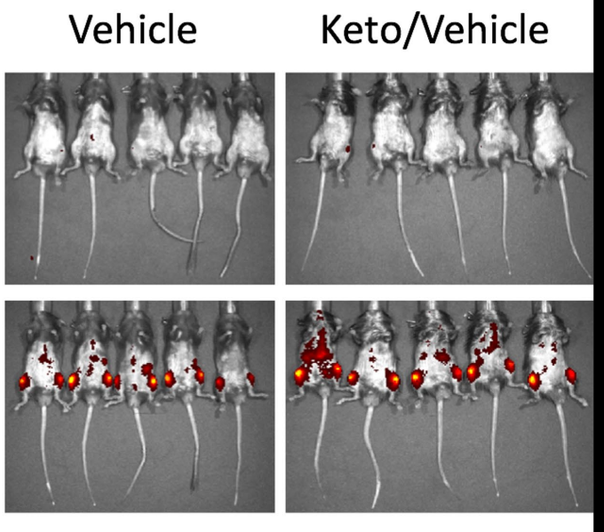
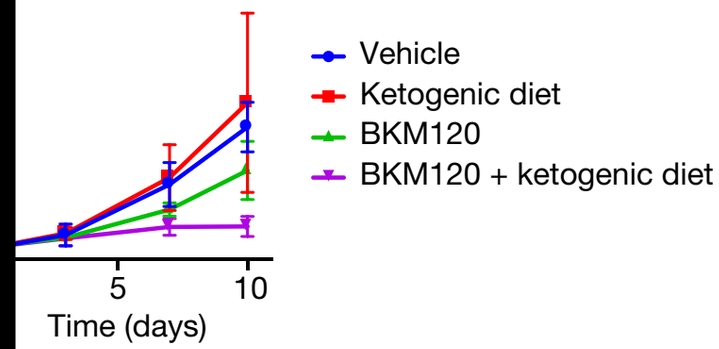


TAKE HOME MESSAGE:

Diet can alter response to therapy



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