Memorial Sloan Kettering Cancer Center

(Cancer) Metabolism

GSK Course
March 31, 2026

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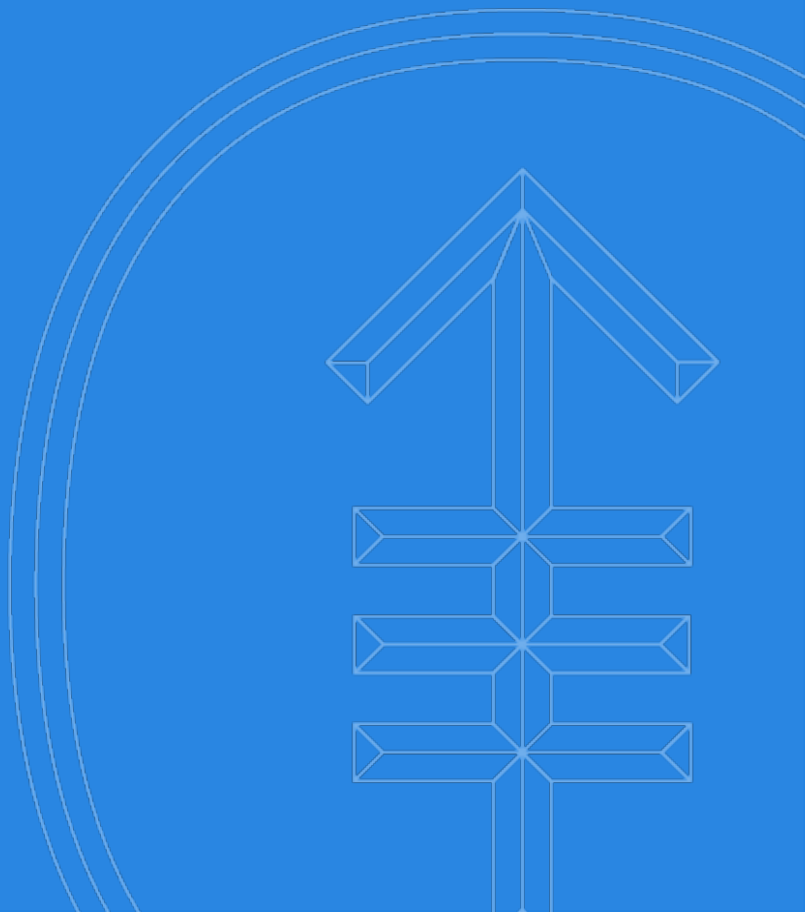
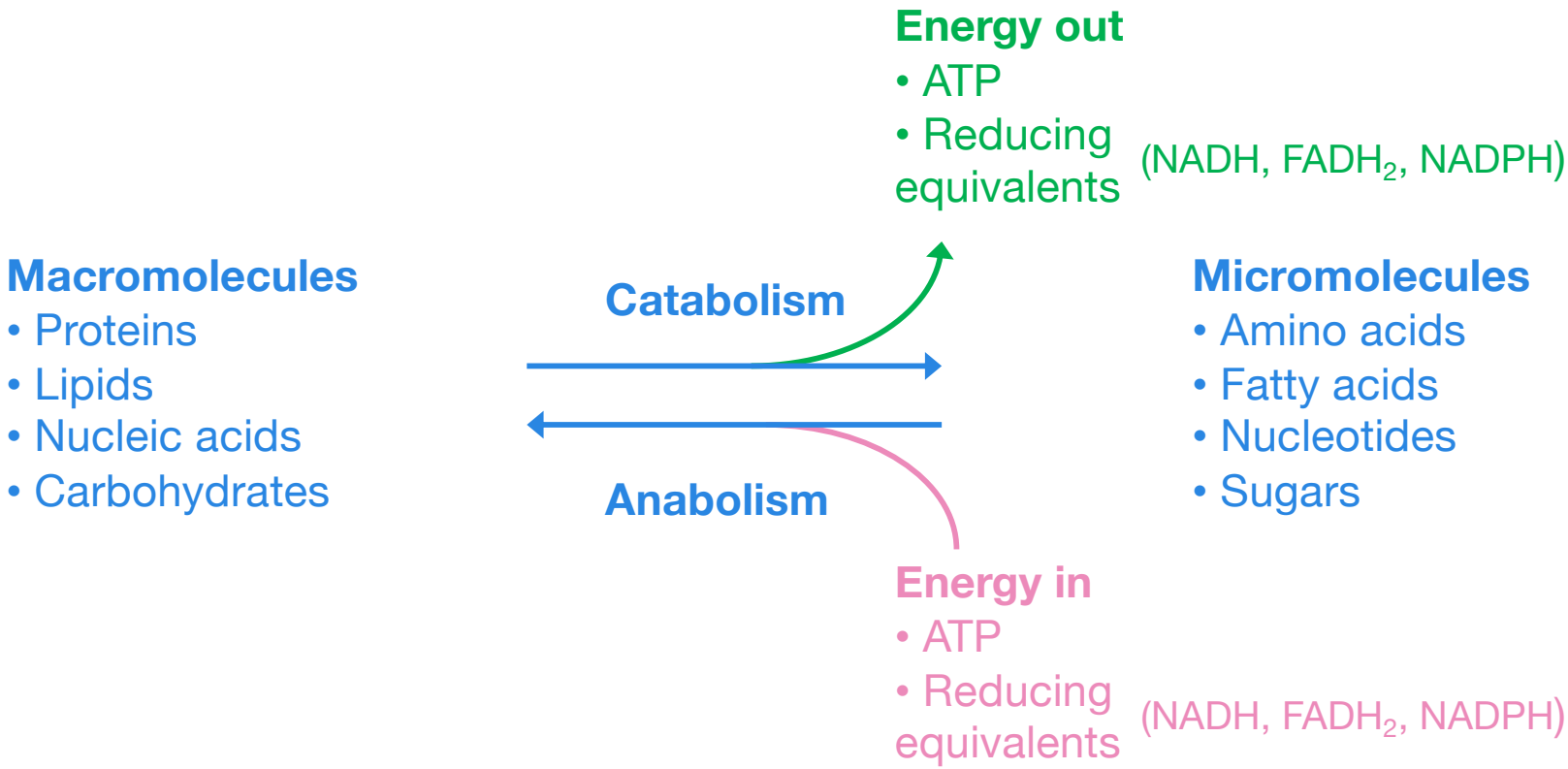
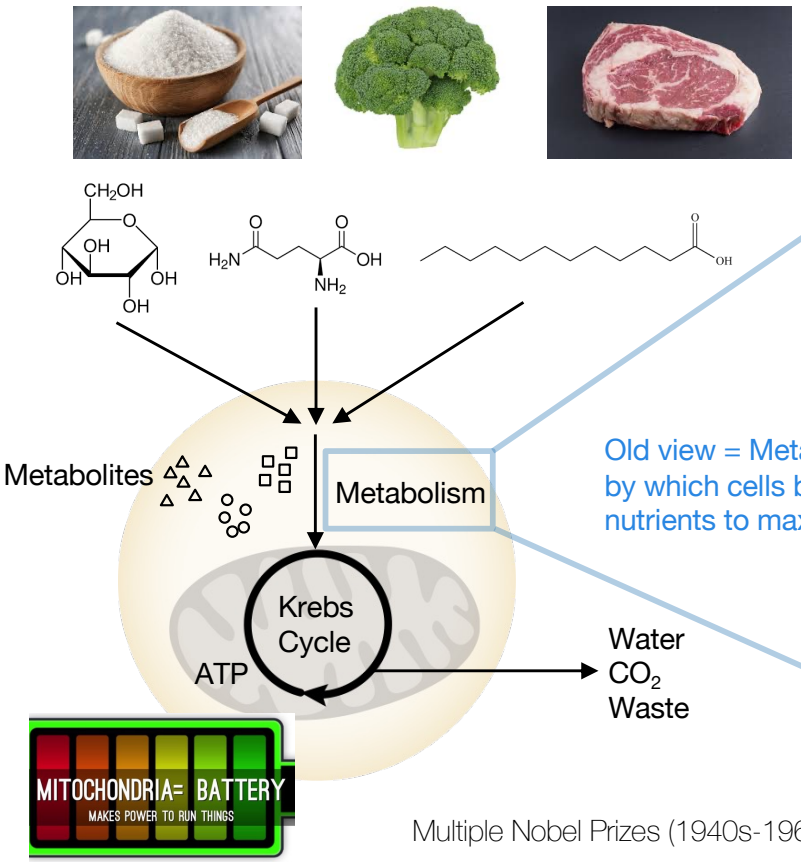


What is cellular metabolism?

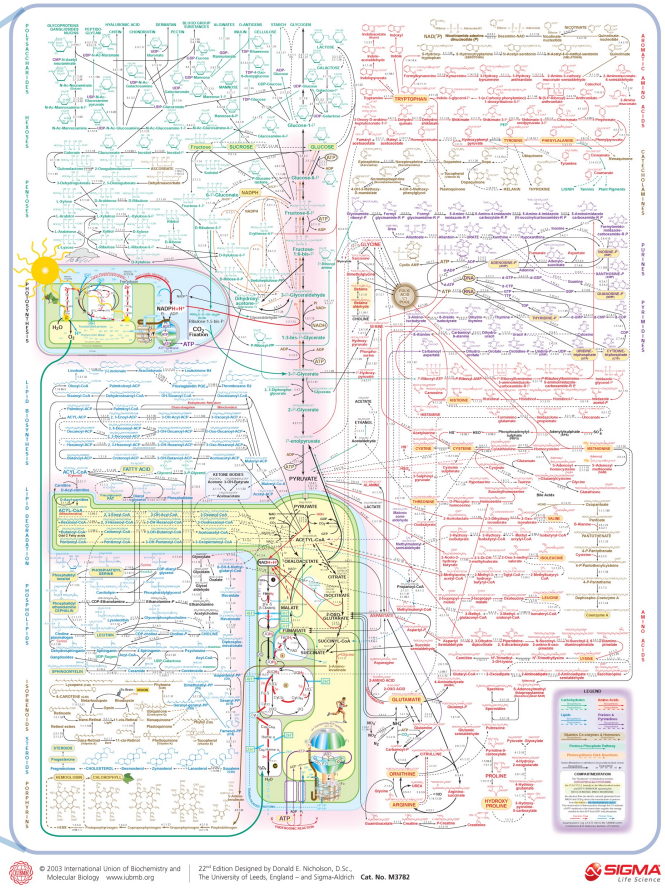
Cellular pathways involved in building or breaking down organic macromolecules



What is cellular metabolism? Old view = energy centric

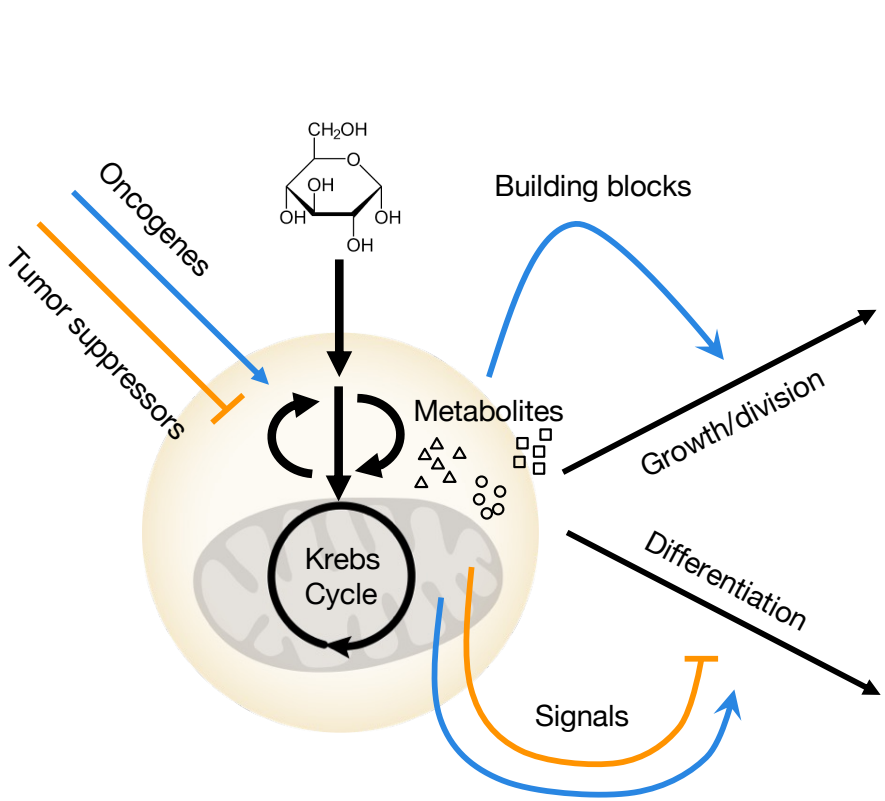


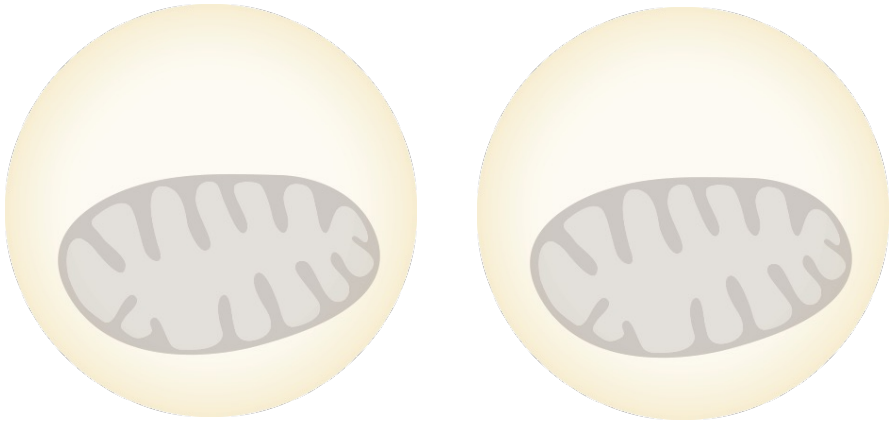
Old view = Metabolism is the process by which cells break down and burn nutrients to maximally extract energy

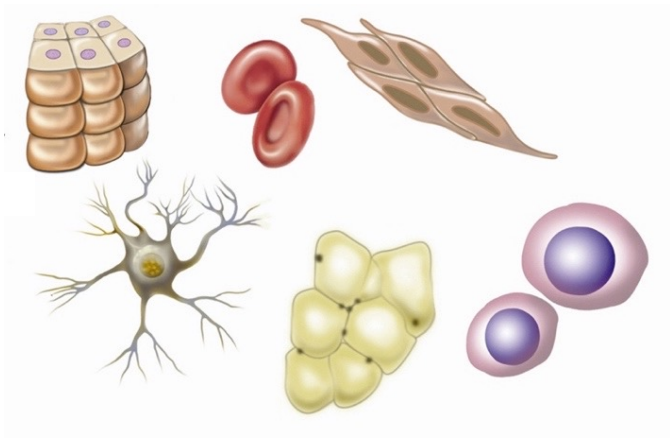


Multiple Nobel Prizes (1940s-1960s)

Metabolism is reprogrammed in proliferating (cancer) and differentiating cells







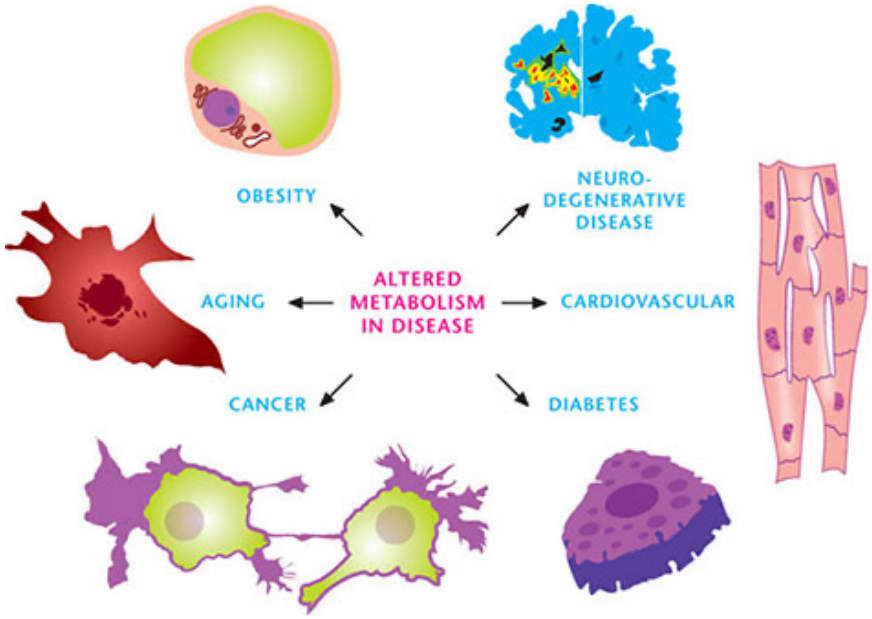
Why study metabolism?

Old view: Metabolism is a housekeeping function that produces energy for the cell

New view: Metabolism is a driver of biology

Normal processes
- Proliferation
- Cell death
- Differentiation
- Gene expression
- Response to stress

Pathology
- Cancer
- Inflammation
- Obesity
- Diabetes
- Neurodegeneration

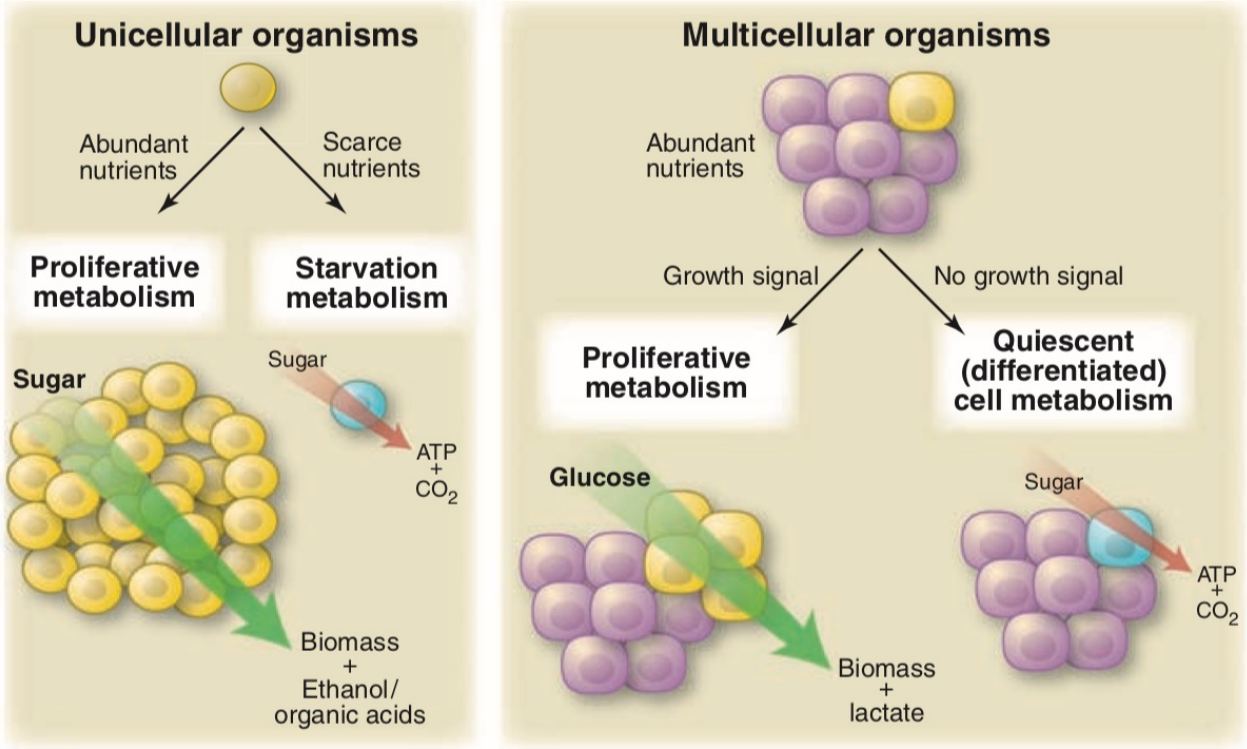


Chandel "Navigating Metabolism"

Proliferating cells (including cancer) ‘reprogram’ their metabolism

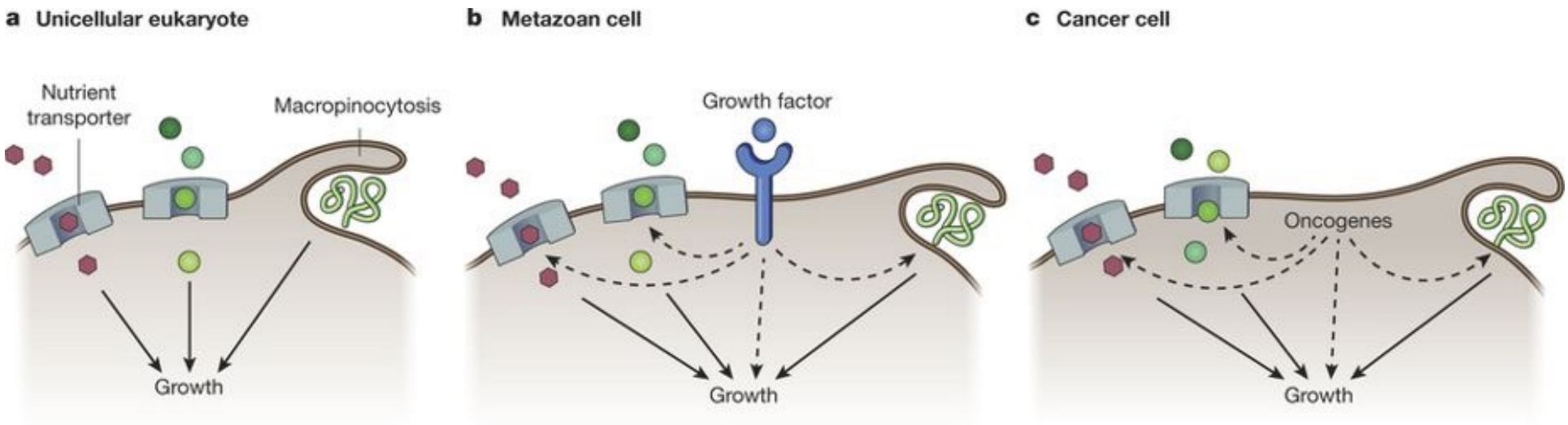
Post-mitotic differentiated cells focus on efficient oxidative metabolism to extract the maximum amount of ATP from nutrients -> ‘manning the pumps’ (ion channels) and executing specialized functions

Proliferating cells (development, immune system, cancer) rewire metabolism to support the biomass accumulation required for cell division



Vander Heiden et al, Science 2009

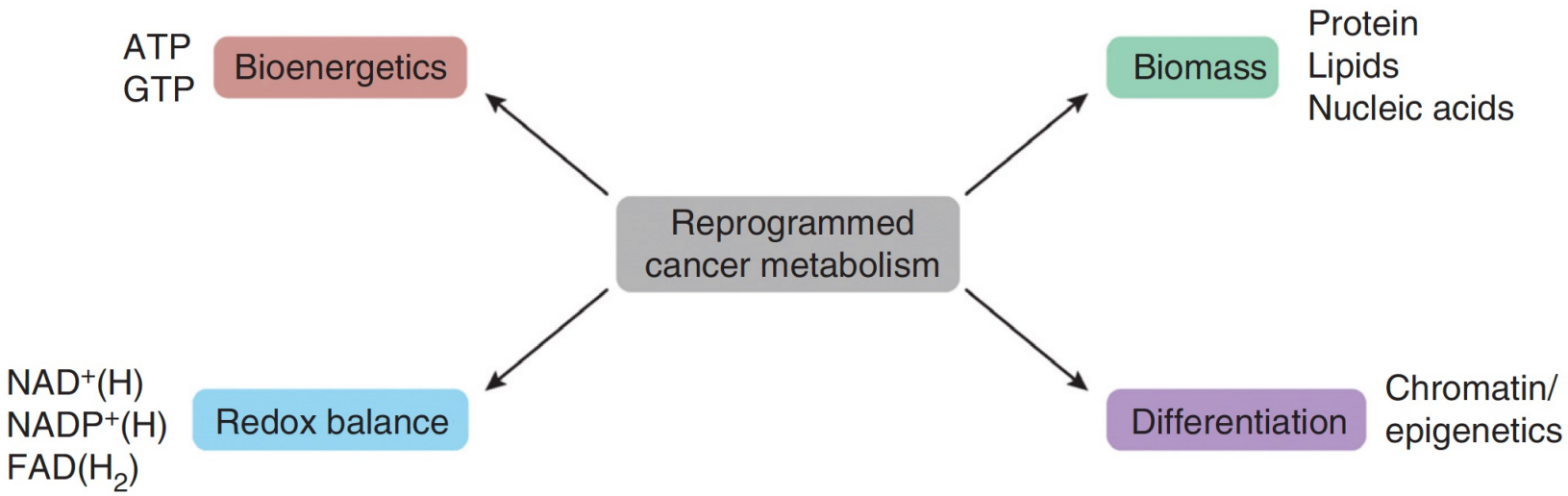
Cancer cells acquire the capacity for unlicensed nutrient uptake



Normal cells depend on growth factors to activate anabolic metabolism; cancer cells activate anabolic metabolism independently of growth factor

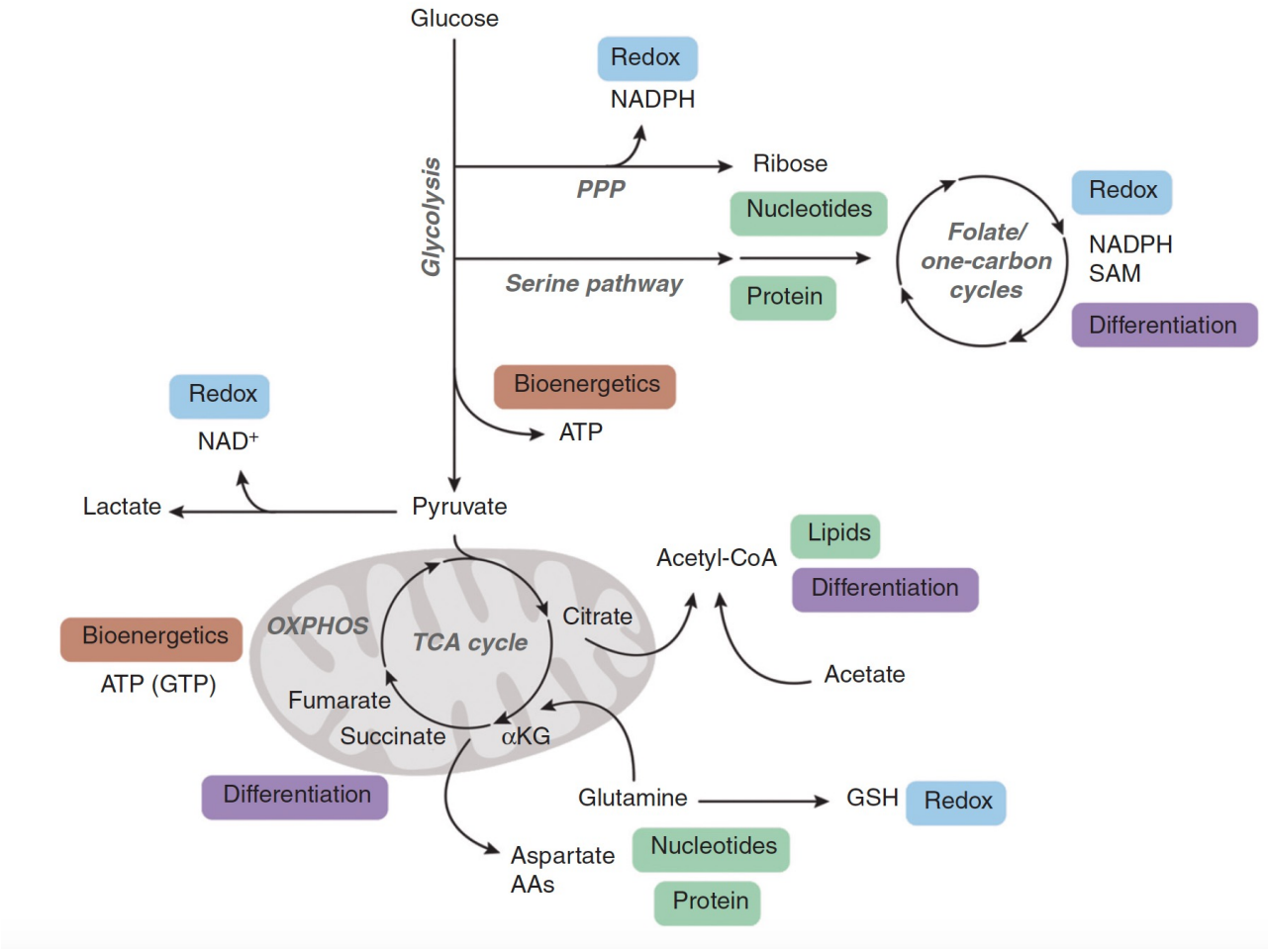
Palm and Thompson, Nature 2017

Key functions of cancer metabolism



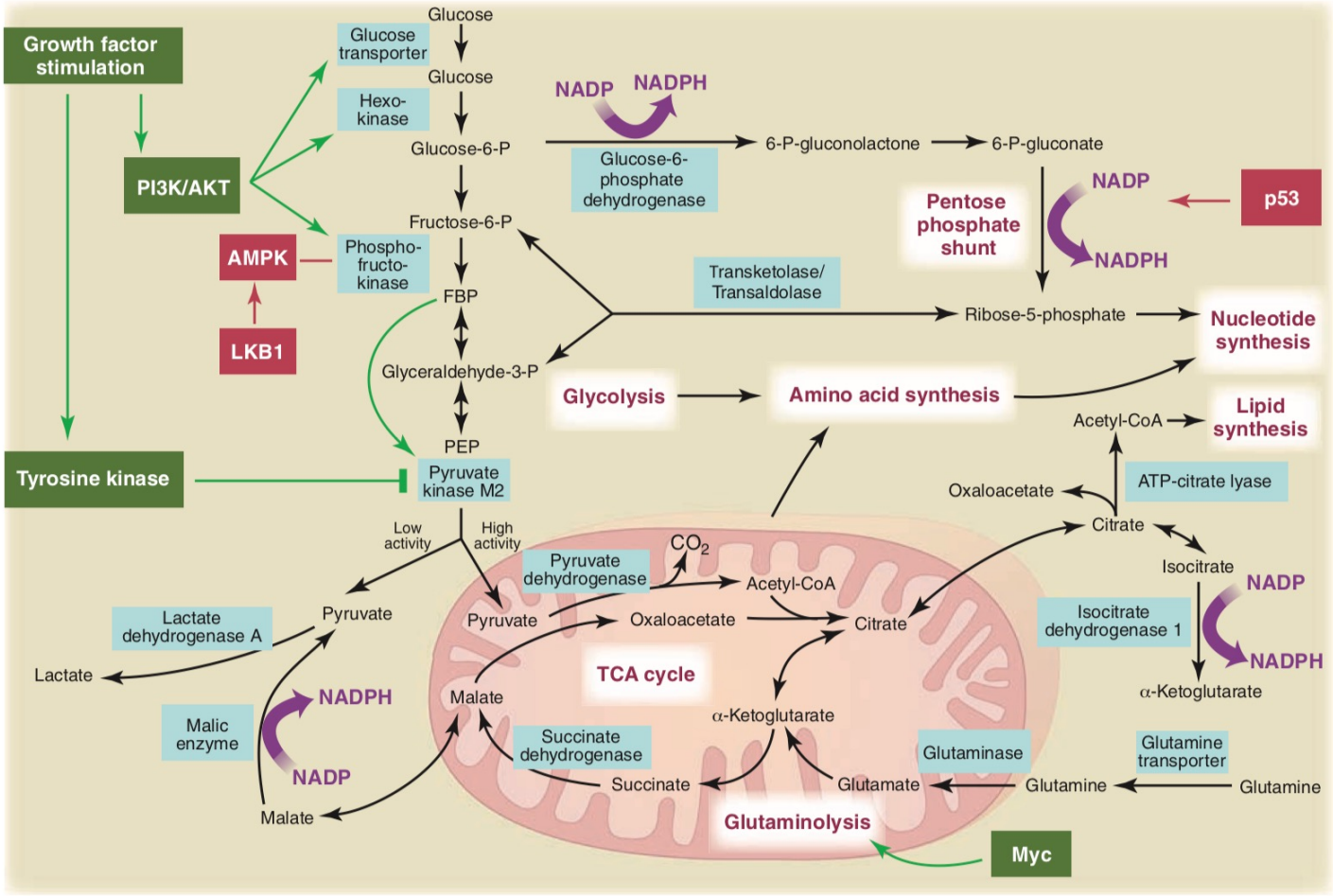
Stahl et al, CSH Press 2020

Simplified schematic of how metabolic demands of cancer cells are fulfilled



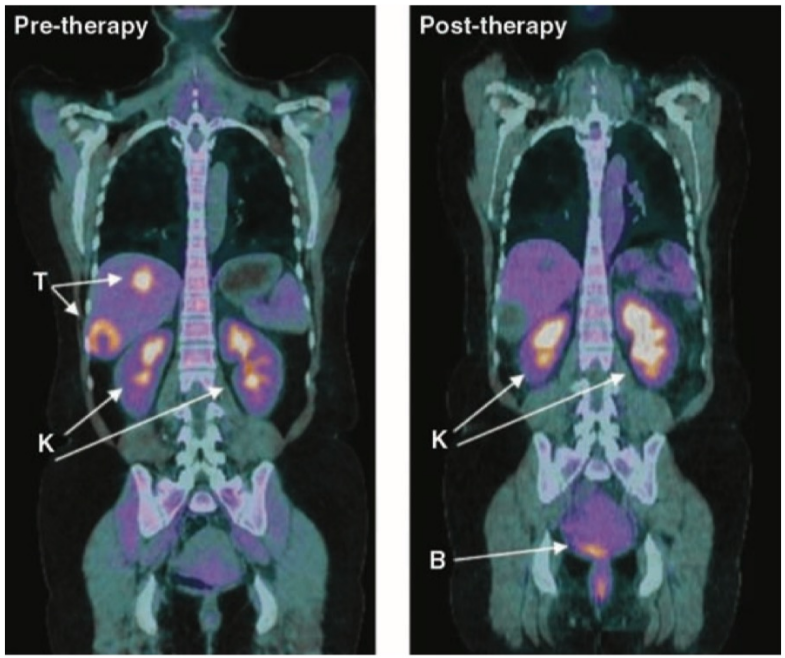
Stahl et al, CSH Press 2020

Oncogenes and tumor suppressors directly regulate metabolism

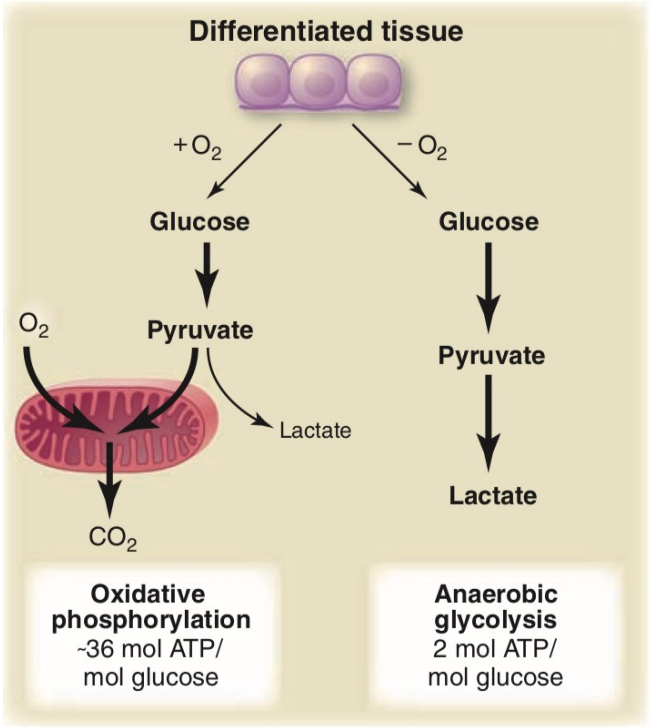


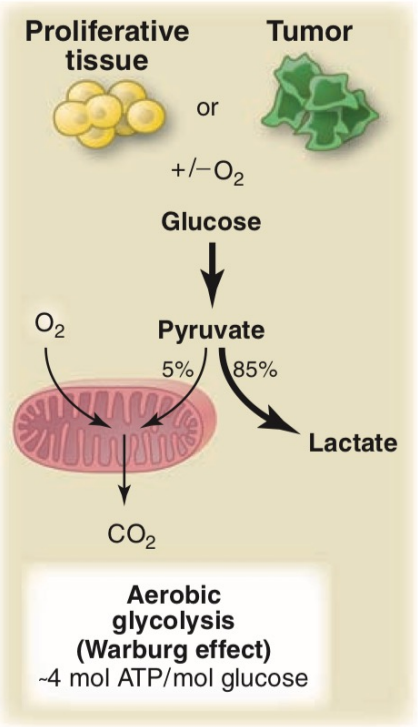
Vander Heiden et al, Science 2009

Cancers exhibit increased glucose uptake but inefficient use? Warburg effect



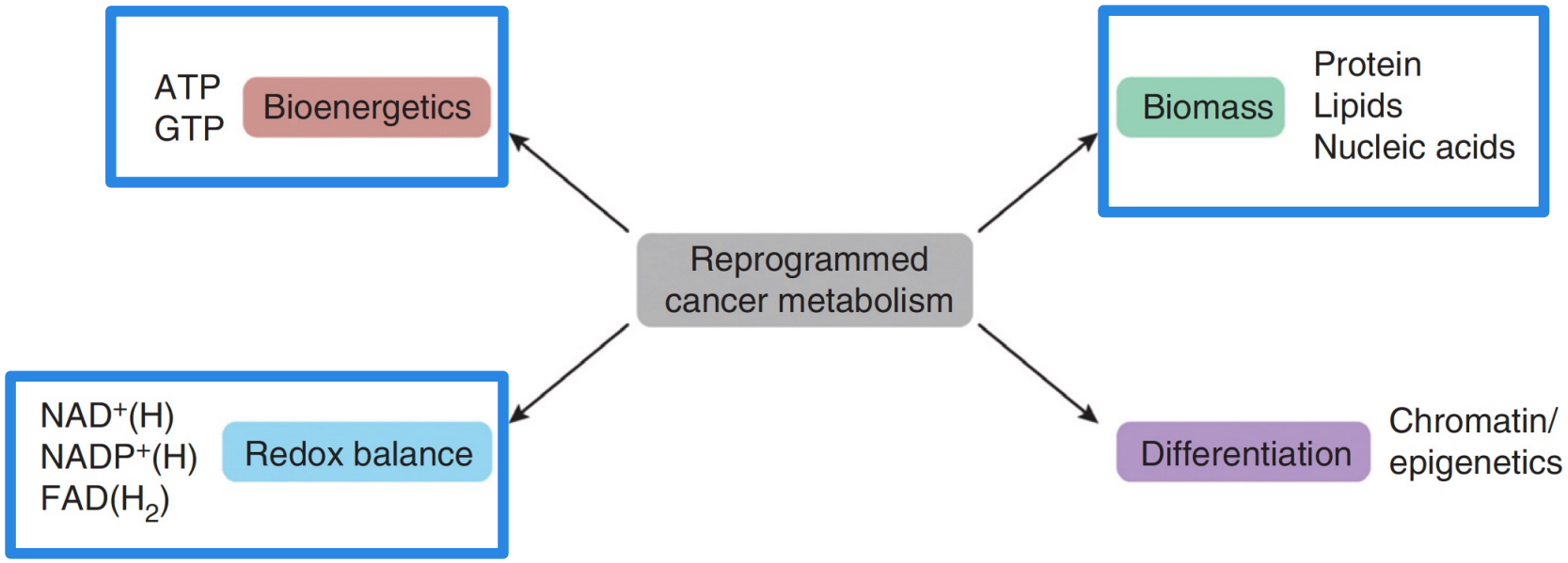
FDG PET scan





Vander Heiden et al, Science 2009

Increased glycolysis achieves multiple goals



Stahl et al, CSH Press 2020

Glycolysis

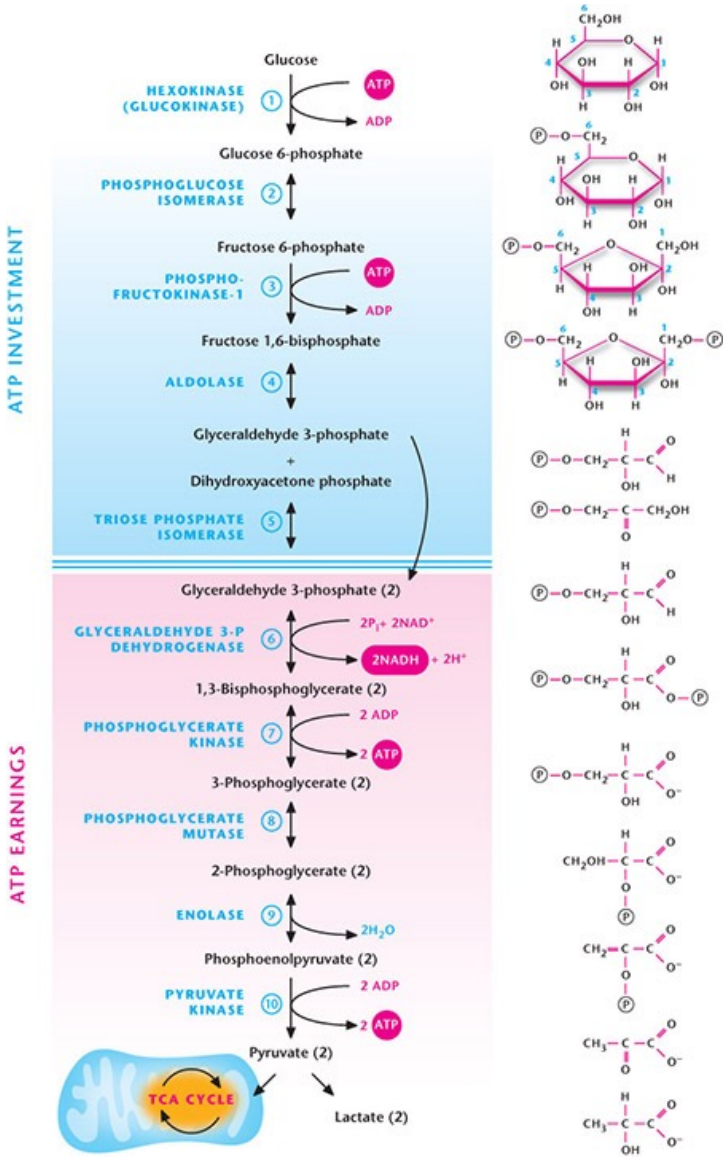
Glucose + **2NAD**$^+$ + 2ADP + 2P_i ⟶
2Pyruvate + **2NADH** + 2H^+ + **2ATP** + 2H_2O

Occurs in cytosol

Glycolysis is essentially a partial oxidation of the reduced carbons in glucose; oxidation of pyruvate is fully completed in the mitochondria

No net loss of carbon or oxygen

Pyruvate and NADH can enter mitochondria for generation of (lots) more ATP (but cancer cells don't really need this as we will see)

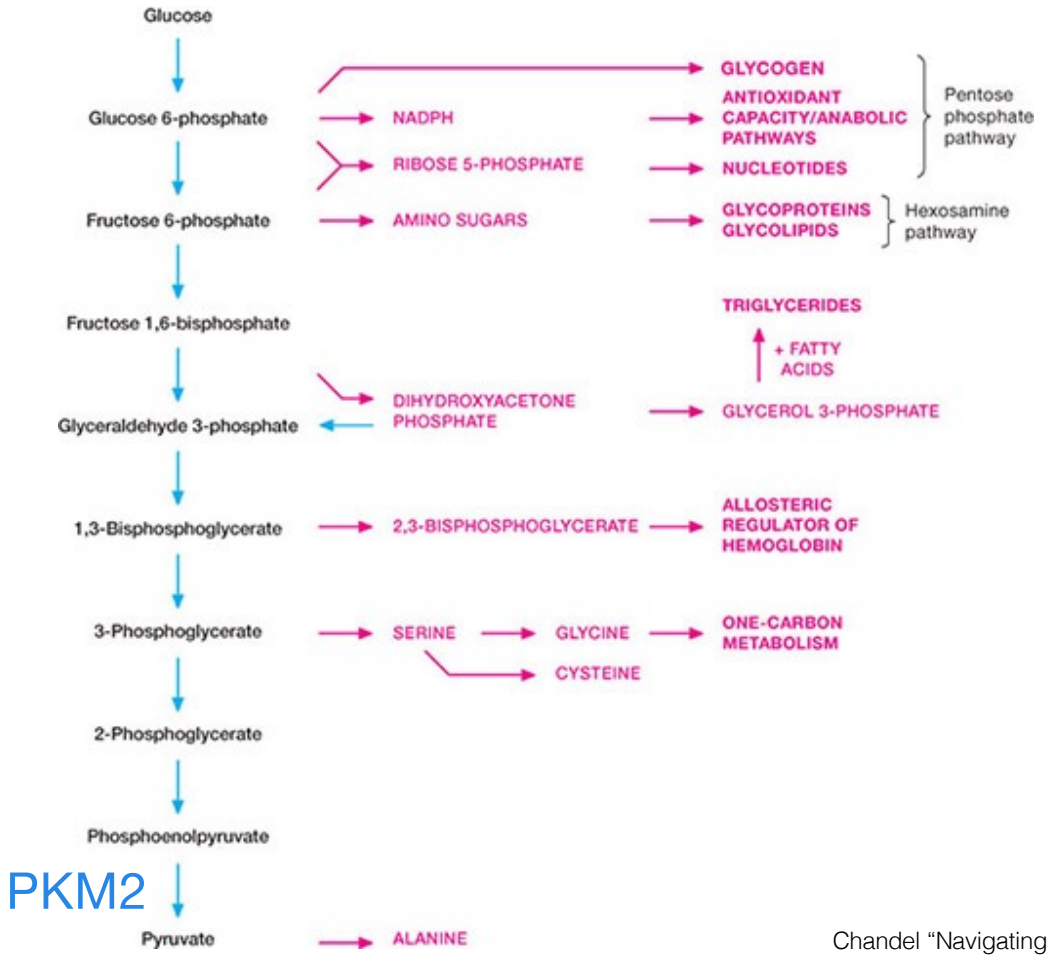


Chandel "Navigating Metabolism"

Glycolysis supports biosynthetic pathways

Proliferating cells (including cancer) paradoxically express an isoform of pyruvate kinase called PKM2 which is slower than conventional PKM1

This creates a bottleneck at the bottom of glycolysis to facilitate exit of upstream intermediates into biosynthetic off-branches, thereby enhancing biomass accumulation required for cell division



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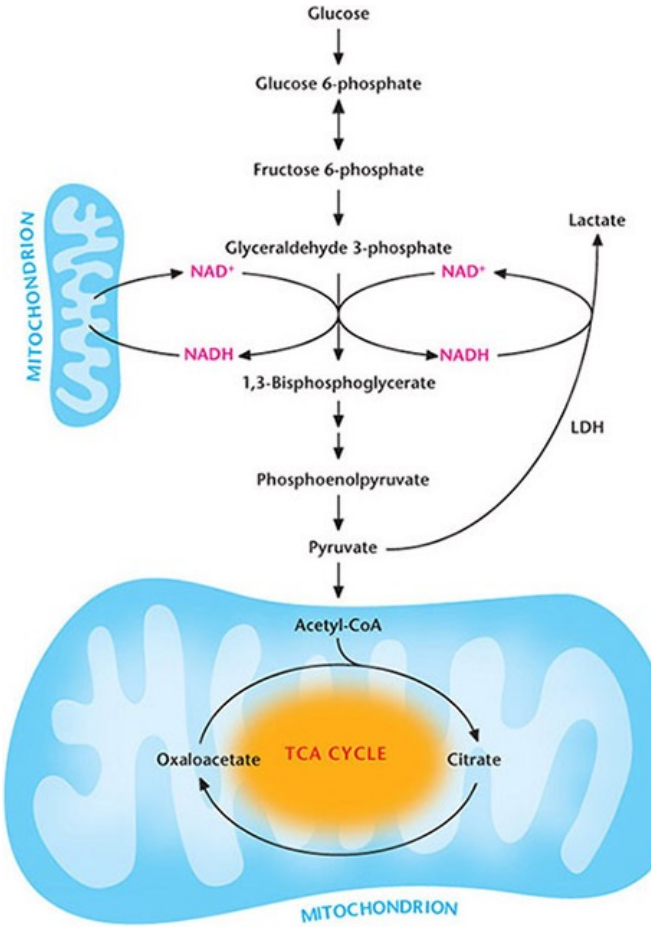
NAD^+ must be regenerated to keep glycolysis going

In cells with functioning mitochondria and oxygen available, NADH is shuttled into the mitochondria via the malate-aspartate shuttle with electrons transferred to the electron transport chain (this is relatively slow)

In hypoxia, mitochondrial dysfunction, or very high rate of glycolysis (cancer), NADH is recycled to NAD^+ via conversion of pyruvate to lactate by lactate dehydrogenase (LDH) -> **Warburg effect**

Glycolysis alone cannot generate net cytosolic NAD^+ (it is redox neutral); NAD^+ is required for macromolecule synthesis, so proliferating cells must have functional ETC to generate the NAD^+ required for biomass accumulation



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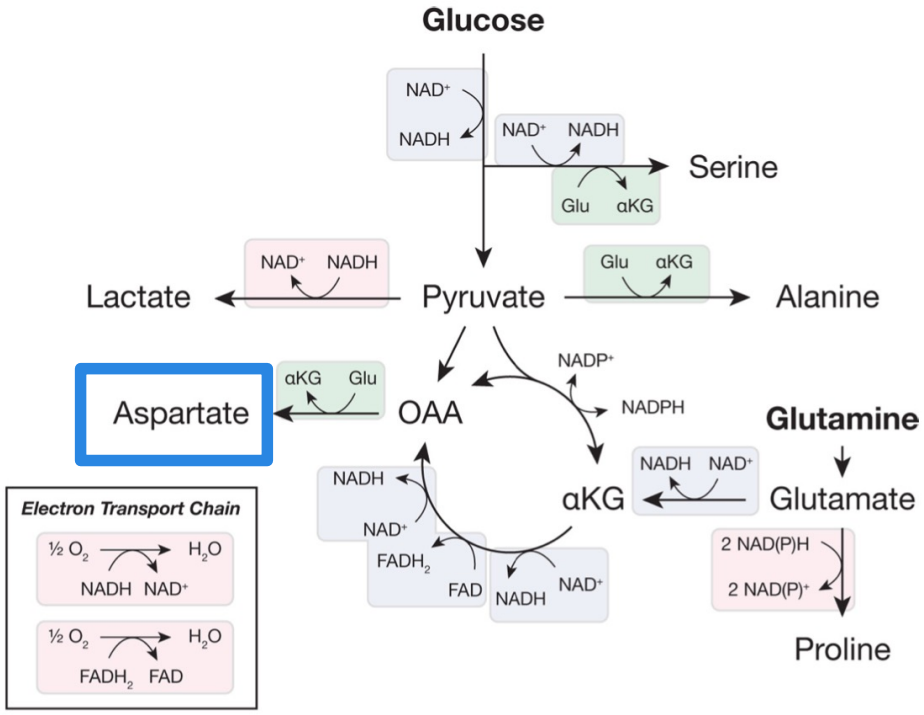
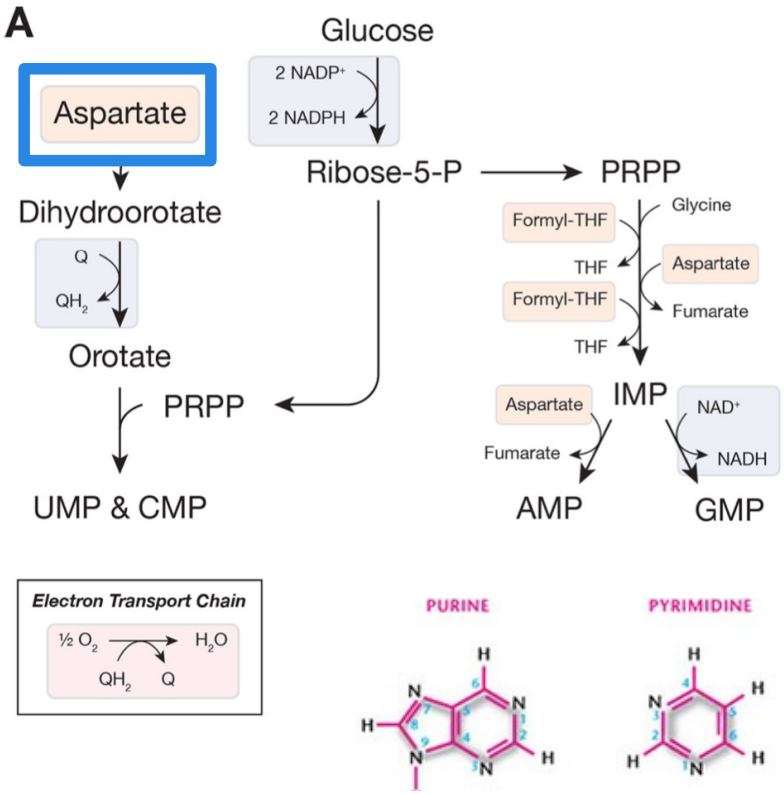
‘Net’ NAD^+ is required to synthesize nucleotides (via aspartate) -> MITOCHONDRIA



‘Net’ NAD^+ also required for synthesis of several non-essential amino acids



Hosios et al, JBC 2018

Mitochondrial metabolism

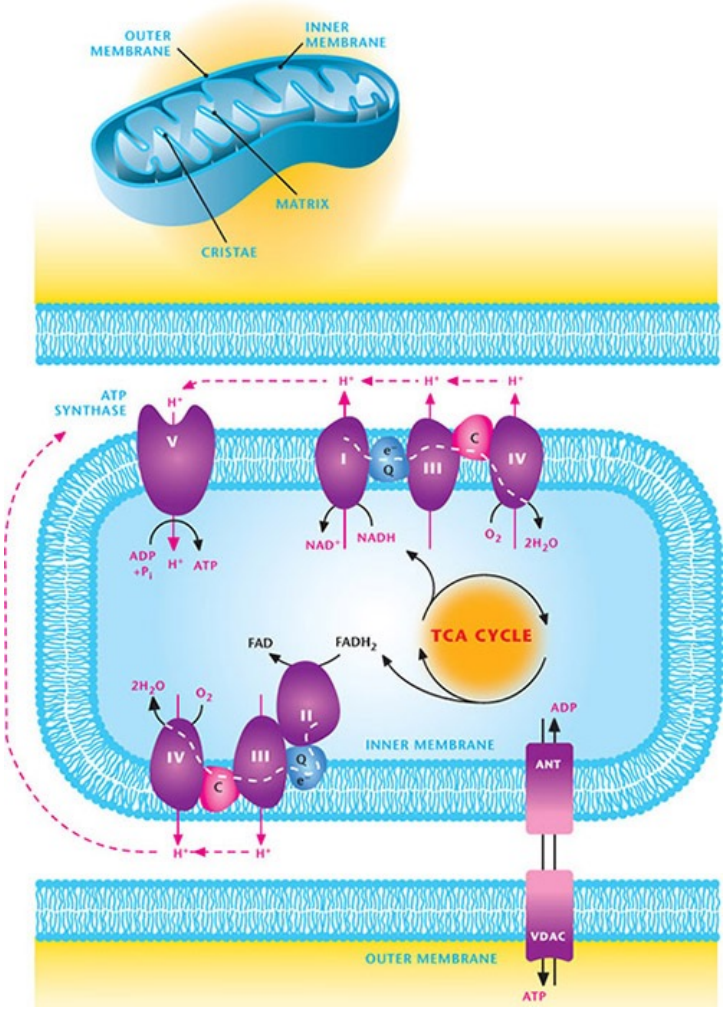
Outer mitochondrial membrane is permeable, inner membrane is impermeable

Mitochondria produce ATP by oxidizing pyruvate, fatty acids, and amino acids

Mitochondria are biosynthetic hubs (indirectly) required for synthesis of lipids, proteins, and nucleotides

Mitochondria are signaling organelles (via ROS, calcium, cytochrome c, mtDNA, acetyl-CoA, metabolites, etc)

Mitochondrial DNA encodes 37 genes (many for OXPHOS); rest of mito proteins are encoded in genomic DNA



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TCA/Krebs cycle

Acetyl-CoA + $3NAD^+$ + 1FAD + 1GDP + P_i ⟶
1CoA-SH + $2CO_2$ + 3NADH + $1FADH_2$ + 1GTP

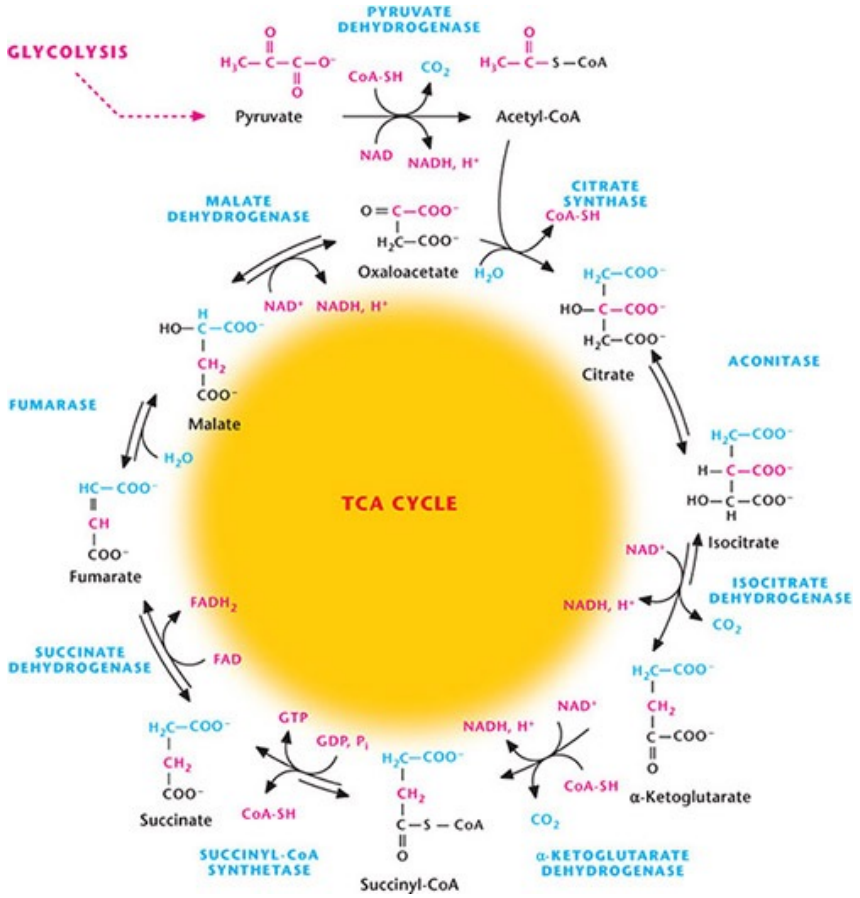
Occurs in mitochondrial matrix

It is a cycle that starts and ends with oxaloacetate

NADH comes from a series of oxidations
- Isocitrate dehydrogenase
- Alpha-ketoglutarate dehydrogenase
- Malate dehydrogenase

$FADH_2$ comes from succinate dehydrogenase

GTP (=ATP) comes from succinyl-CoA synthetase



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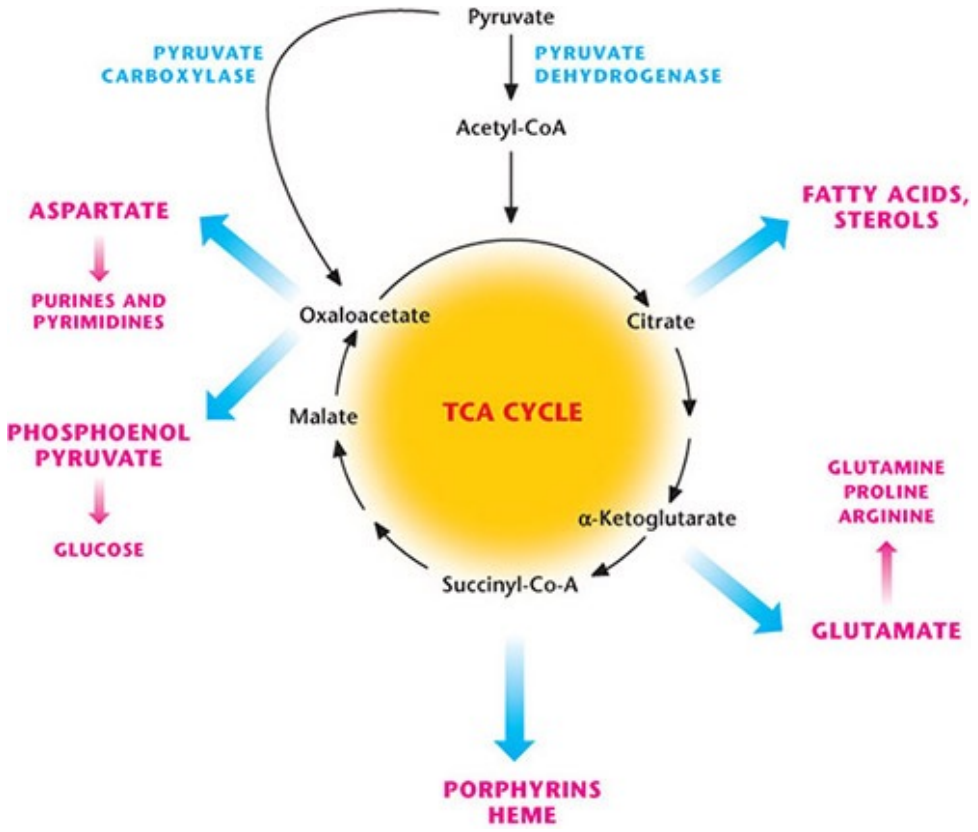
The TCA cycle is a biosynthetic hub

TCA cycle intermediates are required for synthesis of lipids (citrate), proteins (NEAA), nucleotides (aspartate), and glucose (for gluconeogenesis)

Acetyl-CoA cannot cross the mitochondrial membrane so citrate must exit the be converted to acetyl-CoA and oxaloacetate in the cytosol by ATP citrate lyase; essential for:

- Fatty acid synthesis
- Cholesterol synthesis
- Histone and protein acetylation

Note that acetate can be captured by acetyl-CoA synthetase (ACSS2) in cytosol to make acetyl-CoA independently of citrate (think about deacetylation)



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Glutamine is an anaplerotic substrate

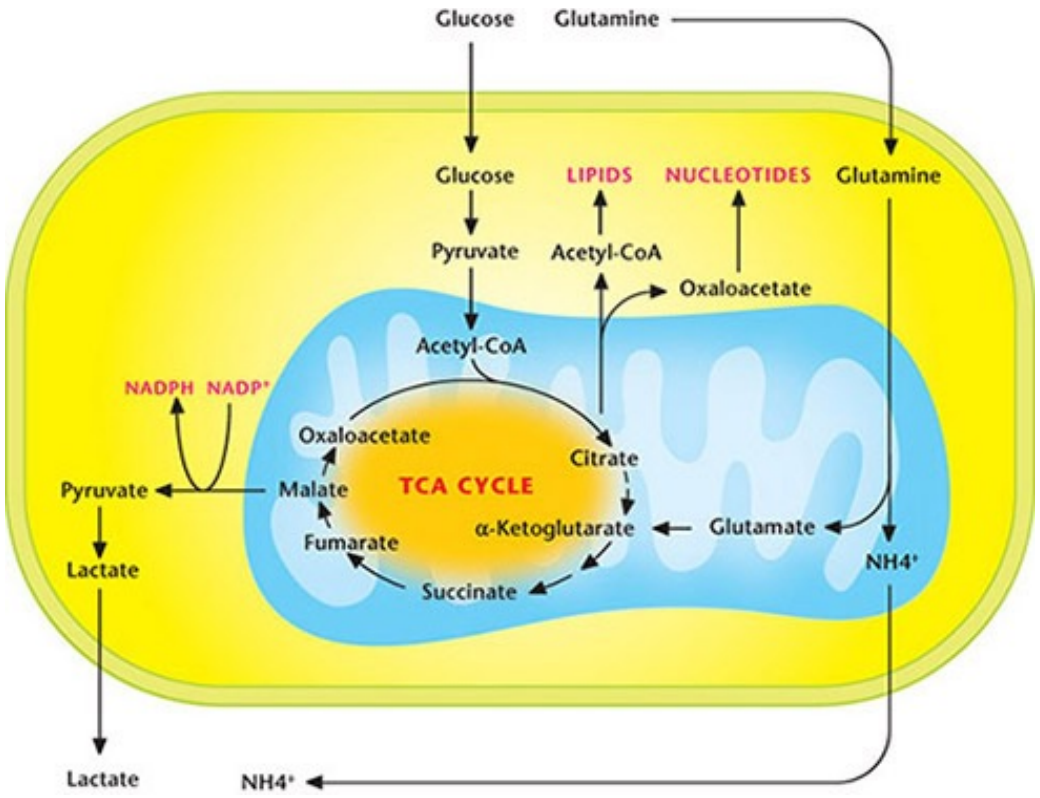
TCA cycle intermediates are constantly existing the TCA cycle for biosynthetic needs

The cycle can only continue if these carbons are replenished (anaplerosis)

Glutamine is a major anaplerotic substrate

Pyruvate can also be an anaplerotic substrate when converted to oxaloacetate by pyruvate carboxylase (not shown)

Glutamine is also key for nucleotide biosynthesis -> nitrogen donor



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Electron transport chain and oxidative phosphorylation (not the same thing!)

NADH donates electrons to complex I

$FADH_2$ donates electrons to complex II

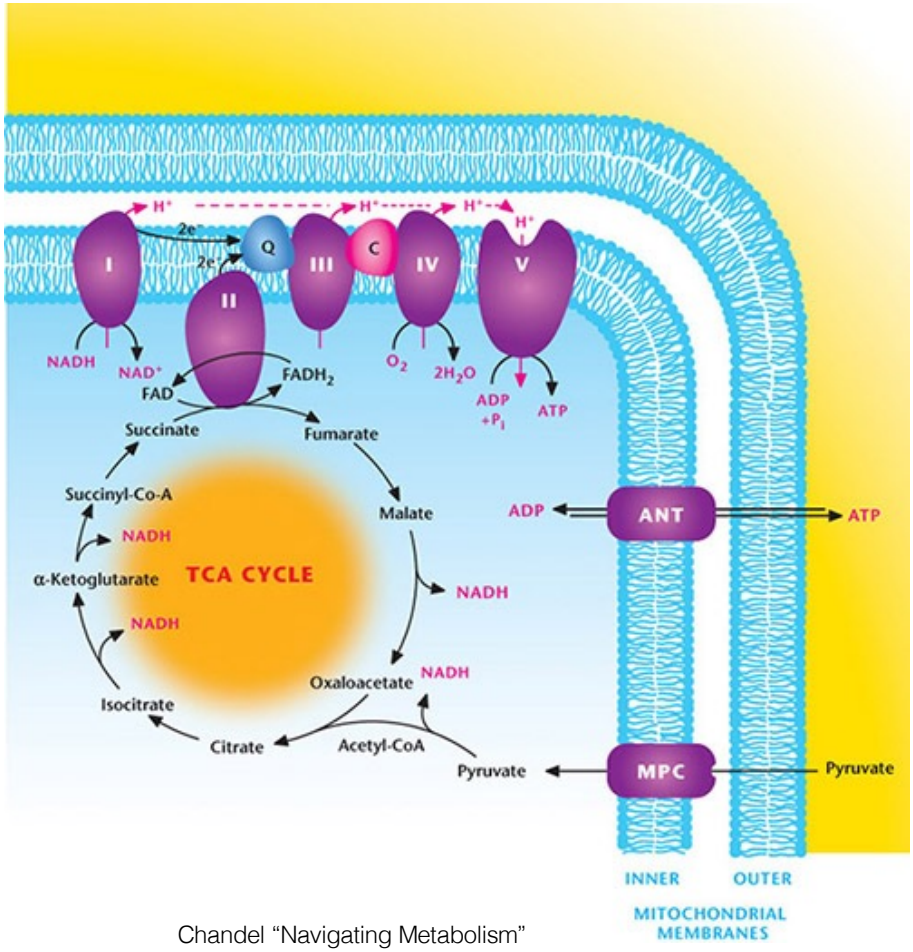
Ubiquinone (Q) bridges complex I and II to III

Cytochrome c bridges complex III to IV

Complex IV transfers electrons to O_2 to make H_2O

Complex I, III, and IV pump H+ into intermembrane space creating chemiosmotic gradient

Complex V produces ATP by controlled reentry of H^+ into mitochondrial matrix



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Net ATP production by complete glucose oxidation

Complete oxidation of glucose:

$$\text{Glucose} + 2H_2O + 10NAD^+ + 2FAD + 4ADP + 4P_i \longrightarrow 6CO_2 + 6H^+ + 10NADH + 1FADH_2 + 4ATP$$

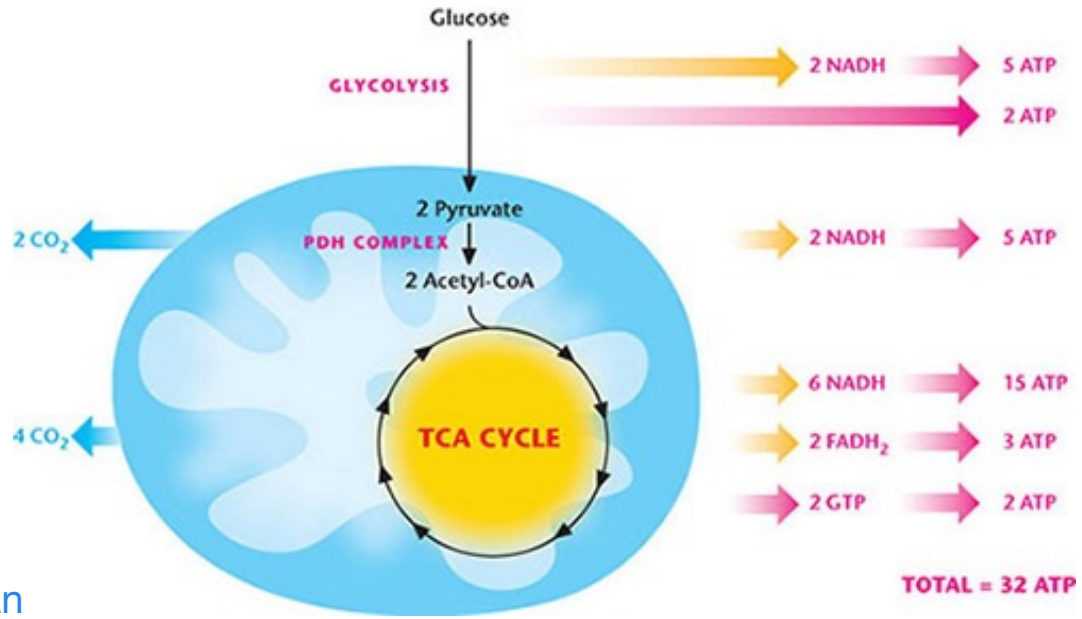
Each NADH gives 2.5 ATP

Each $FADH_2$ give 1.5 ATP

Total = 32 ATP

Important to note that rate of mitochondrial respiration depends on overall rate of ATP consumption by cell; must have continuous supply of ADP to keep making ATP

Surprisingly, recent studies prove that cells can proliferate without any ATP production by mitochondria; critical role of ETC will be discussed



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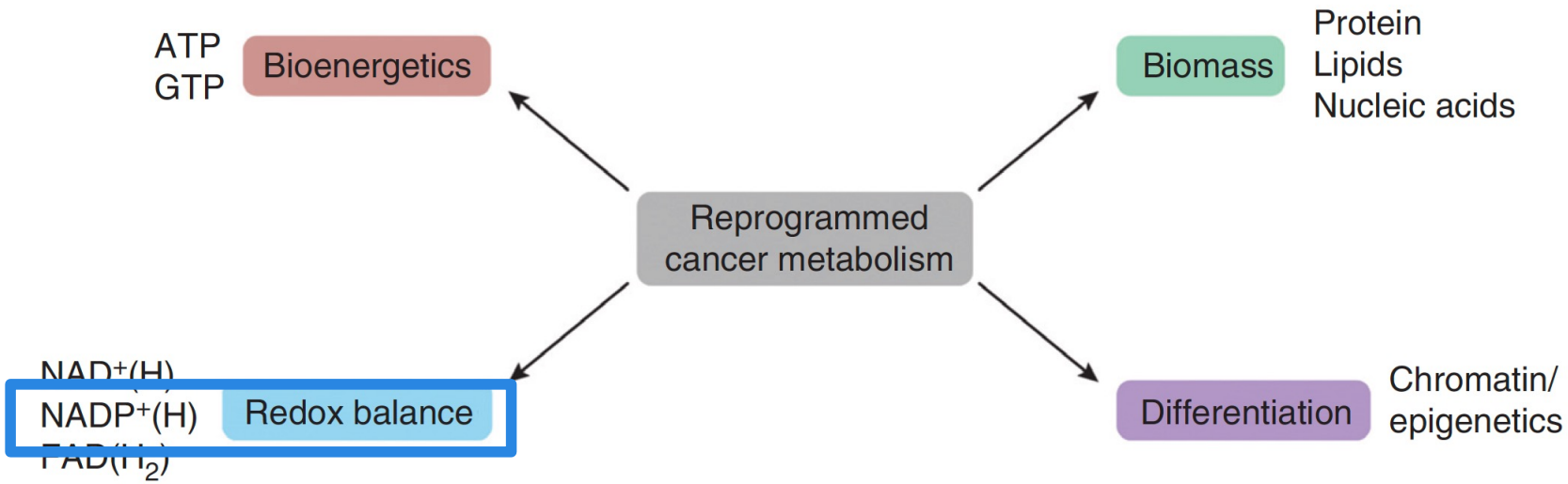
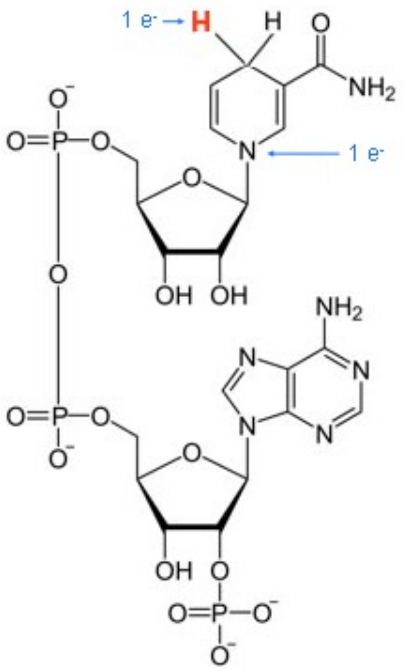
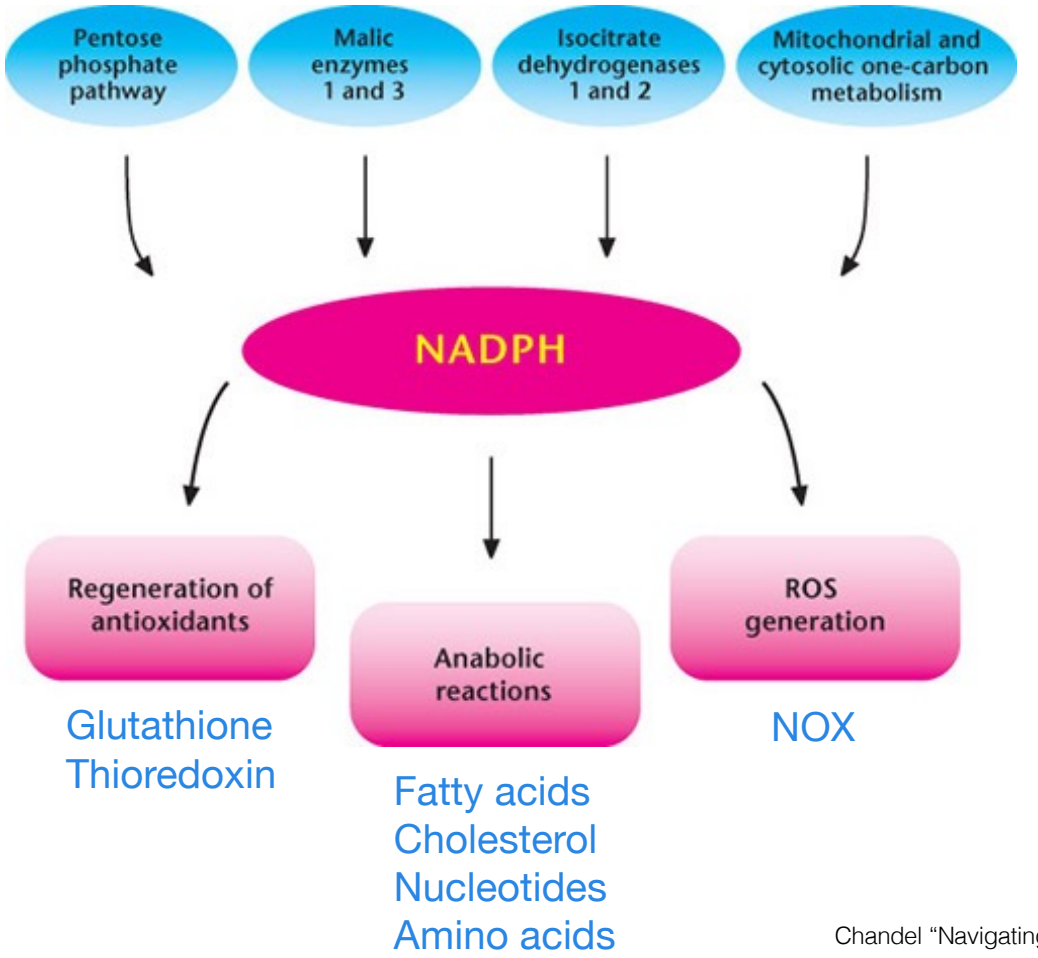
What about NADPH?



Stahl et al, CSH Press 2020

Sources and functions of NADPH





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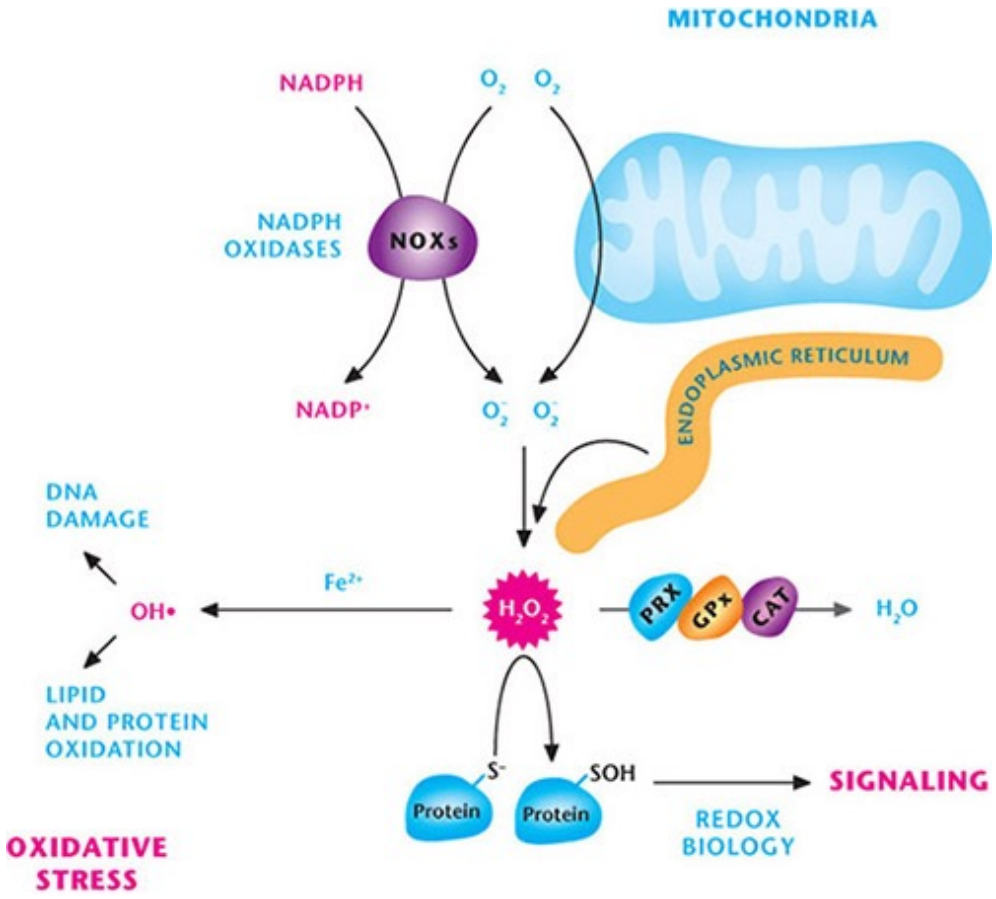
NADPH is critical for buffering oxidative stress

Reactive oxygen species (ROS) come from a variety of sources

ROS are critical signaling mediators

Too much ROS cause oxidative damage (ROS theory of aging)

NADPH both generates ROS through NAPDH oxidases (NOX) and buffers ROS through generation of reduced glutathione and thioredoxin



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NADPH is critical for lipid biosynthesis

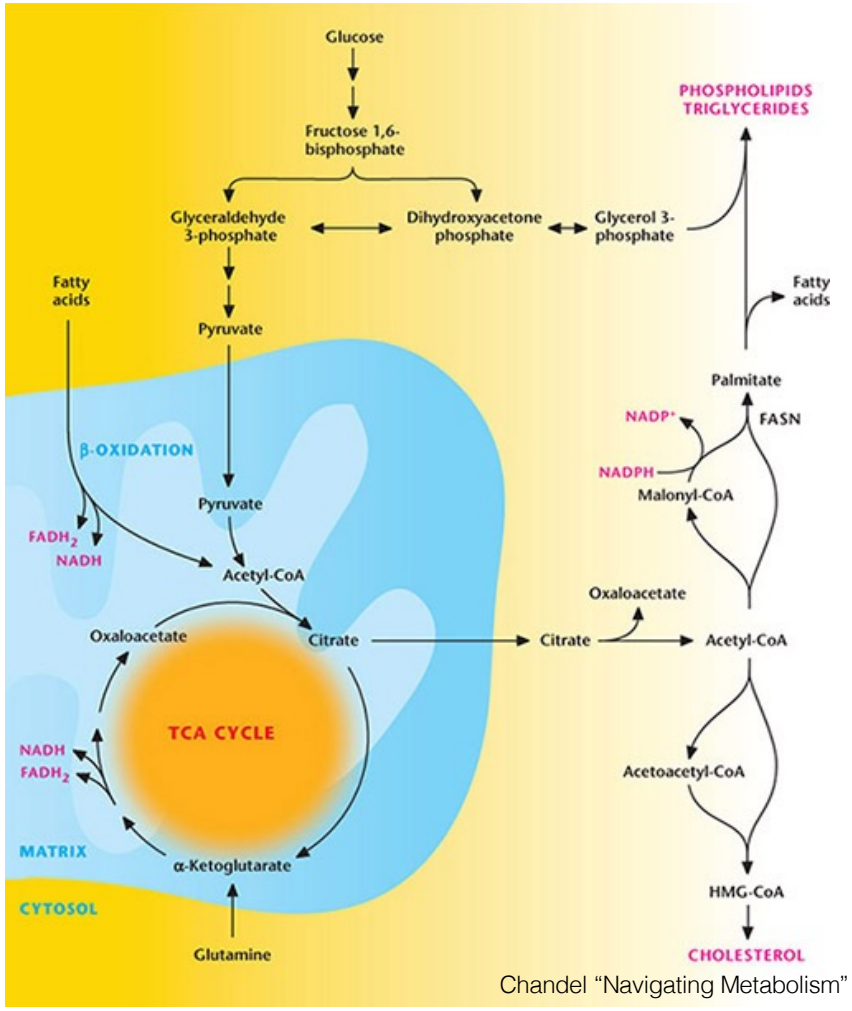
Lipid synthesis is all about citrate and NADPH

Fatty acid synthesis/elongation

- Citrate exits mitochondria
- Cytosolic ATP citrate lyase cleaves citrate to acetyl-CoA and oxaloacetate
- Acetyl-CoA serves as 2-carbon building blocks for long chain fatty acids

Glycerol backbone comes from glycolysis (DHAP->glycerol-3-phosphate)

Cholesterol synthesis also starts with cytosolic acetyl-CoA and requires NADPH to generate the 27-carbon cholesterol molecule (HMG-CoA reductase is target of statins)



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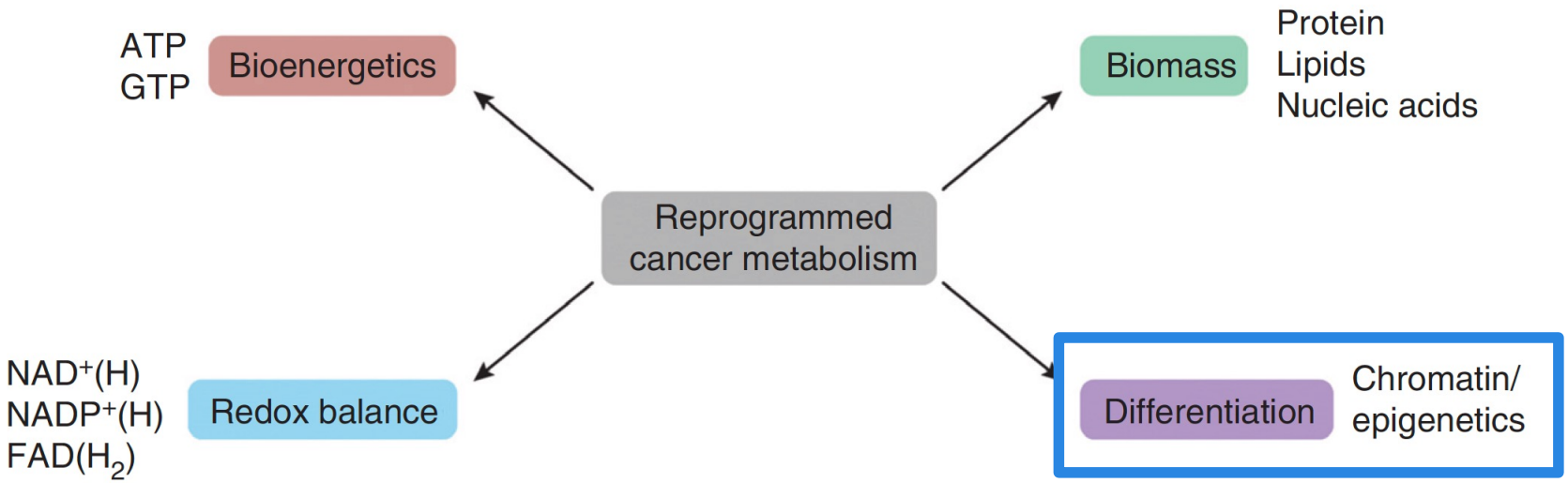
Metabolism regulates the ‘decisions’ that cells make



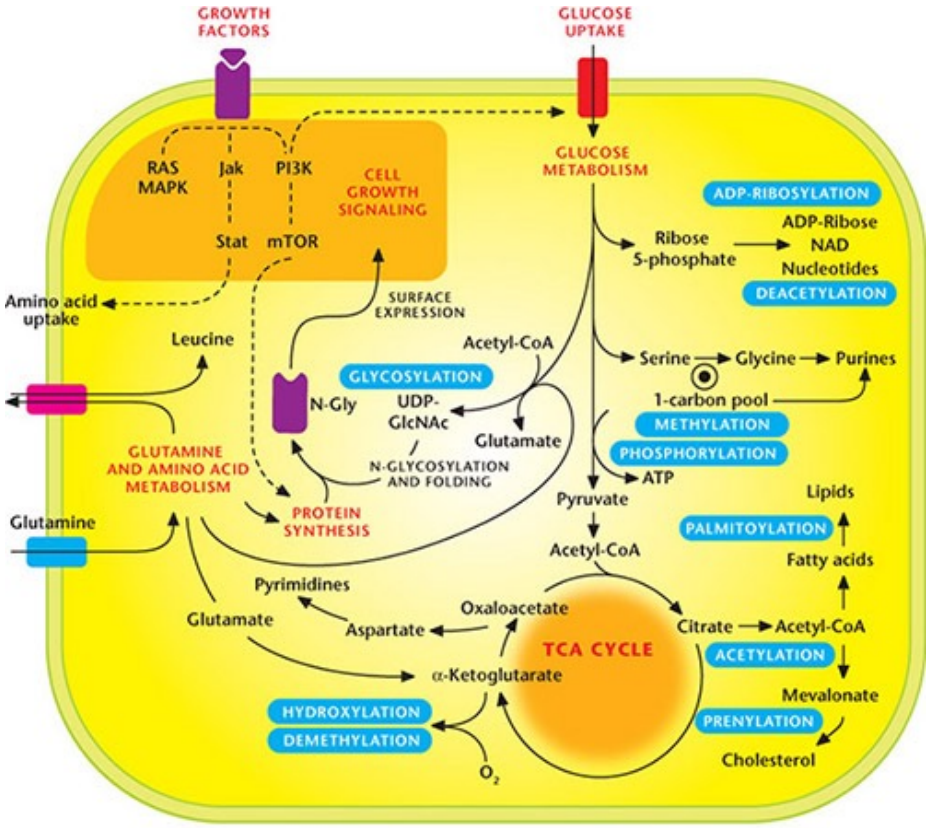
Stahl et al, CSH Press 2020

Metabolic pathways regulate signaling

Every post-translation protein modification (including histones) and every mark placed on DNA/RNA is a piece of a metabolite

Phosphorylation
Acetylation and deacetylation
Methylation and demethylation
Hydroxylation
Glycosylation
ADP-ribosylation
Palmitoylation
Prenylation

All of these modifications are intimately related to the metabolic state of the cell; the cell is telling itself whether or not it has the metabolic resources to engage in energetically costly behaviors/programs



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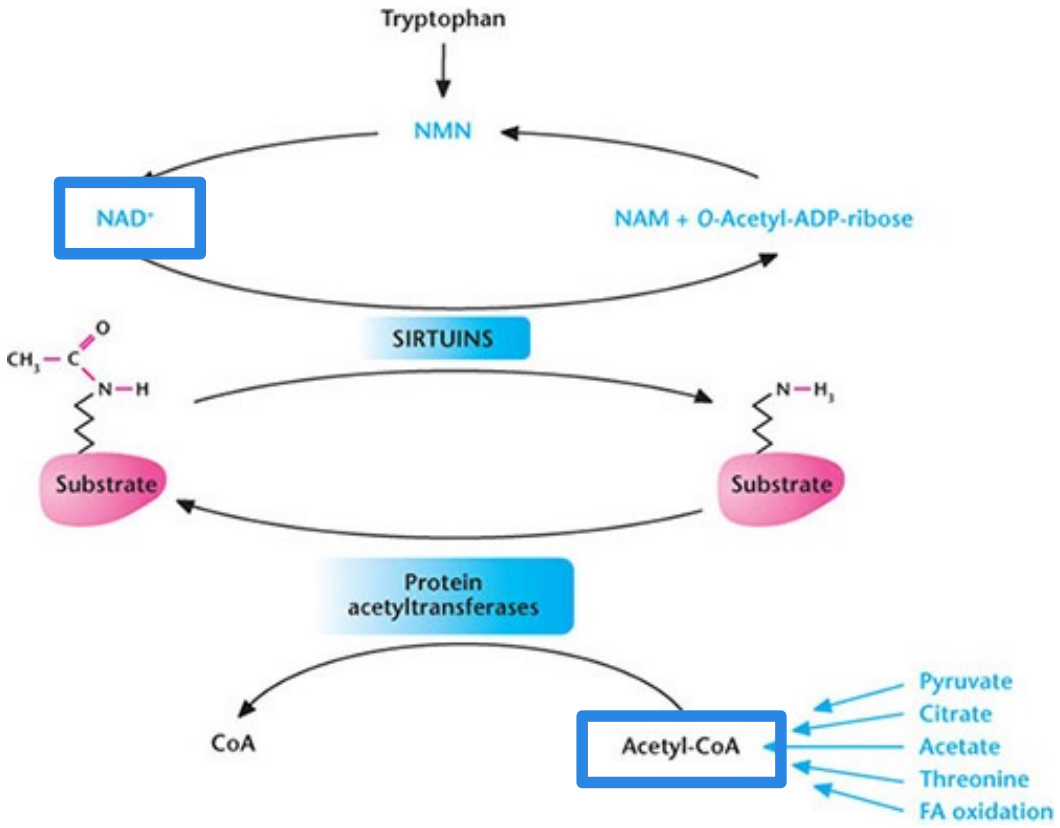
Metabolism regulates acetylation and deacetylation



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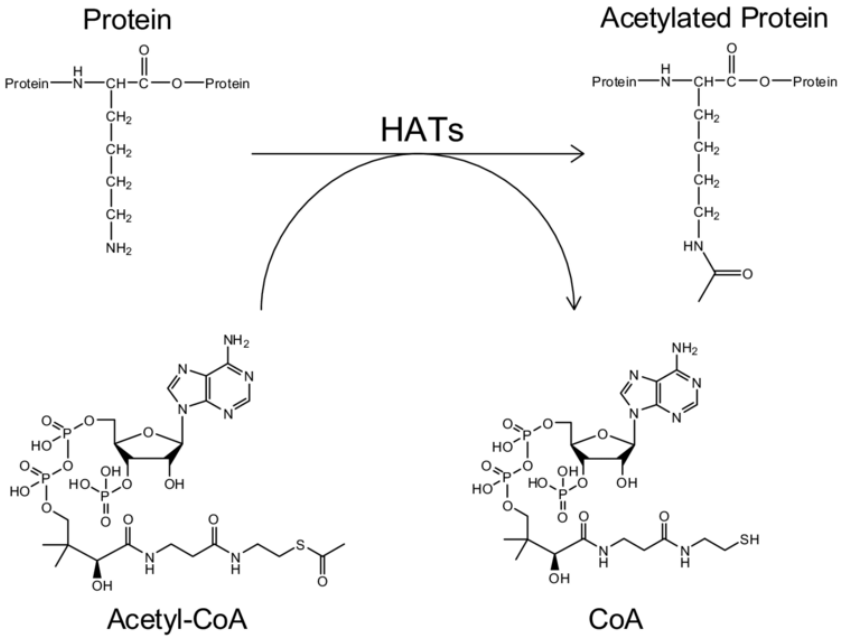
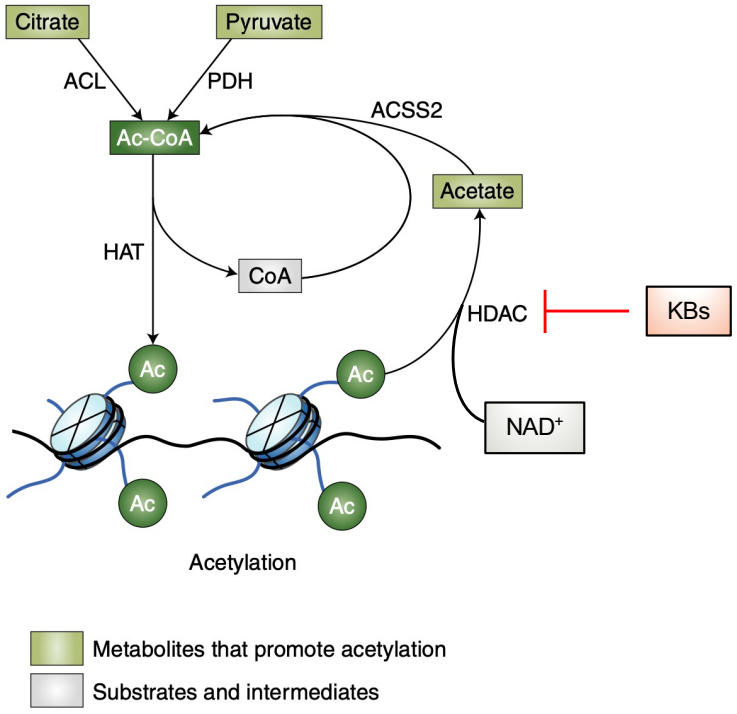
Acetylation and deacetylation

Histone acetylation generally activates transcription

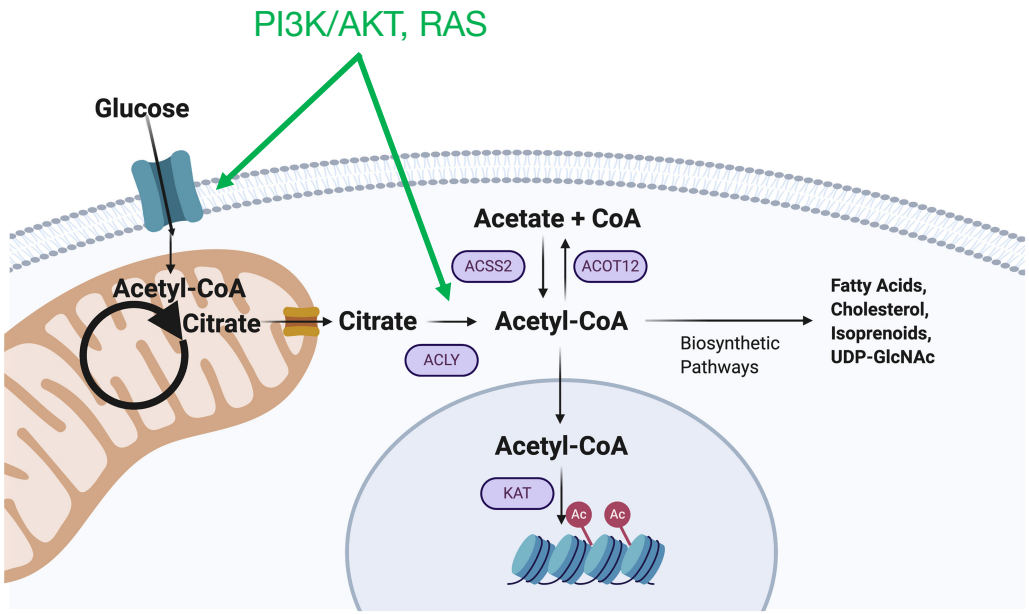


Acetyl-CoA is the currency



Rye et al, J Bio Scr 2011

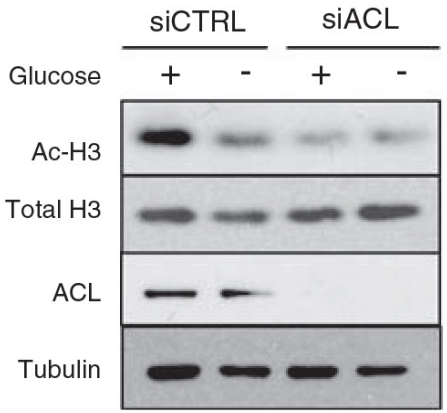
Increased placement: Sources of acetyl-CoA used for histone acetylation



Liu and Wellen, Curr Opin Cell Biol 2020

ATP-Citrate Lyase Links Cellular Metabolism to Histone Acetylation

Kathryn E. Wellen,* Georgia Hatzivassiliou,*† Uma M. Sachdeva, Thi V. Bui, Justin R. Cross, Craig B. Thompson‡



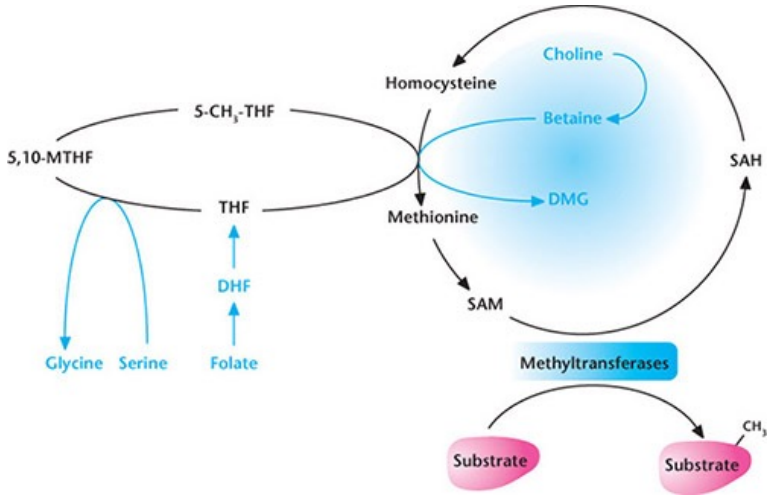
Wellen*, Hatzivassiliou* et al., Science 2009

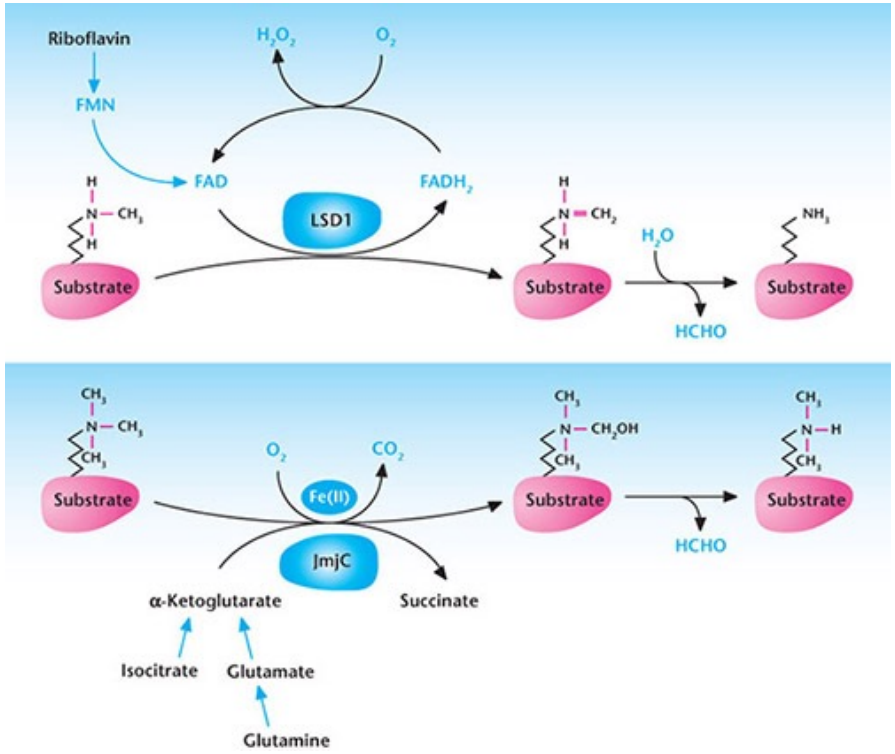
Metabolism regulates methylation and demethylation

S-adenosyl-methionine is the methyl donor for methylation reactions (DNA/RNA/proteins)

Methionine metabolism is intimately linked with one-carbon folate metabolism (and thus serine/glycine metabolism)

αKG and FAD+ are required for demethylation





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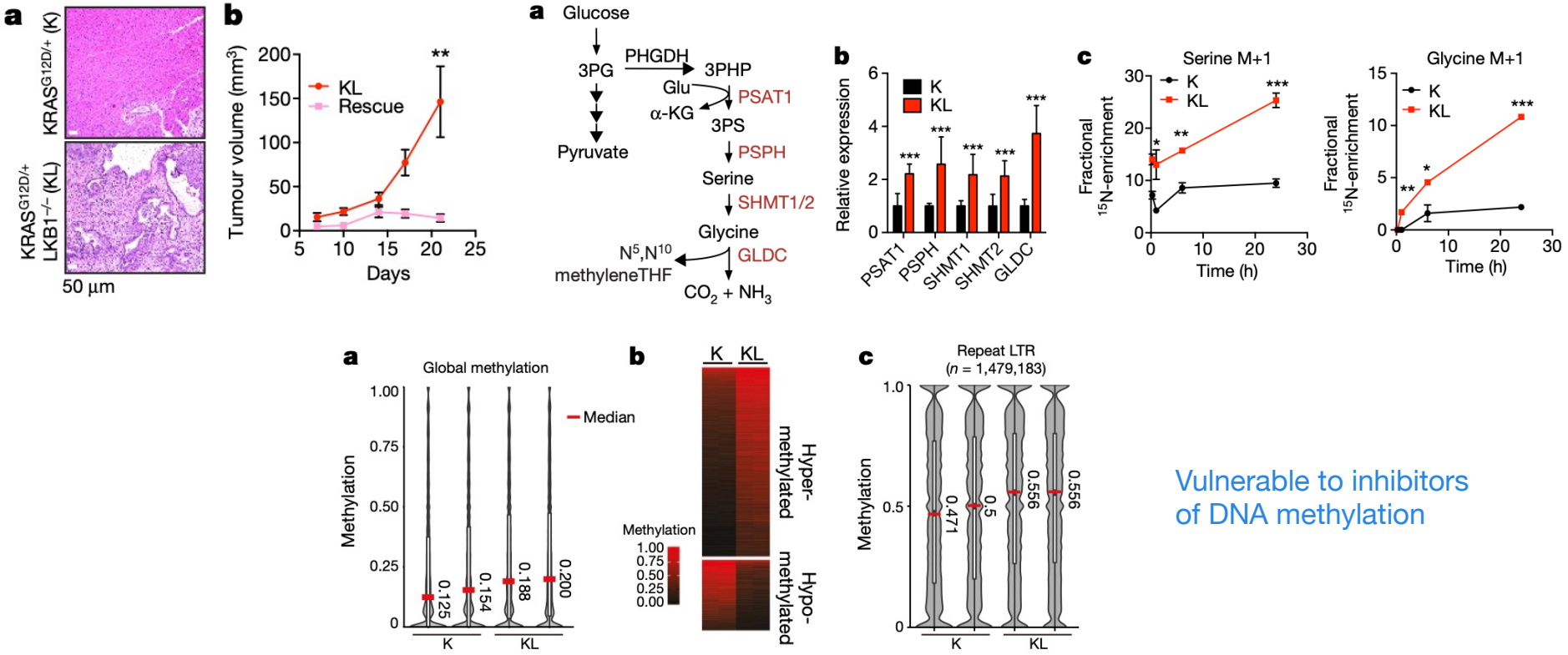
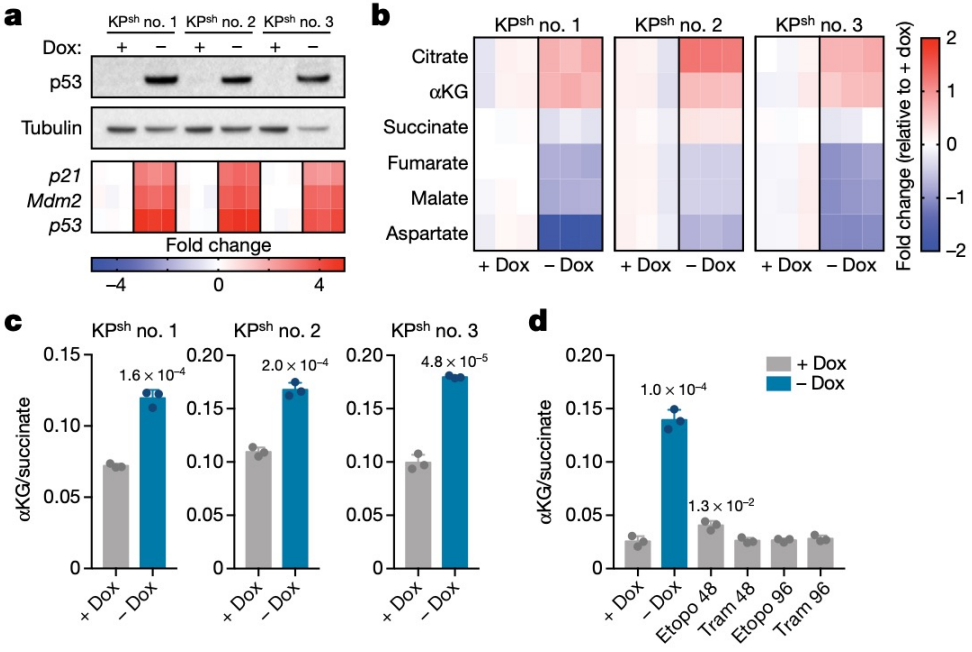
Increased placement: LKB1 loss increases one-carbon metabolism and methylation

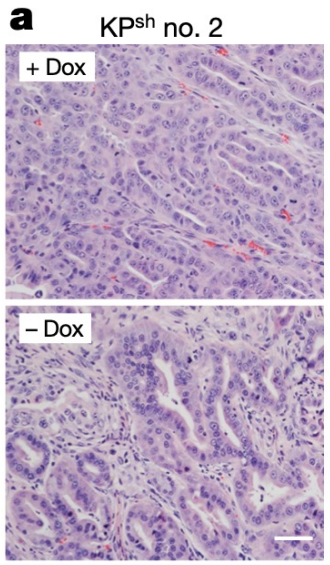


Vulnerable to inhibitors of DNA methylation

Kottakis et al., Nature 2016

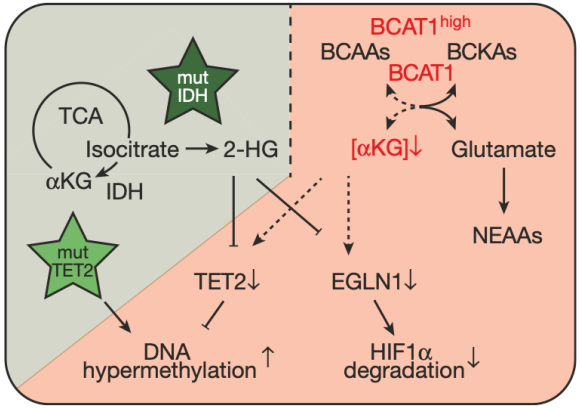
Increased removal: p53 increases αKG/succinate ratio and promotes differentiation

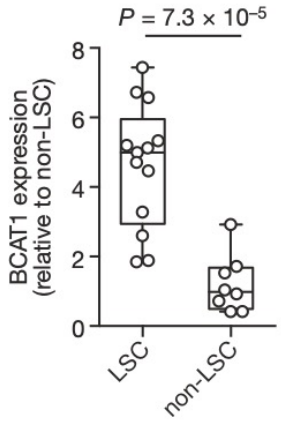


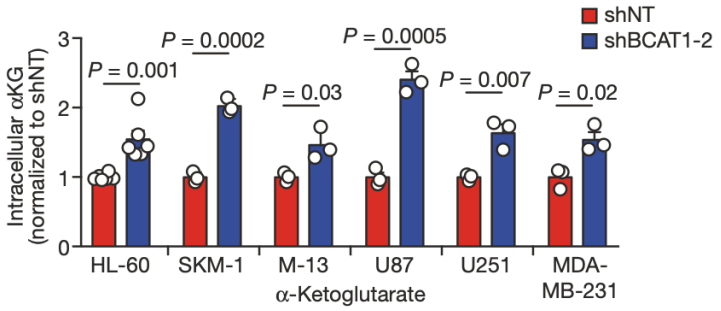


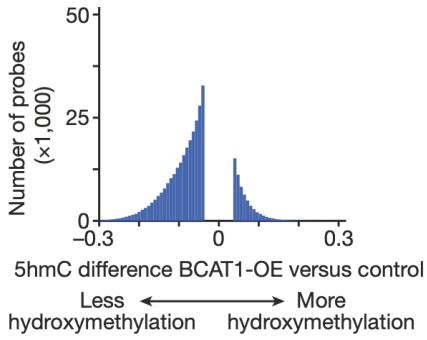
Morris et al. Nature 2019

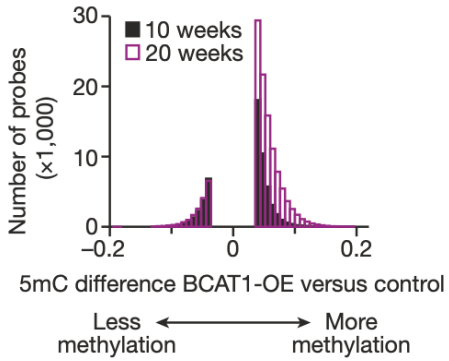
Decreased removal: BCAT1 ‘steals’ αKG to promote hypermethylation in leukemia











Raffel et al, Nature 2017

Mutations/alterations in metabolic enzymes inhibit differentiation

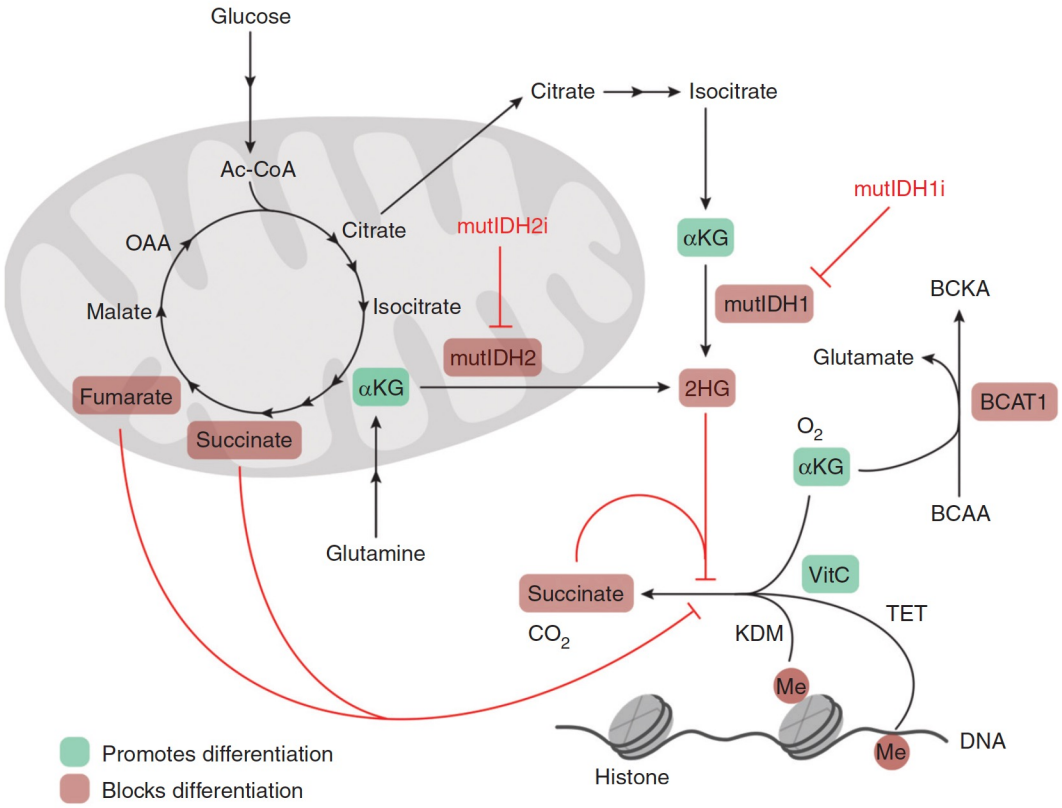
Metabolites are not just building blocks

Repressive methylation of histones and DNA generally prevents differentiation

Cancers exploit this to stay in a stem-like state

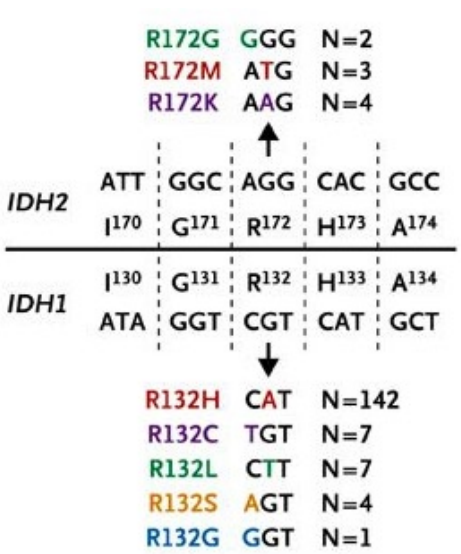
Promote methylation by activating
- Serine/glycine pathway
- Methionine metabolism
- One-carbon folate cycle

Inhibit demethylation (αKG-dependent)
- IDH mutations produce αKG-antagonist 2HG
- SDH and FH loss of function lead to succinate and fumarate accumulation to antagonize αKG

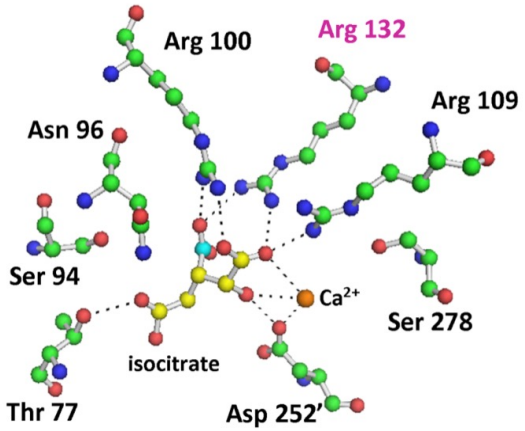


Stahl et al, CSH Press 2020

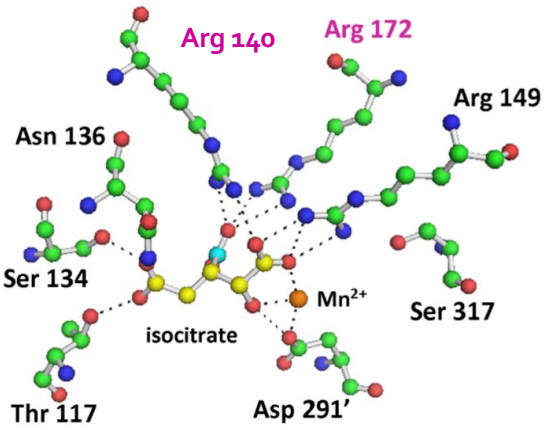
Cancer-associated IDH mutations cluster in the enzyme active site



Cytosolic IDH1



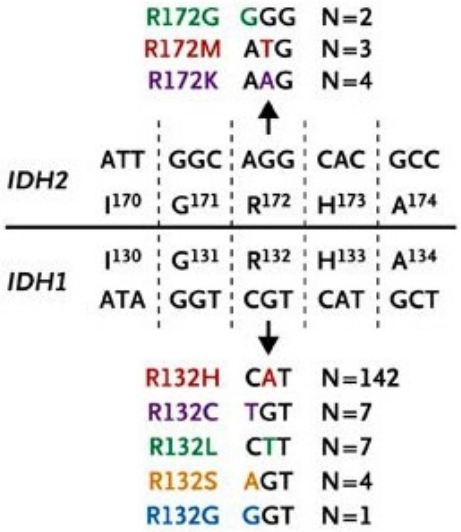
Mitochondrial IDH2

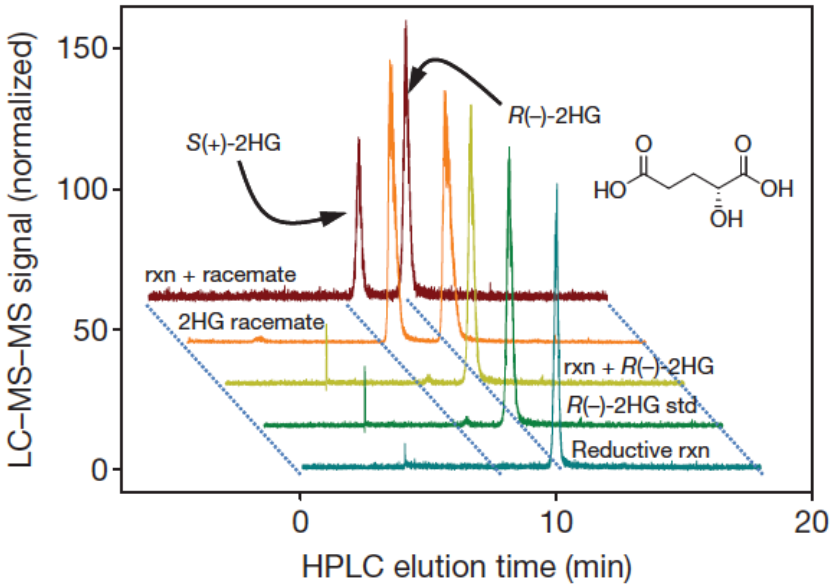


Ward et al, Cancer Cell 2010

- AML, glioma, bile duct, cartilage, T cell lymphoma
- Mutations always heterozygous, preserve wild-type allele
- IDH enzymes function as dimers

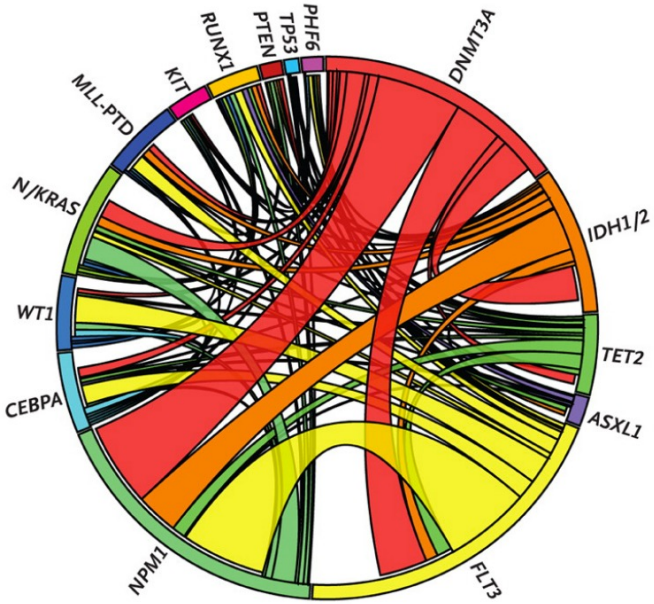
Cancer-associated IDH mutations gain the ability to produce 2-hydroxyglutarate (2HG)





Dang et al, Nature 2009

IDH mutations in AML

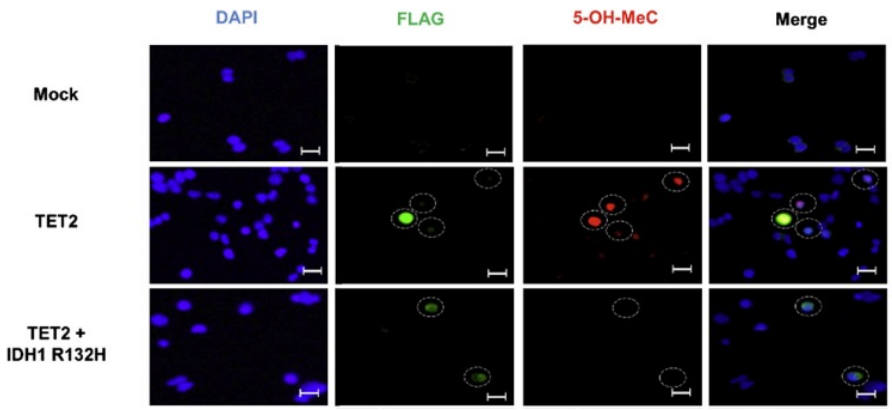


Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

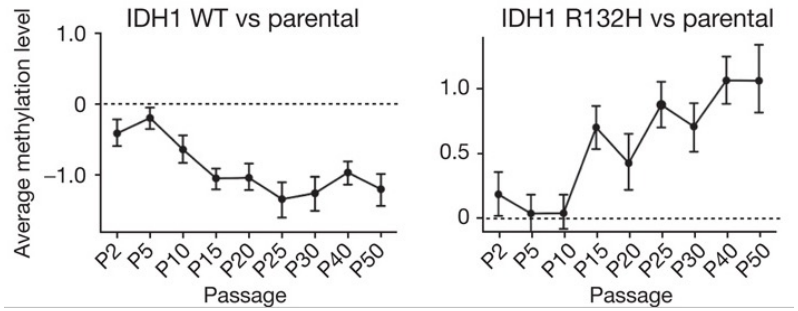
Patel et al, NEJM, 2012

IDH1/2 and Tet2 mutations are mutually exclusive

2HG blocks TET mediated demethylation

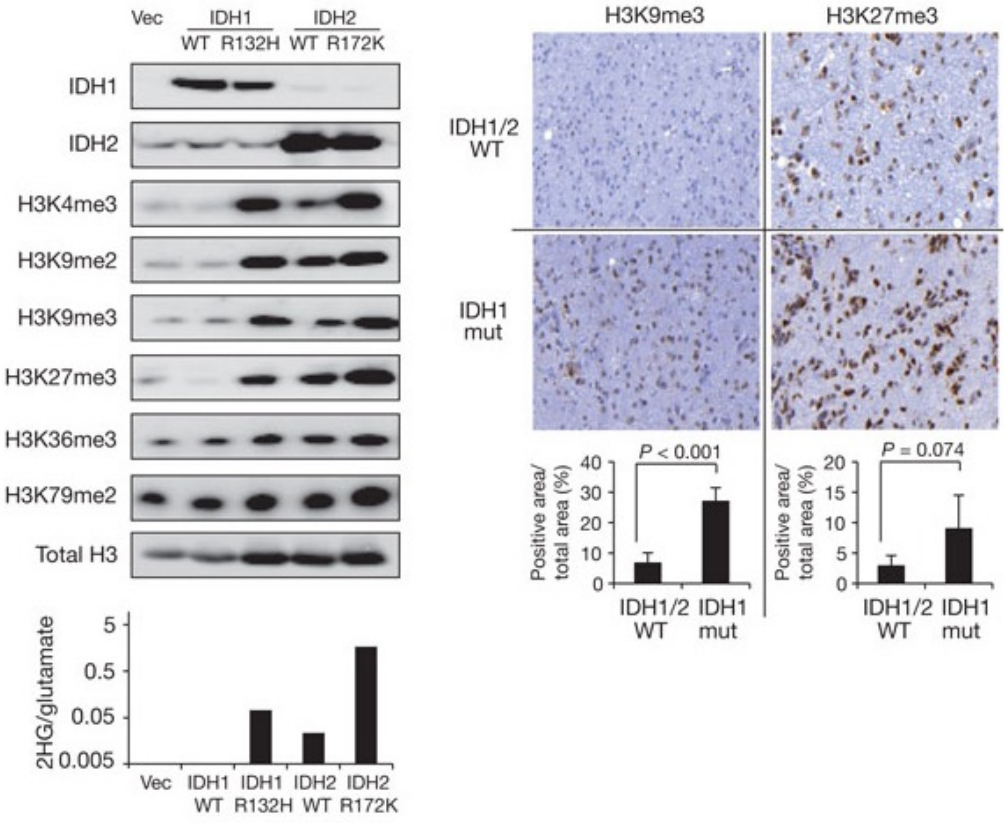


Figueroa et al, Cancer Cell 2010



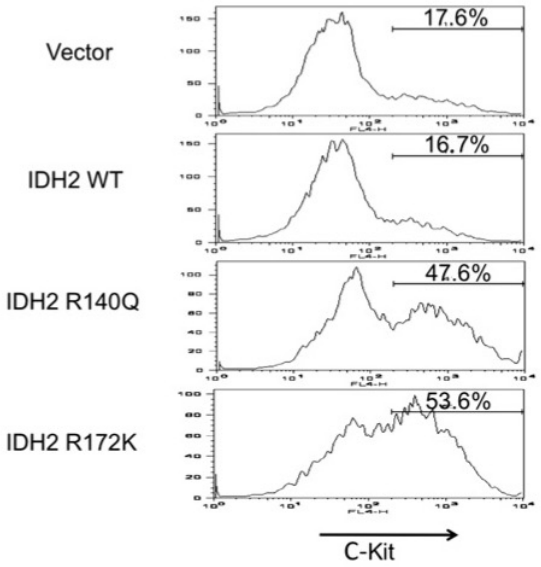
Turcan et al, Nature, 2012

2HG inhibits histone demethylation

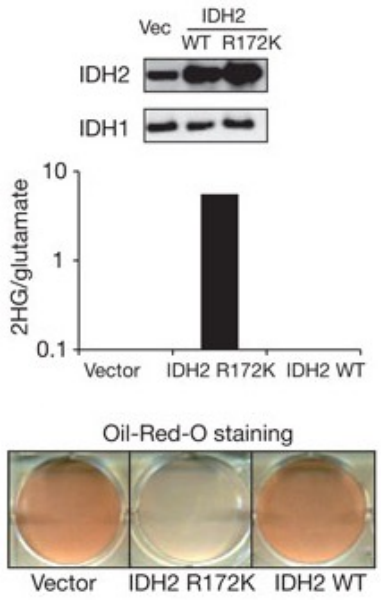


Lu et al, Nature 2012

Mutant IDH and 2HG block differentiation

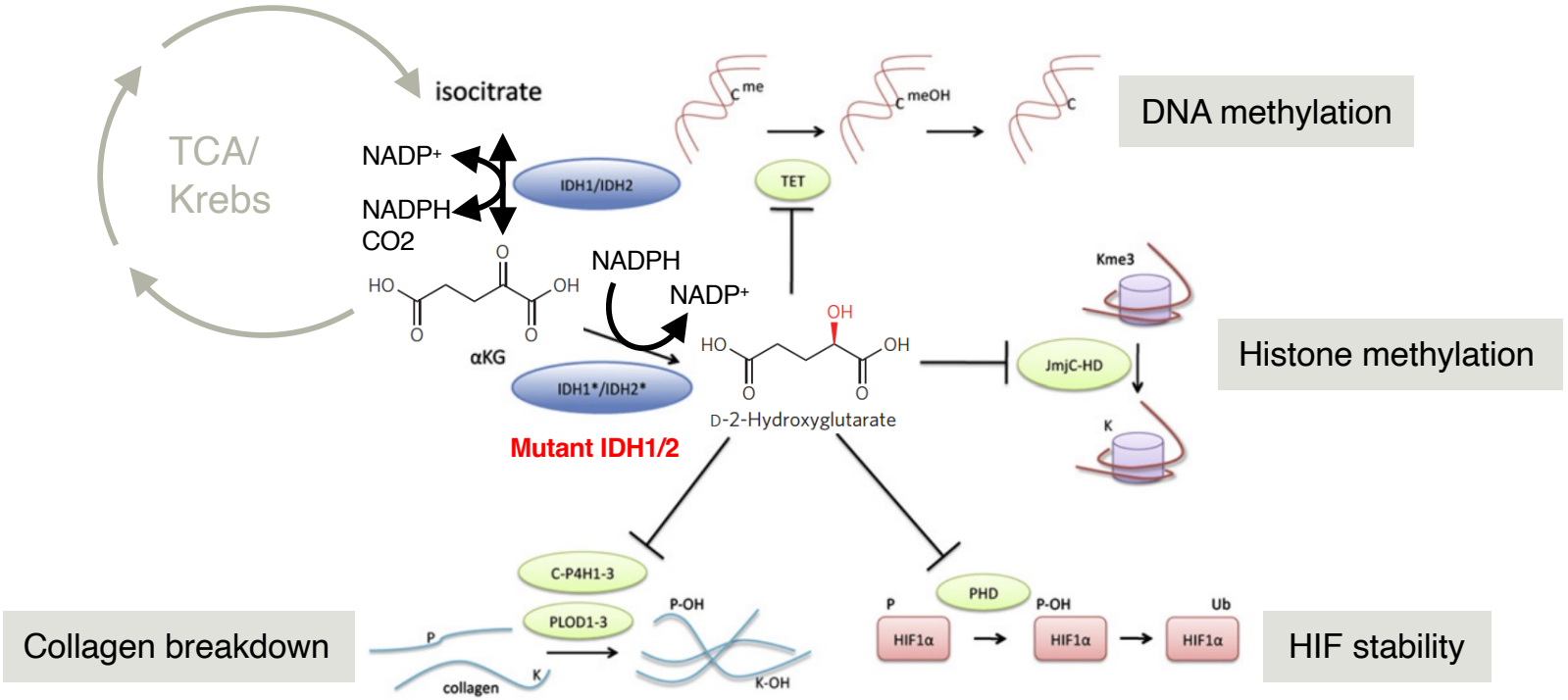


Figueroa et al, Cancer Cell 2010



Lu et al, Nature 2012

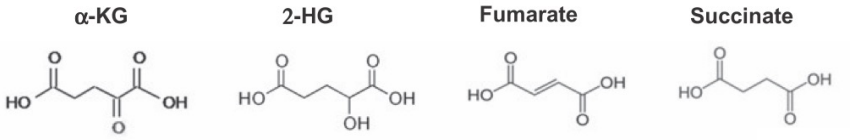
2HG inhibits αKG-dependent enzymes and promotes hypermethylation



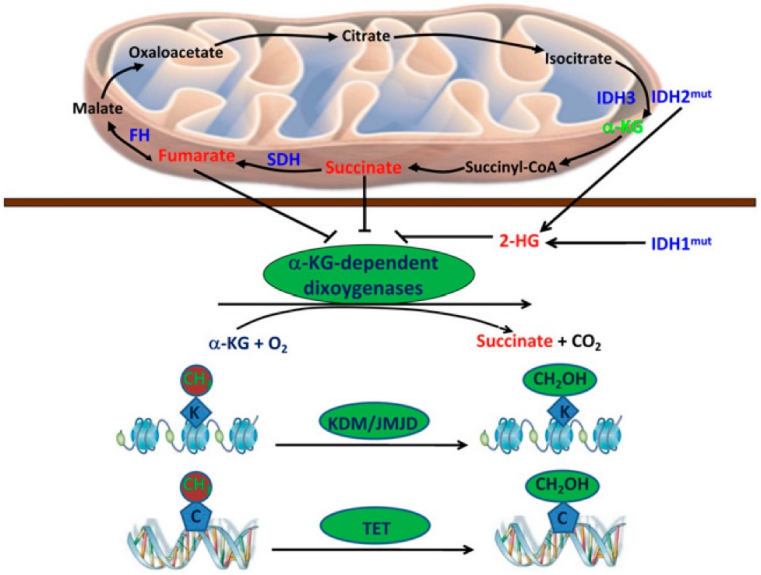
Shih and Levine, Cancer Cell, 2012

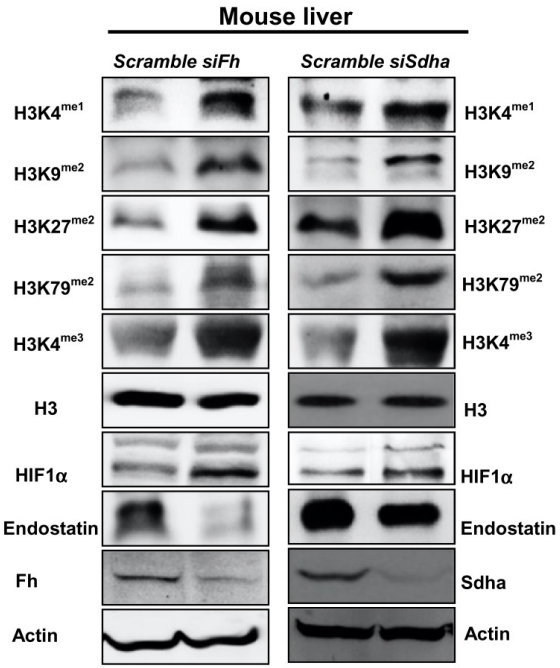
- D-2HG inhibits >70 different α-ketoglutarate-dependent enzymes
- Net effect = repressive chromatin marks -> impaired differentiation

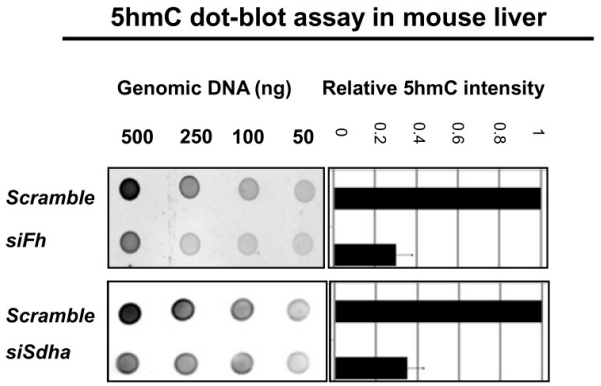
Inhibited removal: Succinate and fumarate promote hypermethylation



SDH or FH loss are drivers of rare cancers

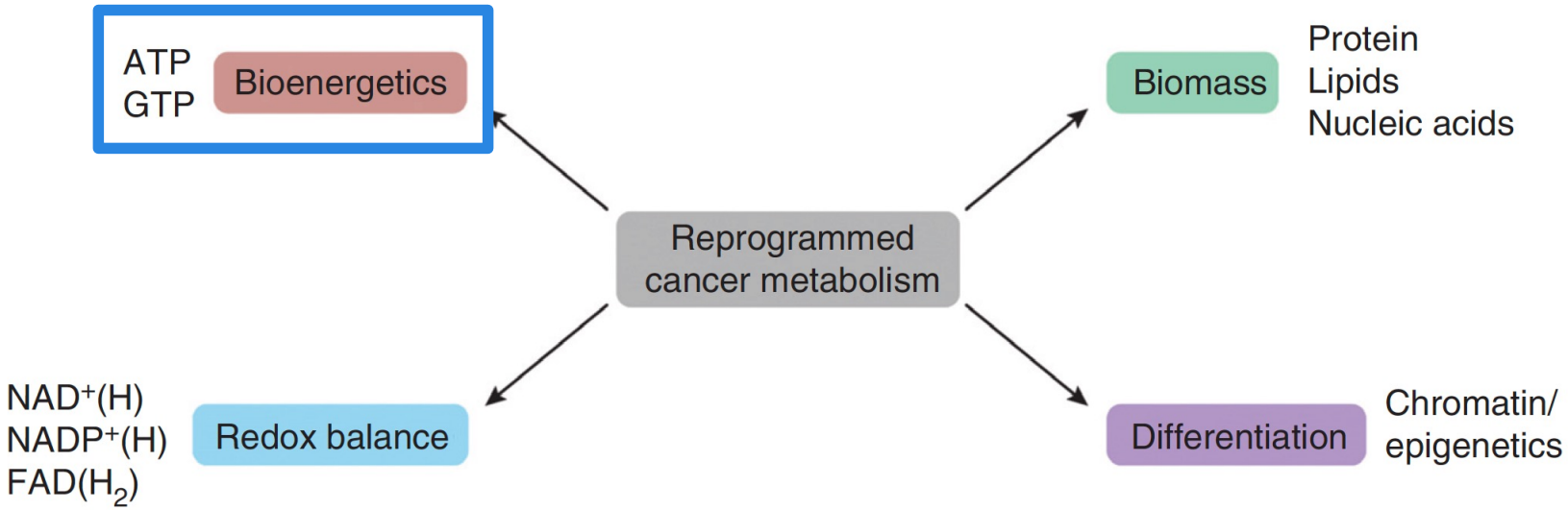






Xiao et al, G&D 2012

In depth look at mitochondria and bioenergetics (hot topic in cancer metabolism)



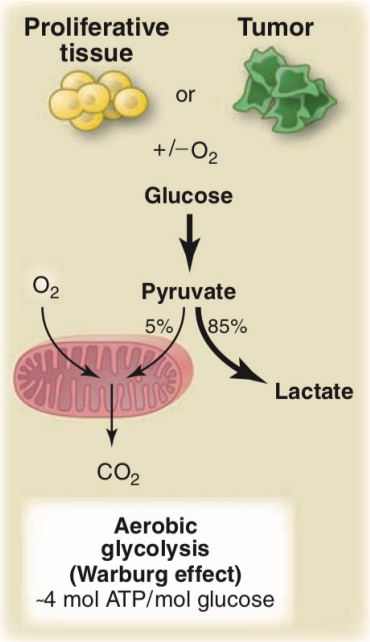
Stahl et al, CSH Press 2020

Why do cancer cells require functional mitochondria? Not for ATP!

Article

Cell

An Essential Role of the Mitochondrial Electron Transport Chain in Cell Proliferation Is to Enable Aspartate Synthesis



Authors

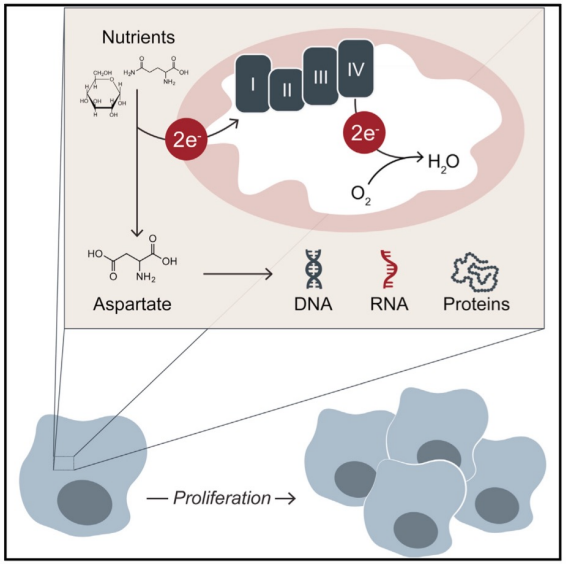
Kıvanç Birsoy, Tim Wang, Walter W. Chen, Elizaveta Freinkman, Monther Abu-Remaileh, David M. Sabatini

Article

Cell

Supporting Aspartate Biosynthesis Is an Essential Function of Respiration in Proliferating Cells

Graphical Abstract



Authors

Lucas B. Sullivan, Dan Y. Gui, Aaron M. Hosios, Lauren N. Bush, Elizaveta Freinkman, Matthew G. Vander Heiden

Correspondence

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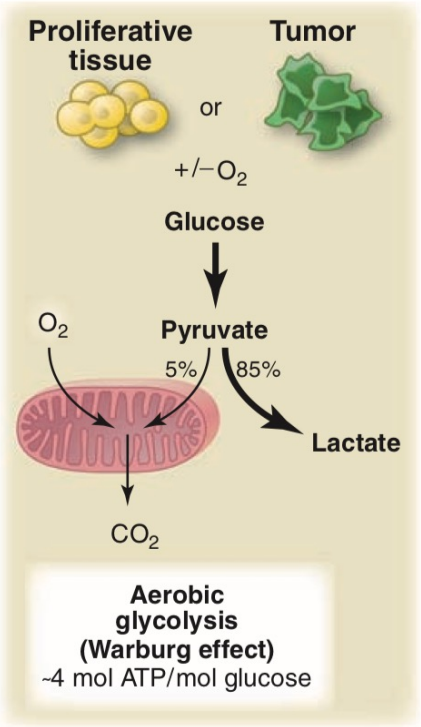
In Brief

A primary role of respiration in proliferating cells is to support aspartate synthesis.

Aspartate production appeared to be the key, but this was *in vitro*

Why do cancer cells require functional mitochondria? More than just aspartate



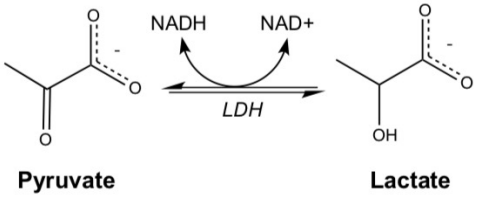
Article

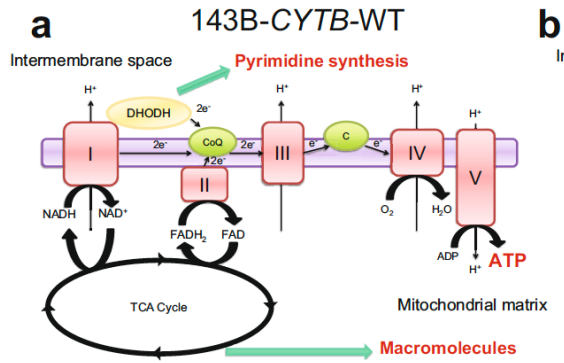
Mitochondrial ubiquinol oxidation is necessary for tumour growth

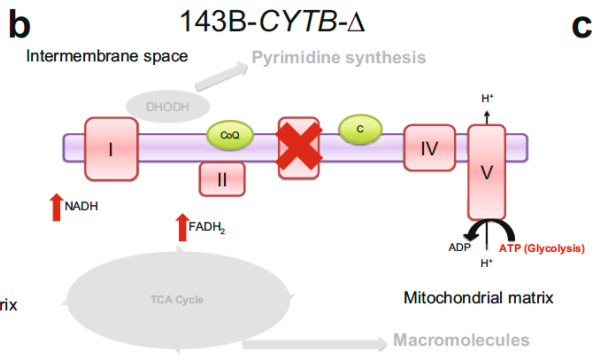
https://doi.org/10.1038/s41586-020-2475-6
Received: 16 December 2018
Accepted: 20 April 2020
Published online: 8 July 2020

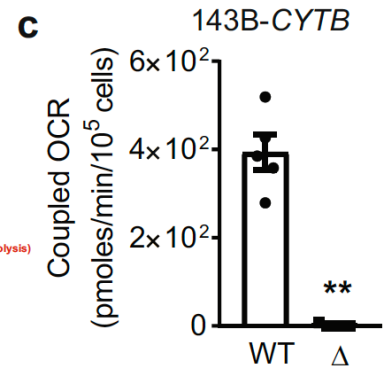
Inmaculada Martínez-Reyes[1], Luzivette Robles Cardona[1], Hyewon Kong[1], Karthik Vasan[1], Gregory S. McElroy[1], Marie Werner[1], Hermon Kihshen[1], Colleen R. Reczek[1], Samuel E. Weinberg[1], Peng Gao[2], Elizabeth M. Steinert[1], Raul Piseaux[1], G. R. Scott Budinger[1] & Navdeep S. Chandel[1,3]✉

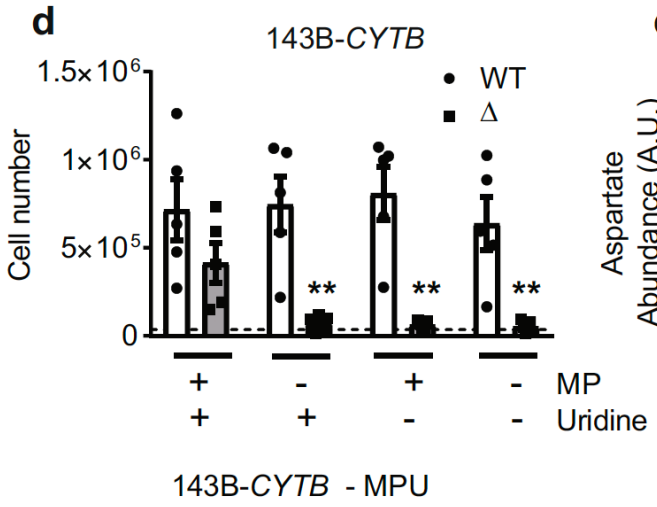
Cancer cells lacking ETC complex III require pyruvate and uridine

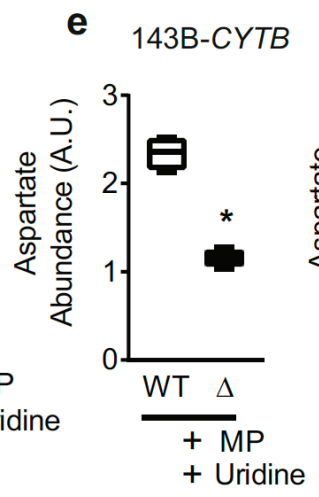


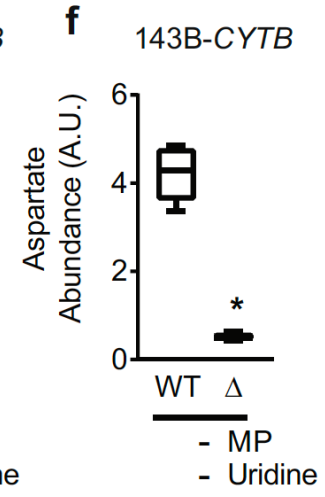


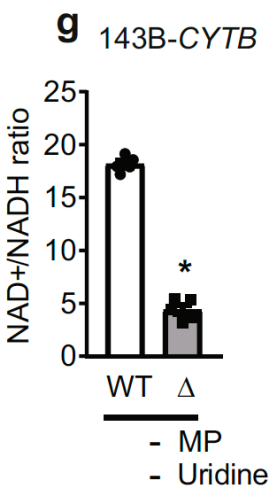




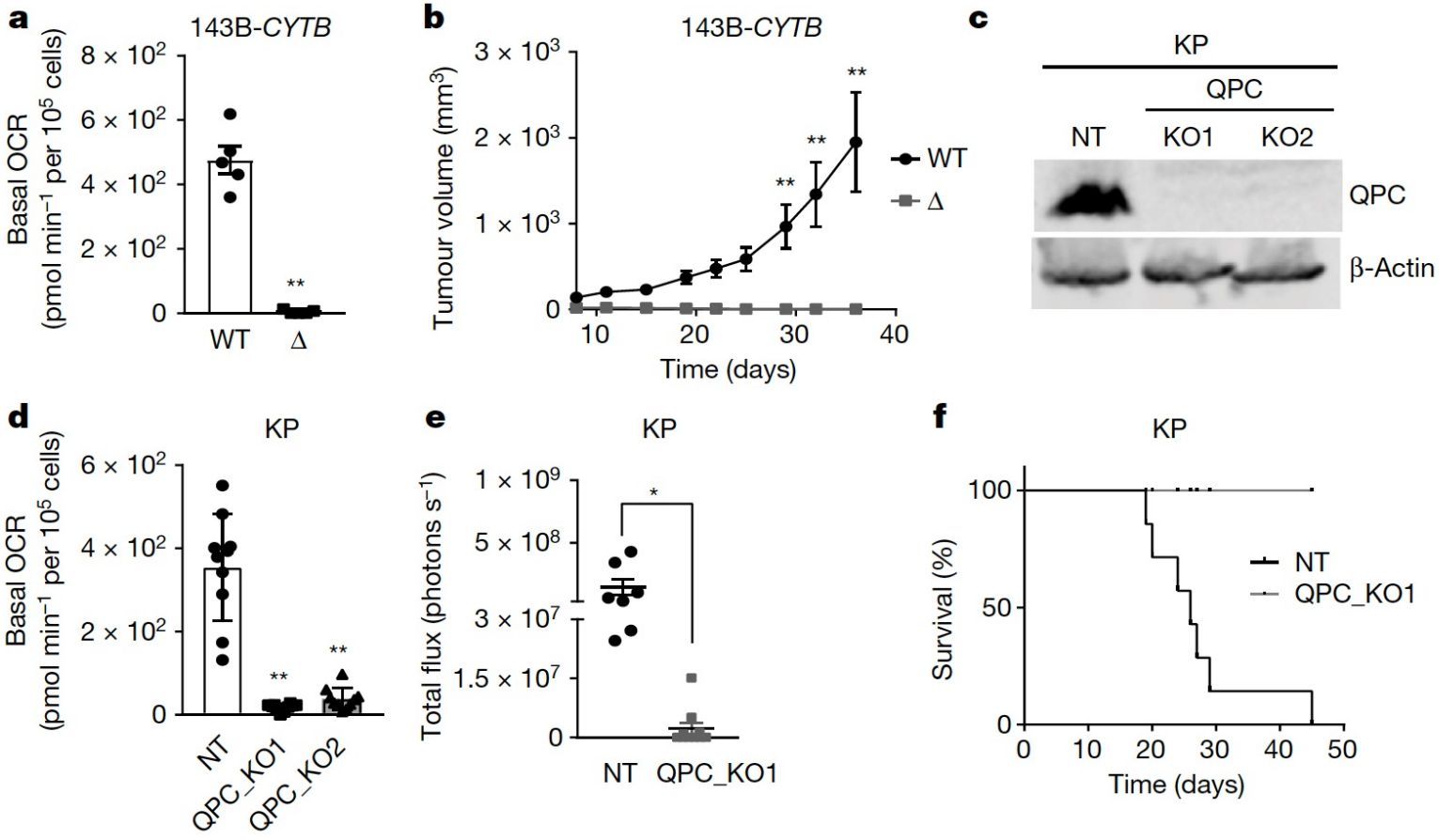




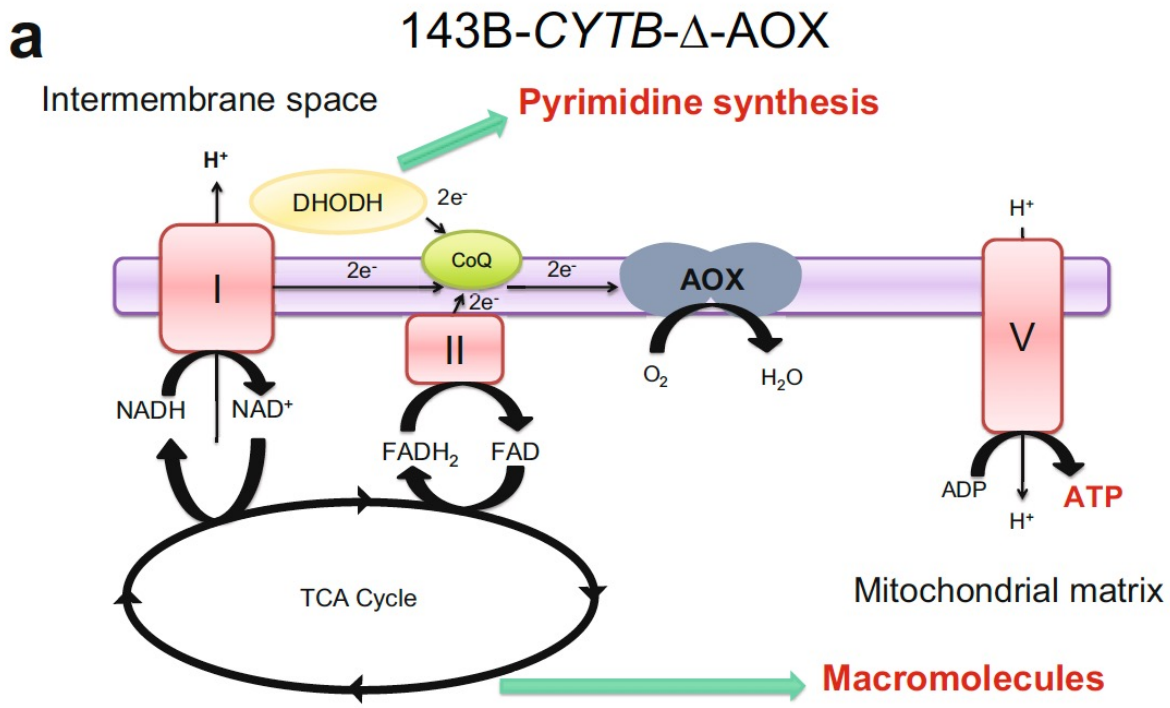




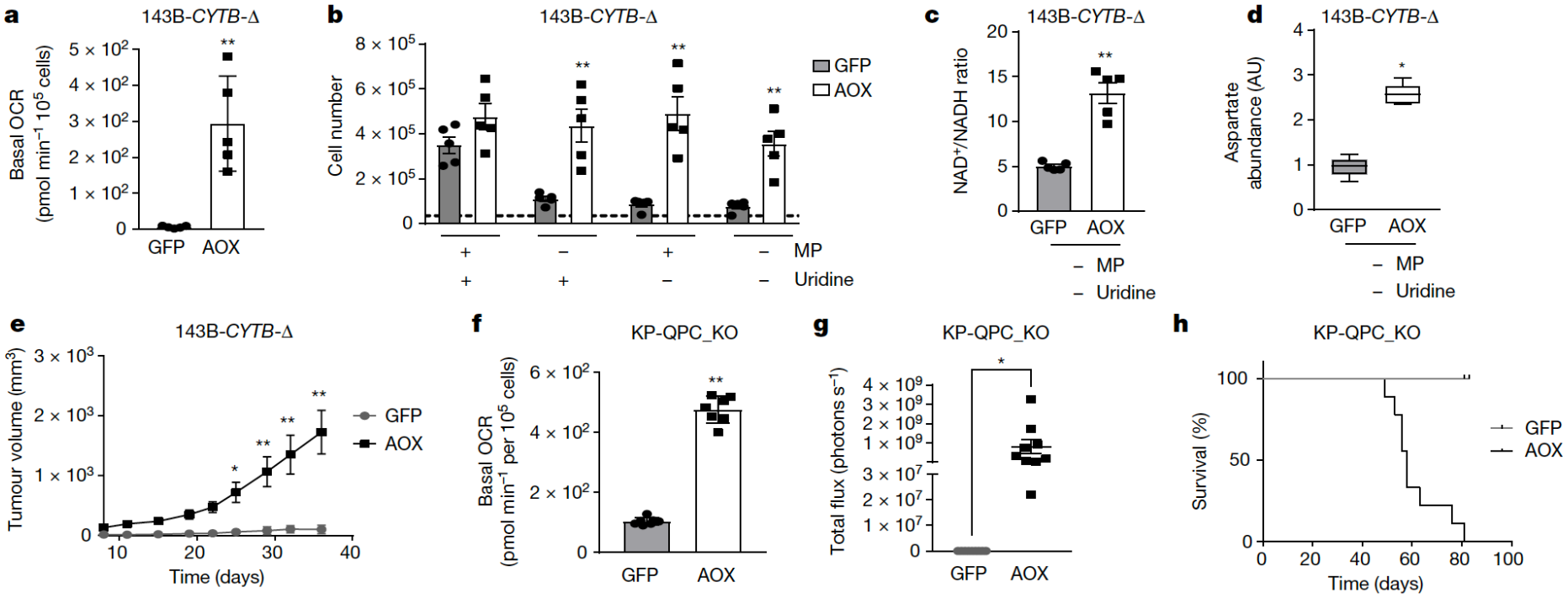
Tumors lacking ETC complex III cannot grow



AOX can accept electrons directly from reduced ubiquinol

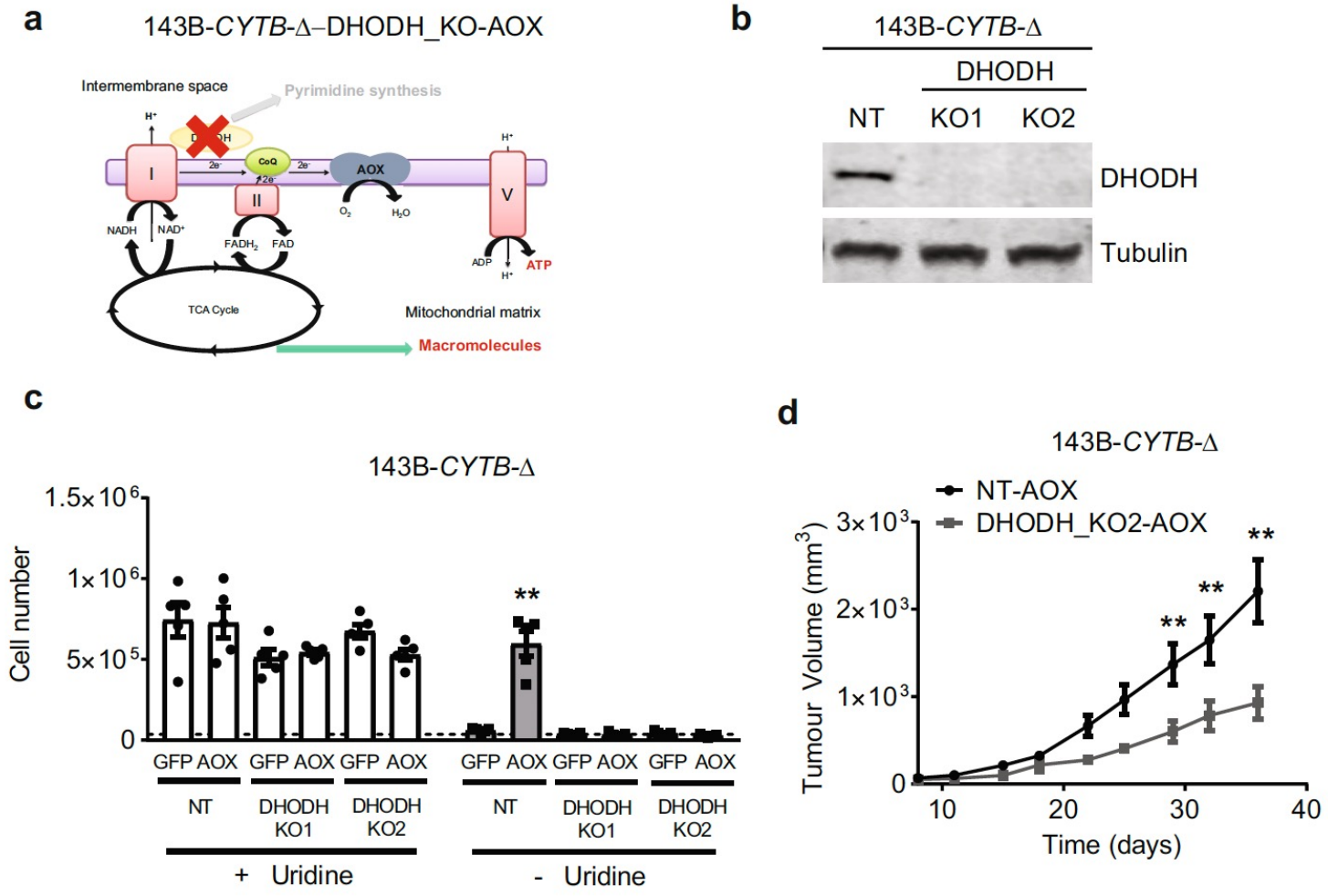


AOX can rescue all of the defects of ETC complex III deficient cells

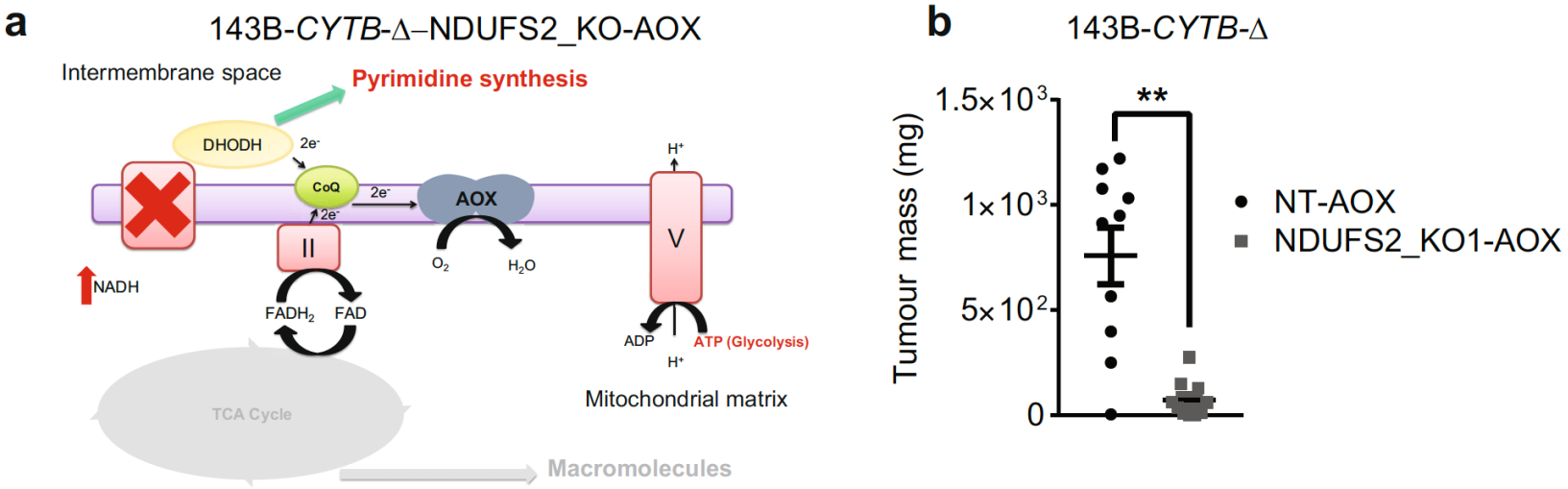


Complex III needed for **ubiquinol oxidation** but not H^+ pumping or e^- transfer to cytC

DHODH is required for pyrimidine biosynthesis



Loss of ETC complex I inhibits growth of AOX-expressing tumors



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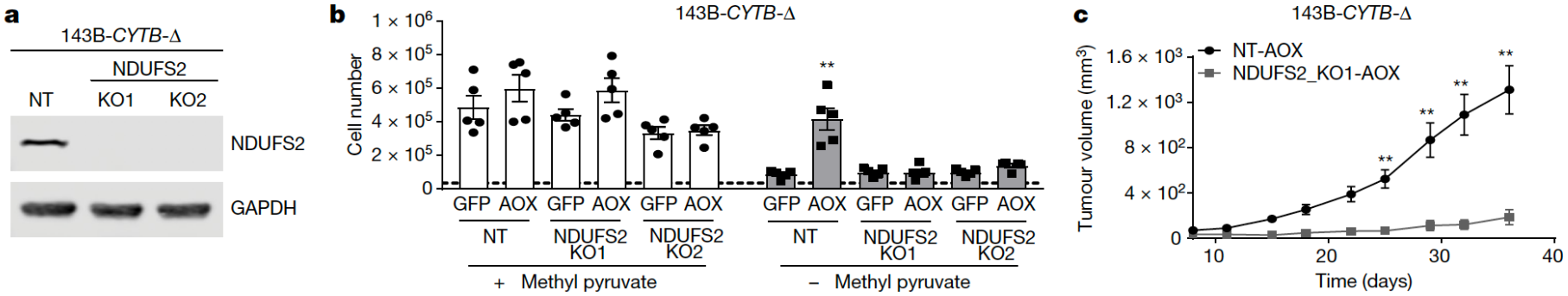
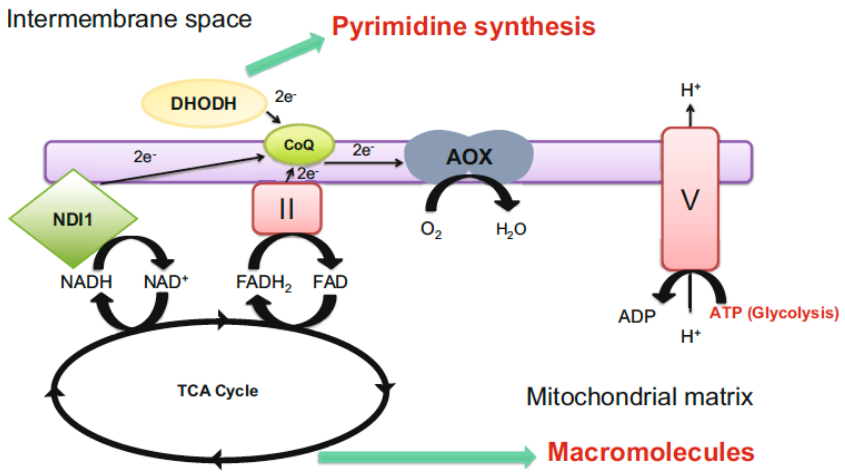


Is it the proton pumping or the NAD^+ regeneration?

NAD^+ regeneration by NDI1 rescues ETC complex I deficient tumors

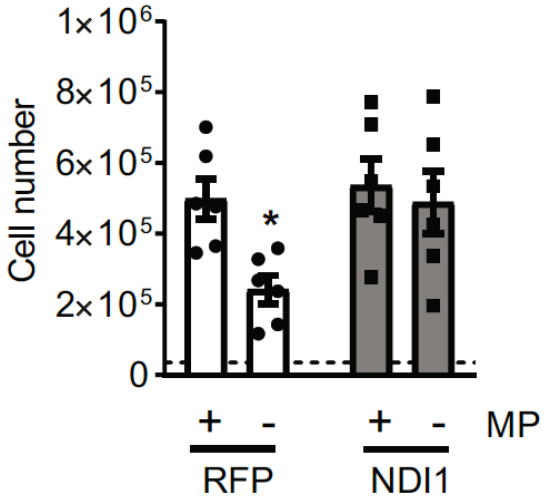
a

143B-*CYTB*-Δ–NDUFS2_KO-AOX-NDI1



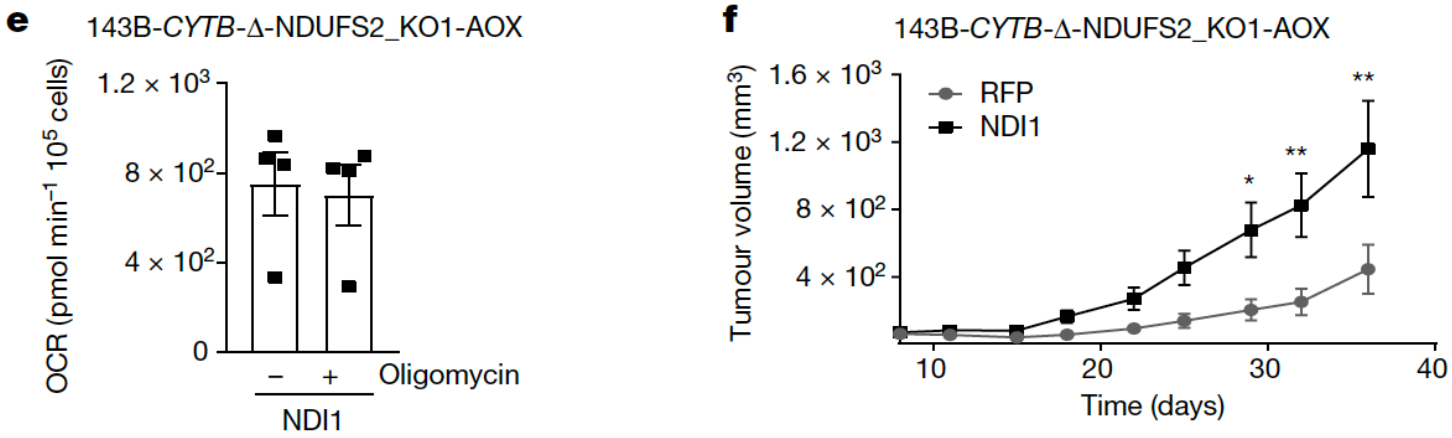
b

143B-*CYTB*-Δ–NDUFS2_KO1-AOX



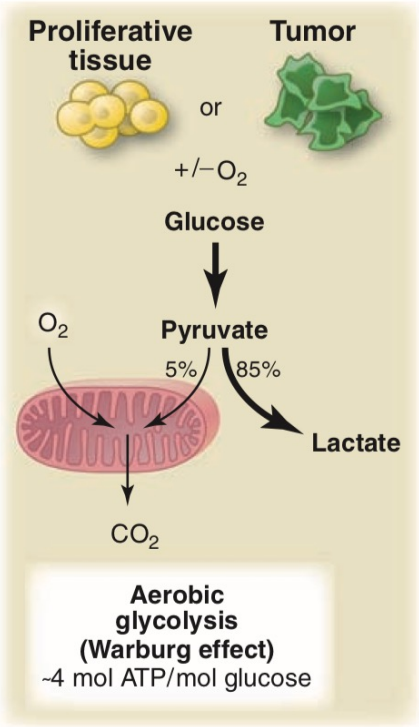
Proton pumping and OXPHOS (ATP) not needed!

NAD^+ regeneration by NDI1 rescues ETC complex I deficient tumors



Proton pumping and OXPHOS (ATP) not needed!

Why do cancer cells require functional mitochondria? Not ATP and more than aspartate



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ETC complex I regenerates NAD^+ and drives oxidative TCA cycle

ETC complex II regenerates FAD^+ and drives oxidative TCA cycle

DHODH requires functioning ETC complex III for pyrimidine biosynthesis