

Metabolism, chromatin biology and cell fate, October 2025

Juanma Schwartzman MD/PhD, Department of Medicine







No service-use **C D Q** Delancey St/Essex St–Metropolitan Av Local in Manhattan, via Manhattan Bridge No service-use **N R** Dyre Av–Bowling Green

Late nights (12:00 midnight to 6:00am, daily)

A	C	E	B	D	F	M	S 42 St
Local, 207 St–Far Rockaway, Euclid Av–Lefferts Blvd Shuttle	No service-use A	Local service	No service-use A D Q	Local in Brooklyn	Local service	Myrtle Av–Metropolitan Av Shuttle	No service-use 7

N	Q	R	W	2	3	4	5
Local, via Financial District	Local service	Whitehall St–95 St	No service-use N	Local service	148 St–Times Sq/42 St	Local, Woodlawn–New Lots Av Skips Hoyt St	Dyre Av–E180 St Shuttle

Q95 free shuttle bus between 21 St–Queensbridge, Queensboro Plaza & Queens Plaza.

Transfer for free out-of-system with MetroCard or OMNY between 21 St–Queensbridge and Queens Plaza or Queensboro Plaza. Have a Single-Ride MetroCard? See agent for a GO Ticket to complete your trip.



No service-use **C D Q**
Delancey St/Essex St—Metropolitan Av
Local in Manhattan, via Manhattan Bridge
No service-use **N R**
Dyre Av—Bowling Green

Late nights (12:00 midnight to 6:00am, daily)

A Local, 207 St—Far Rockaway, Euclid Av—Lefferts Blvd Shuttle	C No service-use A	E Local service	B No service-use A D Q	D Local in Brooklyn	F Local service	M Myrtle Av—Metropolitan Av Shuttle	S 42 St No service-use 7
---	-------------------------------------	---------------------------	---	-------------------------------	---------------------------	---	---

N Local, via Financial District	Q Local service	R Whitehall St—95 St	W No service-use N	2 Local service	3 148 St—Times Sq/42 St	4 Local, Woodlawn—New Lots Av Skips Hoyt St	5 Dyre Av—E180 St Shuttle
---	---------------------------	--------------------------------	-------------------------------------	---------------------------	-----------------------------------	---	-------------------------------------

Q95 free shuttle bus between 21 St—Queensbridge, Queensboro Plaza & Queens Plaza.

Transfer for free out-of-system with MetroCard or OMNY between 21 St—Queensbridge and Queens Plaza or Queensboro Plaza. Have a Single-Ride MetroCard? See agent for a GO Ticket to complete your trip.



No service-use **C D Q** Delancey St/Essex St—Metropolitan Av Local in Manhattan, via Manhattan Bridge No service-use **N R** Dyre Av—Bowling Green

Late nights (12:00 midnight to 6:00am, daily)

A	C	E	B	D	F	M	S 42 St
Local, 207 St—Far Rockaway, Euclid Av—Lefferts Blvd Shuttle	No service-use A	Local service	No service-use A D Q	Local in Brooklyn	Local service	Myrtle Av—Metropolitan Av Shuttle	No service-use 7

N	Q	R	W	2	3	4	5
Local, via Financial District	Local service	Whitehall St—95 St	No service-use N	Local service	148 St—Times Sq/42 St	Local, Woodlawn—New Lots Av Skips Hoyt St	Dyre Av—E180 St Shuttle

Q95 free shuttle bus between 21 St-Queensbridge, Queensboro Plaza & Queens Plaza.

Transfer for free out-of-system with MetroCard or OMNY between 21 St-Queensbridge and Queens Plaza or Queensboro Plaza. Have a Single-Ride MetroCard? See agent for a GO Ticket to complete your trip.



No service-use	Delancey St/Essex St-Metropolitan Av	Local in Manhattan, via Manhattan Bridge	No service-use	Dyre Av-Bowling Green
----------------	--------------------------------------	--	----------------	-----------------------

Late nights (12:00 midnight to 6:00am, daily)						
A	C	E	B	D	F	M
Local, 207 St-Far Rockaway, Euclid Av-Lefferts Blvd Shuttle	No service-use	Local service	No service-use	Local in Brooklyn	Local service	Myrtle Av-Metropolitan Av Shuttle

N	Q	R	W	2	3	4	5
Local, via Financial District	Local service	Whitehall St-95 St	No service-use	Local service	148 St-Times Sq/42 St	Local, Woodlawn-New Lots Av Skips Hoyt St	Dyre Av-E180 St Shuttle

Q95 free shuttle bus between 21 St-Queensbridge, Queensboro Plaza & Queens Plaza.

Transfer for free out-of-system with MetroCard or OMNY between 21 St-Queensbridge and Queens Plaza or Queensboro Plaza. Have a Single-Ride MetroCard? See agent for a GO Ticket to complete your trip.



No service-use C D Q	Delancey St/Essex St–Metropolitan Av	Local in Manhattan, via Manhattan Bridge	No service-use N R	Dyre Av–Bowling Green
-----------------------------	--------------------------------------	--	---------------------------	-----------------------

Late nights (12:00 midnight to 6:00am, daily)

A	C	E	B	D	F	M	S 42 St
Local, 207 St–Far Rockaway, Euclid Av–Lefferts Blvd Shuttle	No service-use A	Local service	No service-use A D Q	Local in Brooklyn	Local service	Myrtle Av–Metropolitan Av Shuttle	No service-use 7

N	Q	R	W	2	3	4	5
Local, via Financial District	Local service	Whitehall St–95 St	No service-use N	Local service	148 St–Times Sq/42 St	Local, Woodlawn–New Lots Av Skips Hoyt St	Dyre Av–E180 St Shuttle



No service-use **C D Q** Delancey St/Essex St—Metropolitan Av Local in Manhattan, via Manhattan Bridge No service-use **N R** Dyre Av—Bowling Green

Late nights (12:00 midnight to 6:00am, daily)

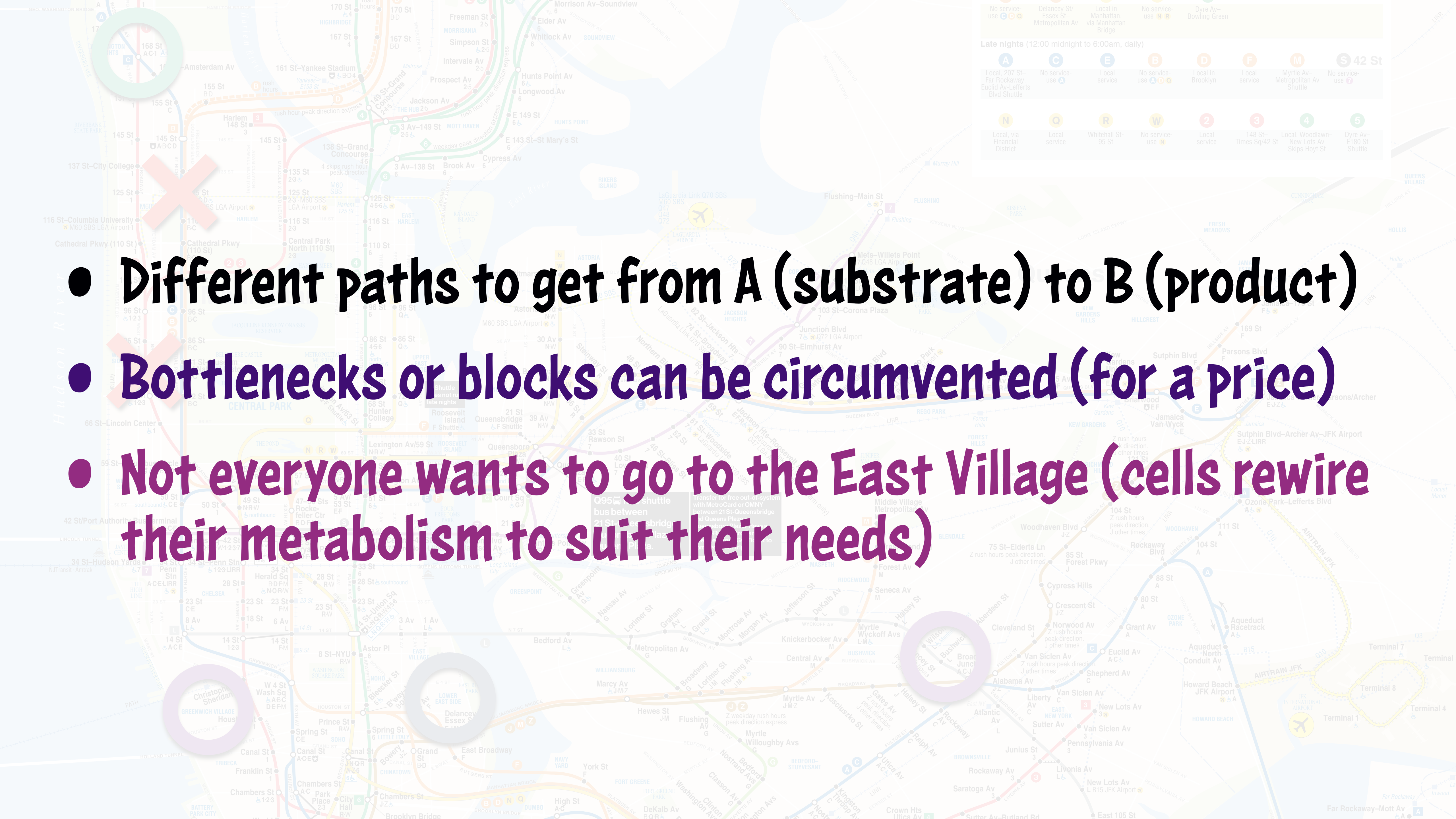
A	C	E	B	D	F	M	S 42 St
Local, 207 St—Far Rockaway, Euclid Av—Lefferts Blvd Shuttle	No service-use A	Local service	No service-use A D Q	Local in Brooklyn	Local service	Myrtle Av—Metropolitan Av Shuttle	No service-use 7

N	Q	R	W	2	3	4	5
Local, via Financial District	Local service	Whitehall St—95 St	No service-use N	Local service	148 St—Times Sq/42 St	Local, Woodlawn—New Lots Av Skips Hoyt St	Dyre Av—E180 St Shuttle

Q95 free shuttle bus between 21 St—Queensbridge, Queensboro Plaza & Queens Plaza.

Transfer for free out-of-system with MetroCard or OMNY between 21 St—Queensbridge and Queens Plaza or Queensboro Plaza. Have a Single-Ride MetroCard? See agent for a GO Ticket to complete your trip.

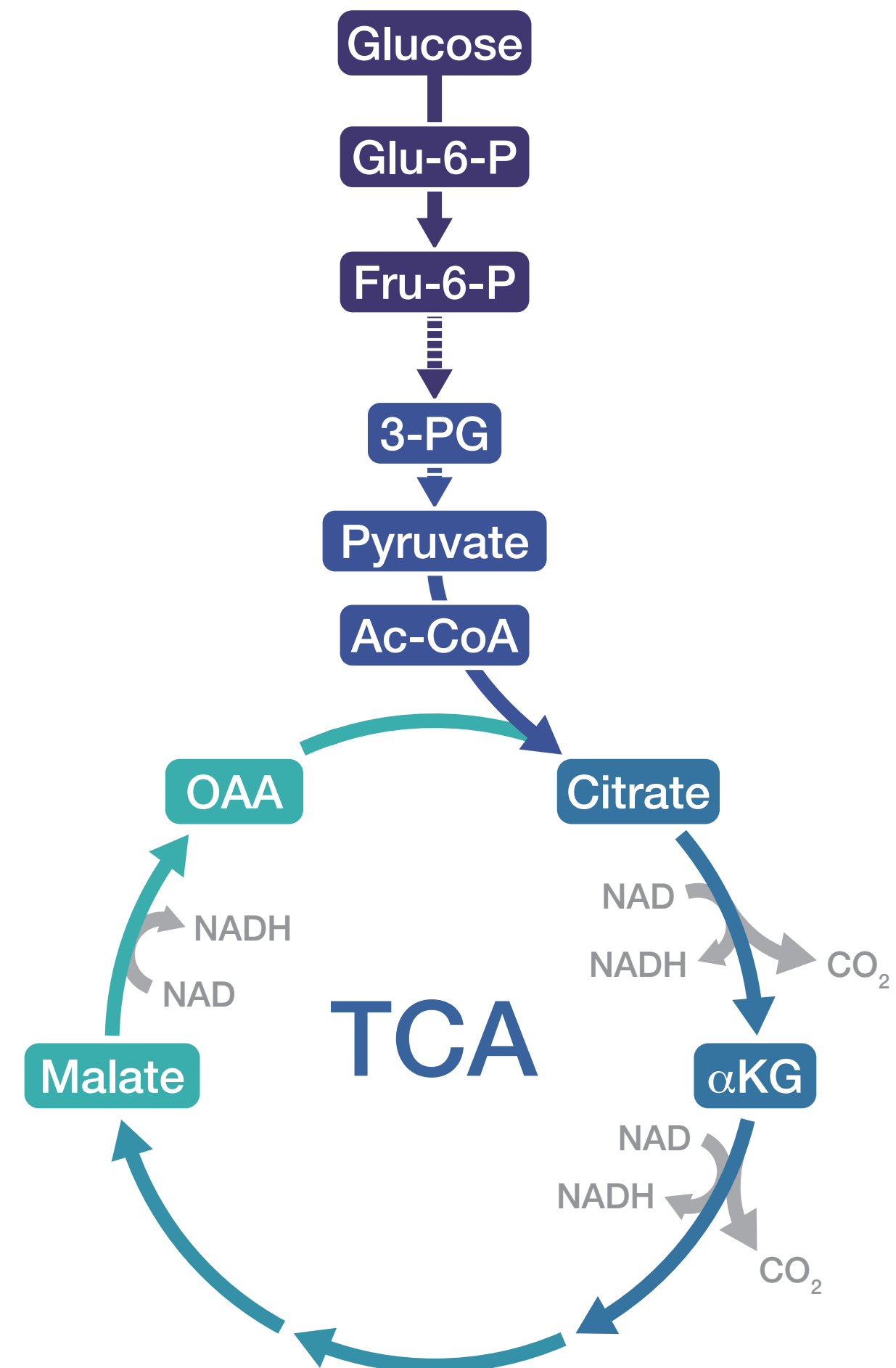


- 
- Different paths to get from A (substrate) to B (product)
 - Bottlenecks or blocks can be circumvented (for a price)
 - Not everyone wants to go to the East Village (cells rewire their metabolism to suit their needs)

Carbon Metabolism



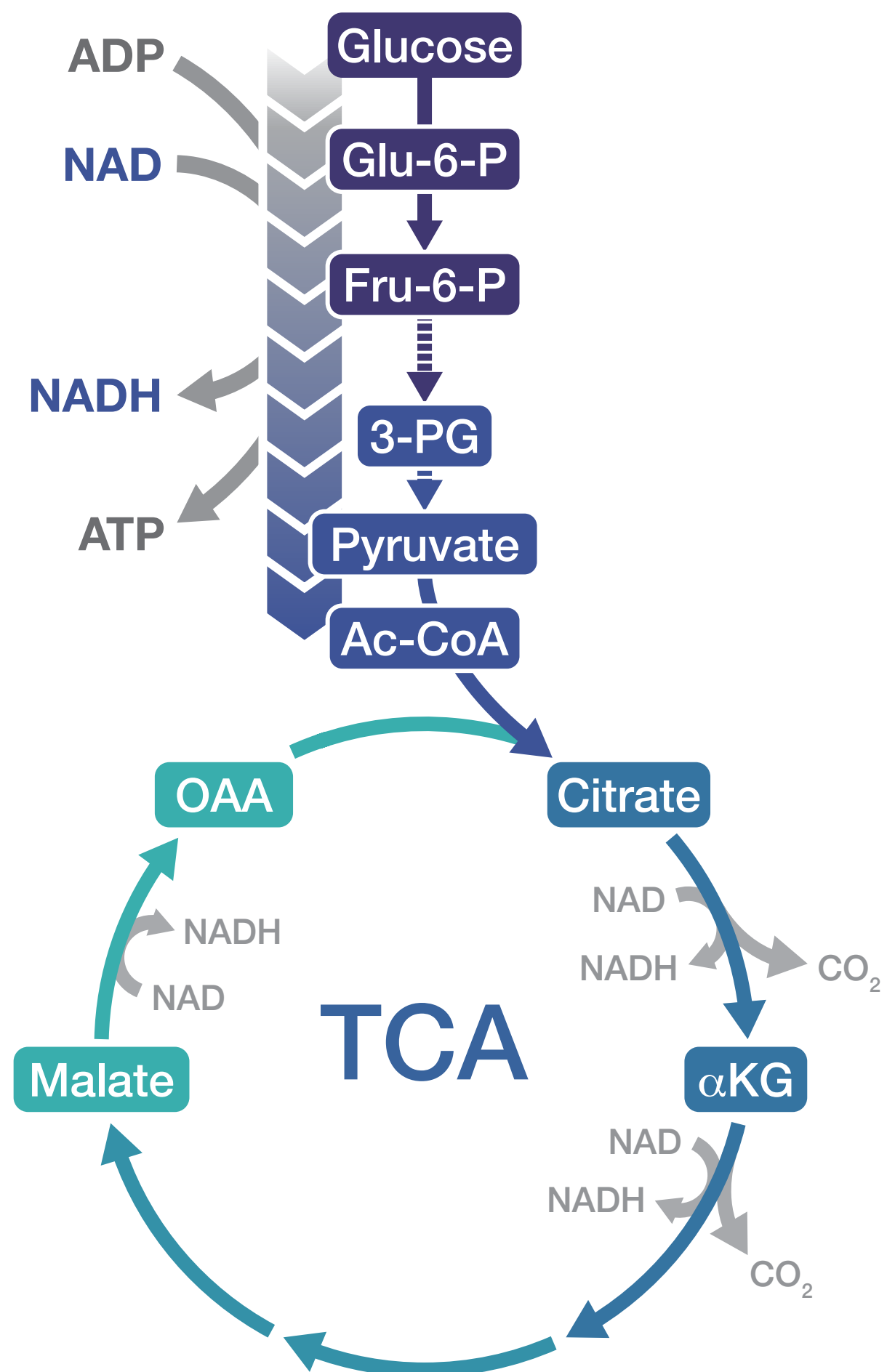
Hans Krebs



Carbon Metabolism



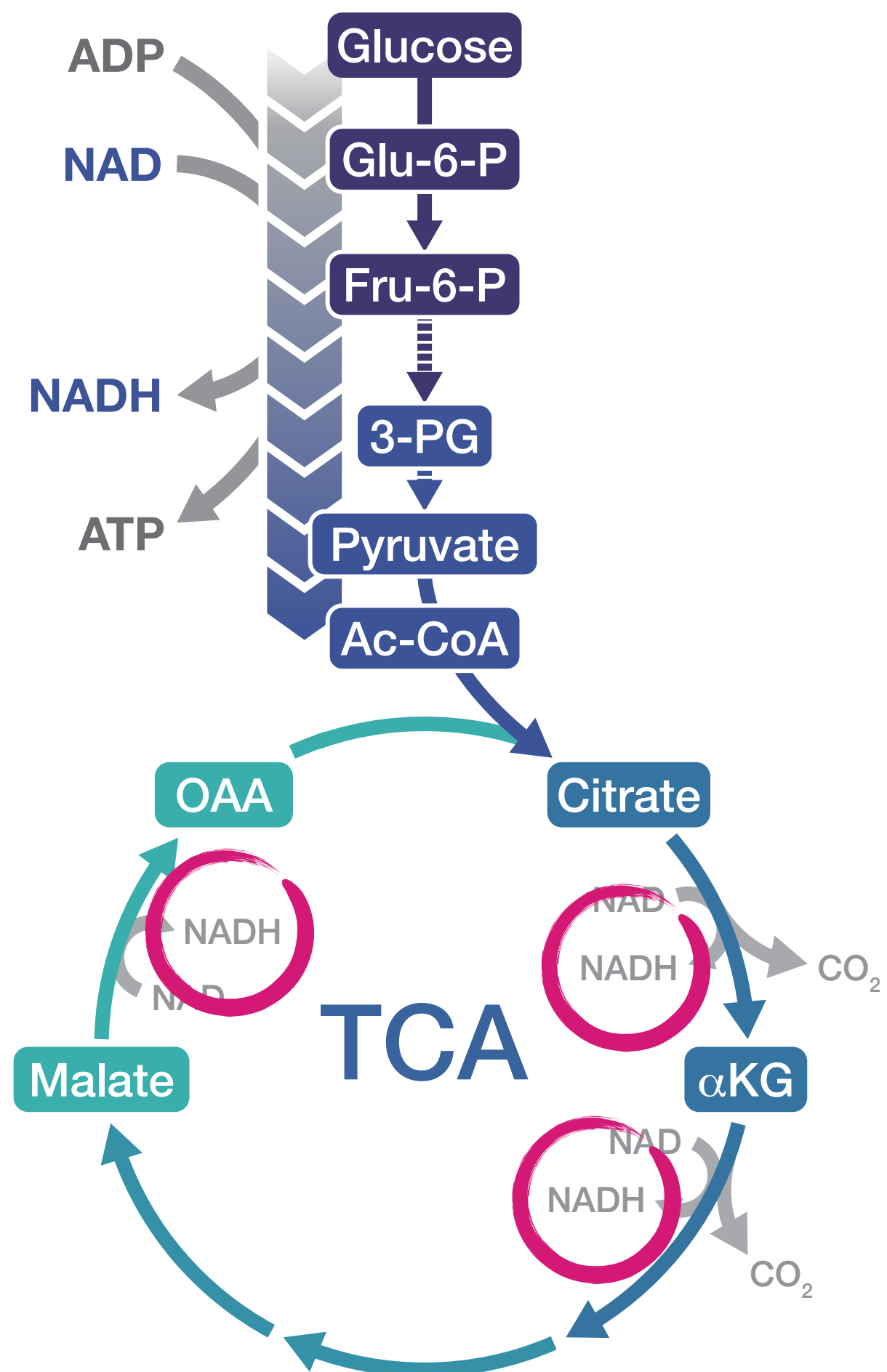
Hans Krebs



Carbon Metabolism



Hans Krebs

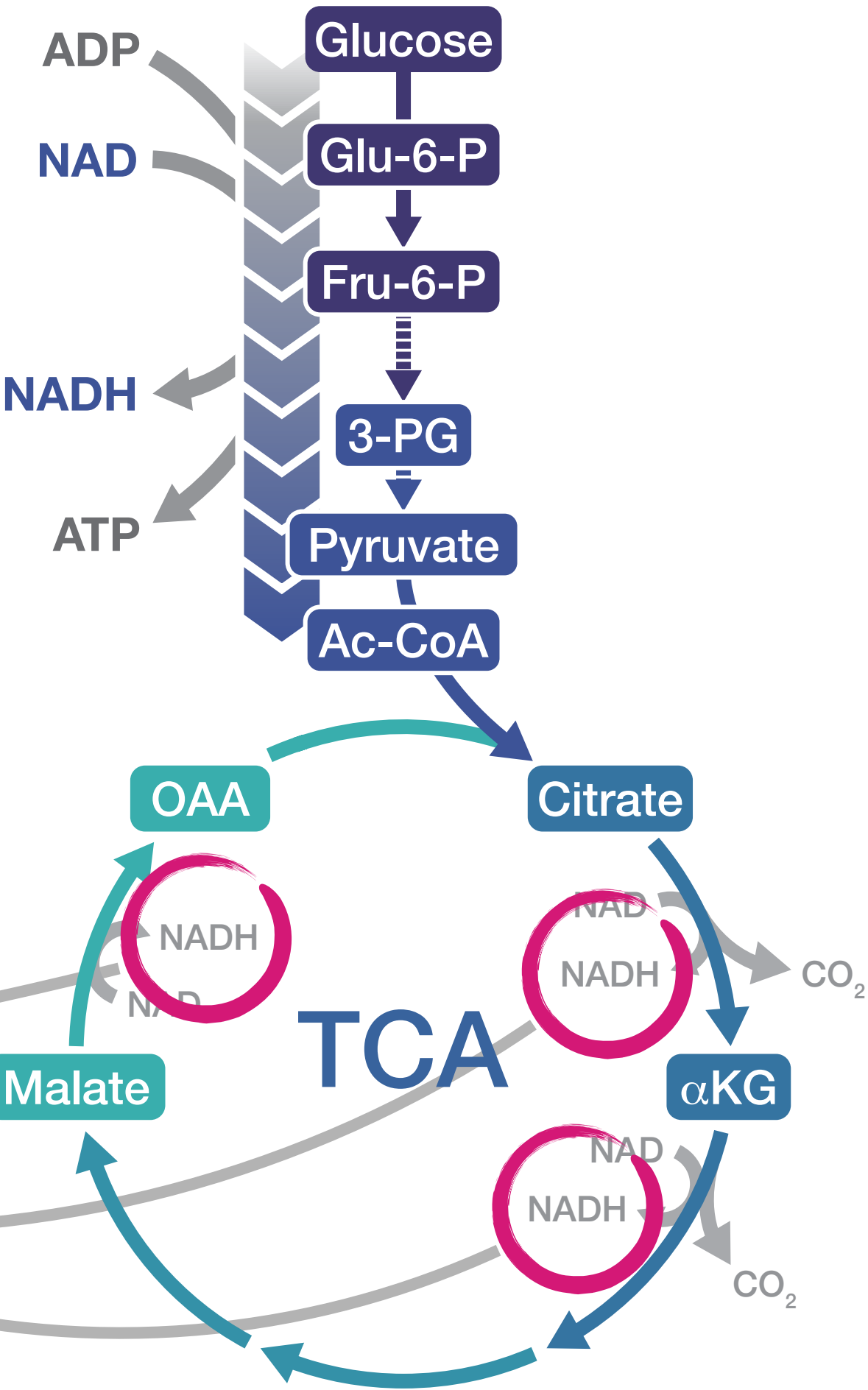
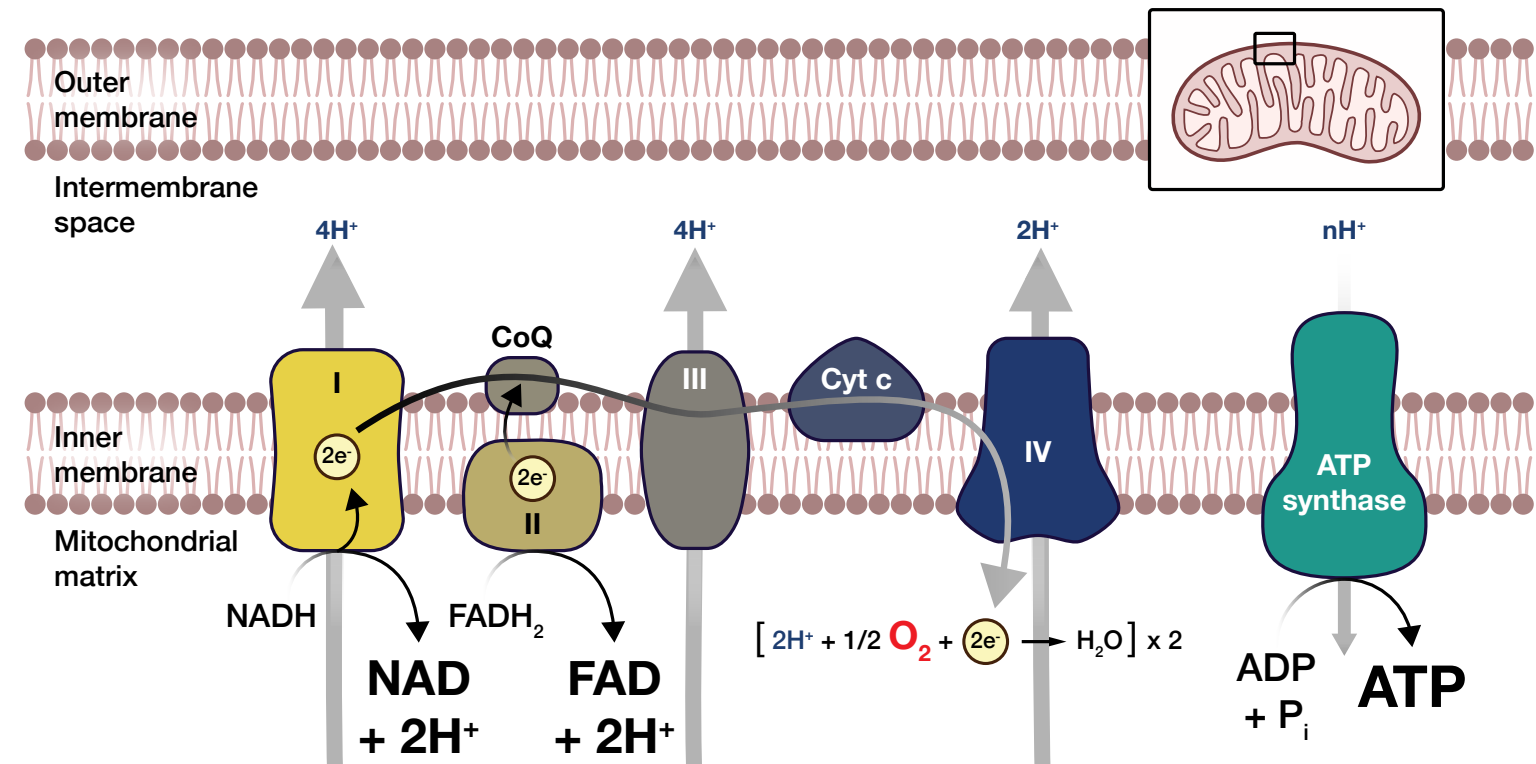


Carbon Metabolism



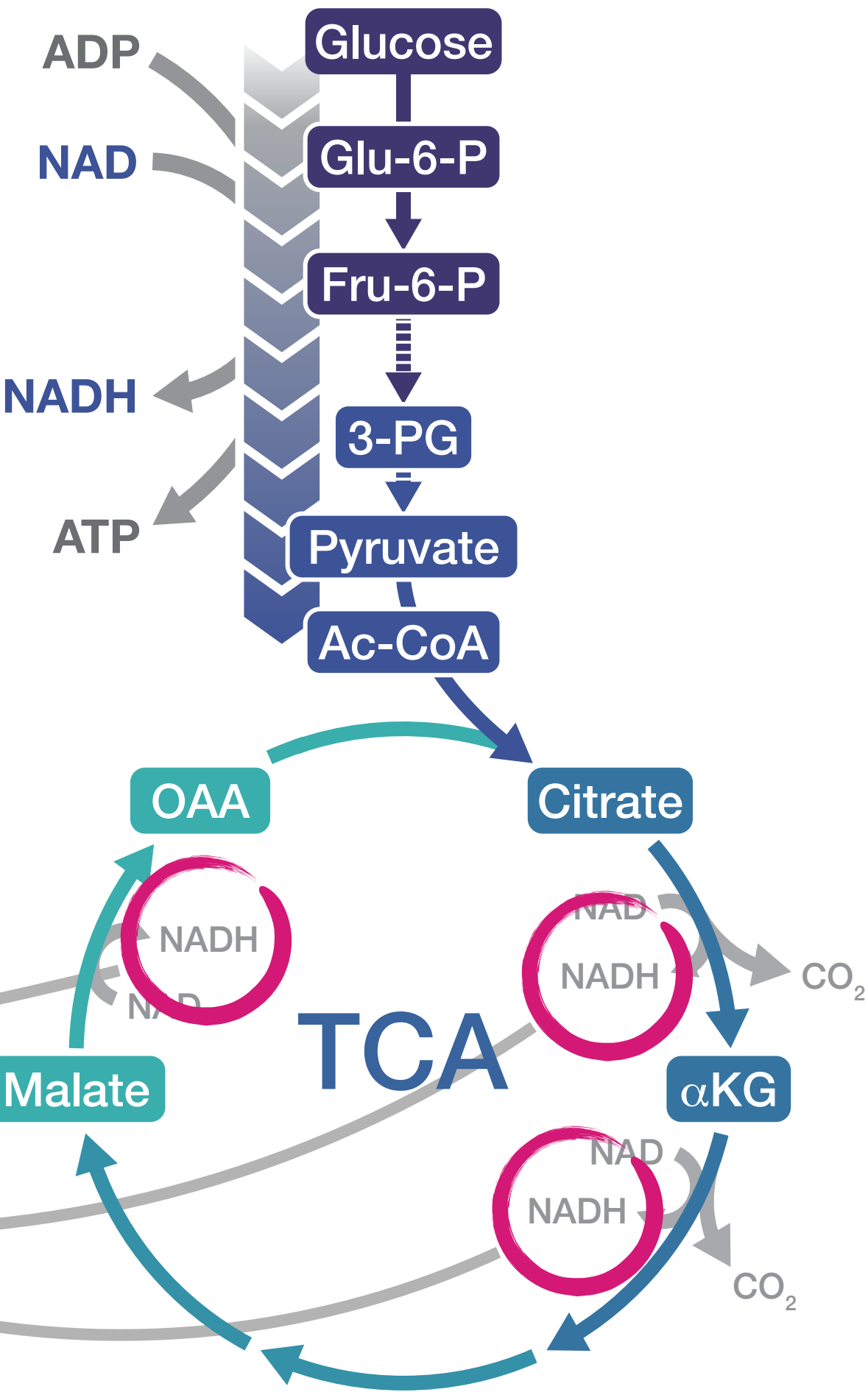
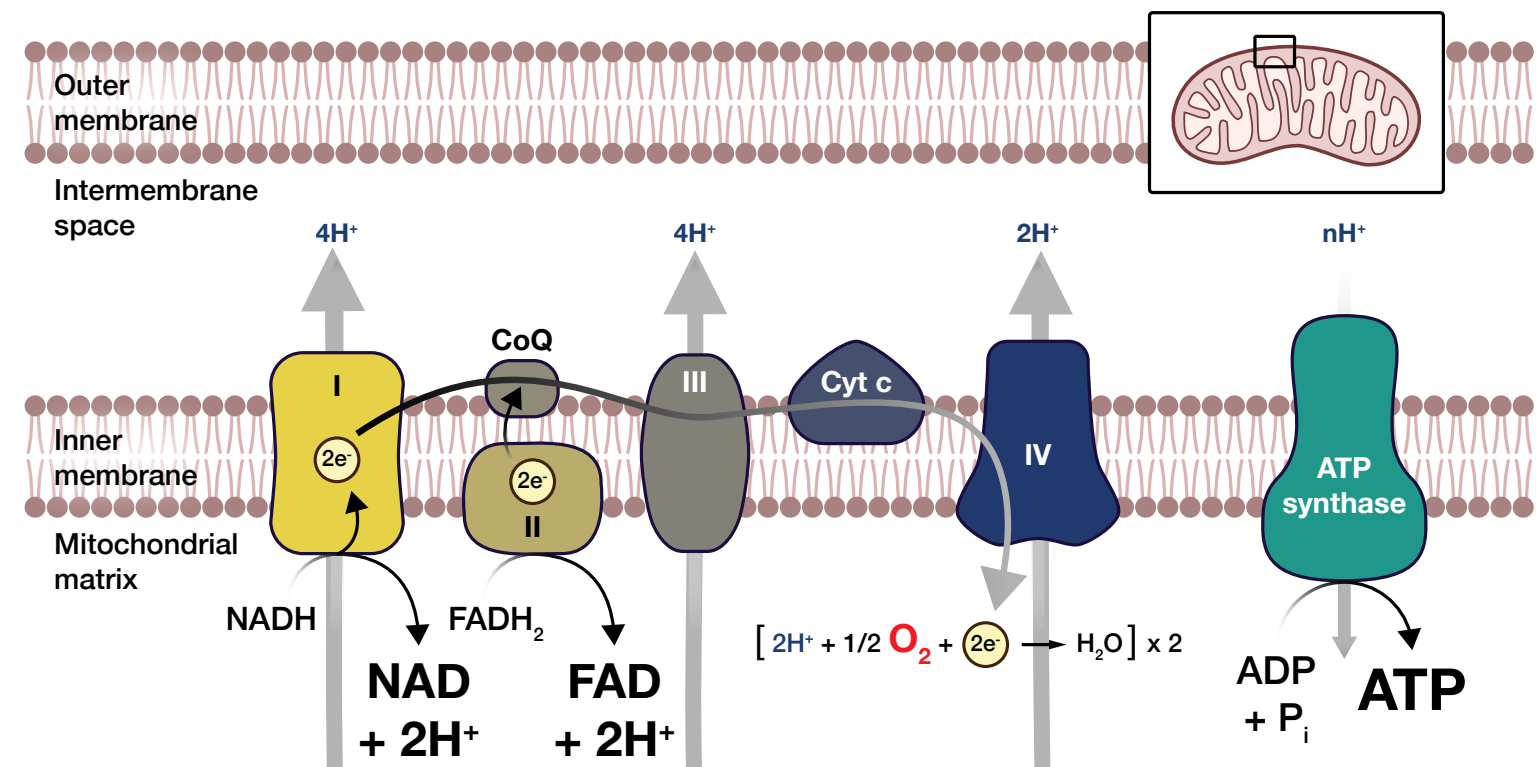
Hans Krebs

Electron Transport Chain (ETC)

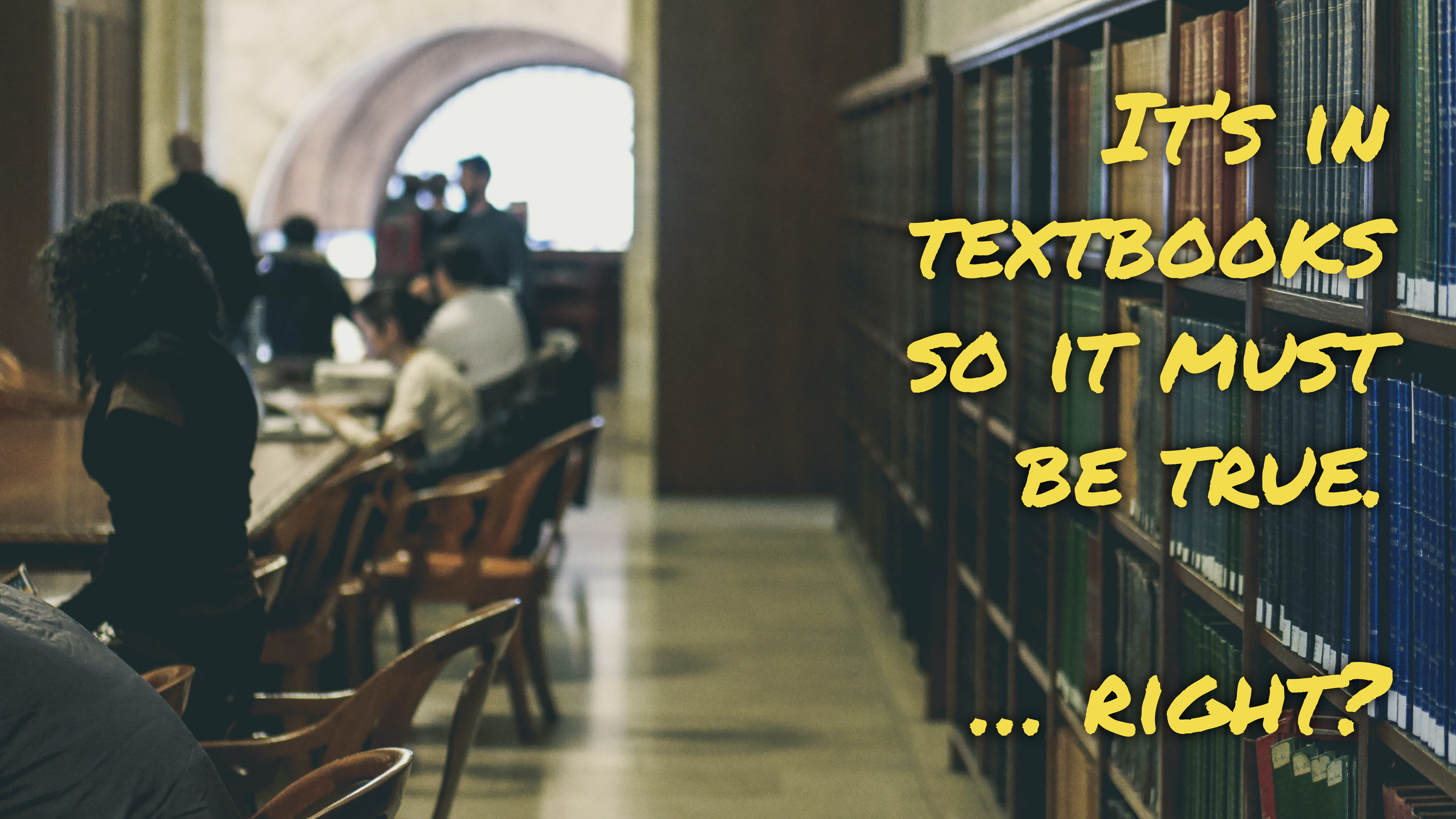


Carbon Metabolism

Electron Transport Chain (ETC)



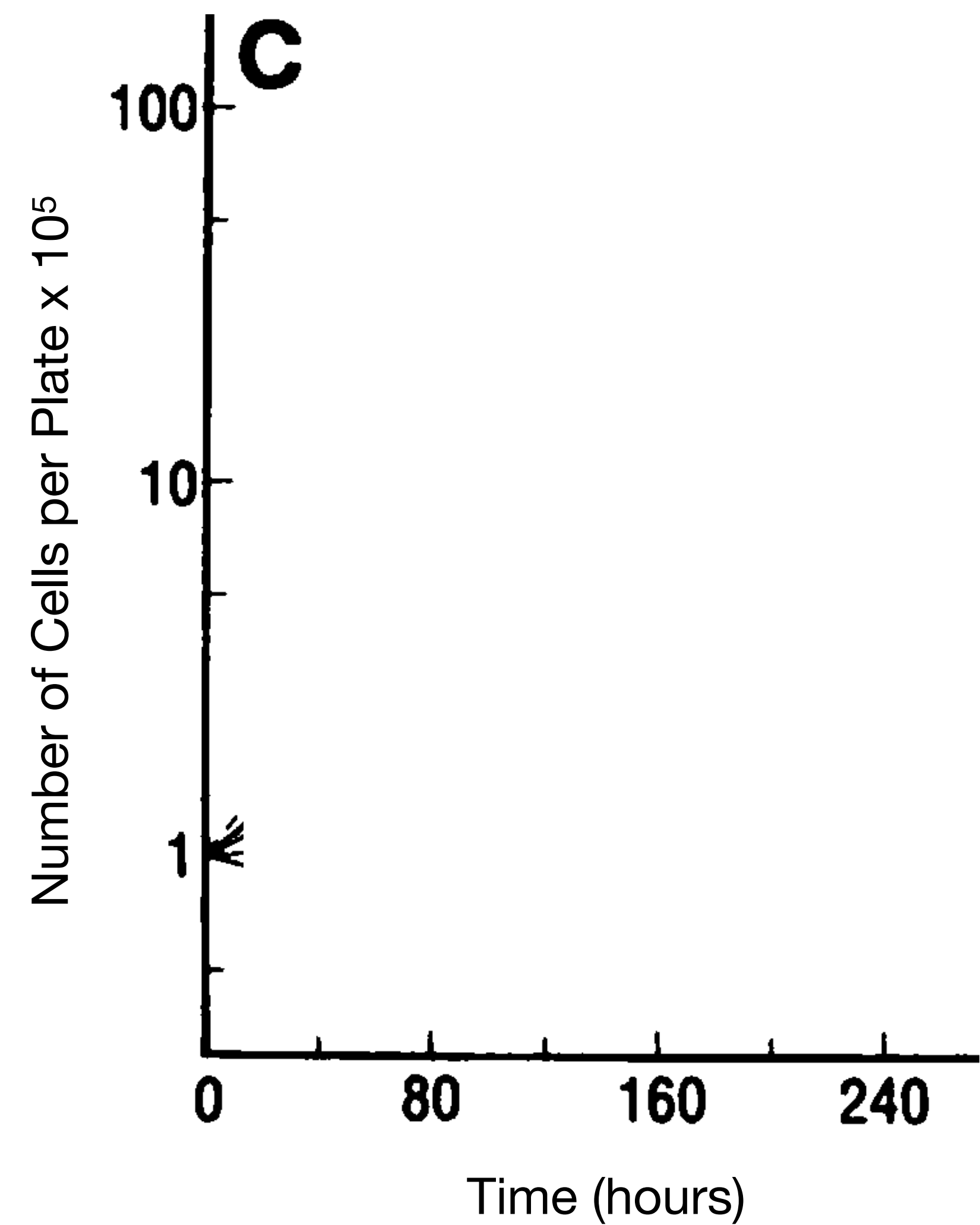
Hans Krebs

A photograph of a library interior. On the right, tall wooden bookshelves are filled with books, mostly with blue and green spines. On the left, several people are seated at wooden tables, studying. The background features a large, arched window that lets in bright light, creating a soft glow. The overall atmosphere is quiet and scholarly.

IT'S IN
TEXTBOOKS
SO IT MUST
BE TRUE.

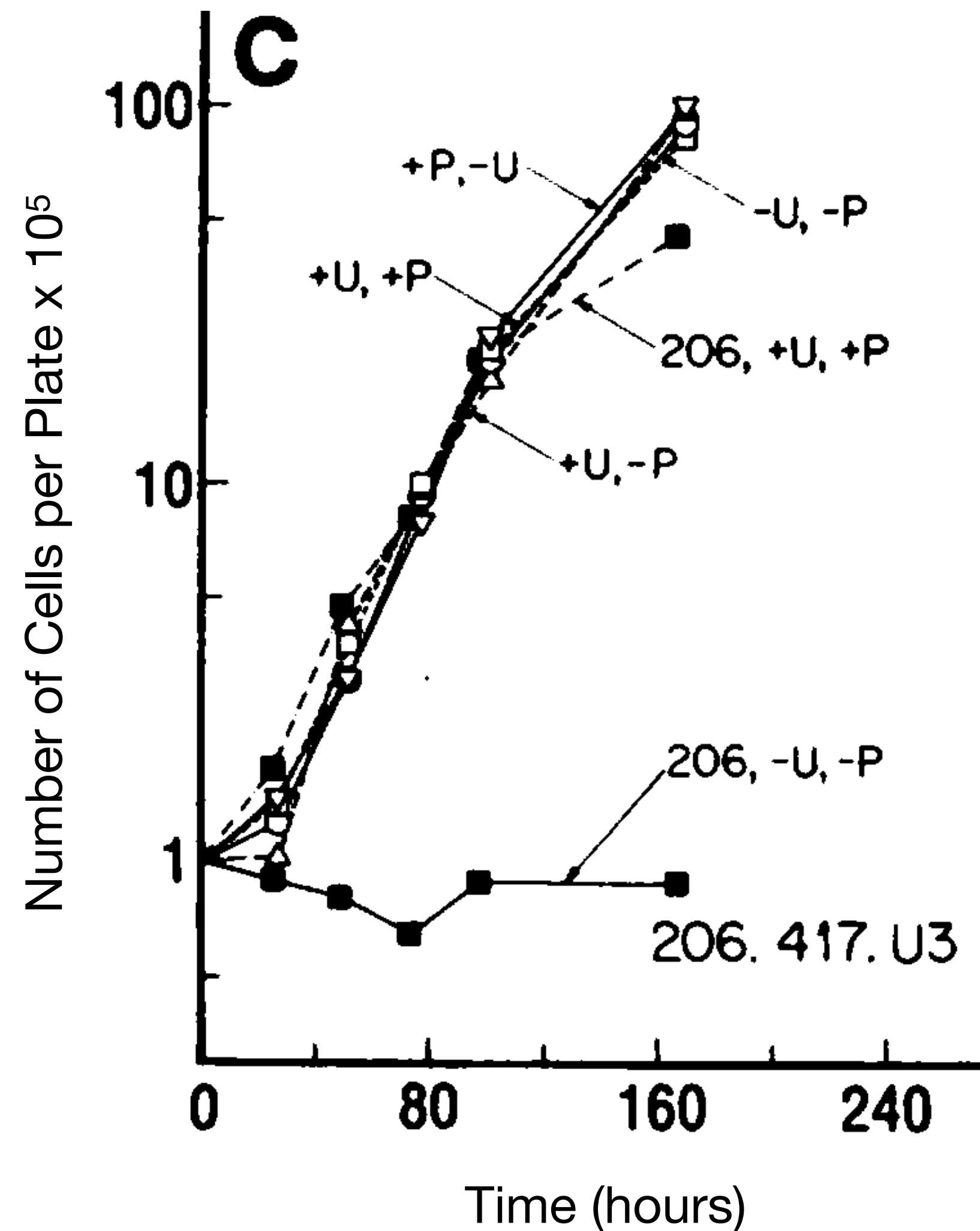
... RIGHT?

U = uridine
P = pyruvate
206 = 143B Rho0 cells (no mtDNA)



Oxidative Phosphorylation is dispensable for cell proliferation

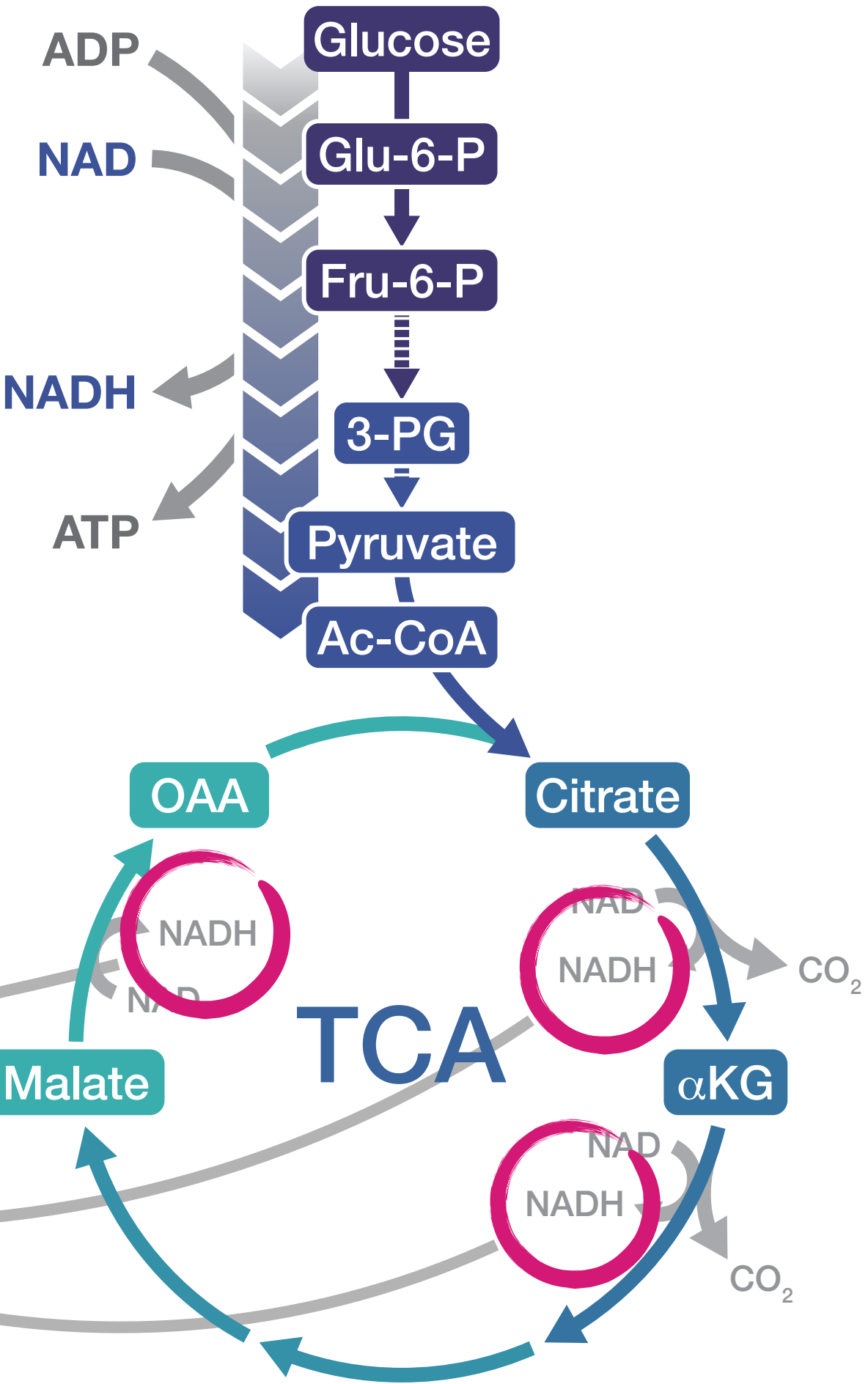
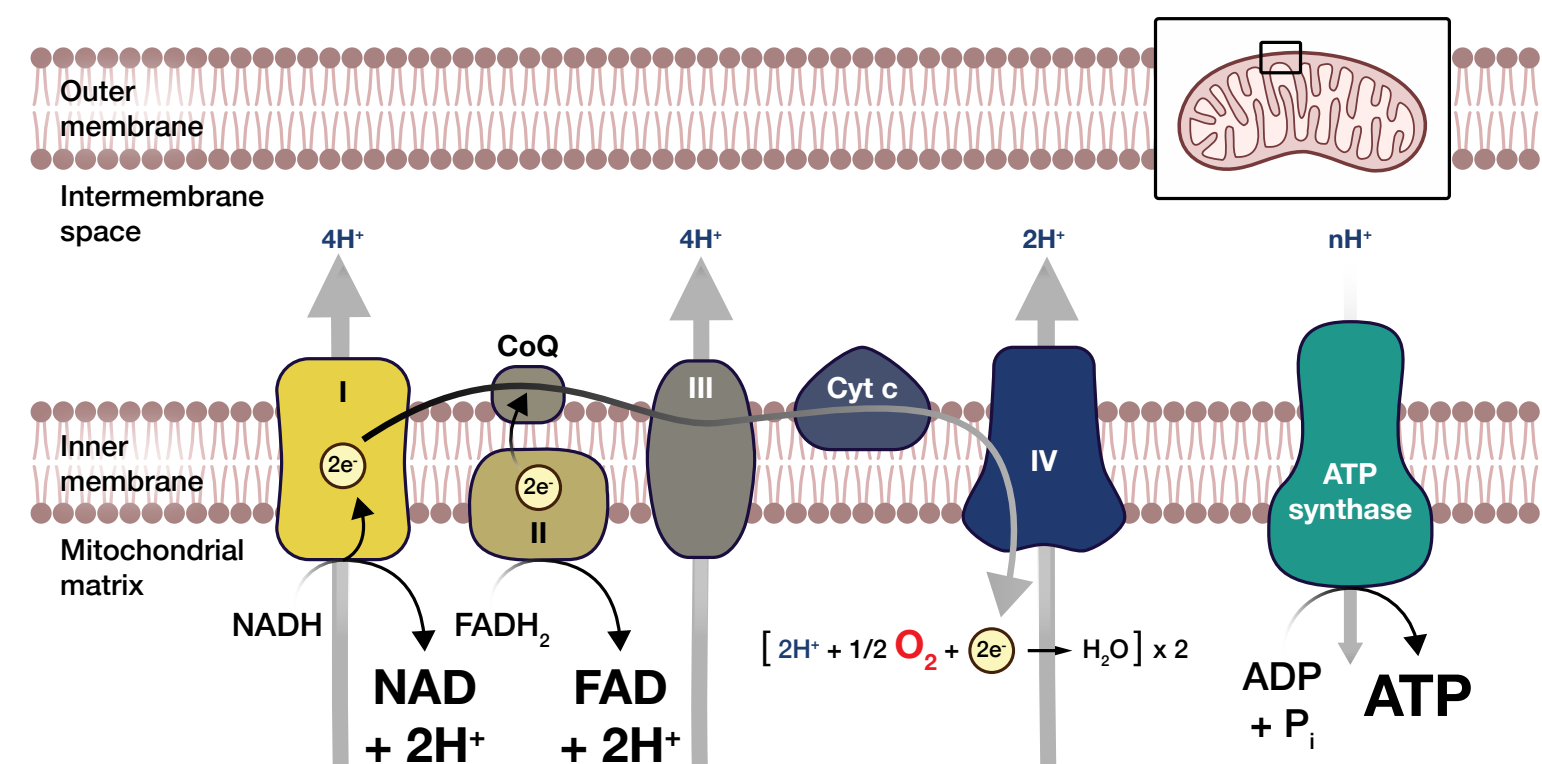
U = uridine
P = pyruvate
206 = 143B Rho0 cells (no mtDNA)



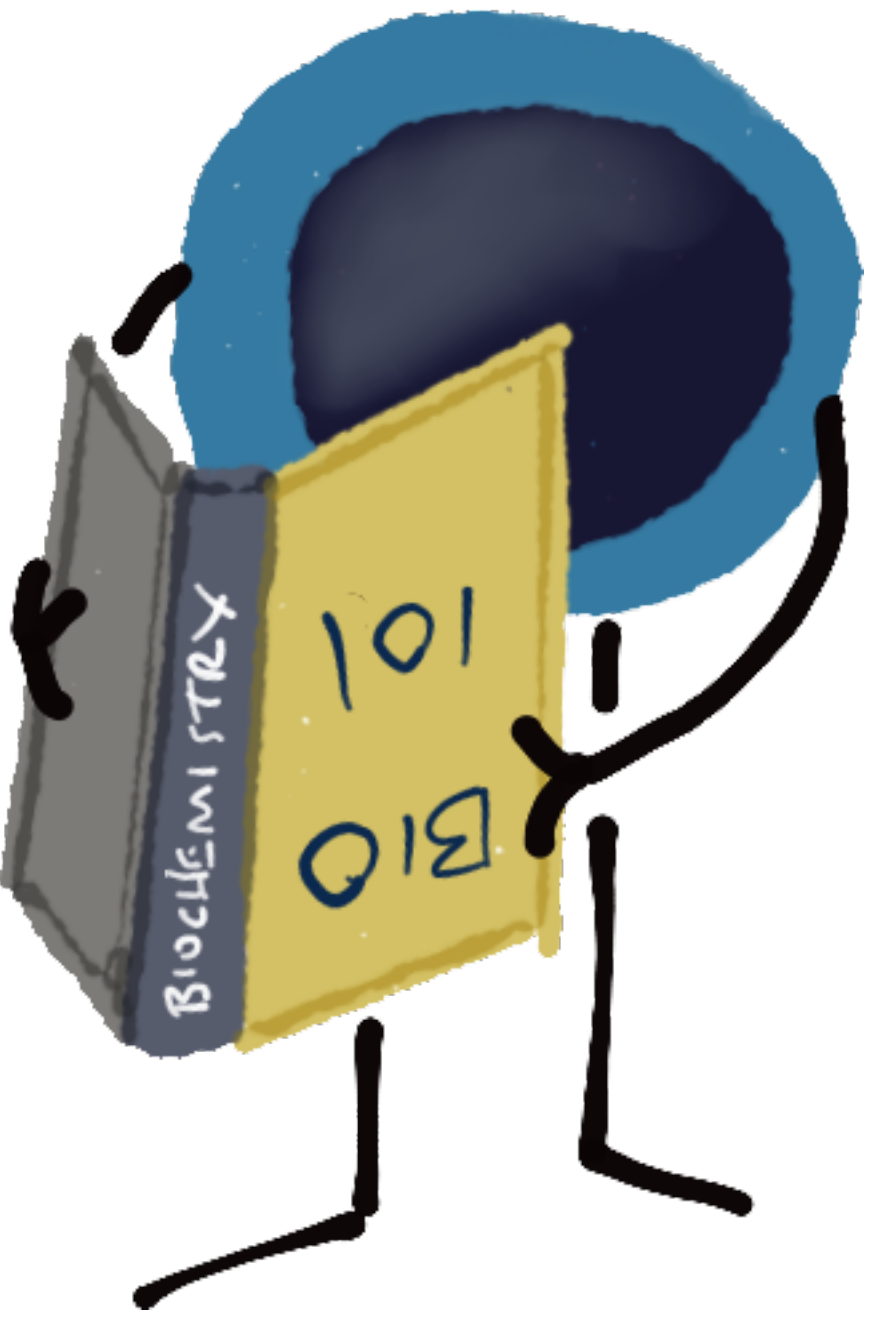
**CELLS WITHOUT AN
ELECTRON TRANSPORT
CHAIN CAN GROW,
AS LONG AS THEY HAVE PYRUVATE AND URIDINE**

Carbon Metabolism

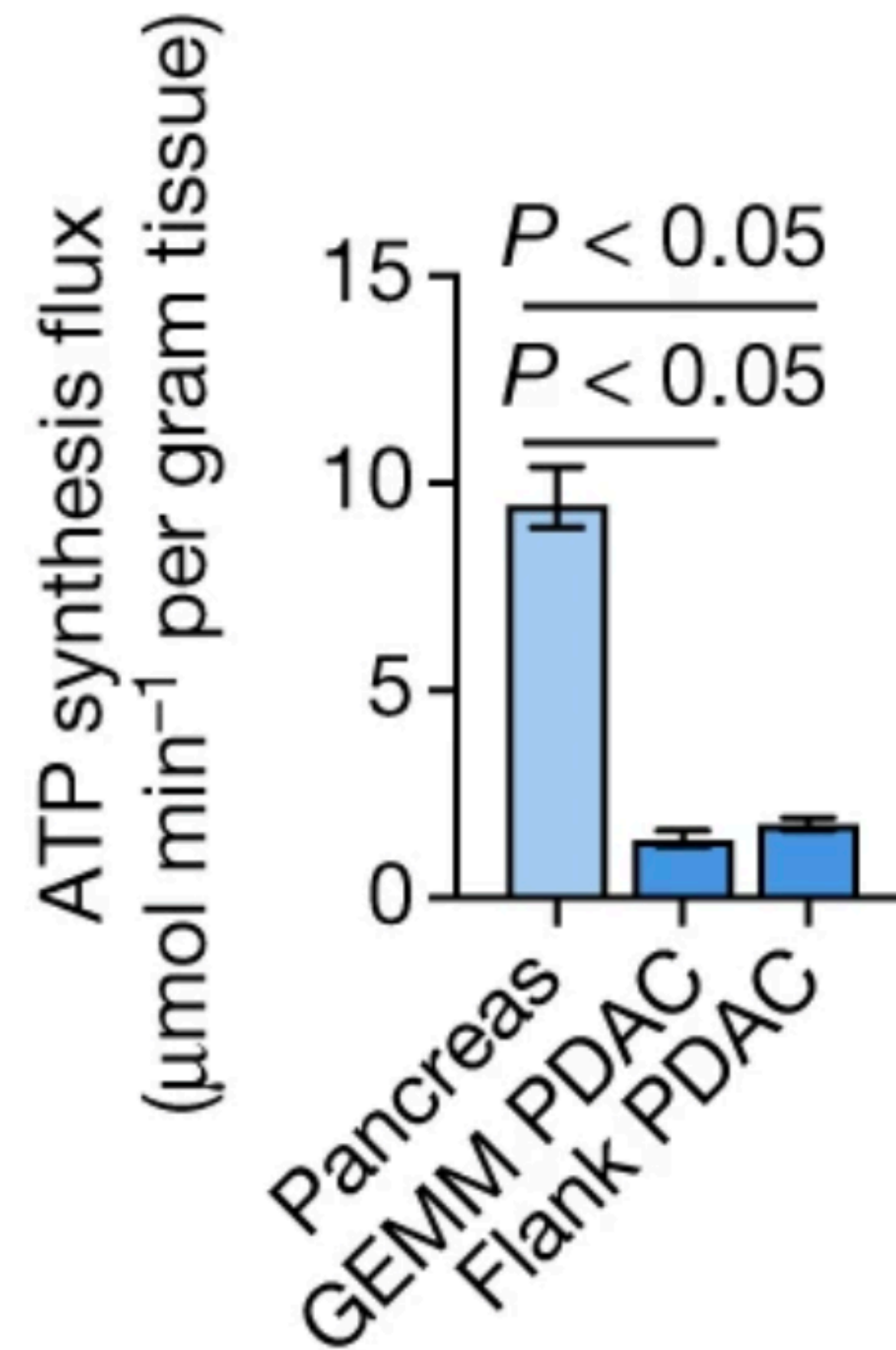
Electron Transport Chain (ETC)



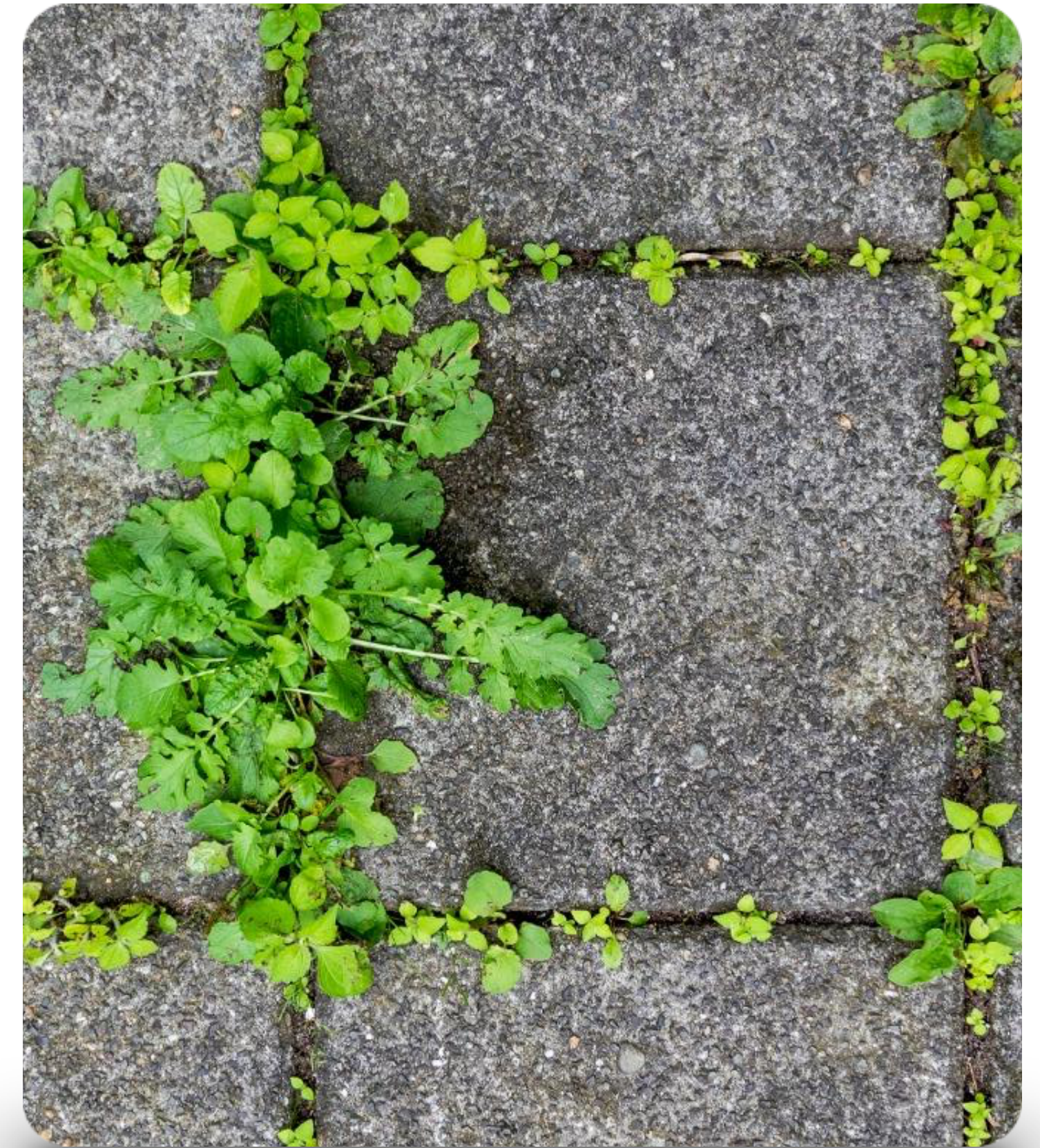
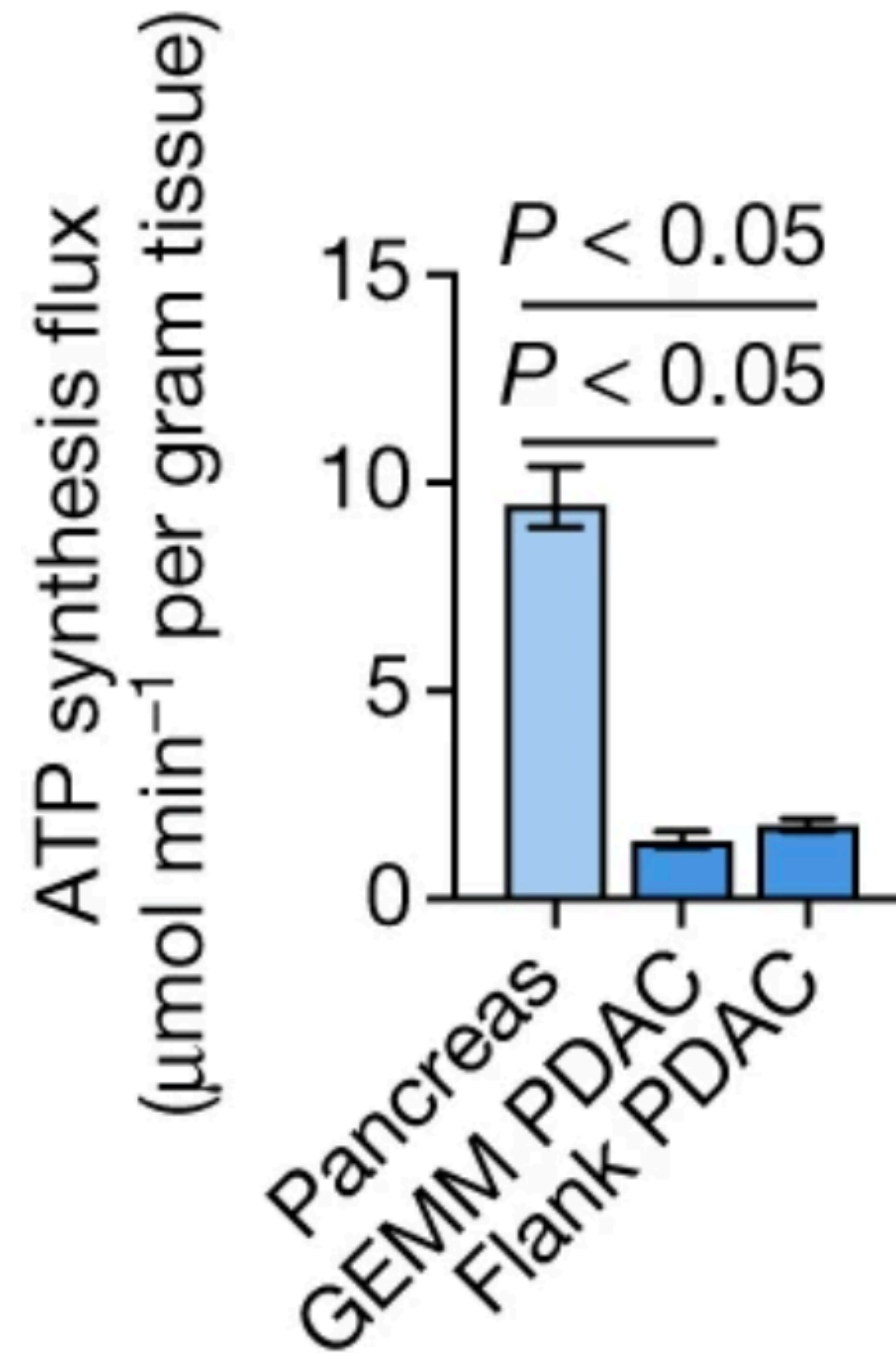
**Turns out
cells don't
read textbooks**



Proliferating cells need **LESS** ATP than differentiated tissues

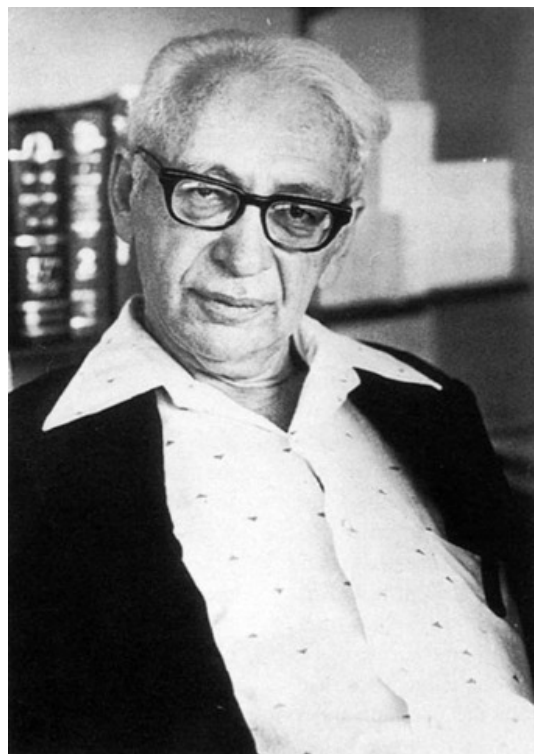
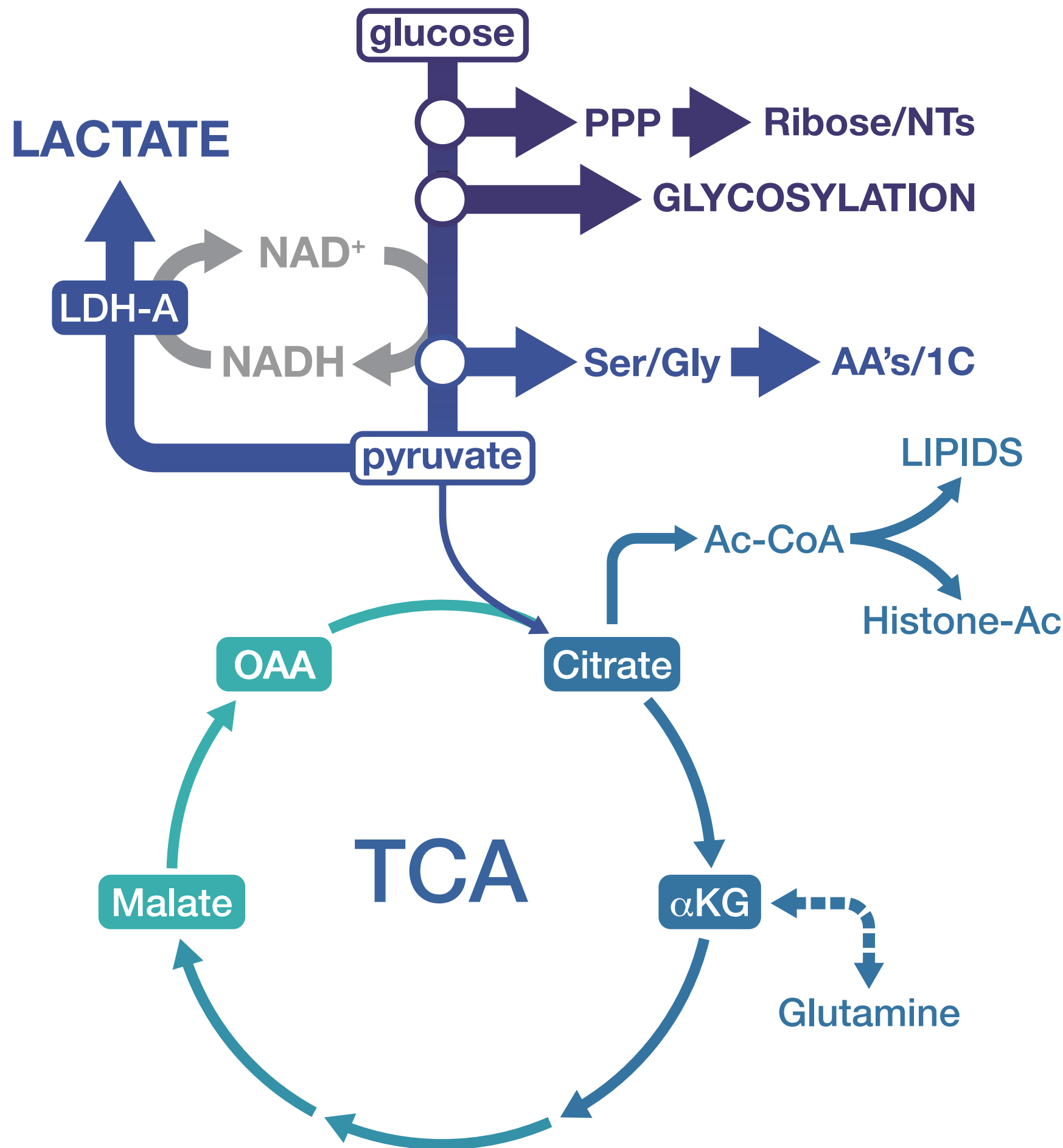


Proliferating cells need **LESS** ATP than differentiated tissues



Classic Warburg Aerobic Glycolysis

(e.g. highly glycolytic tumors)



Ephraim Racker



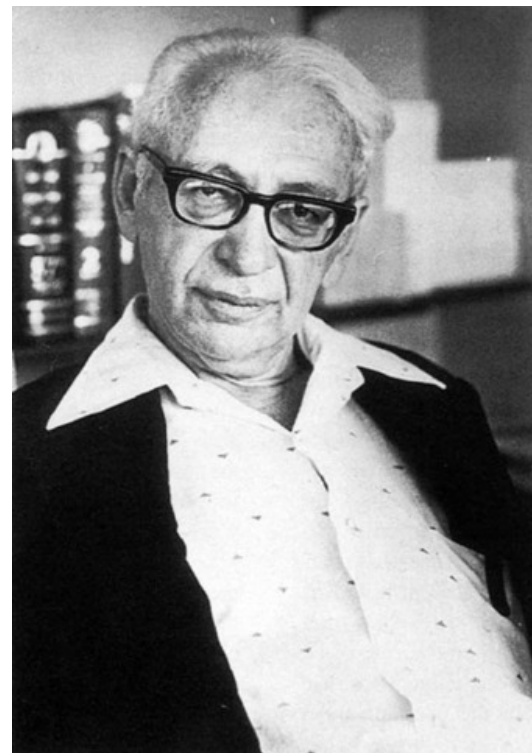
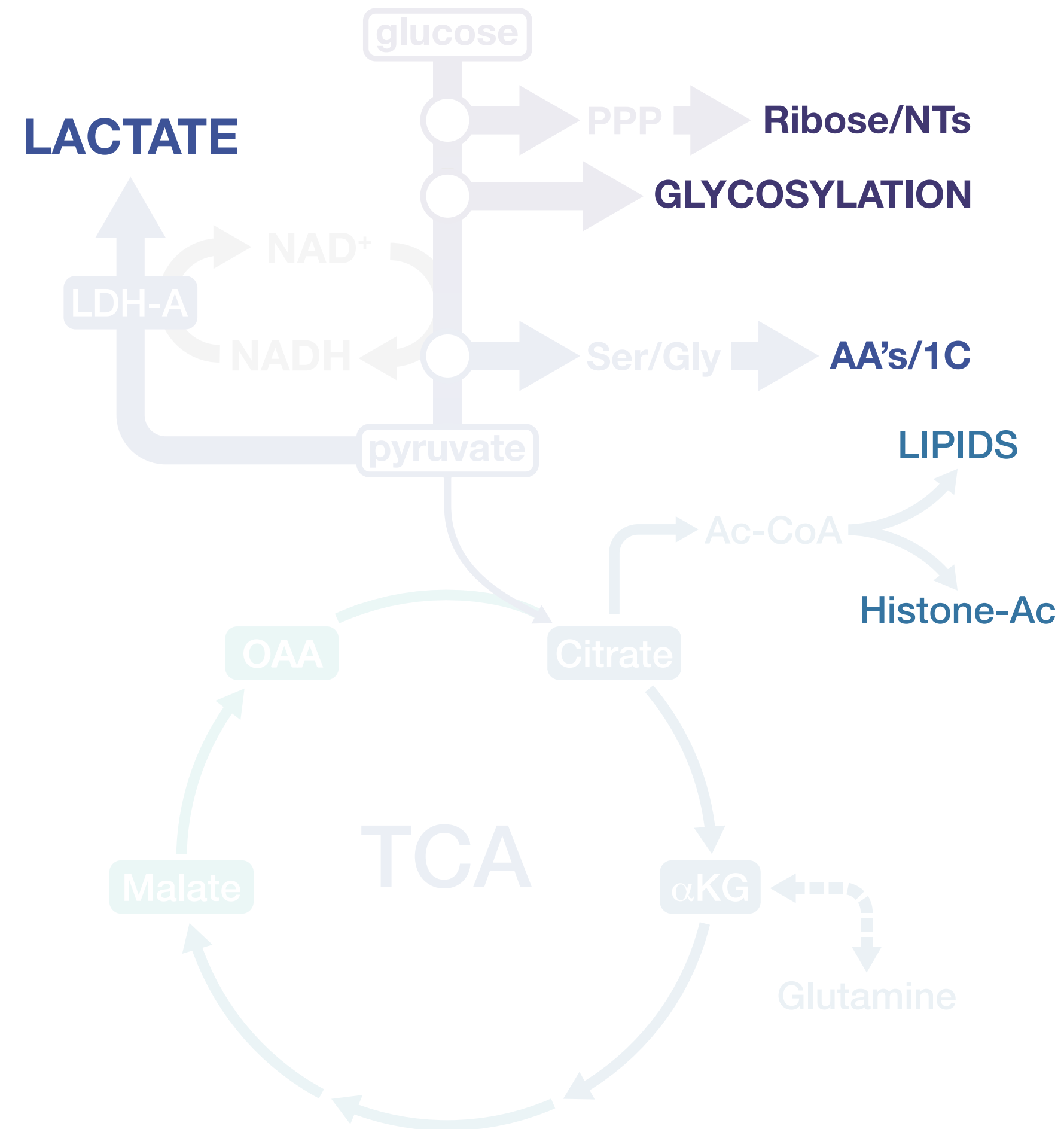
Otto Warburg

Bioenergetics and the Problem
of Tumor Growth

*An understanding of the mechanism of the generation and control of
biological energy may shed light on the problem of tumor growth*

Classic Warburg Aerobic Glycolysis

(e.g. highly glycolytic tumors)



Ephraim Racker



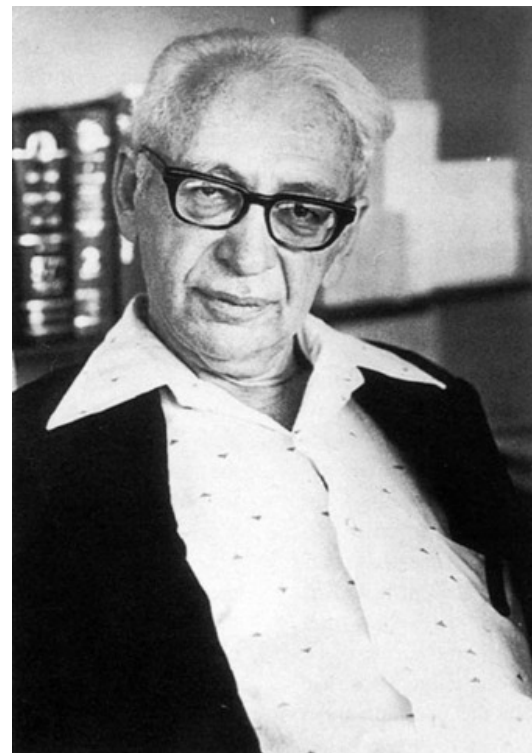
Otto Warburg

Bioenergetics and the Problem
of Tumor Growth

*An understanding of the mechanism of the generation and control of
biological energy may shed light on the problem of tumor growth*

NB THE WARBURG EFFECT IS NOT THE BASIS FOR WHY PET SCANS ARE USEFUL TO IMAGE TUMORS.

FDG-PET → GLUCOSE UPTAKE (BROWN FAT LIGHTS UP!)



Ephraim Racker



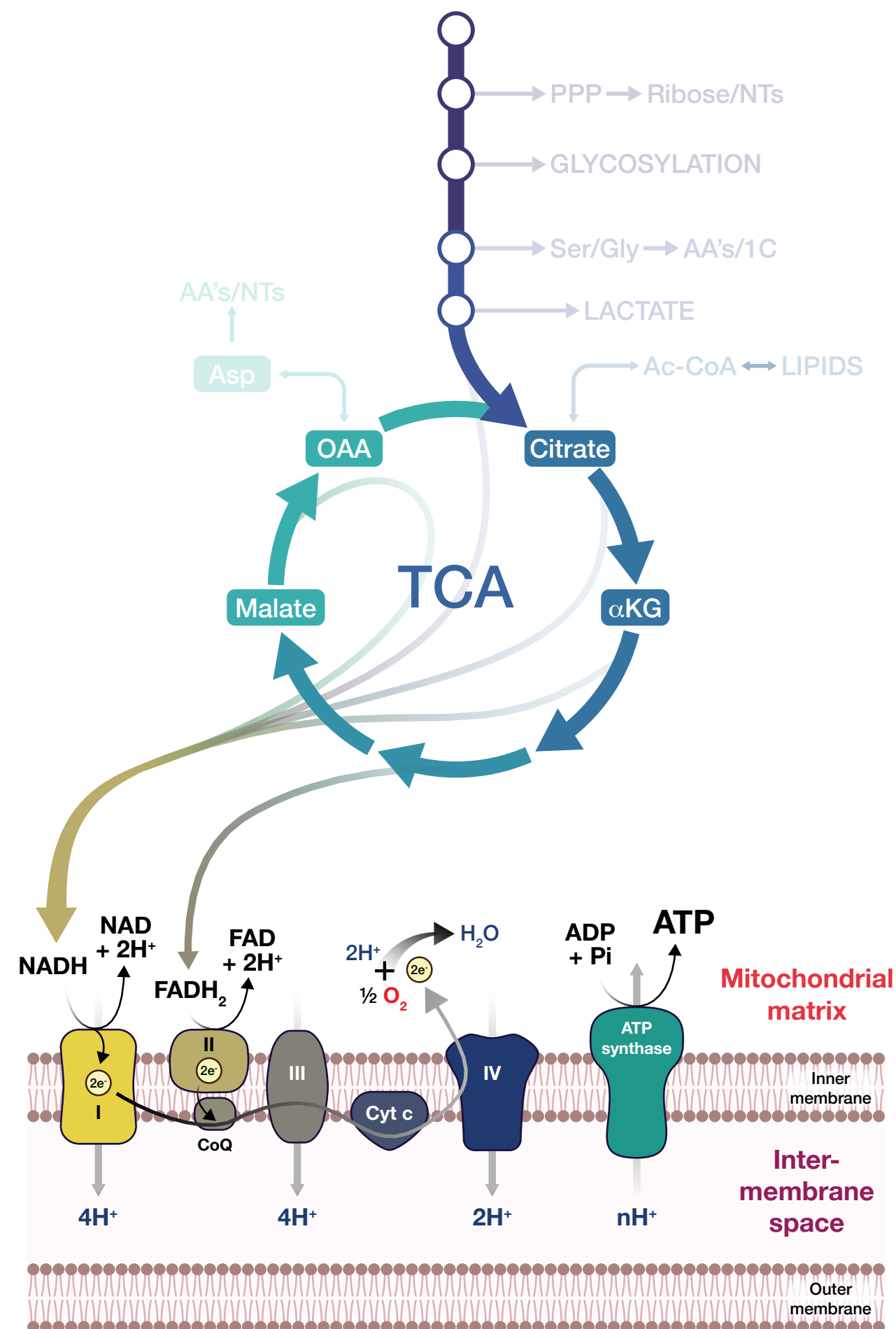
Otto Warburg

Bioenergetics and the Problem of Tumor Growth

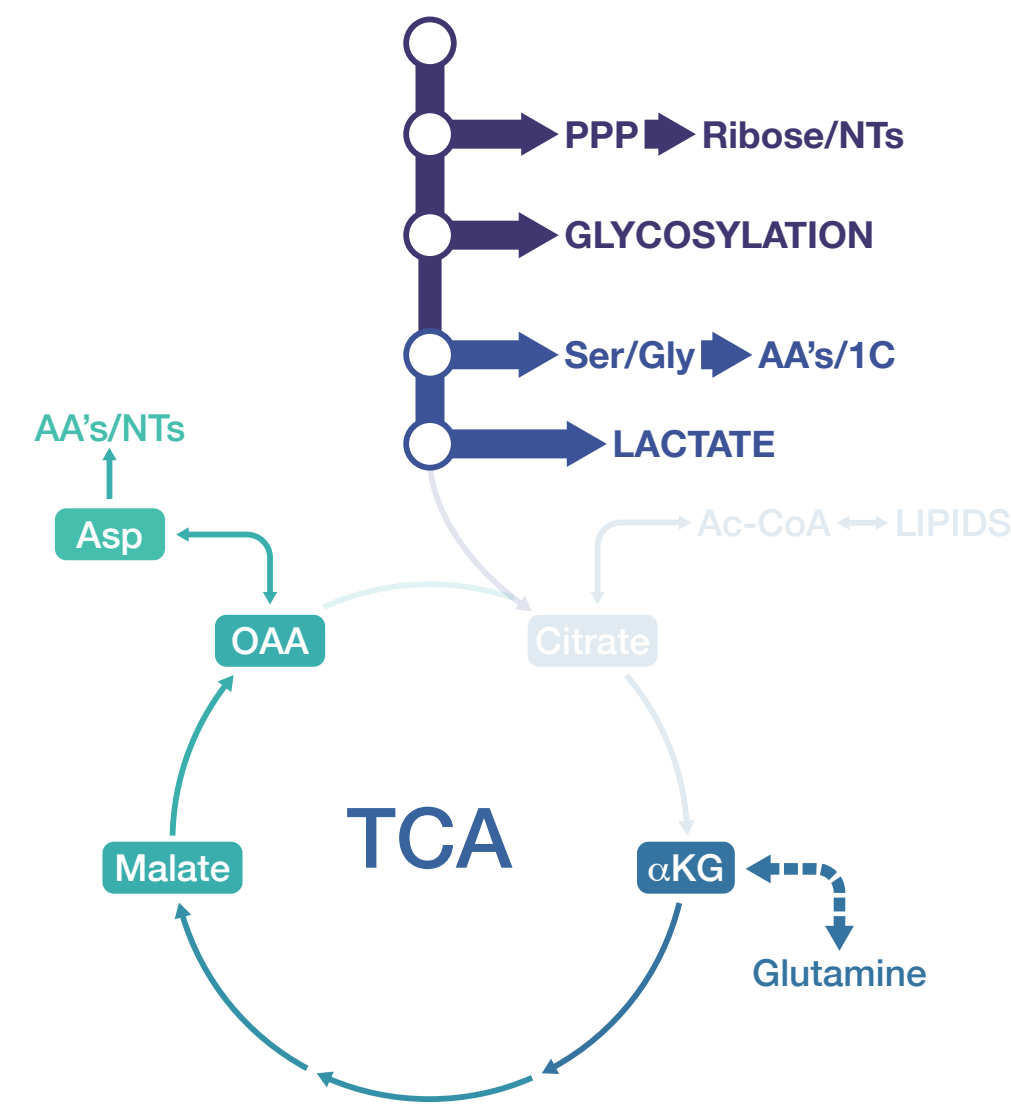
An understanding of the mechanism of the generation and control of biological energy may shed light on the problem of tumor growth

Cells rewire metabolic pathways to fulfill anabolic, catabolic and regulatory needs

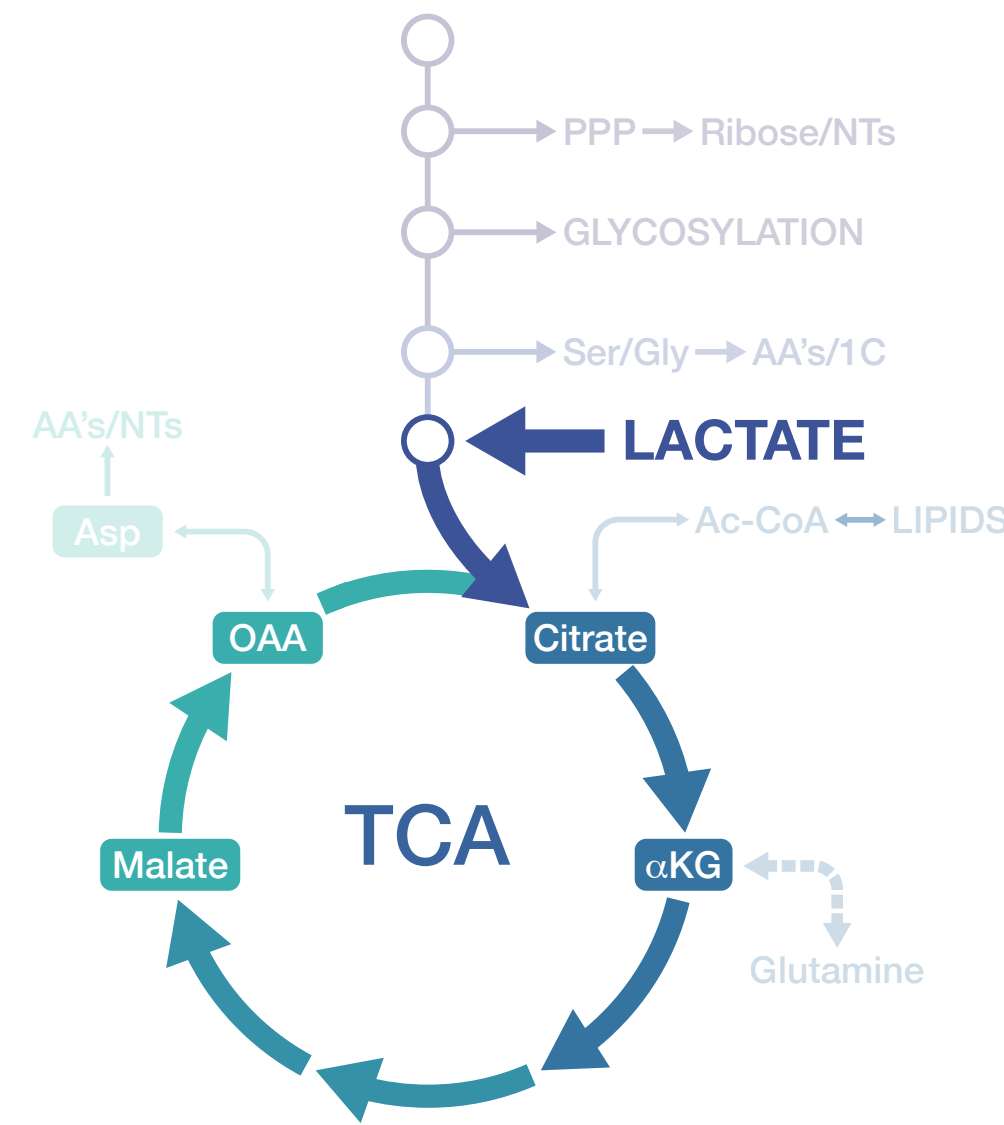
**Canonical Krebs Cycle
Oxidative Phosphorylation**
(e.g. muscle, neurons)



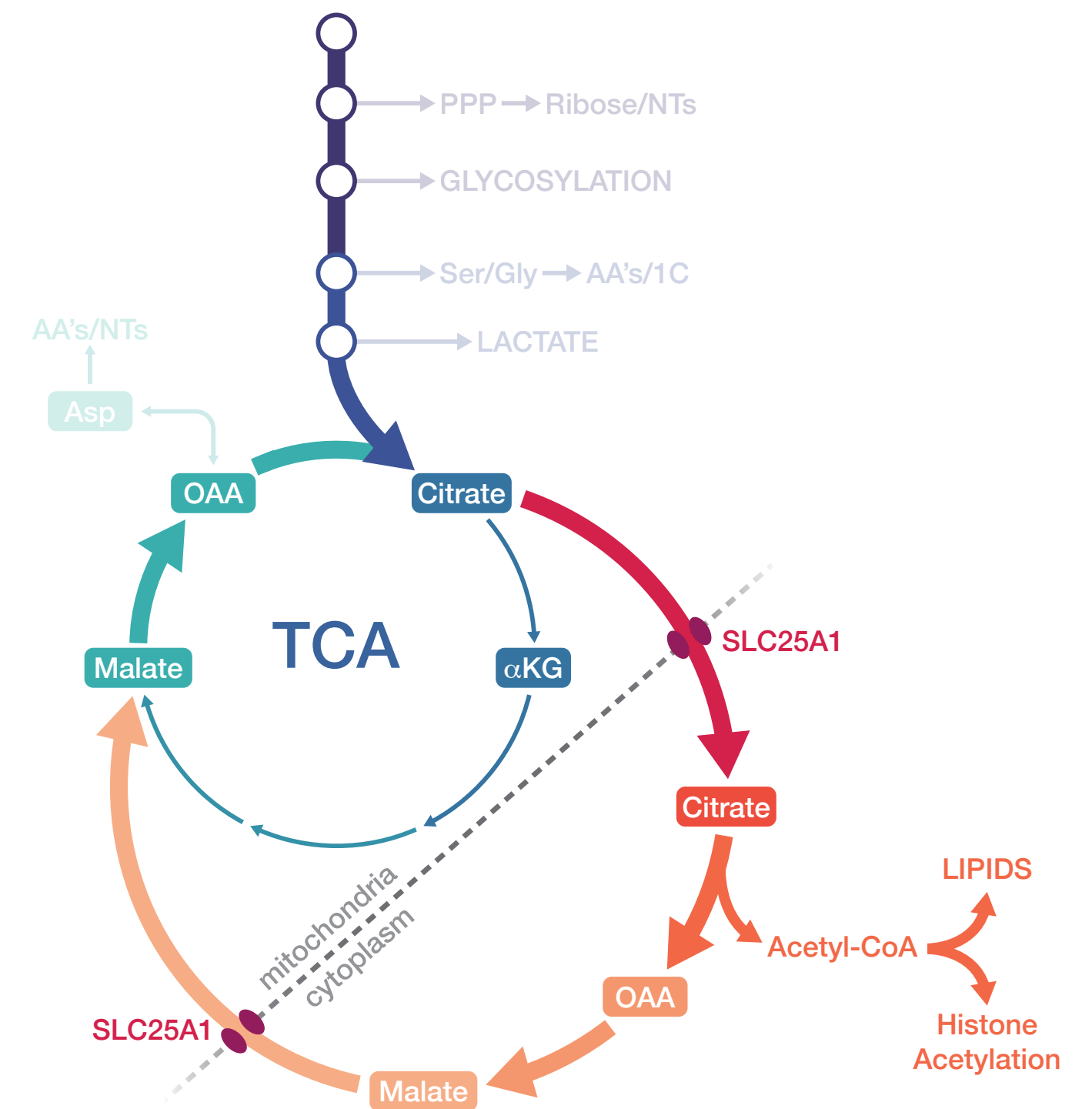
**Classic Warburg
Aerobic Glycolysis**
(e.g. highly glycolytic tumors)



**Lactate
Oxidation**
(e.g. cancer cells in normoxia, neurons)



**Non-Canonical
Krebs Cycle**
(e.g. ES cells, myoblasts)

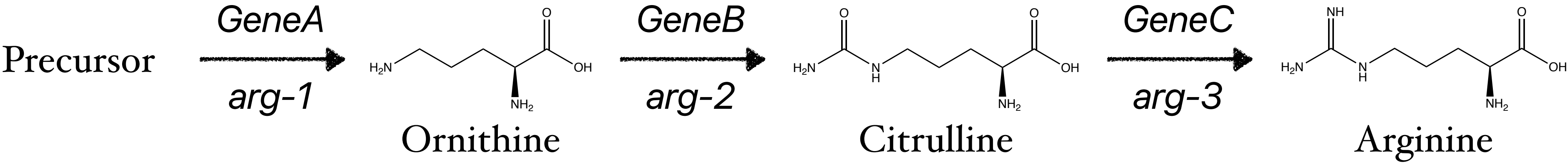
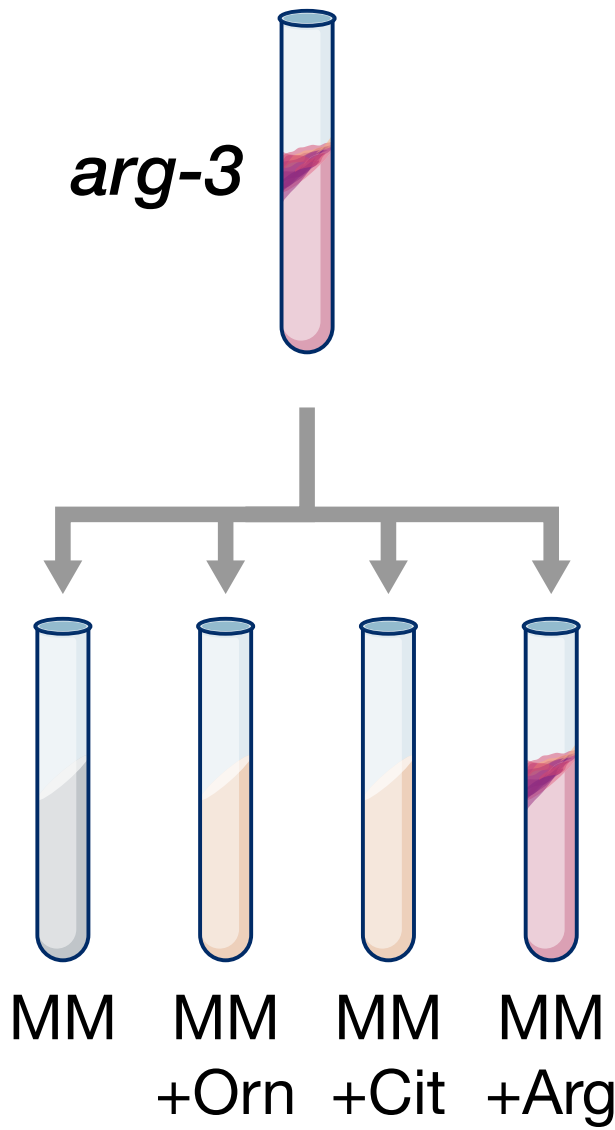
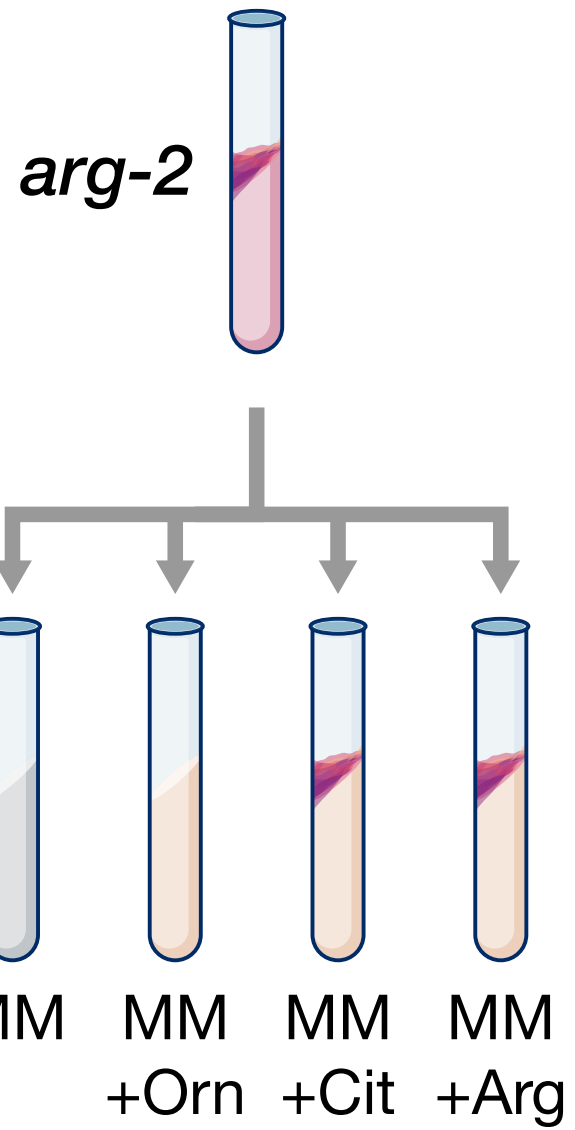
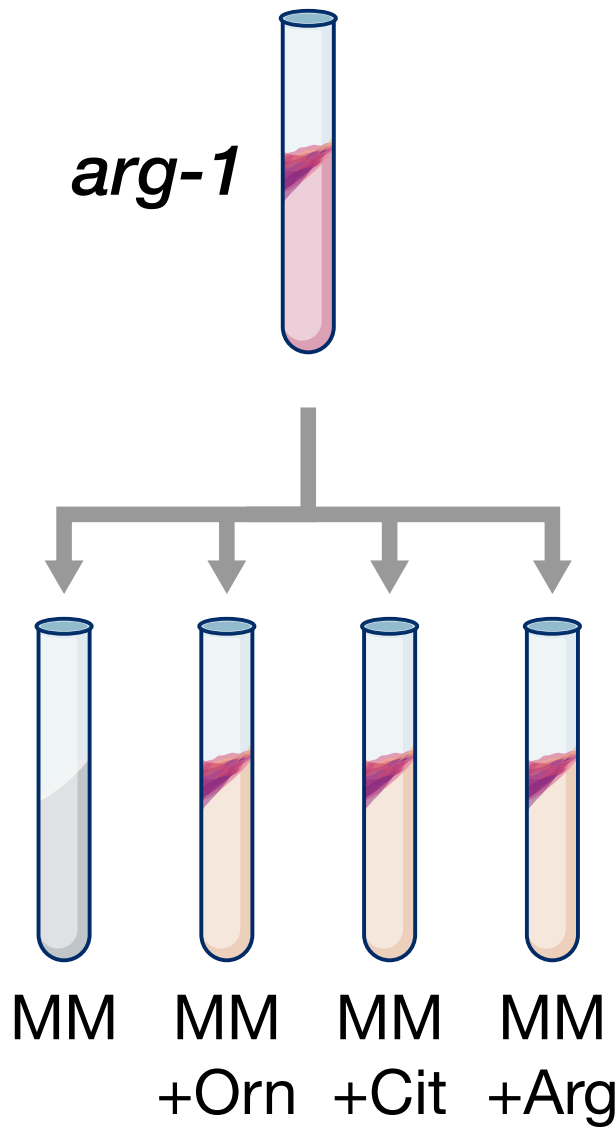
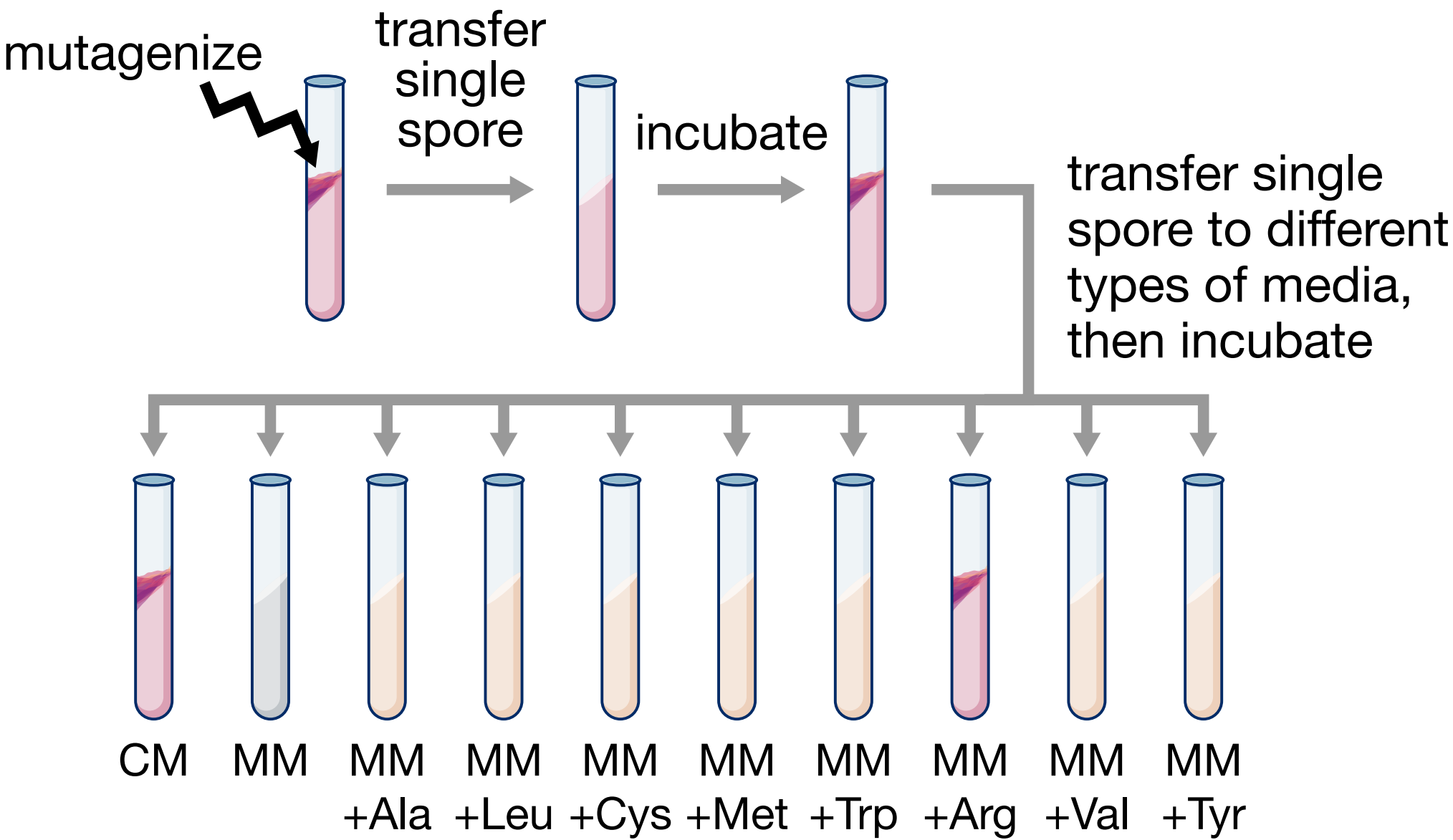


Takehome points 1

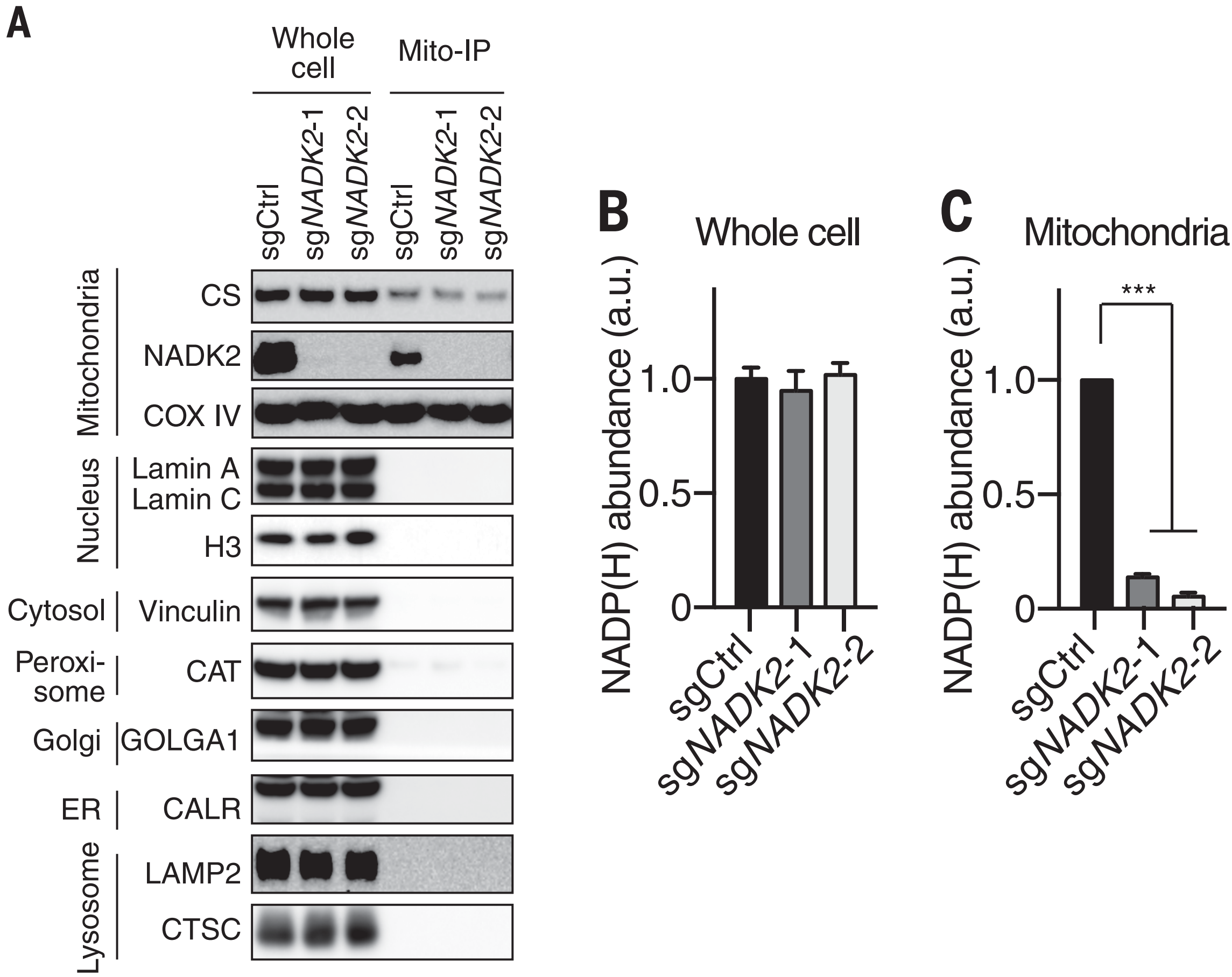
1. **Metabolic flux is malleable (many ways to make a product)**
2. **Metabolism is not ALWAYS about energy**
3. **Growth (anabolic metabolism) requires SUBSTRATES >>> ENERGY**
4. **Cells (and organisms) rewire their metabolism to suit their needs**

**METABOLISM AFFECTS ALL CELLULAR PROCESSES... BUT
HOW DO WE FIND OUT WHICH METABOLITES INFLUENCE
SPECIFIC PROCESSES AND HOW?**

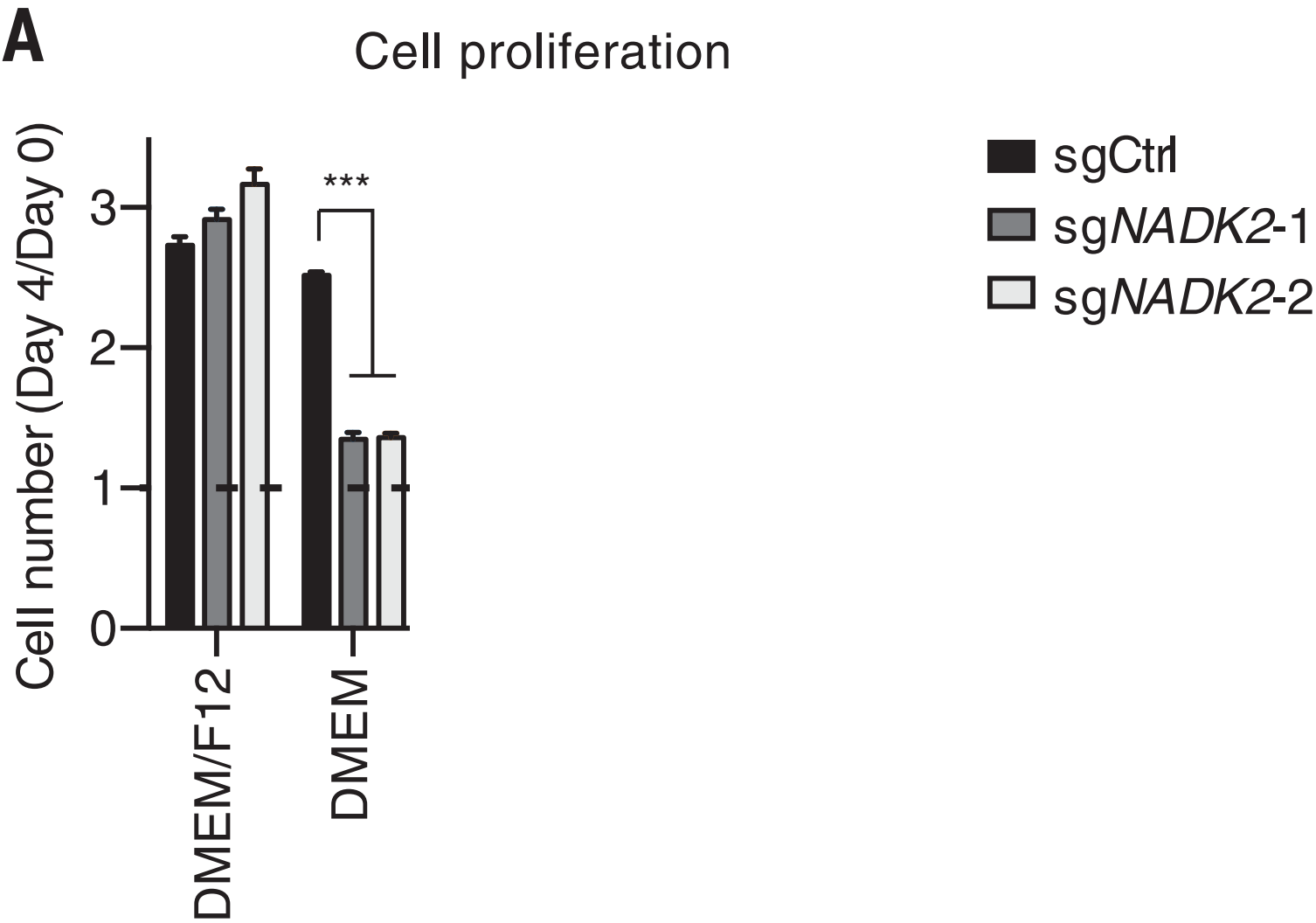
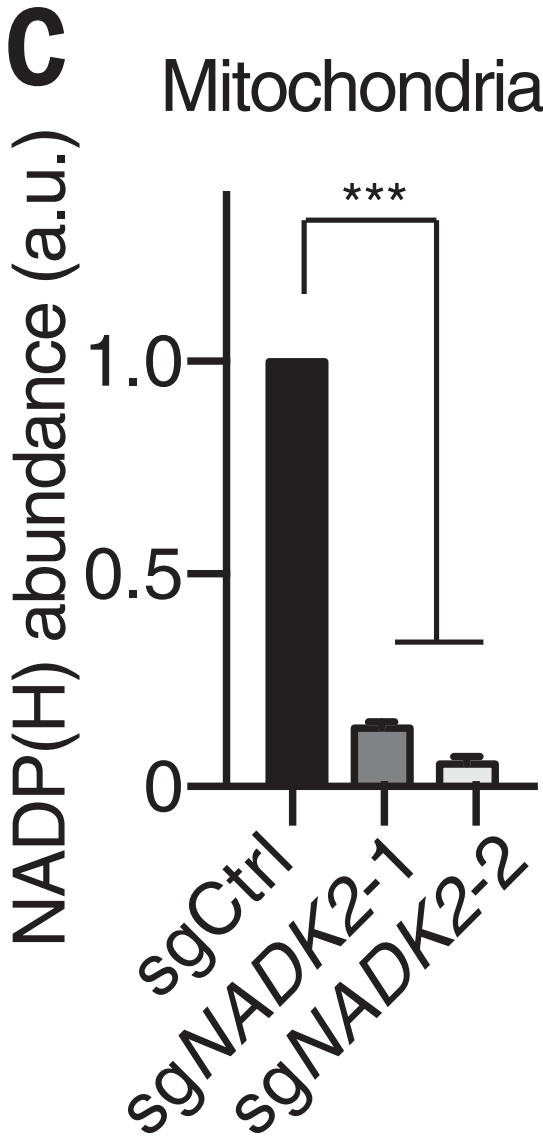
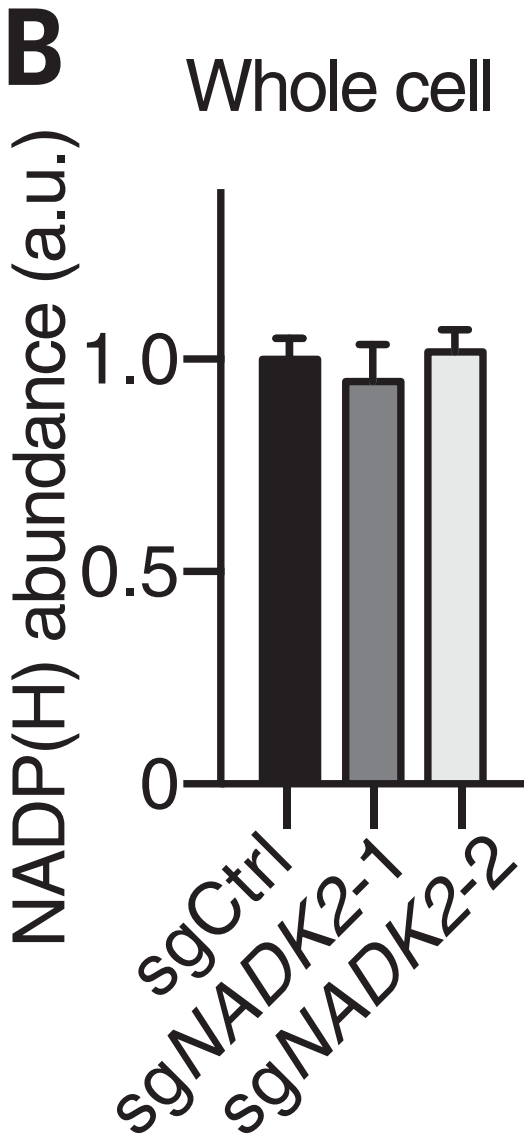
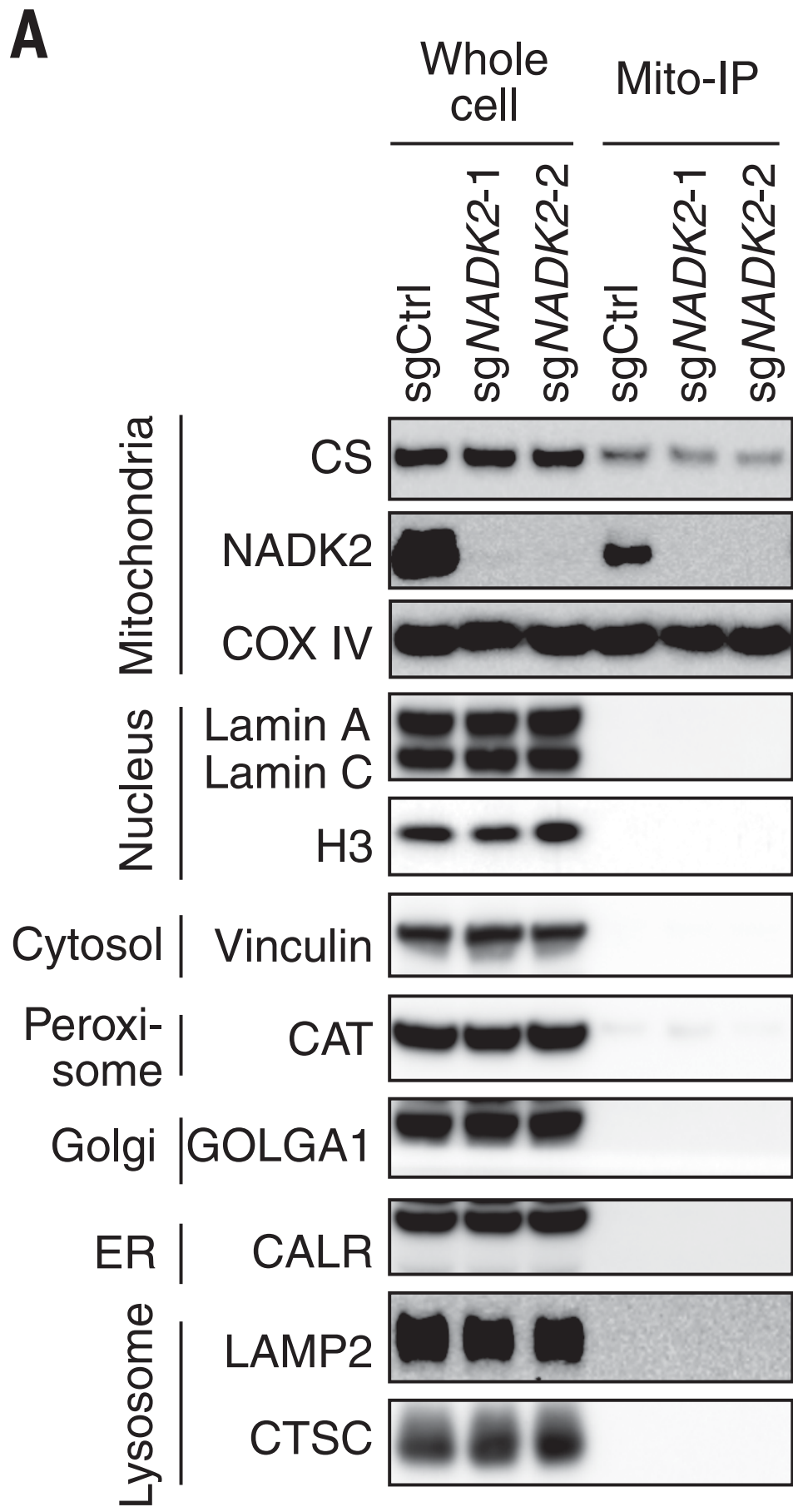
Auxotrophs & Prototrophs: the genetics of biochemistry



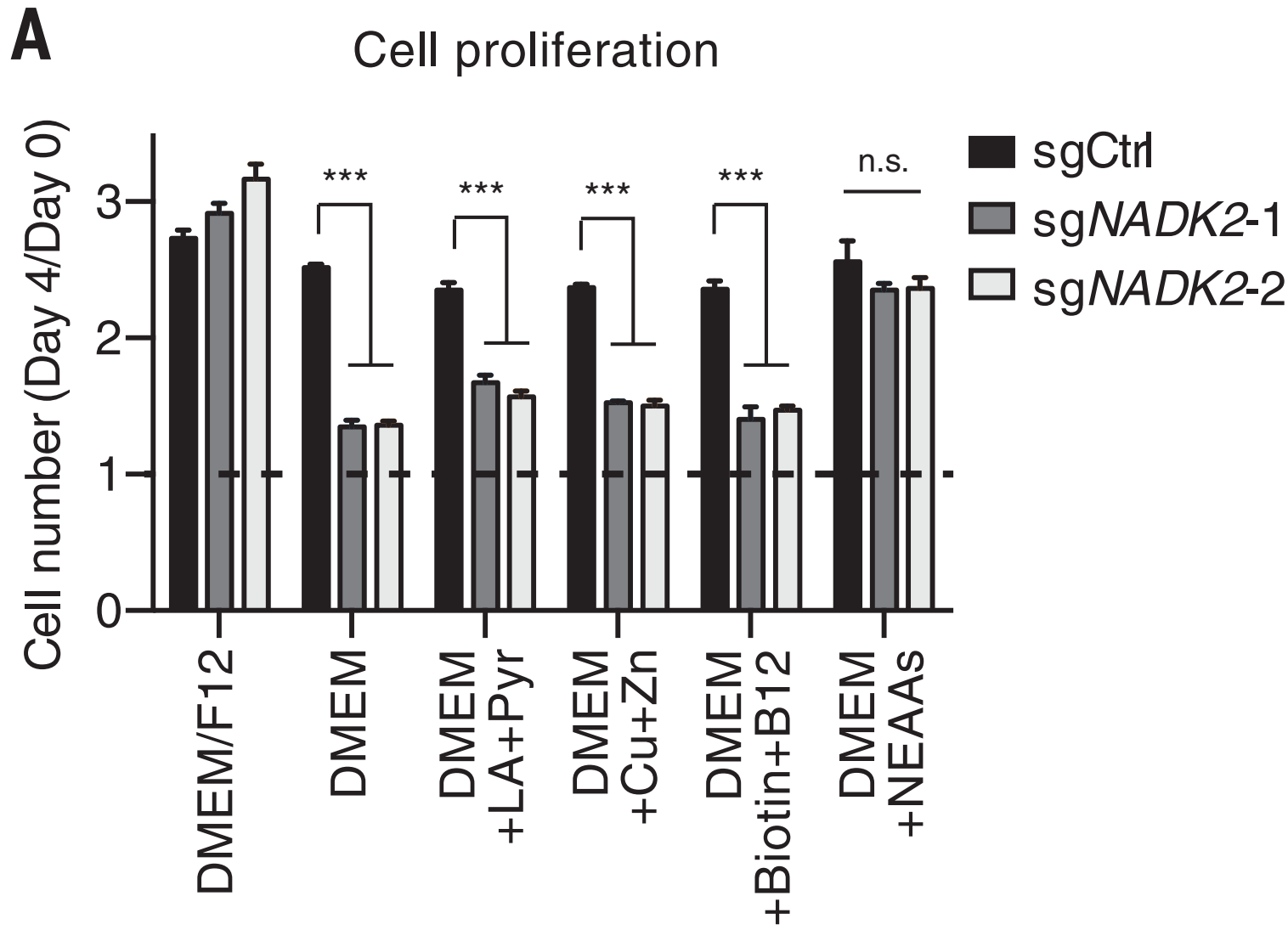
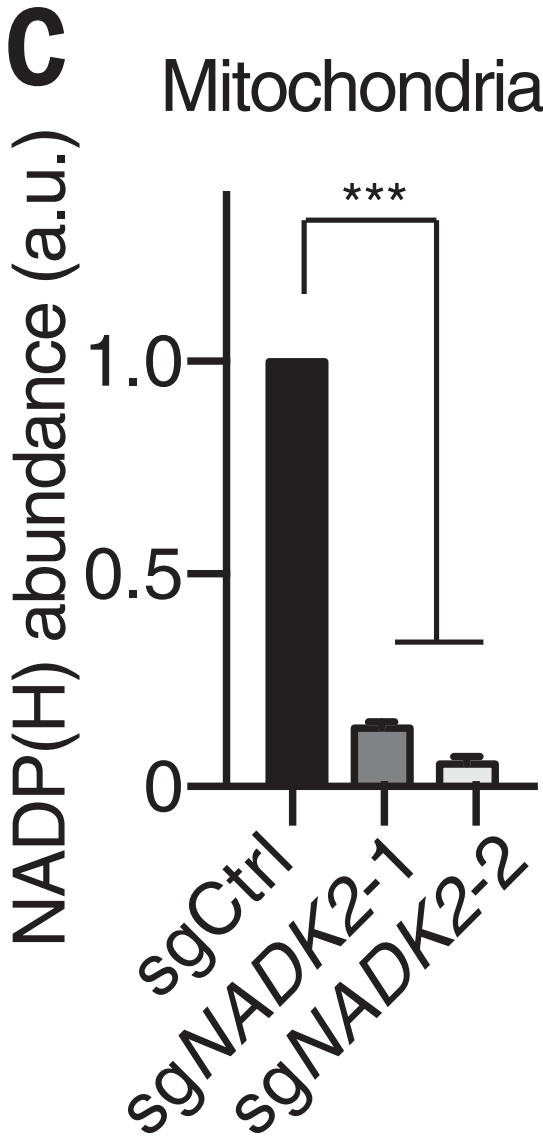
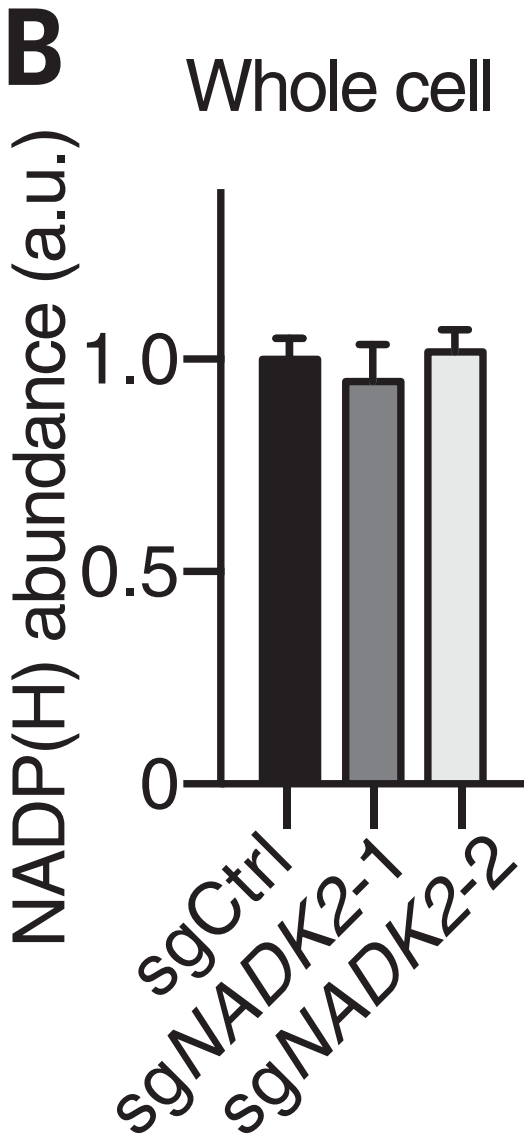
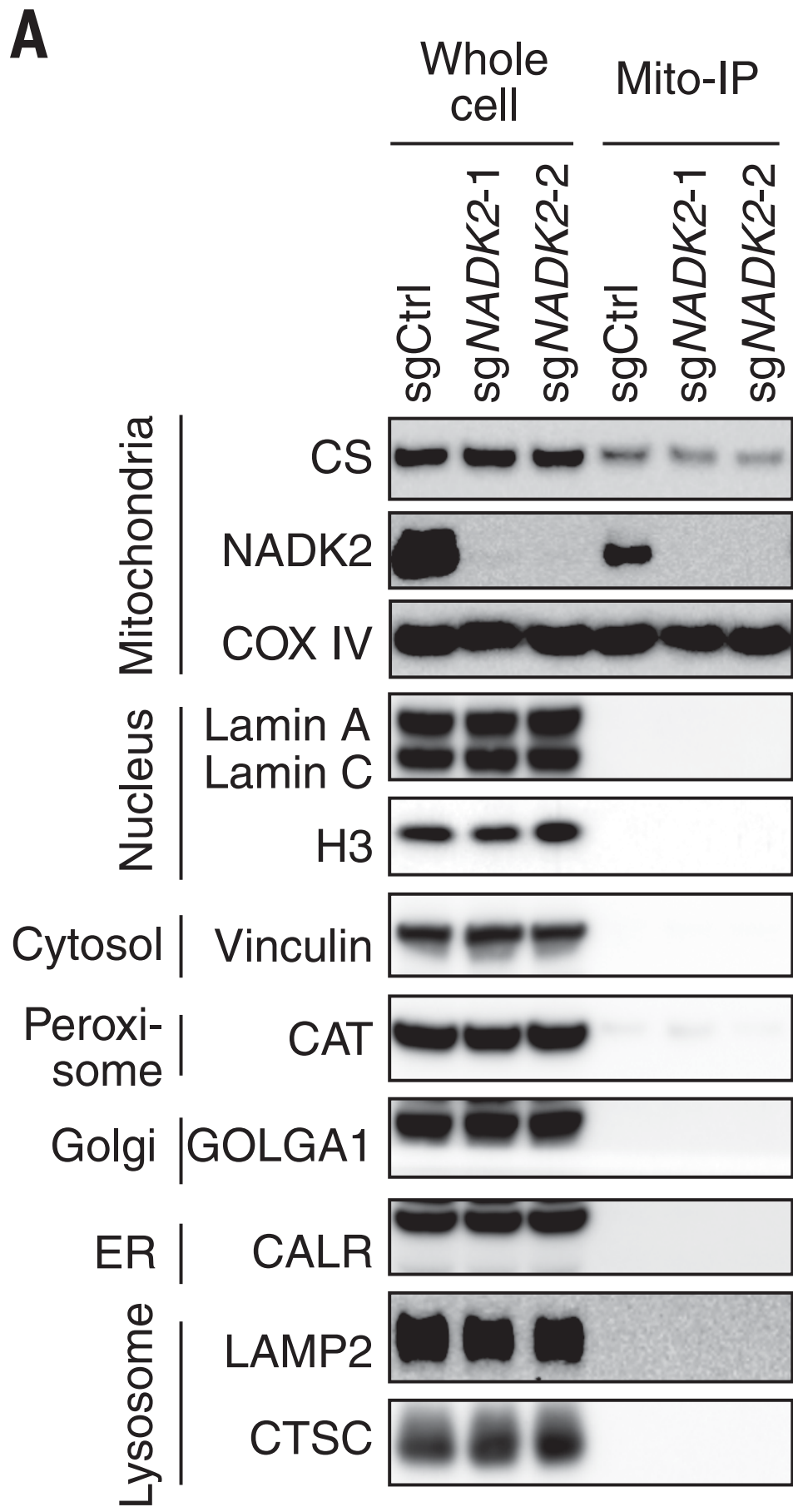
Auxotrophs are a powerful tool to study metabolic pathways



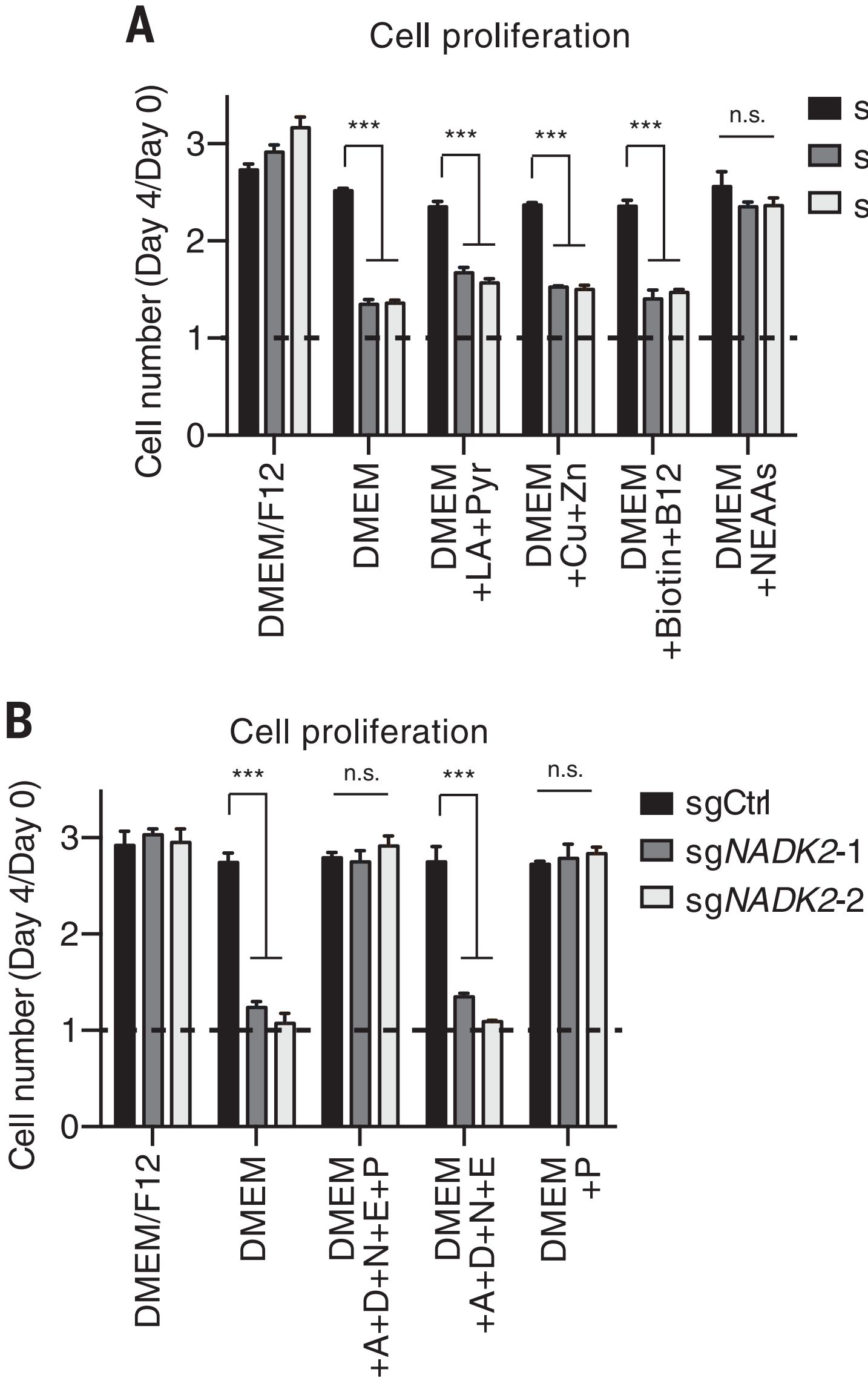
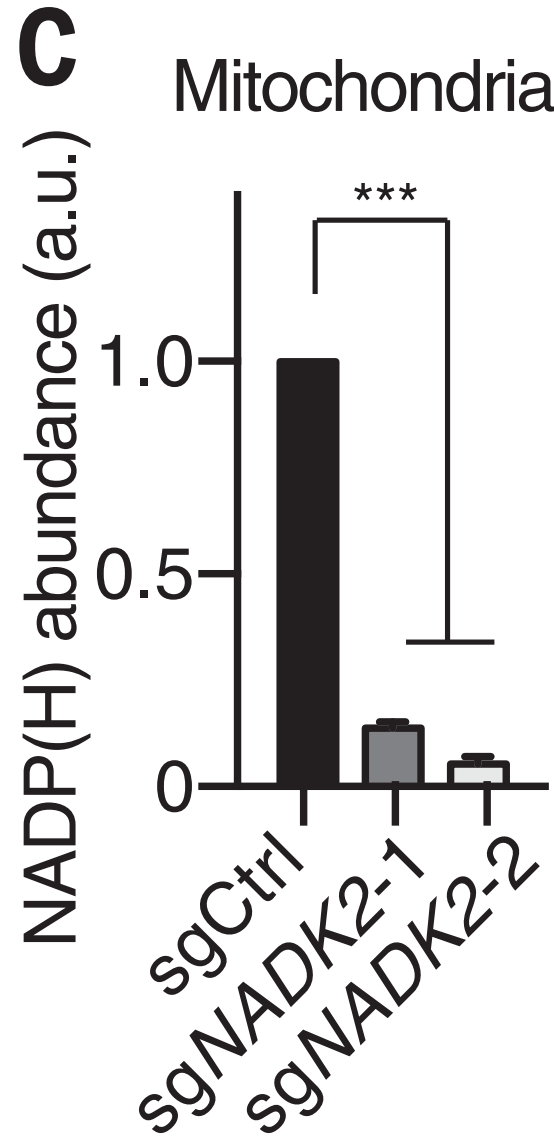
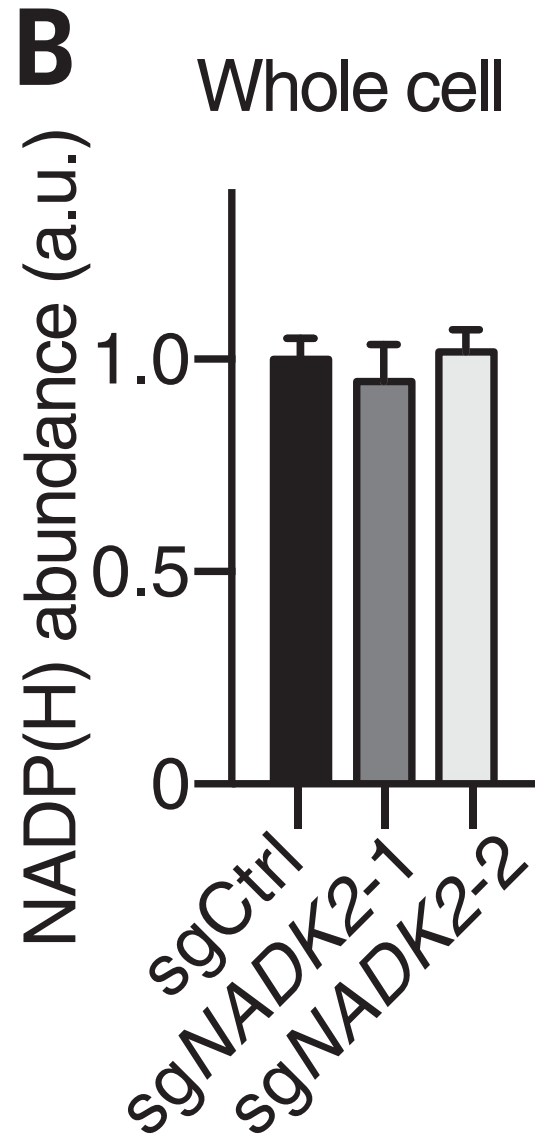
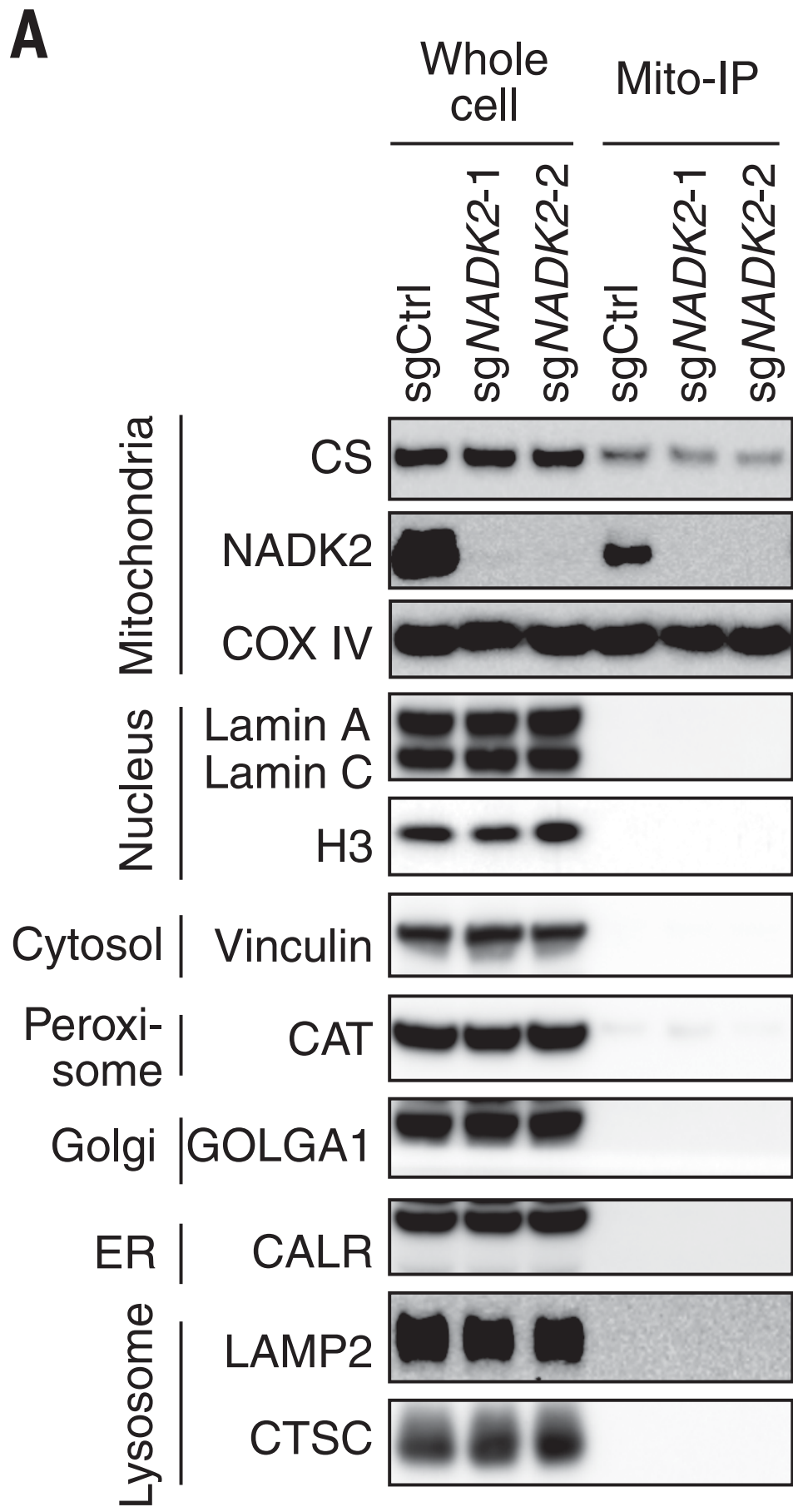
Auxotrophs are a powerful tool to study metabolic pathways



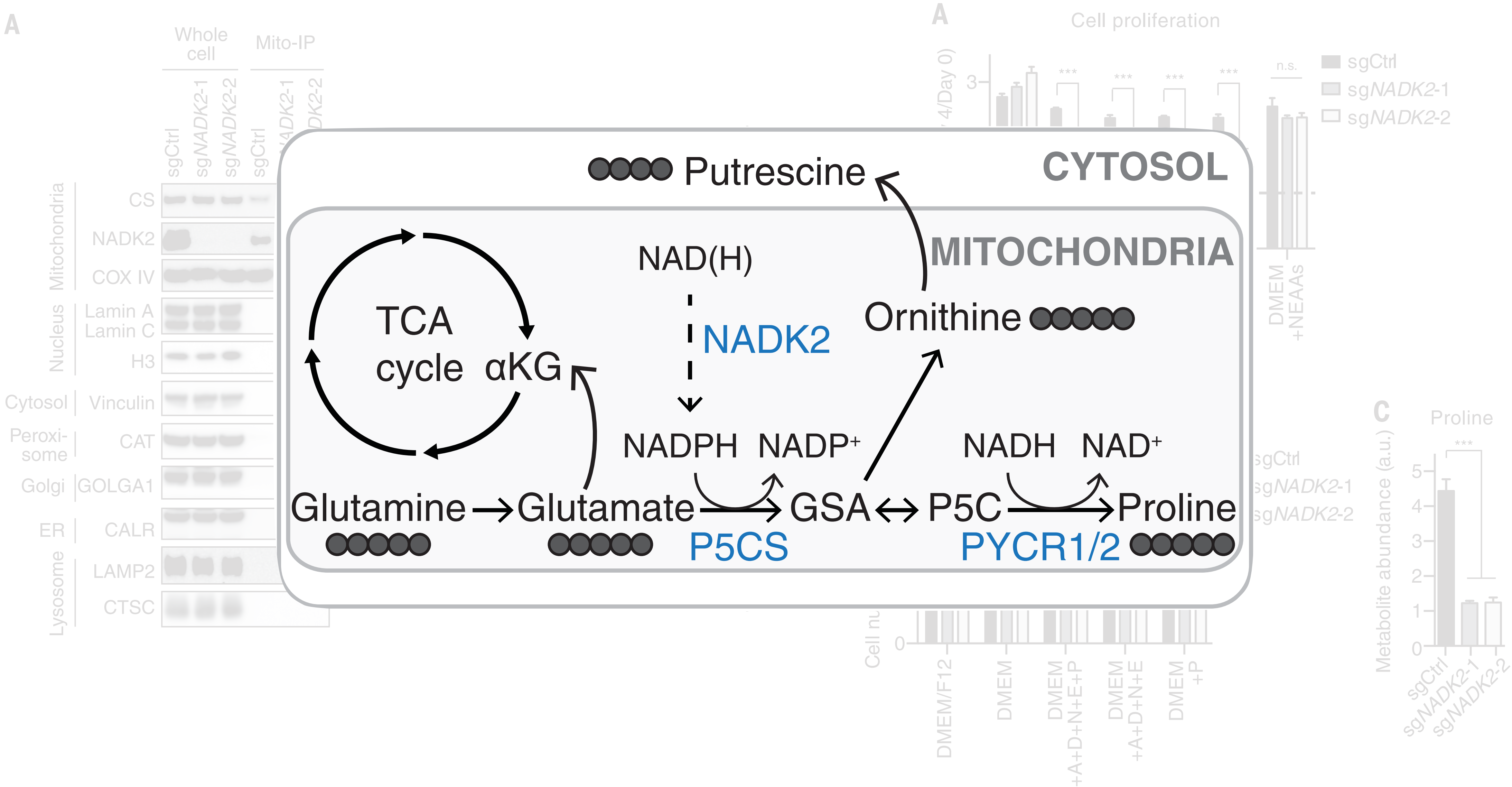
Auxotrophs are a powerful tool to study metabolic pathways



Auxotrophs are a powerful tool to study metabolic pathways

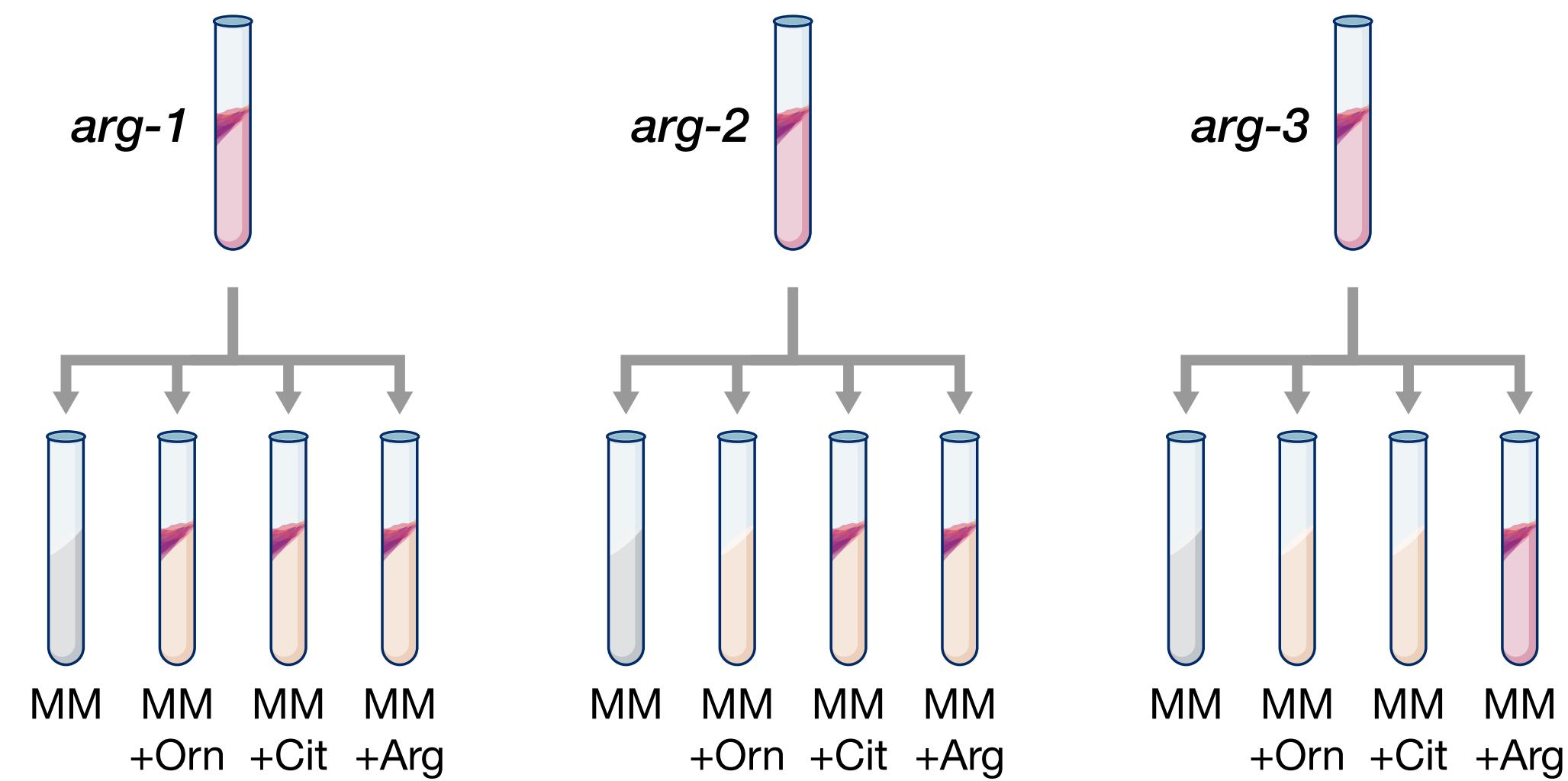


Auxotrophs are a powerful tool to study metabolic pathways



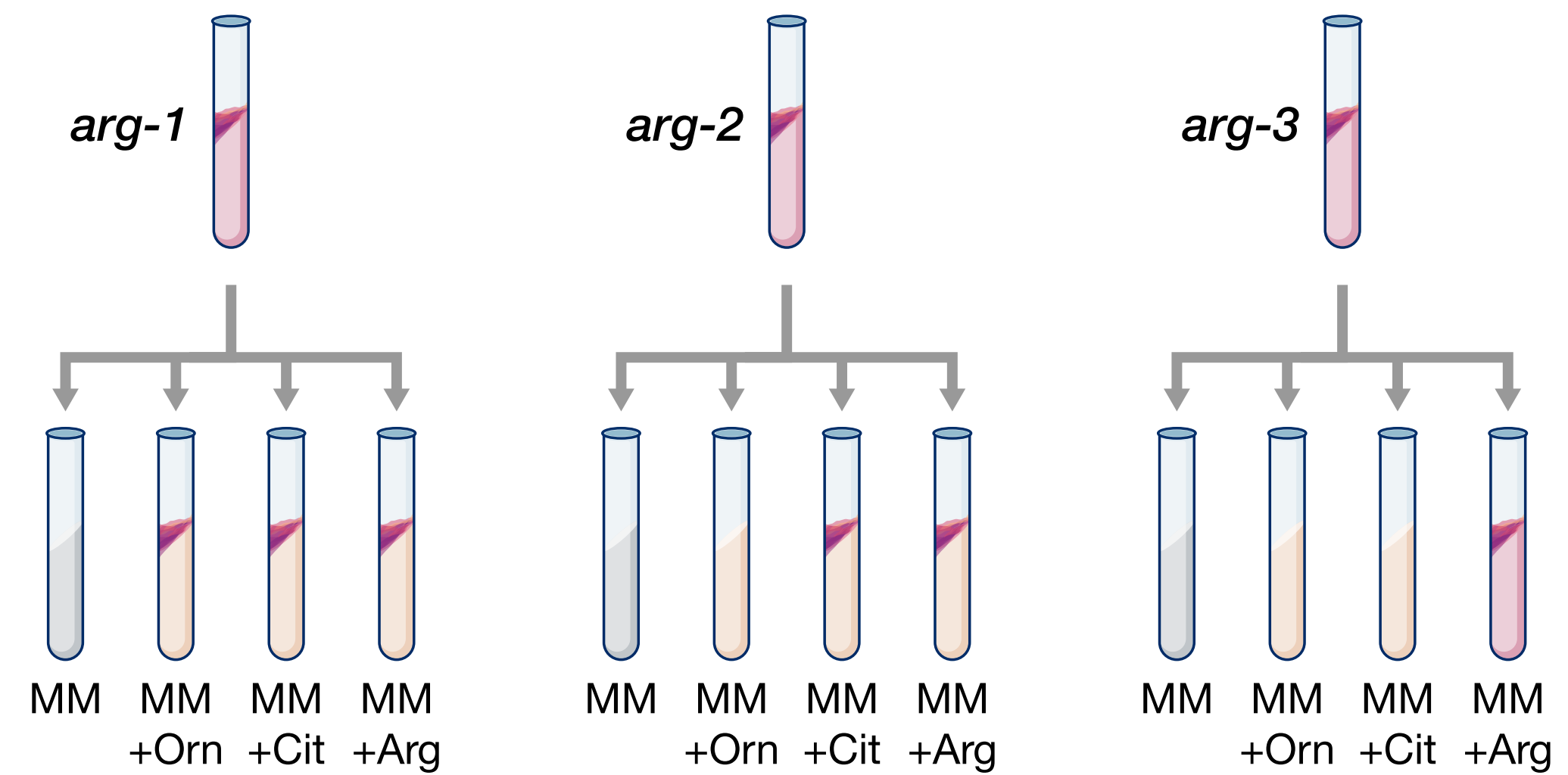
What about screens? (1)

SINGLE CELL CLONES (1941)



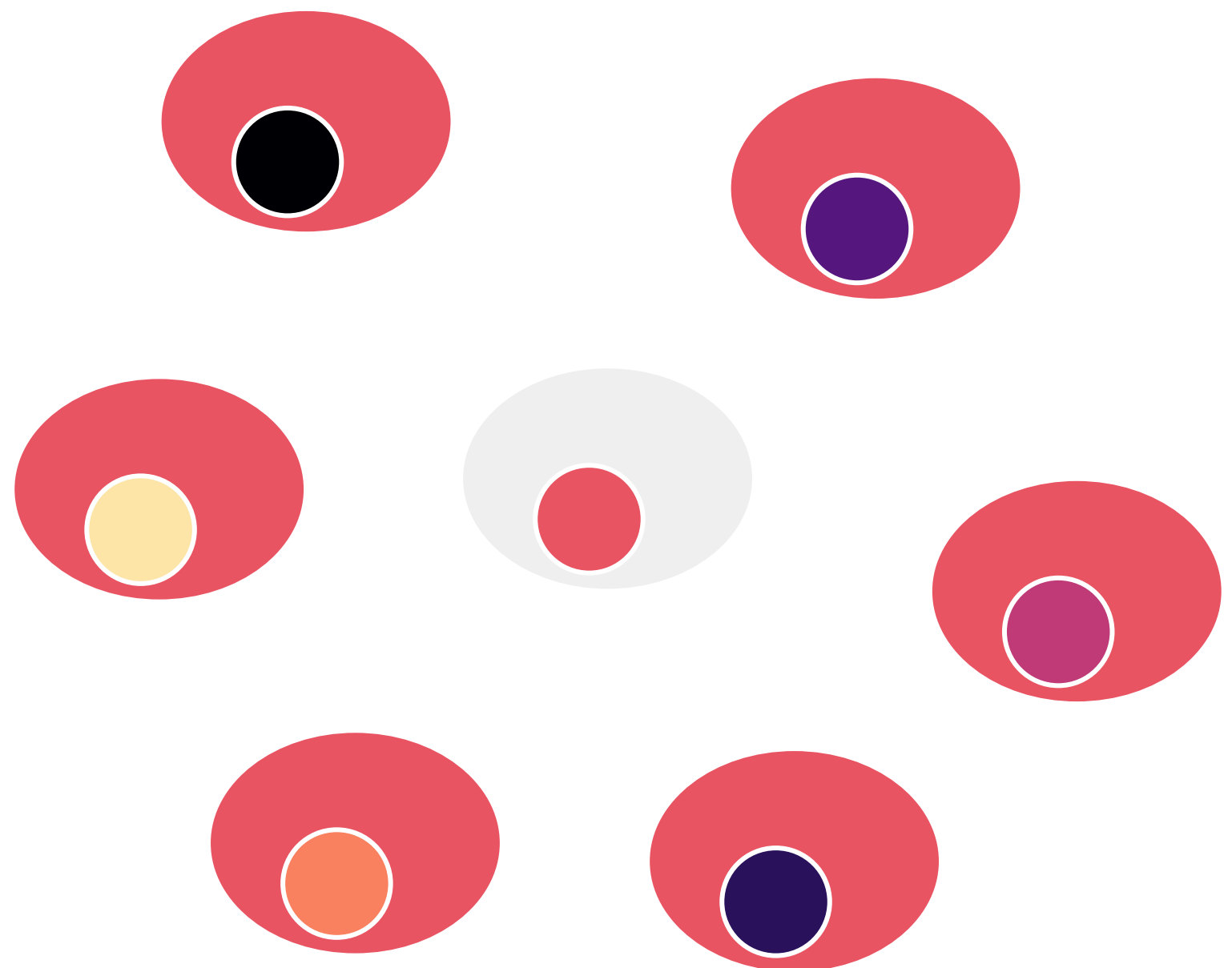
What about screens? (1)

SINGLE CELL CLONES (1941)



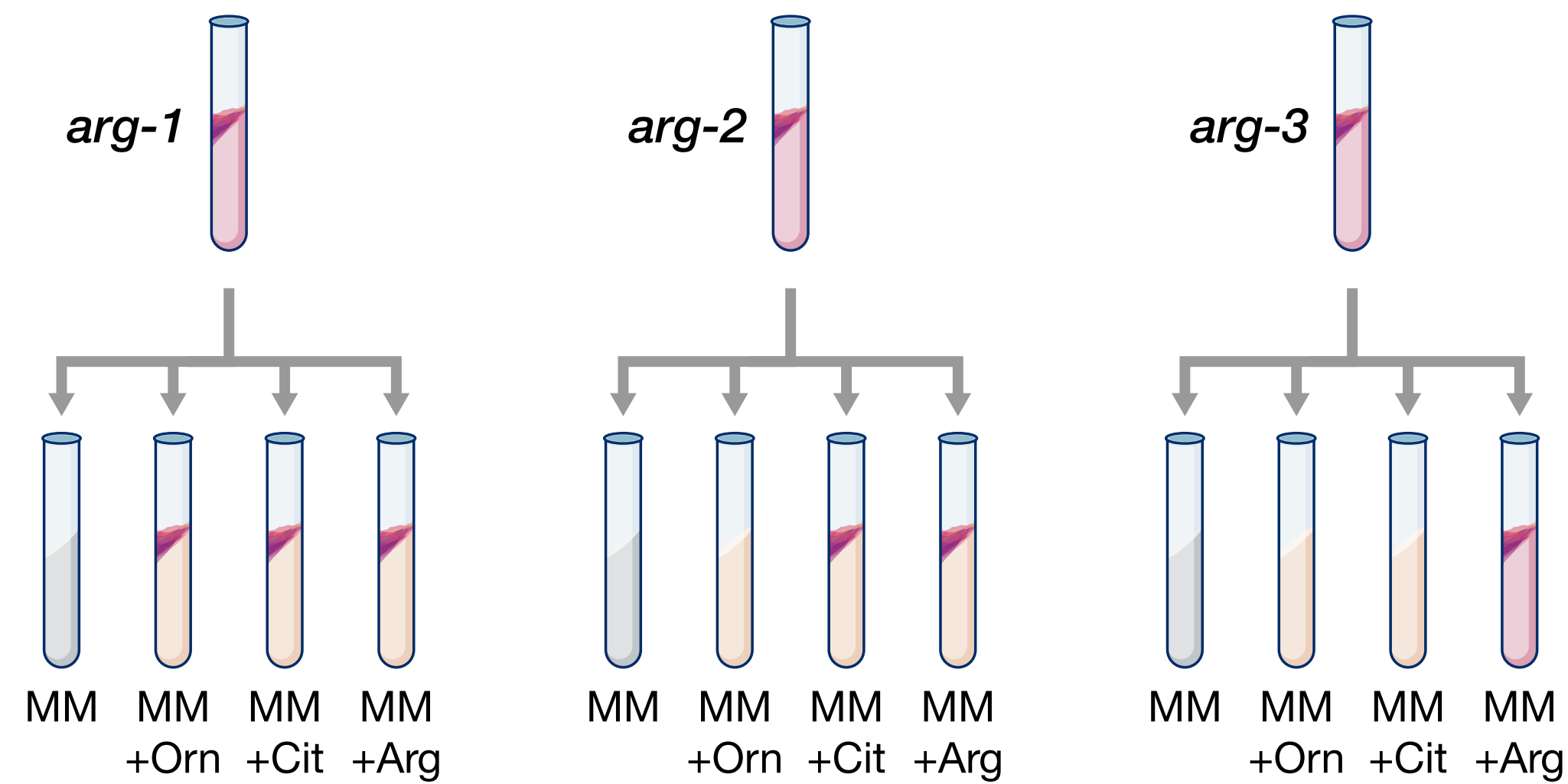
VS

POOLED LIBRARIES (2025)



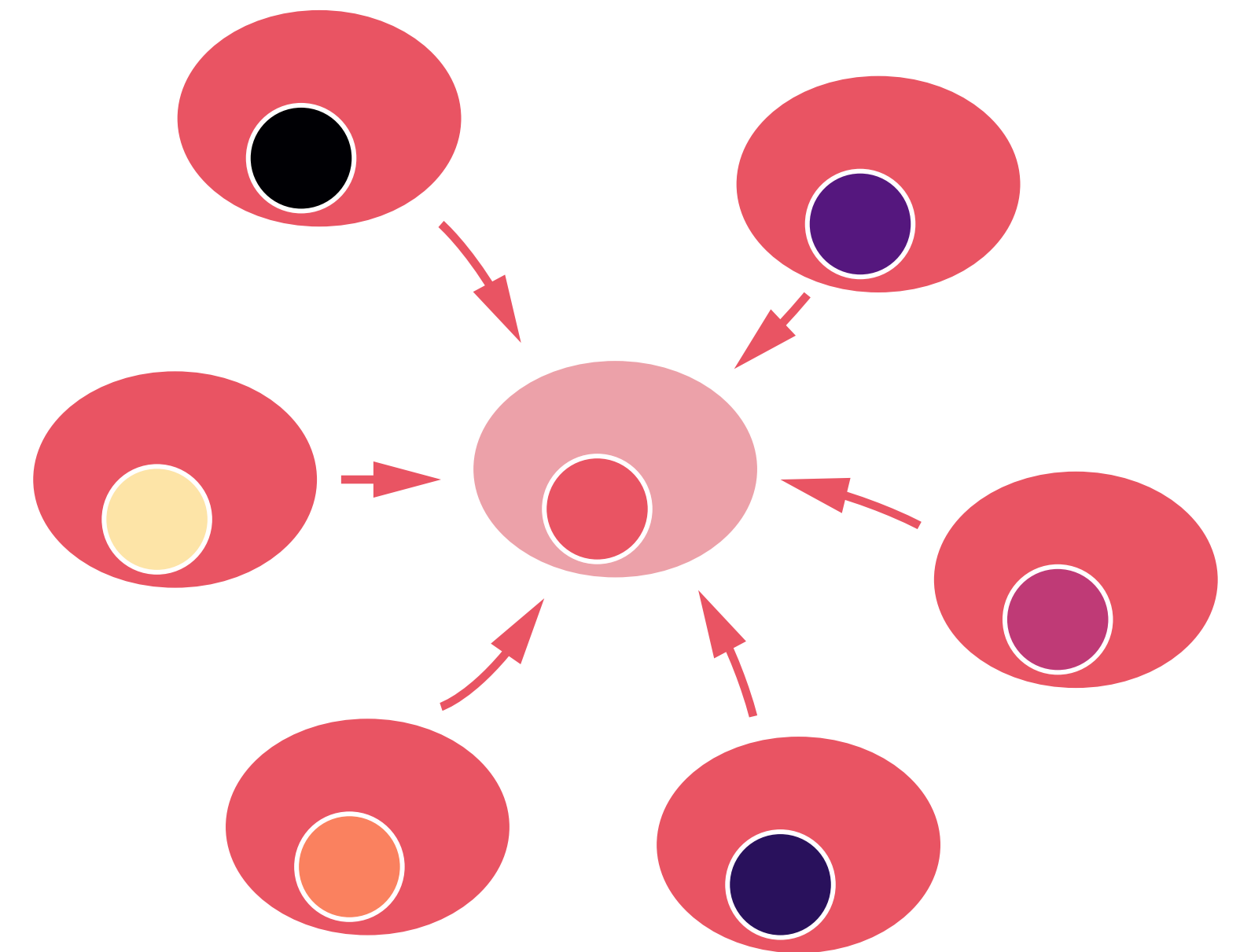
What about screens? (1)

SINGLE CELL CLONES (1941)



POOLED LIBRARIES (2025)

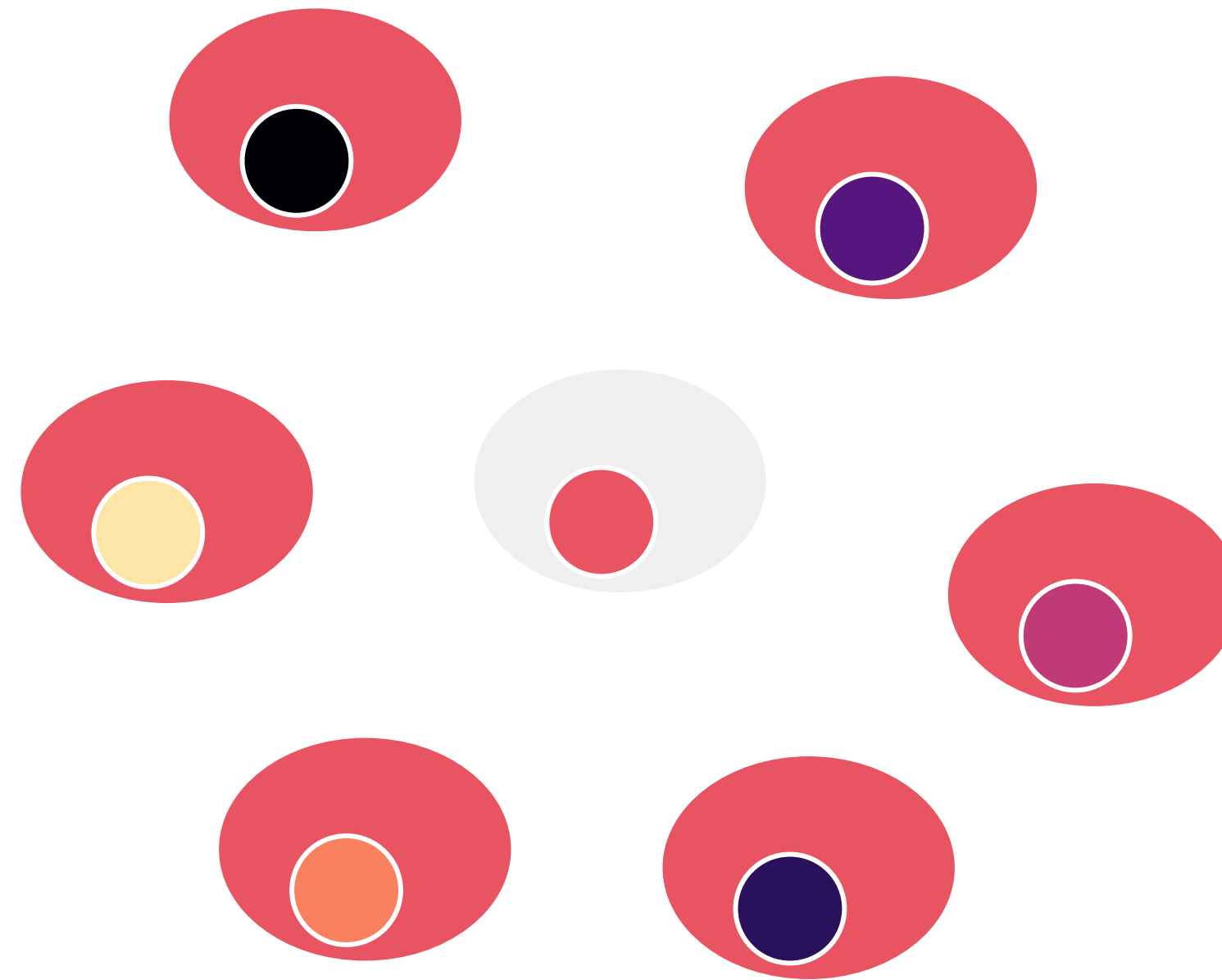
VS



NEIGHBORS CAN RESCUE

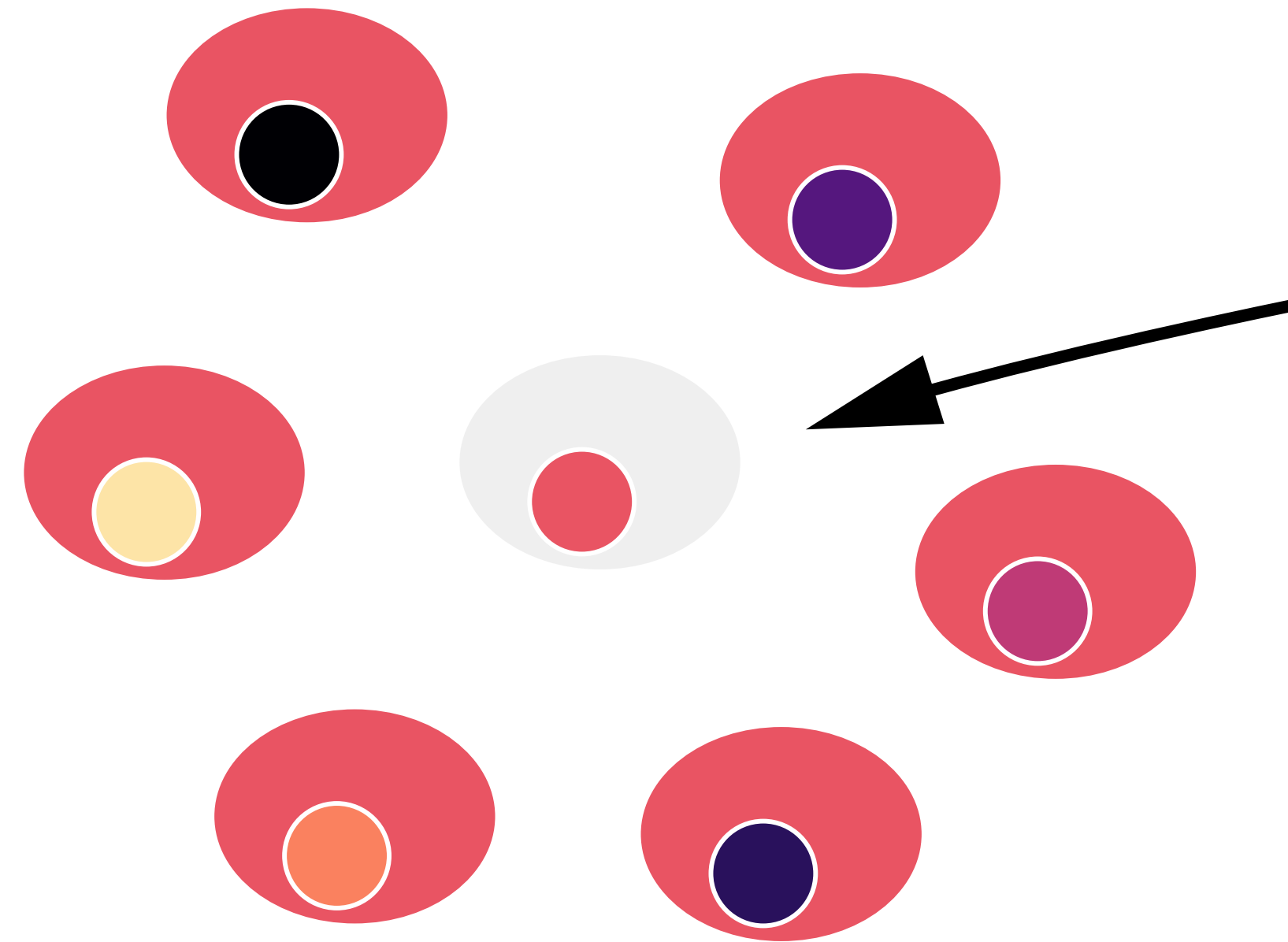
What about screens? (2)

POOLED
LIBRARIES



What about screens? (2)

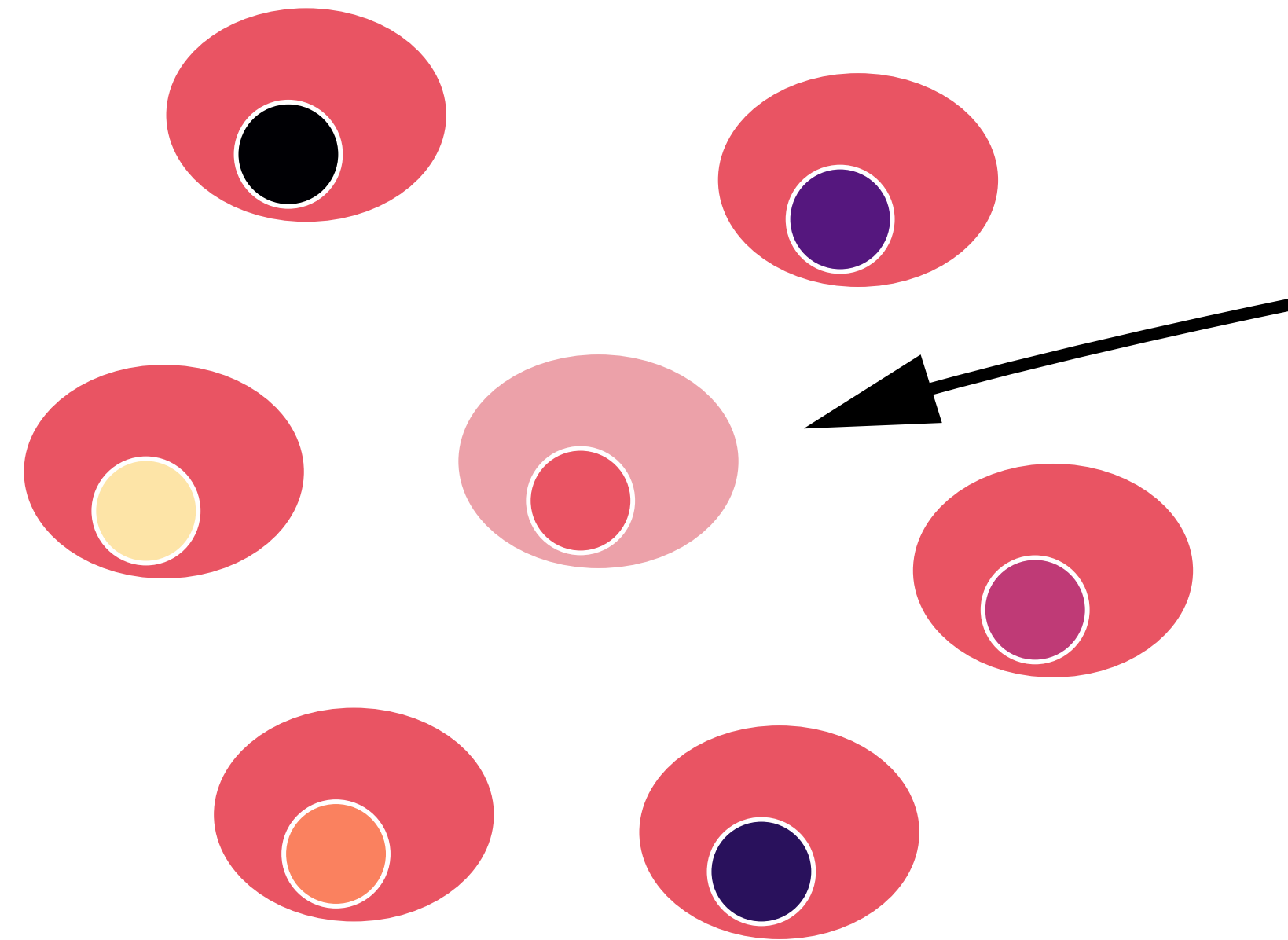
POOLED
LIBRARIES



What about screens? (2)

**SERUM
METABOLITES
CAN RESCUE**

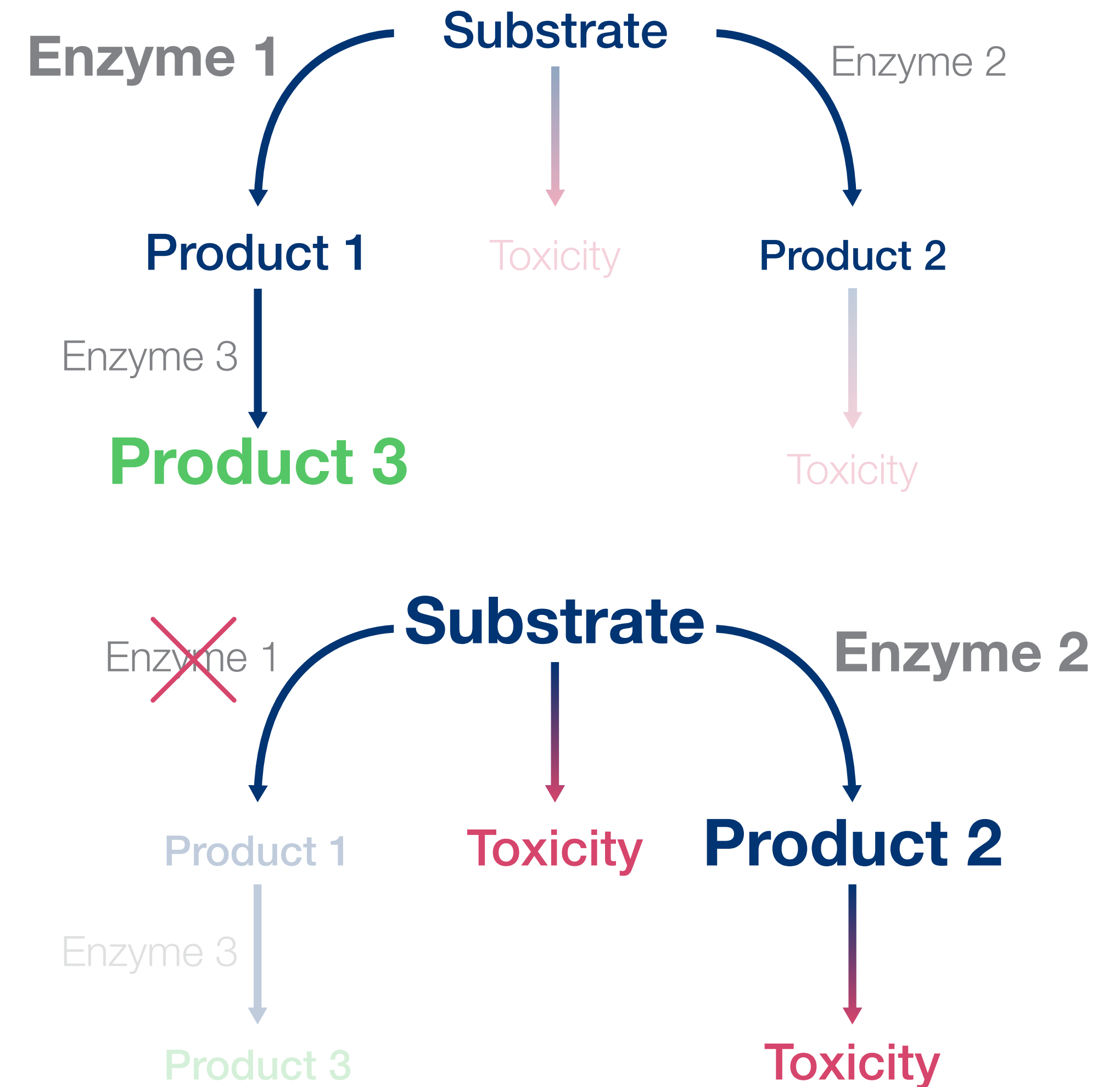
**POOLED
LIBRARIES**



Inborn errors of metabolism (IEMs): a window in to what matters and where

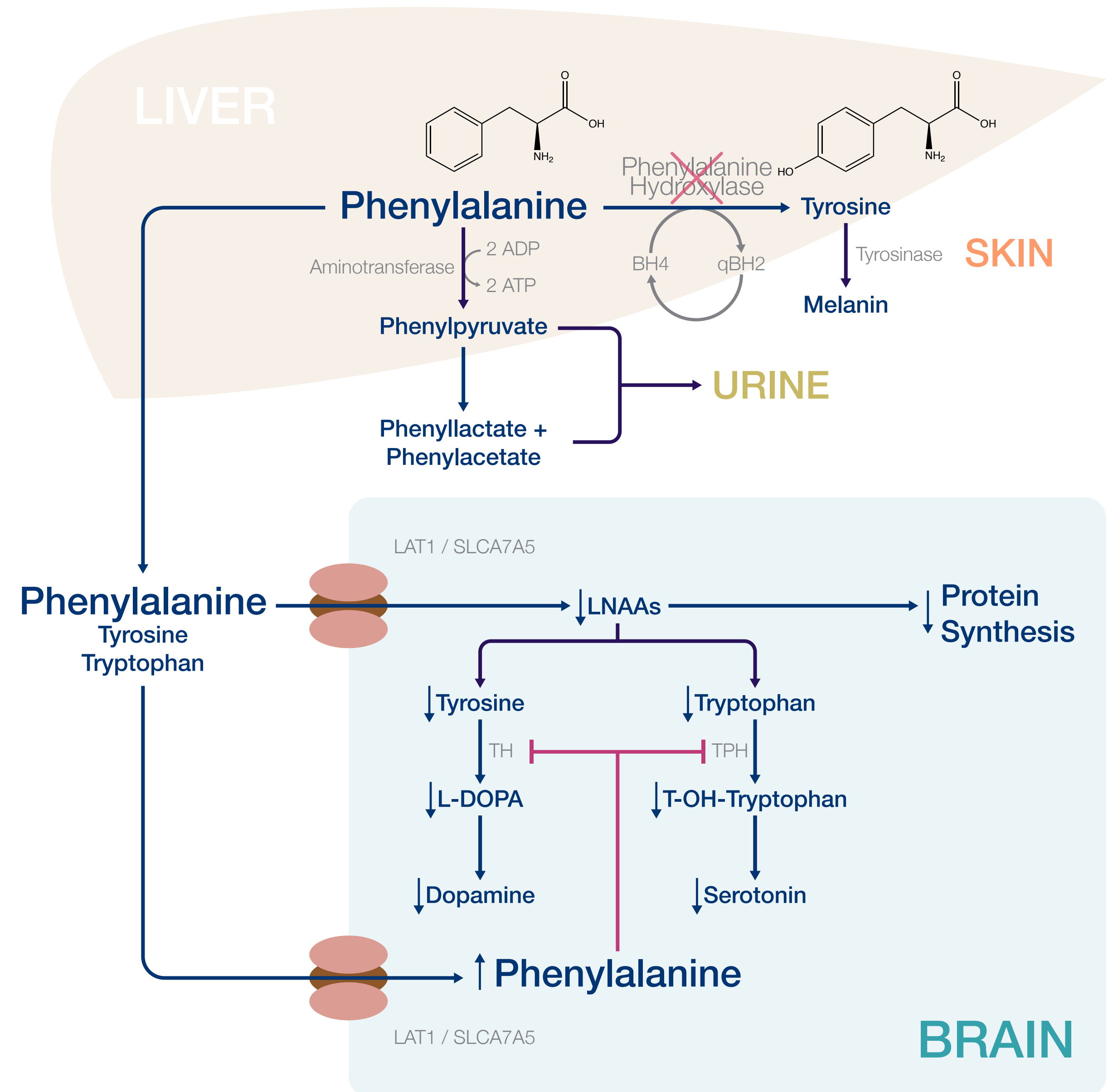
Inborn errors of metabolism (IEMs): a genetic aberration that disrupts a single metabolic pathway

1. End-product depletion
2. Substrate accumulation
3. Activation of alternative pathways producing toxic by-products
4. A combination of the above



Phenylketonuria

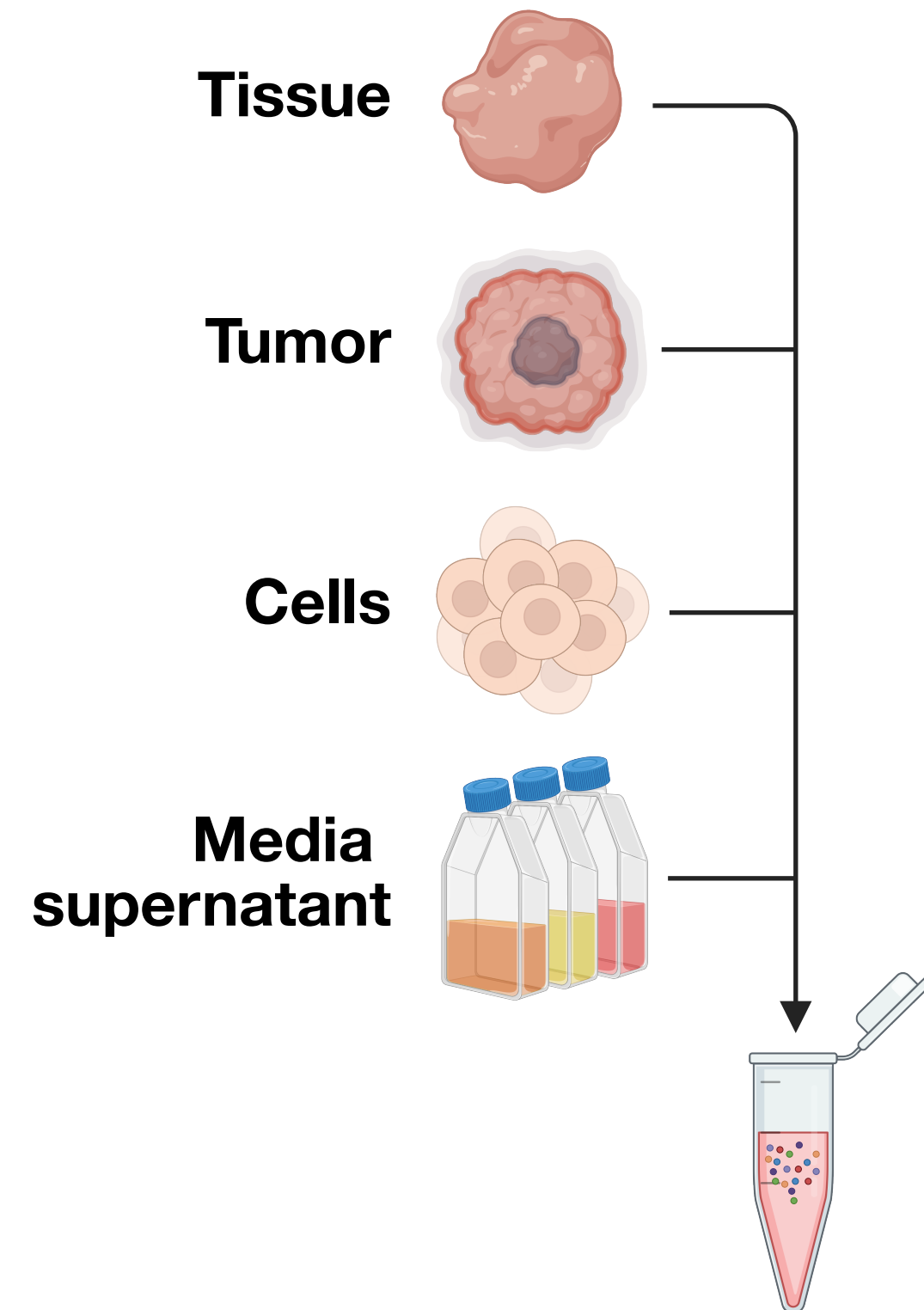
1. Deficiency of **Phenylalanine Hydroxylase** from mutations in *PAH*
2. Inheritance: **autosomal recessive**
3. $\uparrow\uparrow\uparrow$ levels of dietary **phenylalanine** in plasma
4. Clinical features:
 - **CNS**: intellectual disability, seizures, behavioral problems
 - **Urine**: musty smell (breakdown products)
 - **Skin**: decreased melanin
5. Treatment: dietary phenylalanine avoidance



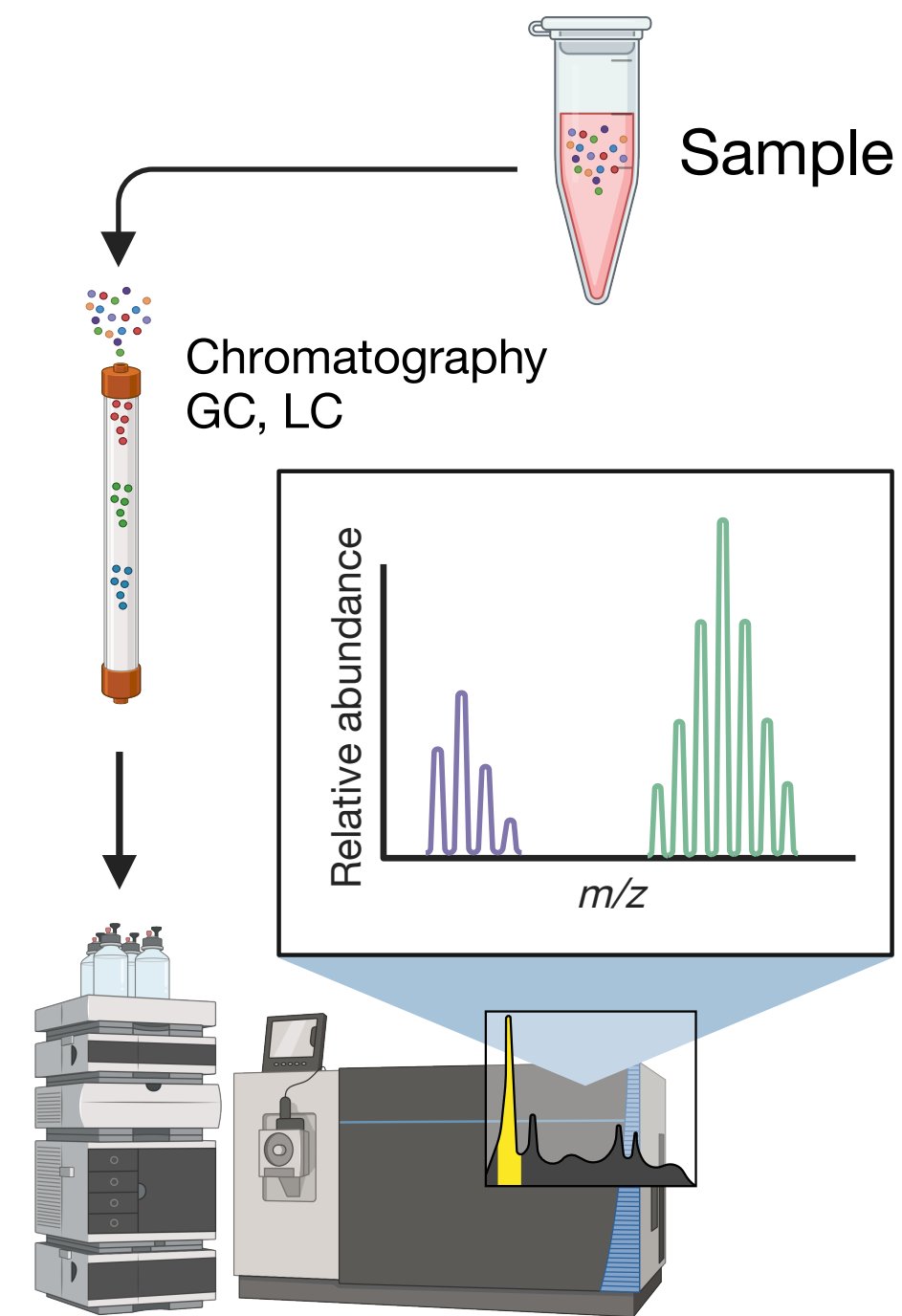
Measuring Metabolism

Bulk metabolomics (GC or LC/MS)

1 Sample collection

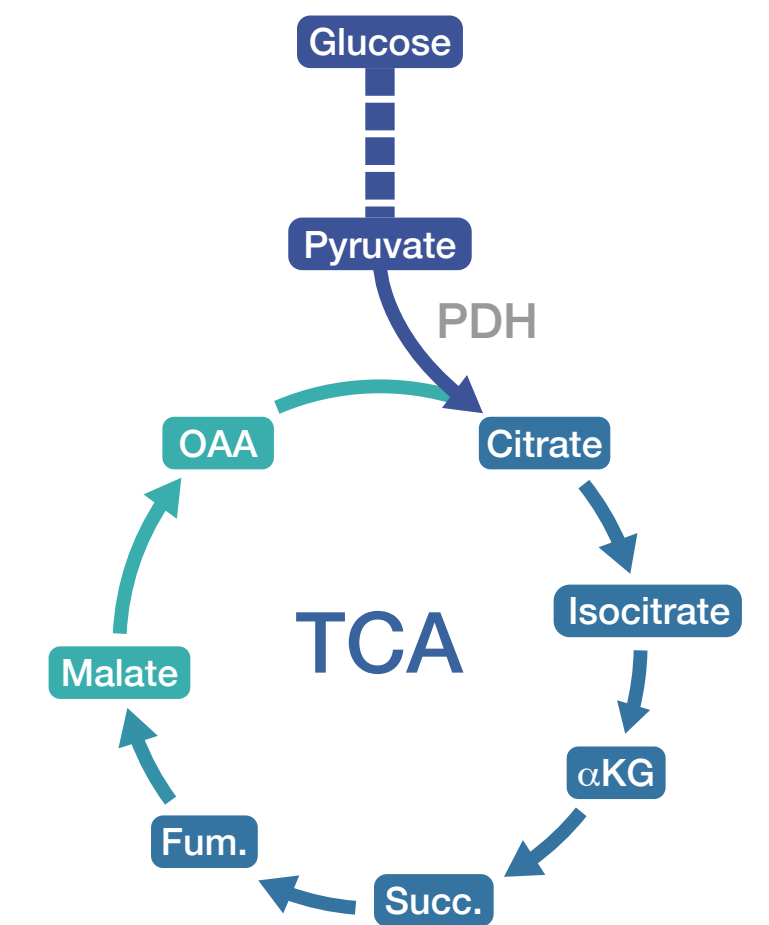
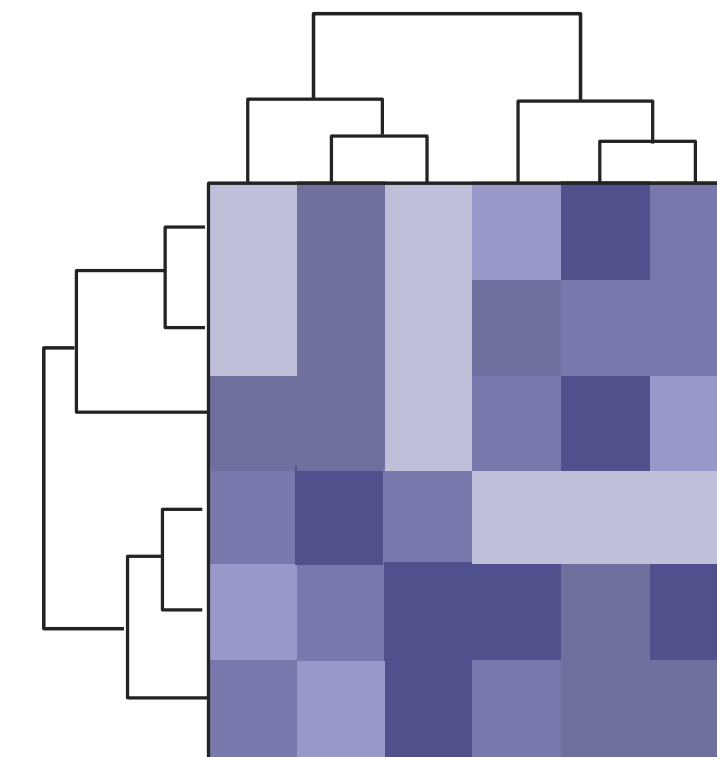


2 Chromatography + MS

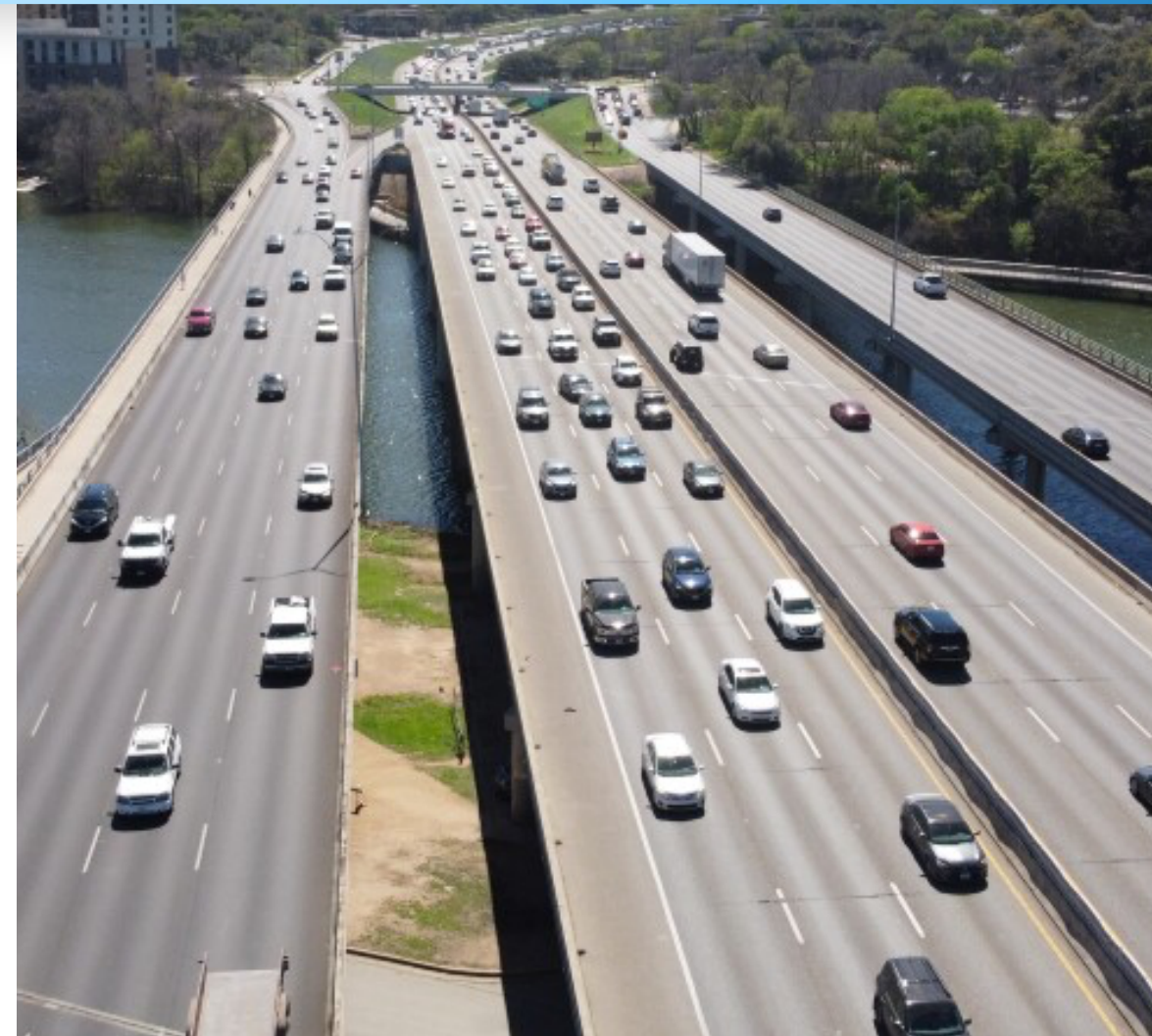


3 Data analysis

Metabolites in central carbon metabolism representing major metabolic pathways



What is metabolic flux? (And how to measure)



Direction matters. What is flux and how do you measure it?



Direction matters. What is flux and how do you measure it?



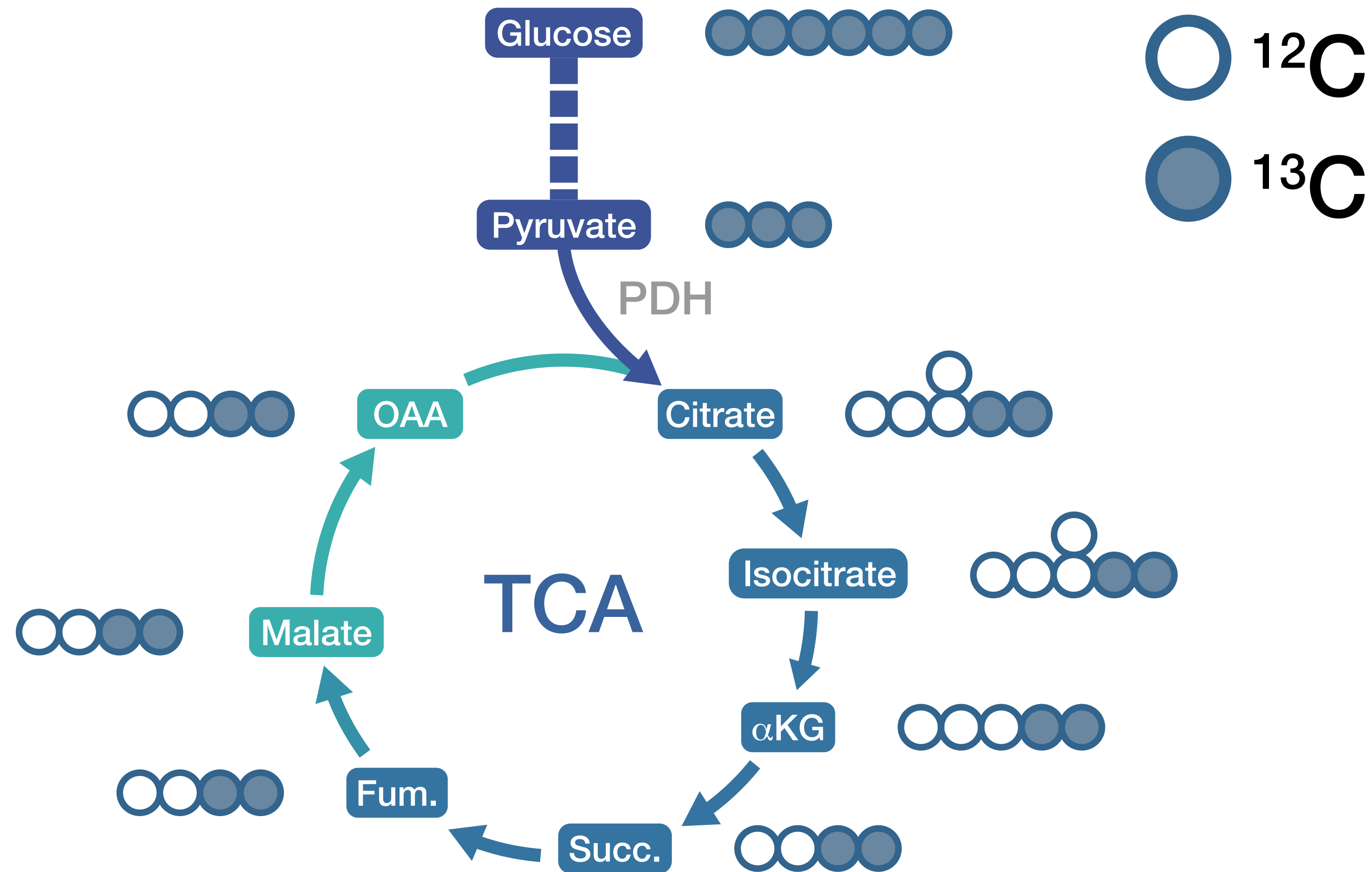
Direction matters. What is flux and how do you measure it?



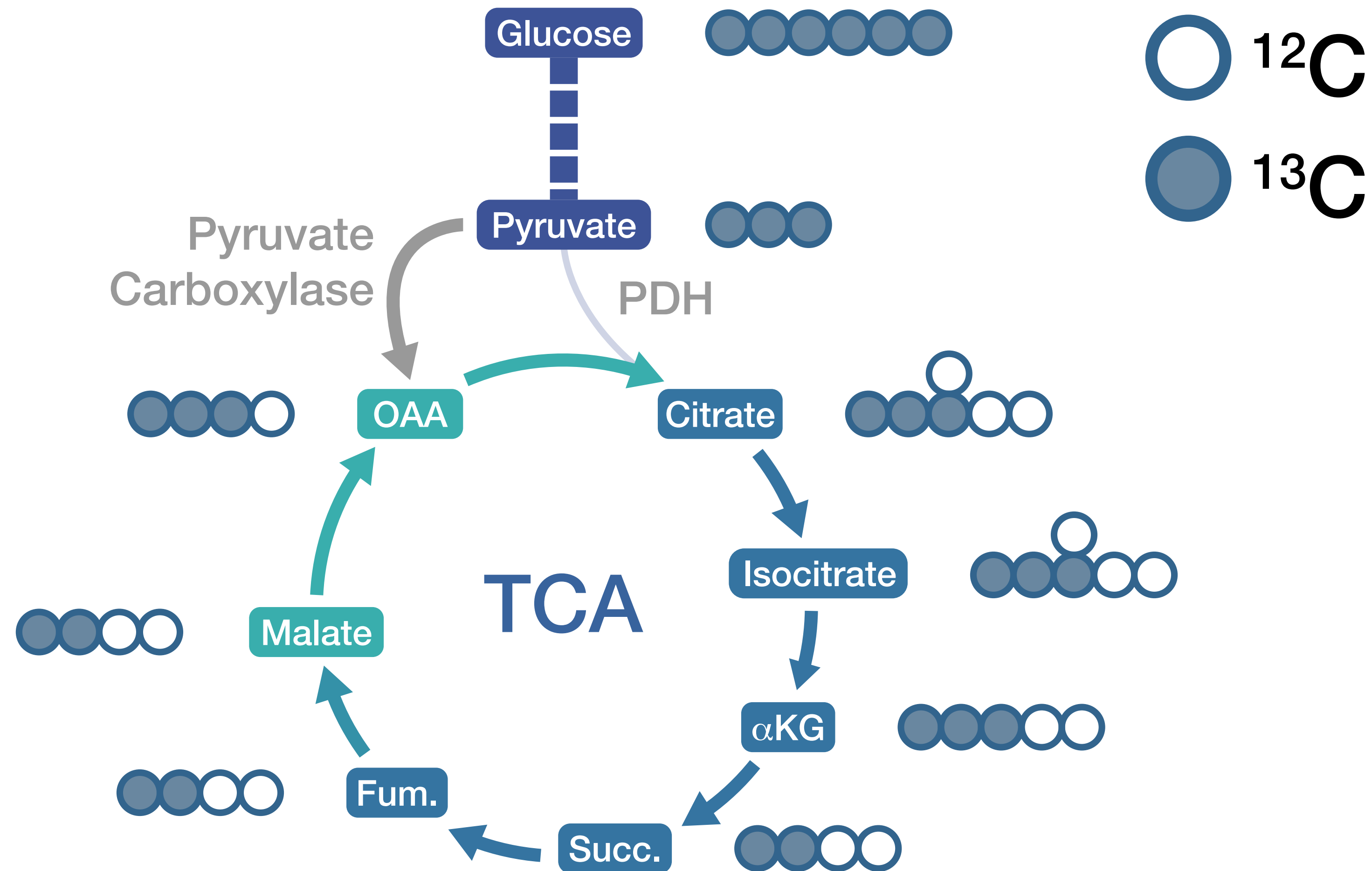
Direction matters. What is flux and how do you measure it?



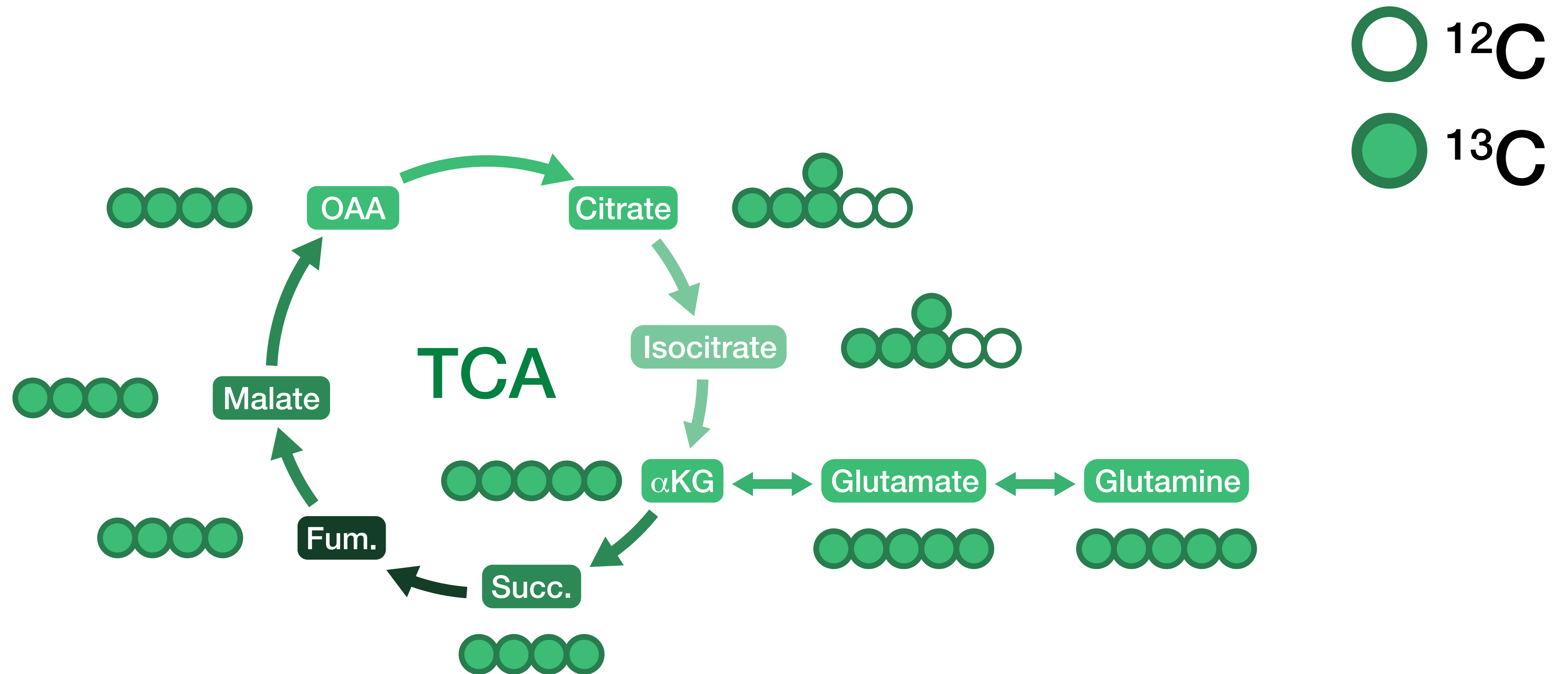
Isotope tracing enables measurement of flux through metabolic pathways



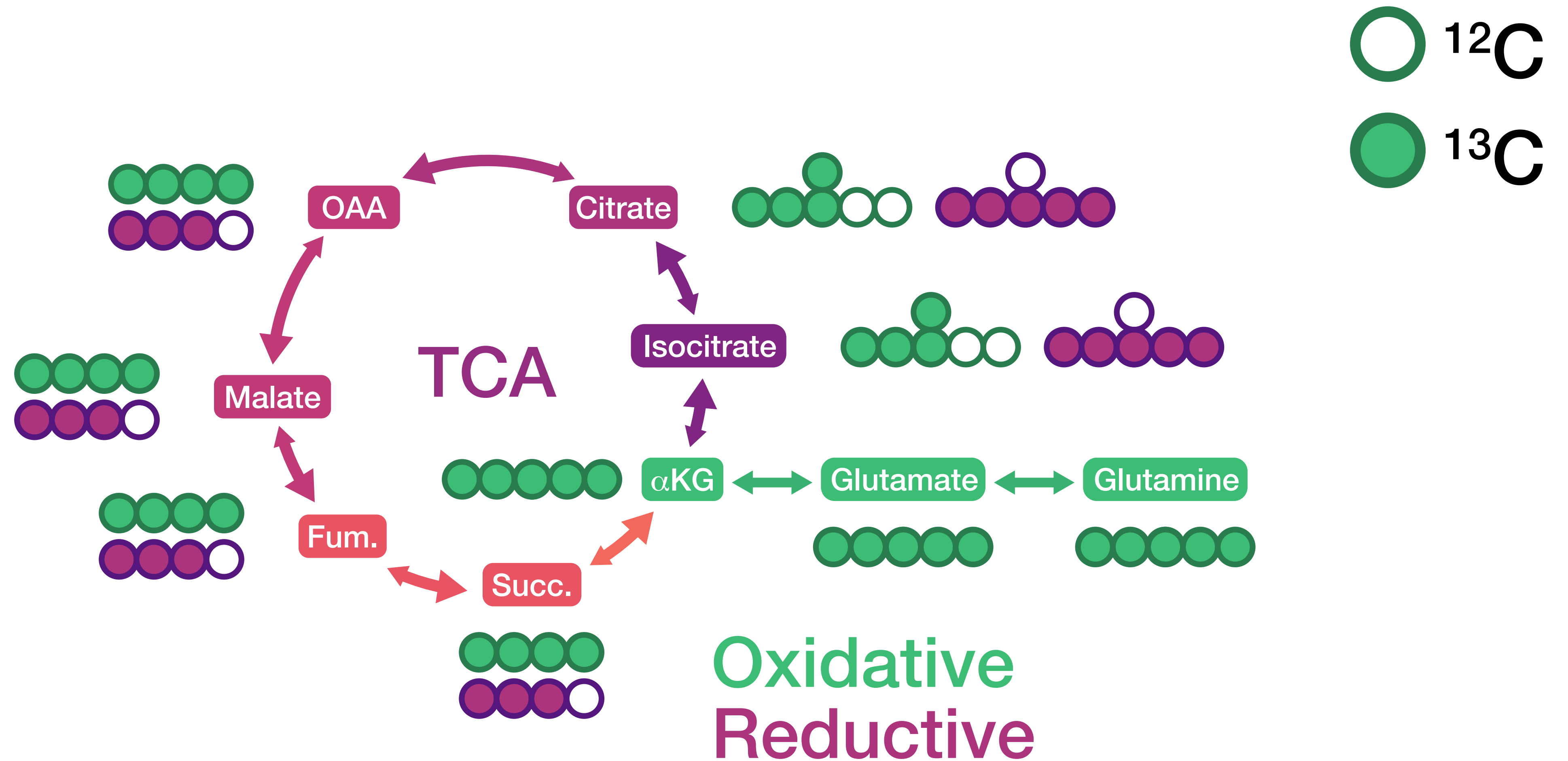
Isotope tracing enables measurement of flux through metabolic pathways



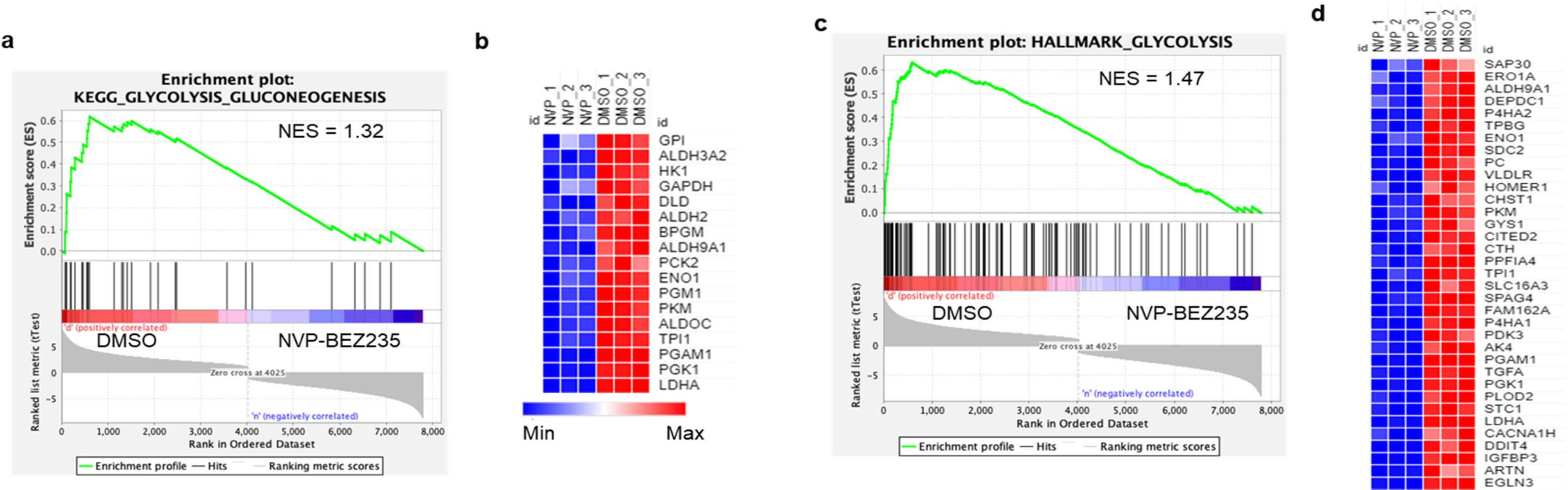
Isotope tracing enables measurement of flux through metabolic pathways



Isotope tracing enables measurement of flux through metabolic pathways



Gene expression as a proxy for metabolic flux

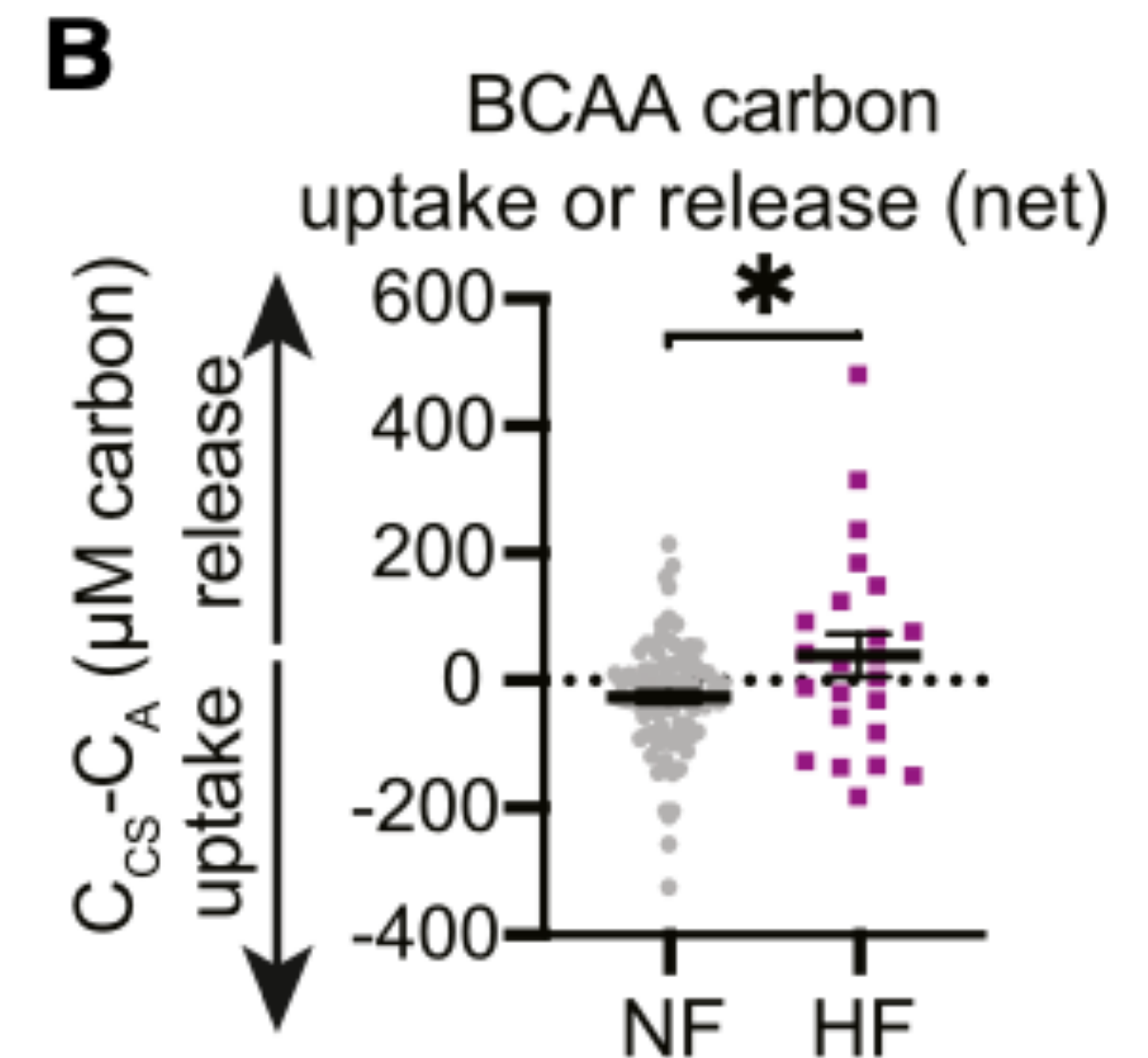
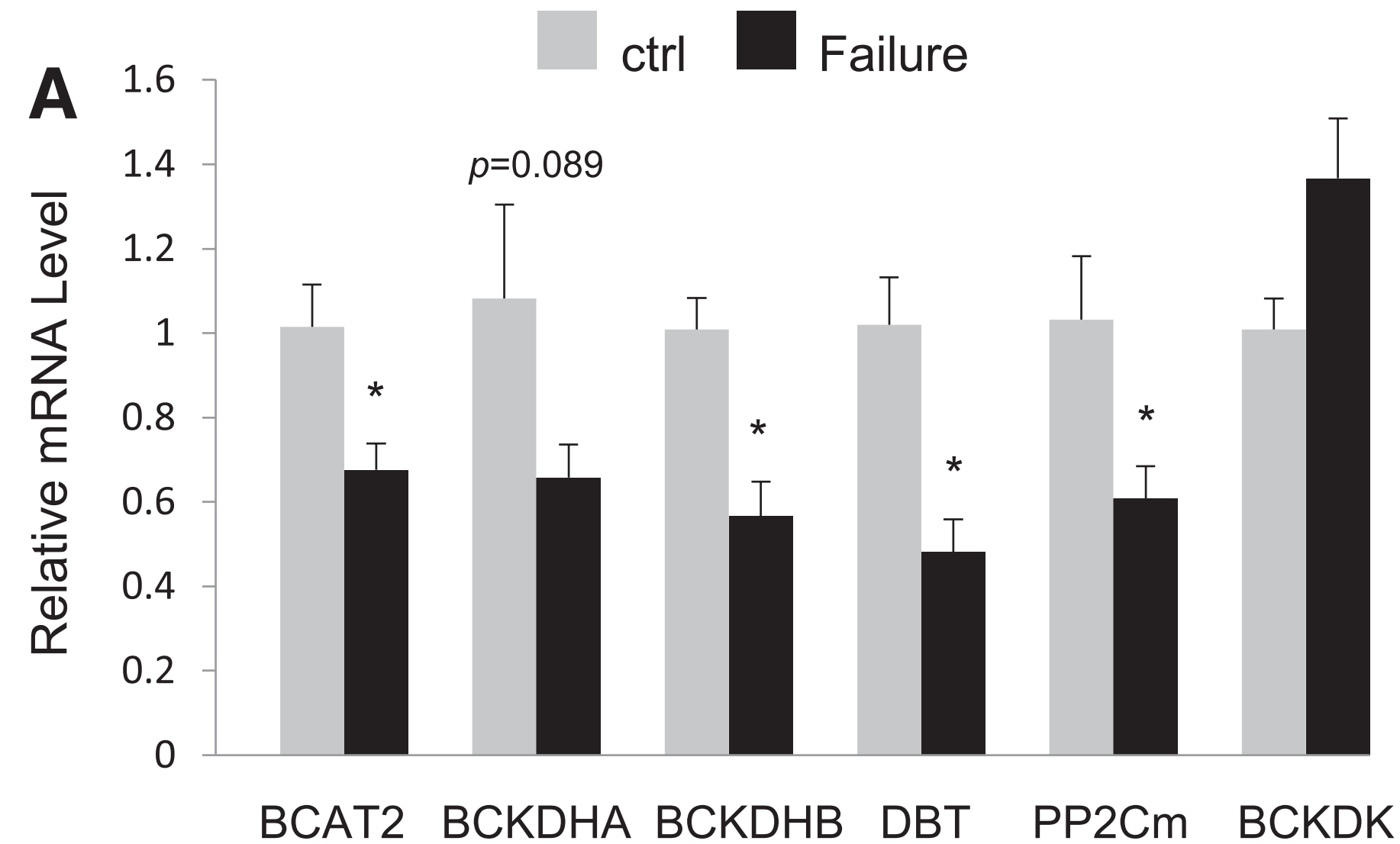
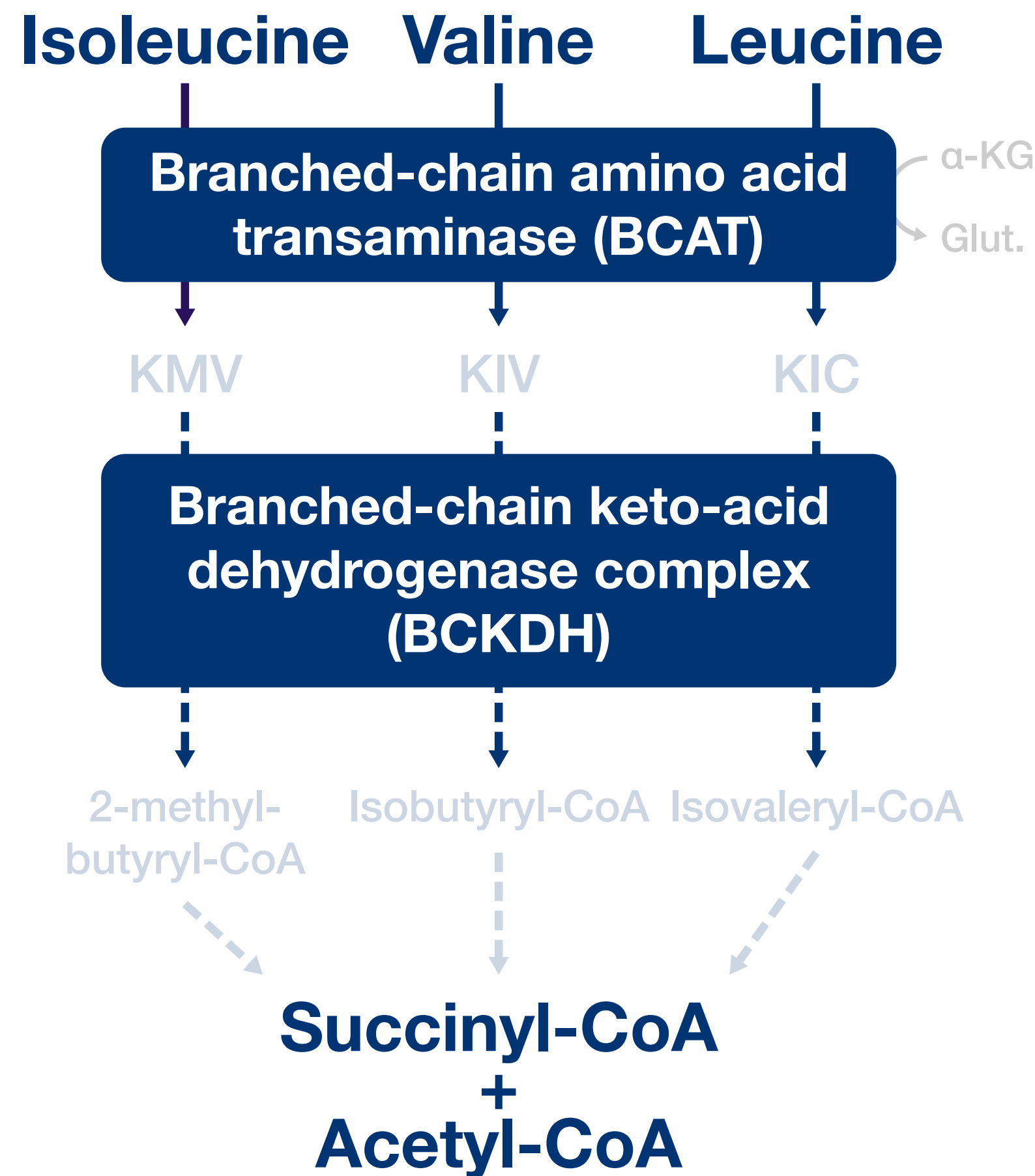


28,501 Metabolism-related Gene-Sets in GSEA Molecular Signatures Database



Metabolic flux **CANNOT!!!**

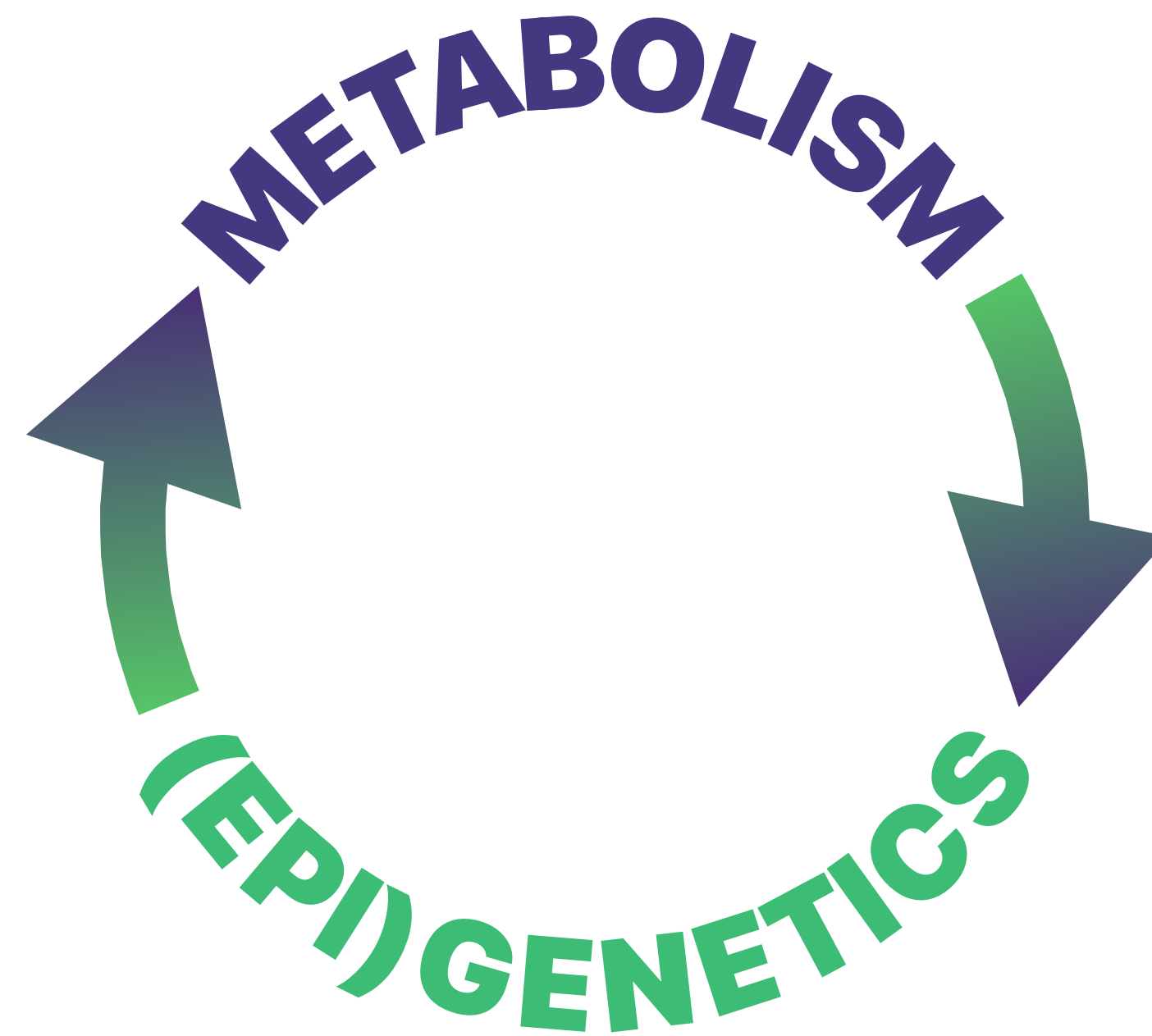
be extrapolated from expression of enzymatic gene loci



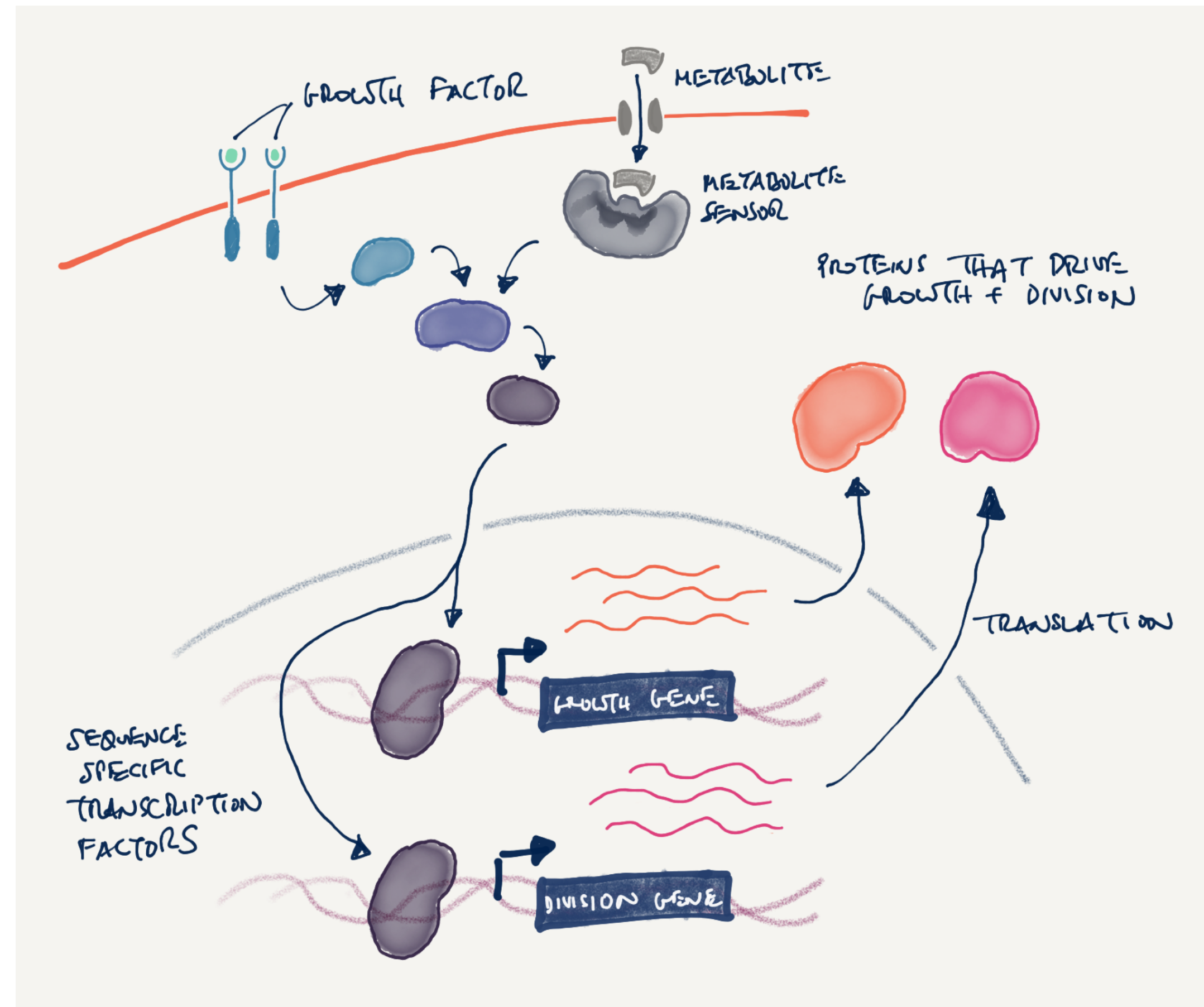
Takehome points 2

1. Forward genetics can be used to study metabolic pathways in auxotrophic systems/organisms
2. Inborn errors of metabolism are the clinical manifestations of blocks in metabolic flux
3. Metabolomics shows us the snapshot AMOUNT of each metabolite in a population
4. Flux analysis reveals directionality and the contribution of one metabolite to different pathways
5. Metabolic flux CANNOT be extrapolated from gene expression data

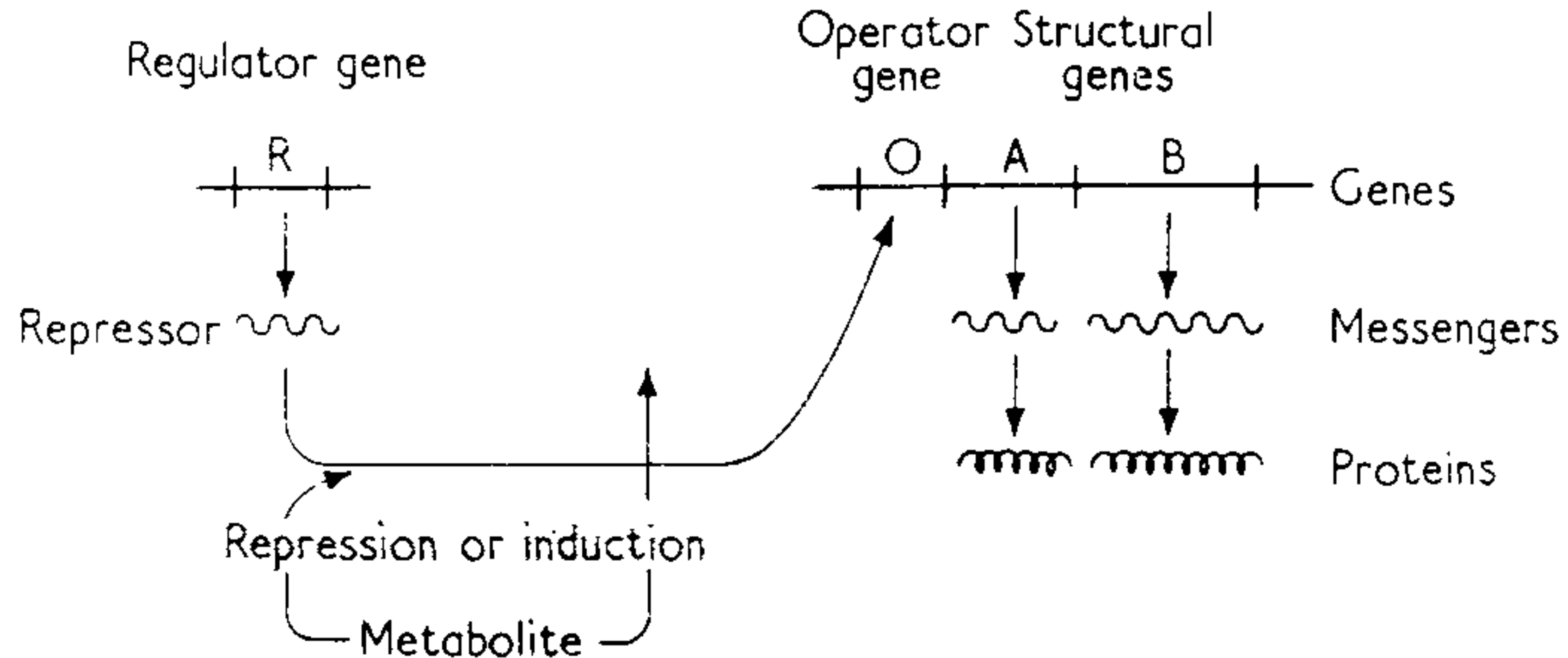
A DIVE INTO HOW METABOLISM AFFECTS CHROMATIN



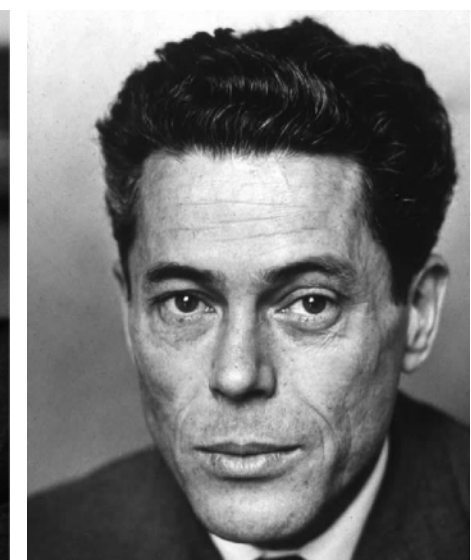
The classic view of transcriptional regulation hinges on DNA-sequence specificity of activators and repressors



Bacterial gene-expression is **DIRECTLY** regulated by metabolites



François Jacob

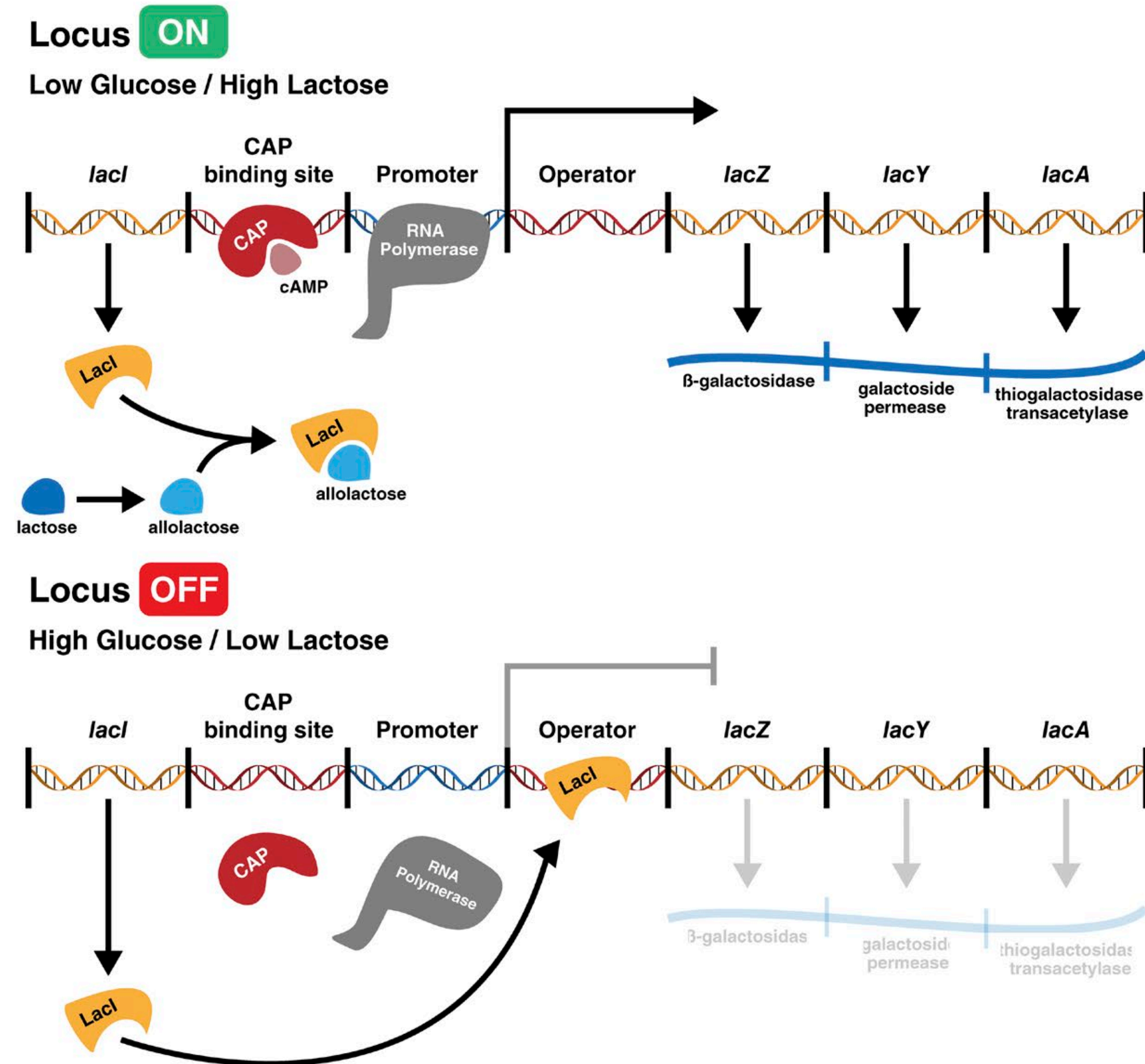


Jacques Monod



André Lwoff

Bacterial gene-expression is **DIRECTLY** regulated by metabolites

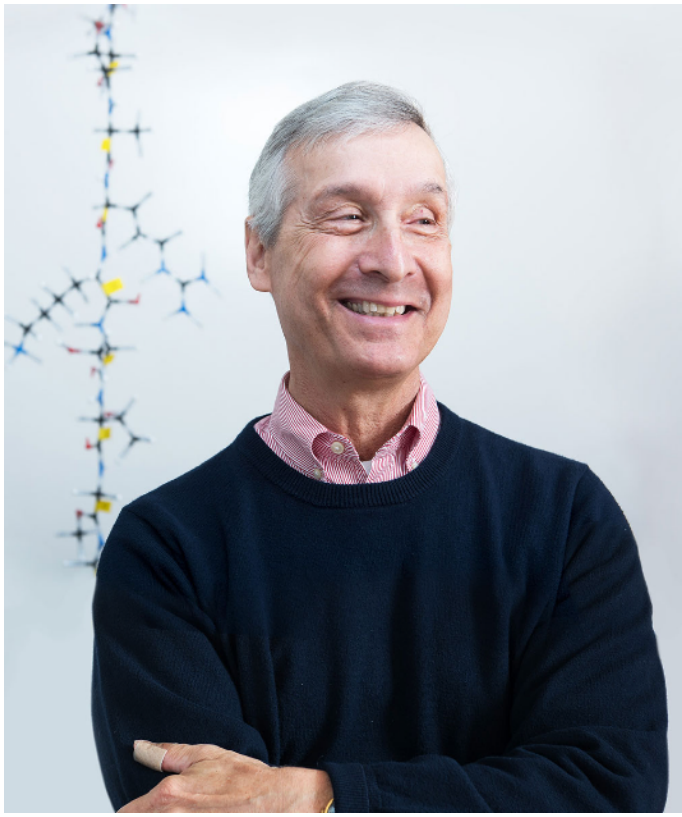


OK BUT THAT'S PROKARYOTES, NO NUCLEUS AND NO CHROMATIN...

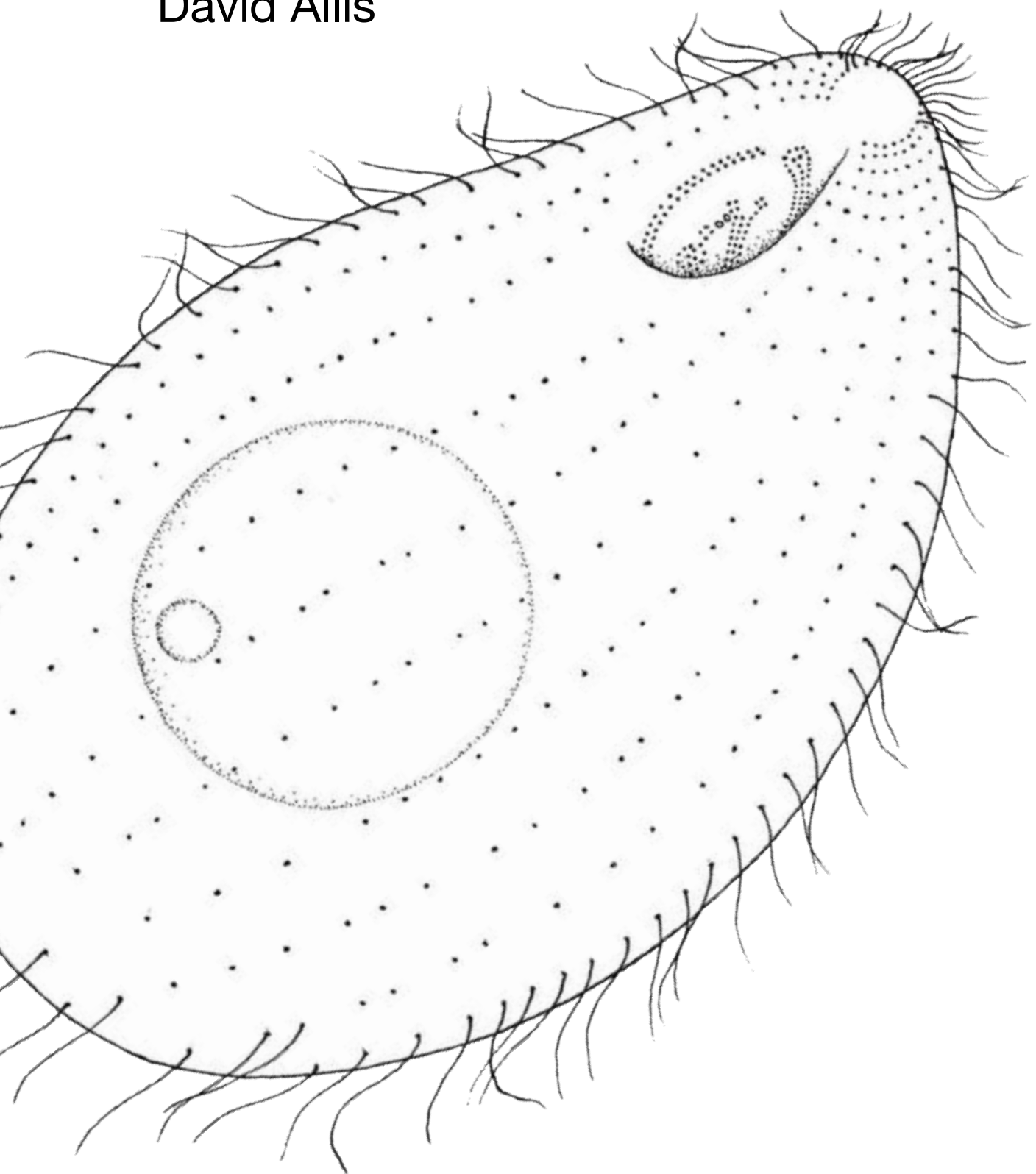


Chromatin is heavily decorated with the products of metabolic reactions



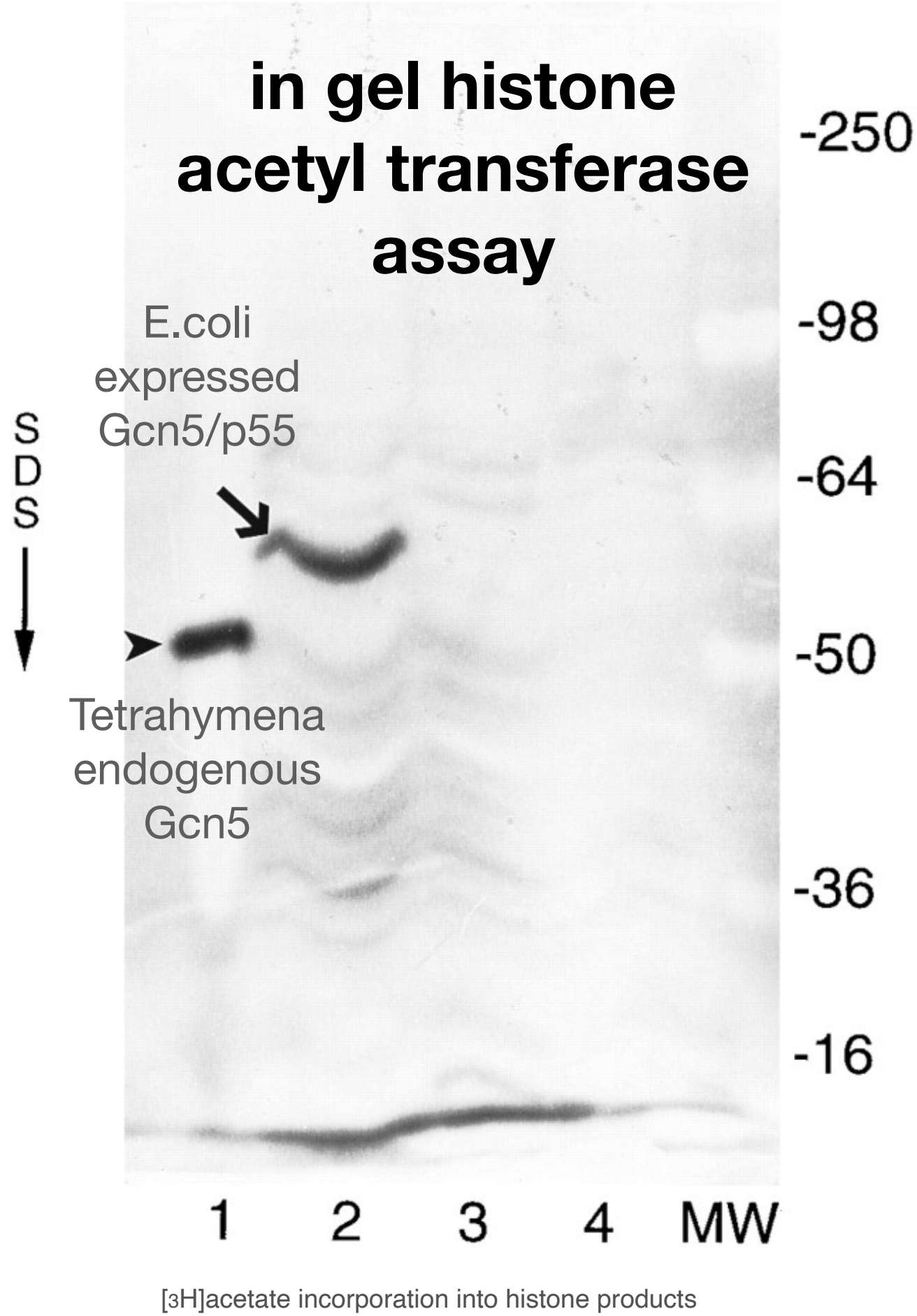


David Allis



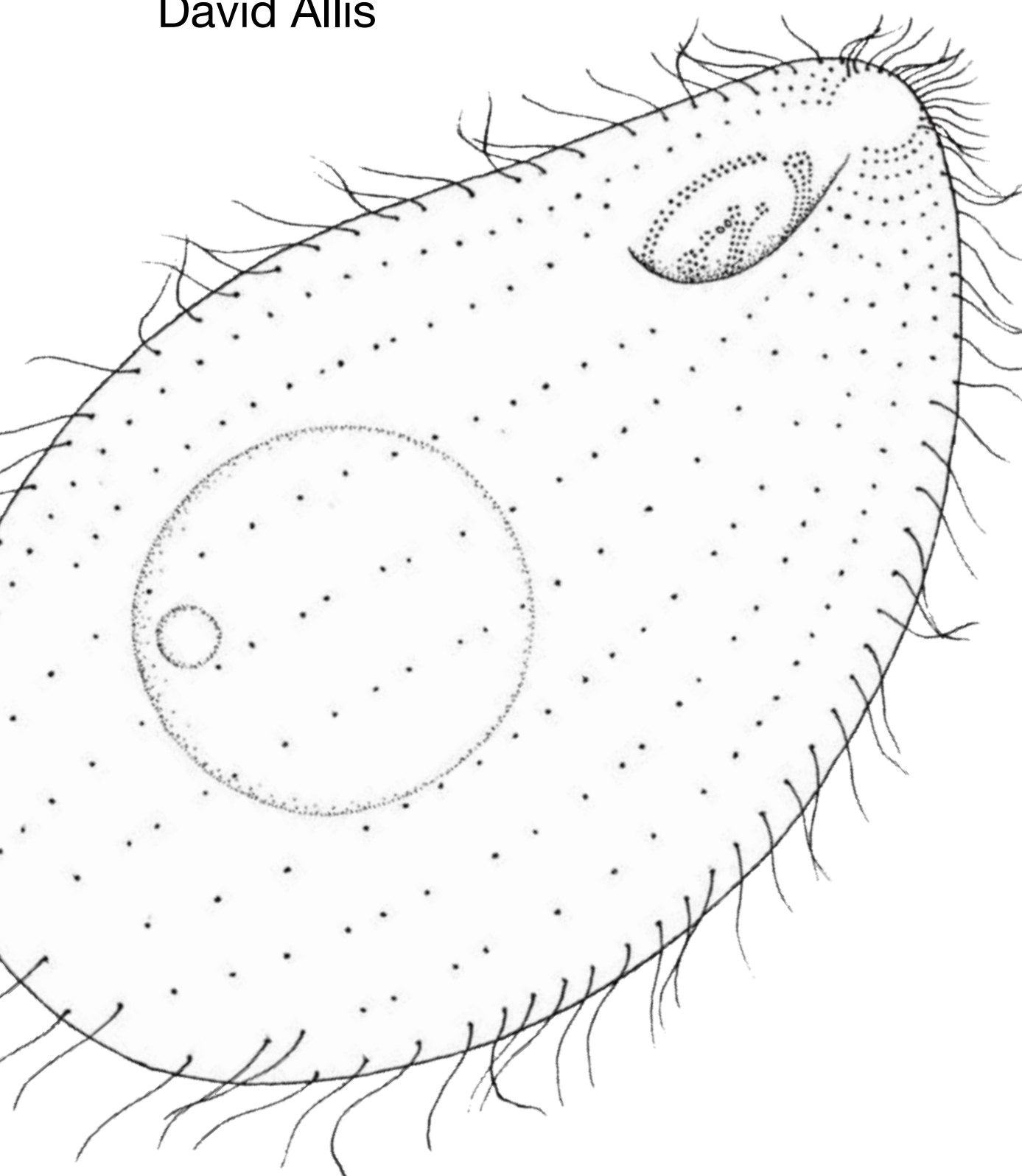
Tetrahymena thermophila

So why are histones acetylated?



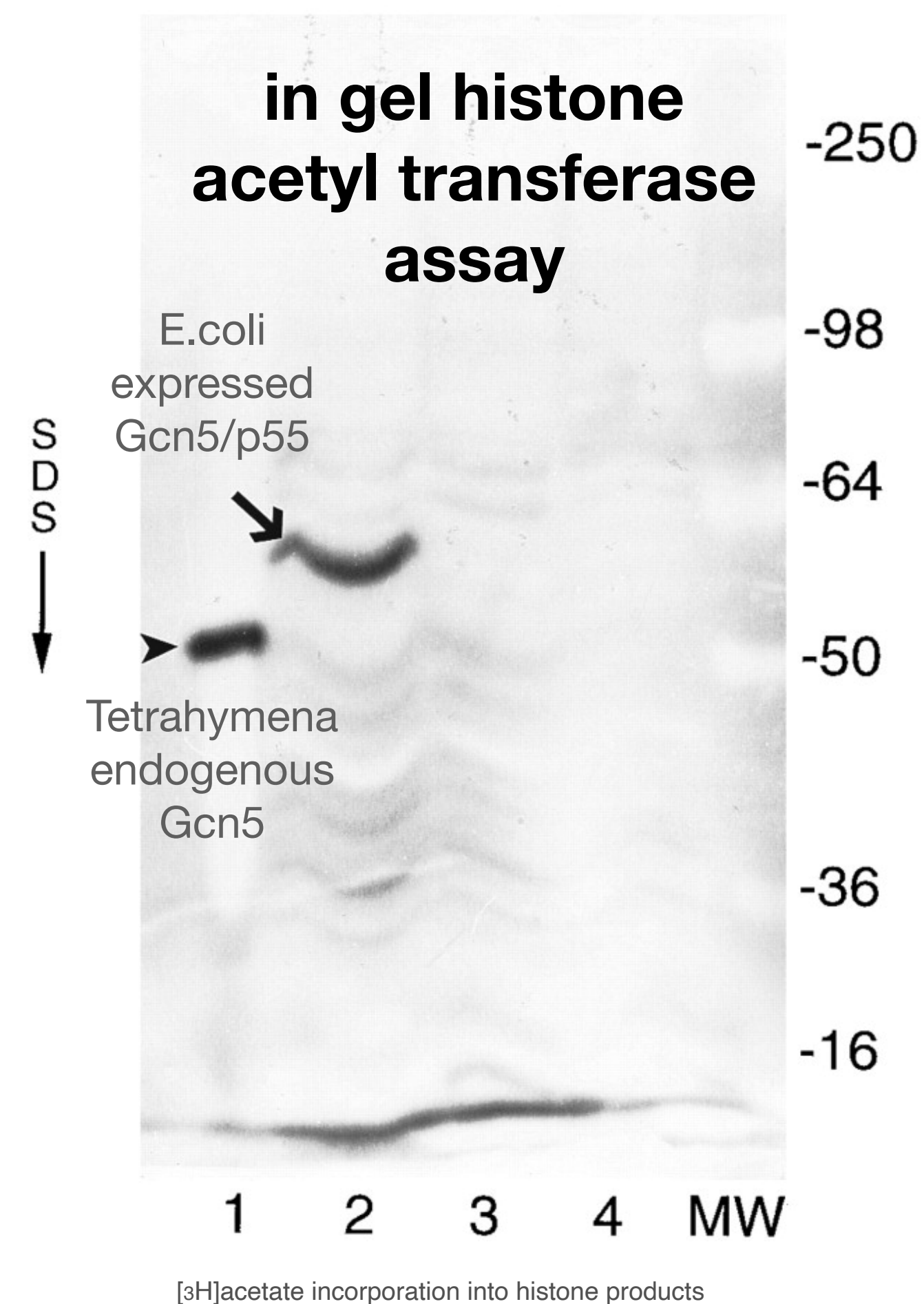


David Allis



Tetrahymena thermophila

So why are histones acetylated?



**METABOLITE-
DEPENDENT ENZYMATIC
MODIFICATION OF
CHROMATIN CAN
CHANGE GENE
EXPRESSION**

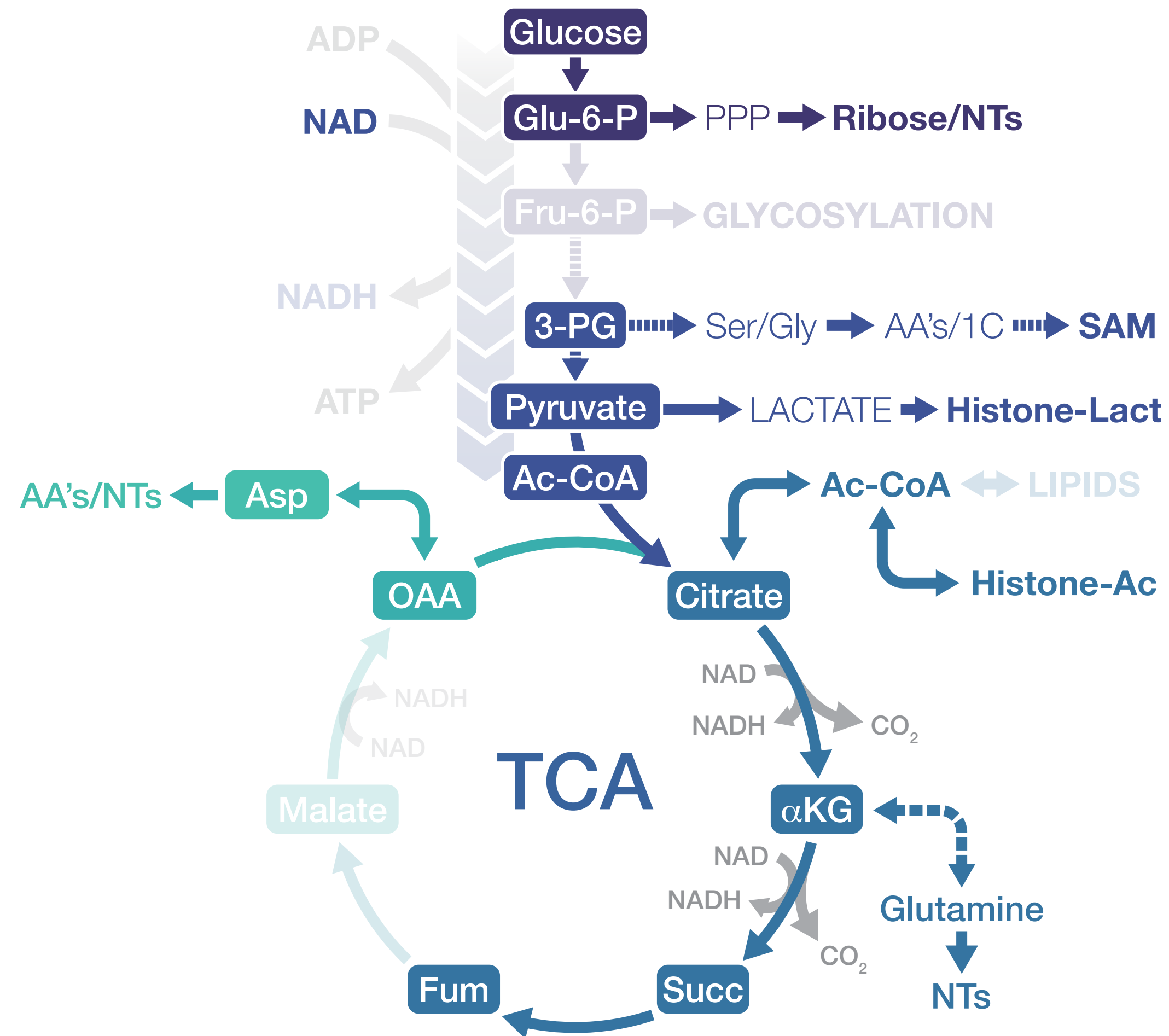
Chromatin modifications respond to the metabolic state of the cell



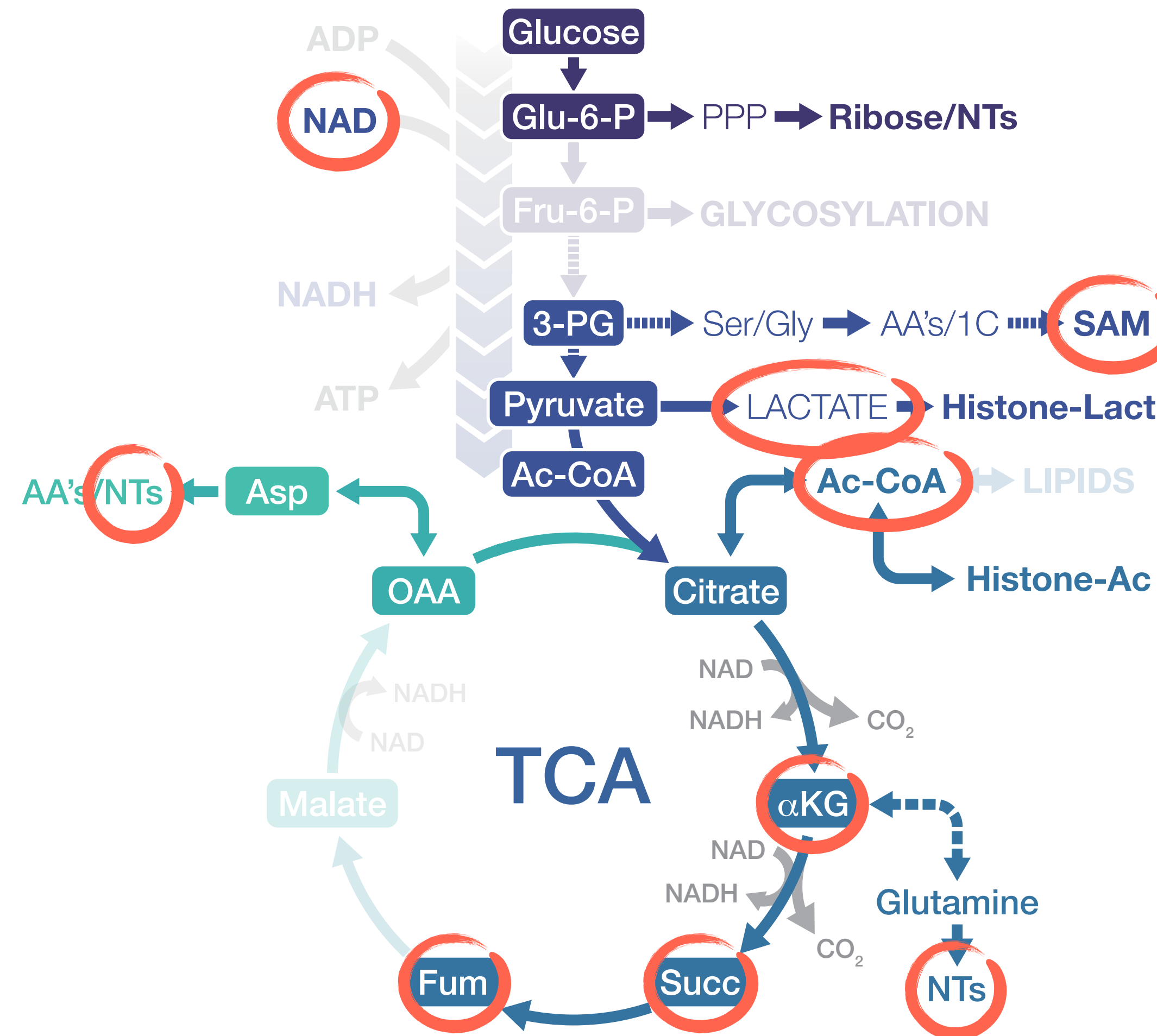
Implications:

- Changes in intracellular metabolism affect gene expression
 - Gene expression programs can be altered through inhibition of the metabolic pathways they are dependent on
- i.e. **TFS CAN'T BE DRUGGED BUT ENZYMES CAN**

Central Carbon Metabolism: Links to Chromatin

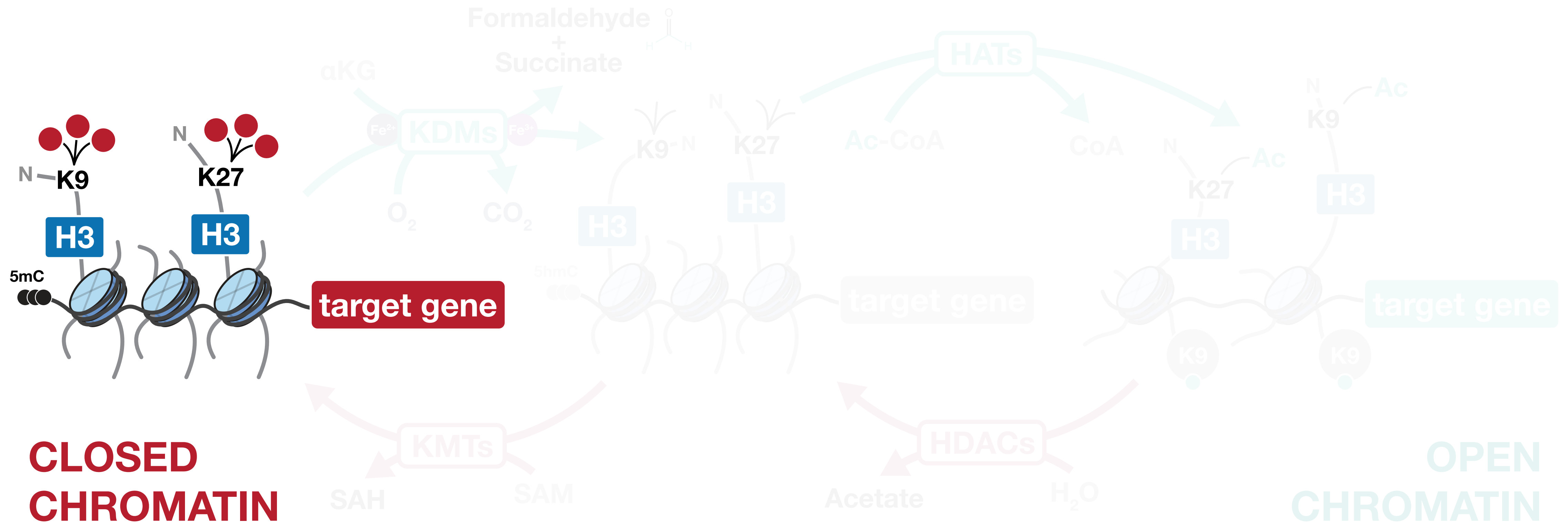


Central Carbon Metabolism: Links to Chromatin



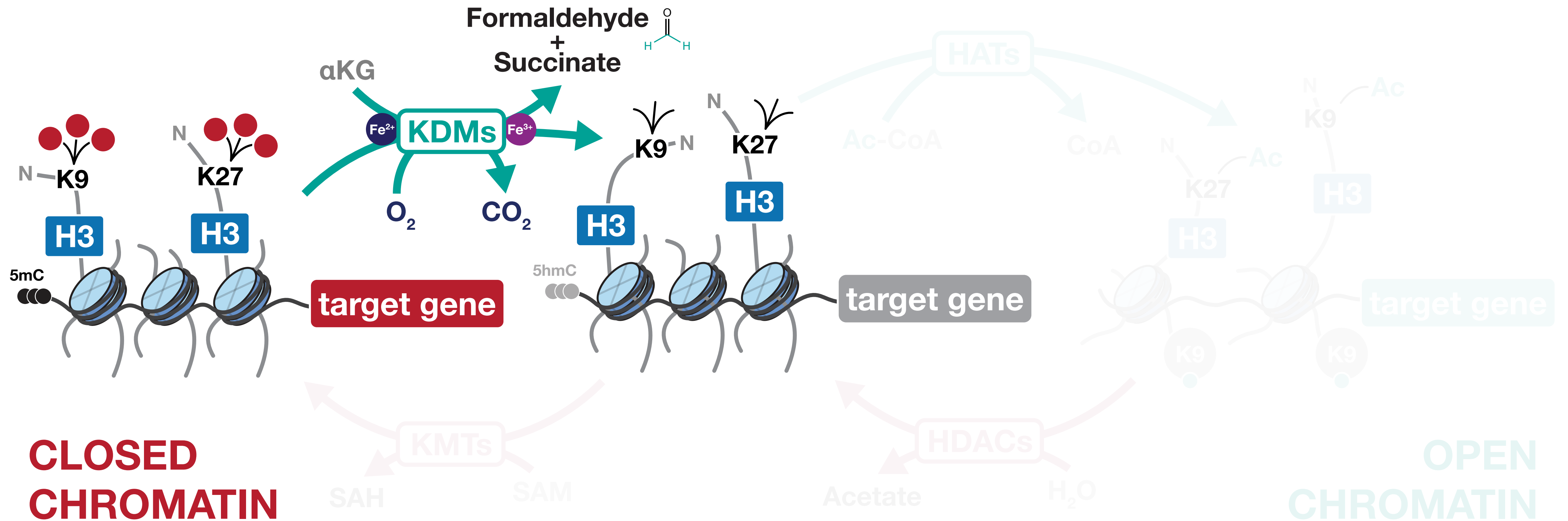
Chromatin modifications respond to the metabolic state of the cell

OFF



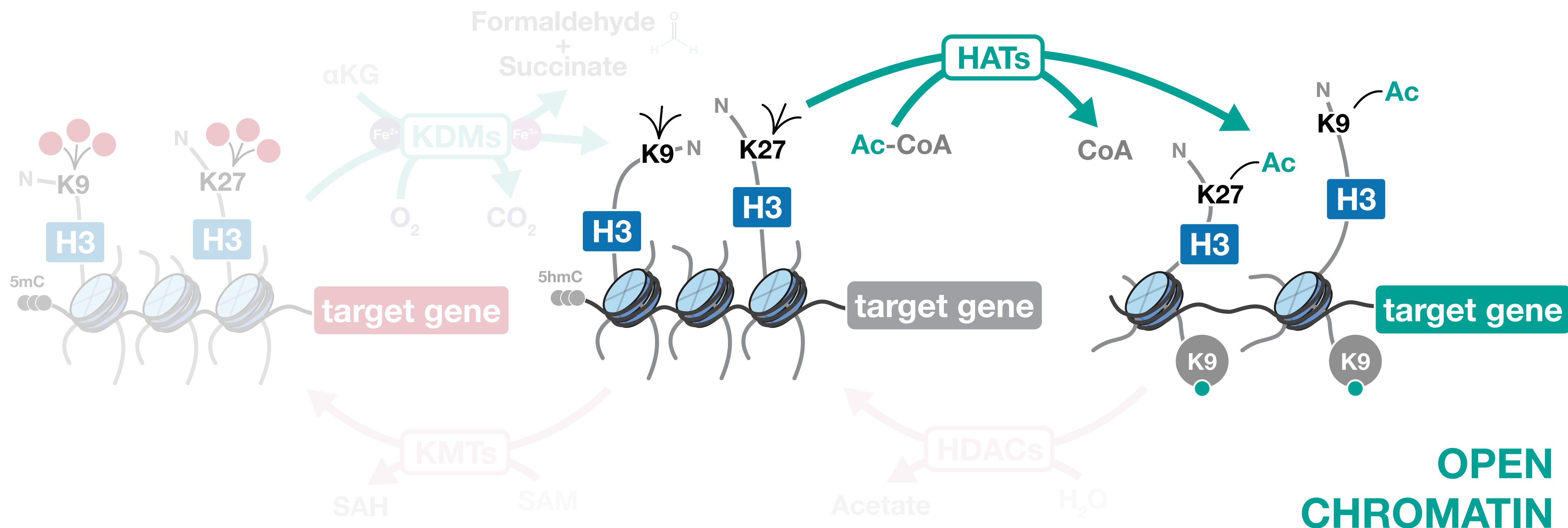
Chromatin modifications respond to the metabolic state of the cell

OFF



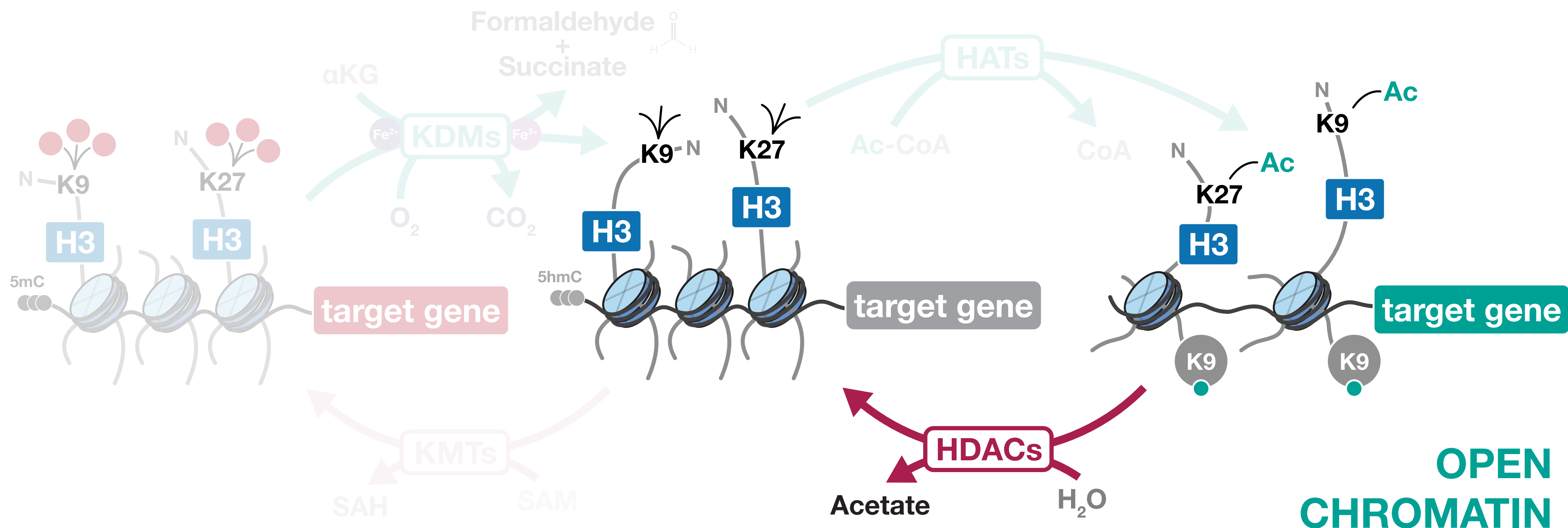
Chromatin modifications respond to the metabolic state of the cell

ON



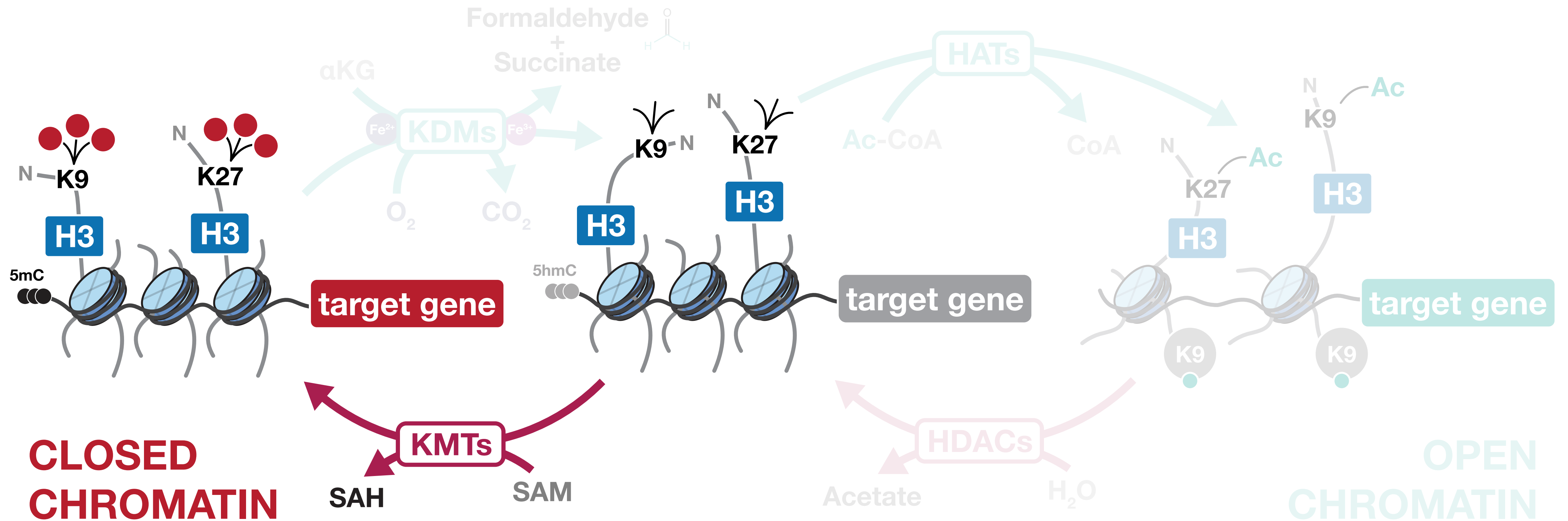
Chromatin modifications respond to the metabolic state of the cell

ON



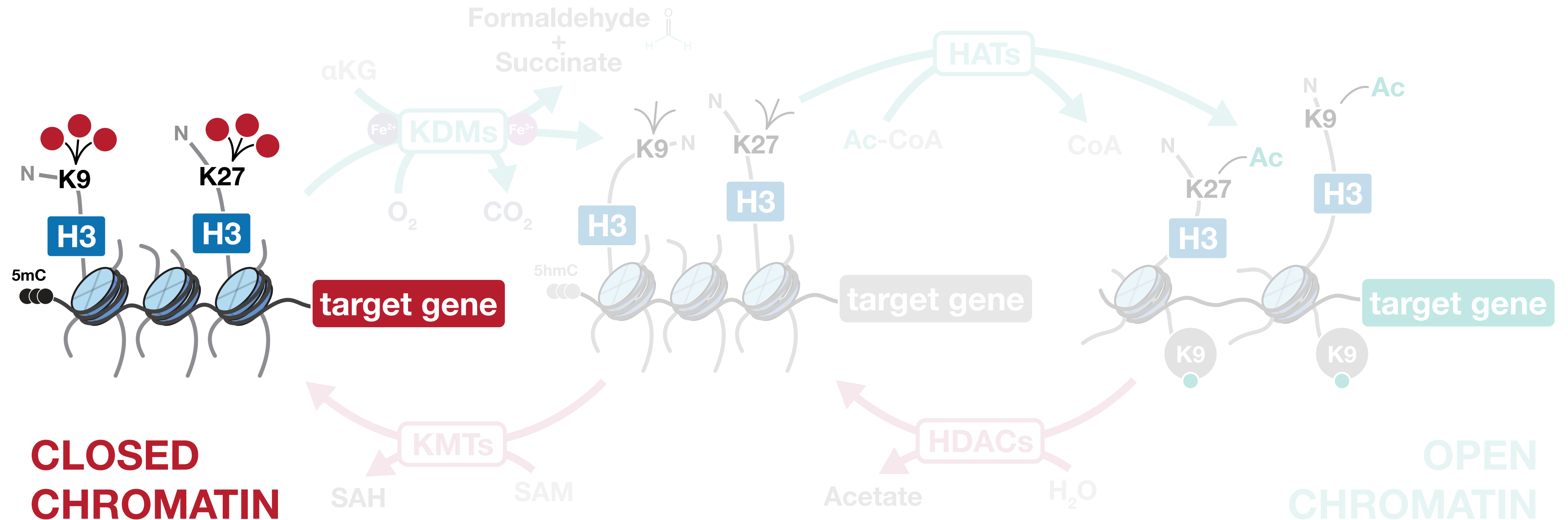
Chromatin modifications respond to the metabolic state of the cell

OFF



Chromatin modifications respond to the metabolic state of the cell

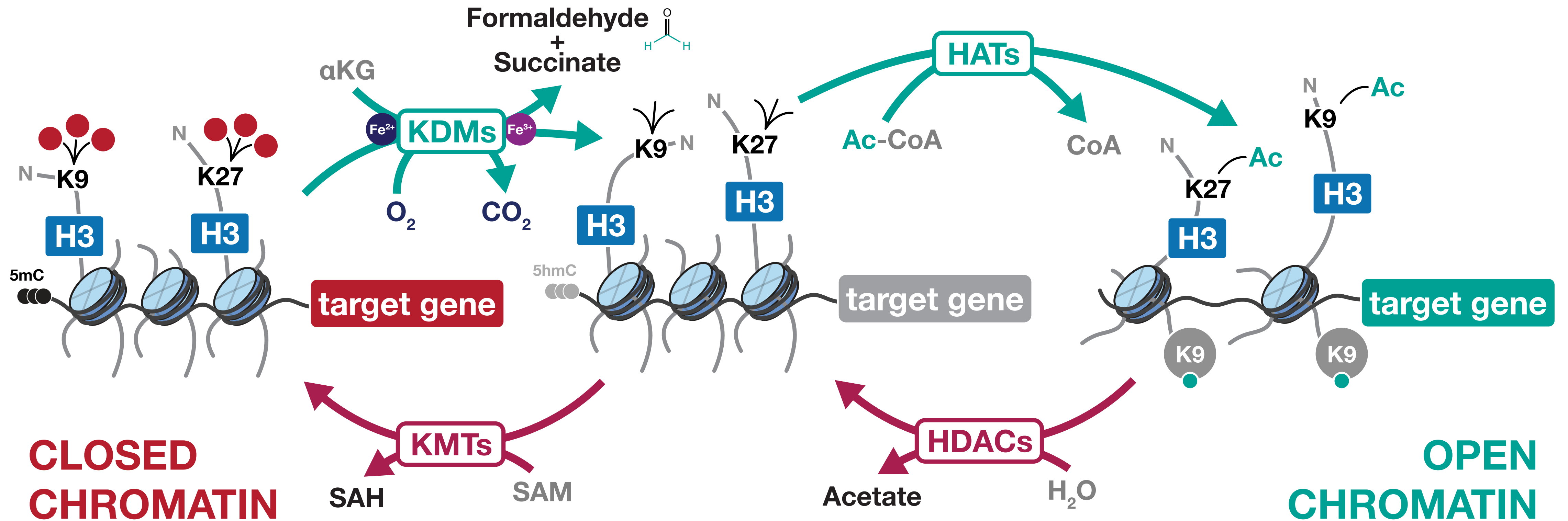
OFF



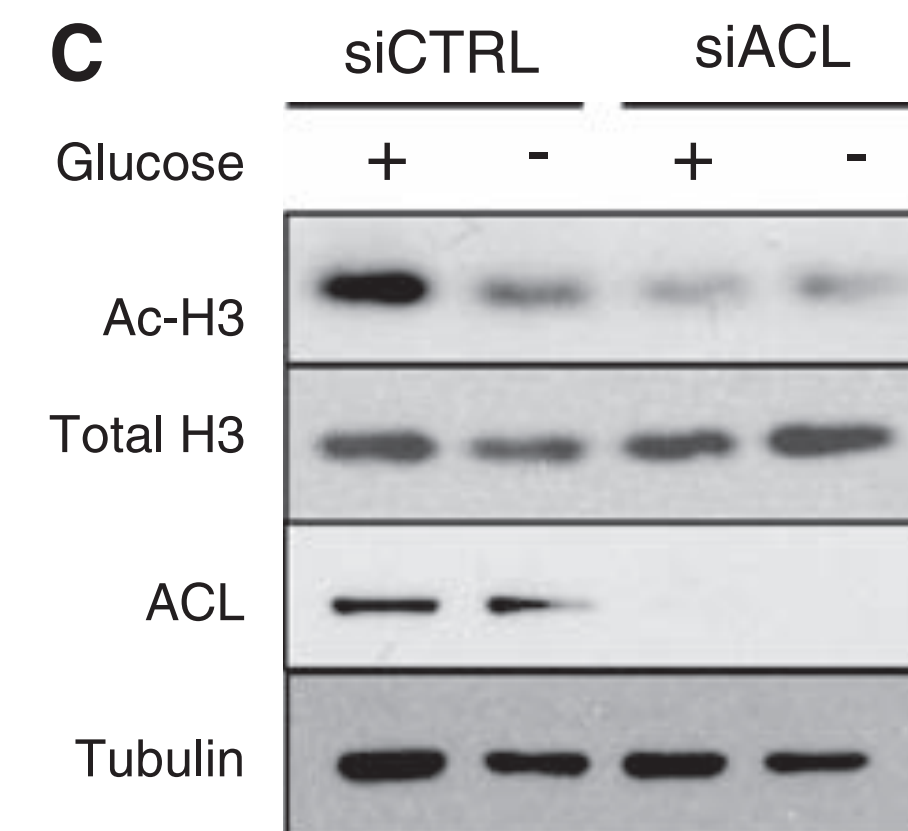
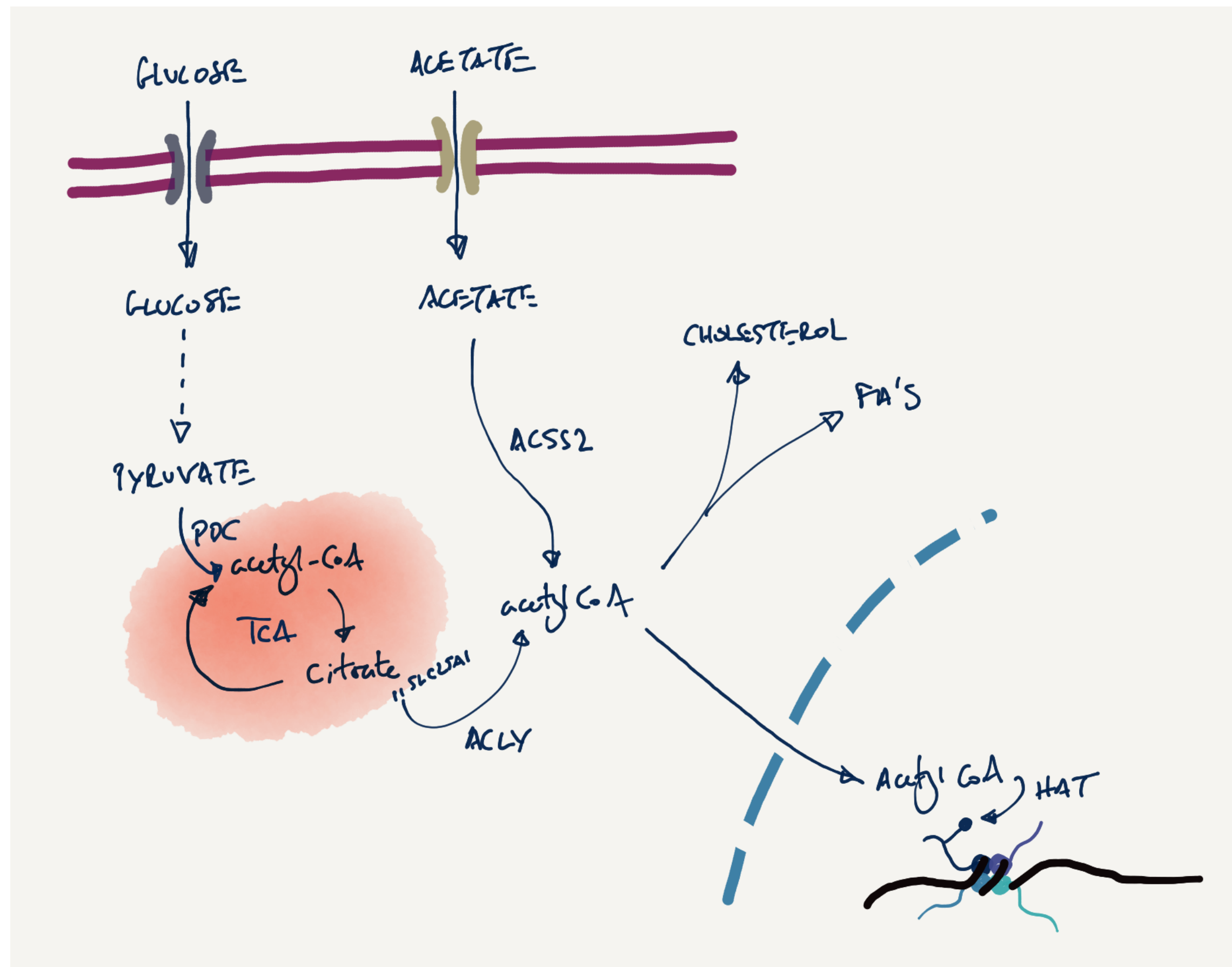
Chromatin modifications respond to the metabolic state of the cell

OFF

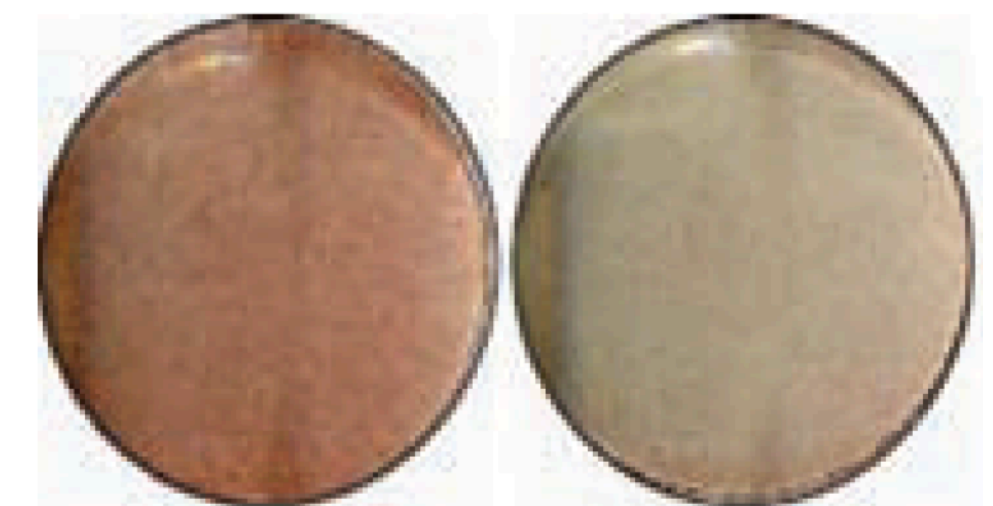
ON



Does acetyl-CoA concentration affect histone acetylation / gene expression?

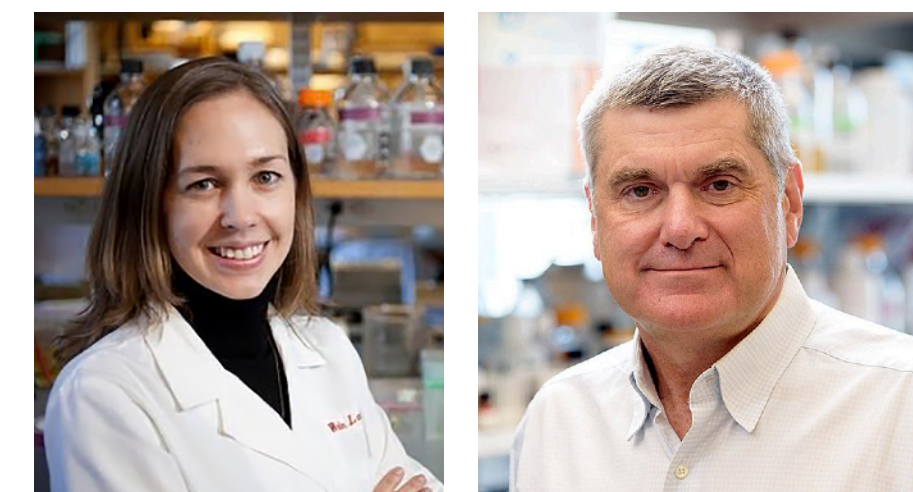


Adipocyte Differentiation
(Oil Red O)



siCTRL

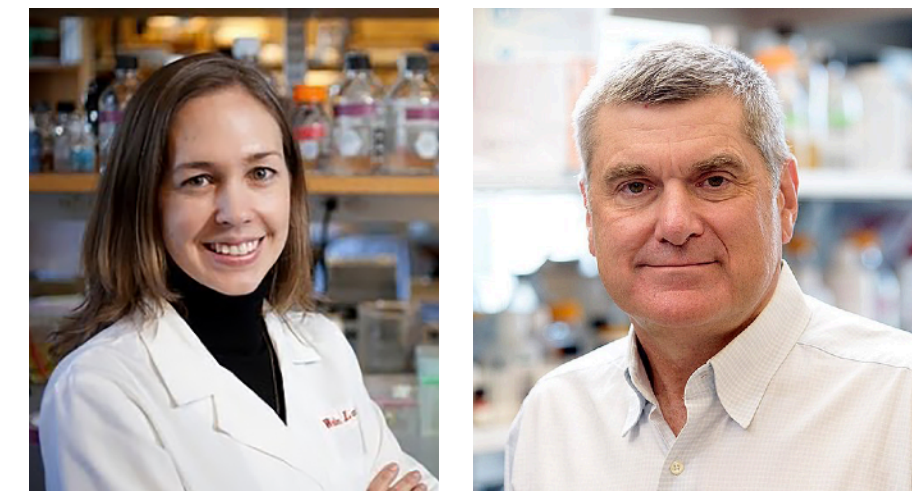
siACL



Katy Wellen Craig Thompson

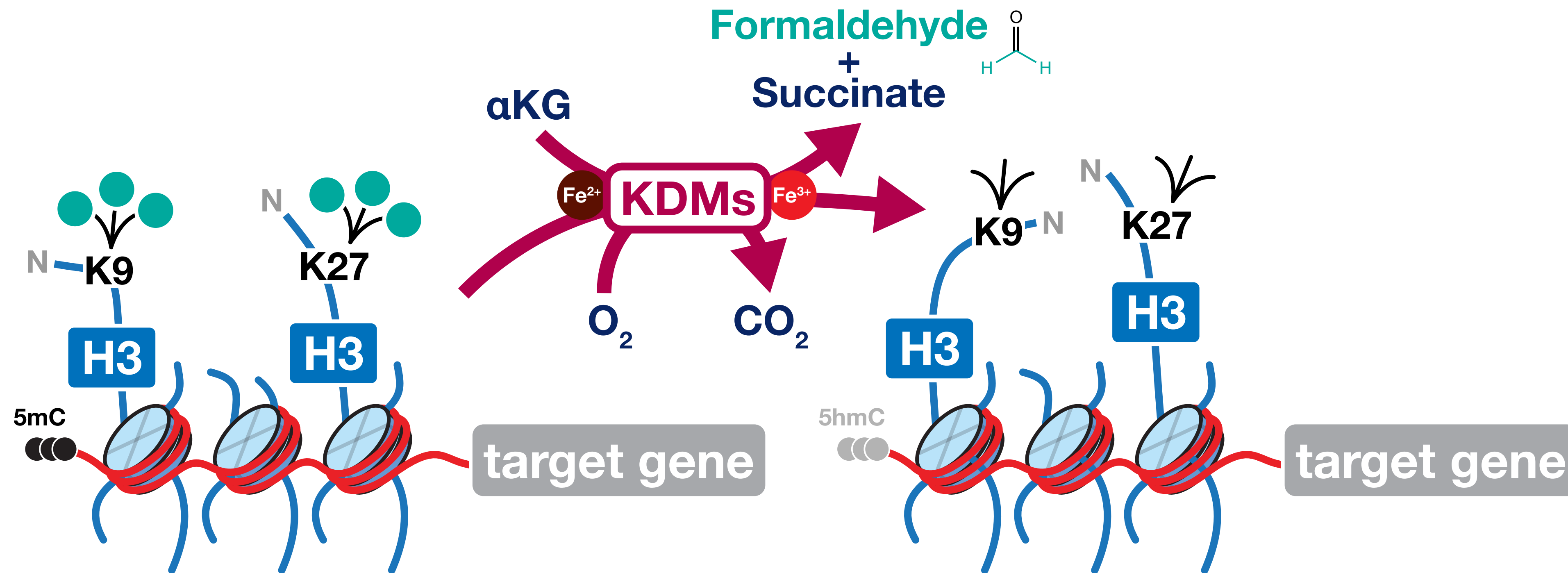
**Does acetyl-CoA concentration affect histone
acetylation / gene expression?**

[SUBSTRATES] MATTER!!!!



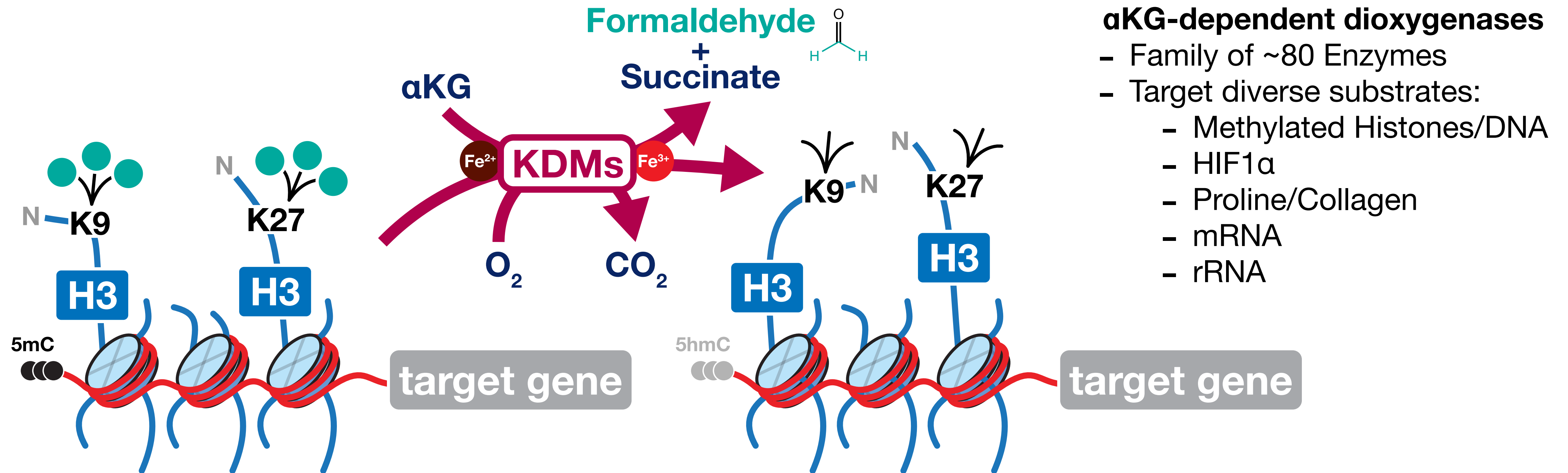
Katy Wellen Craig Thompson

α KG-dependent dioxygenases remove methyl marks from methylated histones



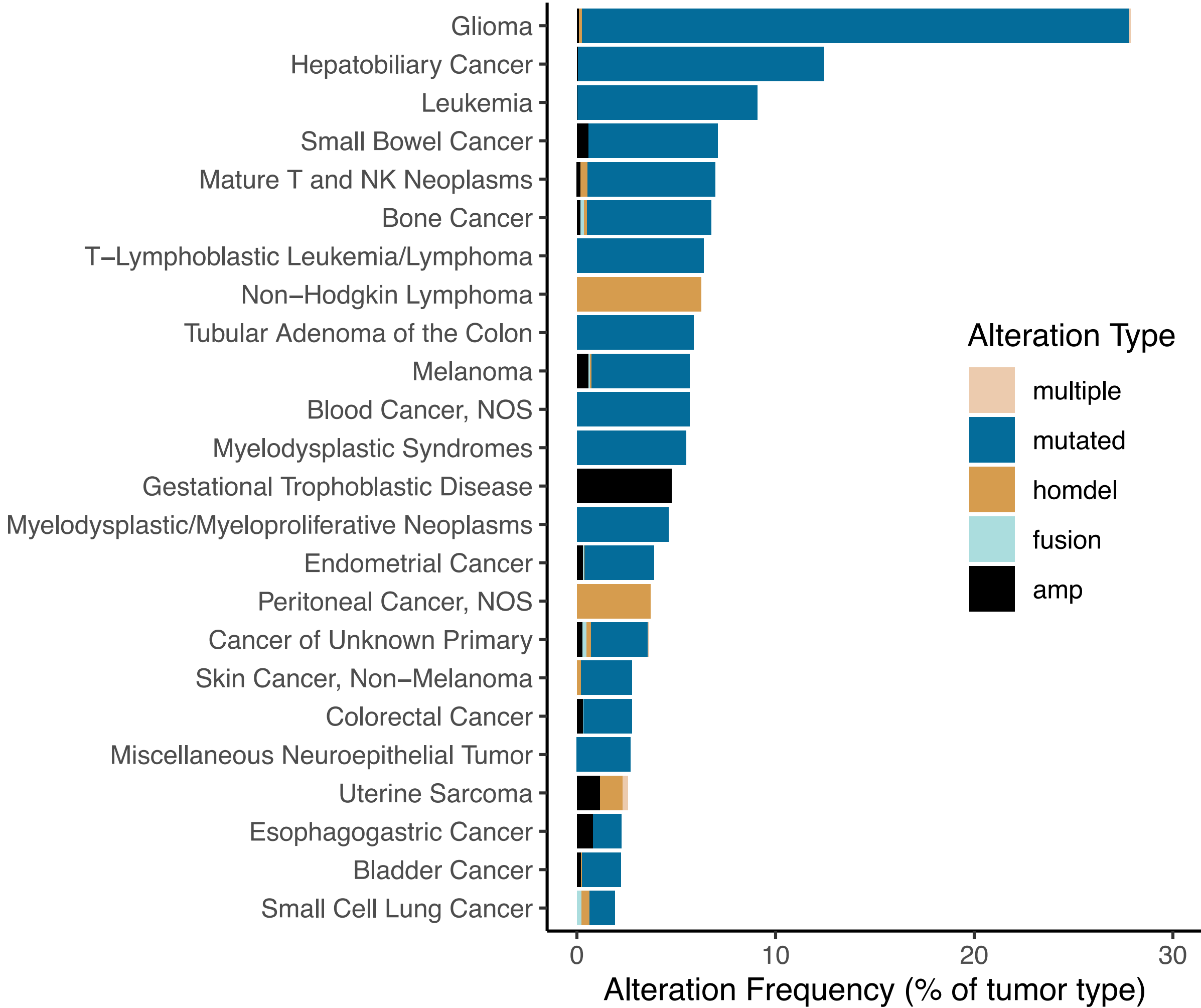
KDMs = Lysine Demethylase
 α KG = alpha-Ketoglutarate

α KG-dependent dioxygenases remove methyl marks from methylated histones

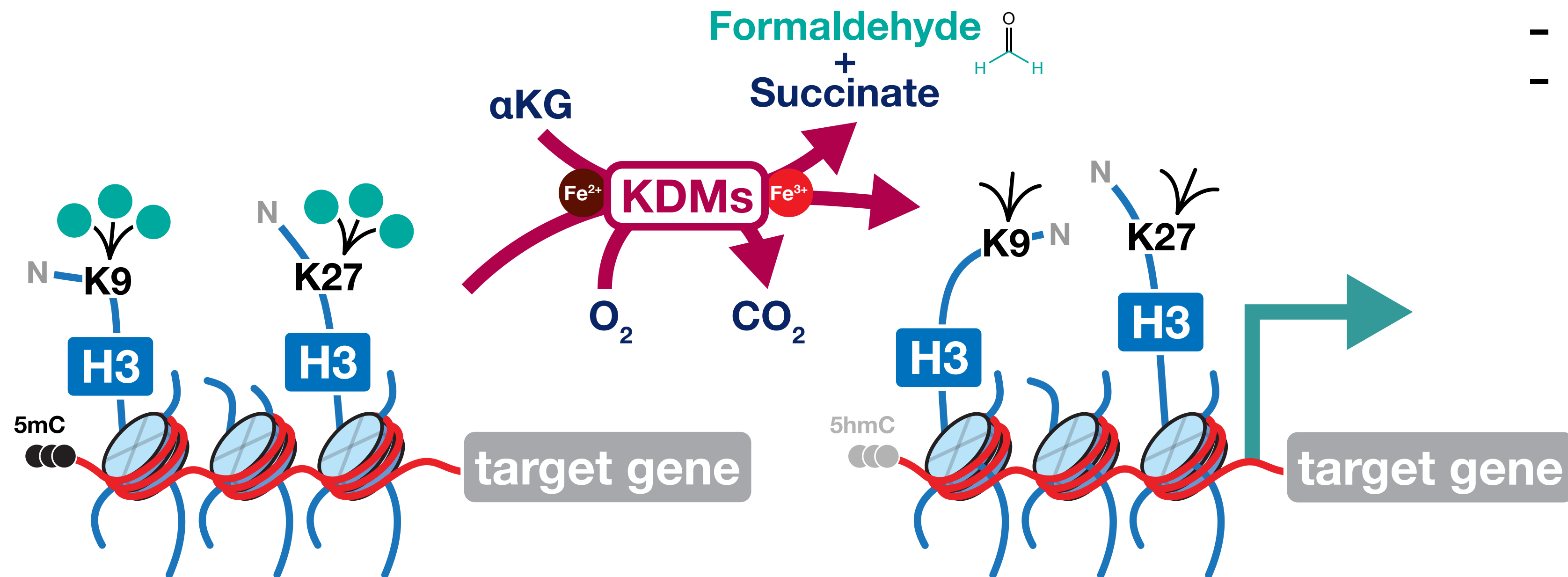


KDMs = Lysine Demethylase
 α KG = alpha-Ketoglutarate

Isocitrate Dehydrogenase 1/2 (IDH1/2) neomorphic mutations are found in a diverse set of malignancies derived from all germ layers



IDH mutations block differentiation by impairing the removal of heterochromatic H3K9me2/3 methyl marks

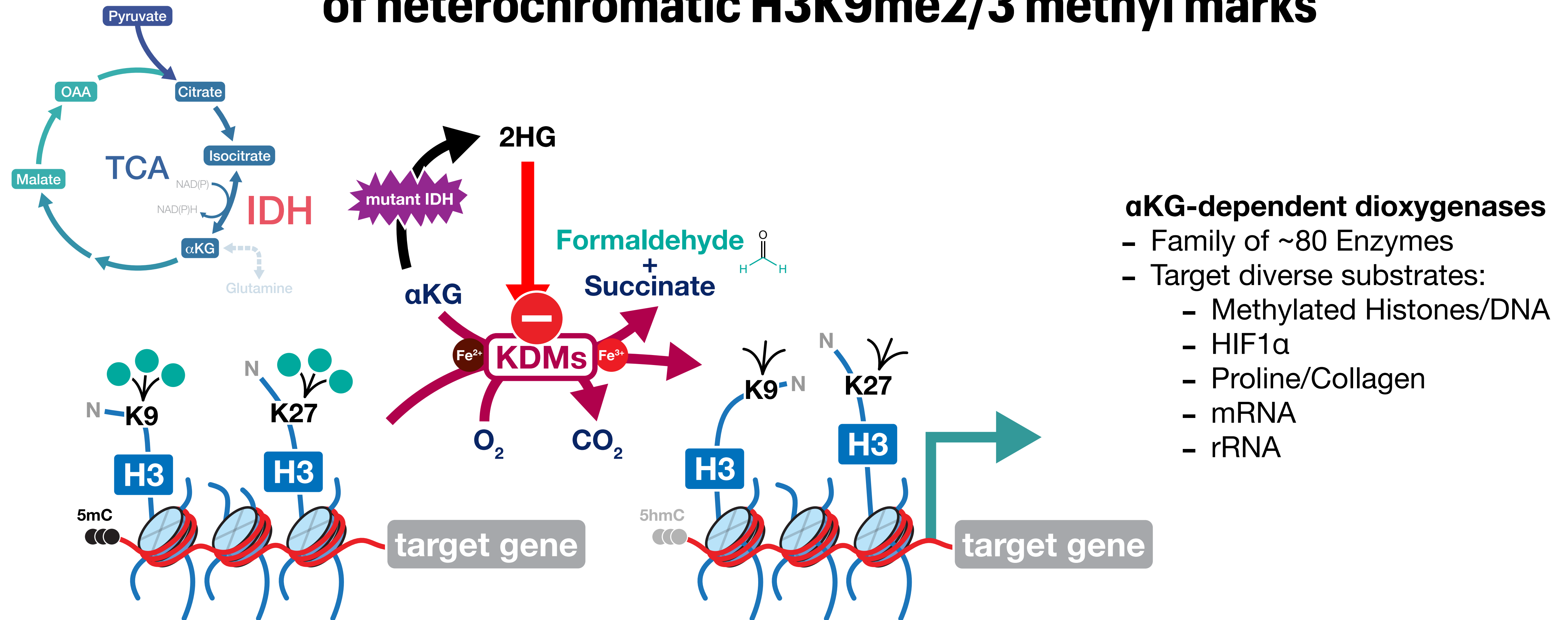


αKG-dependent dioxygenases

- Family of ~80 Enzymes
- Target diverse substrates:
 - Methylated Histones/DNA
 - HIF1α
 - Proline/Collagen
 - mRNA
 - rRNA

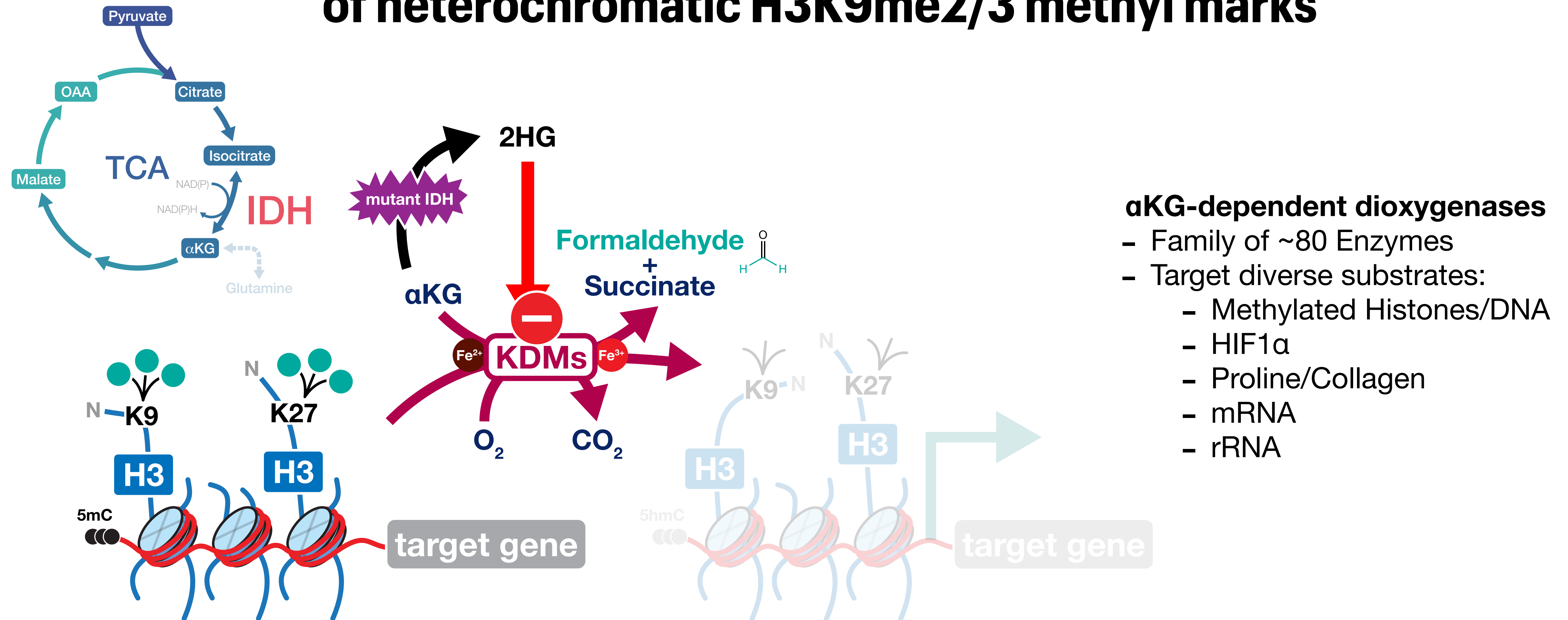
KDMs = Lysine Demethylase
αKG = alpha-Ketoglutarate

IDH mutations block differentiation by impairing the removal of heterochromatic H3K9me2/3 methyl marks



KDMs = Lysine Demethylase
αKG = alpha-Ketoglutarate

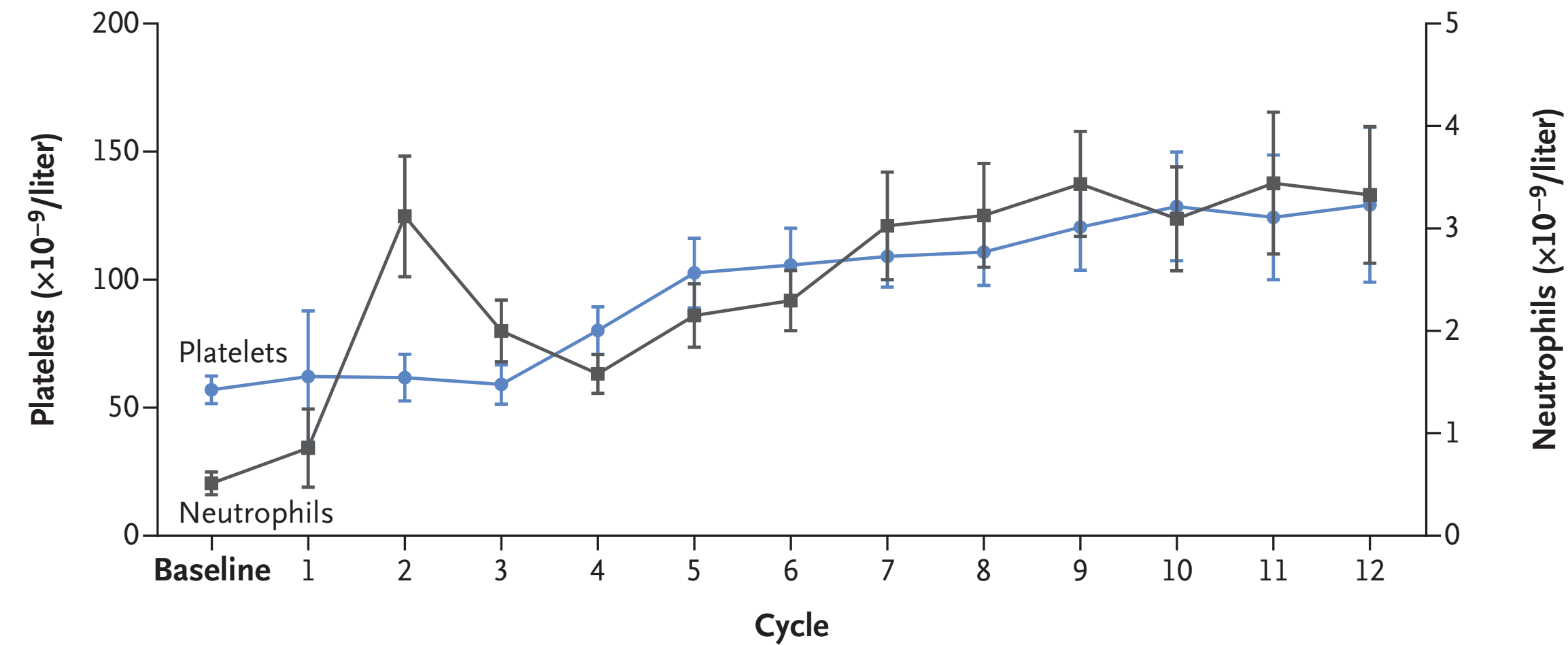
IDH mutations block differentiation by impairing the removal of heterochromatic H3K9me2/3 methyl marks



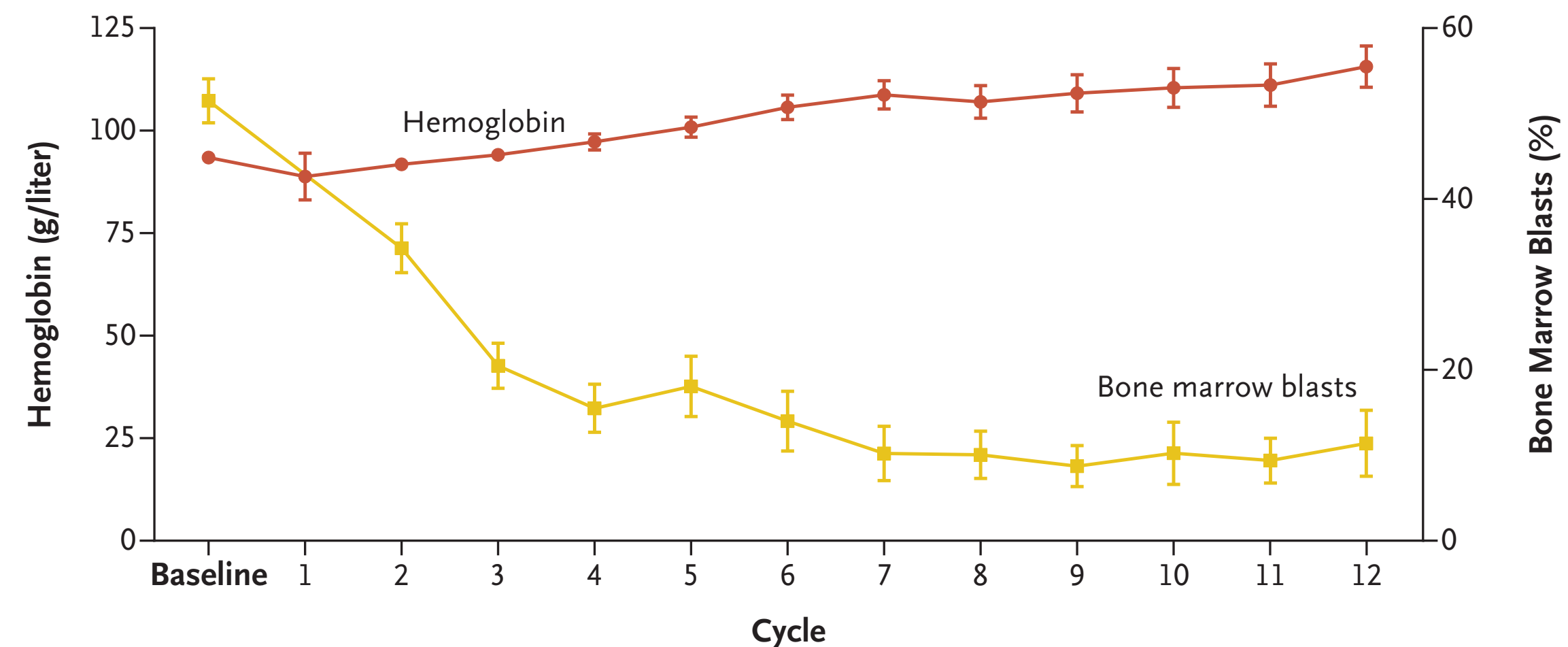
KDMs = Lysine Demethylase
αKG = alpha-Ketoglutarate

IDH inhibitors are effective in IDH-mutated Leukemia and they work by differentiating leukemic cells

A Platelets and Neutrophils

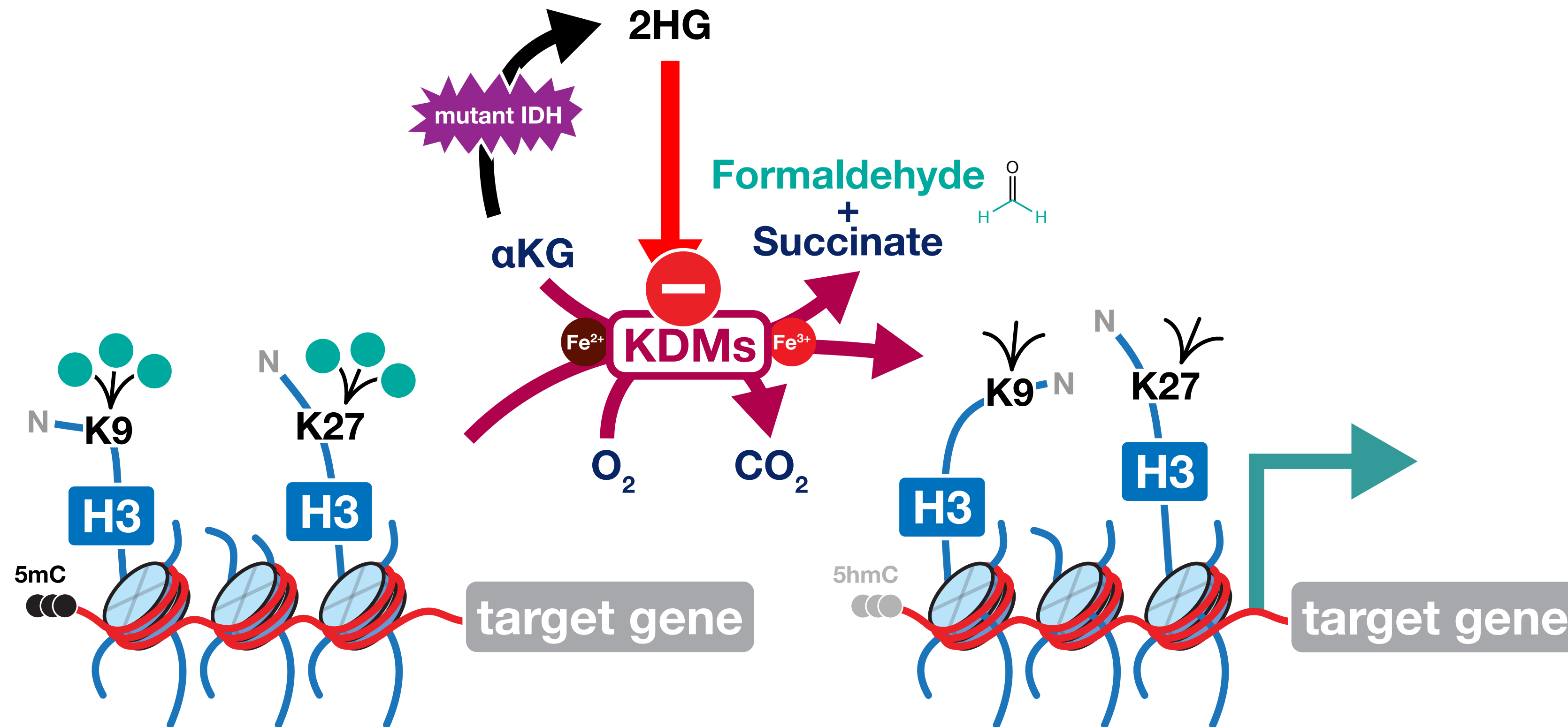


B Hemoglobin and Bone Marrow Blasts



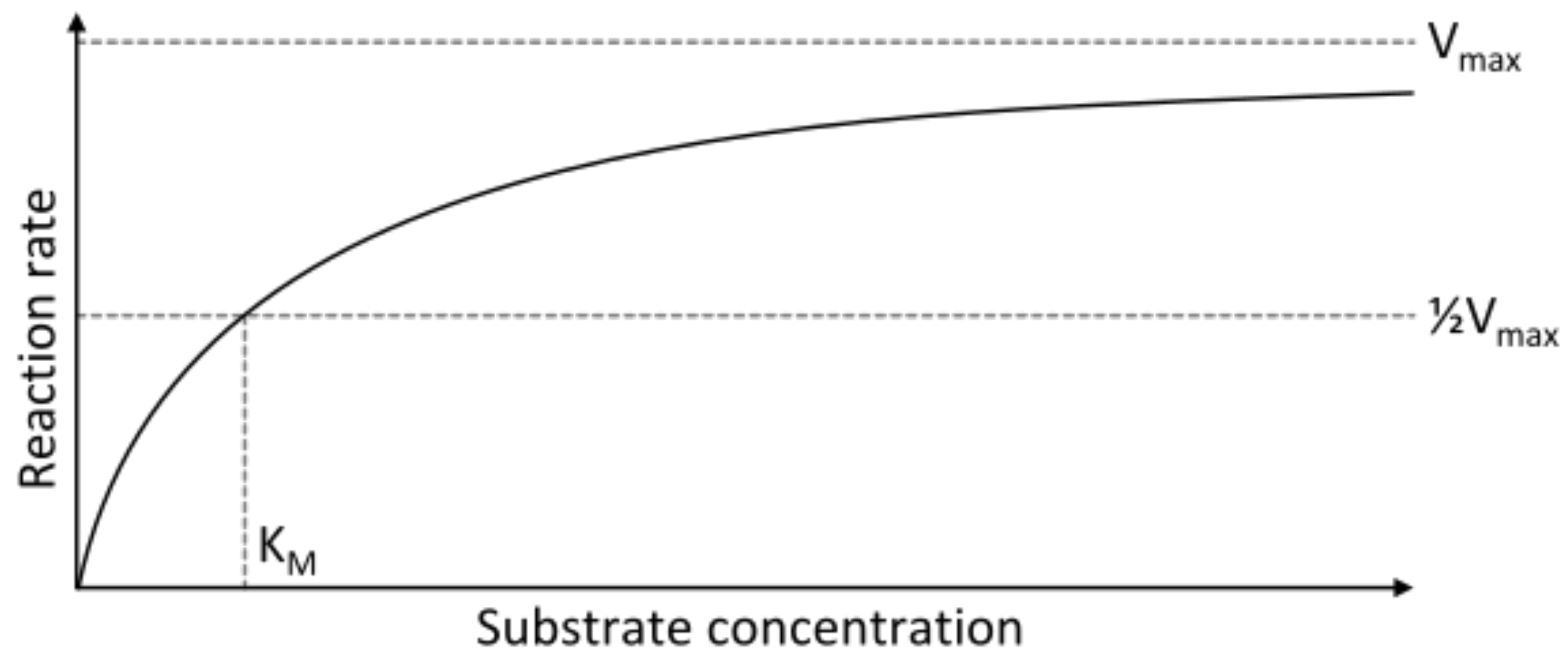
**IDH MUTATIONS OCCUR IN A SMALL FRACTION OF PATIENTS;
ARE THESE CONCEPTS GENERALIZABLE?**

Can dioxygenases act as sensors of metabolism?

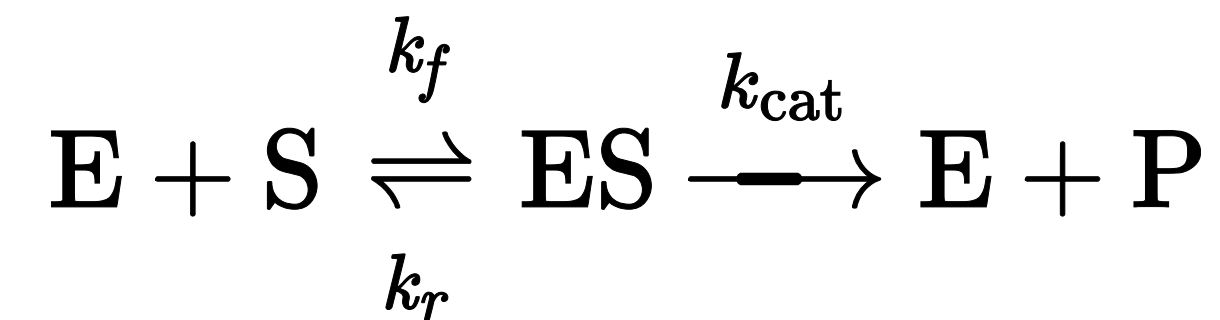
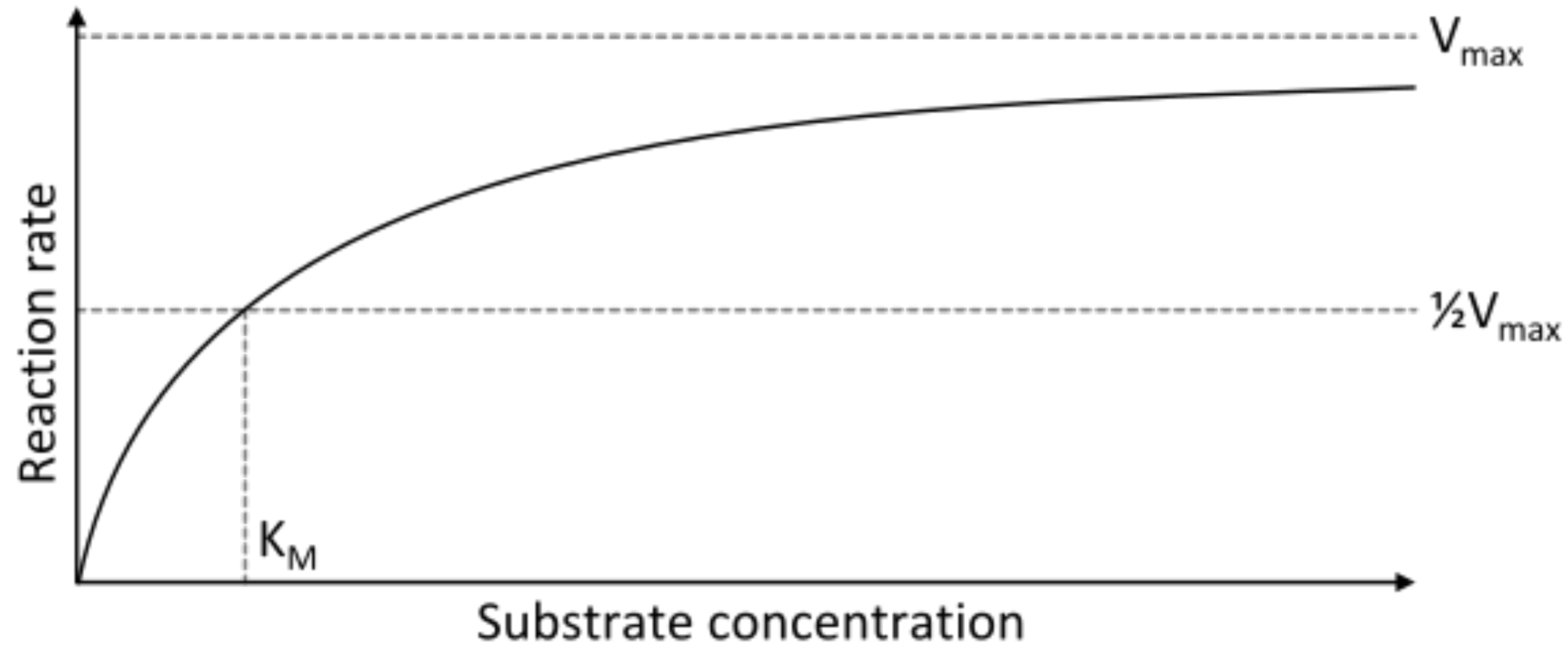


KDMs = Lysine Demethylase
αKG = alpha-Ketoglutarate

PMID: 31182575
PMID: 29760106



Michaelis–Menten kinetics:



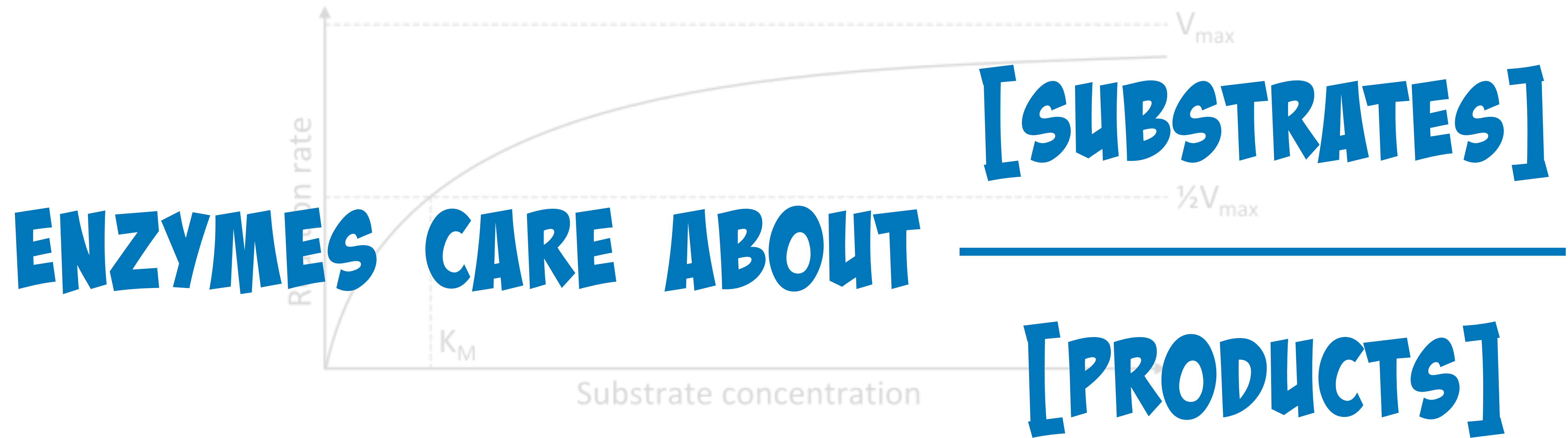
$$v = \frac{d[\text{P}]}{dt} = V_{\max} \frac{[\text{S}]}{K_M + [\text{S}]}$$



Leonor Michaelis



Maud Menten

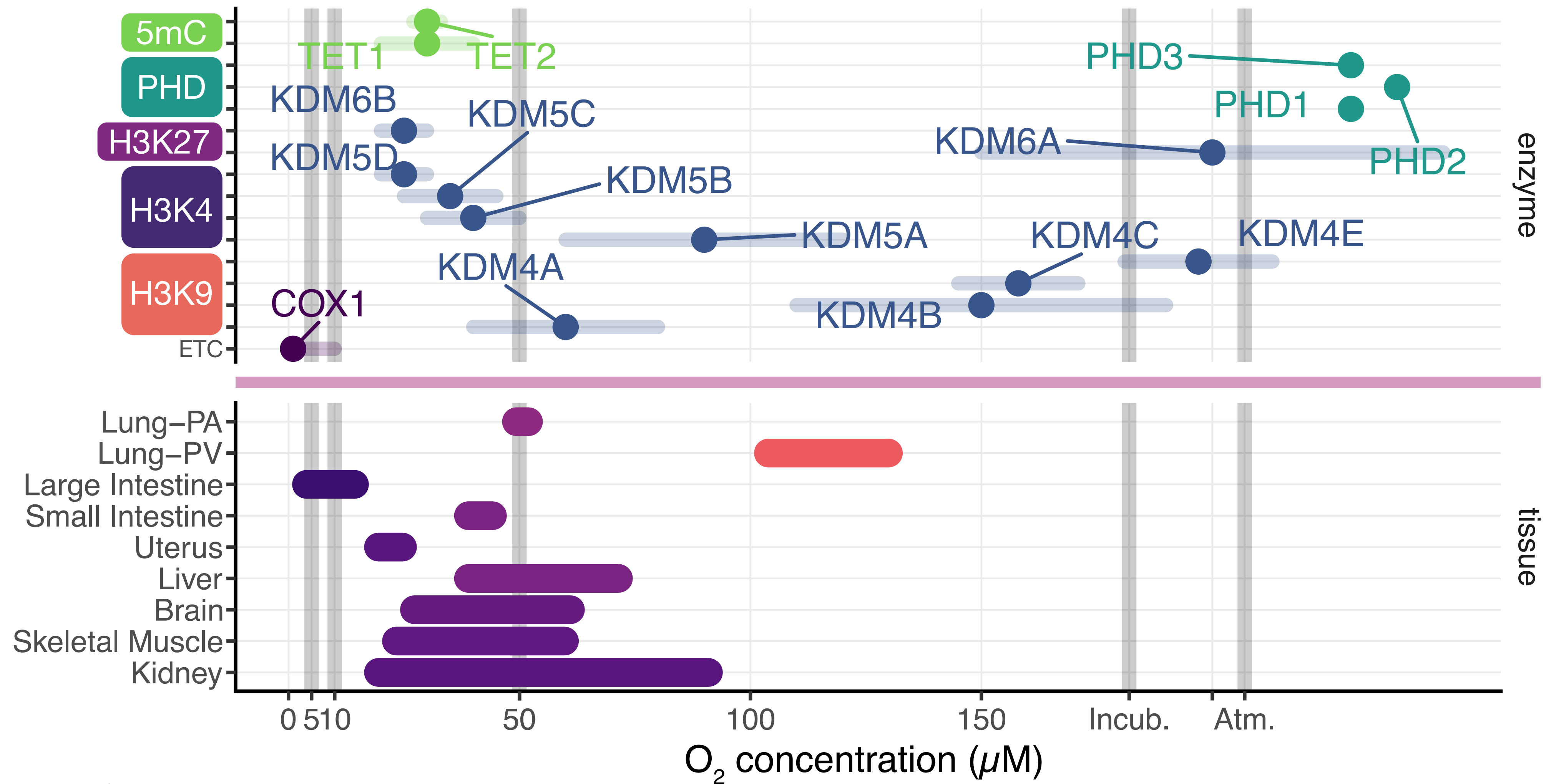


Leonor Michaelis



Maud Menten

The 'regulatable' space of chromatin metabolism

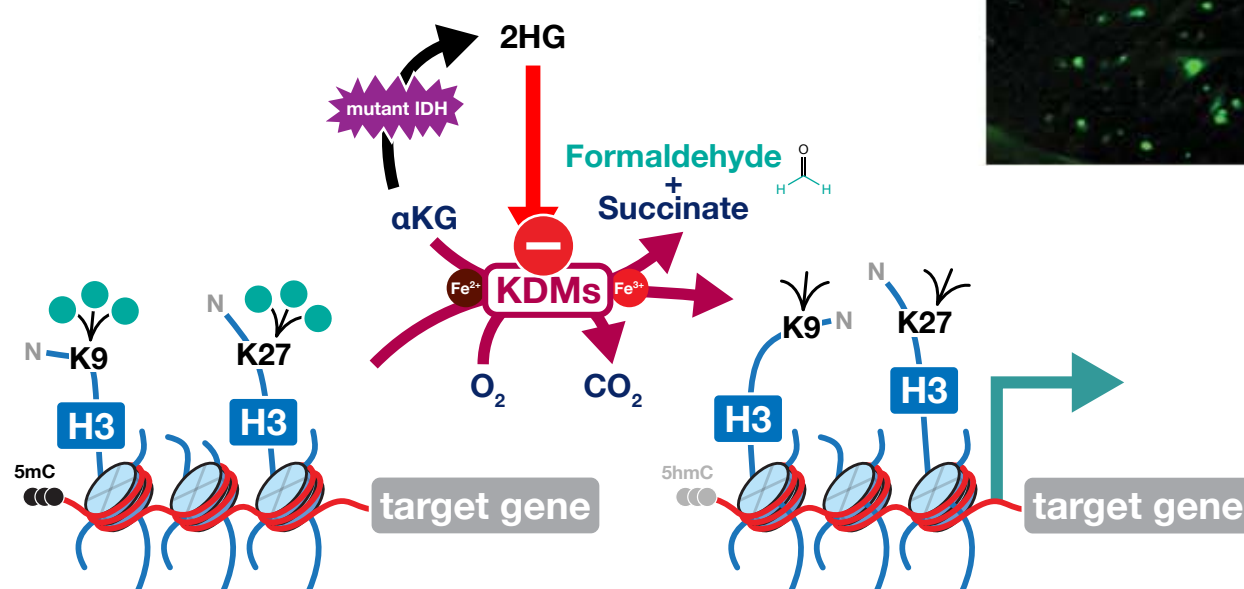
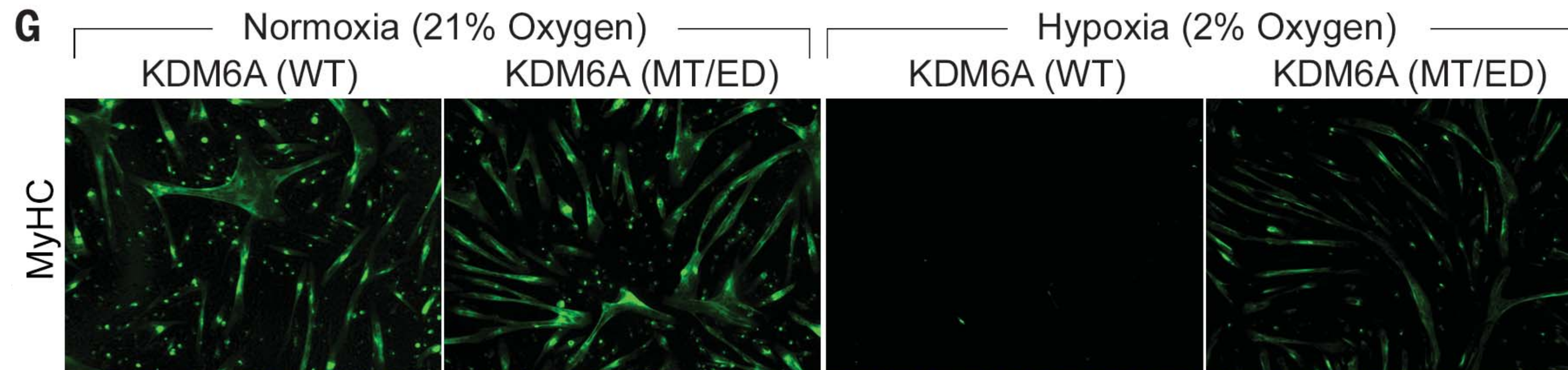


Tsilil Ast and Vamsi K. Mootha
 Oxygen and mammalian cell culture: are we
 repeating the experiment of Dr. Ox?

Are dioxygenases oxygen sensors?

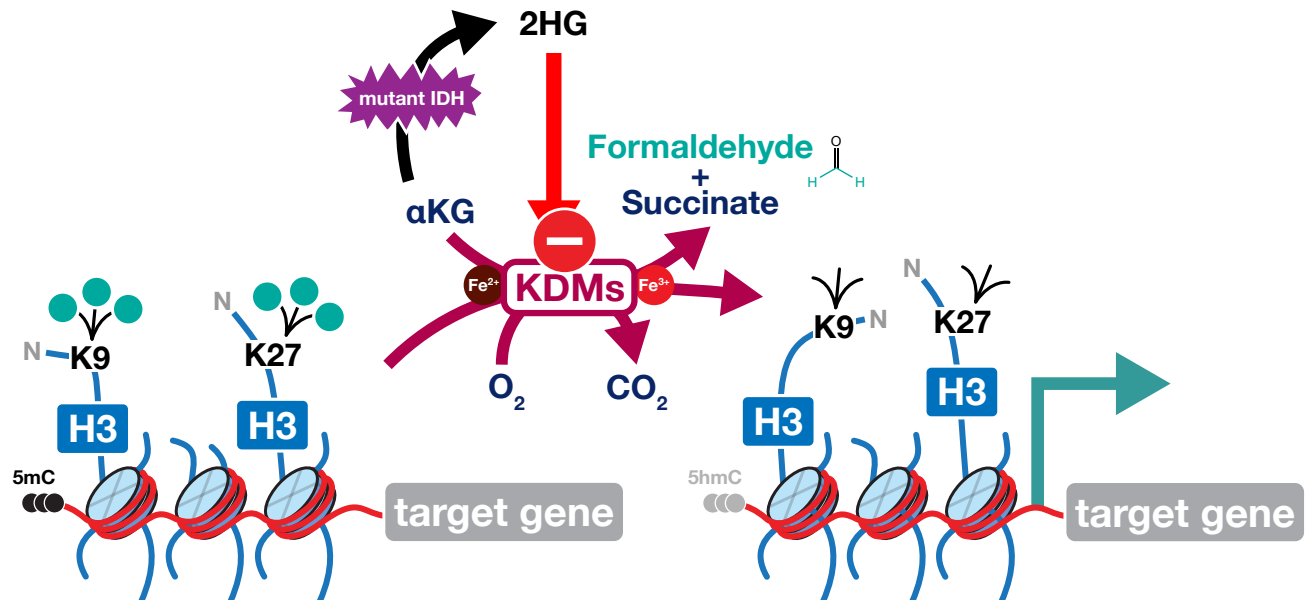
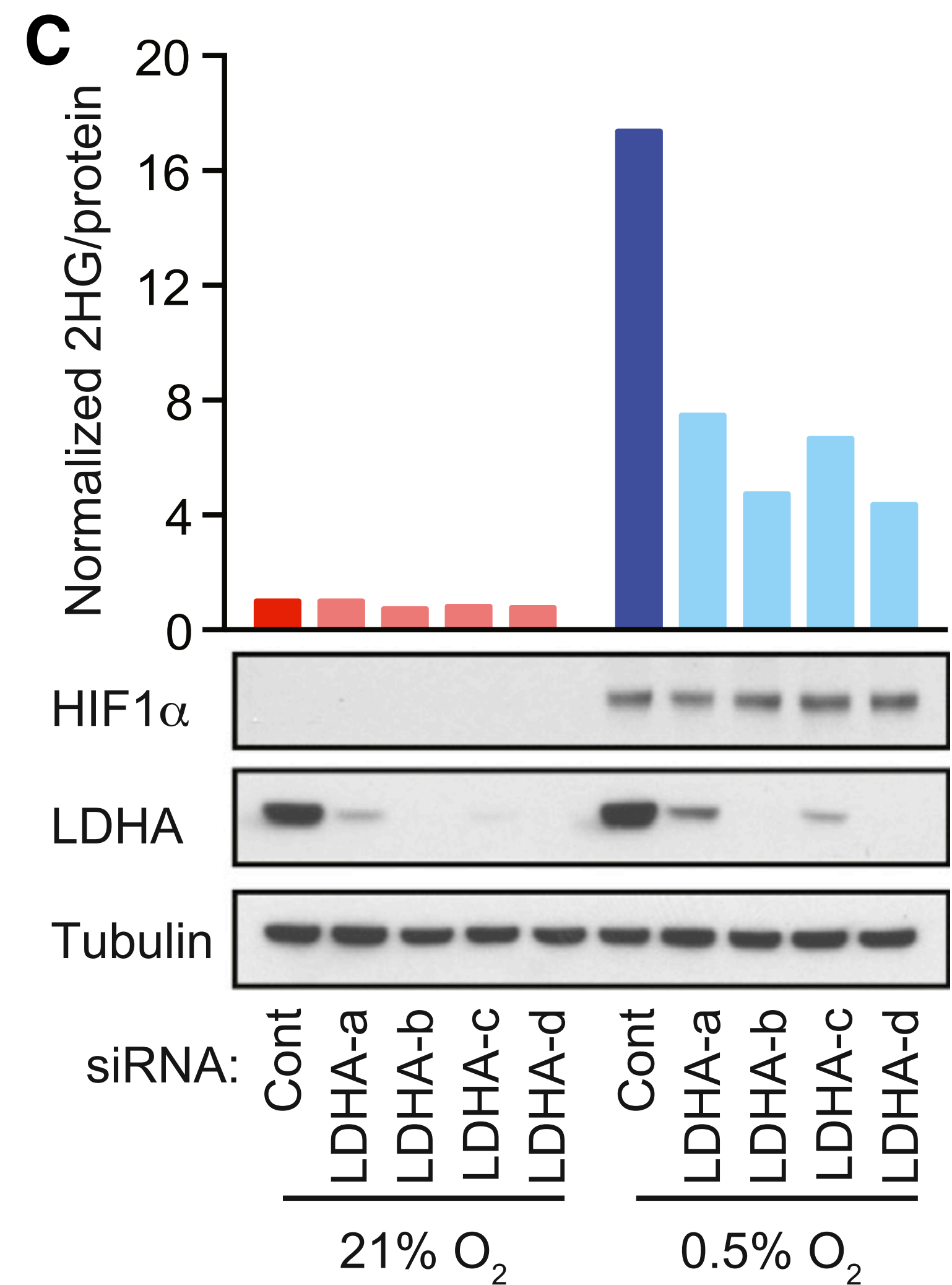


William Kaelin

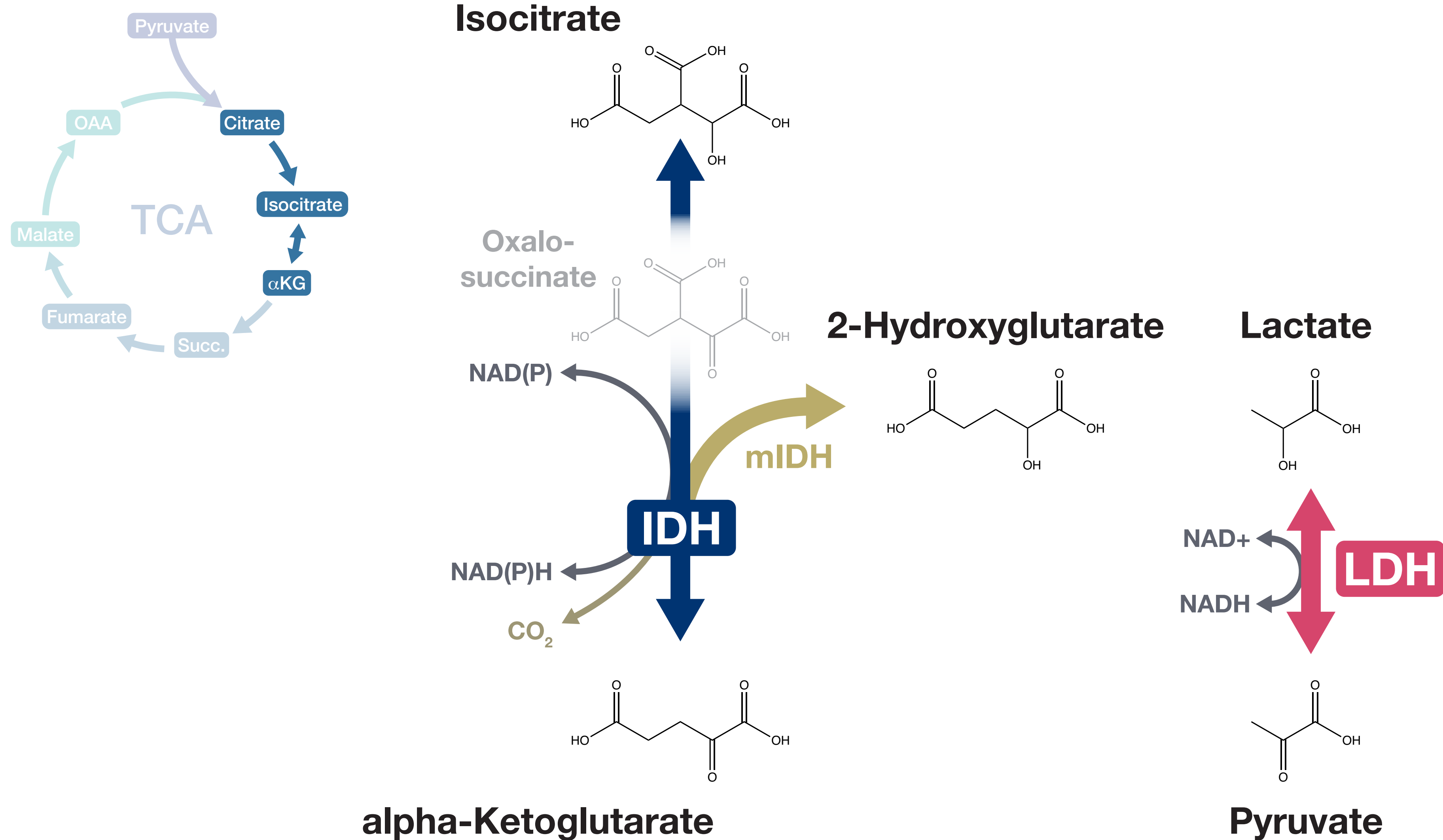


**ENZYMES DON'T READ
TEXTBOOKS EITHER**

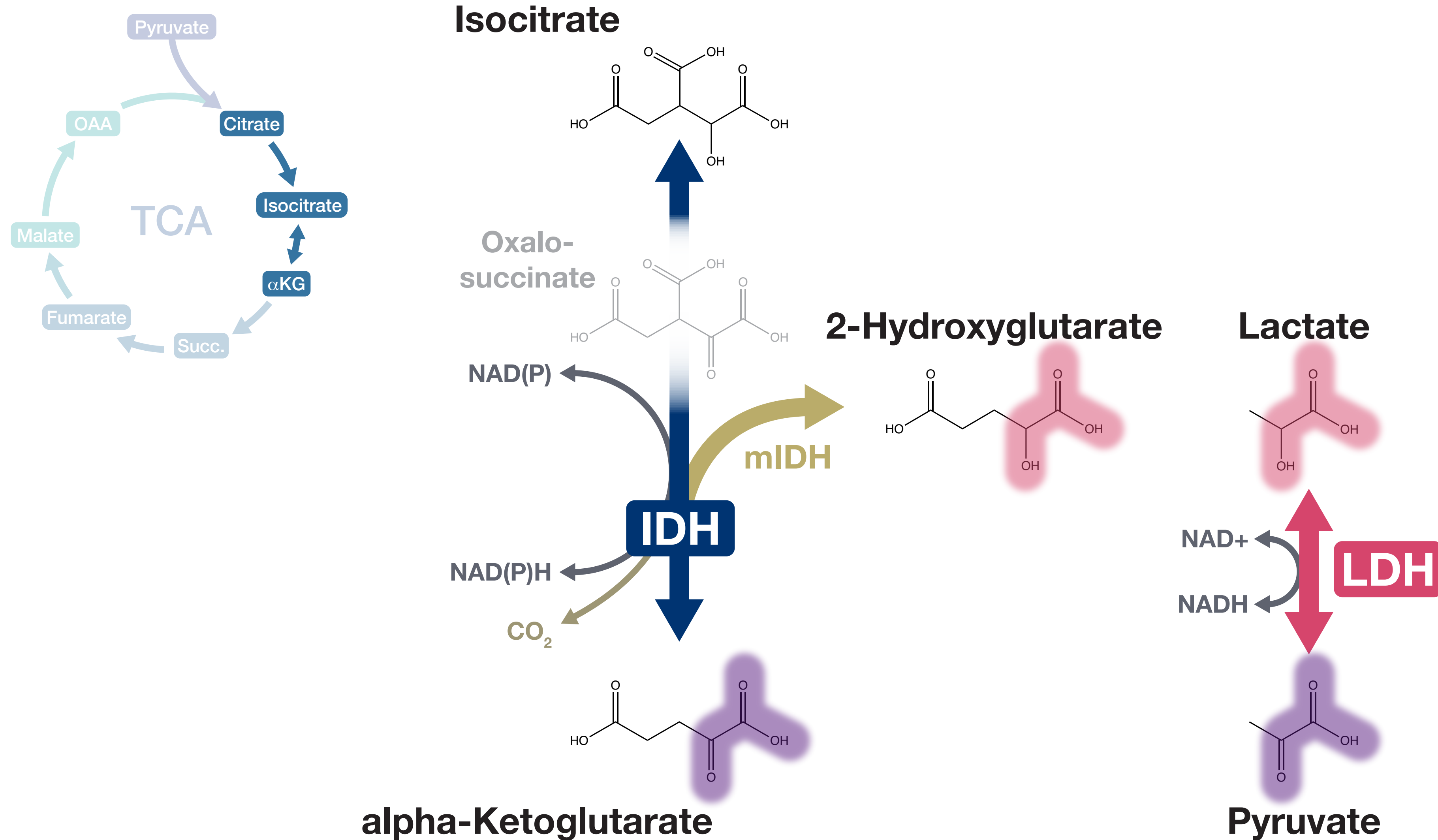
2HG can be produced in **hypoxia** and **acidosis** independently of IDH mutations



2HG can be produced in **hypoxia** and **acidosis** independently of IDH mutations



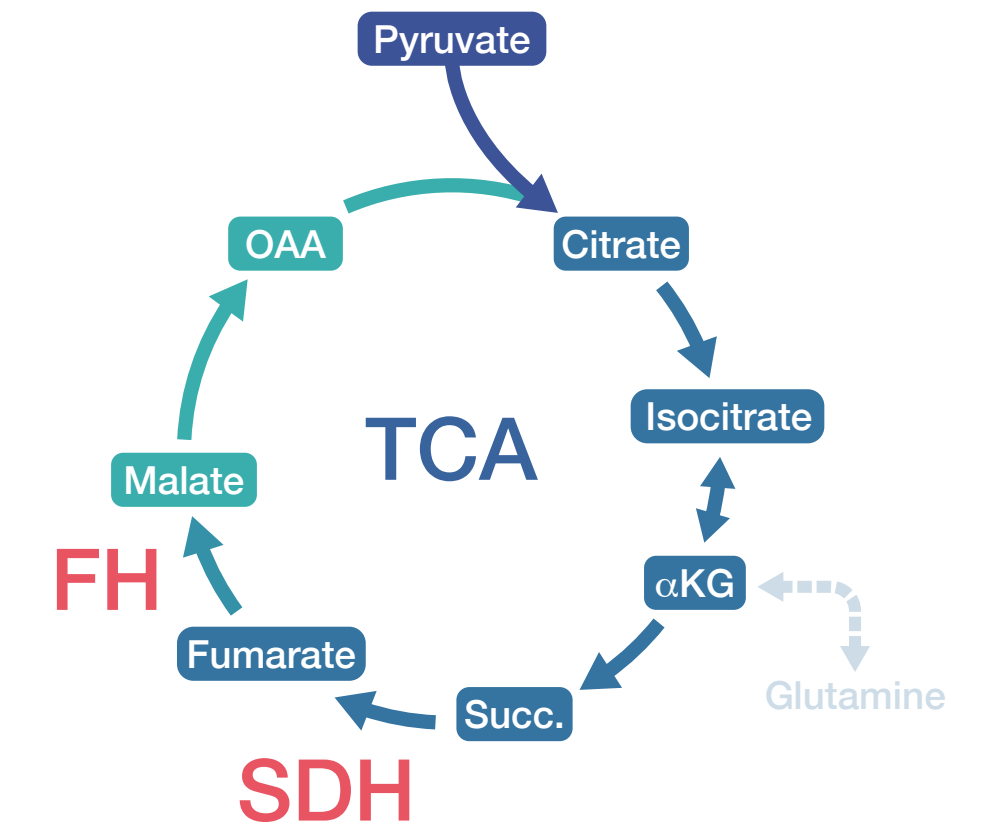
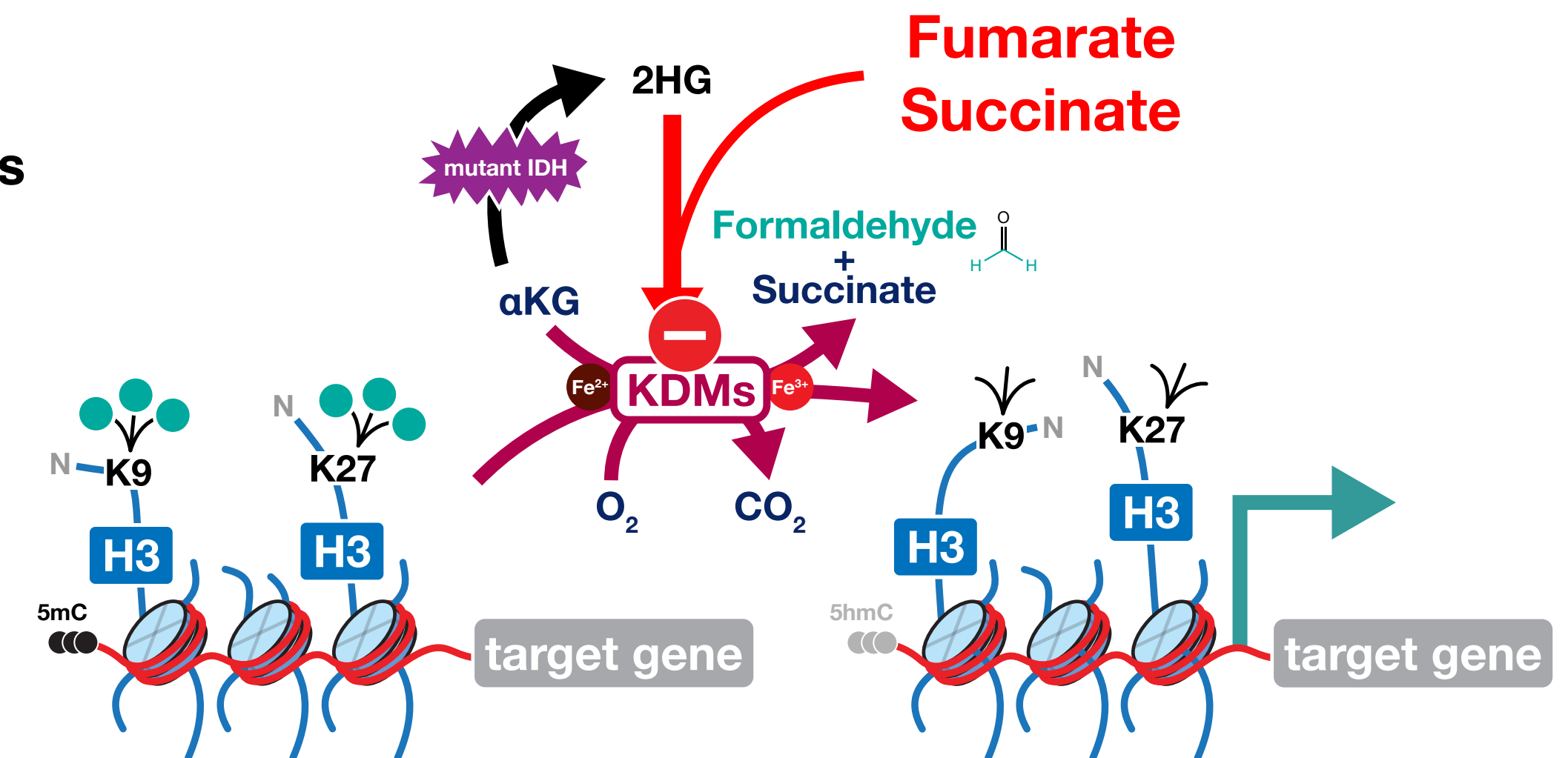
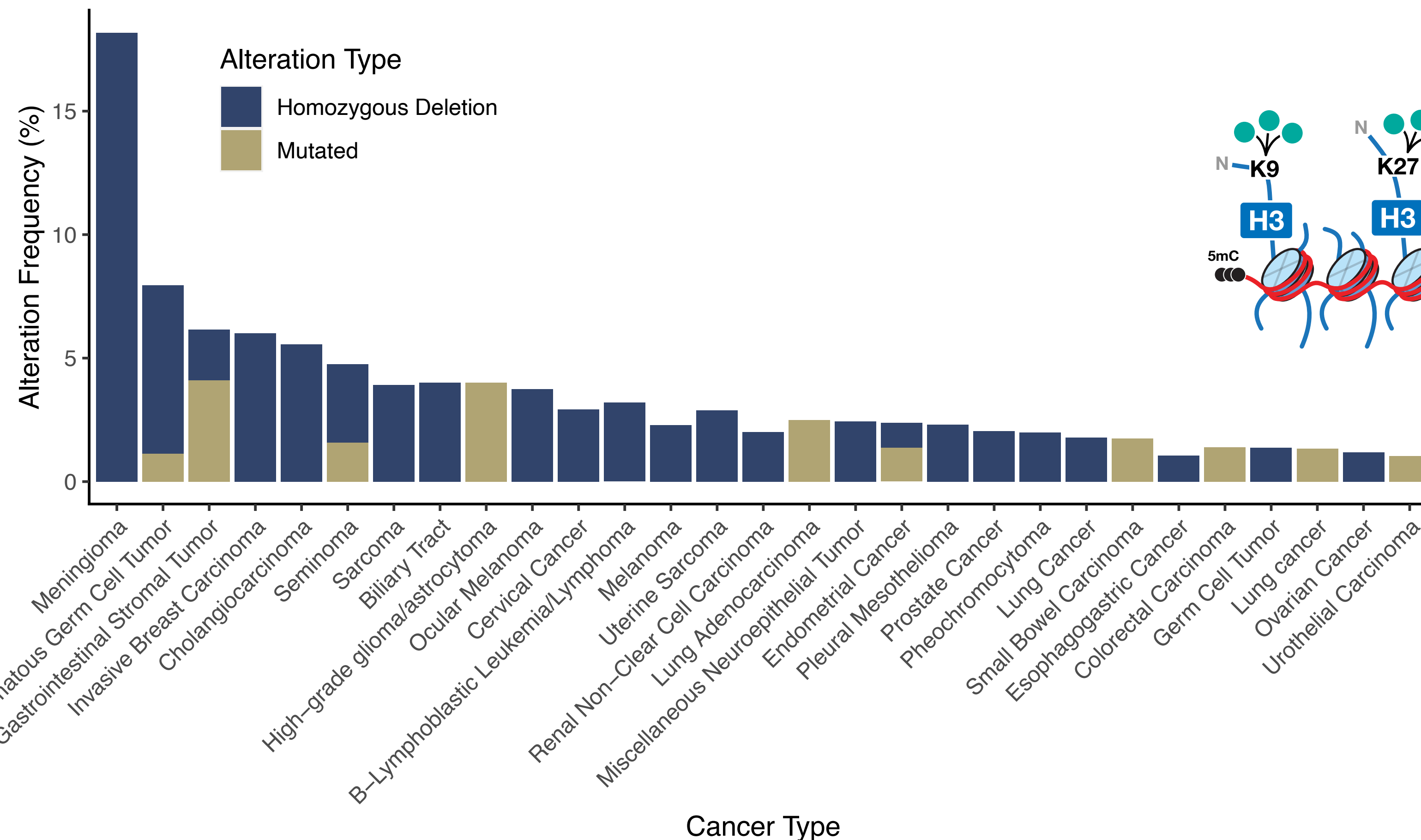
2HG can be produced in **hypoxia** and **acidosis** independently of IDH mutations



PRODUCTS MATTER TOO!!!

Succinate (and Fumarate) can also inhibit dioxygenase function

Frequency of SDH and FH Mutations across tumor types



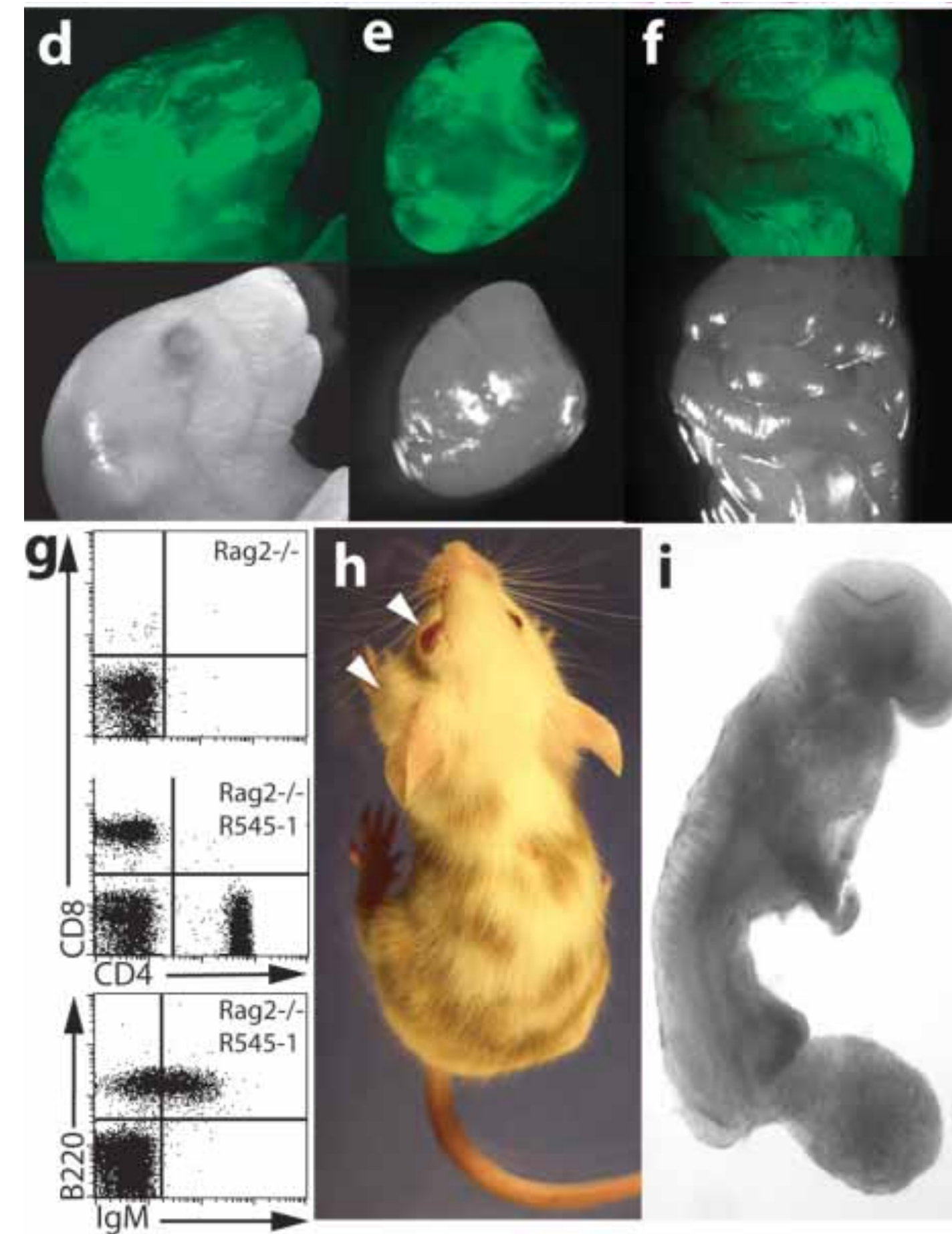
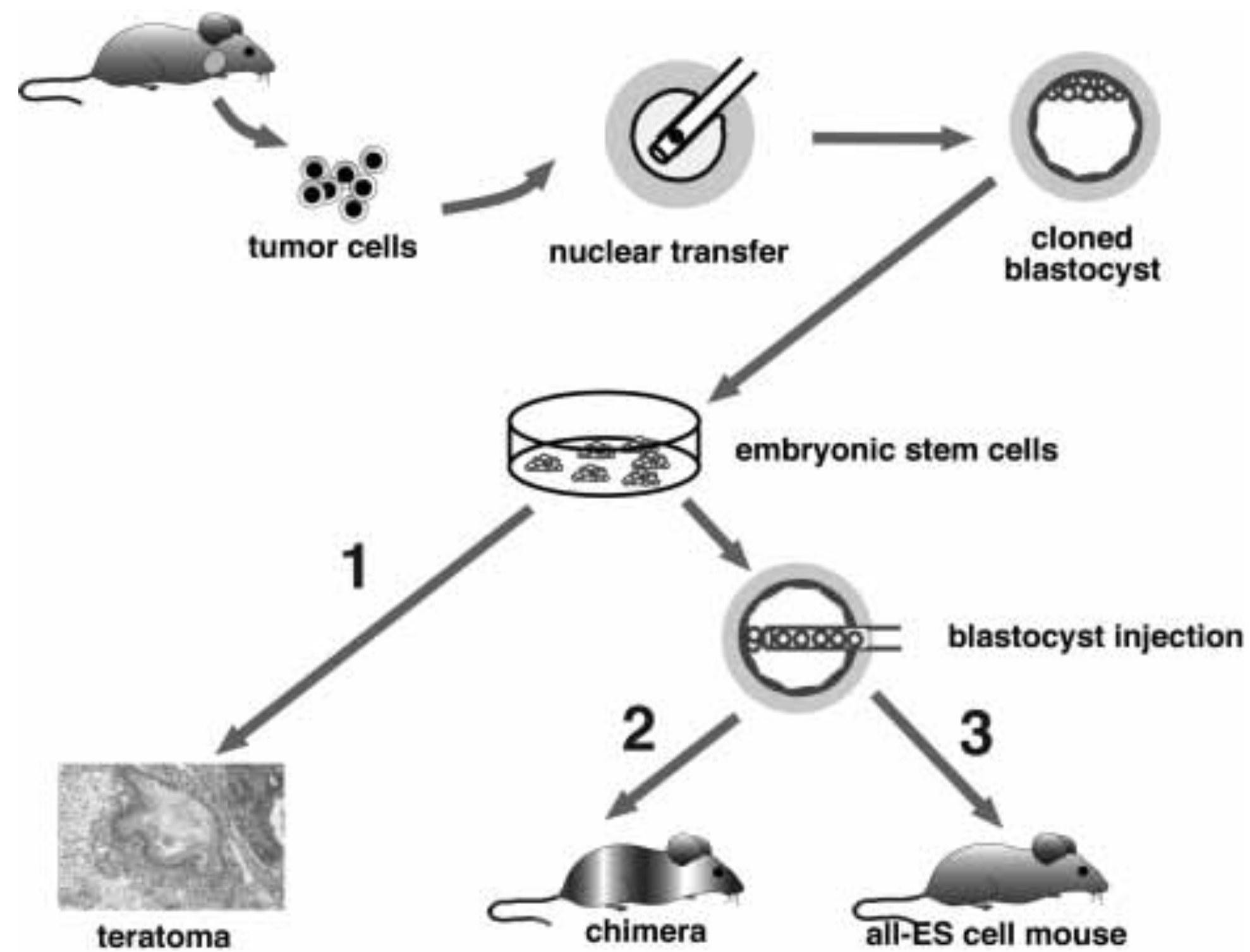
Takehome points 3

1. **Chromatin is a substrate for many metabolic enzymes**
2. **Chromatin modifications have meaning/impart function**
3. **Substrates Matter: altering the levels of metabolites can affect chromatin function**
4. **Mutations can alter metabolism → alter chromatin / cell states**
5. **Remember the K_M !!!**
6. **Enzymes also care about products**
7. **Enzymes don't read textbooks**

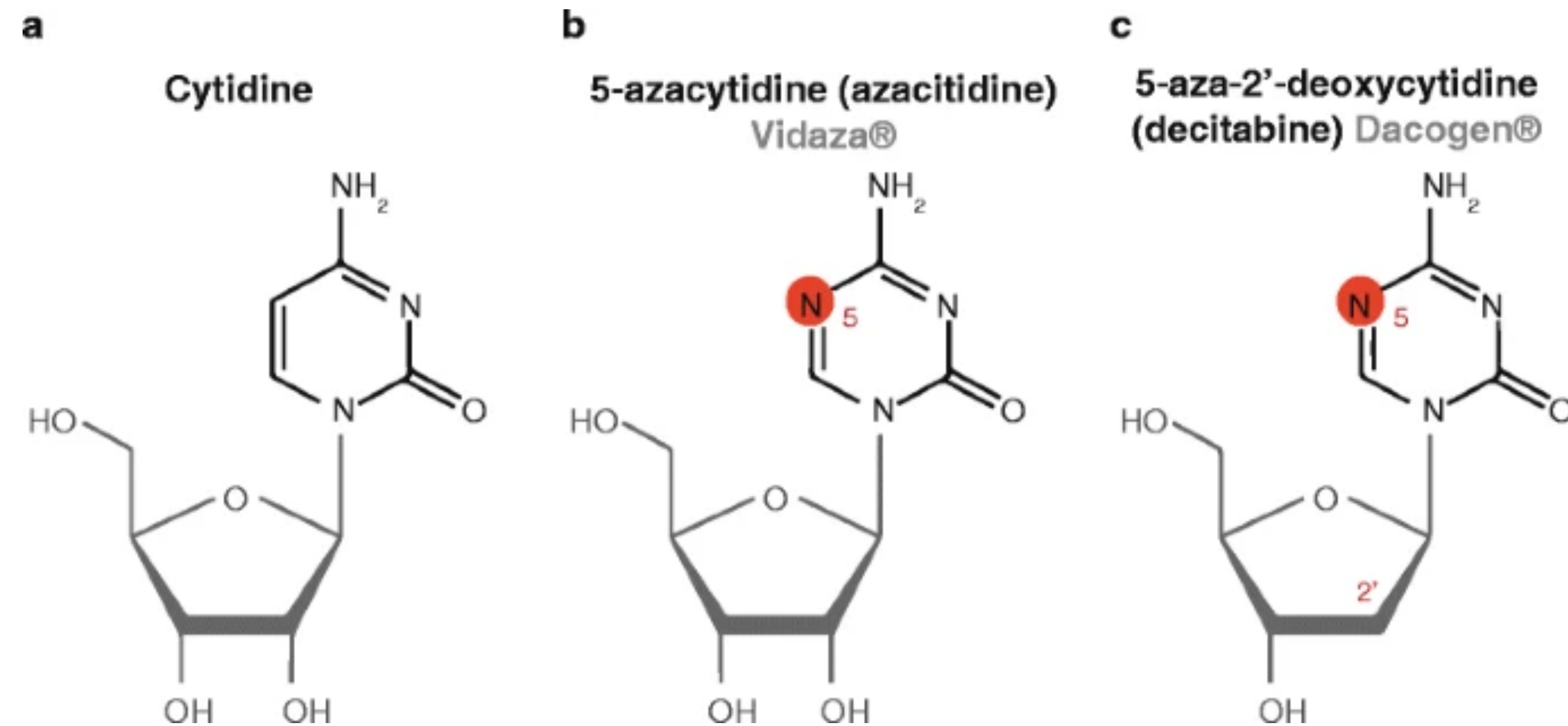


UGH!!! I JUST DON'T
KNOW HERE WE GO
FROM HERE.

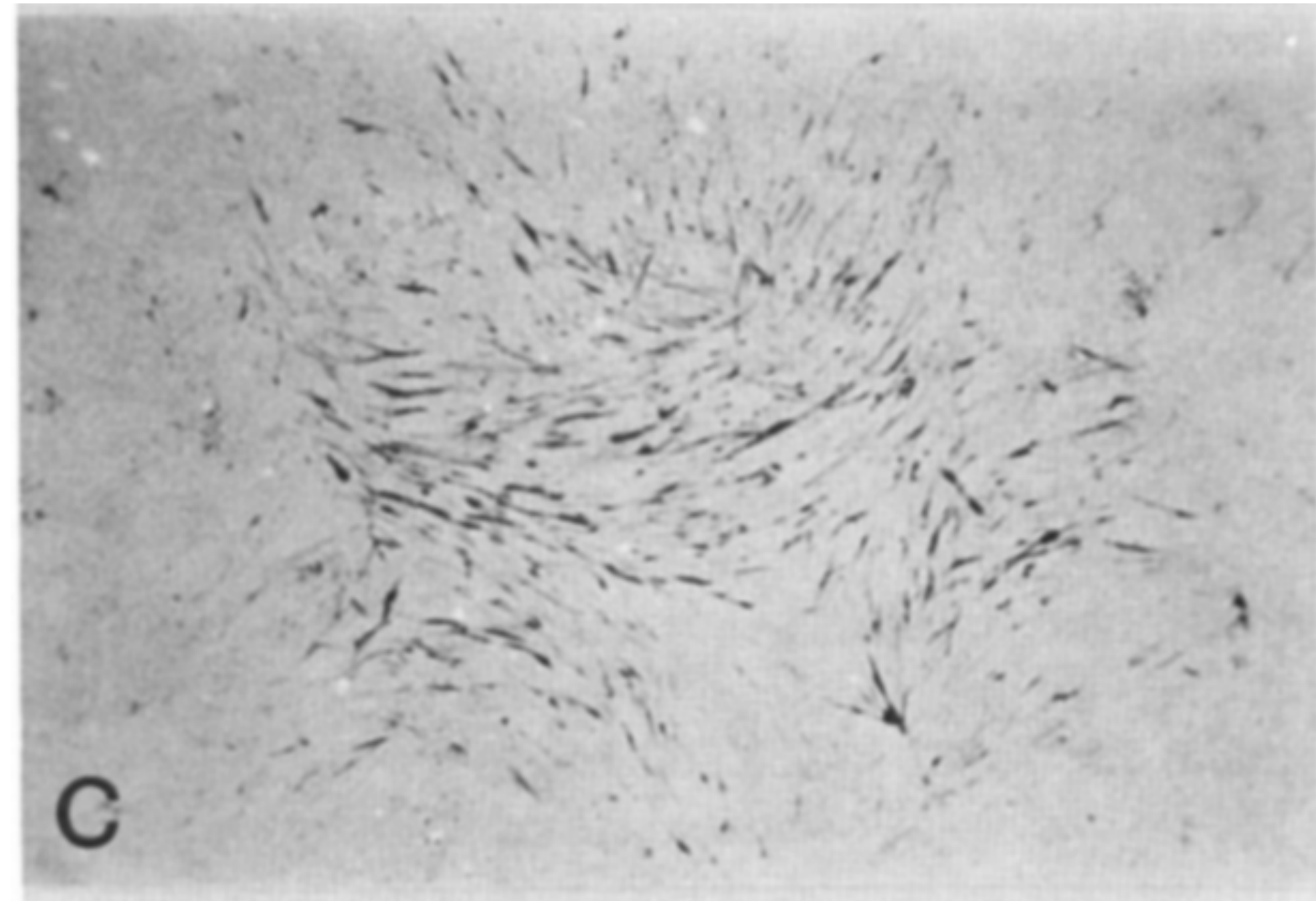
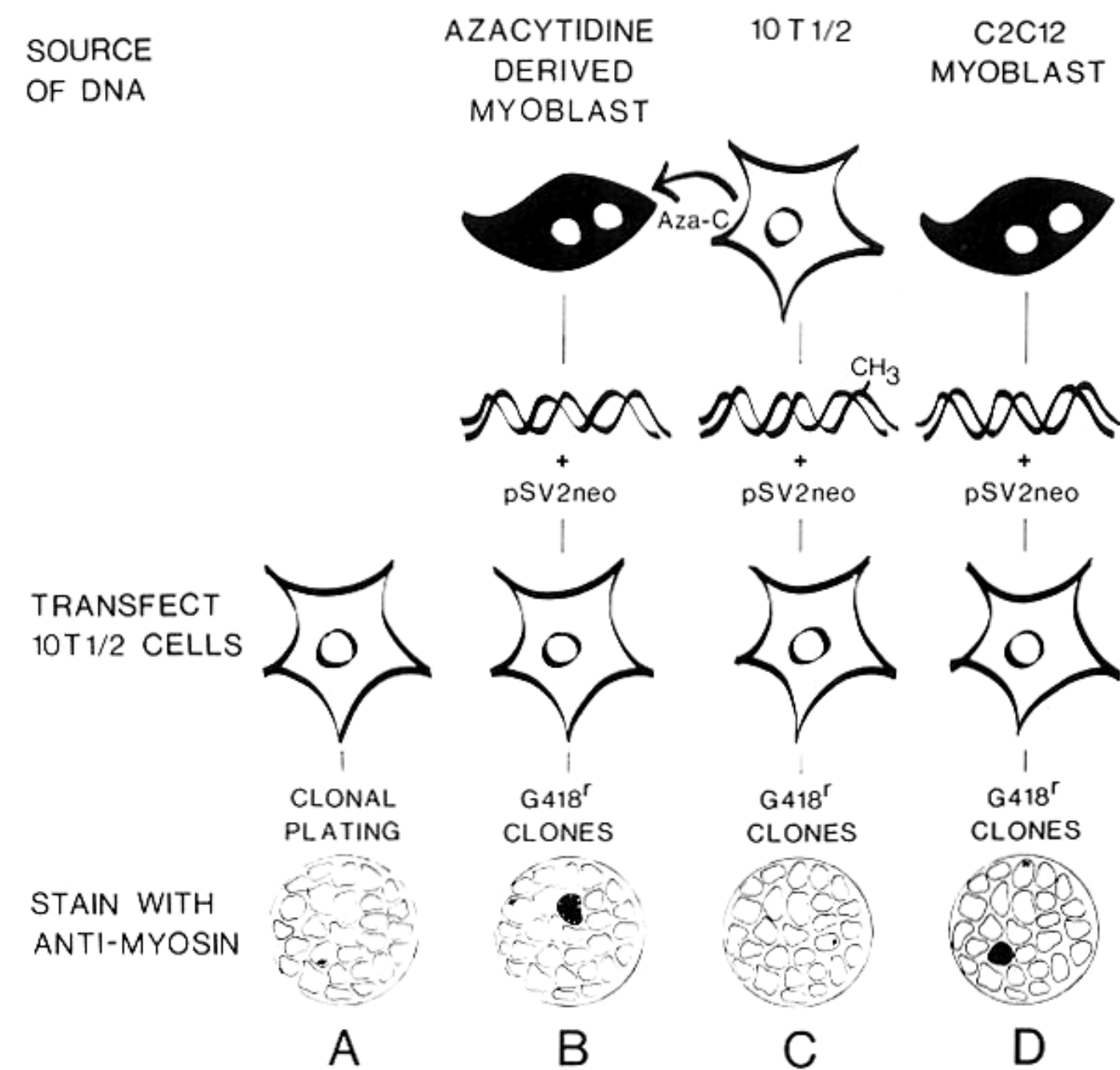
Even a cancer cell line (melanoma) can be reprogrammed



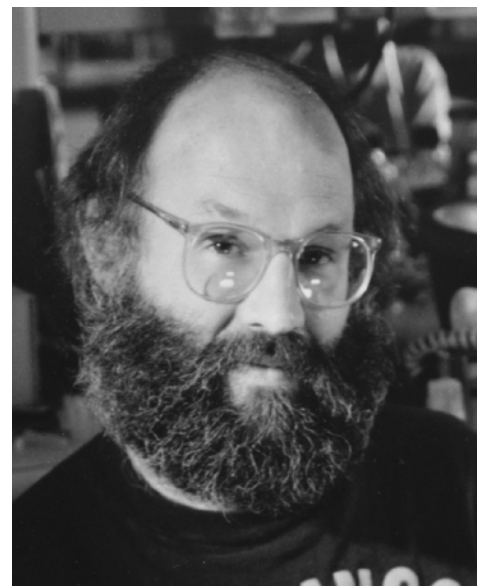
Inhibition of DNA methylation can lead to differentiation through derepression of lineage-specifying transcription factors



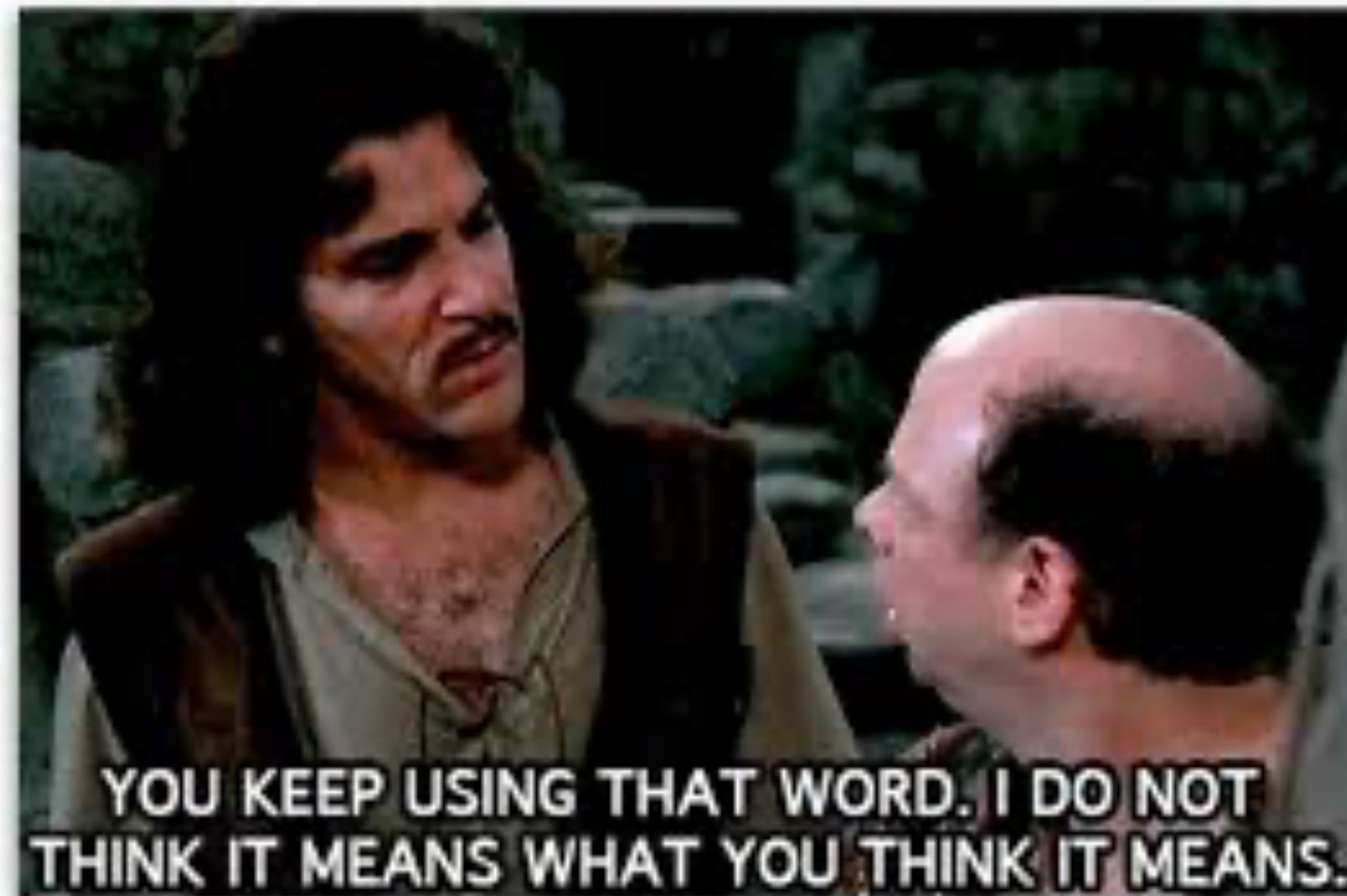
Inhibition of DNA methylation can lead to differentiation through derepression of lineage-specifying transcription factors



Peter Jones



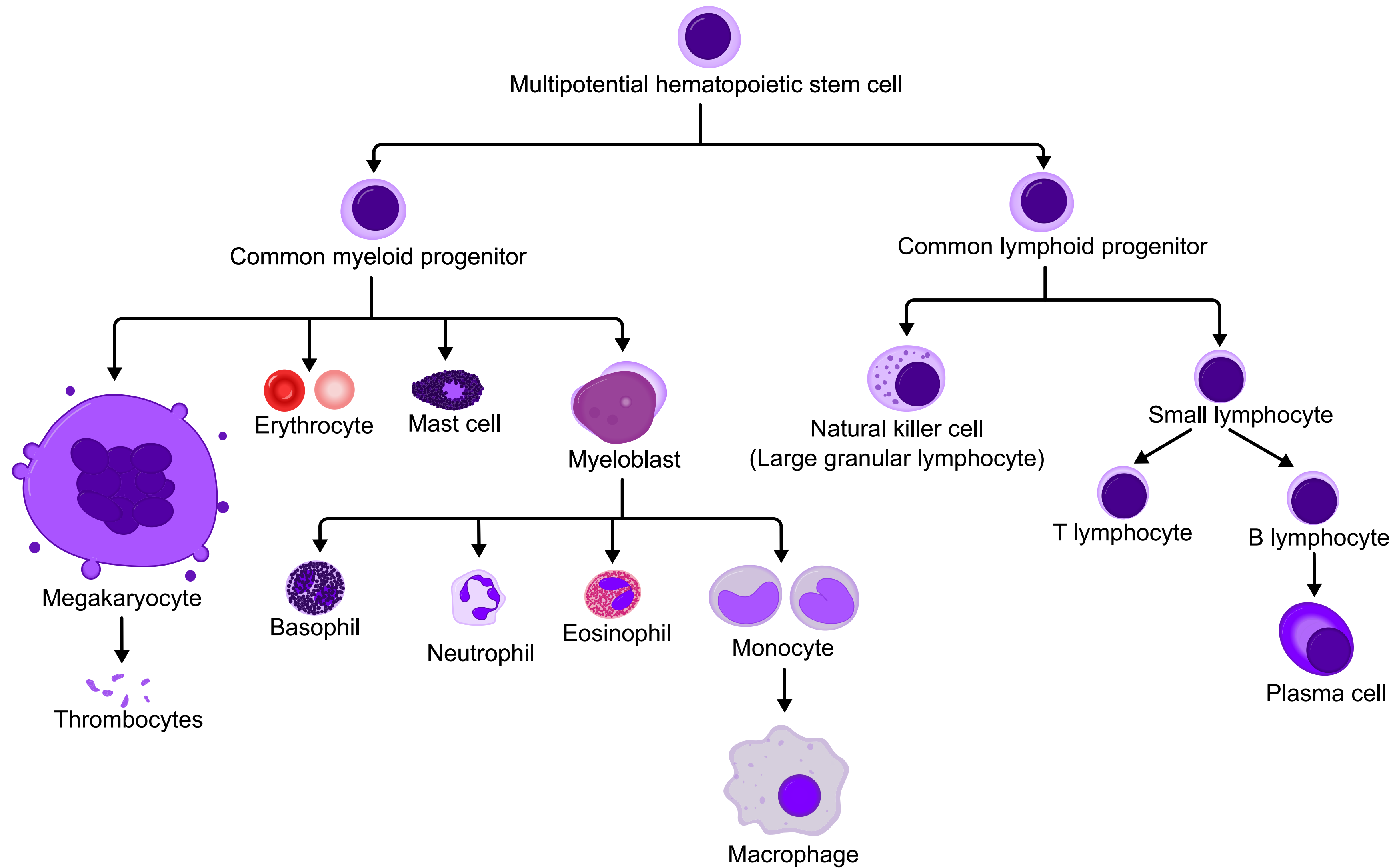
Harold Weintraub



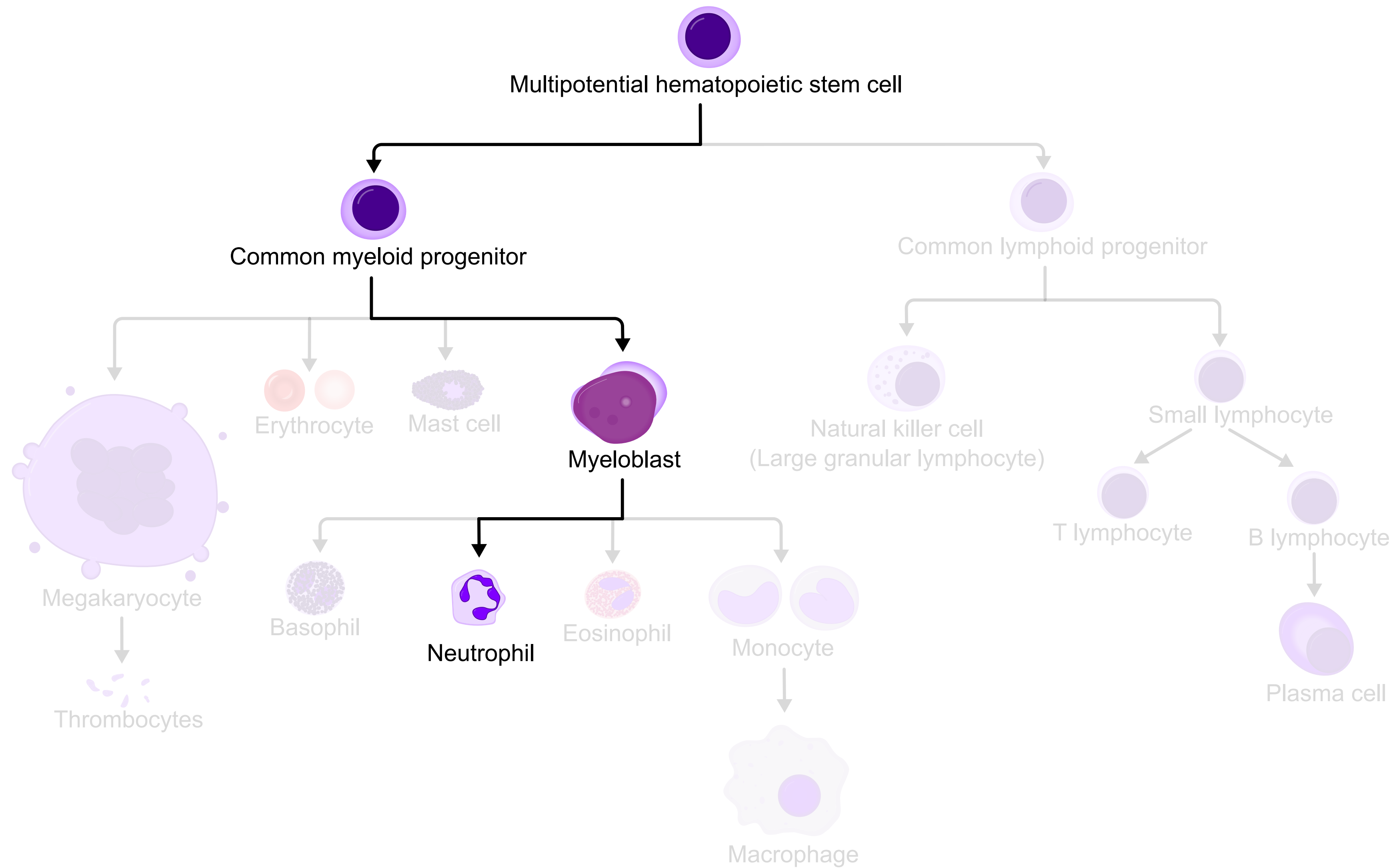
REVISITING ANTIMETABOLITES

5-azacytidine
Decitabine
5-fluorouracil
Capecitabine
Floxuridine
Fludarabine
Cytarabine
Gemcitabine
Azathioprine
Mercaptopurine
Methotrexate
Pemetrexed
(Hydroxyurea NB RNri)

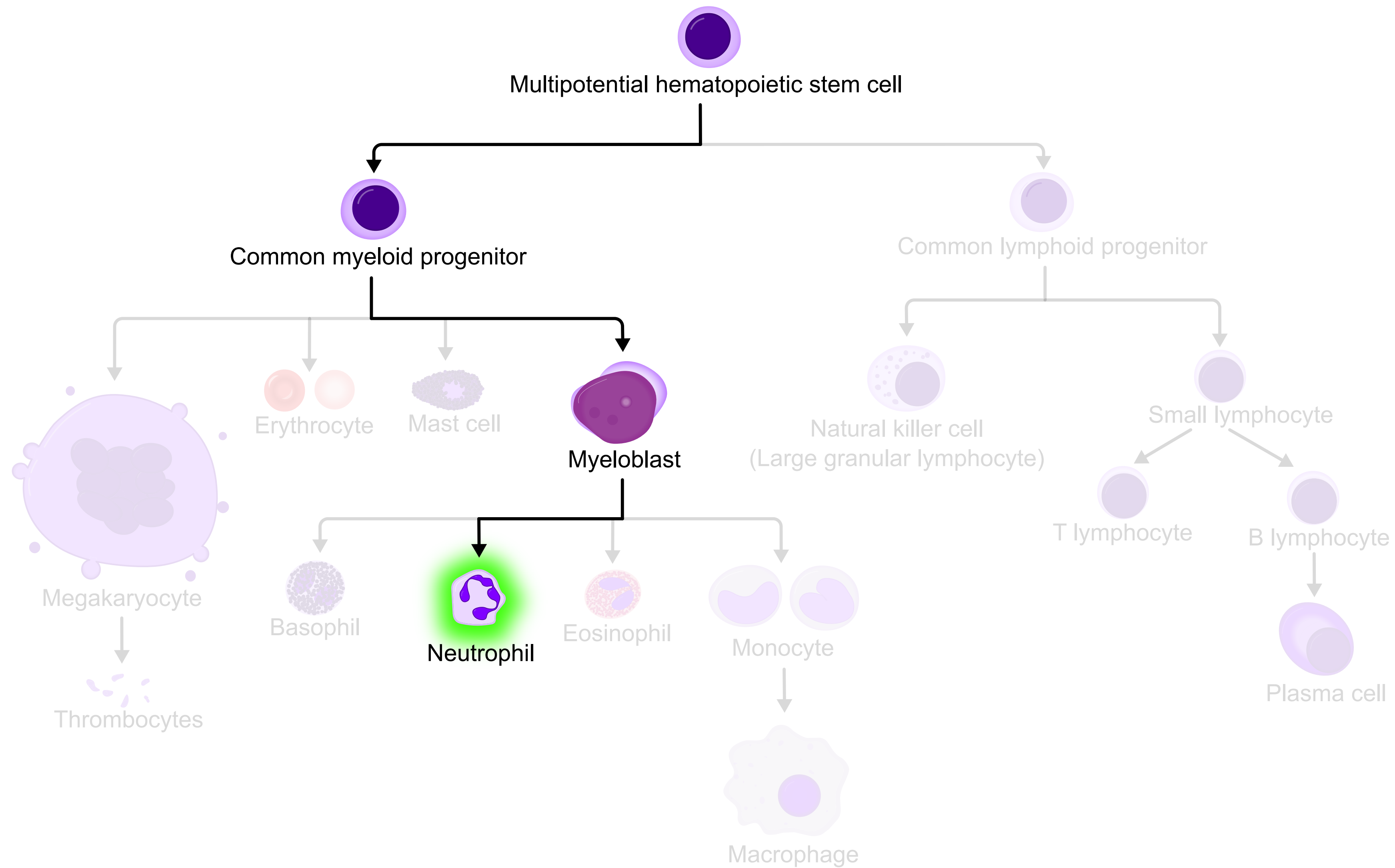
Nucleotide pool imbalance can alter cell fate



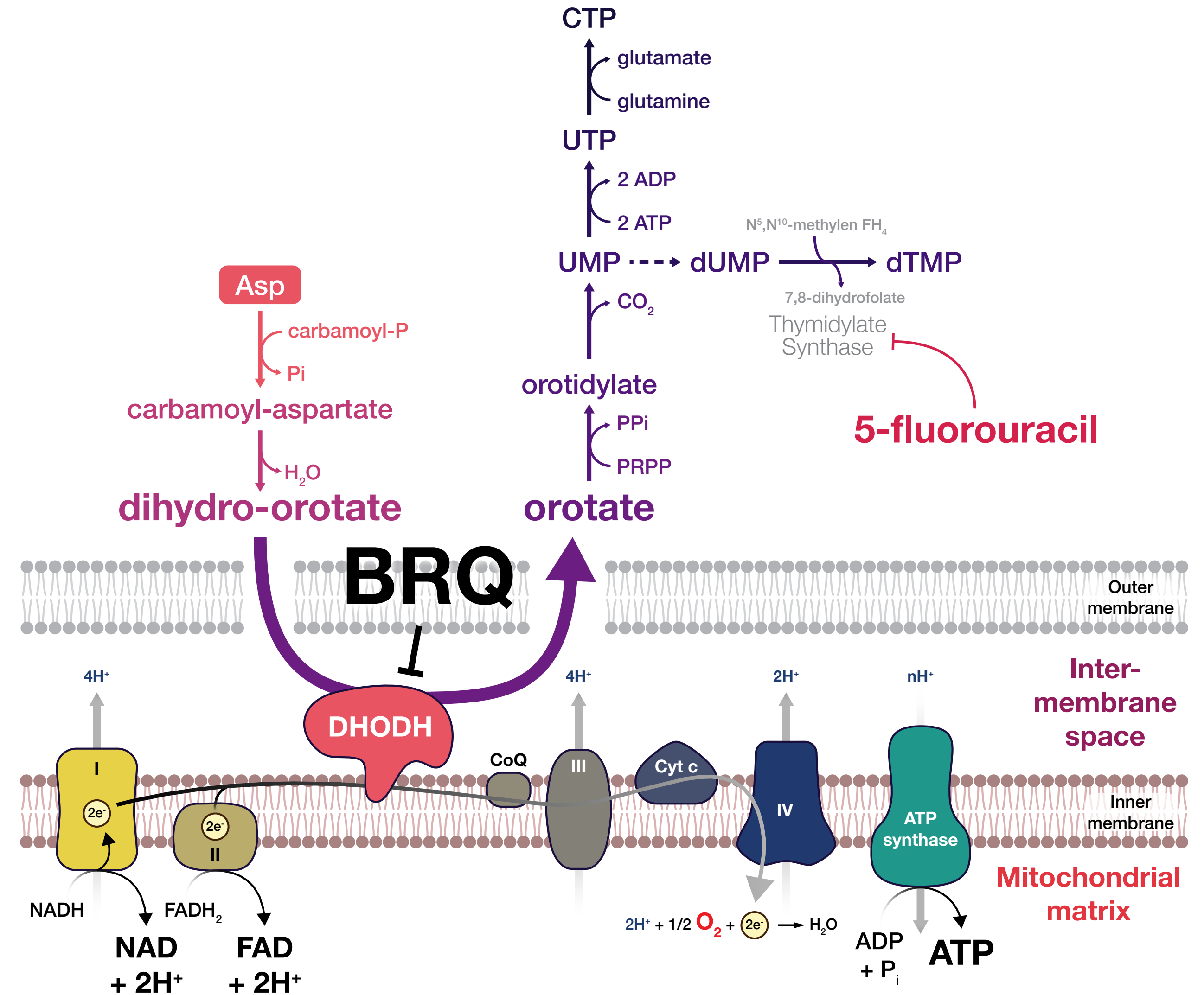
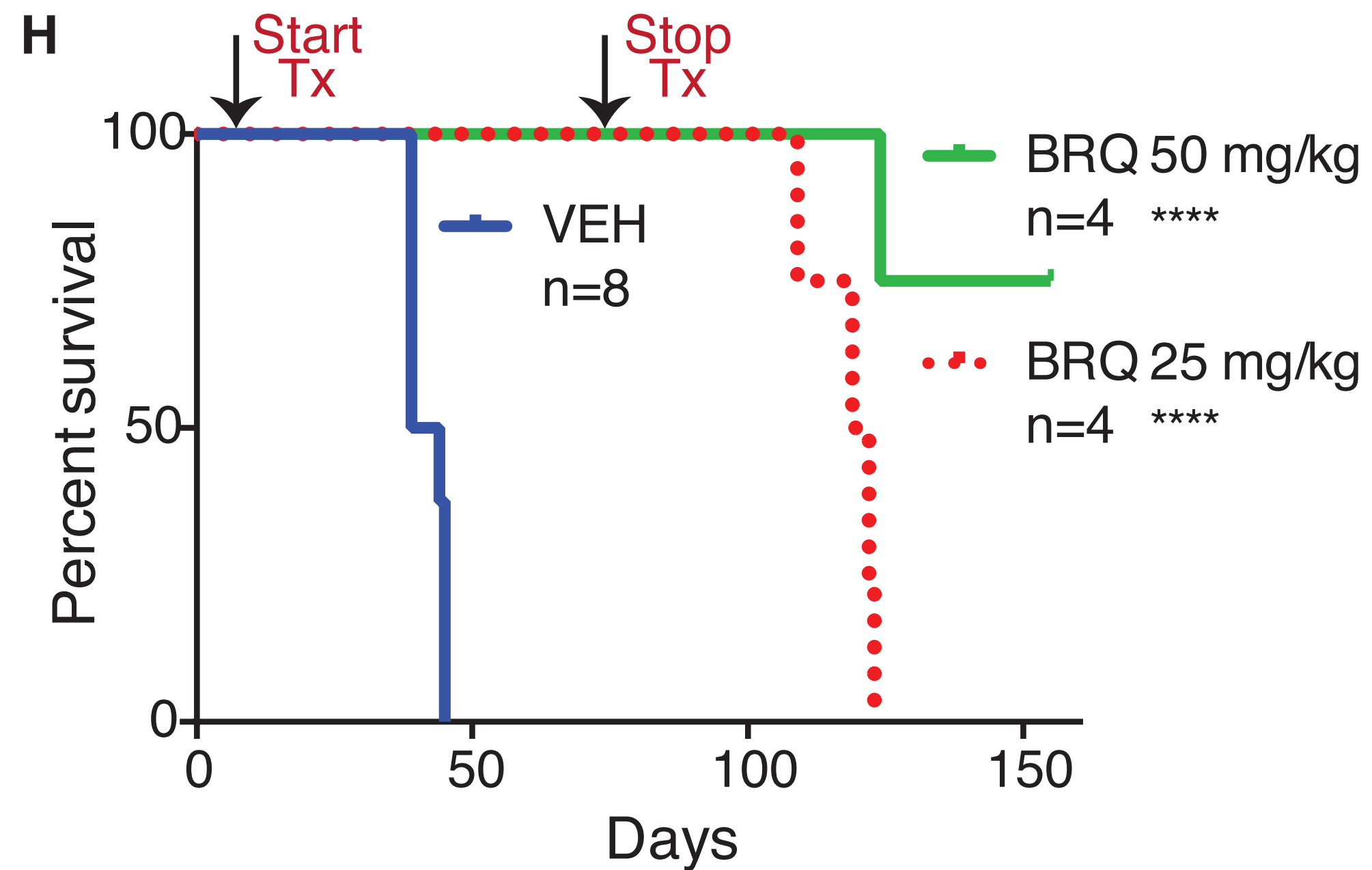
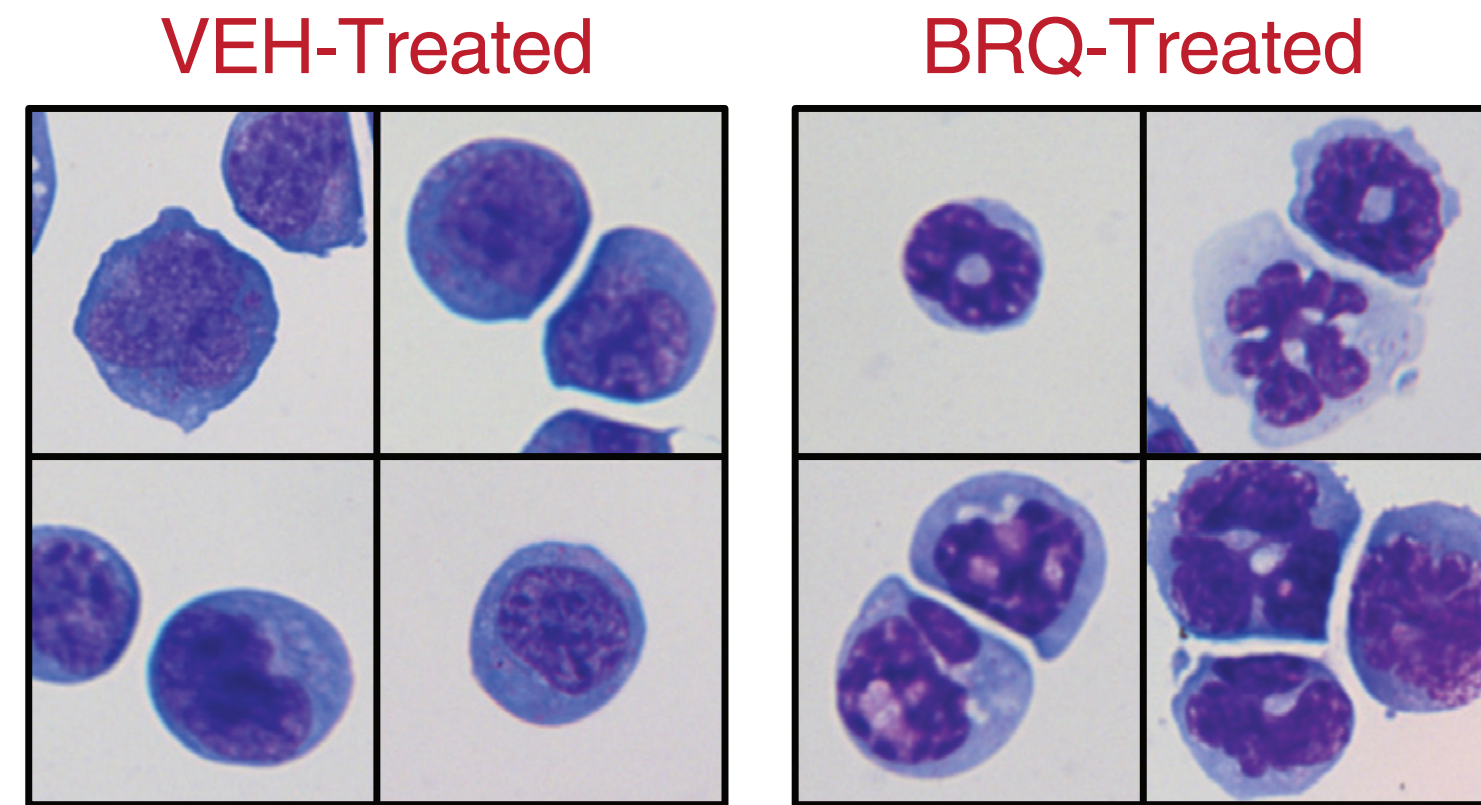
Nucleotide pool imbalance can alter cell fate



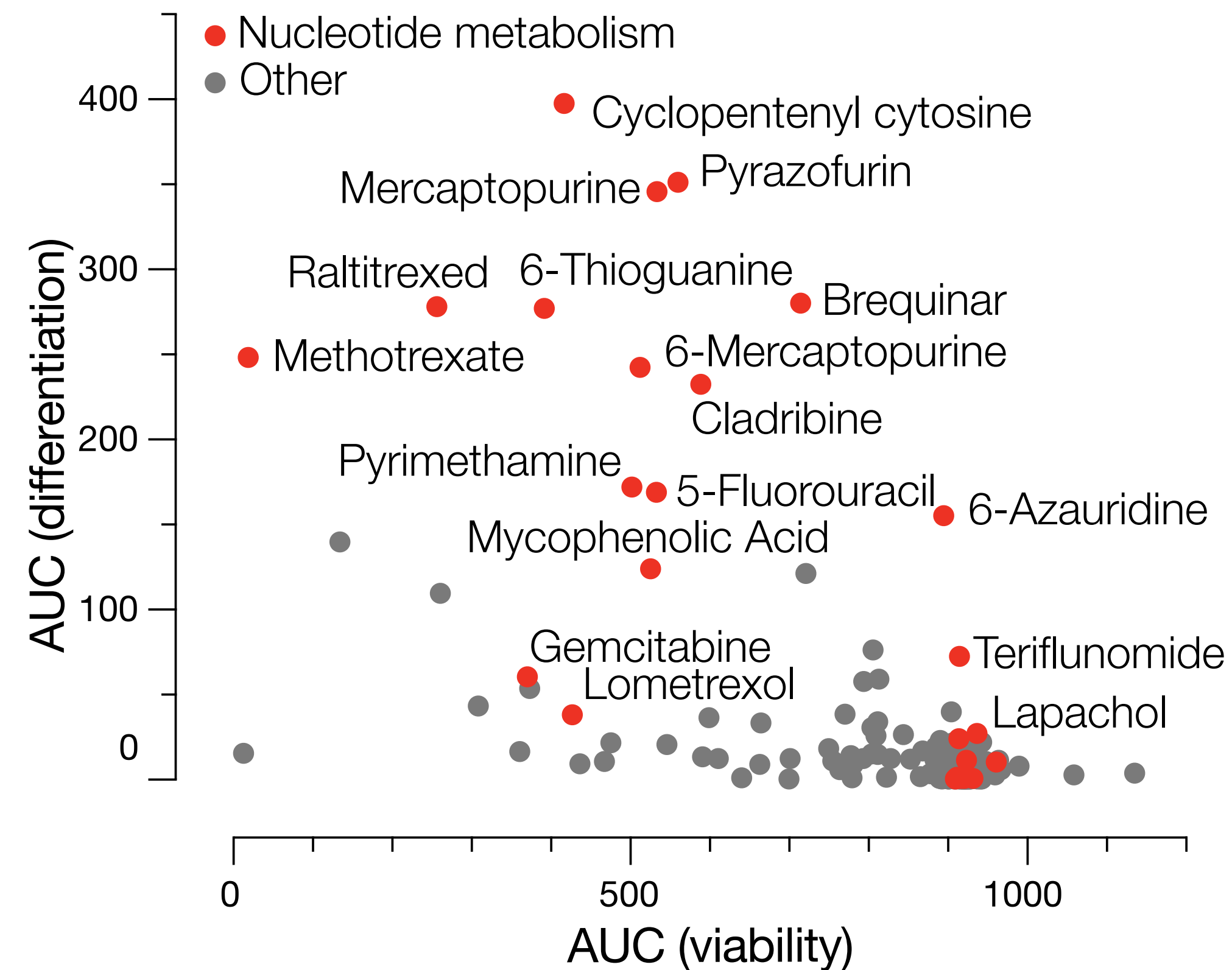
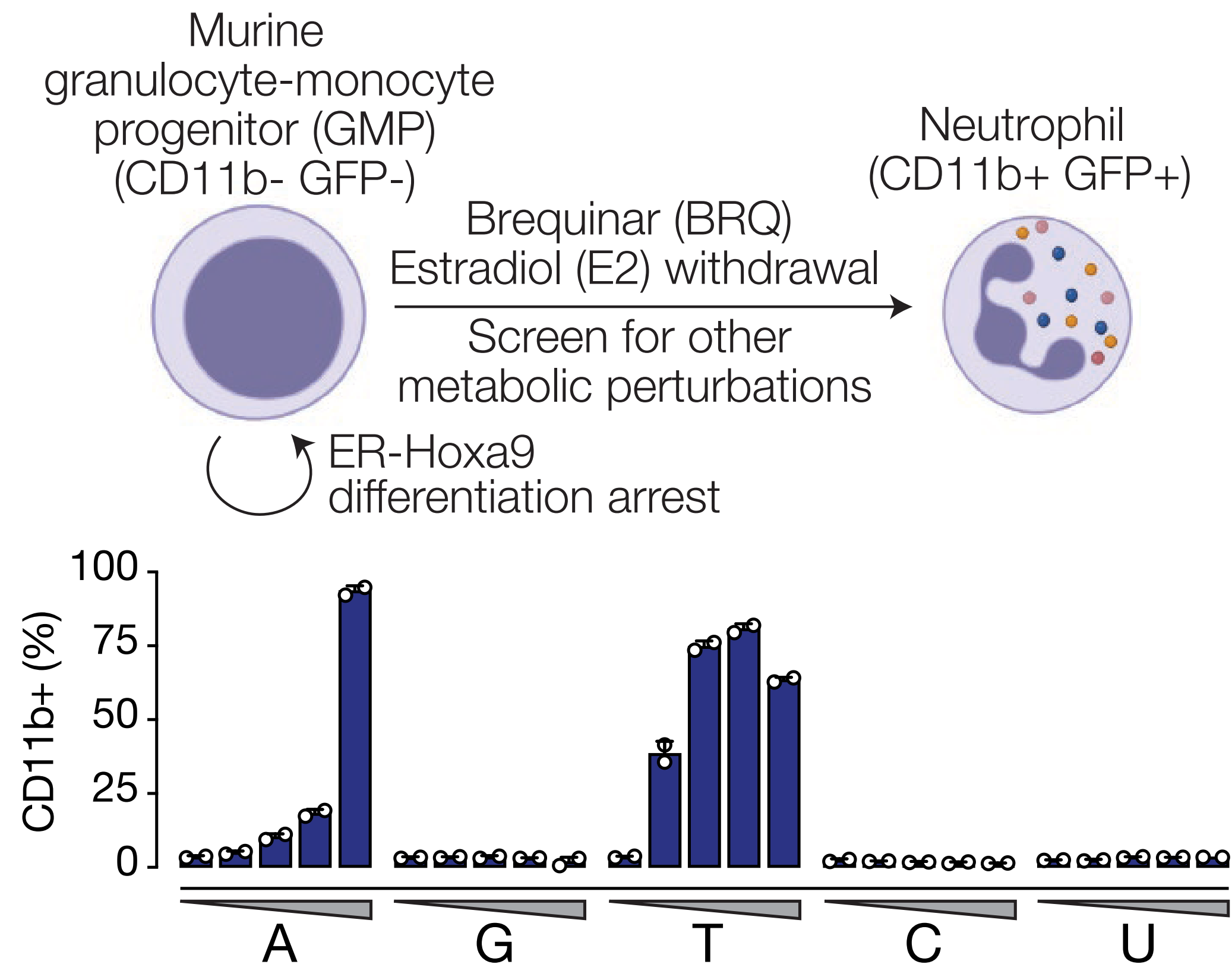
Nucleotide pool imbalance can alter cell fate



Nucleotide pool imbalance can alter cell fate



Nucleotide pool imbalance can alter cell fate

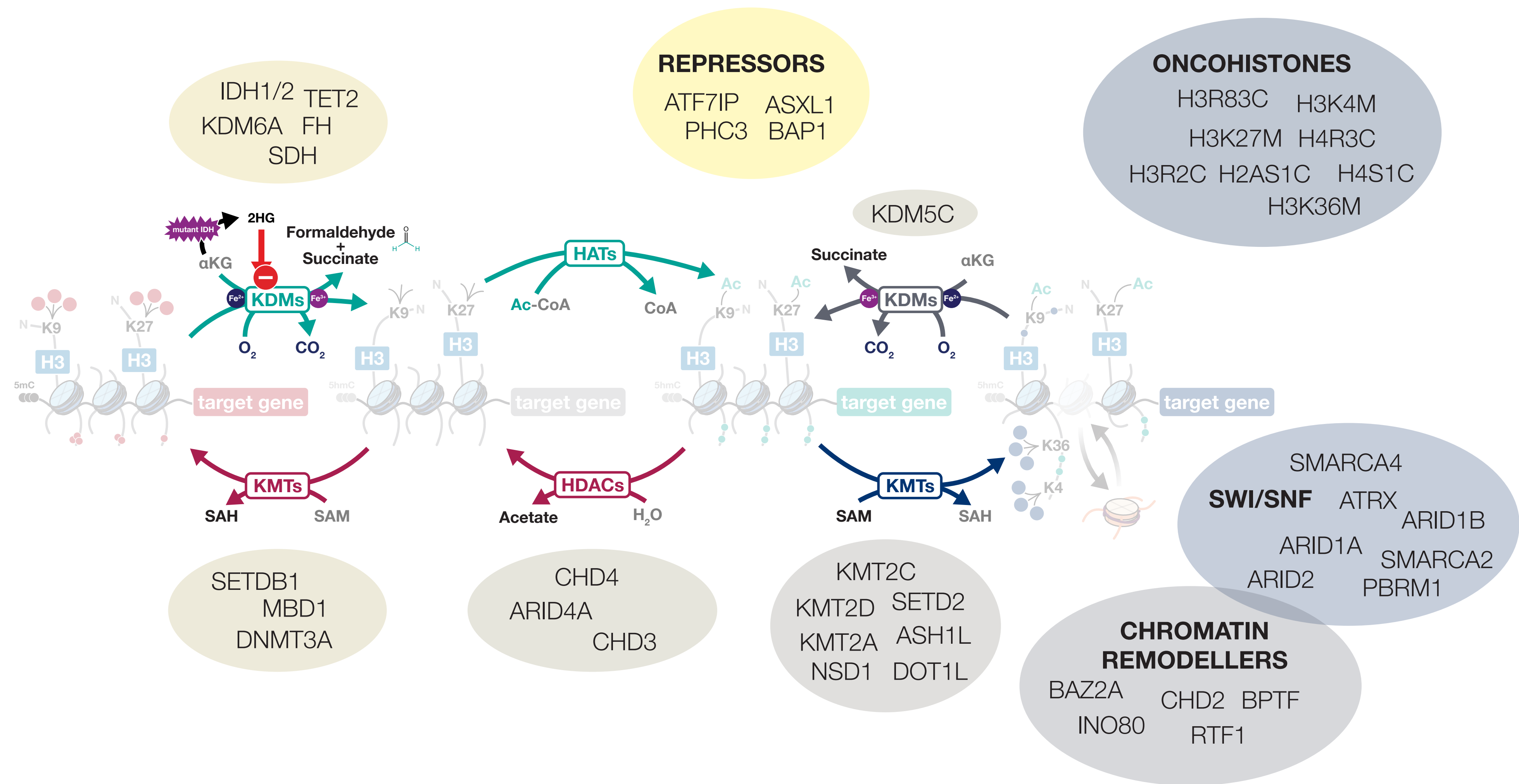


Nucleotide pool imbalance can alter cell fate

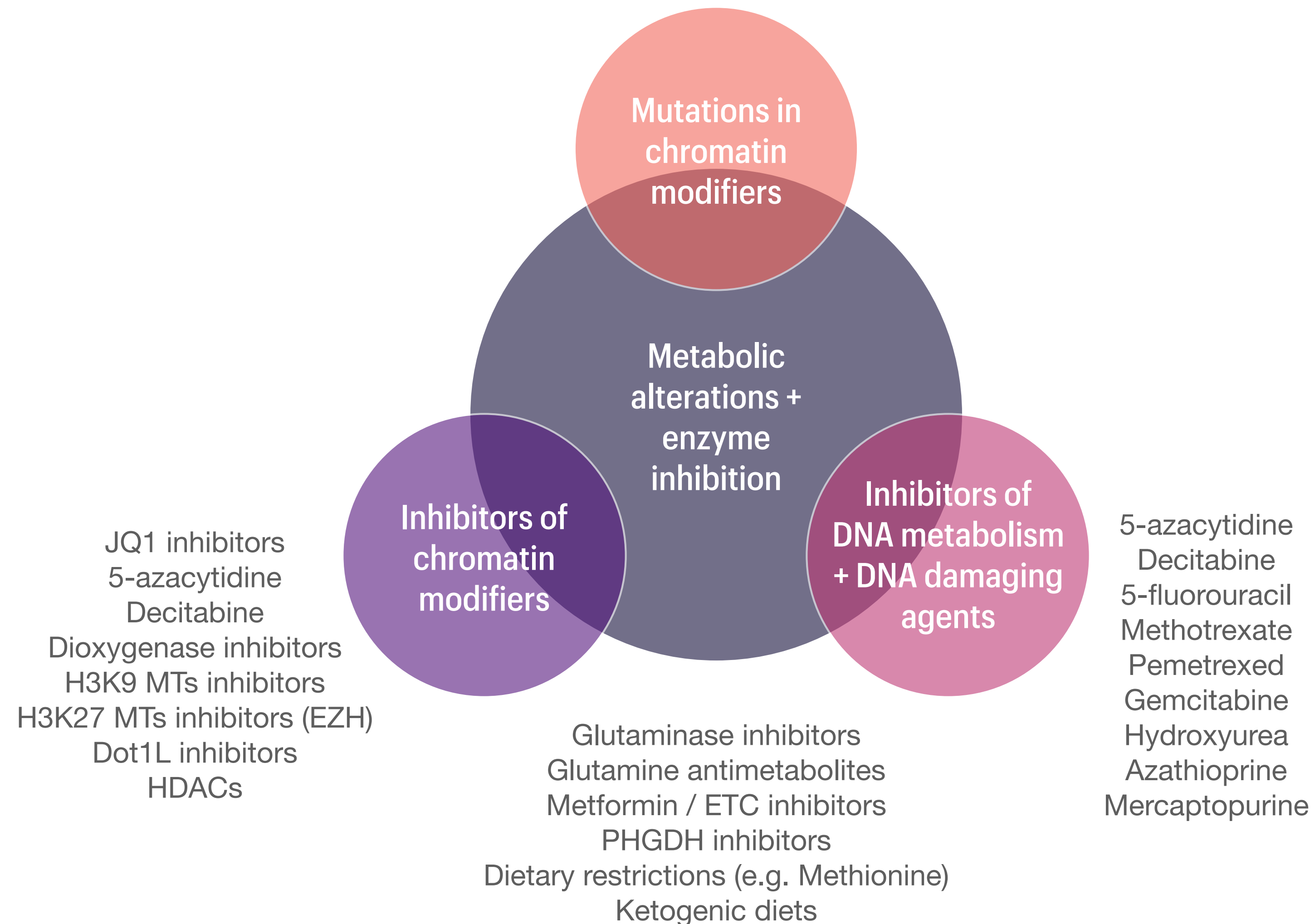
**ALTERING NUCLEOTIDES CAN
DIFFERENTIATE CELLS?????**



A wide range of chromatin modifying enzymes are mutated in cancers



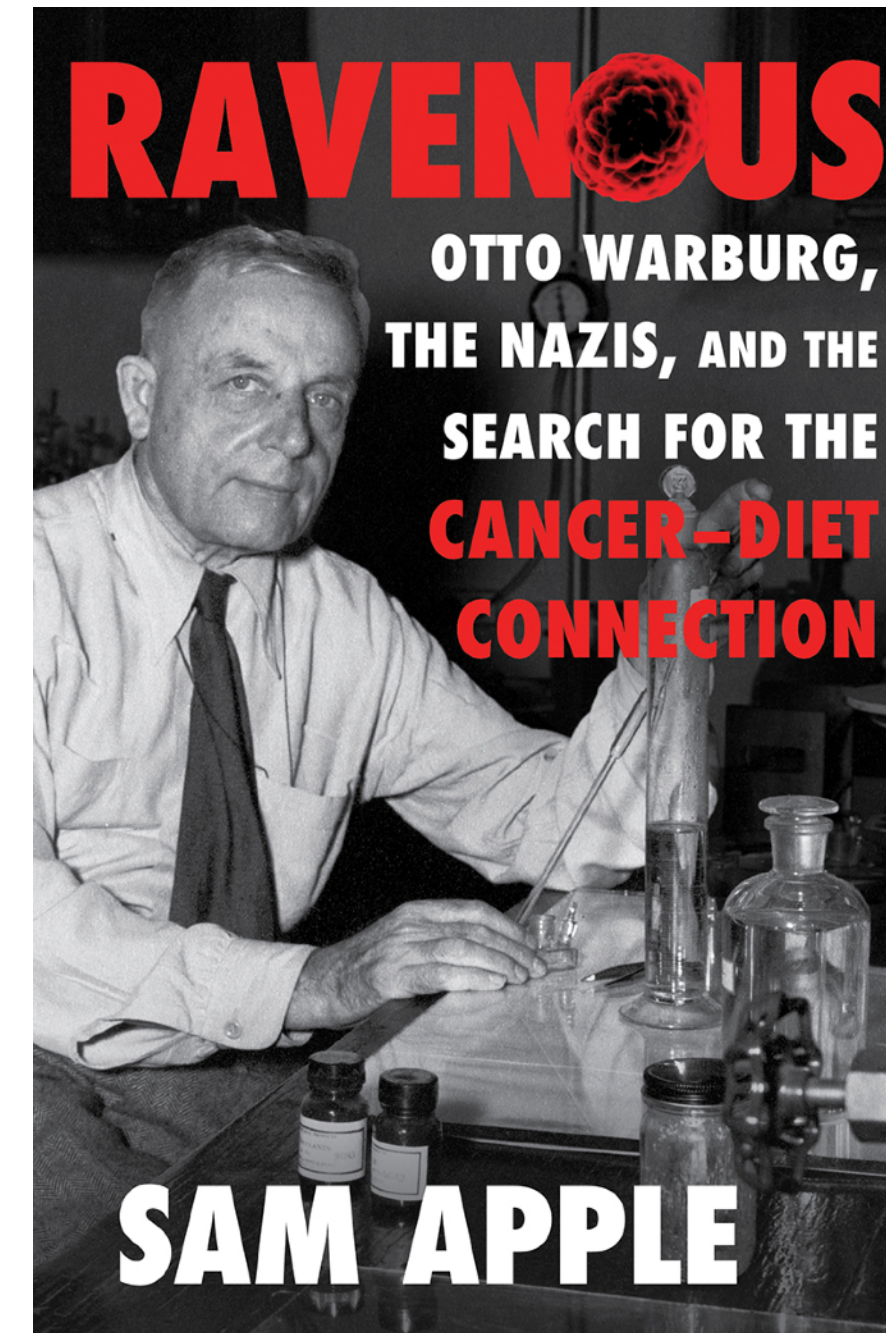
Metabolic pathways as a therapeutic handle for chromatin biology in cancer



Final Takehome points

1. Cells don't read textbooks
2. Metabolism is wired to meet different anabolic/catabolic needs
3. Many pathways are redundant → Auxotrophy + forward genetics to understand metabolic pathways
4. If you want to look at metabolism, look at metabolism:
 - metabolomics and flux analysis; NOT RNA!!
5. K_M : Enzymes care about [substrates] / [products]
6. All substrates/products matter
7. Enzymes also don't read textbooks

If you want to learn more:



CHROMETAB

CHROMATIN | METABOLISM | CANCER
SCHVARTZMAN LAB @
COLUMBIA  UNIVERSITY

CHROMETAB

CHROMATIN | METABOLISM | CANCER
SCHVARTZMAN LAB @
COLUMBIA  UNIVERSITY

schvartzmanlab.org

@Schvartzman_JM
js5279@columbia.edu