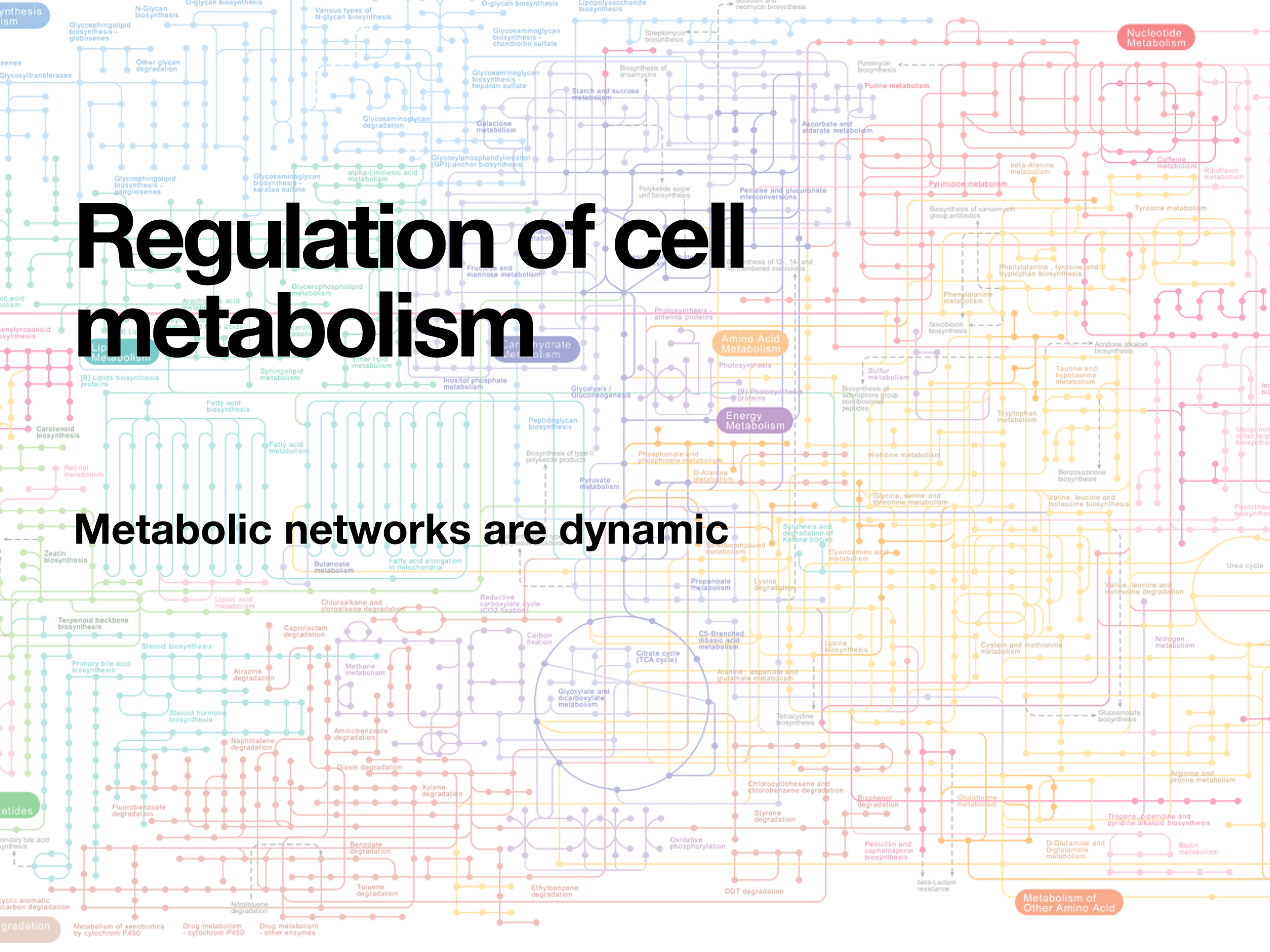
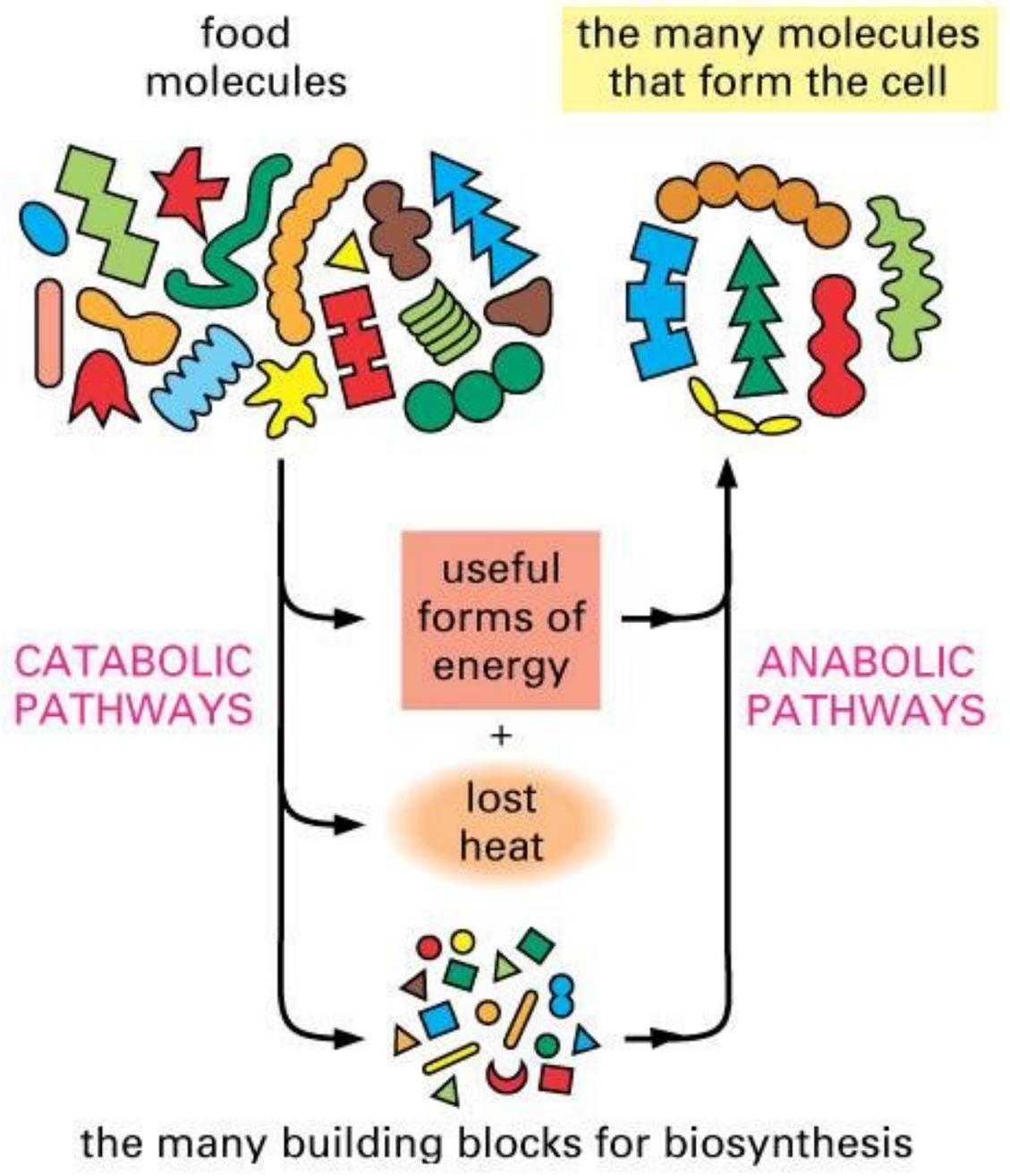
Regulation of cell metabolism

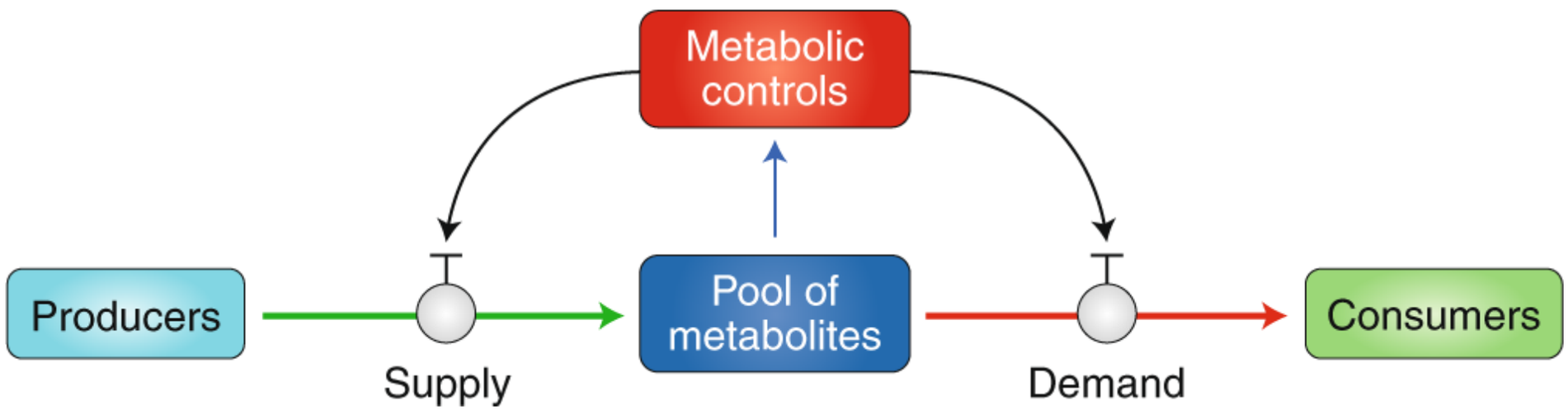
Metabolic networks are dynamic



Catabolism and Anabolism determine the metabolic status of the cell



Supply and demands dictate metabolism



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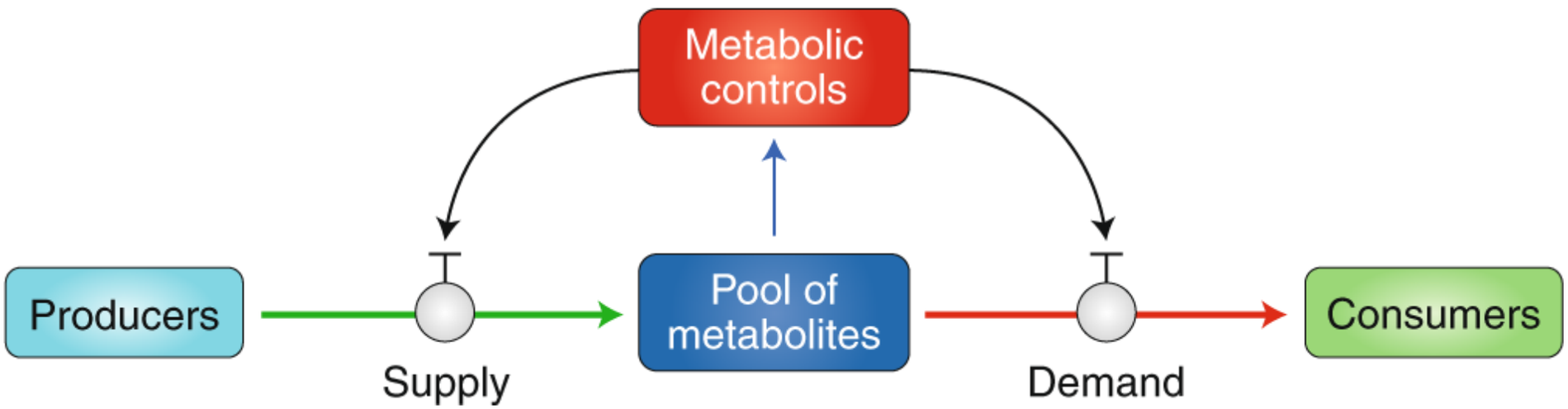
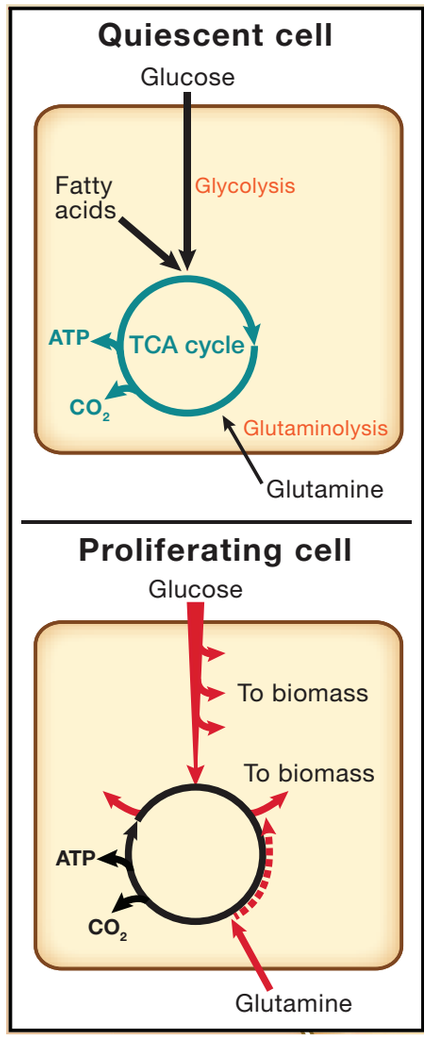


1. **METABOLIC DEMANDS**
   - Growth and proliferation
   - Differentiation

2. **METABOLIC SUPPLY**
   - Tissue specificity
   - Hormonal stimulation
   - Diet
   - Perfusion

Proliferation presents metabolic challenges



Finley LY, Thompson CB, ***Cell****, 2012*

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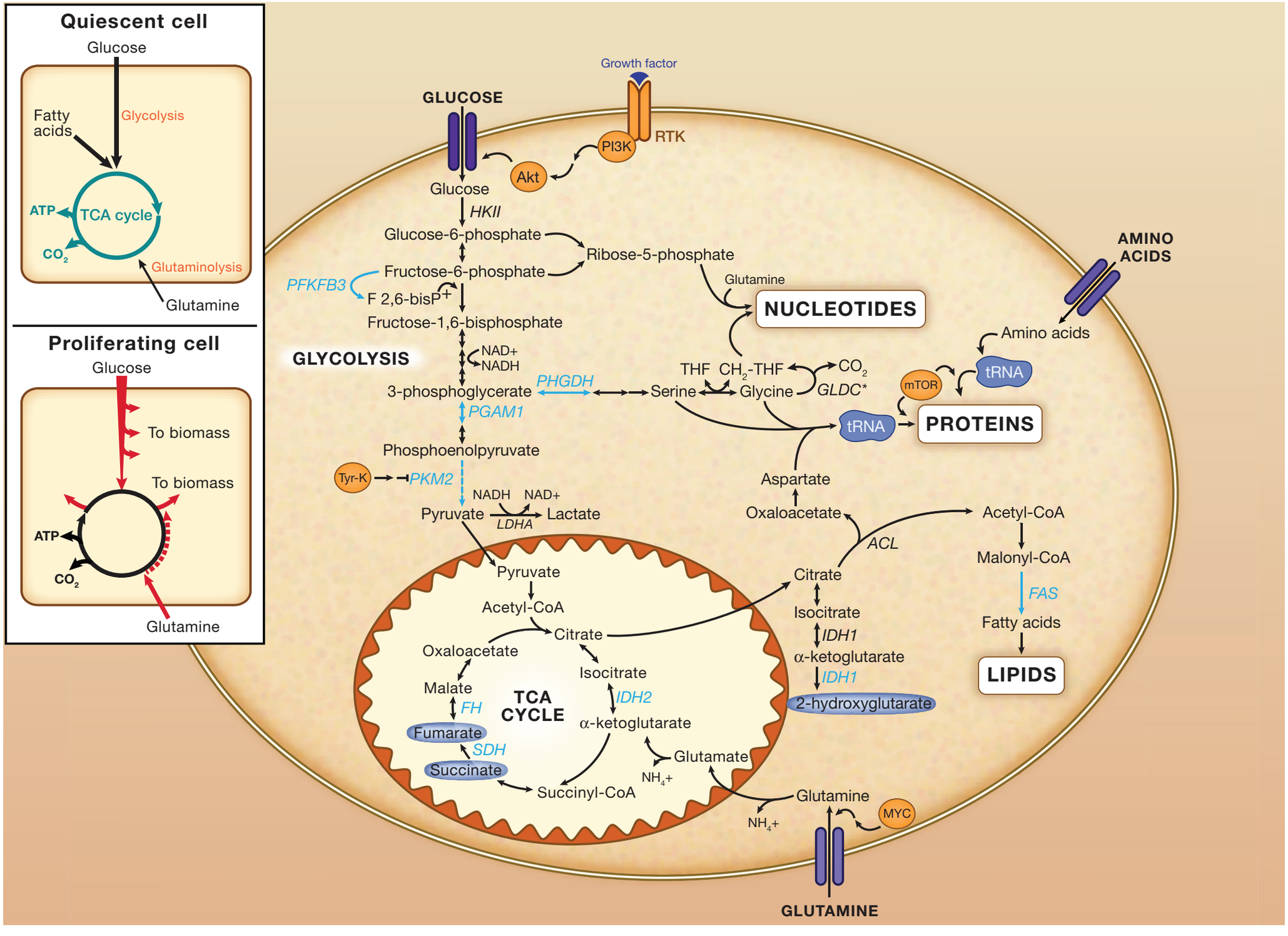

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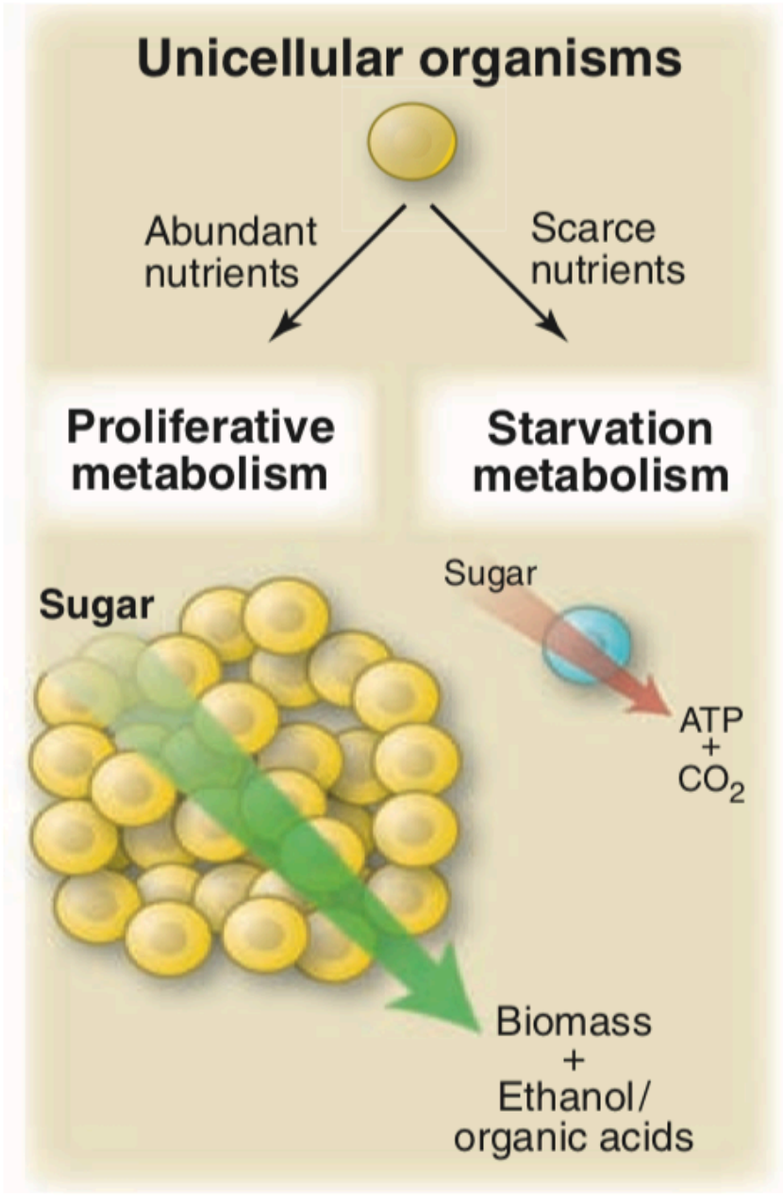
Organisms gauge environmental conditions to decide cell fate



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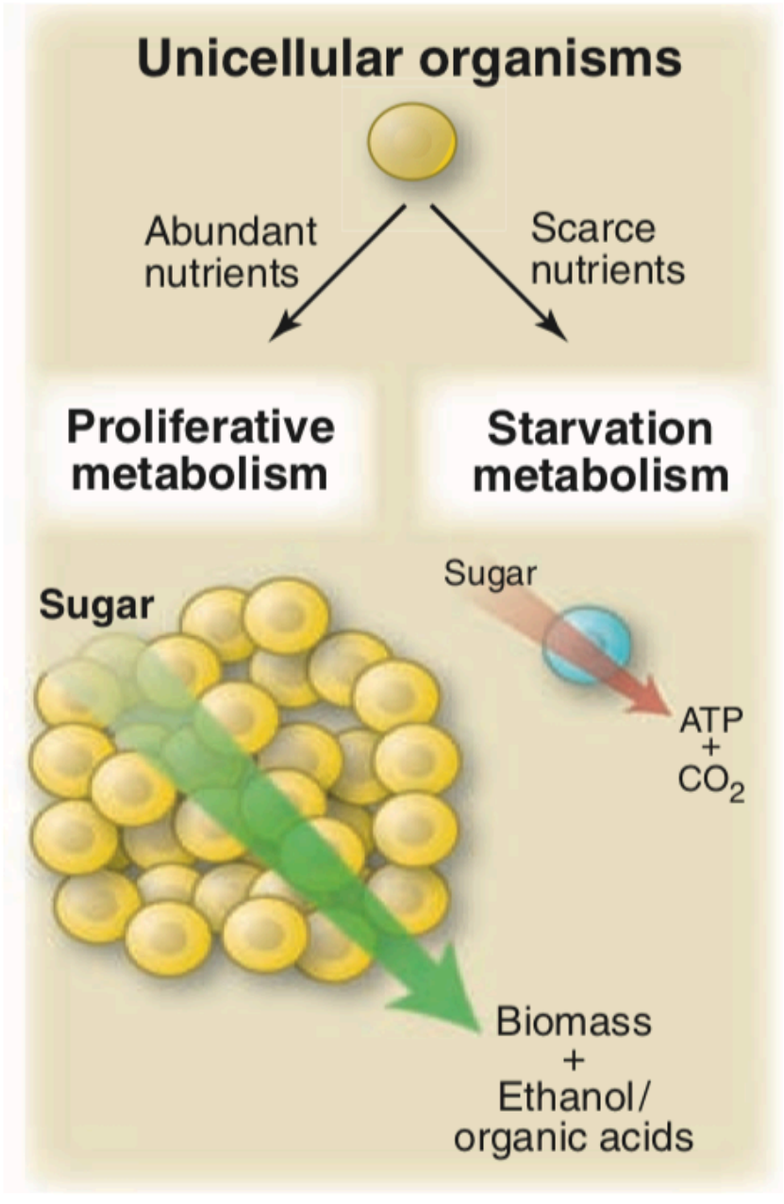

Nutrient sensing regulates growth in unicellular organisms
Growth factor signals induce proliferation in multicellular organisms

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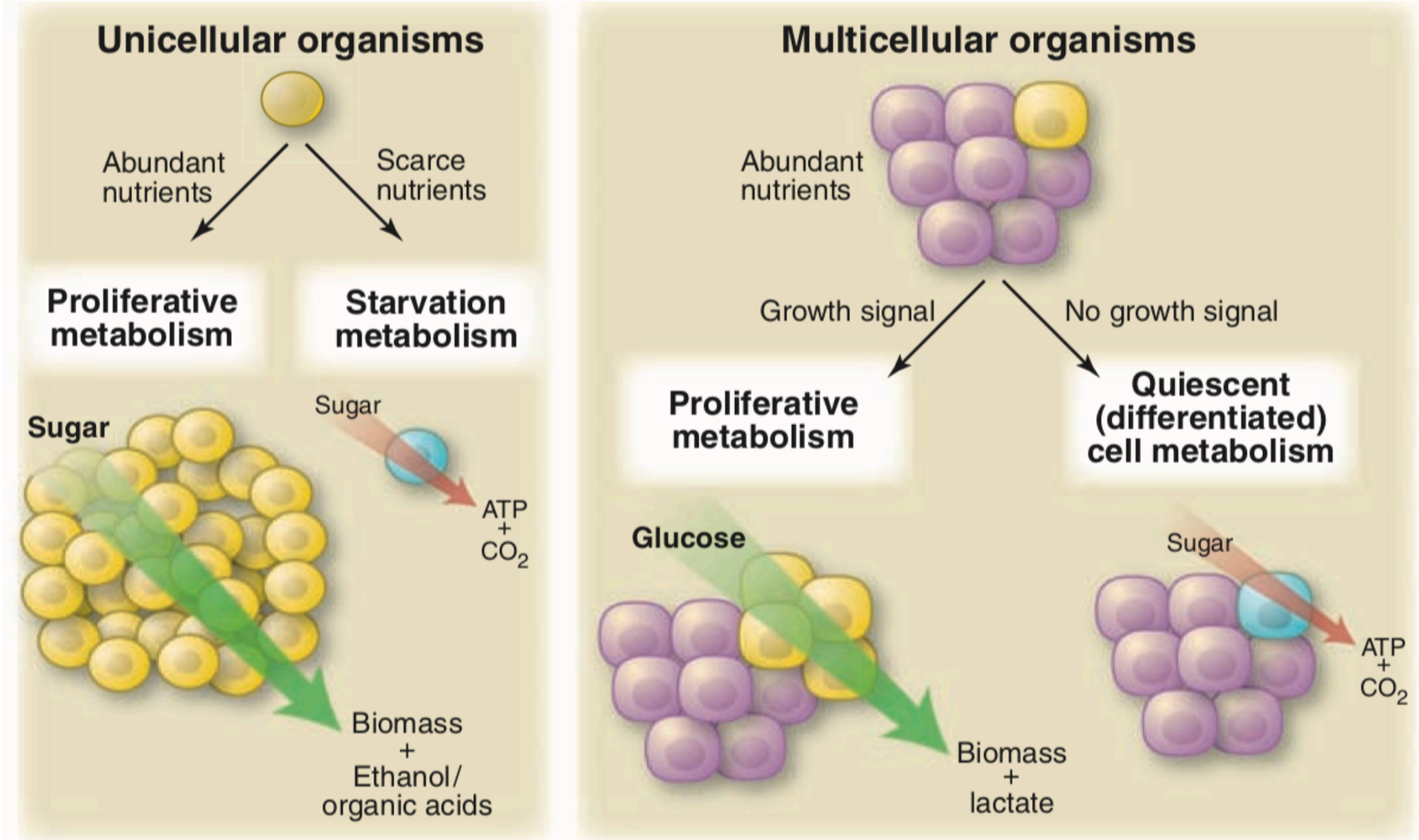

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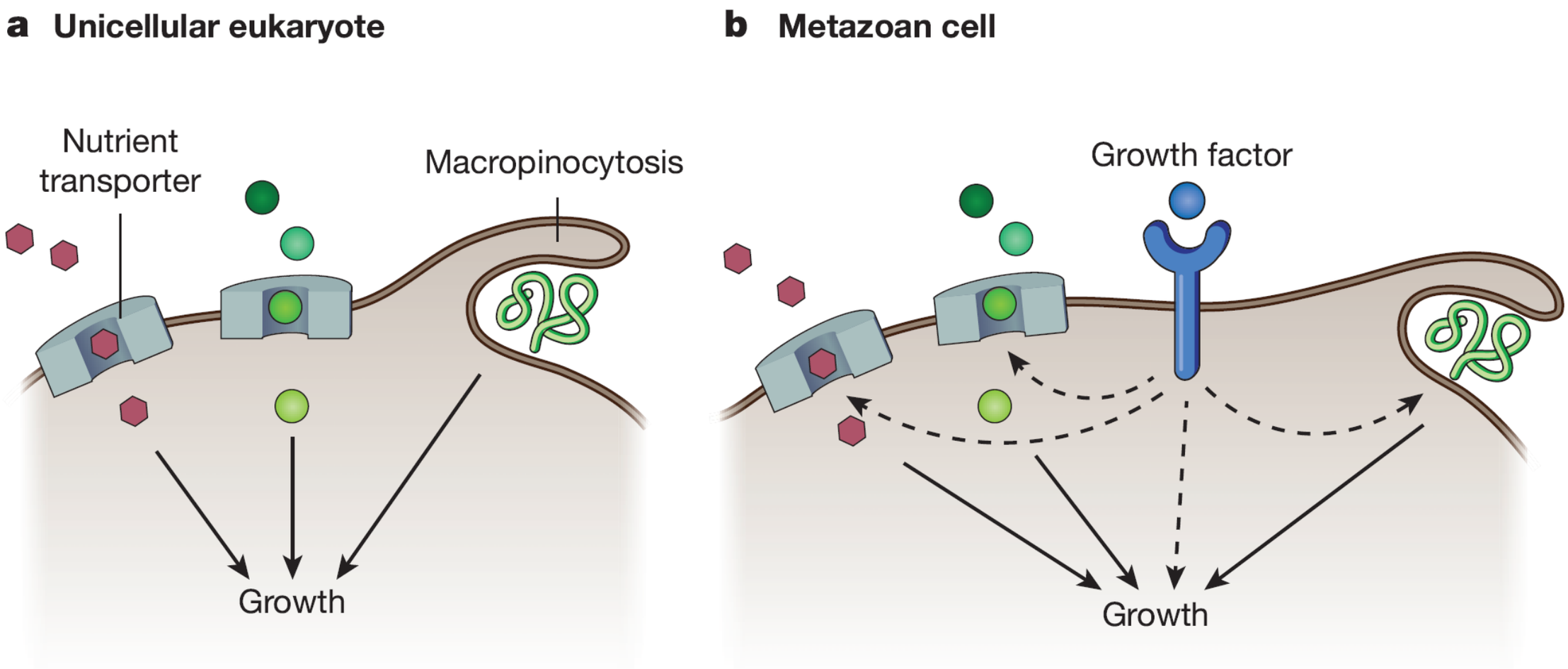
Multicellular organisms integrate hormonal signaling



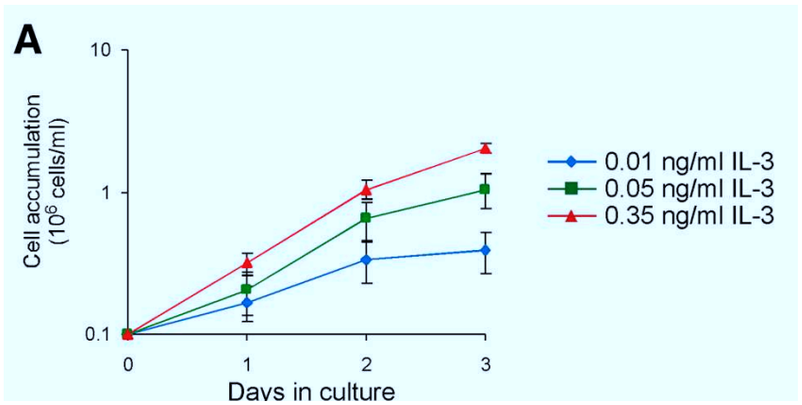
Abundant nutrients → Proliferation
Scarce nutrients → Growth arrest

Presence of signals → Proliferation
Absence of signals → Growth arrest

The FASEB Journal express article 10.1096/fj.03-1001fje. Published online June 4, 2004.

Cytokine stimulation of aerobic glycolysis in hematopoietic cells exceeds proliferative demand

Daniel E. Bauer,* Marian H. Harris,* David R. Plas, Julian J. Lum, Peter S. Hammerman, Jeffrey C. Rathmell, James L. Riley, and Craig B. Thompson



FL5.12 are immortalized but non-tumorigenic lyphoblastoid cells that depend on the presence of IL-3 for growth and proliferation

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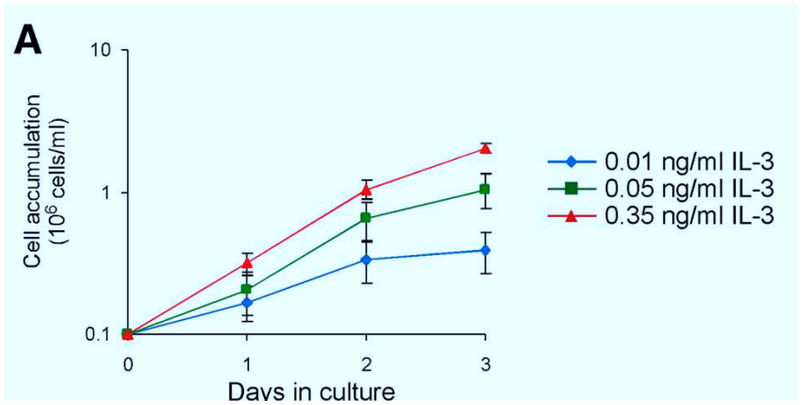

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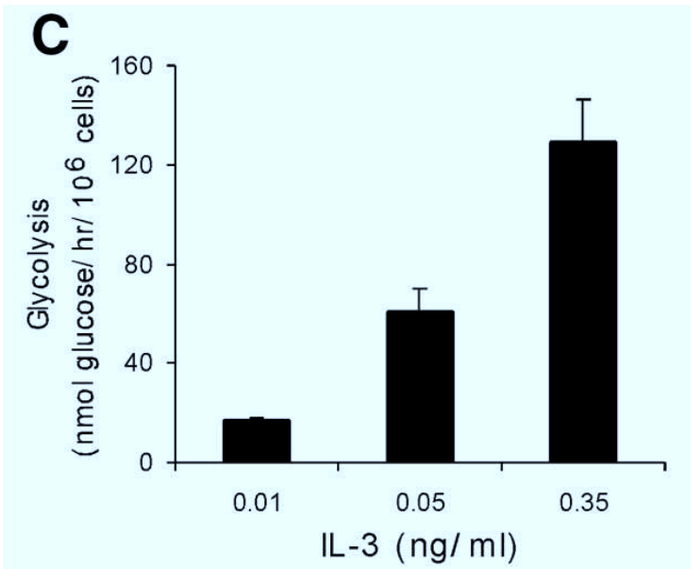

IL-3 addition promotes glycolysis (conversion of radioactive glucose to water)

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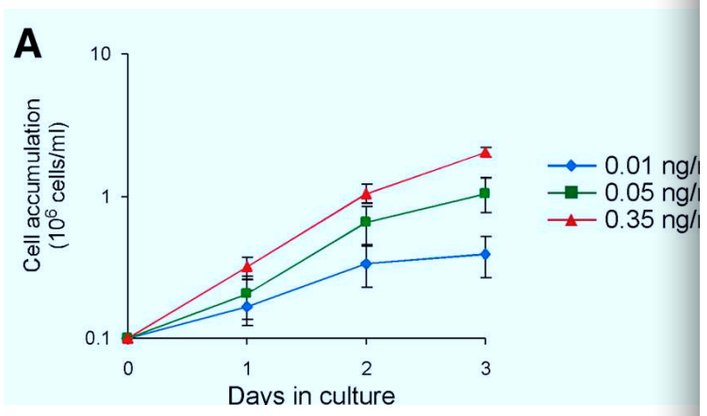

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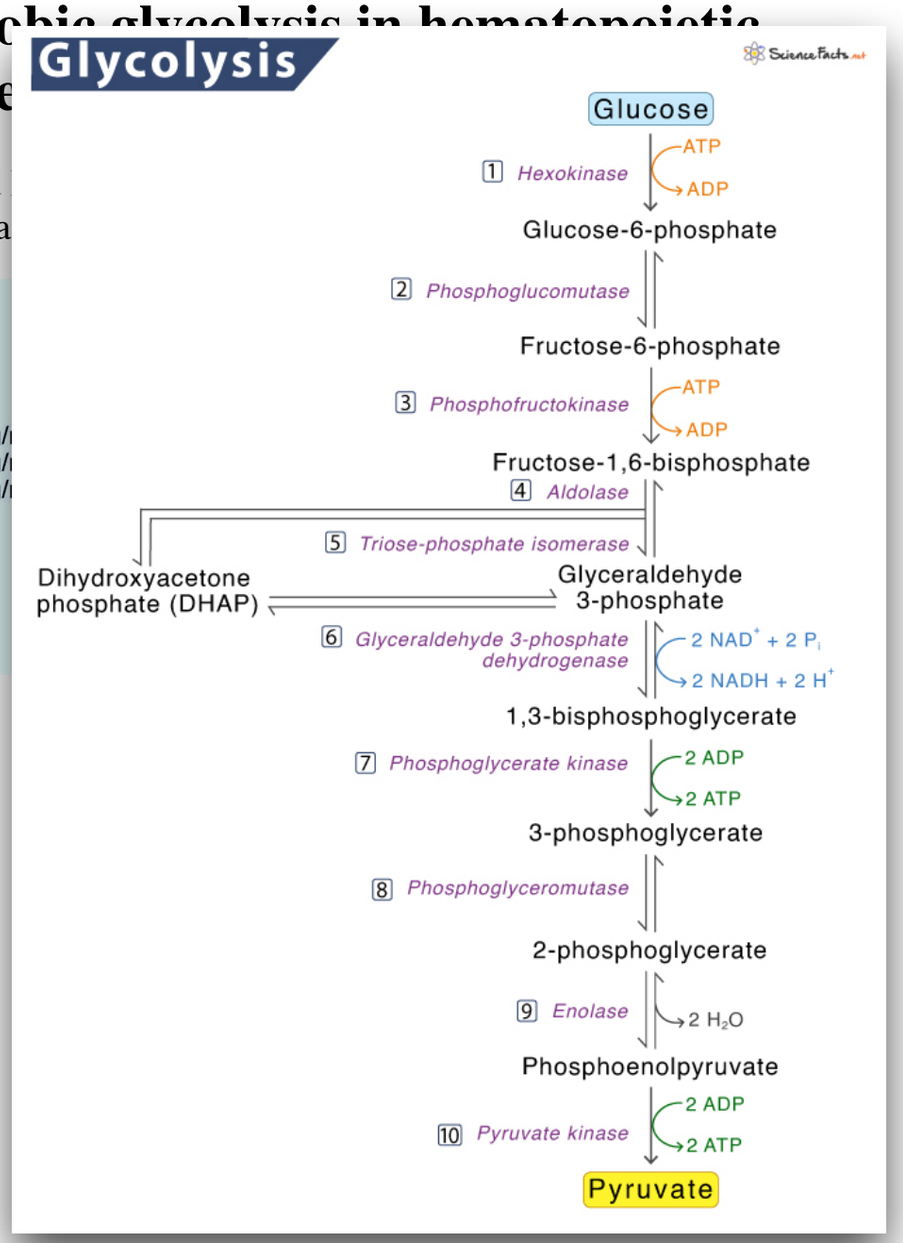

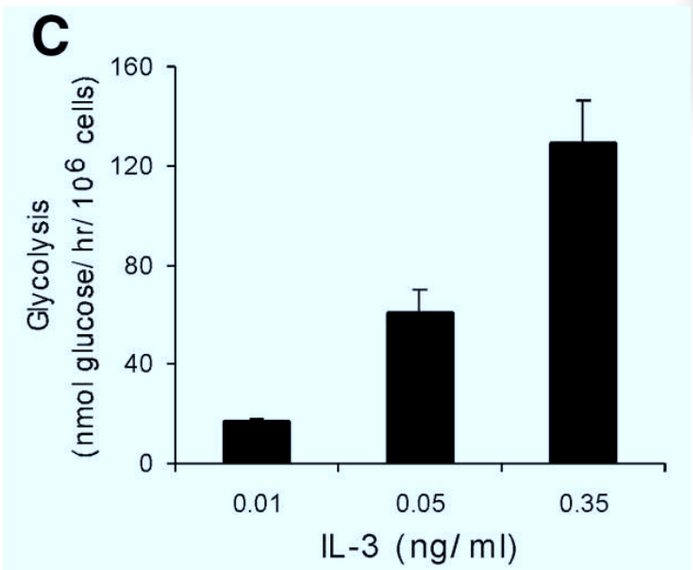

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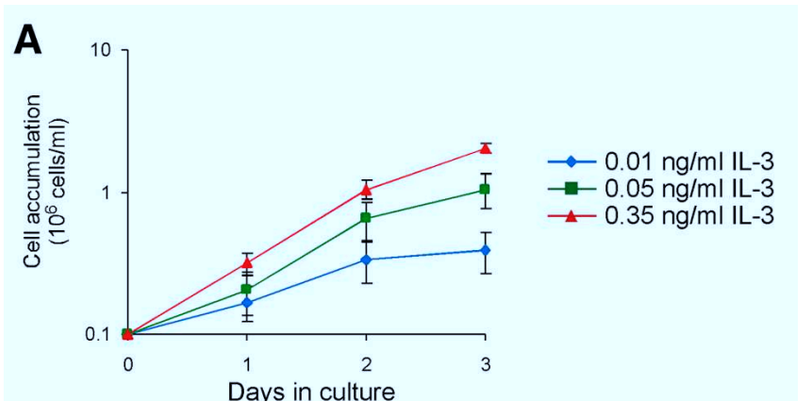

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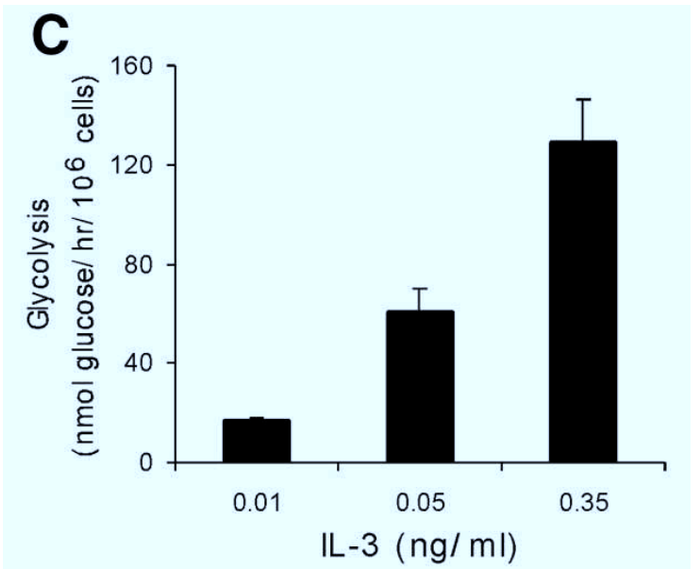

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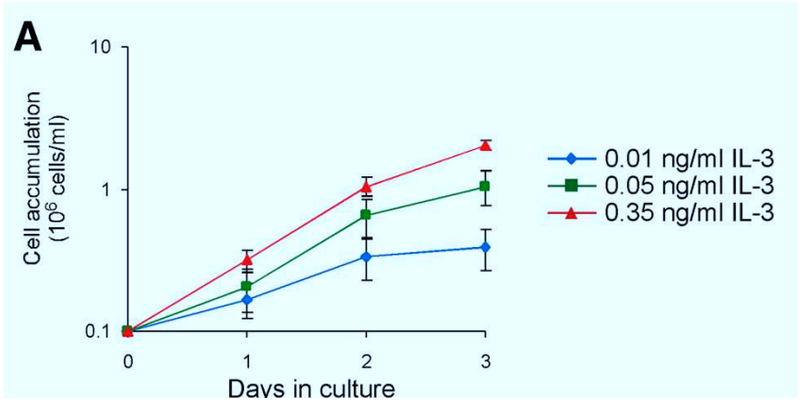

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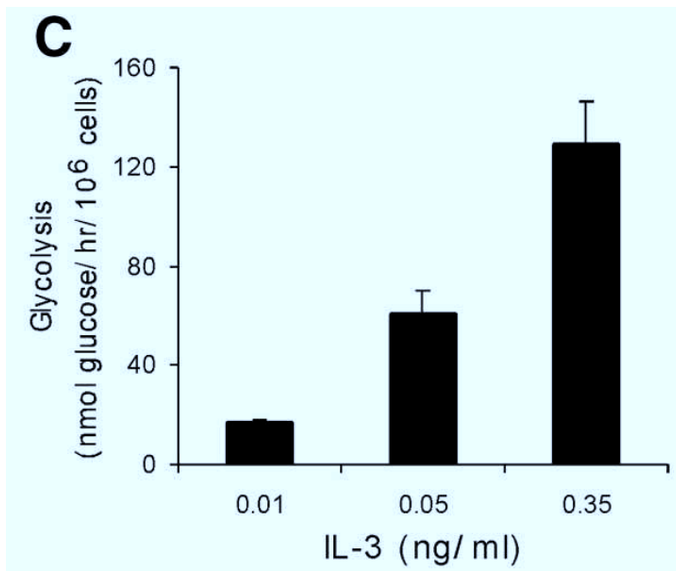

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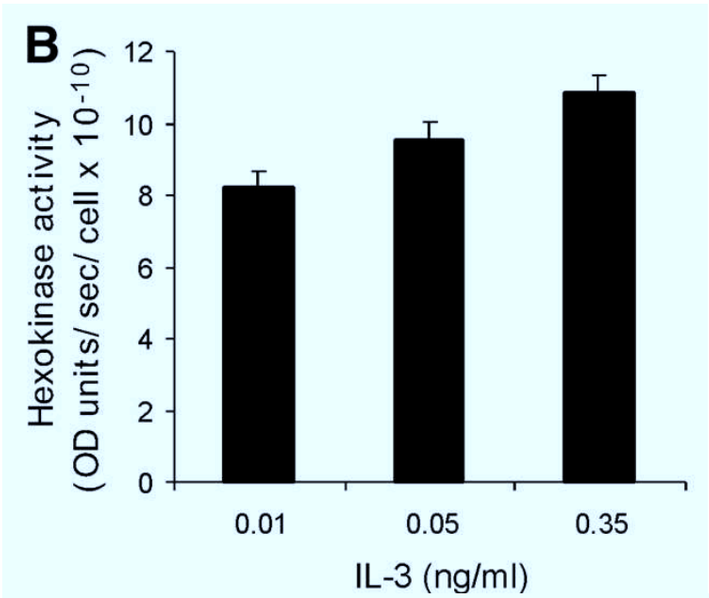

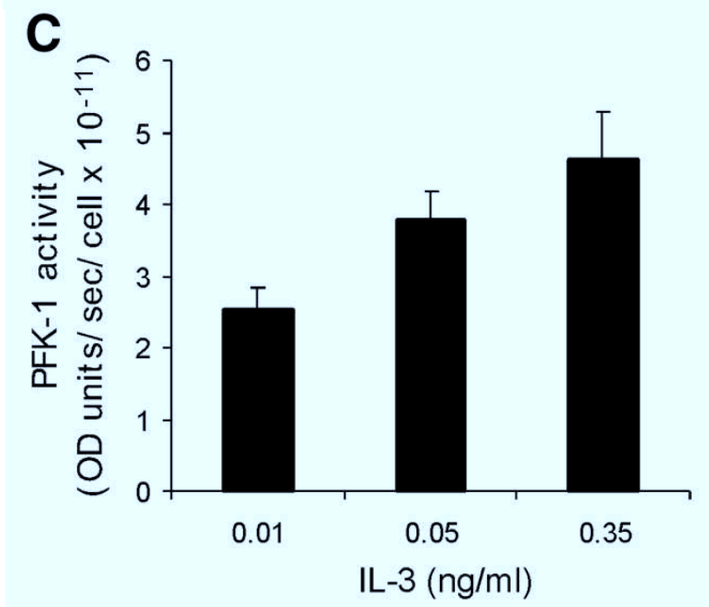

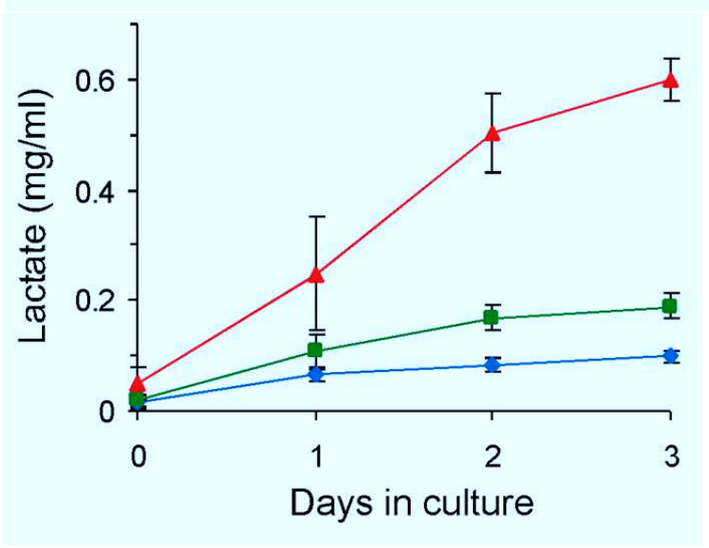

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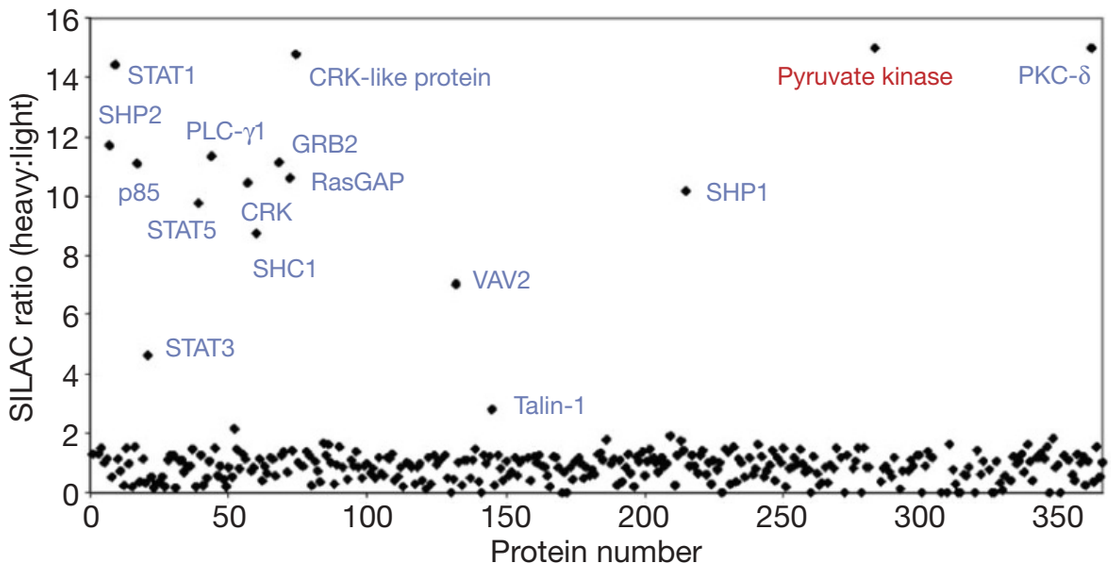
Pyruvate kinase M2 is a phosphotyrosine-binding protein

Heather R. Christofk[1], Matthew G. Vander Heiden[1,3], Ning Wu[1], John M. Asara[2,4] & Lewis C. Cantley[1,4]



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Christofk et al, ***Nature****, 2008*

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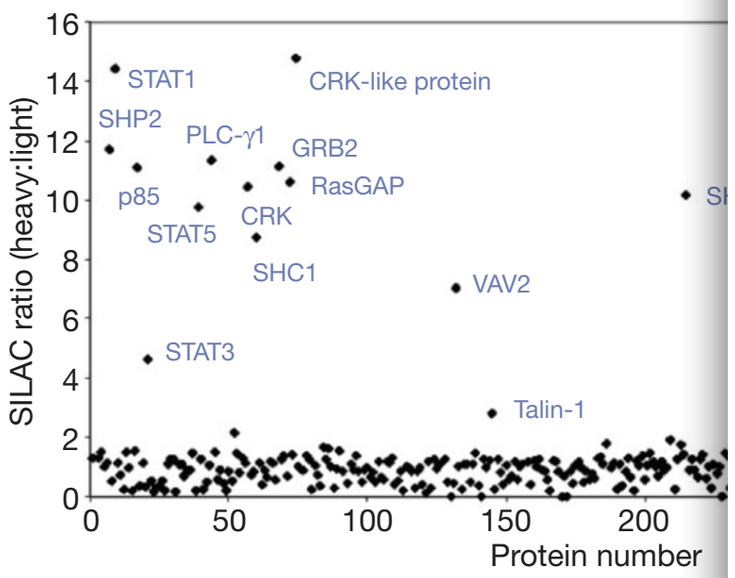

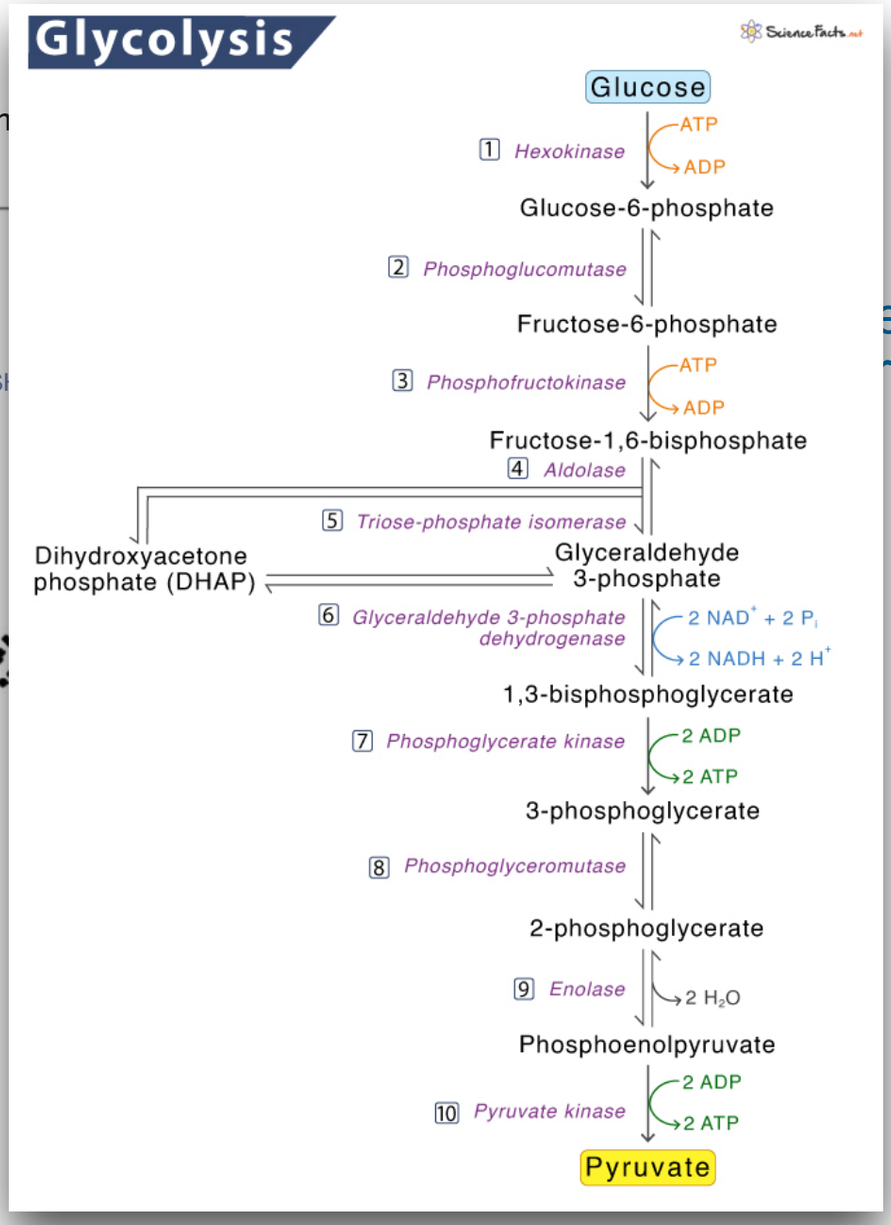

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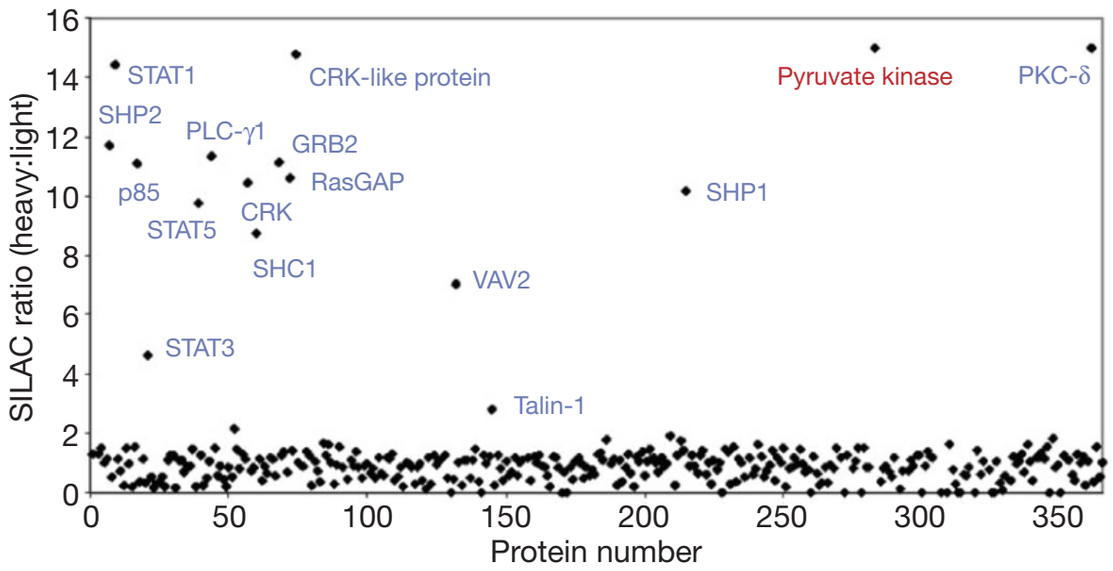

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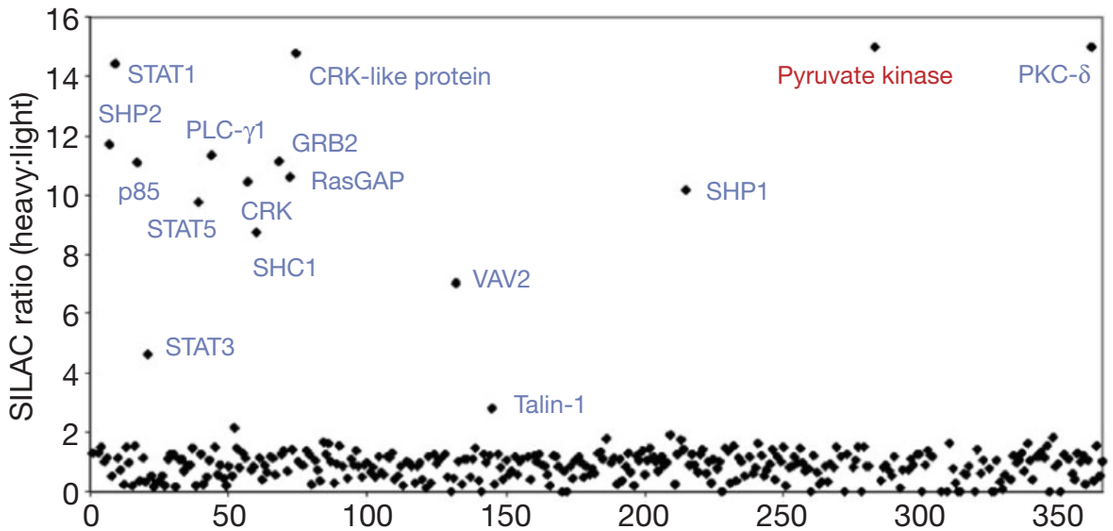

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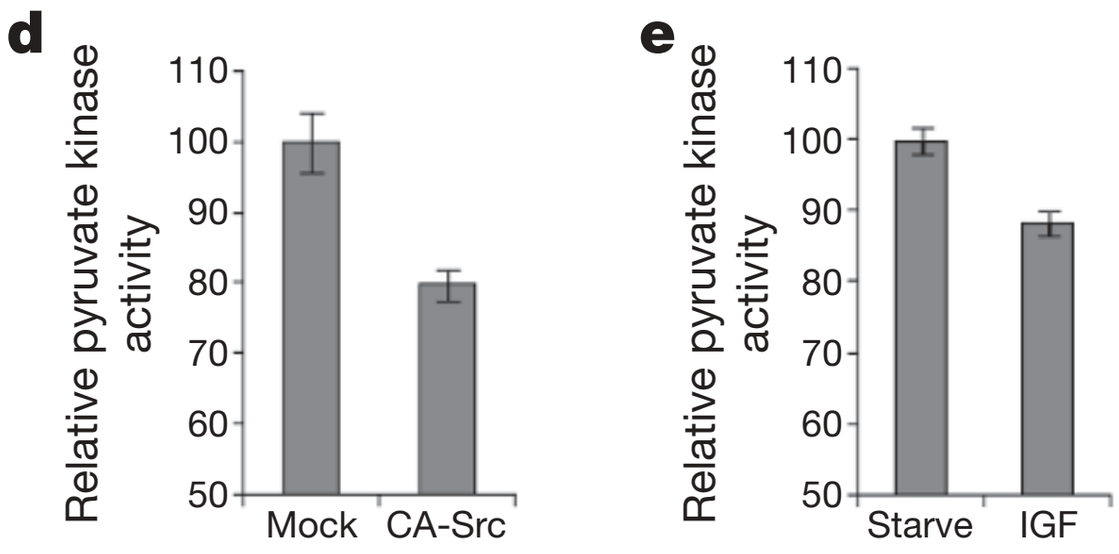

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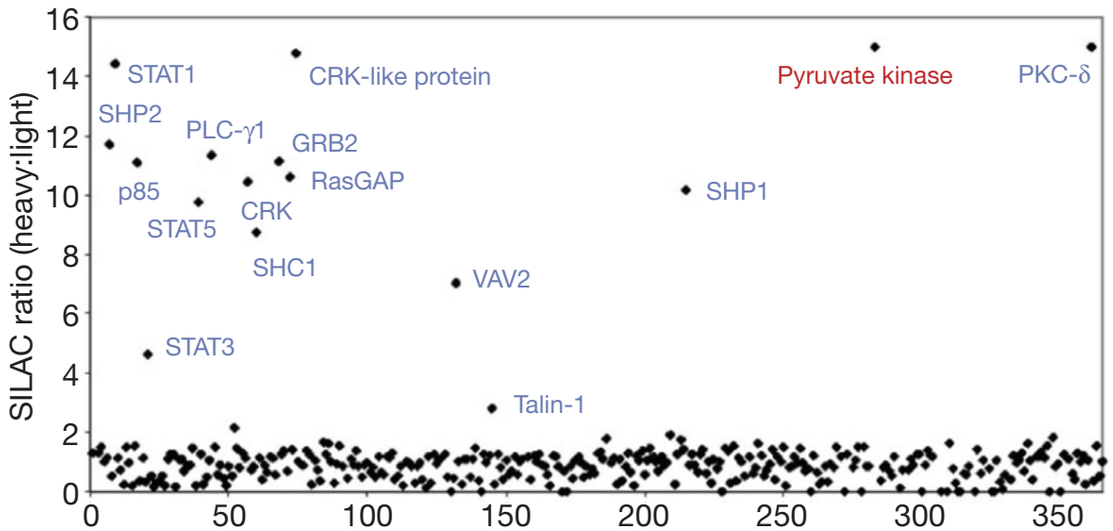

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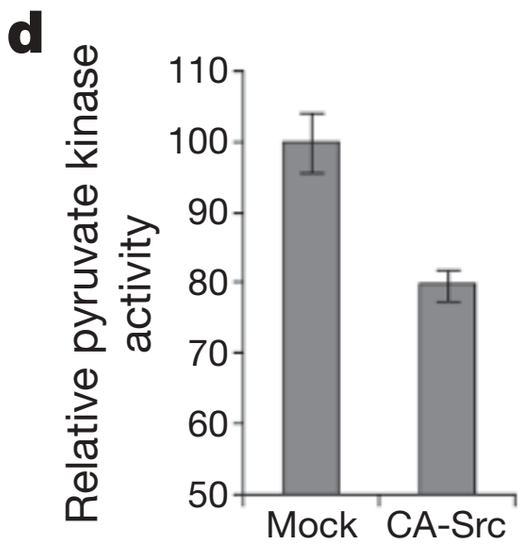

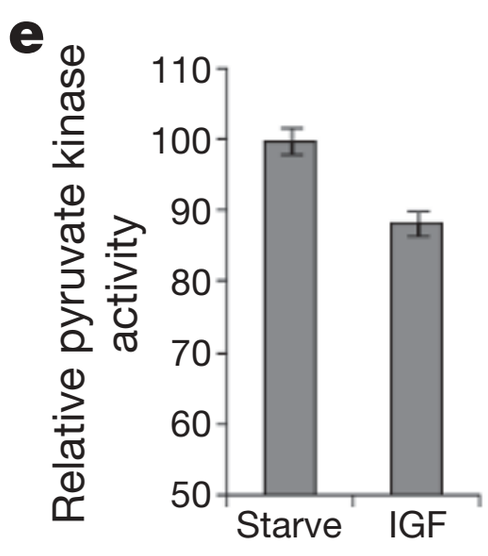

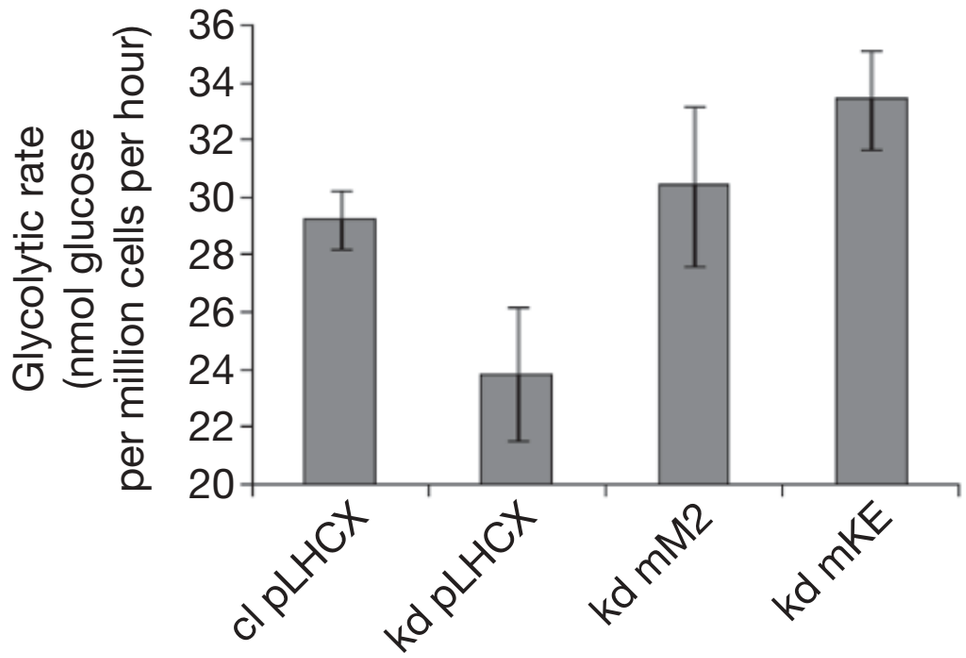

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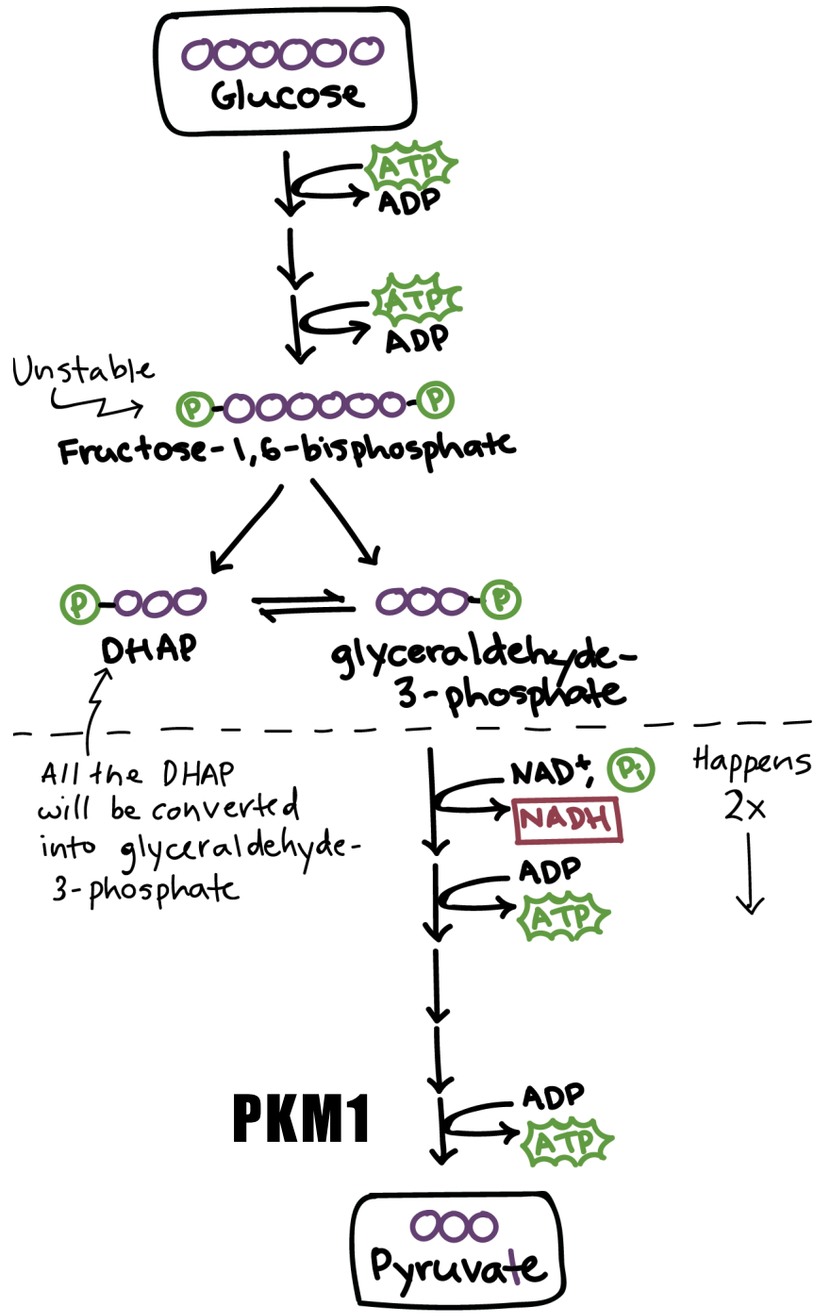
Fast proliferating cells express an alternative form of Pyruvate Kinase



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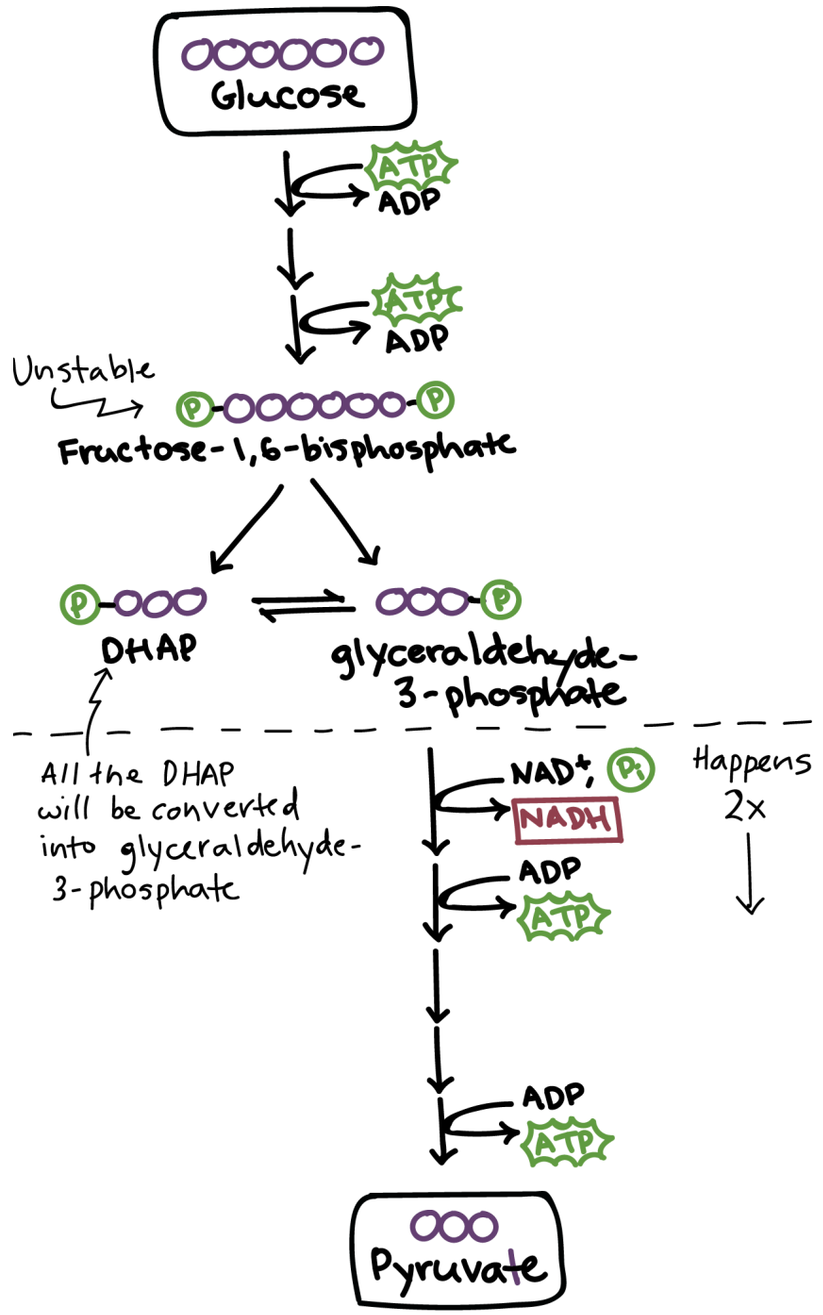

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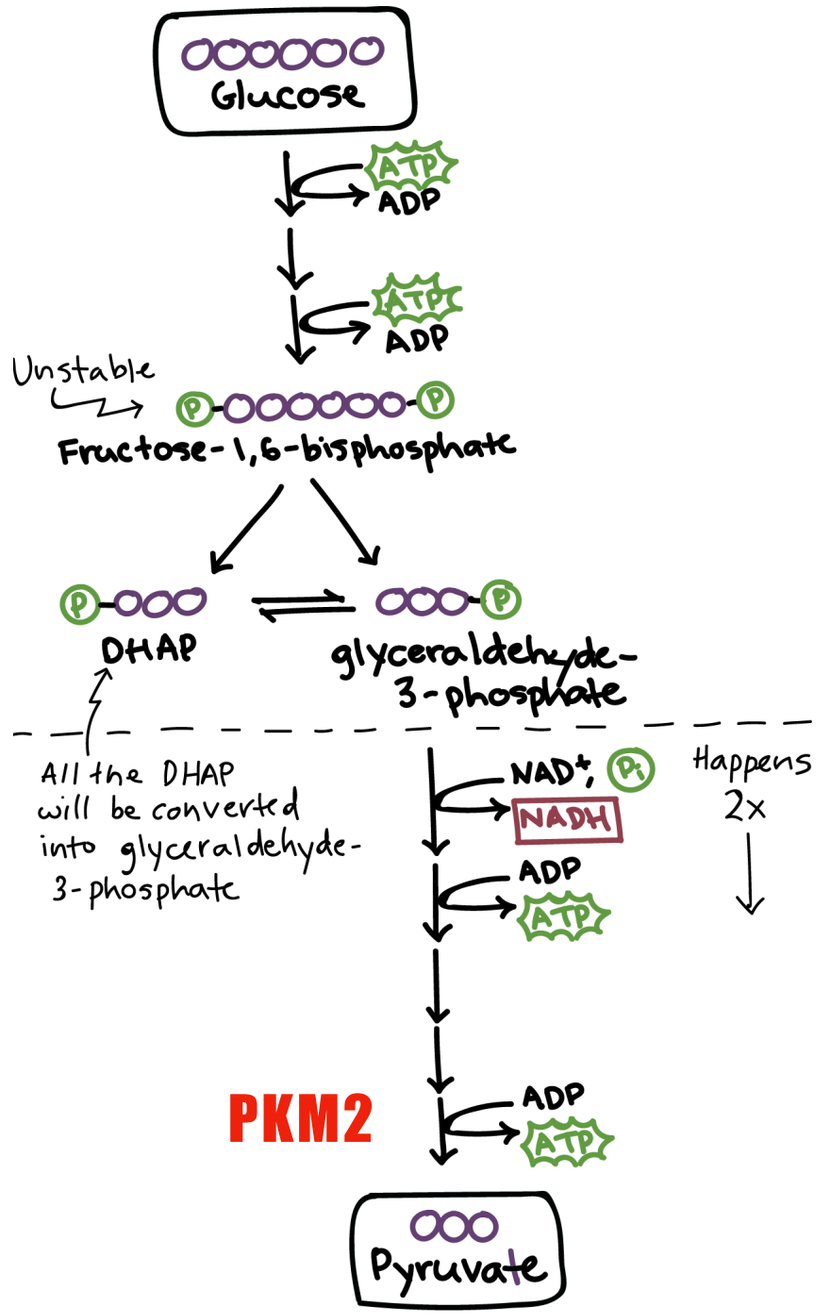

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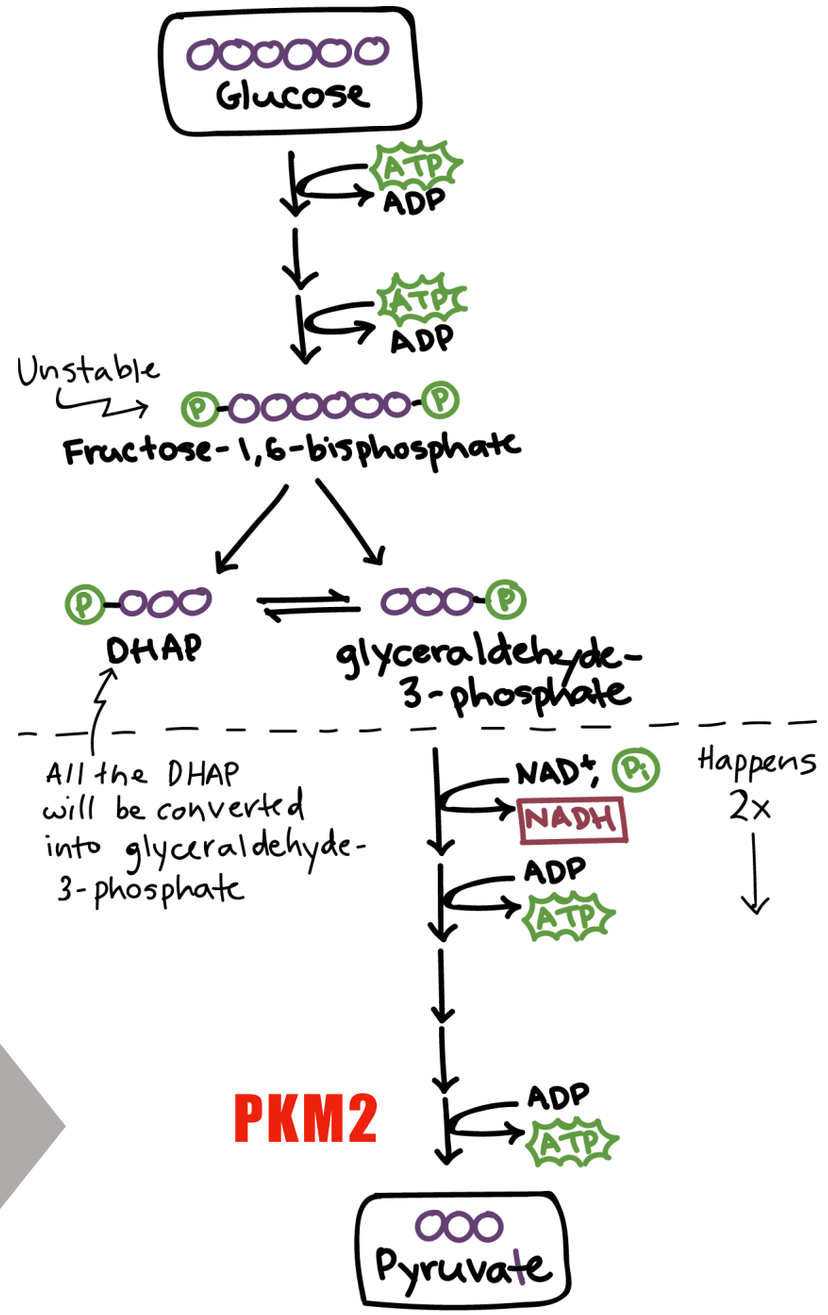
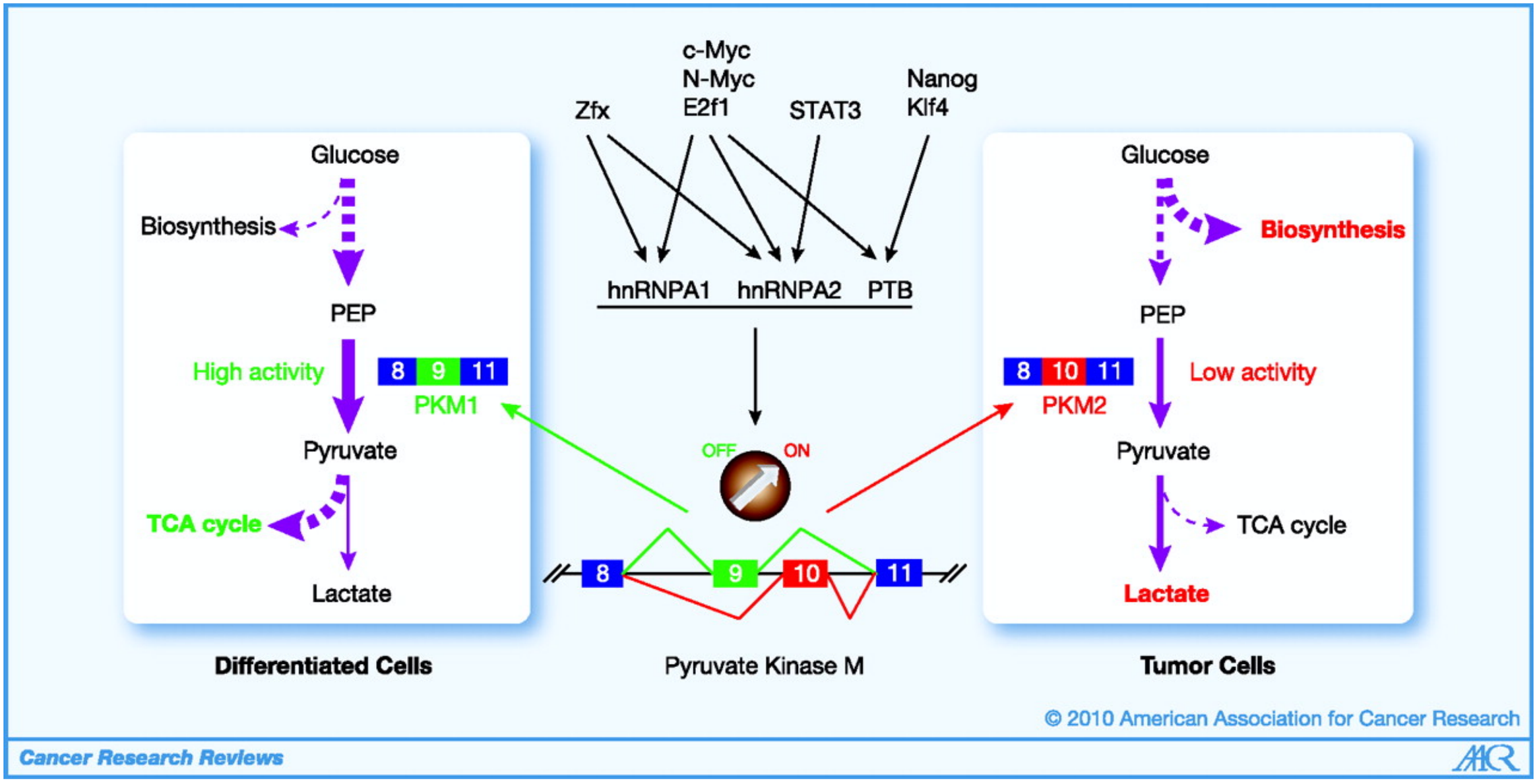
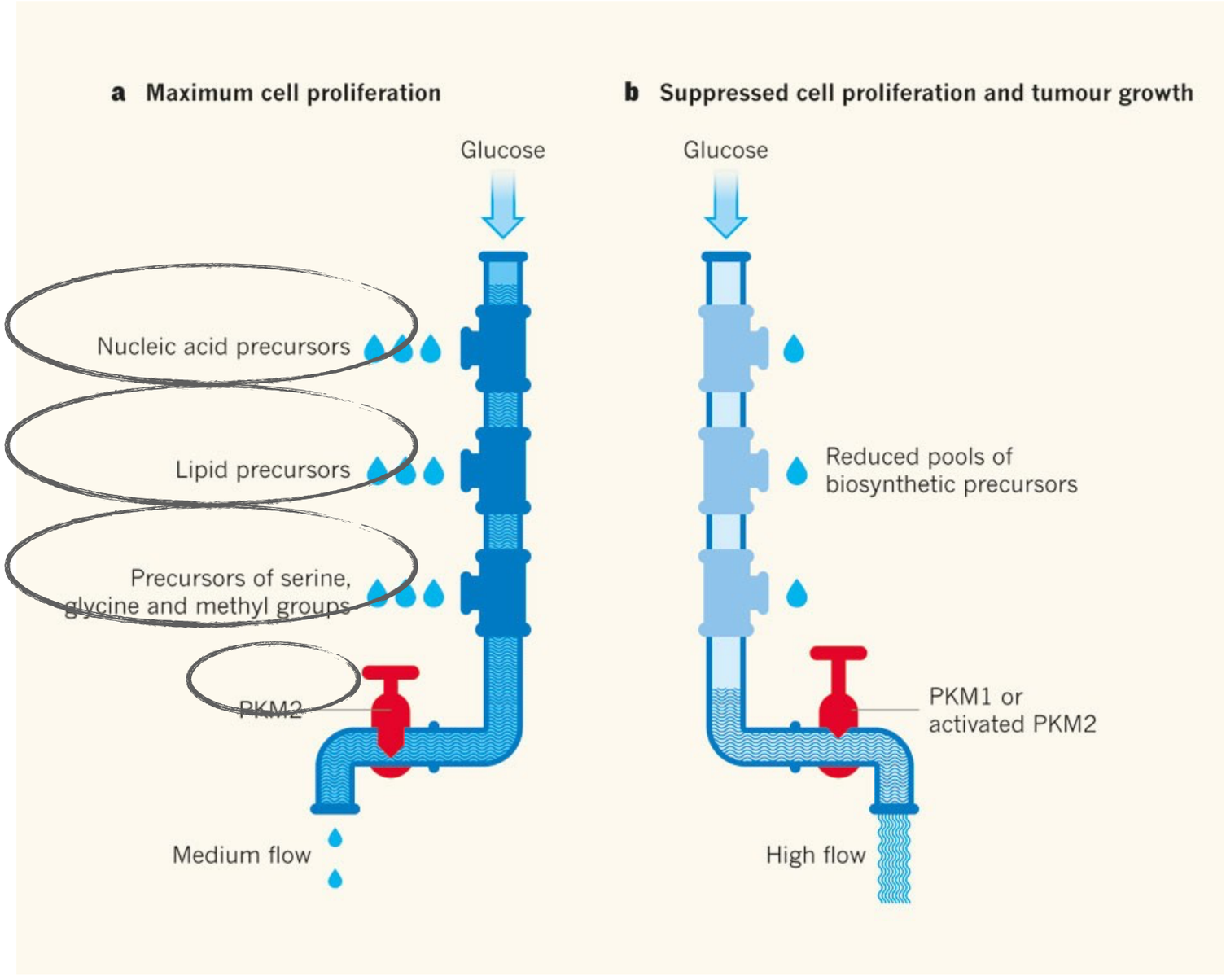


1. Allosteric/metabolic
2. Transcription (Growth Factor Signaling)
3. Phosphorylation

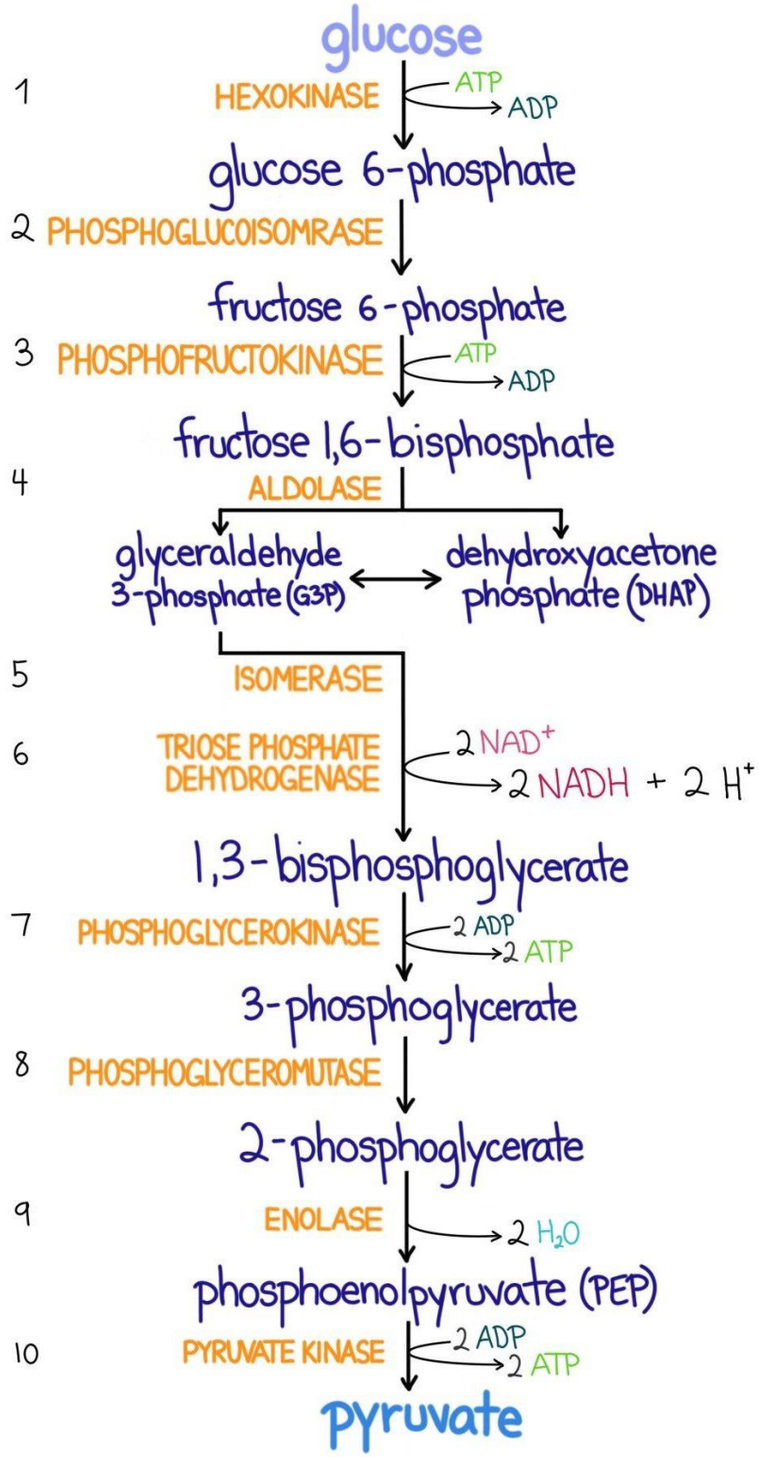
PKM2 has LOWER activity



Lower PKM activity leads to accumulation of glycolytic intermediates



Glycolytic flux is regulated and provides substrates for biosynthetic pathways



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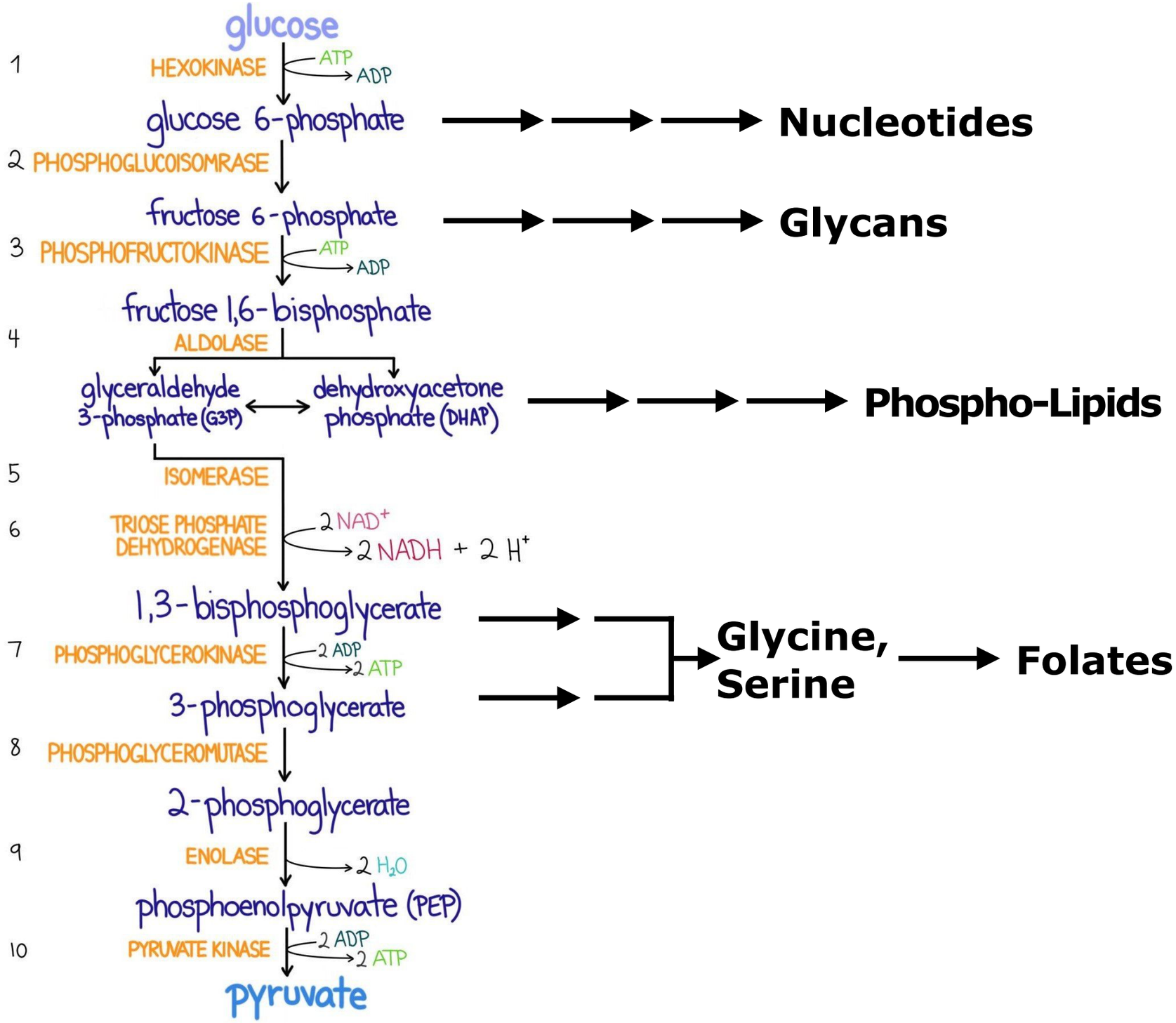
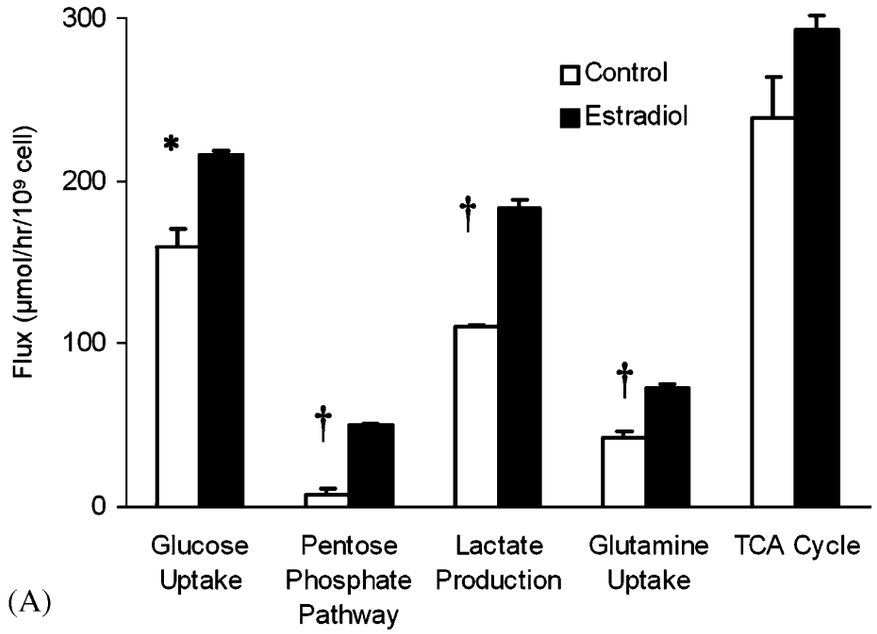


Estradiol stimulates the biosynthetic pathways of breast cancer cells: Detection by metabolic flux analysis

Neil S. Forbes*, Adam L. Meadows, Douglas S. Clark, Harvey W. Blanch



NMR measurements of major metabolites inside and outside (medium) the cell

Forbes et al, ***Metabol Engin****, 2006*

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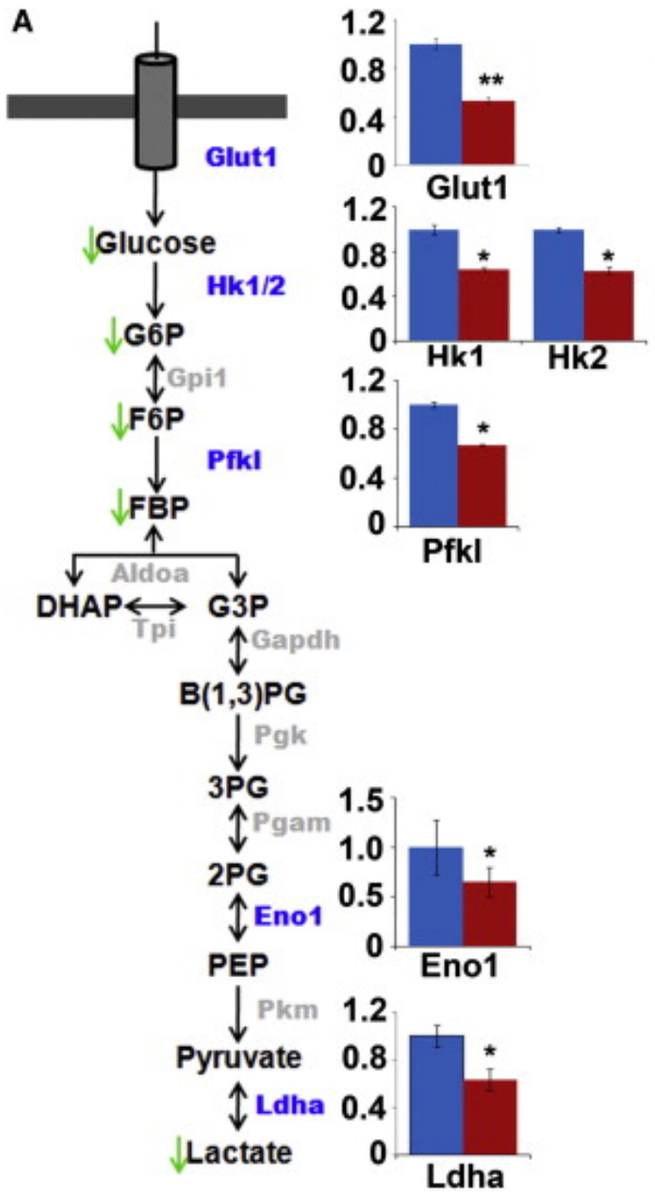
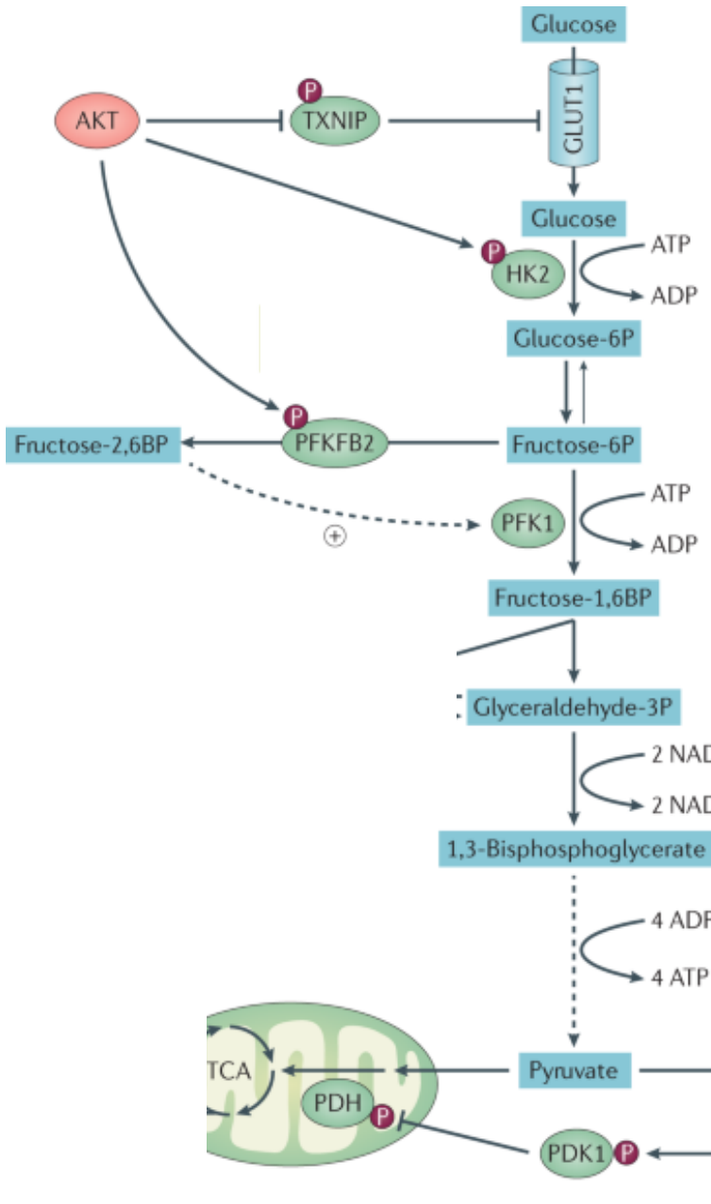




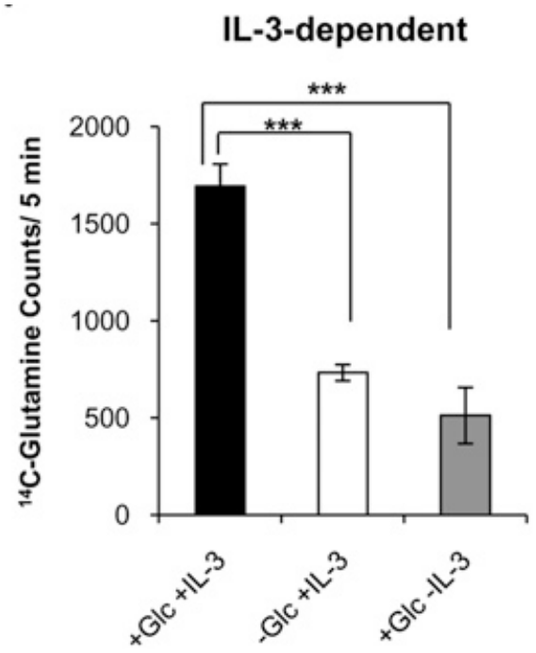
Ying H et al, ***Cell****, 2012*

KRAS mutant
KRAS wild-type

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

The hexosamine biosynthetic pathway couples growth factor-induced glutamine uptake to glucose metabolism

Kathryn E. Wellen,[1] Chao Lu,[1] Anthony Mancuso,[1] Johanna M.S. Lemons,[2] Michael Ryczko,[3] James W. Dennis,[3] Joshua D. Rabinowitz,[4] Hilary A. Coller,[5] and Craig B. Thompson[1,6]



FL5.12 cells supplemented with IL-3 enhance their glutamine uptake

Wellen et al, ***Genes Dev****, 2010*

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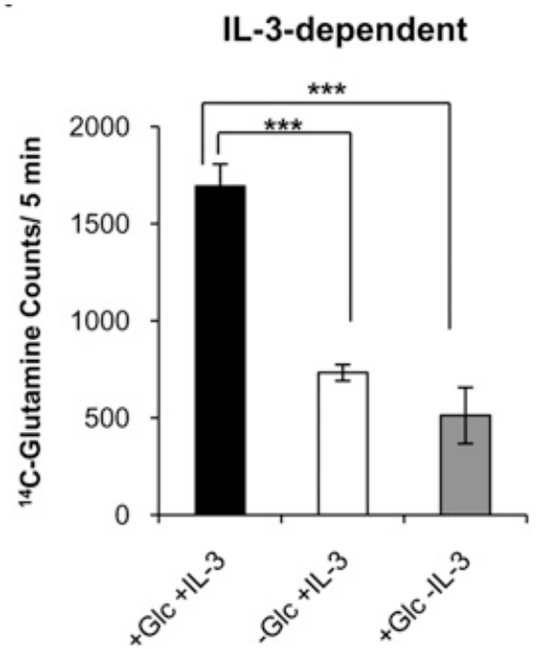

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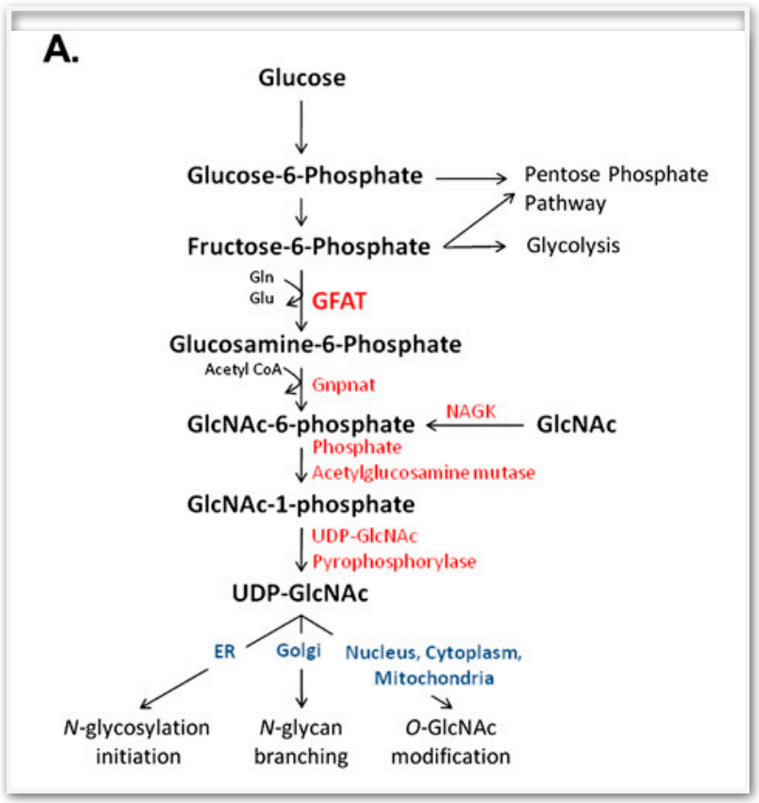

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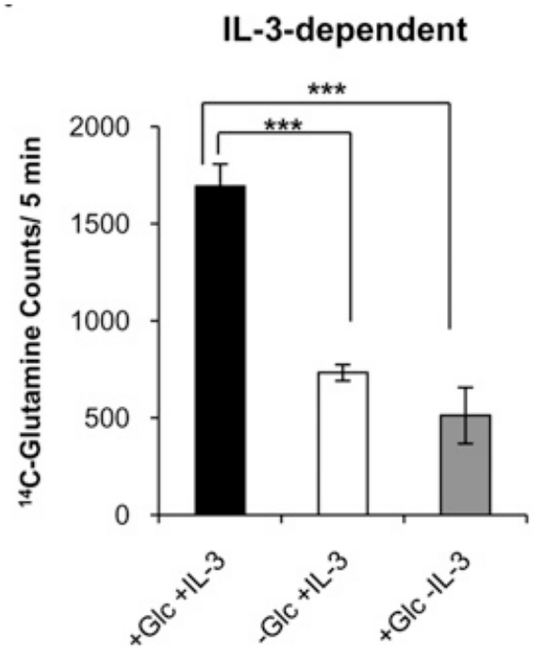

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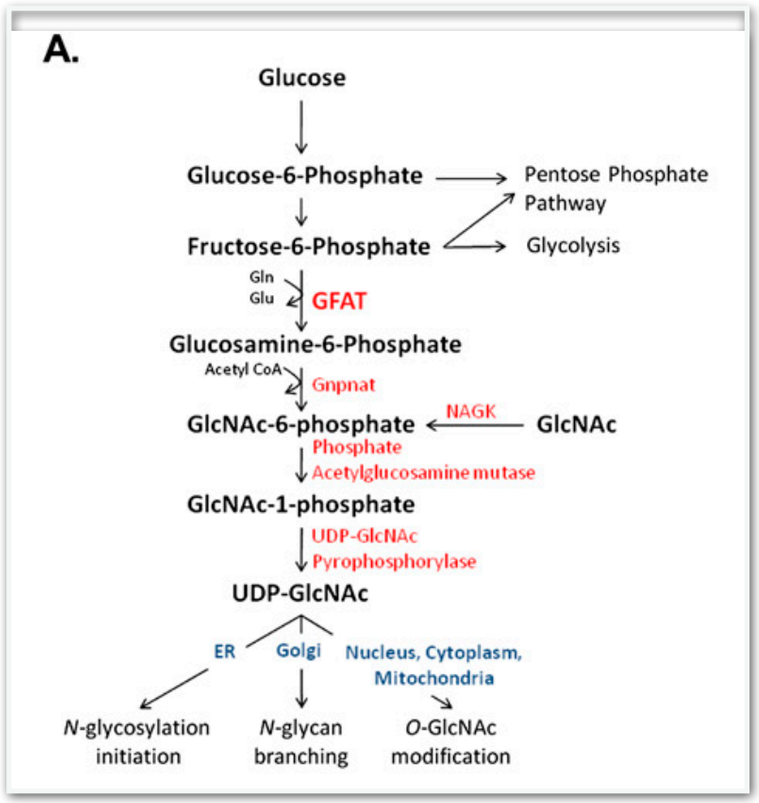

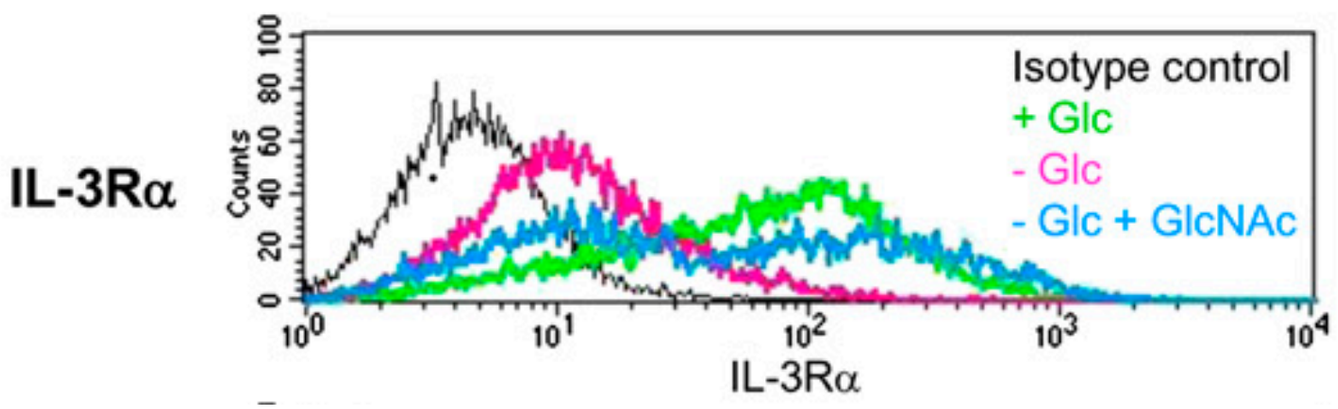

Glucose deprivation impairs glycosylation of IL-3R

Wellen et al, ***Genes Dev****, 2010*

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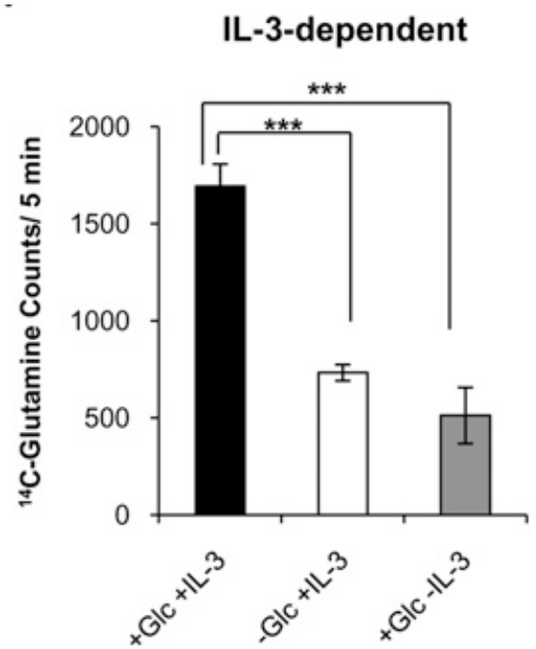

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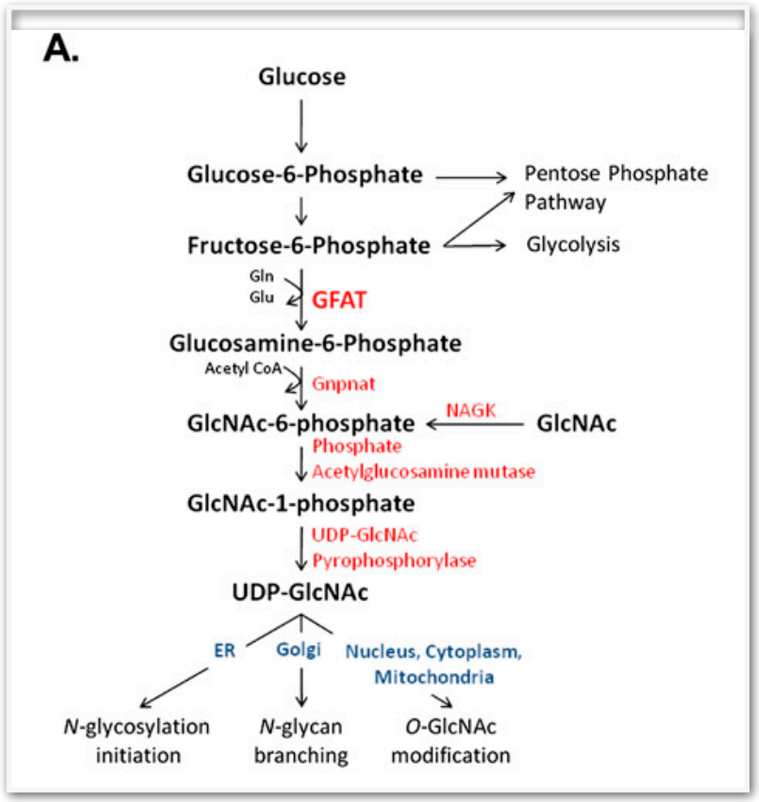
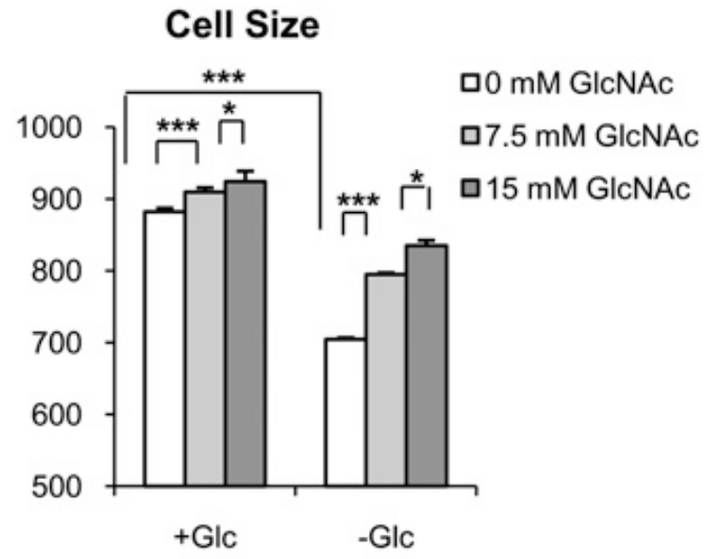
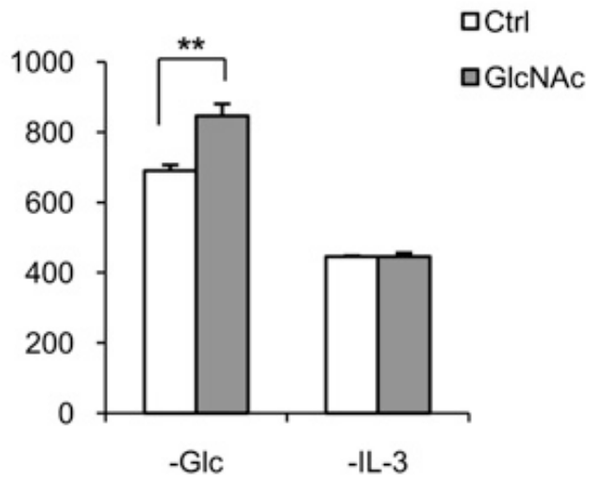
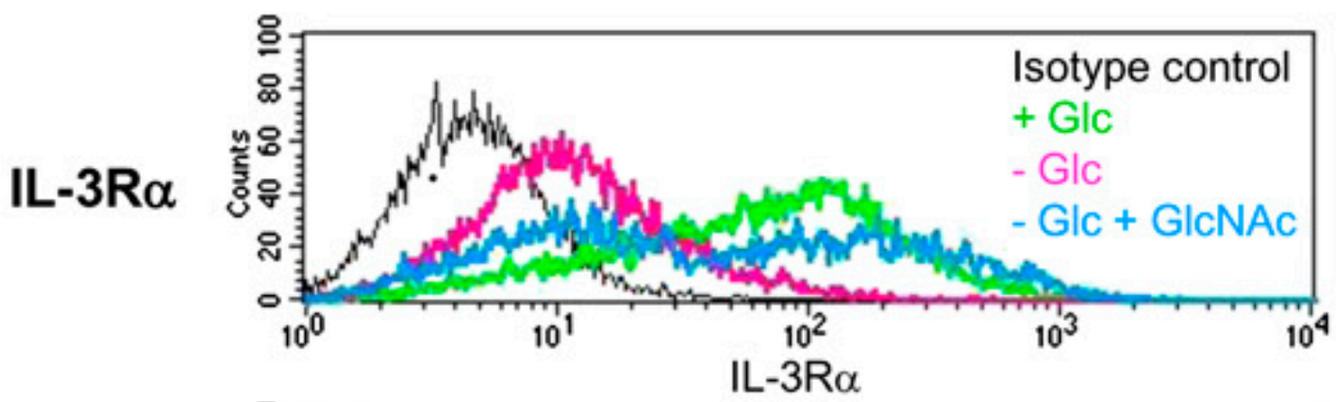






HexP intermediates rescue cell growth in glucose-deprived conditions



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Multi-level regulation of intracellular metabolism

Nutrient availability

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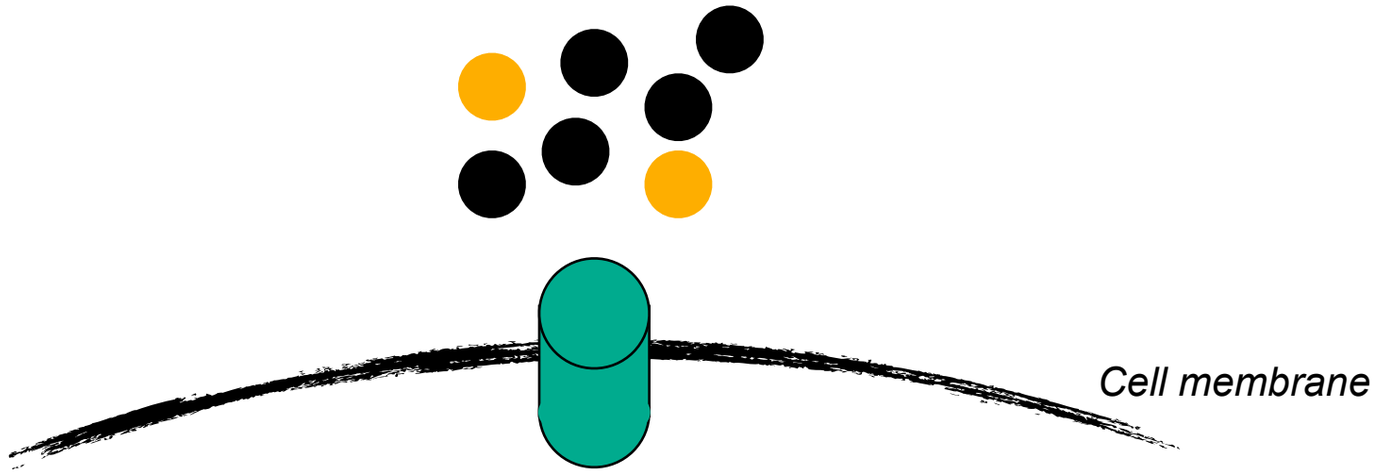
Nutrient availability

Nutrient uptake



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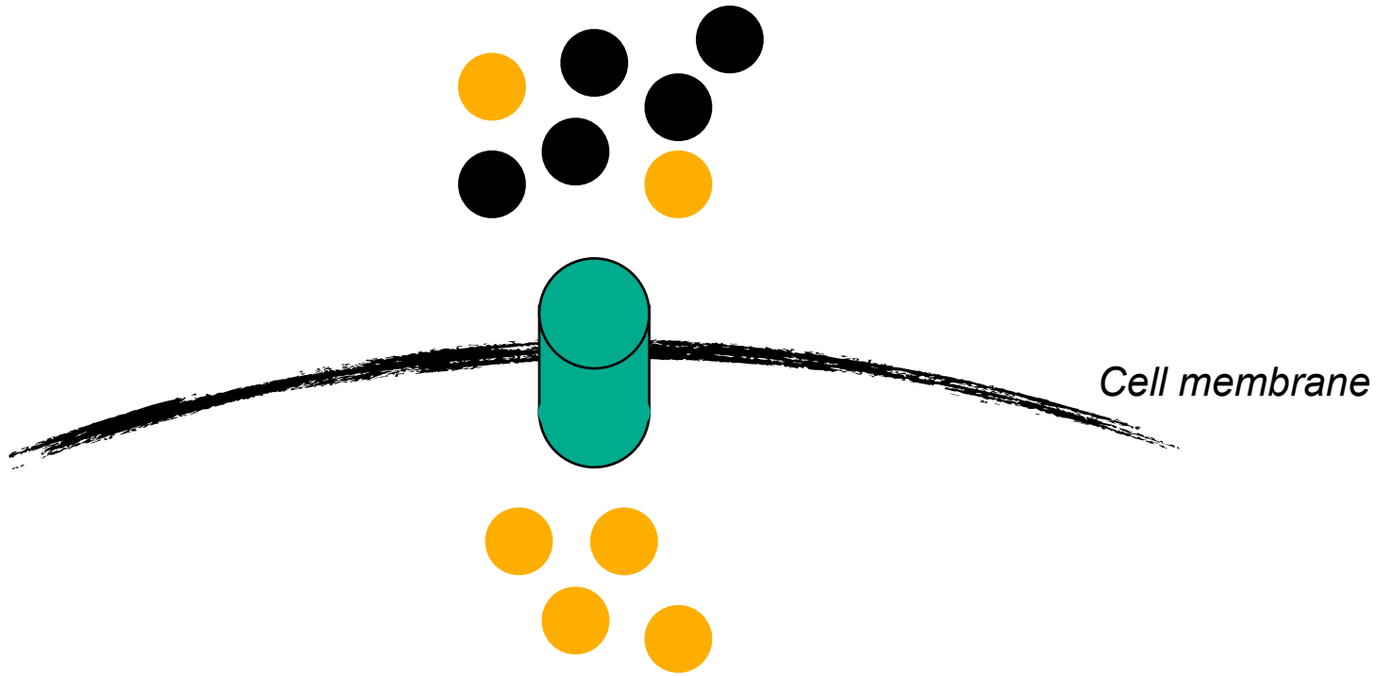

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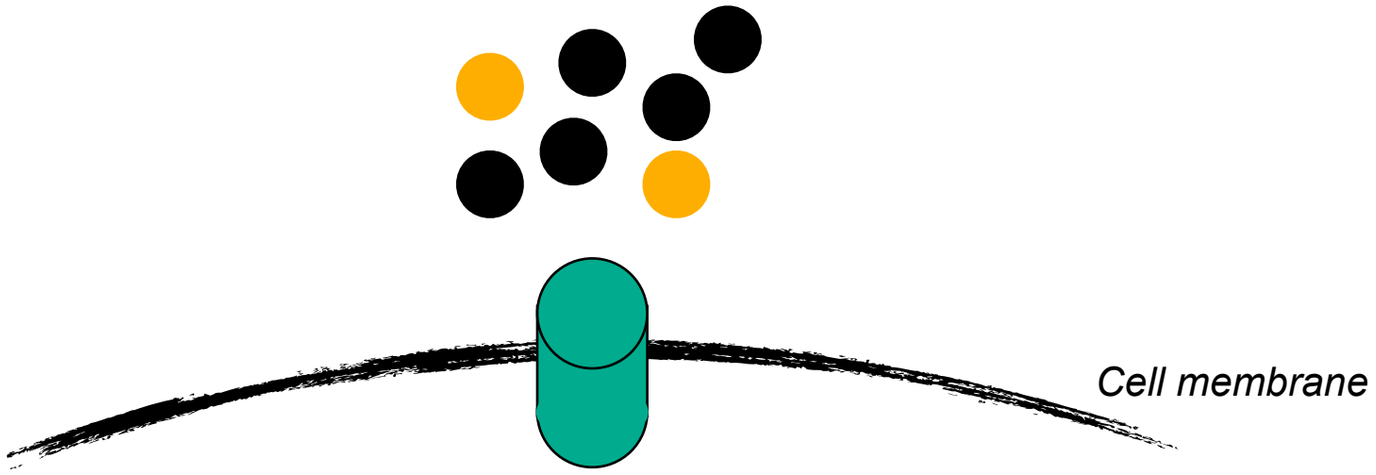
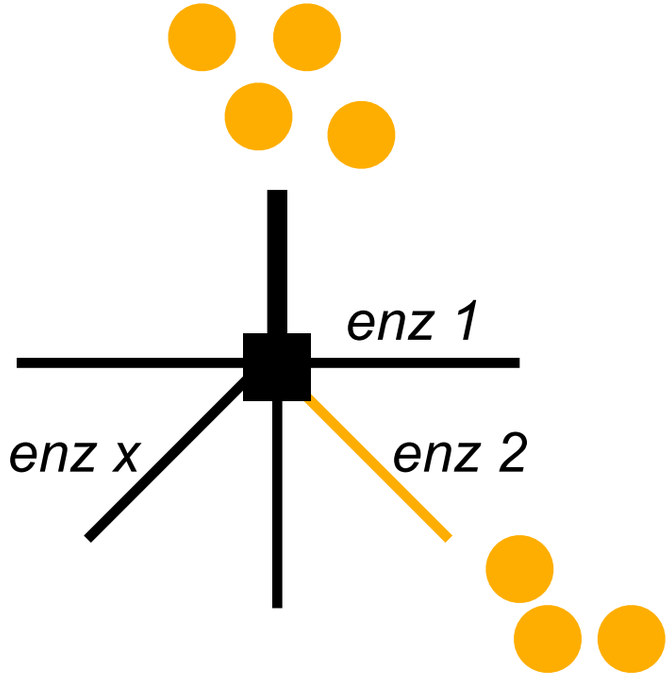


Nutrient channeling (wiring)



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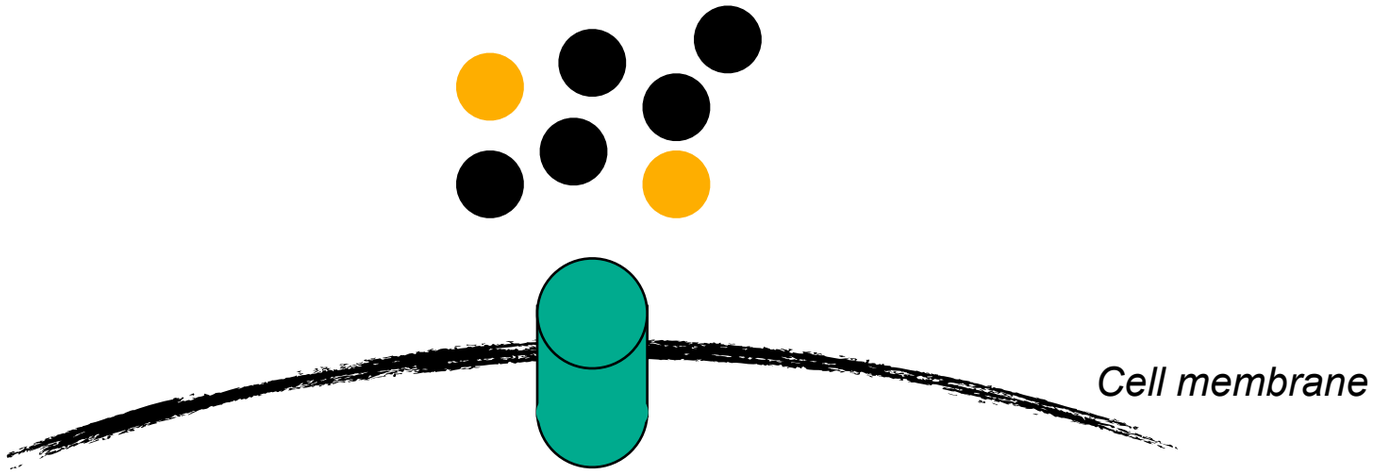

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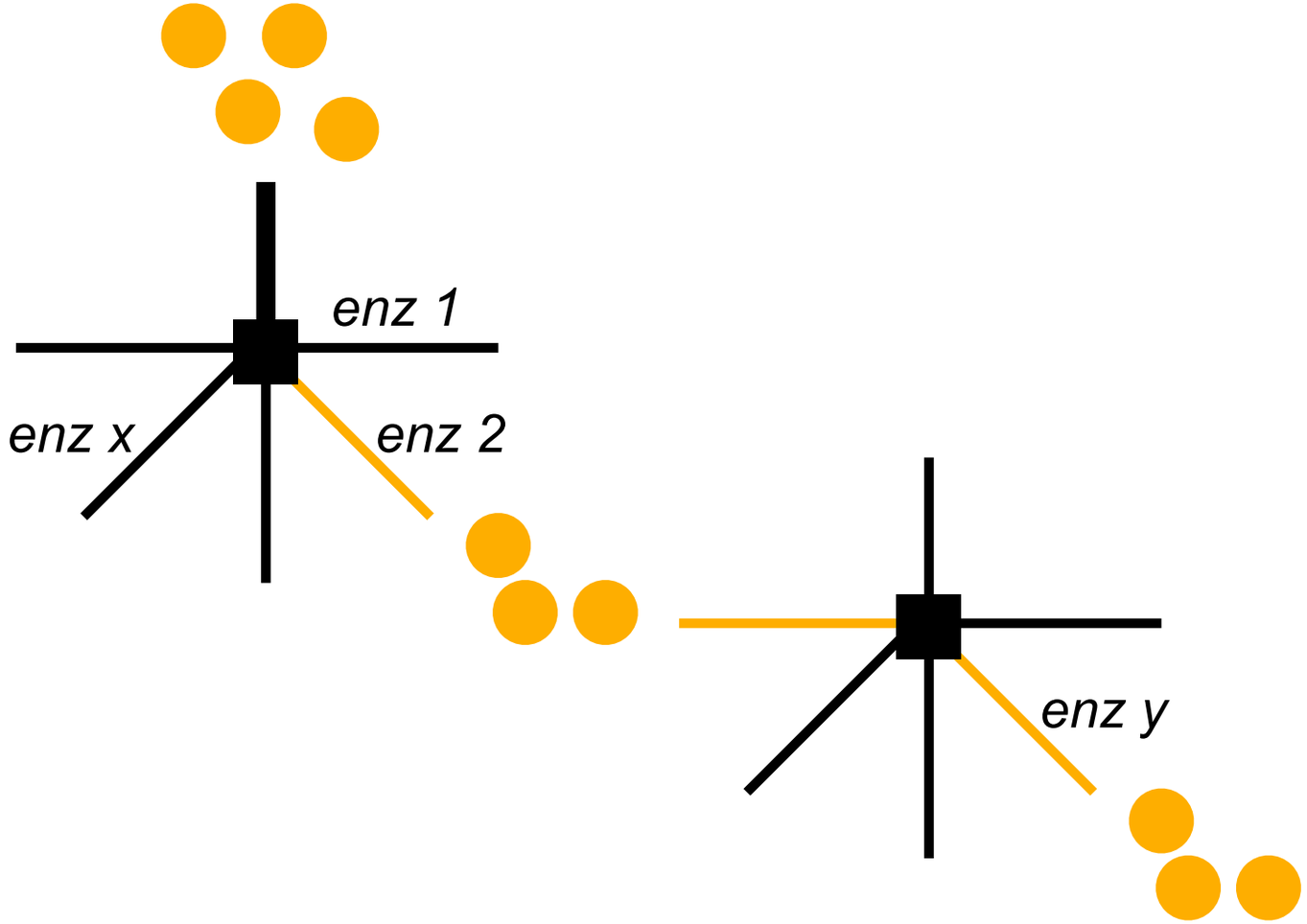
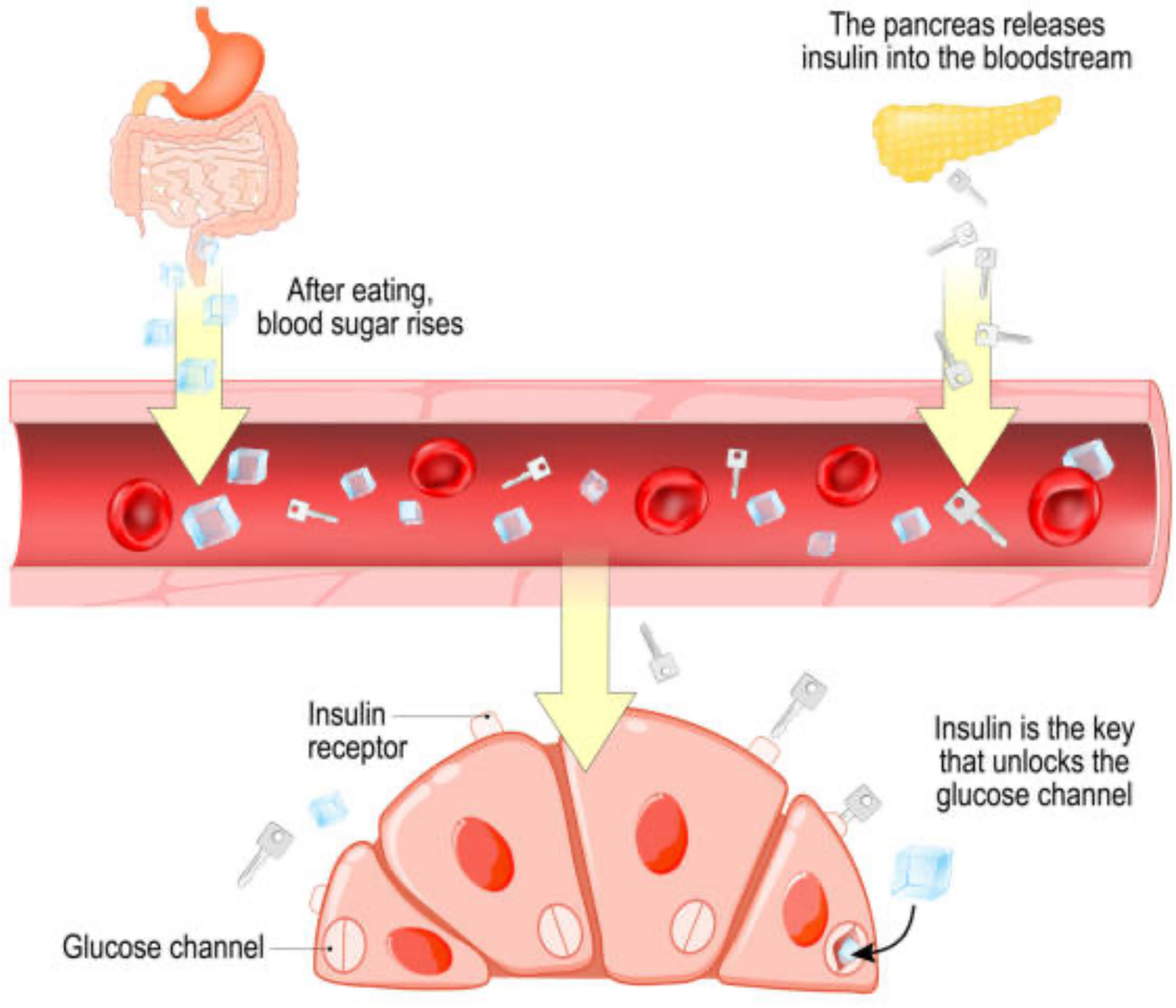
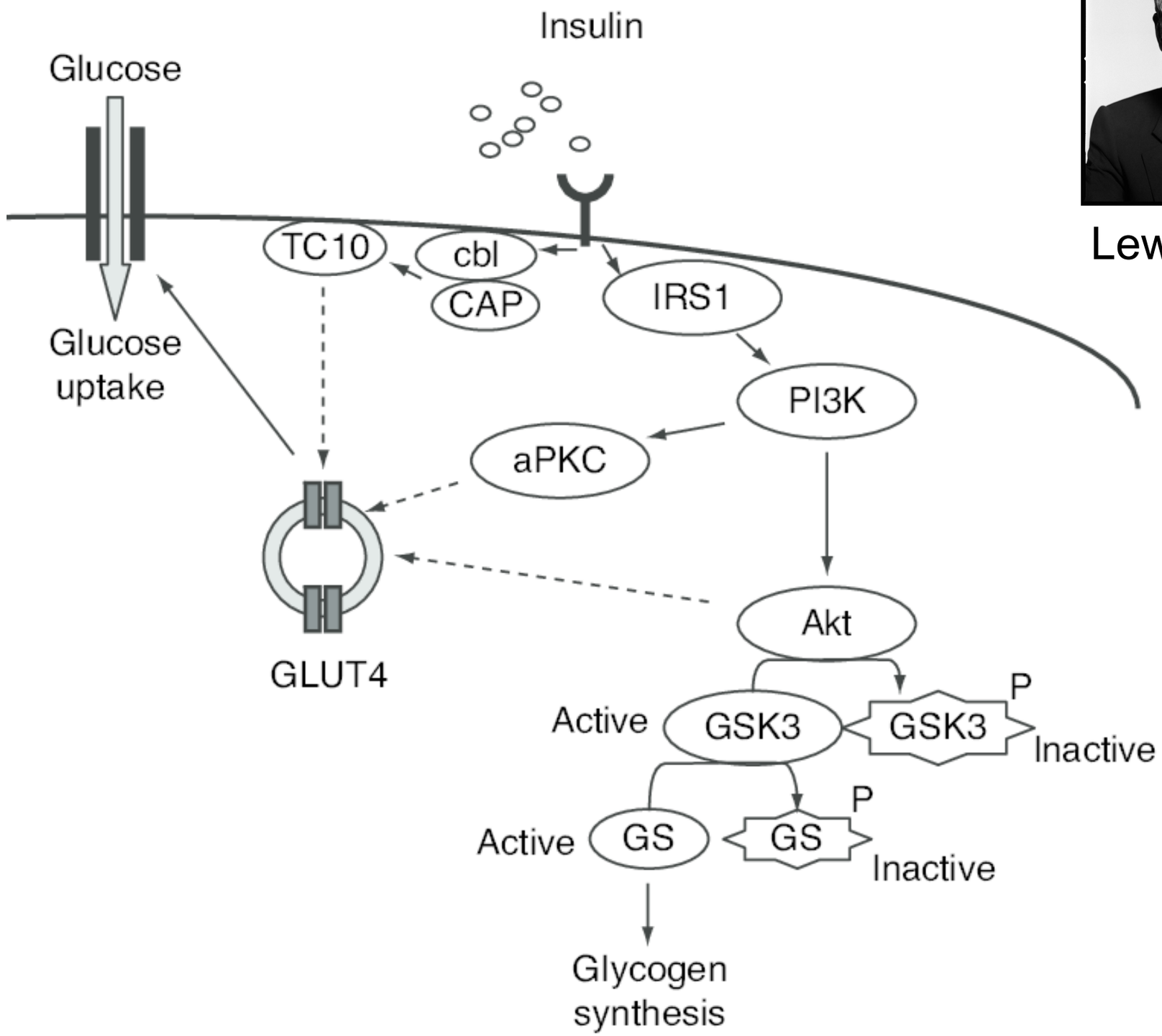


Glucose uptake: the case of INSULIN



Insulin triggers membrane-associated GTPases and phosphatidylinositol 3-kinase

Lew Cantley



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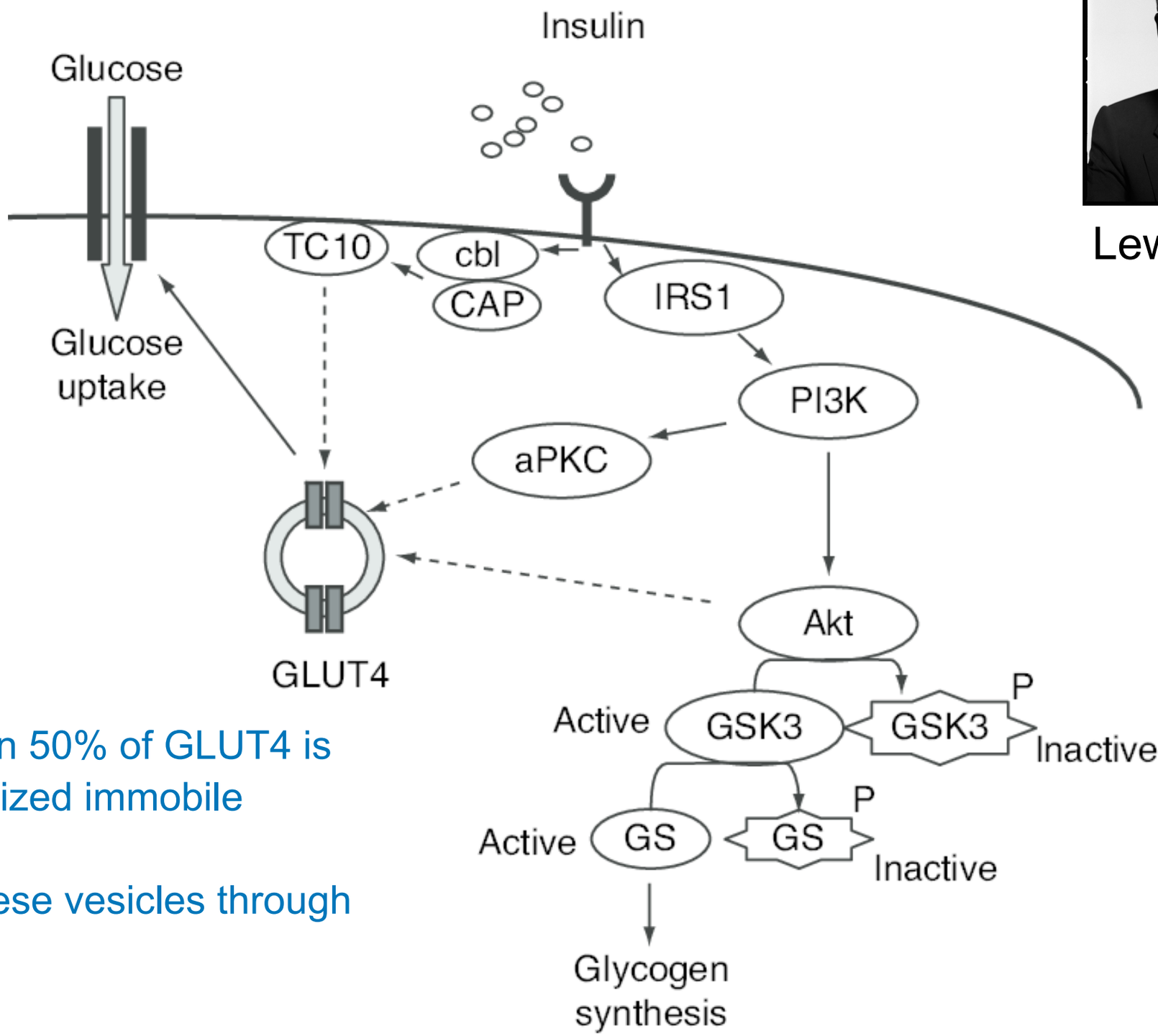

At rest state, more than 50% of GLUT4 is sequestered in specialized immobile storage vesicles.
Signaling mobilizes these vesicles through multiple mechanisms.

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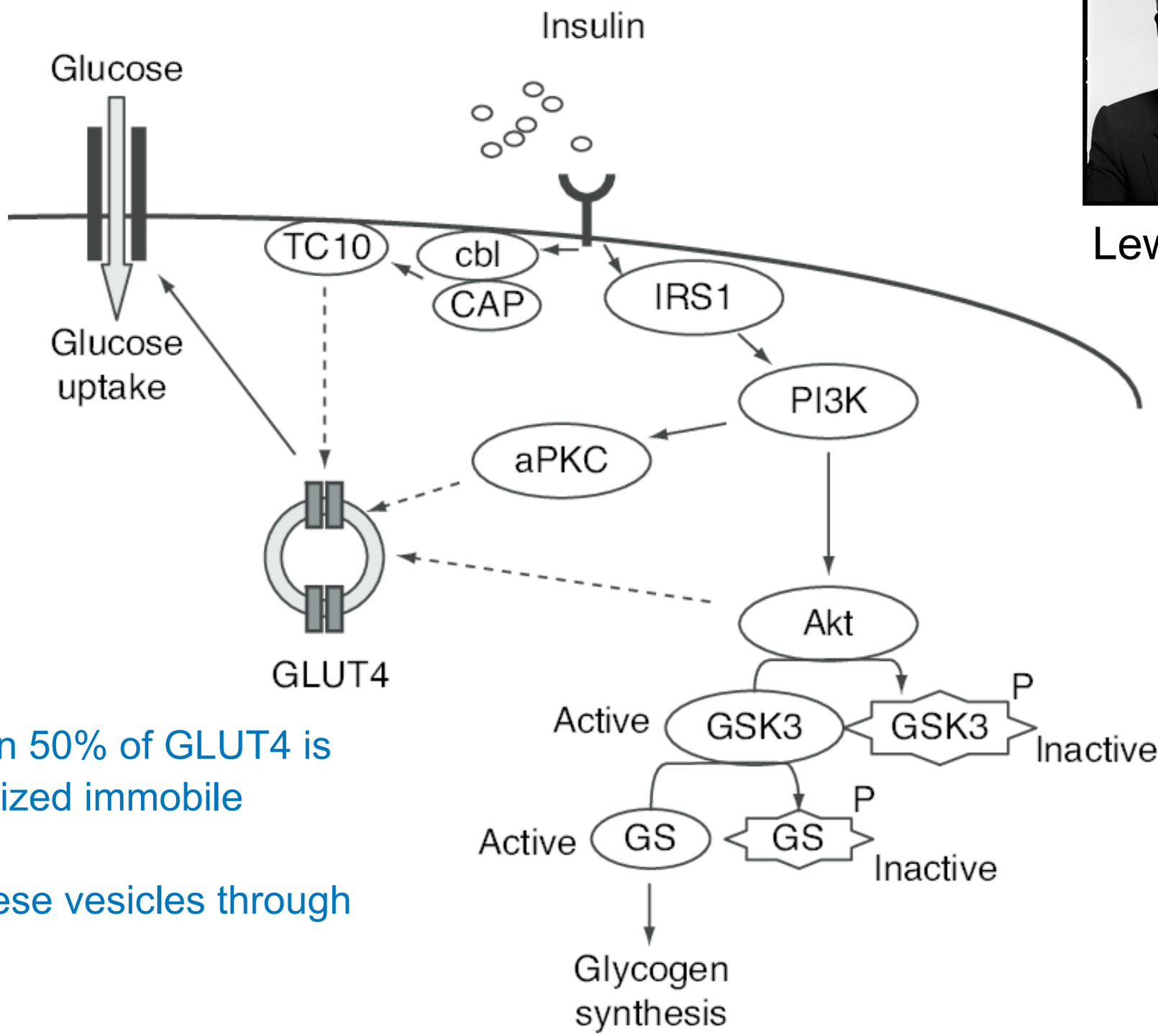

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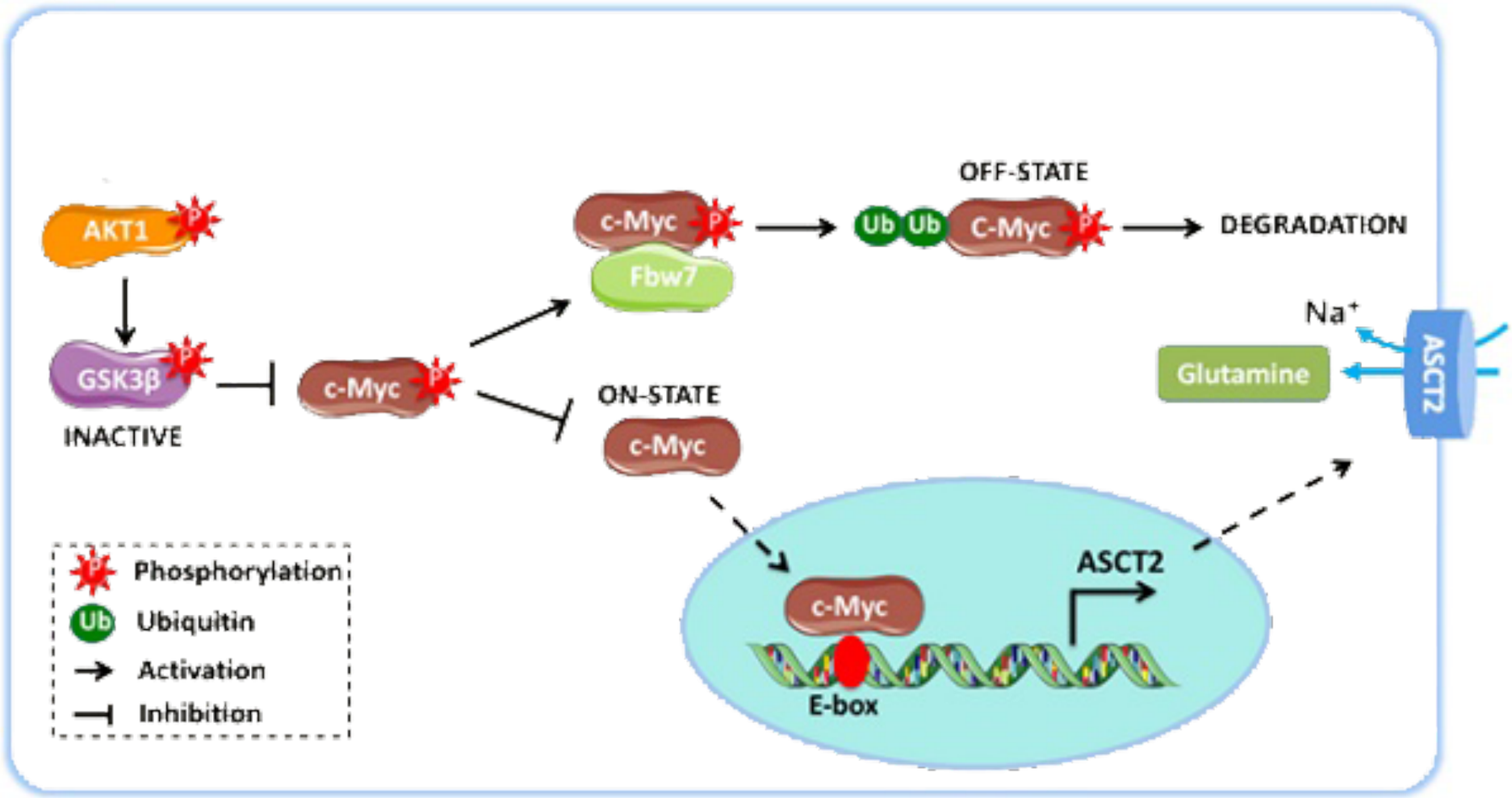
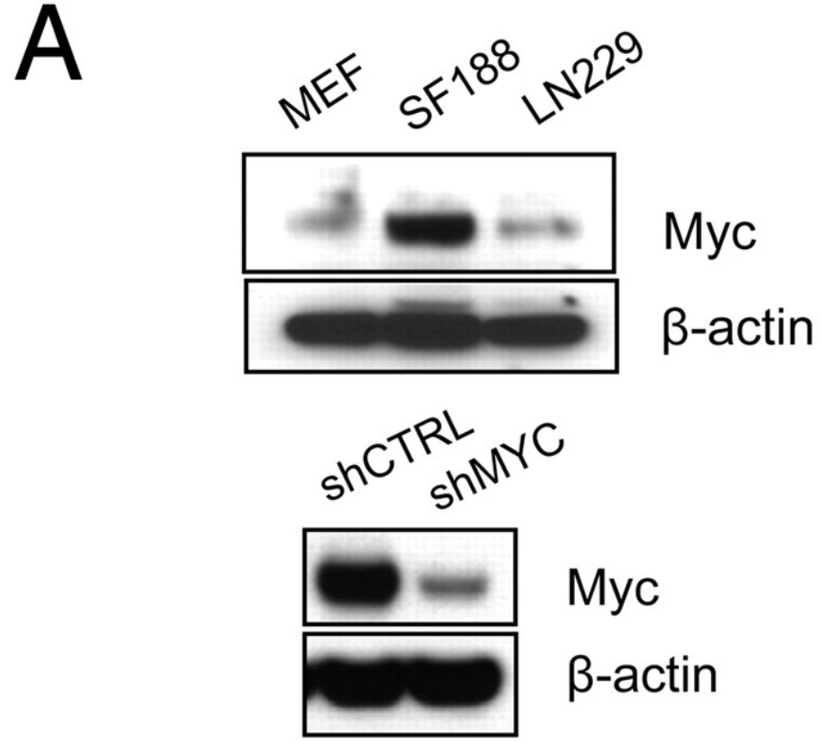
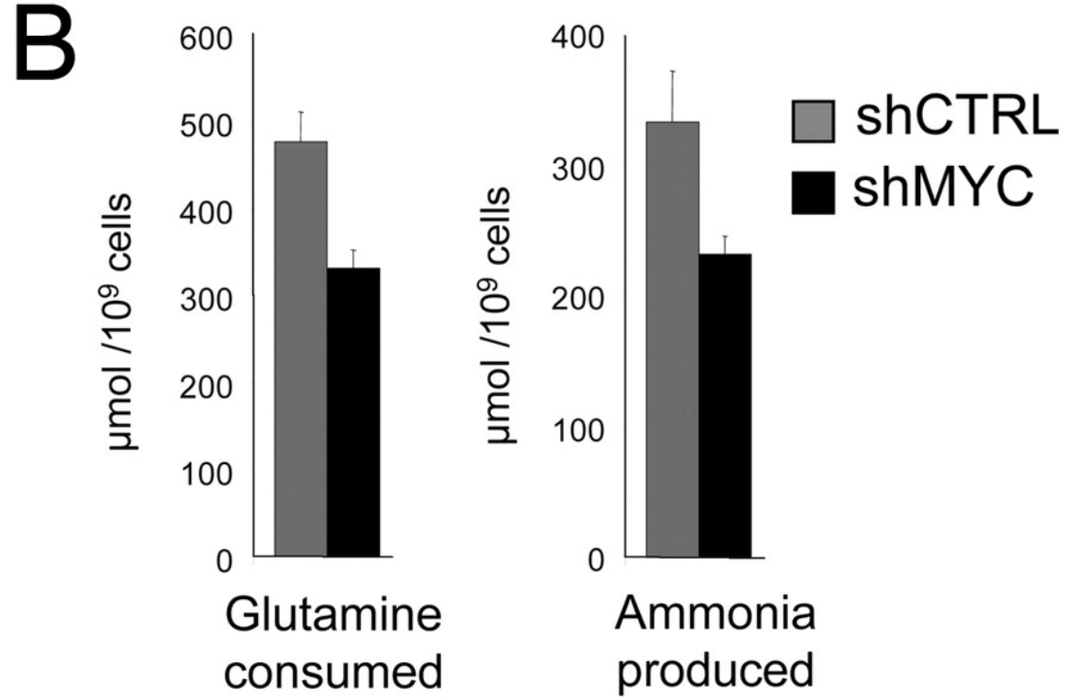
GLUT4 on the PM

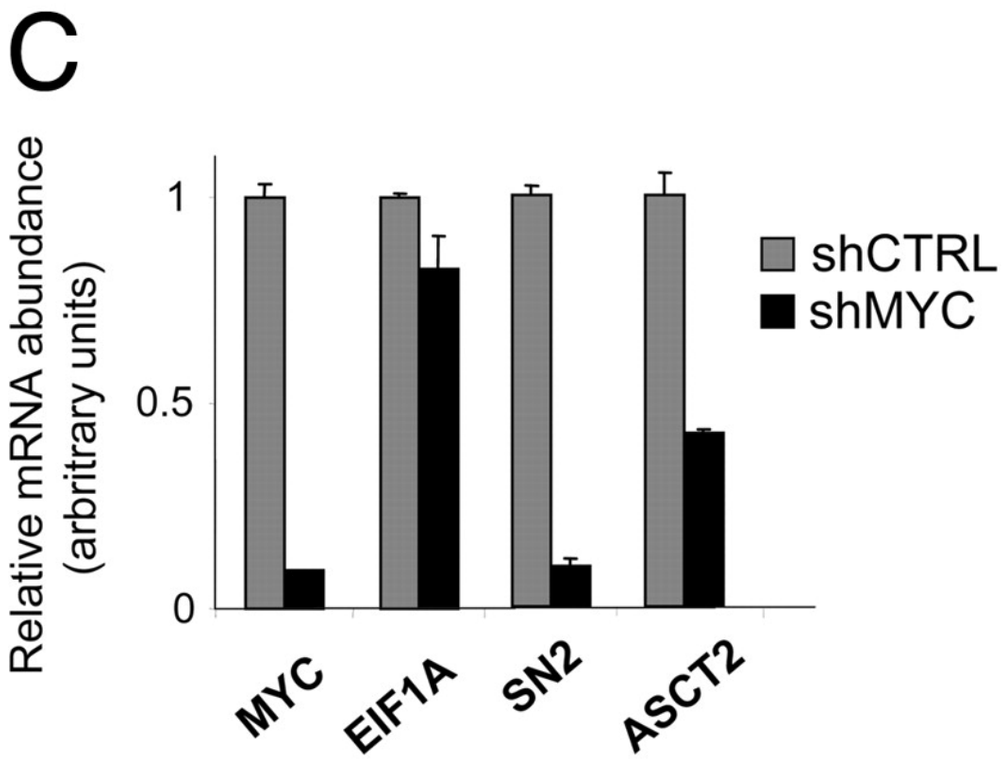
++ glucose uptake

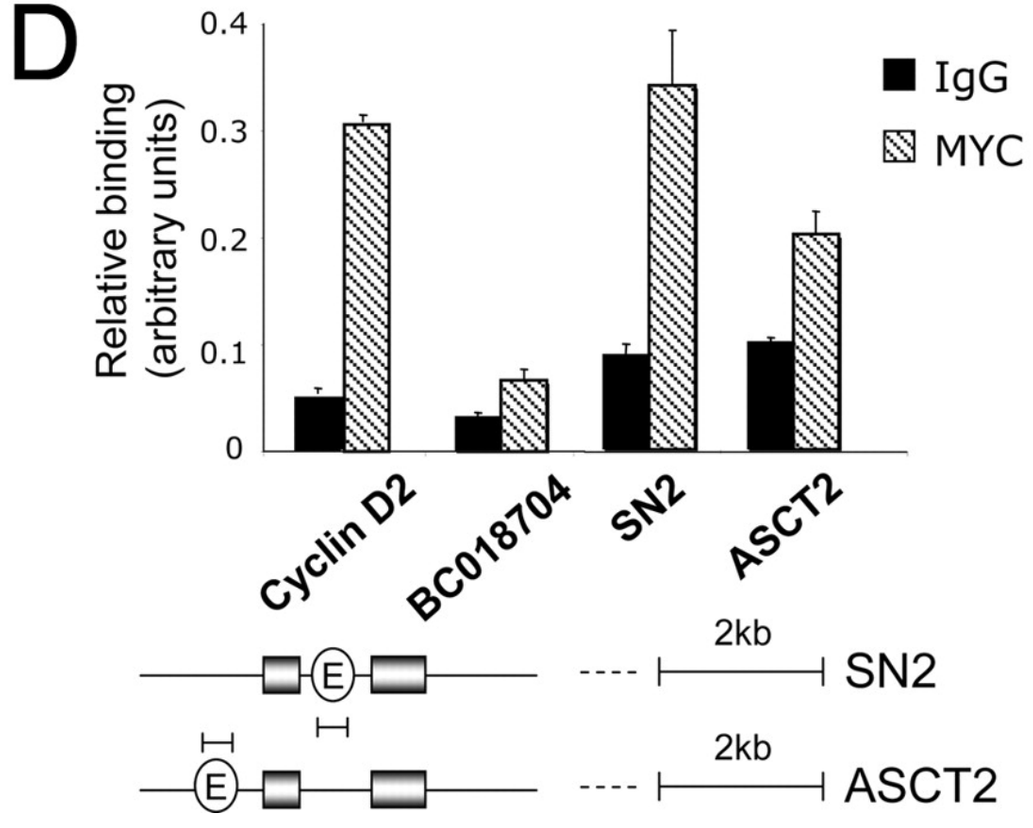
MYC mediates GLUTAMINE uptake through transcriptional upregulation of *SLC1A5*



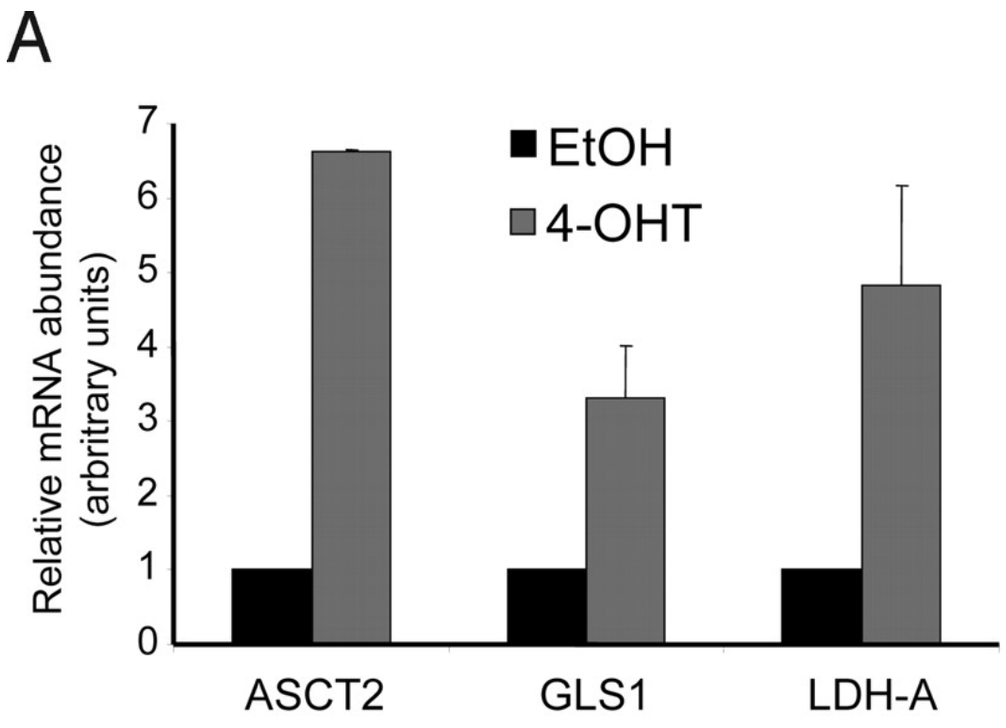


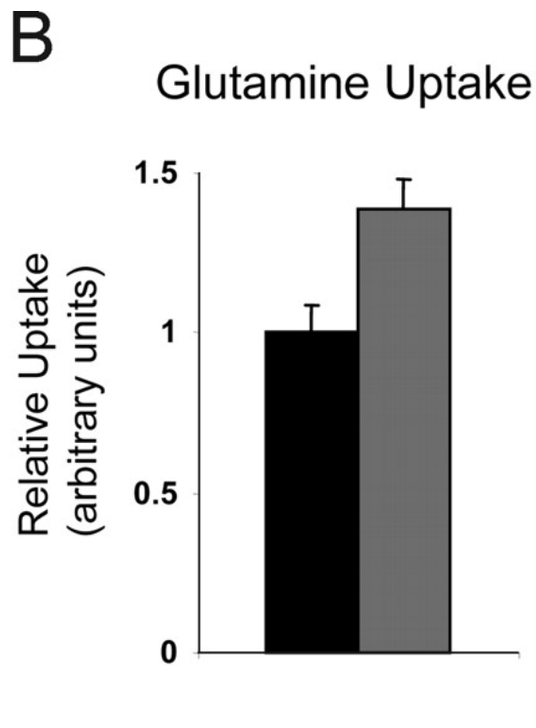


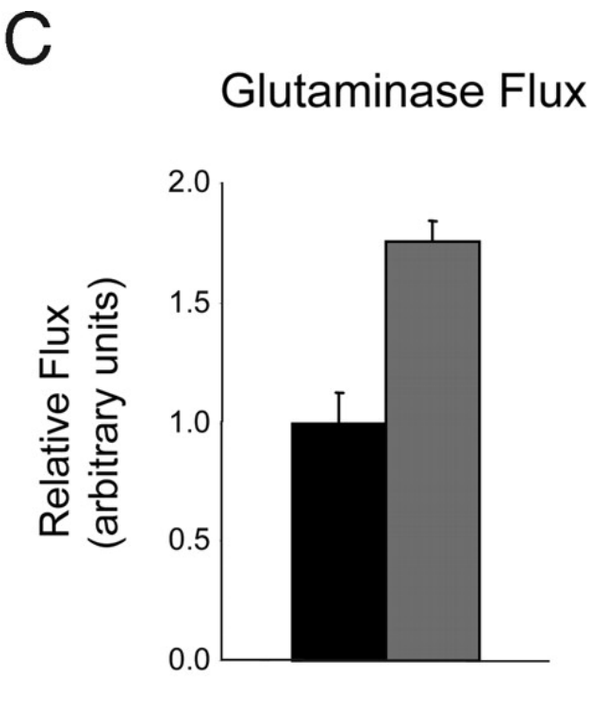


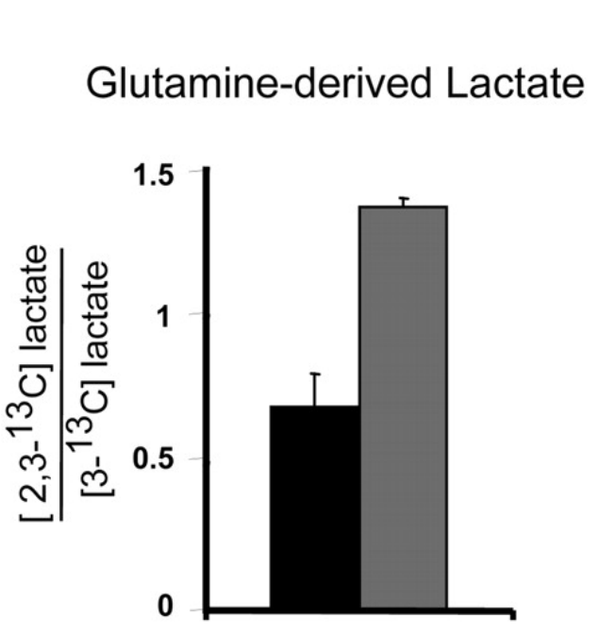


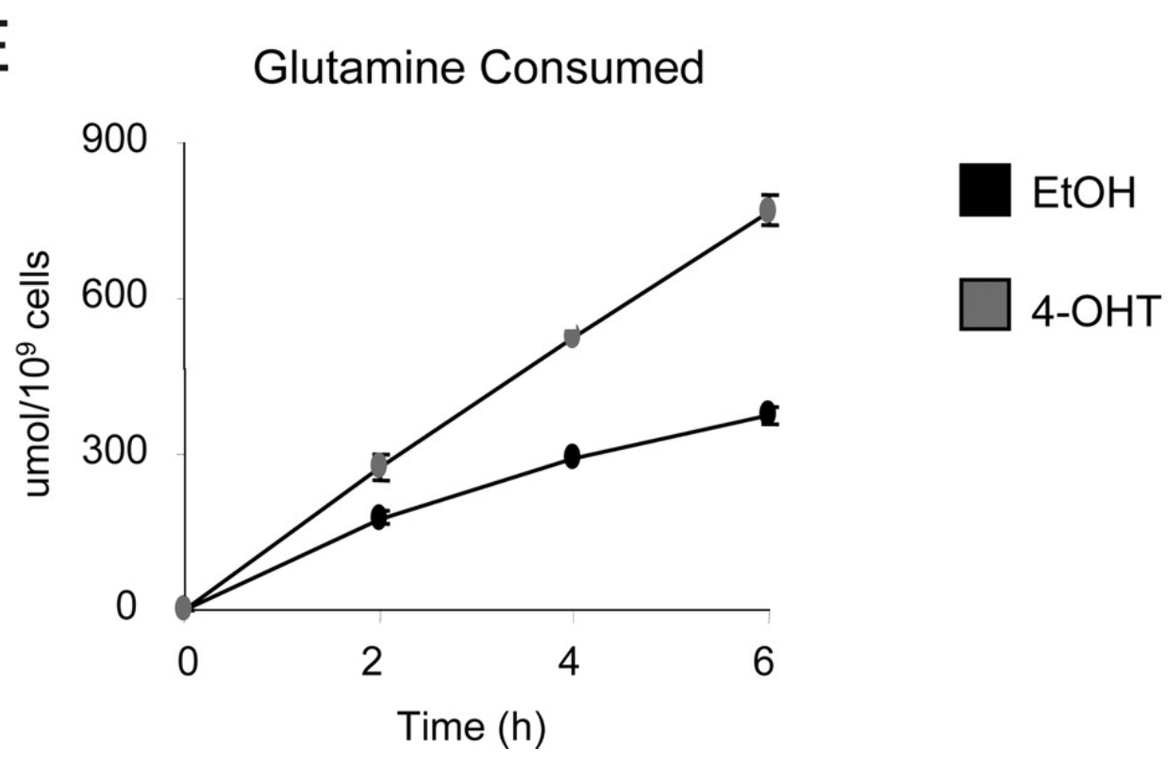
*Wise, DeBerardinis et al, **PNAS**, 2008*









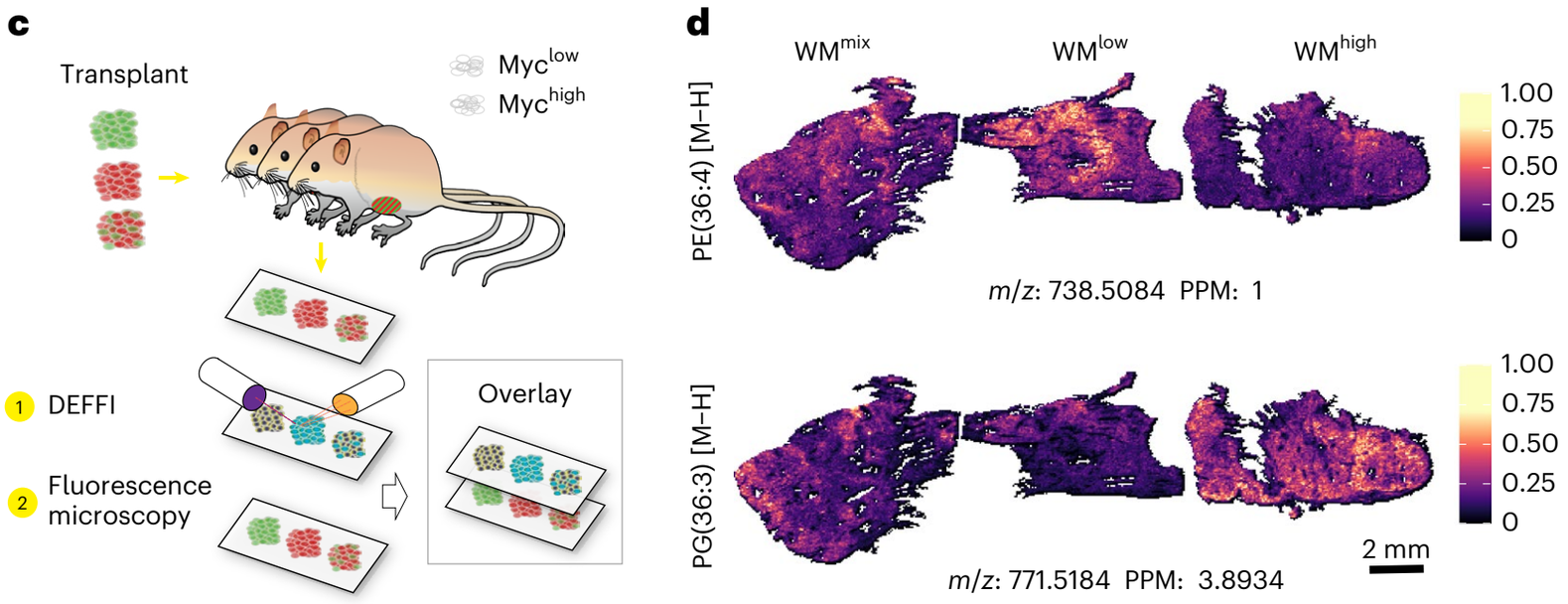


Wise, DeBerardinis et al, ***PNAS****, 2008*

https://doi.org/10.1038/s42255-023-00915-7

Vitamin B_5 supports MYC oncogenic metabolism and tumor progression in breast cancer

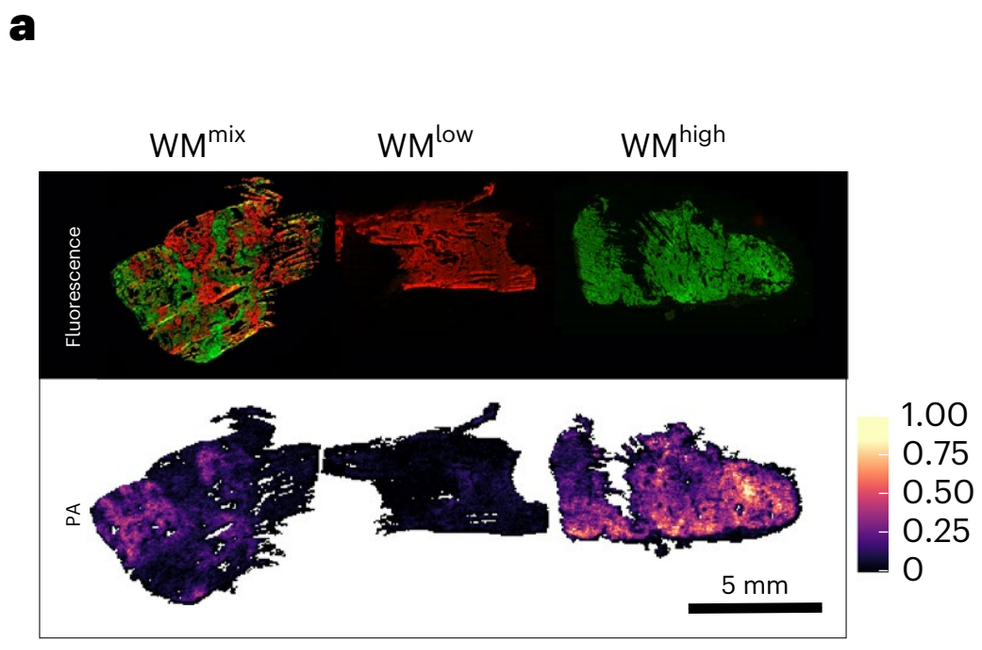
While MYC is recognized as a master regulator of metabolism, inducing glycolytic flux and increas- ing glutaminolysis among others, the true metabolic signature of these malignant subclones in the pathophysiologically relevant context of multiclonality remains unknown.



MYC^{high} (GFP+) and MYC^{low} (TdTomato+) clones were mixed together and injected in mice to form polyclonal tumors.

To dissect metabolites and metabolic pathways most closely associated with the individual WM clones in situ. To this end they combined desorption electro-flow focusing ionization (DEFFI)-mass spectrometric imaging (MSI) with fluorescence microscopy

Kreuzaler et al, ***Nature Metab****, 2023*



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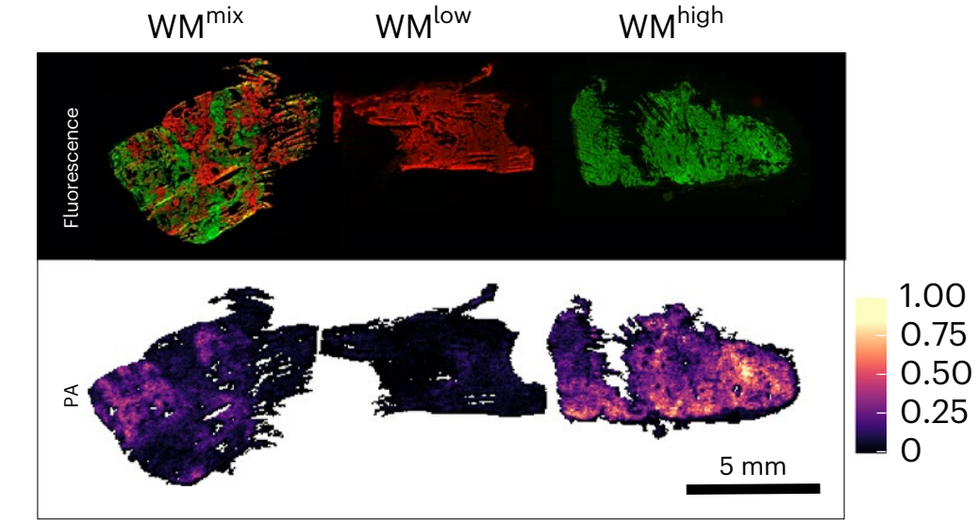
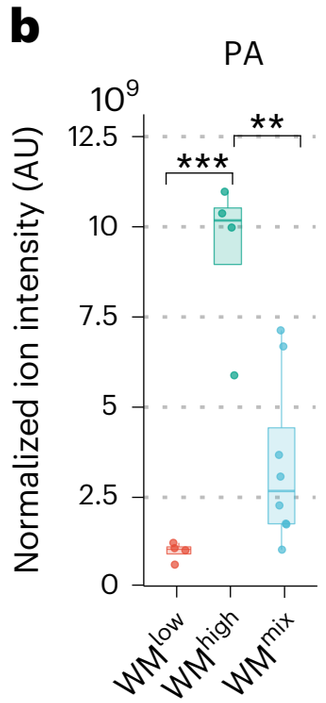
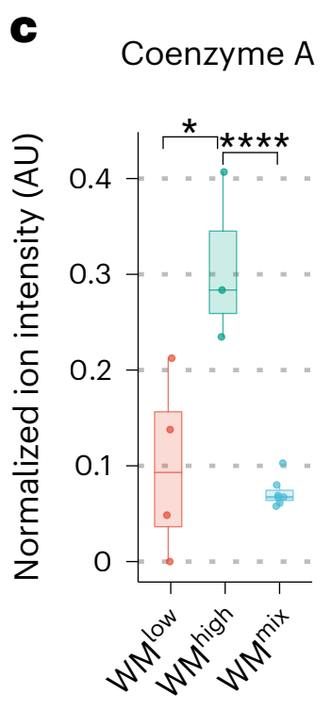
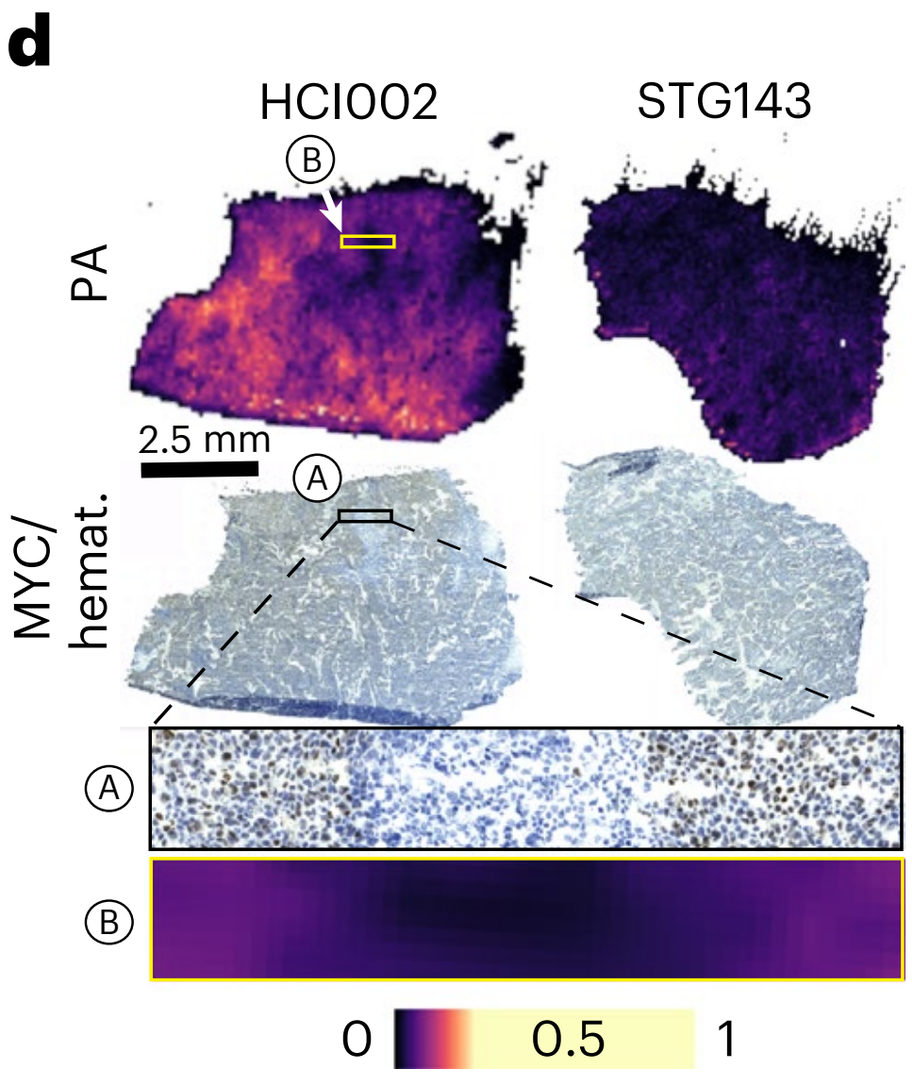
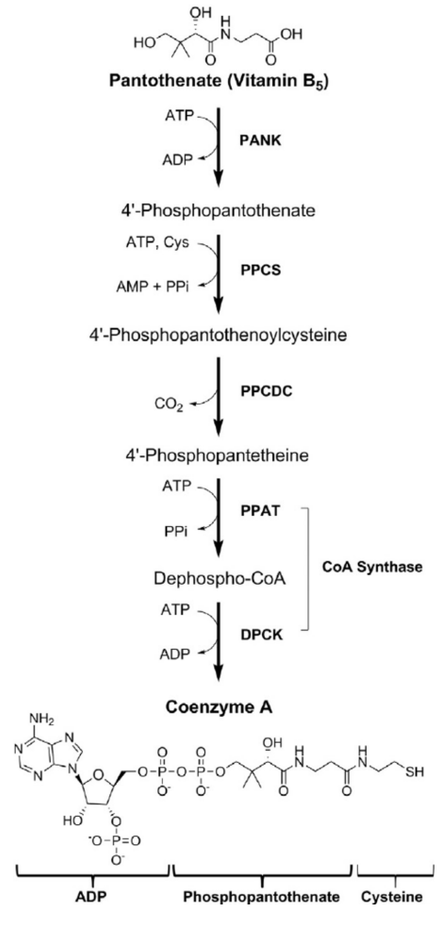








Uptake of Pantothenic Acid (PA, Vitamin B5) spatially correlates with MYC^{high} clones.



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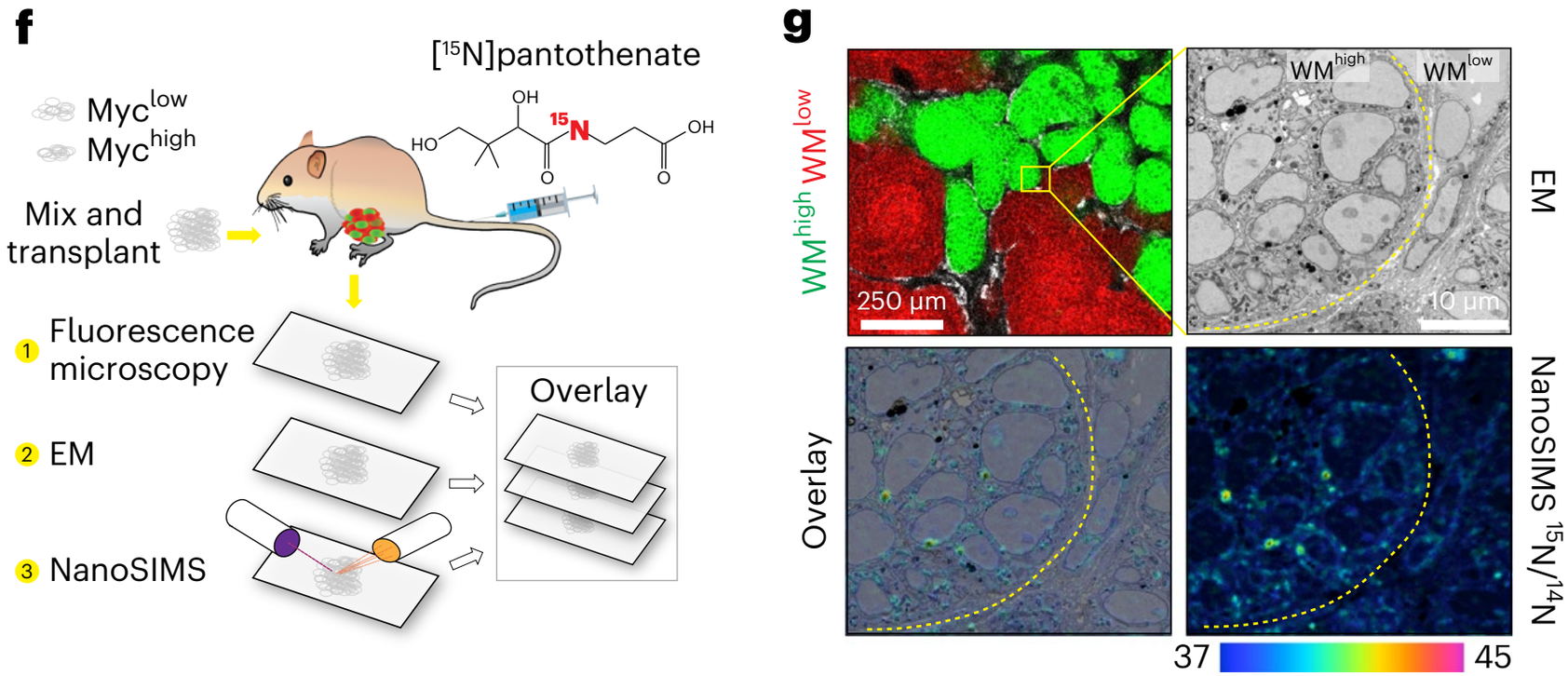
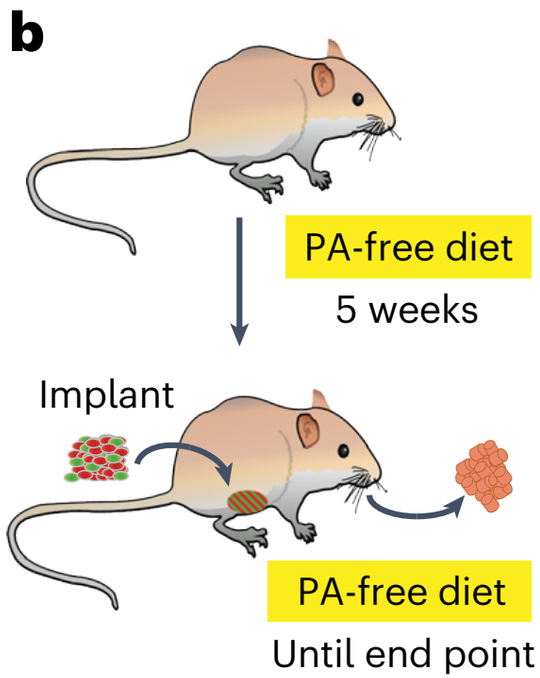
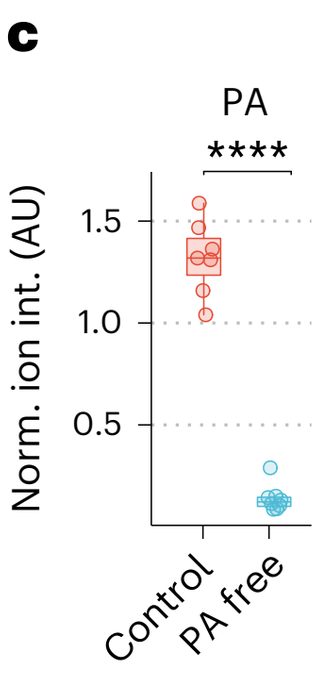


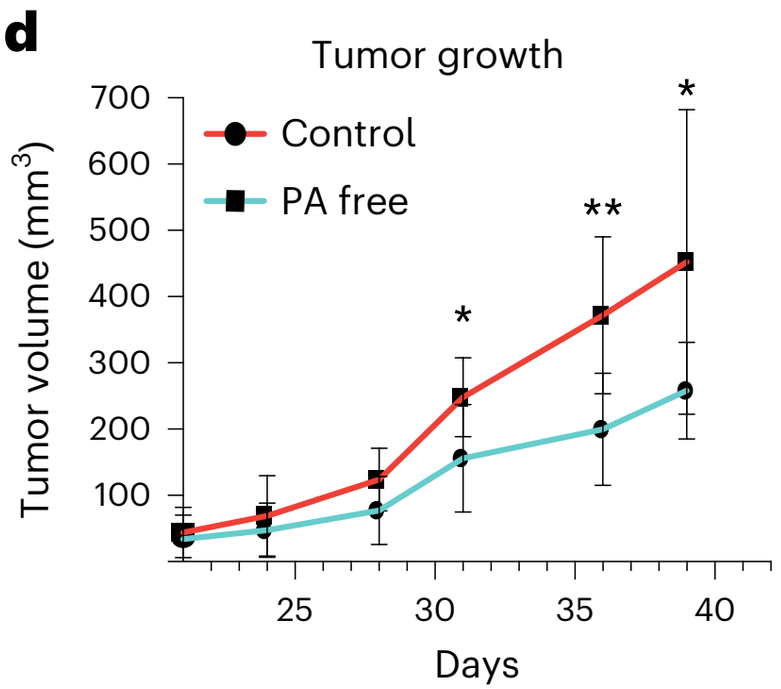
MYC^{high} (GFP+) and MYC^{low} (TdTomato+) clones were mixed together and injected in mice to form polyclonal tumors.

Isotopically-labelled pantothenate was injected in tumor bearing mice and consecutive tissue slides were images with different methods (fluorescence, electron microscopy, mass-spectrometry)

Kreuzaler et al, ***Nature Metab****, 2023*







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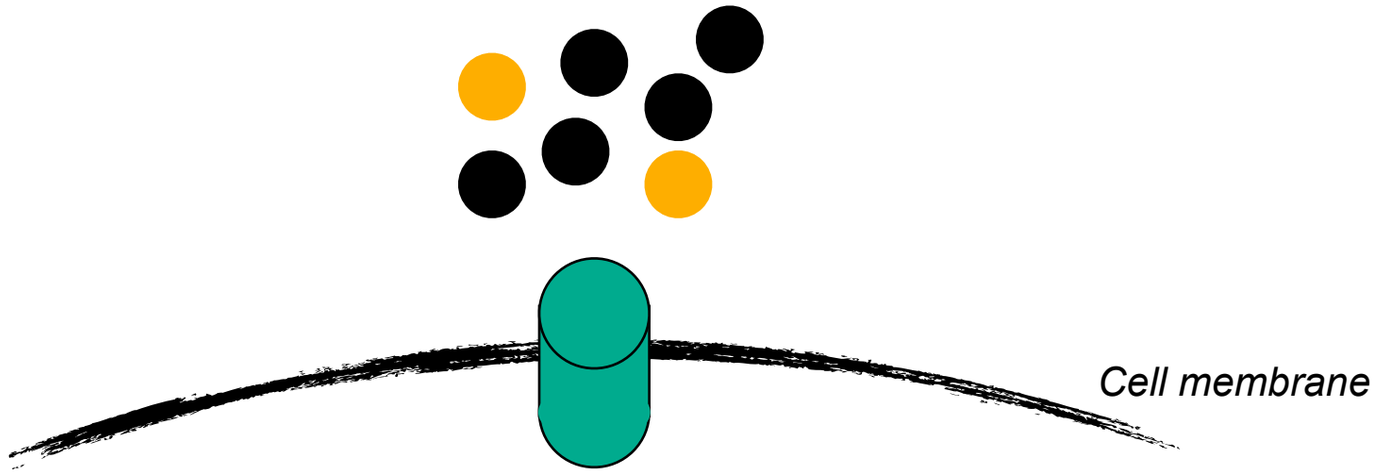
Tumor bearing mice were provided wither regular chow (food) or a diet deficient of PA.

Kreuzaler et al, ***Nature Metab****, 2023*

Multi-level regulation of intracellular metabolism

Nutrient availability

Nutrient uptake



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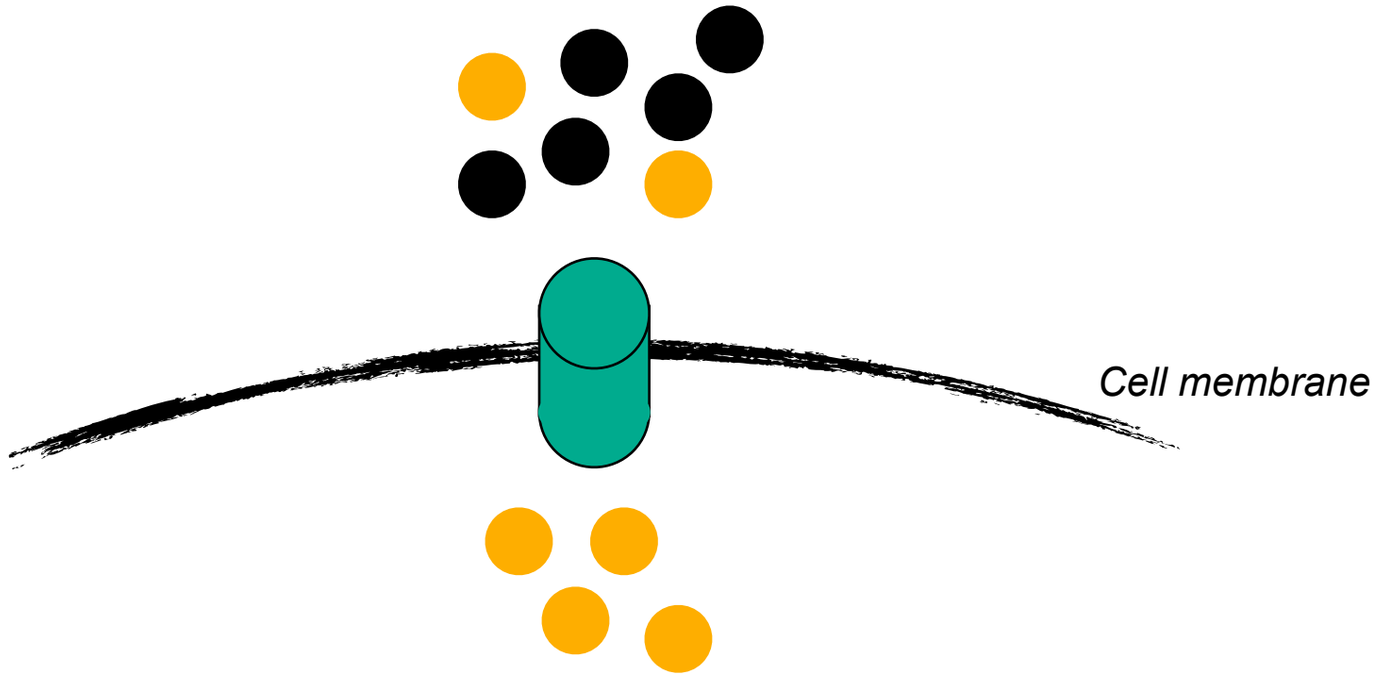

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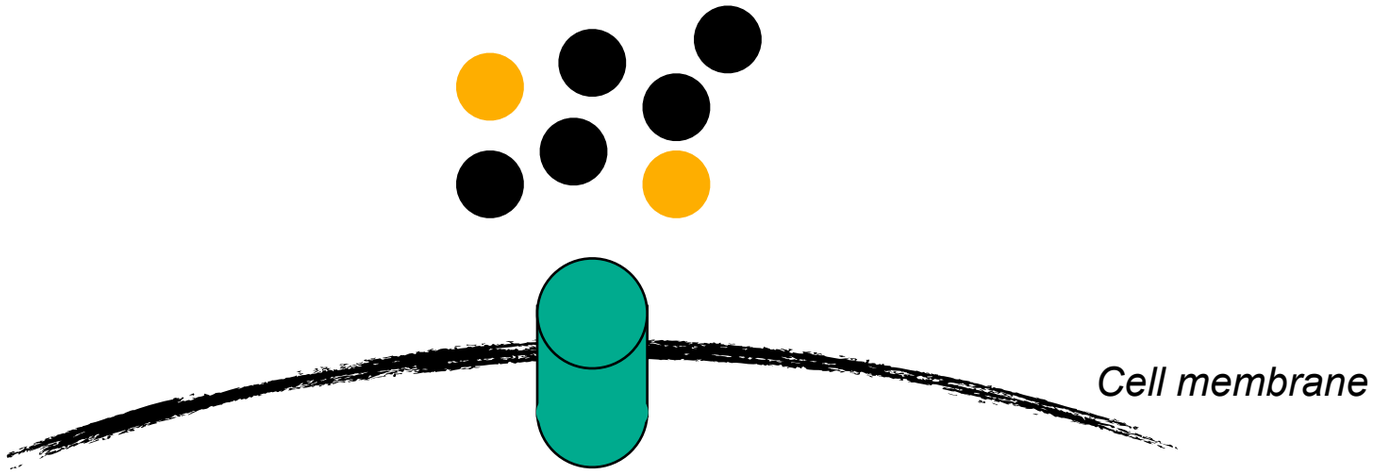
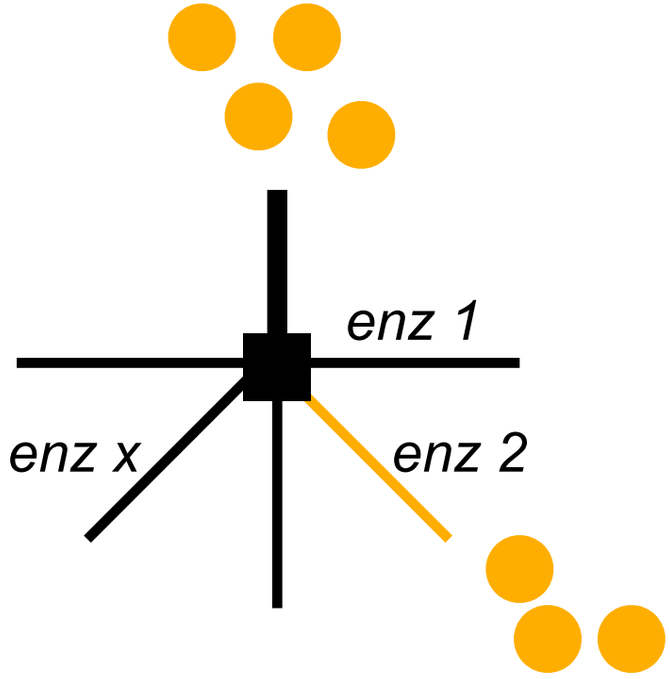


Nutrient channeling (wiring)



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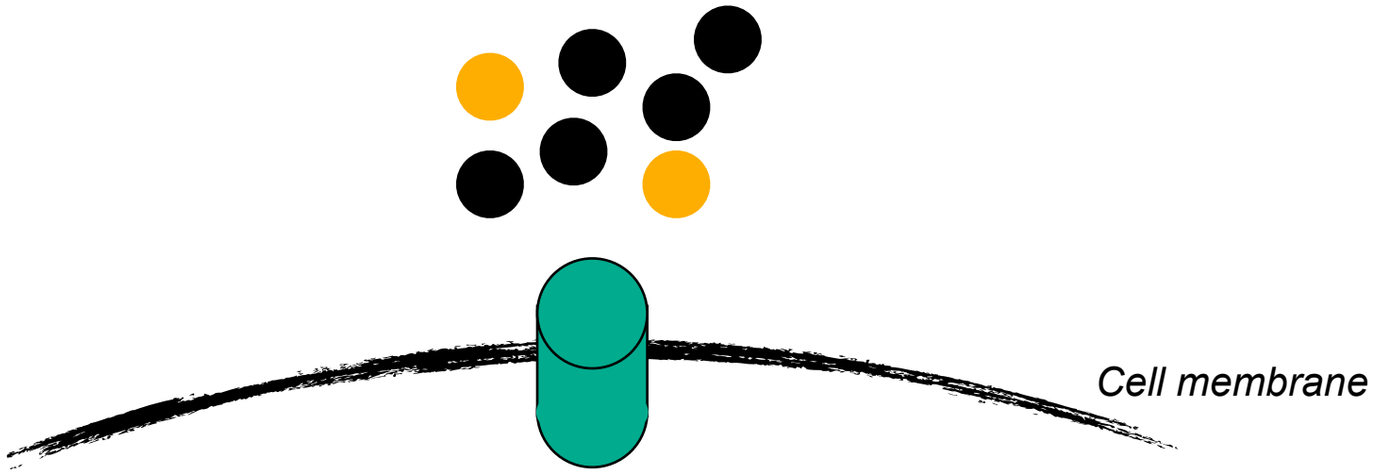

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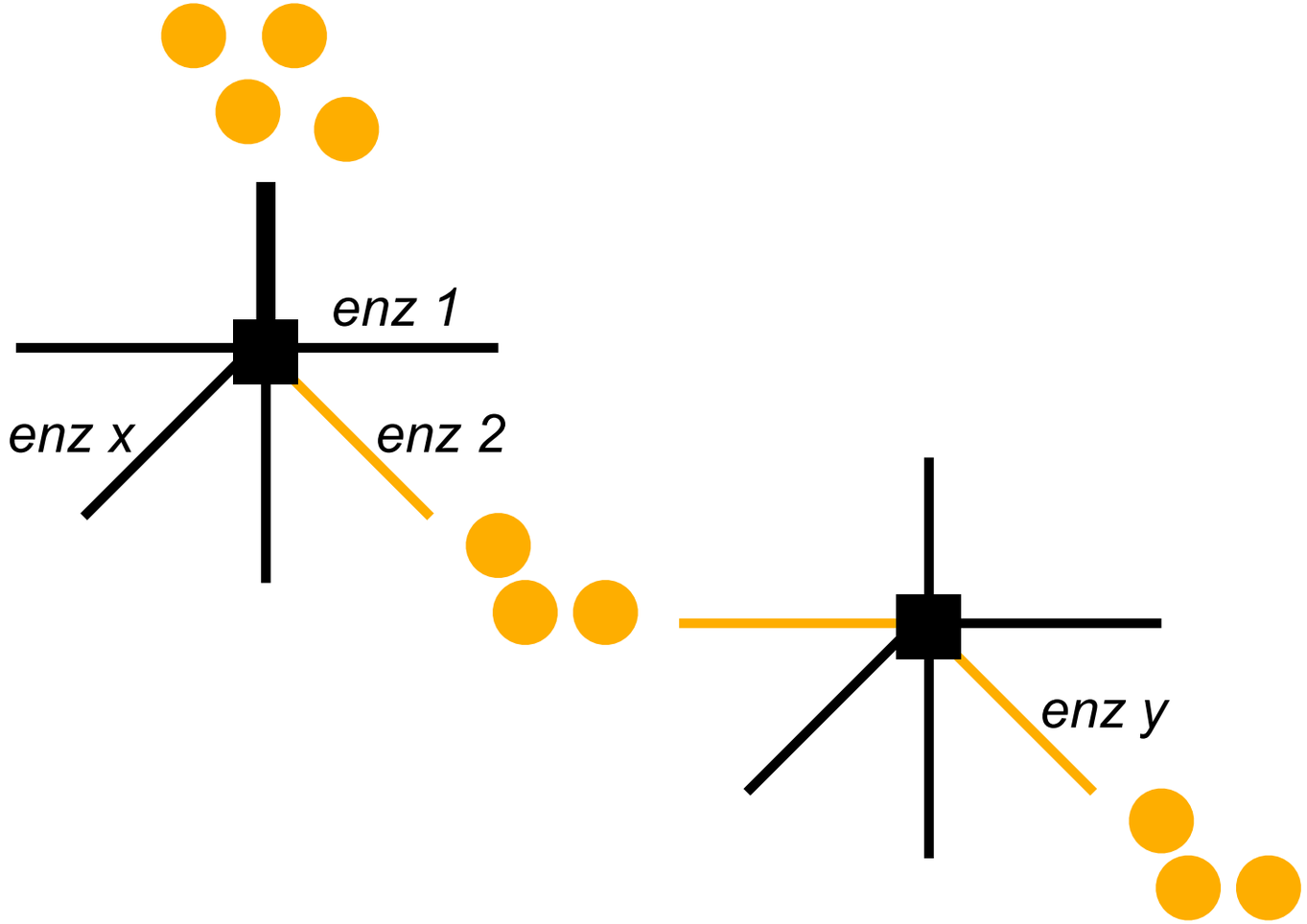
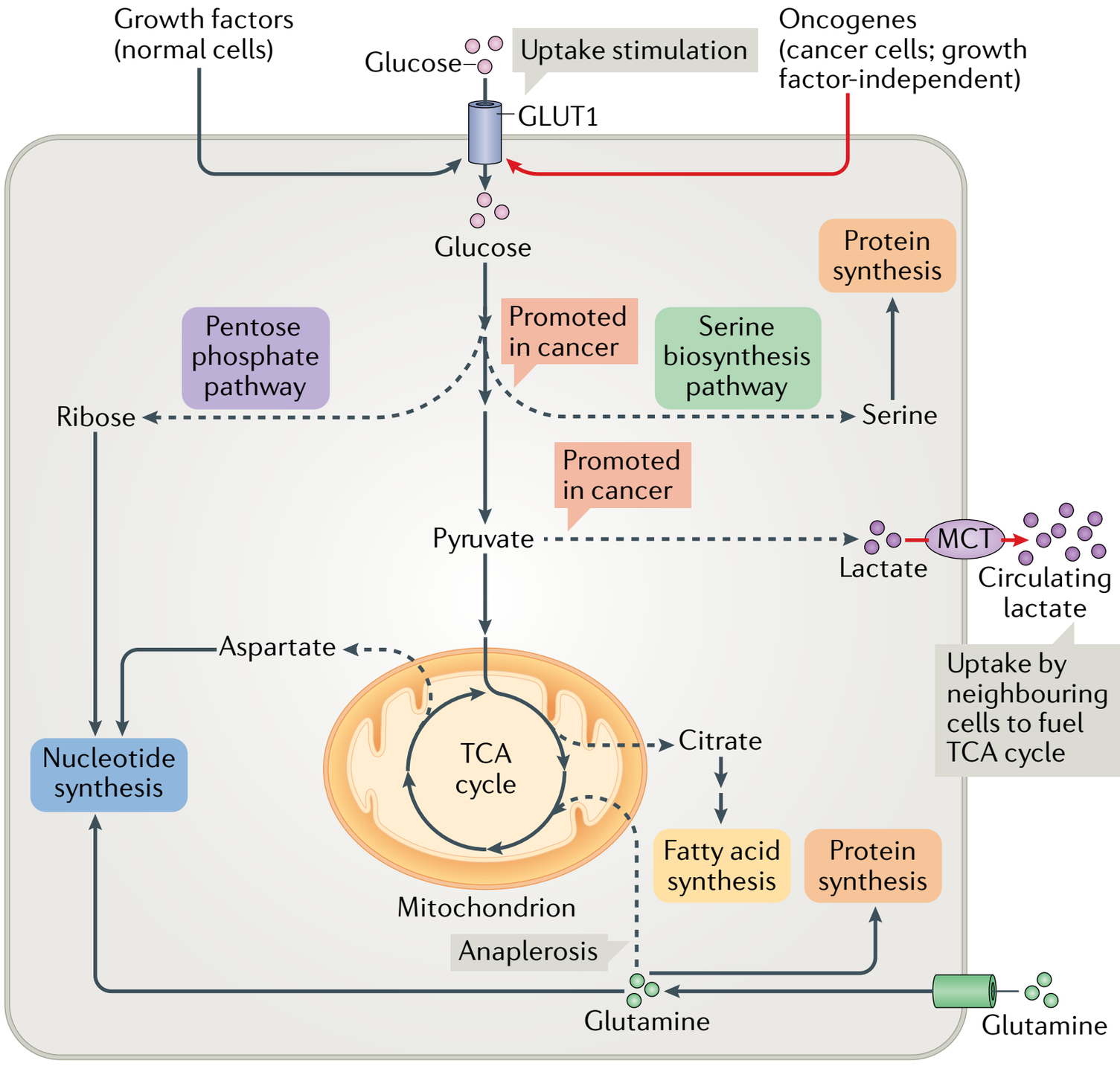
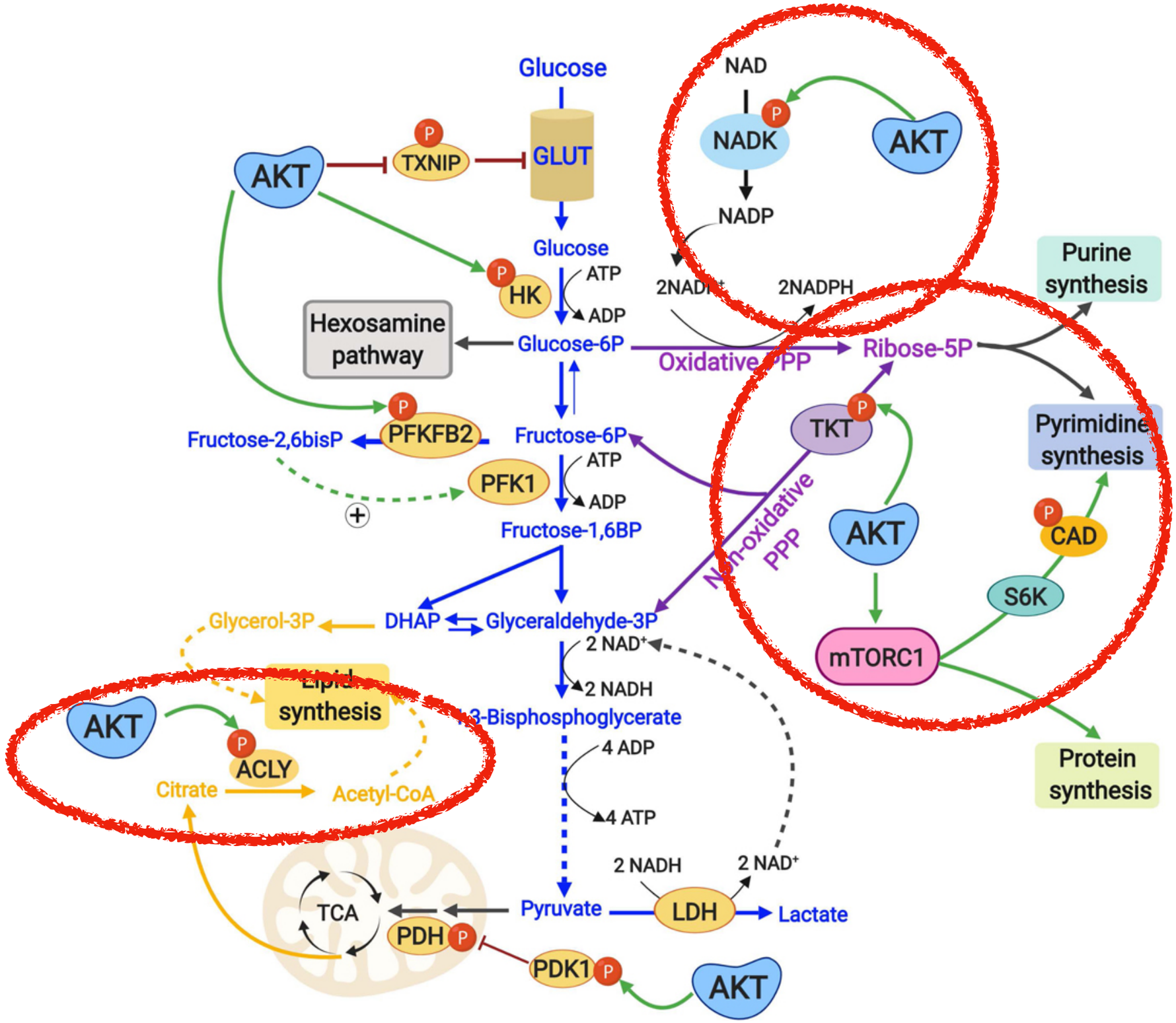


Glucose and glutamine carbons can be differentially utilized for anabolic purposes



Zhu & Thompson, ***Nat Rev Mol Cell Biol****, 2019*

PI3K/AKT signal transduction coordinates reprogramming of cell metabolism



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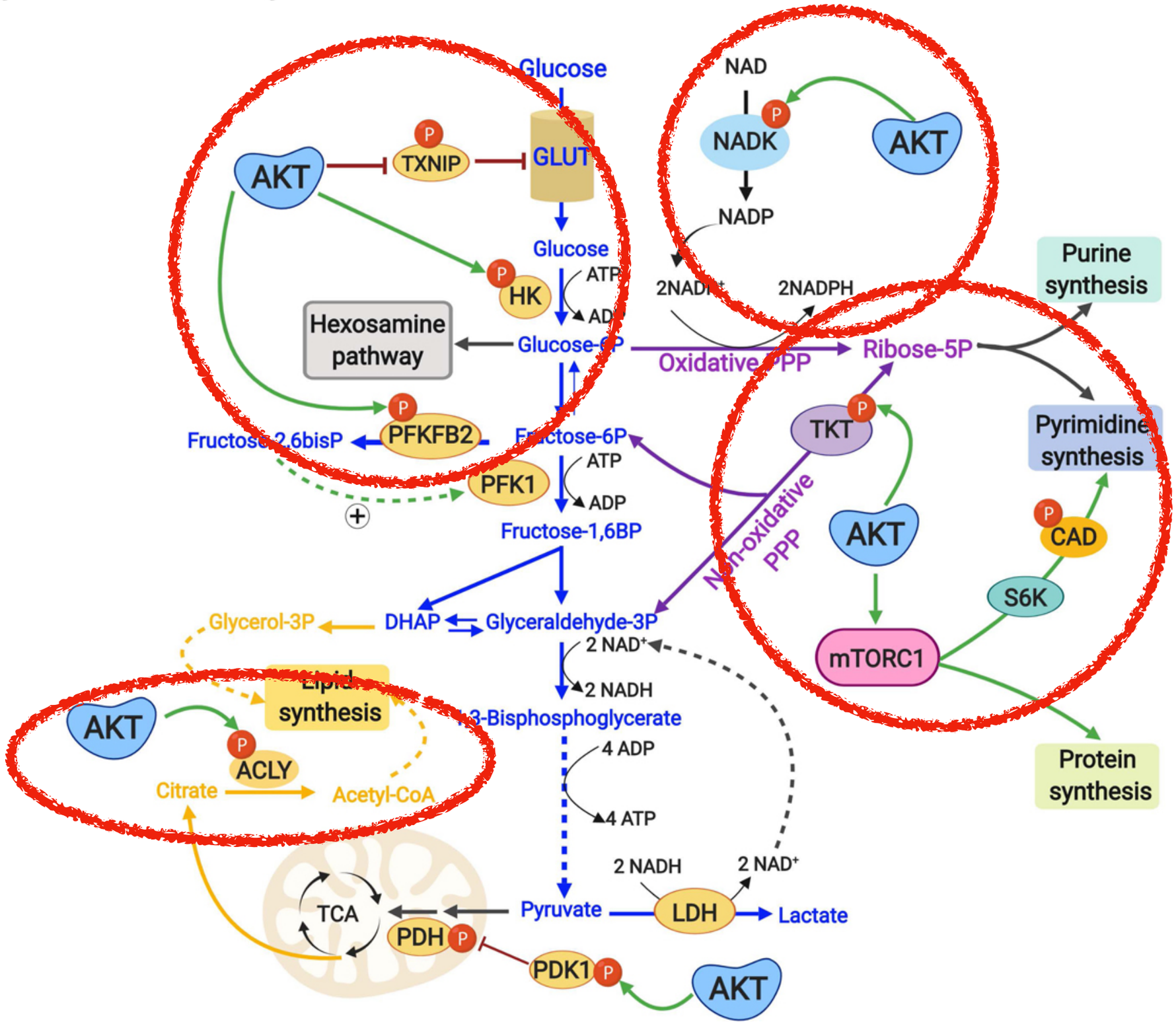
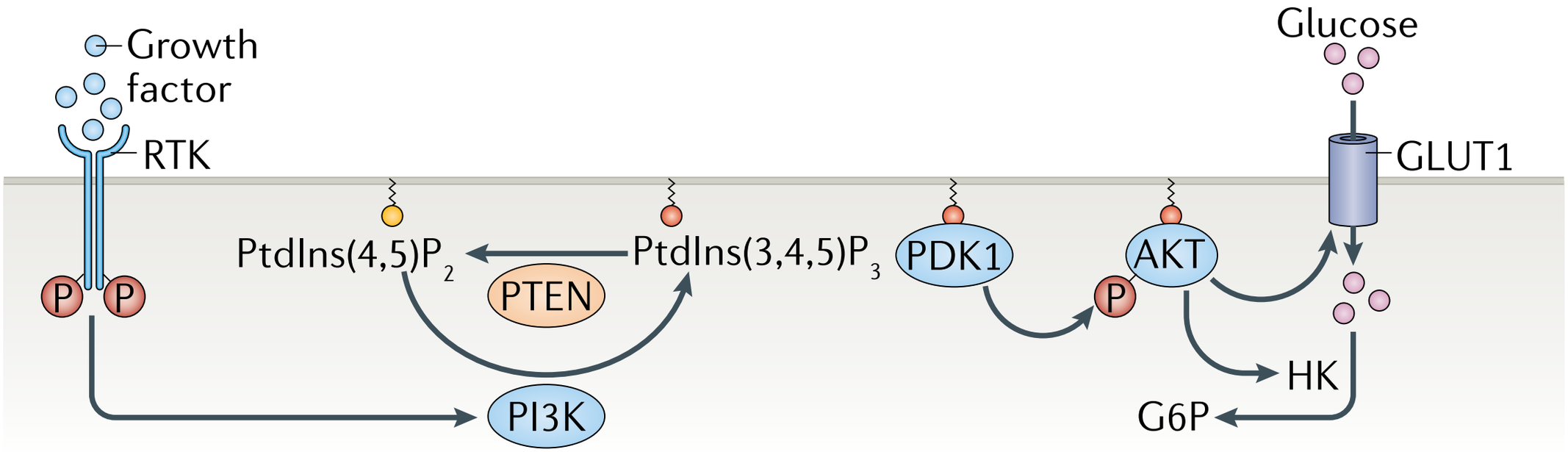


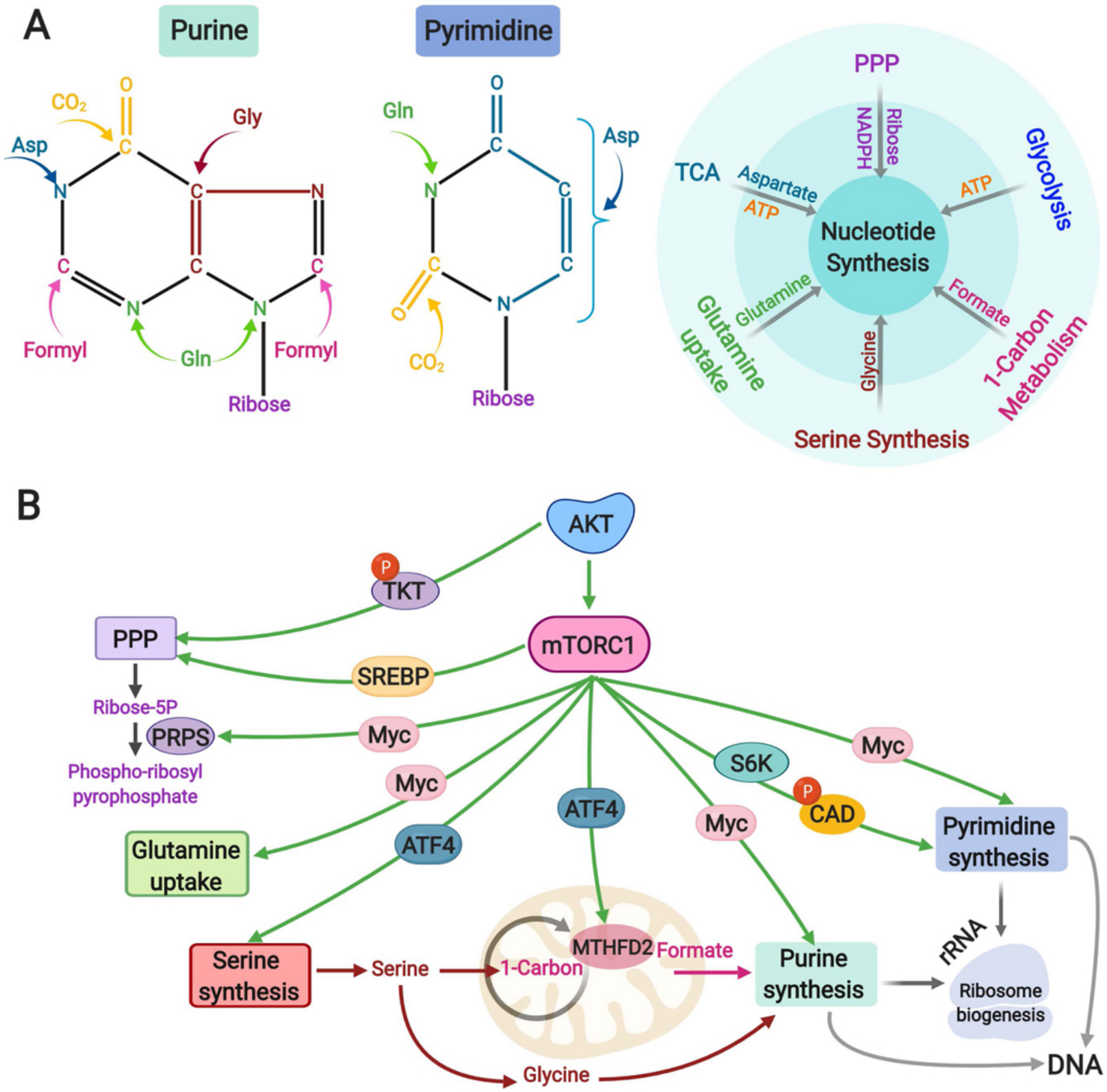
PI3K/AKT signal transduction promotes glucose metabolism (glycolysis)



AKT activates Hexokinase that activates GLC, locking sugars for catabolism

Zhu & Thompson, ***Nat Rev Mol Cell Biol****, 2019*

PI3K/AKT signal transduction enhances nucleotide synthesis

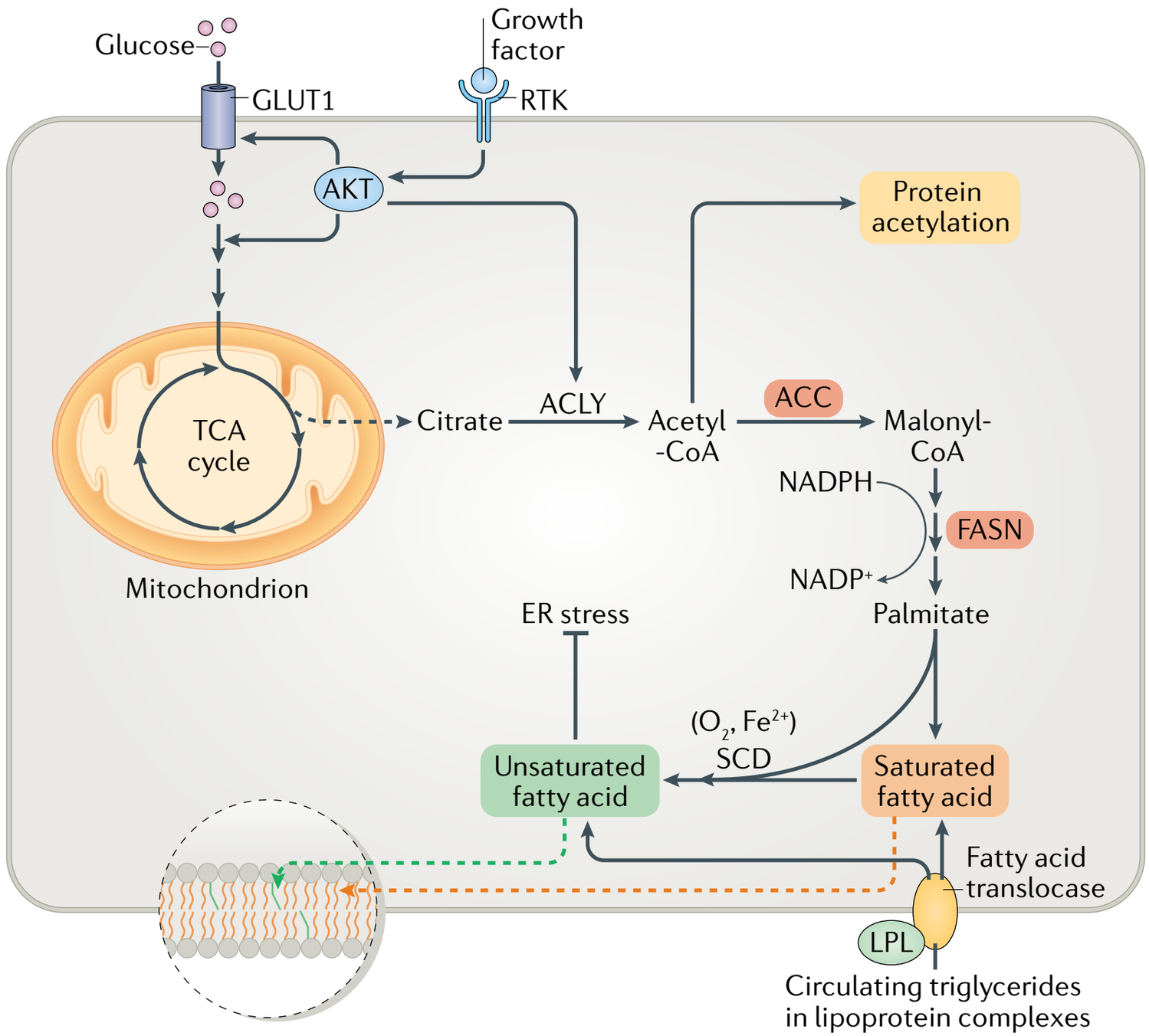


Hoxhaj & Manning, ***Nat Rev Cancer****, 2020*

PI3K/AKT signal transduction enhances FA synthesis

AKT / Protein Kinase B (PKB) is a Sereine/Threonine Kinase activated by many TM receptor through phosphatidylinositol-3-kinase (PI3K). AKT is hyper activated in about 80% of human cancers (also in Proteus syndrome, aka “elephant man”).

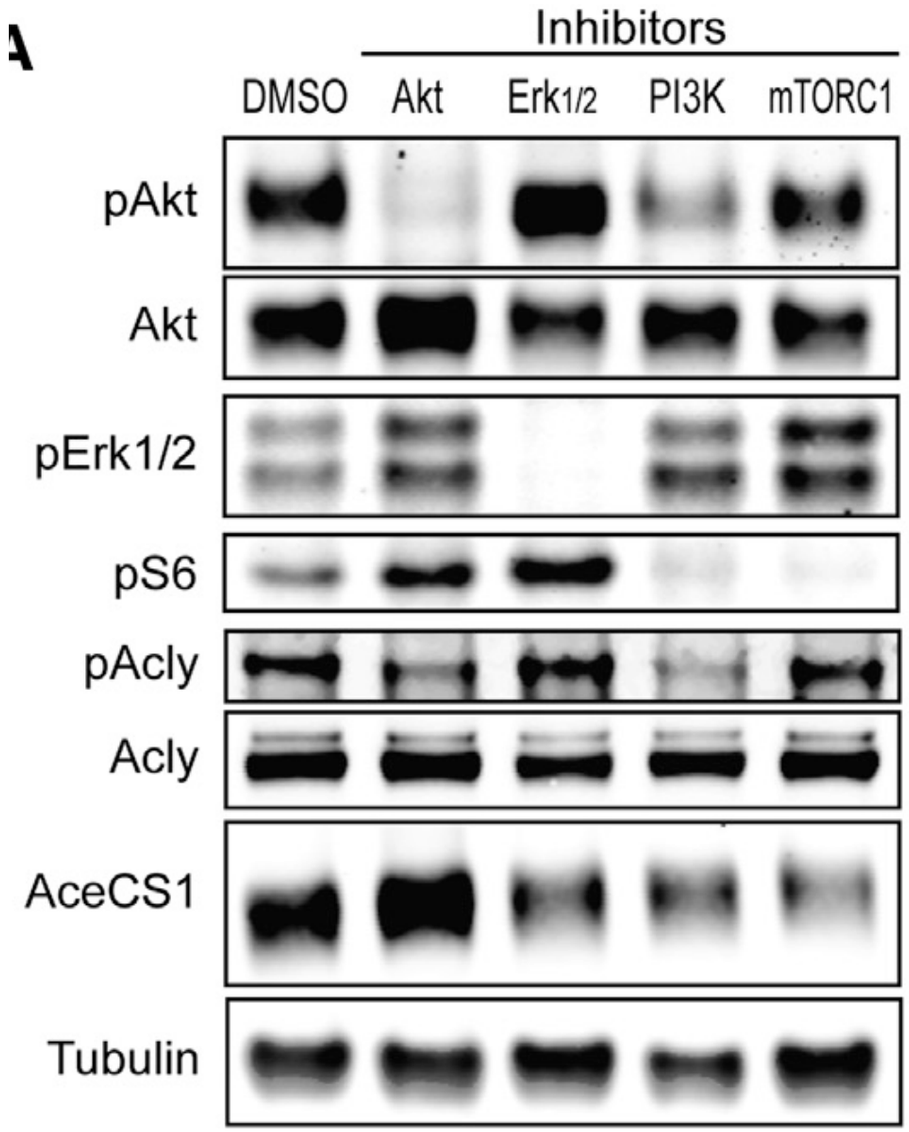
AKT actions:
- Activates glucose uptake and glycolysis
- Activates ACLY
- Activates mTORC1 (cell anabolism)
- Promotes cell growth and survival
- Promotes cancer

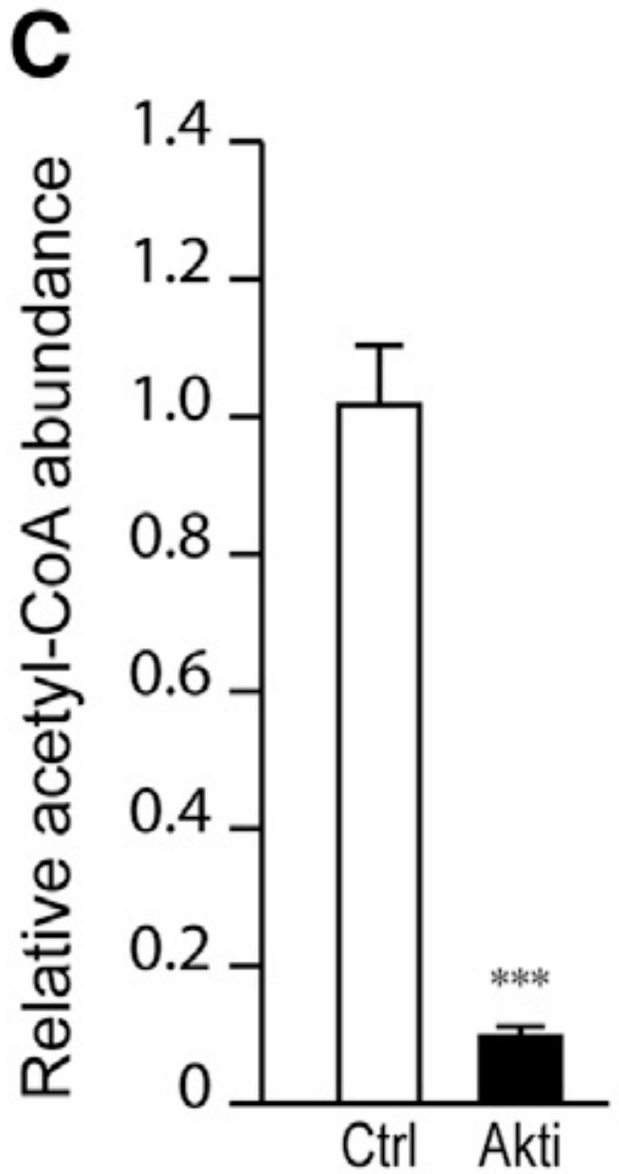


Zhu & Thompson, ***Nat Rev Mol Cell Biol****, 2019*

Akt-Dependent Metabolic Reprogramming Regulates Tumor Cell Histone Acetylation

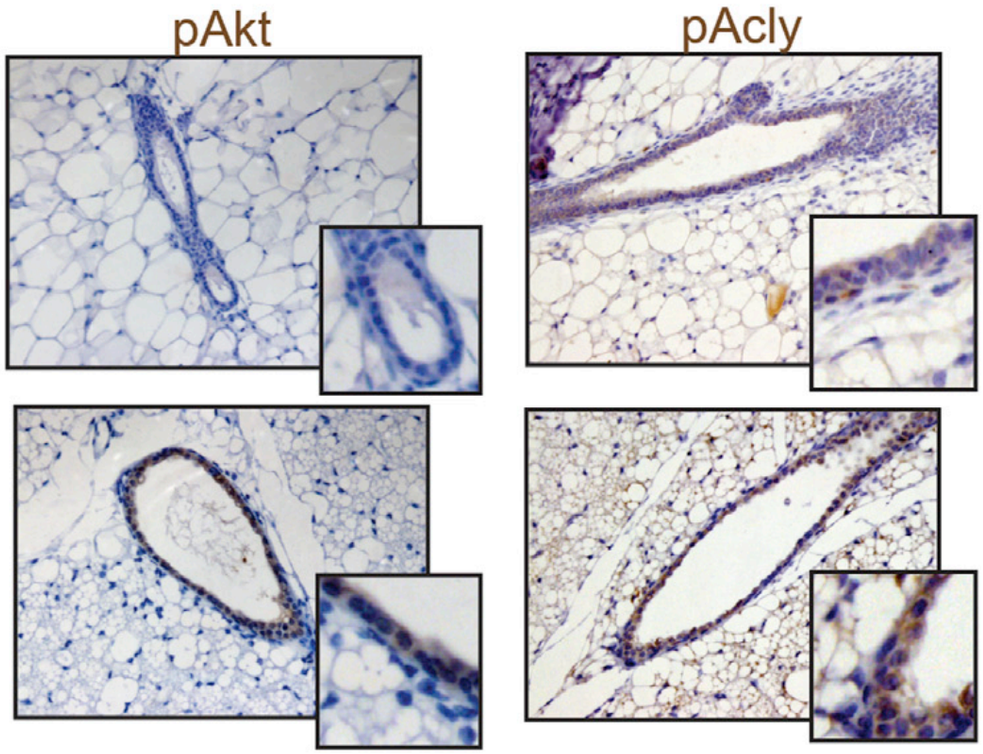
Joyce V. Lee,[1,2,11] Alessandro Carrer,[1,2,11] Supriya Shah,[1,2,11] Nathaniel W. Snyder,[3] Shuanzeng Wei,[4] Sriram Venneti,[5] Andrew J. Worth,[3] Zuo-Fei Yuan,[6] Hee-Woong Lim,[7] Shichong Liu,[6] Ellen Jackson,[1,2] Nicole M. Aiello,[2,8] Naomi B. Haas,[8] Timothy R. Rebbeck,[9] Alexander Judkins,[10] Kyoung-Jae Won,[7] Lewis A. Chodosh,[1,2] Benjamin A. Garcia,[6] Ben Z. Stanger,[2,8] Michael D. Feldman,[4] Ian A. Blair,[3] and Kathryn E. Wellen[1,2,*]

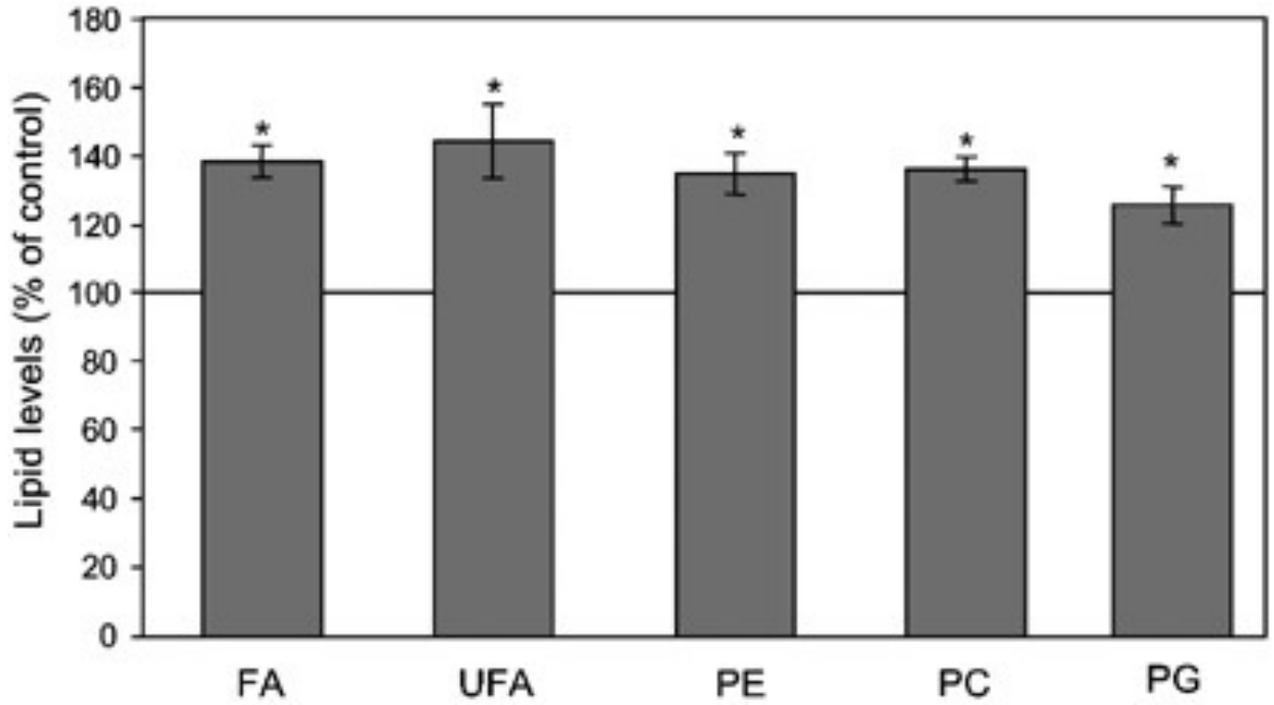




Lee, Carrer et al, ***Cell Metab****, 2014*

Cells with constitutively active AKT (myr-AKT) have sustained ACLY phosphorylation and more abundant lipid species





Lee, Carrer et al, ***Cell Metab****, 2014*

Porstmann et al, ***Oncogene****, 2005*

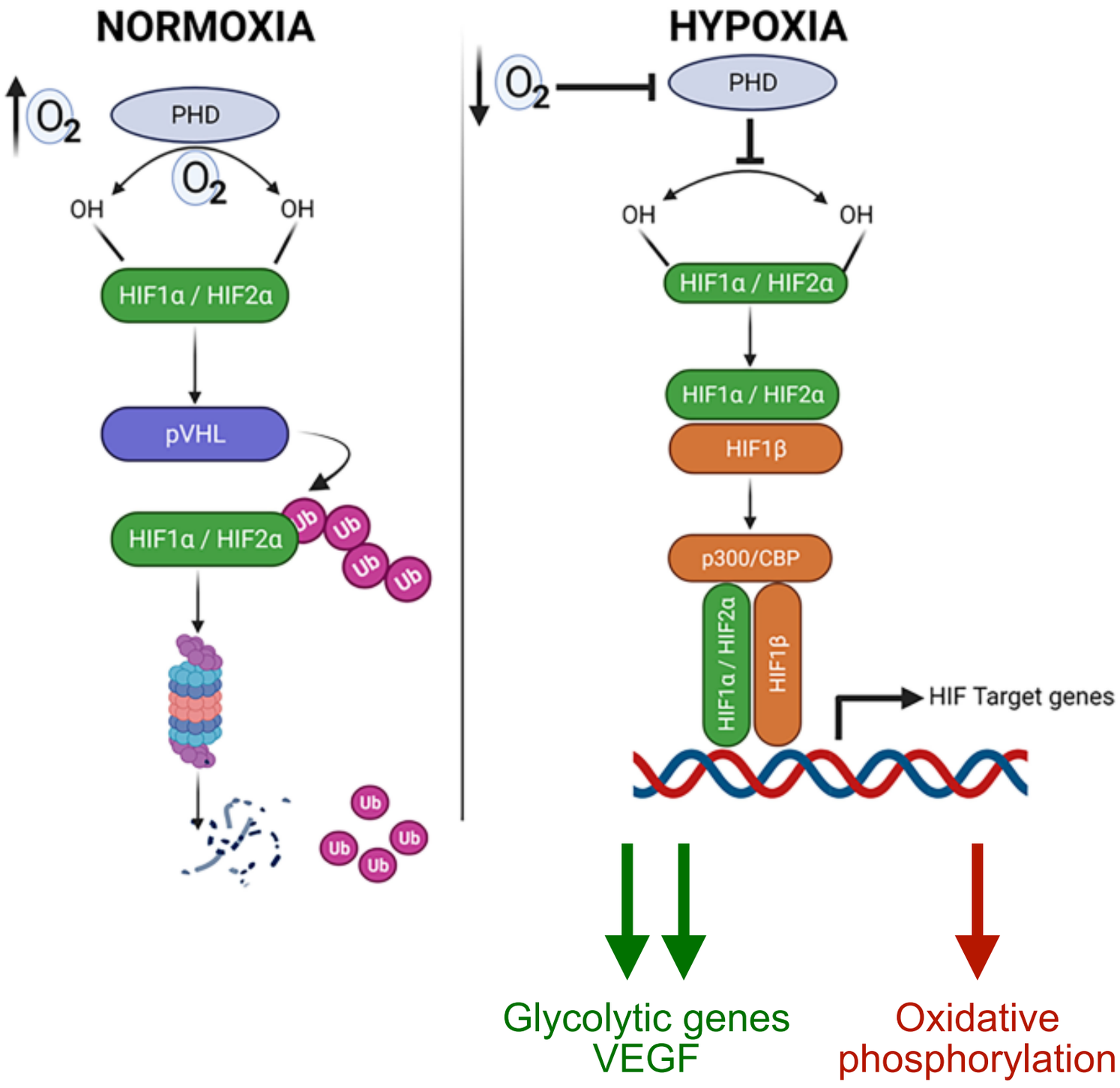
Hypoxia induces switch to glycolytic metabolism

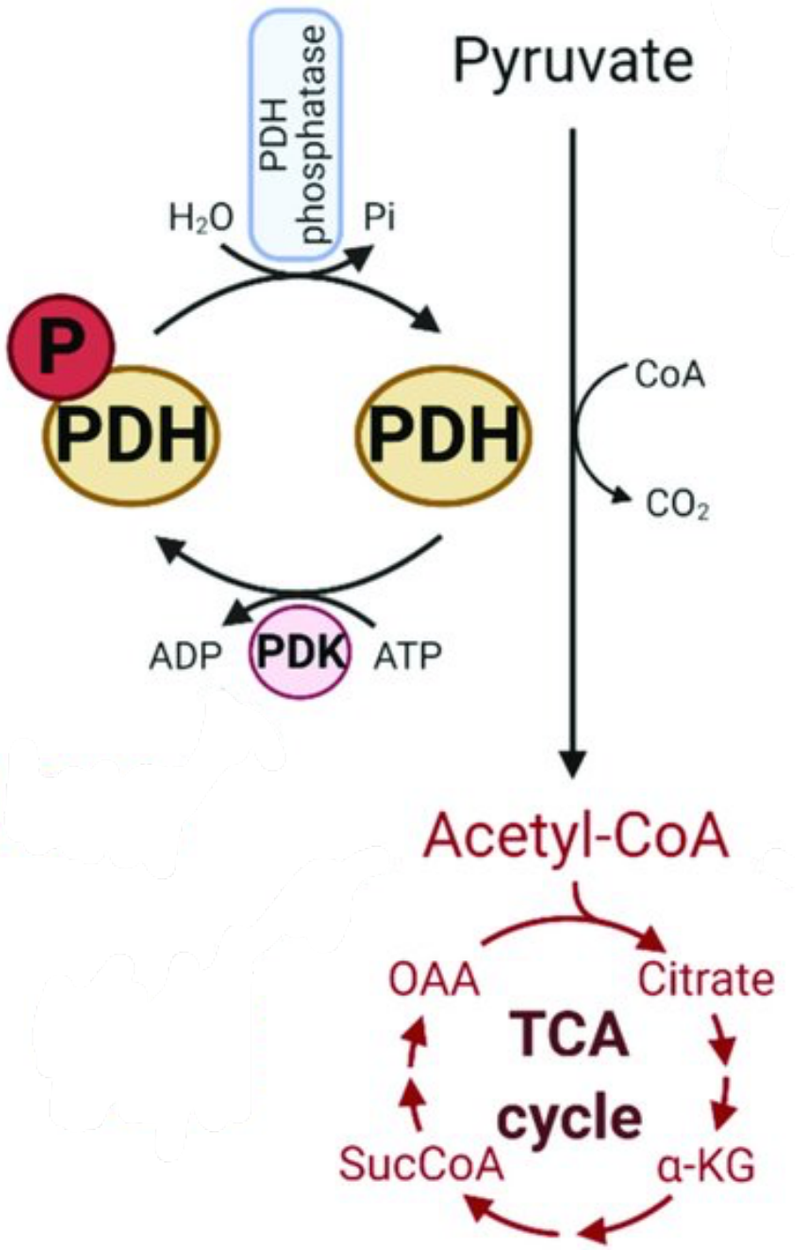
Hypoxia-inducible factors (HIFs) are transcription factors that control the cell response to hypoxia

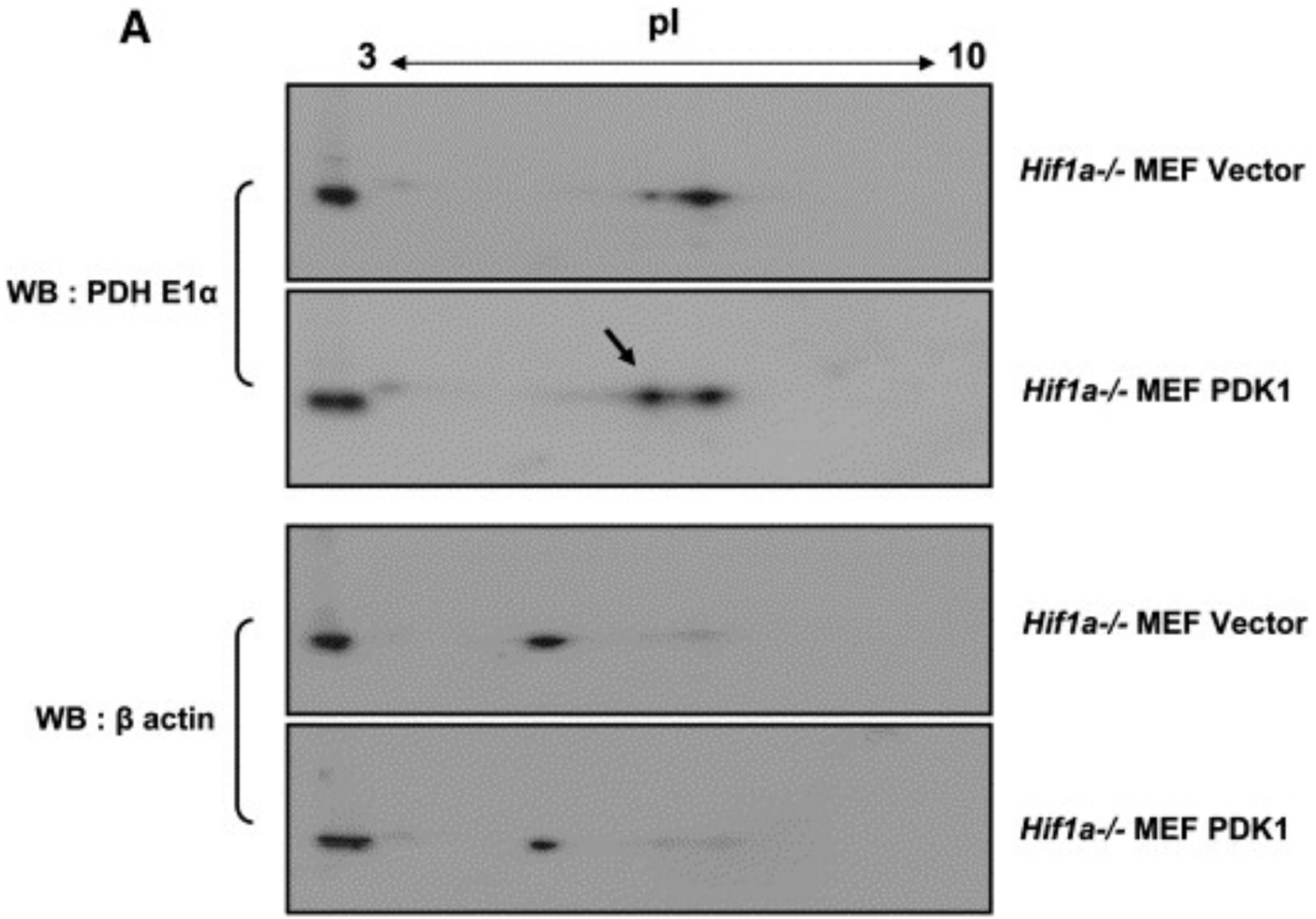
In presence of oxygen, prolyl hydroxylases (PHDs) target HIF for degradation (*interestingly aKG, Fe2+ and ascorbate are cofactors for this reaction*)

When oxygen becomes limited, HIFs are no longer degraded and can act

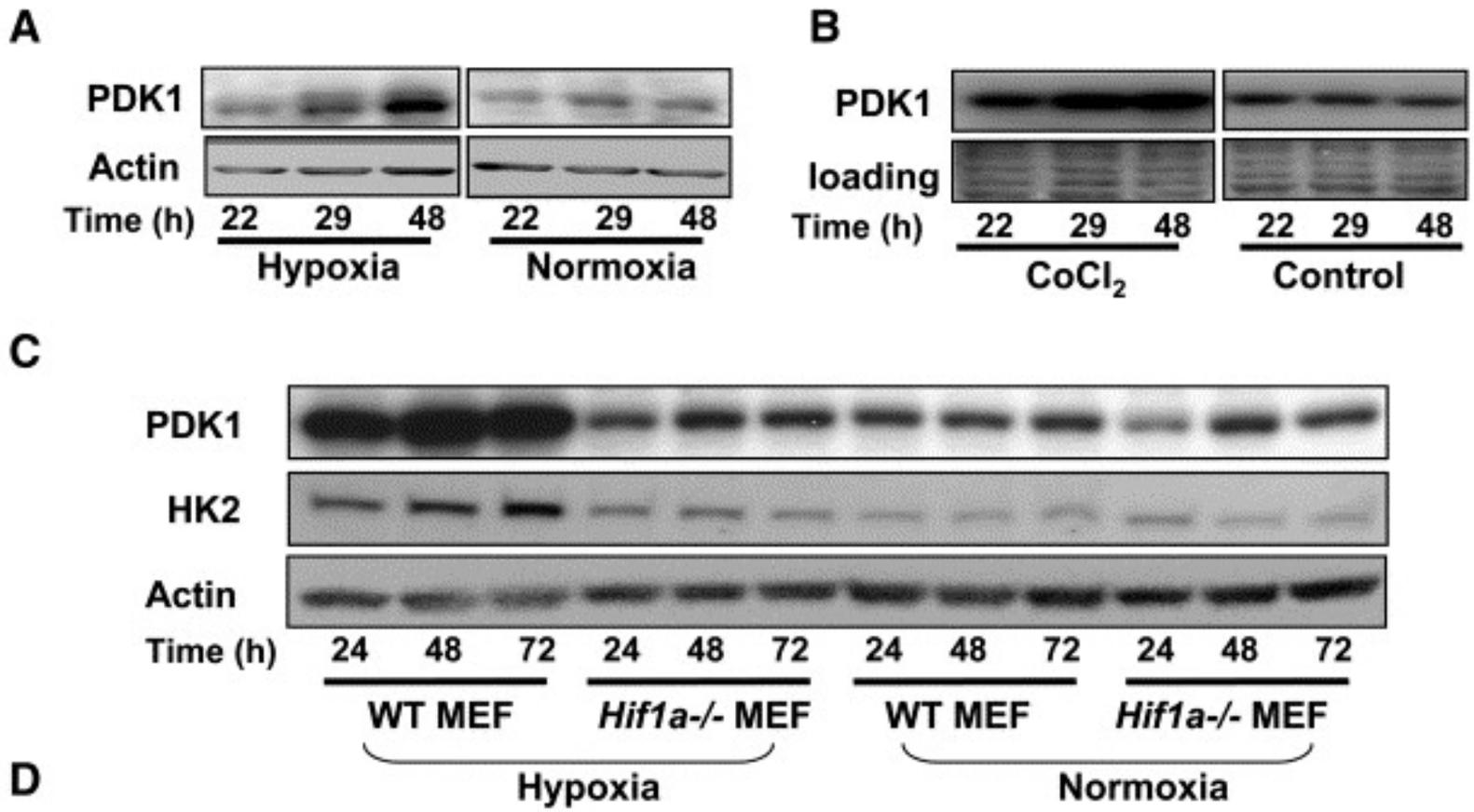
HIF actions:
•Activate glucose uptake and glycolysis
•Inhibit pyruvate entry into mitochondria
•Balance intracellular pH (drops in hypoxia)
•Promote erythropoiesis
•Promote angiogenesis



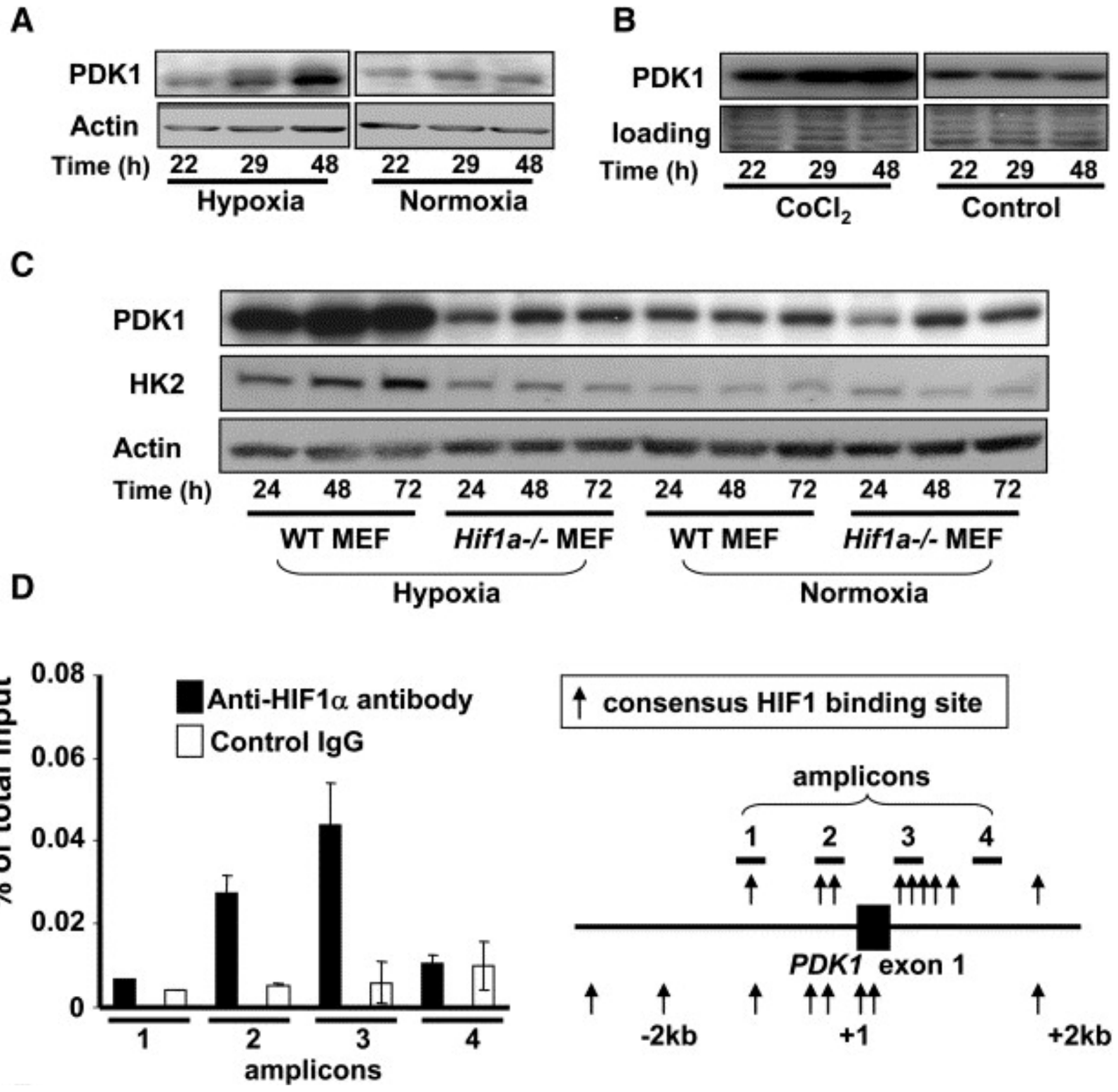




Kim et al, ***Cell Metabol****, 2006*



Kim et al, ***Cell Metabol****, 2006*



Kim et al, ***Cell Metabol****, 2006*

CONCLUSIONS (1)

Growth and proliferation need nutrients AND signals

Nutrient uptake and usage are REGULATED by signal transduction

Most growth signals induce nutrient uptake and anabolic pathways

Nutrient uptake is DIVERSE

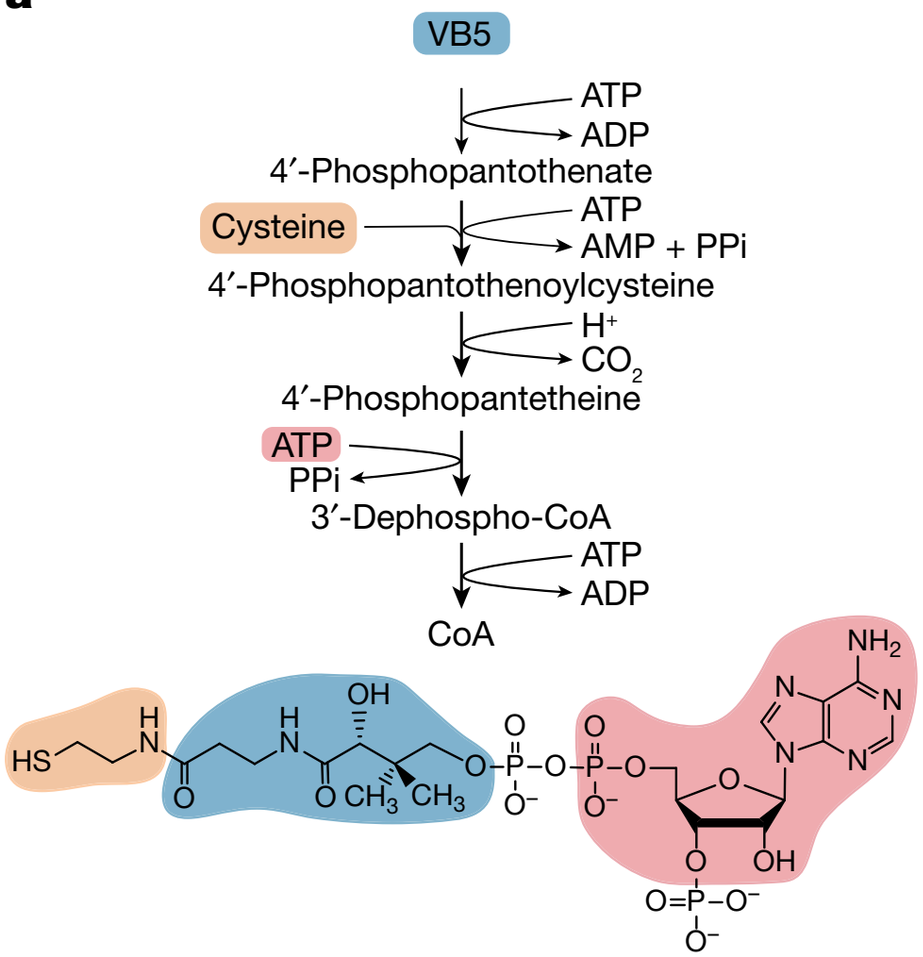
AKT and MYC promote similar yet distinct metabolic reprogramming

Article

PI3K drives the de novo synthesis of coenzyme A from vitamin B5

In response to hormones and growth factors, PI3K signaling network functions as a major regulator of metabolism and growth, governing (…). Many of the driver mutations in cancer with the highest recurrence, including (…), pathologically activate PI3K signaling. **However, our understanding of the core metabolic program controlled by PI3K is almost certainly incomplete.**

a



Dibble et al, ***Nature****, 2022*

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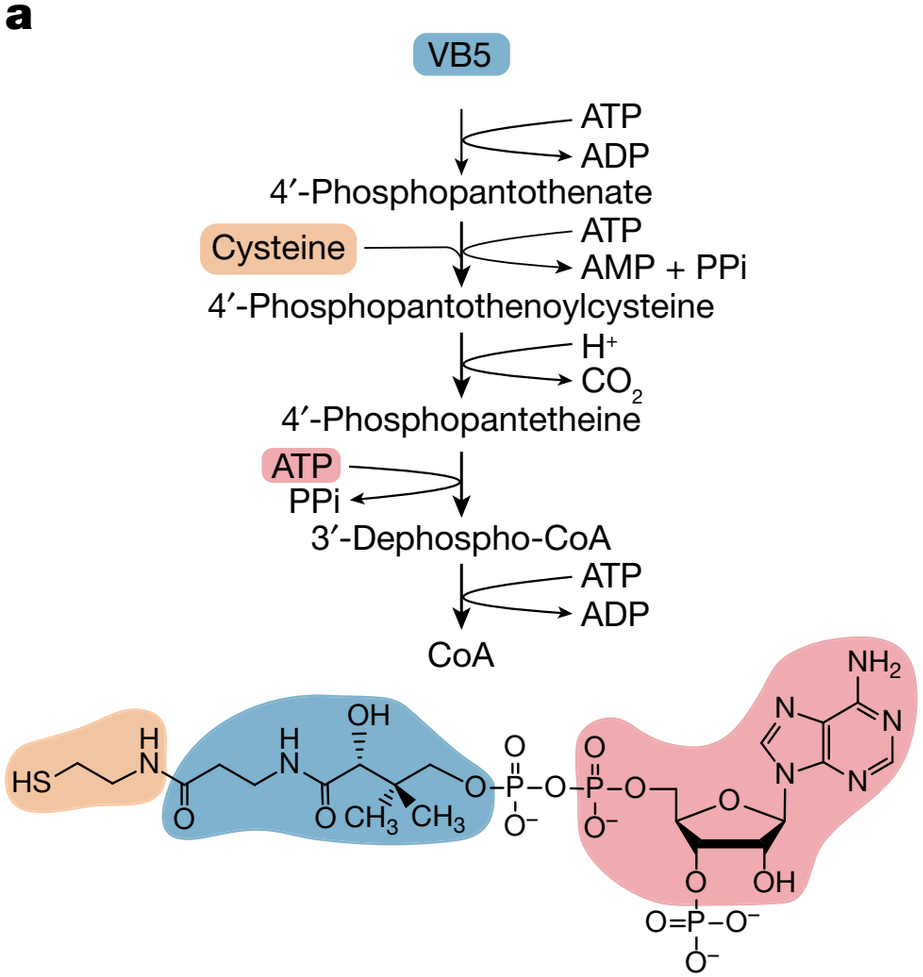

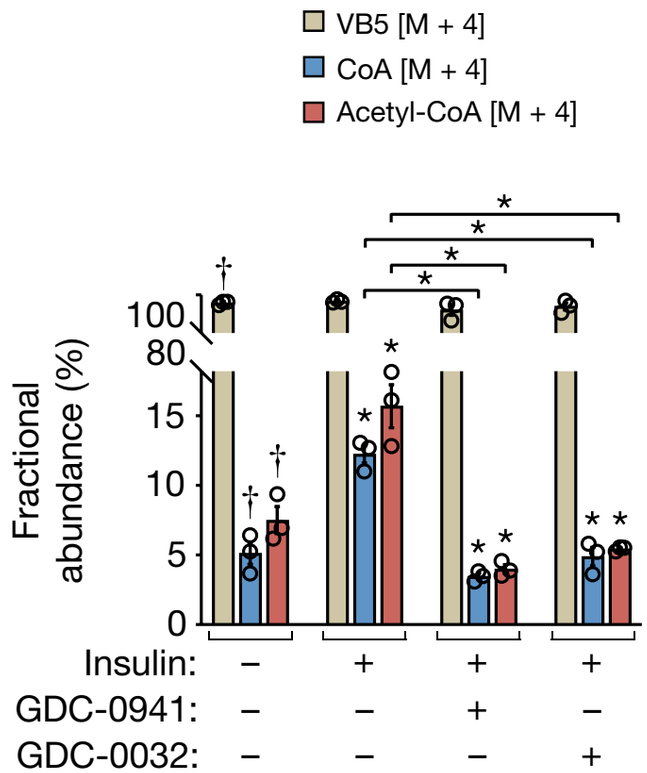

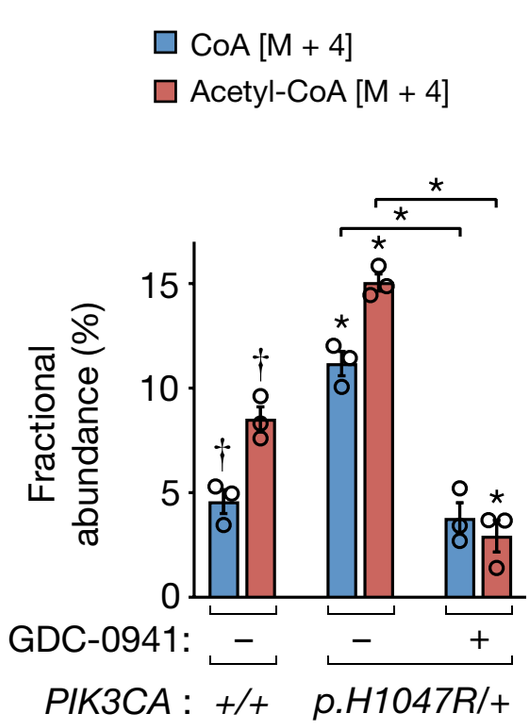

Dibble et al, ***Nature****, 2022*

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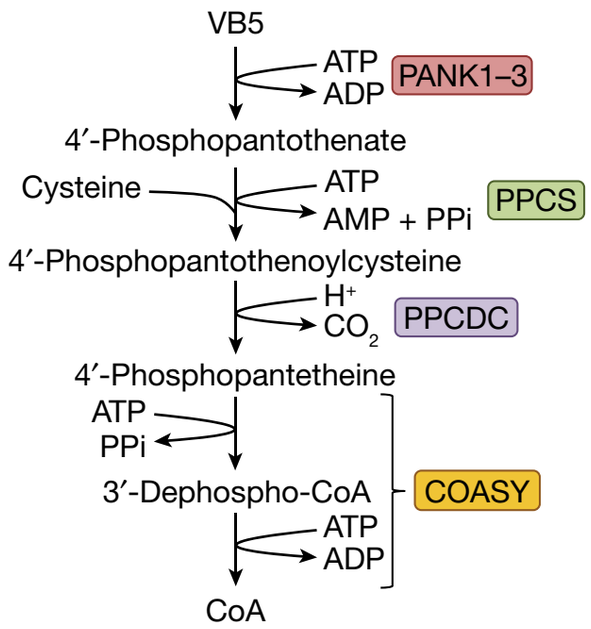
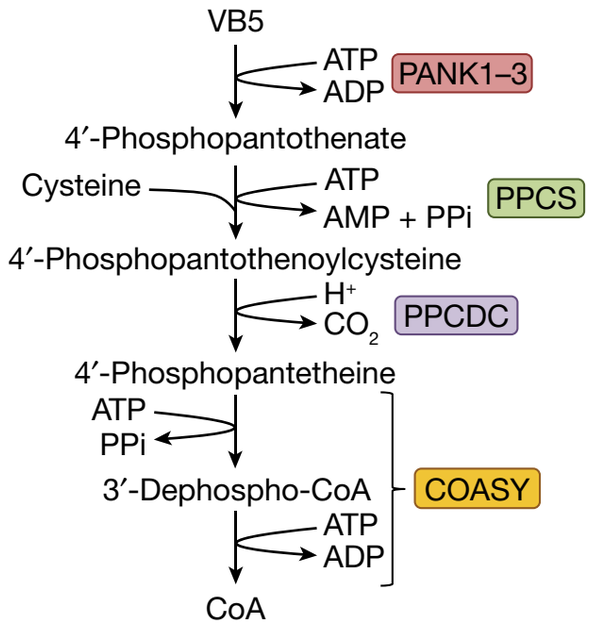


b

Enzyme	p-site	Amino acid sequence										Substrate quality
		–7	–6	–5	–4	–3	–2	–1	0	+1	+2	
PANK1	S228	R	L	R	R	R	M	D	S	G	R	Low
PANK2	S169	P	L	R	R	R	A	S	S	A	S	High
PANK2	S189	T	R	R	D	R	L	G	S	Y	S	High
PANK2	S203	V	S	R	Q	R	V	E	S	L	R	Low
PANK3	–	–	–	–	–	–	–	–	–	–	–	–
PANK4	T406	A	Q	R	A	R	S	G	T	F	D	High
PPCS	–	–	–	–	–	–	–	–	–	–	–	–
PPCDC	–	–	–	–	–	–	–	–	–	–	–	–
COASY	–	–	–	–	–	–	–	–	–	–	–	–
AKT substrate motif:				R	X	R	X	X	S/T			

PI3K drives the de novo synthesis of coenzyme A from vitamin B5



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PANK2	S203	V	S	R	Q	R	V	E	S	L	R	Low
PANK3	–	–	–	–	–	–	–	–	–	–	–	–
PANK4	T406	A	Q	R	A	R	S	G	T	F	D	High
PPCS	–	–	–	–	–	–	–	–	–	–	–	–
PPCDC	–	–	–	–	–	–	–	–	–	–	–	–
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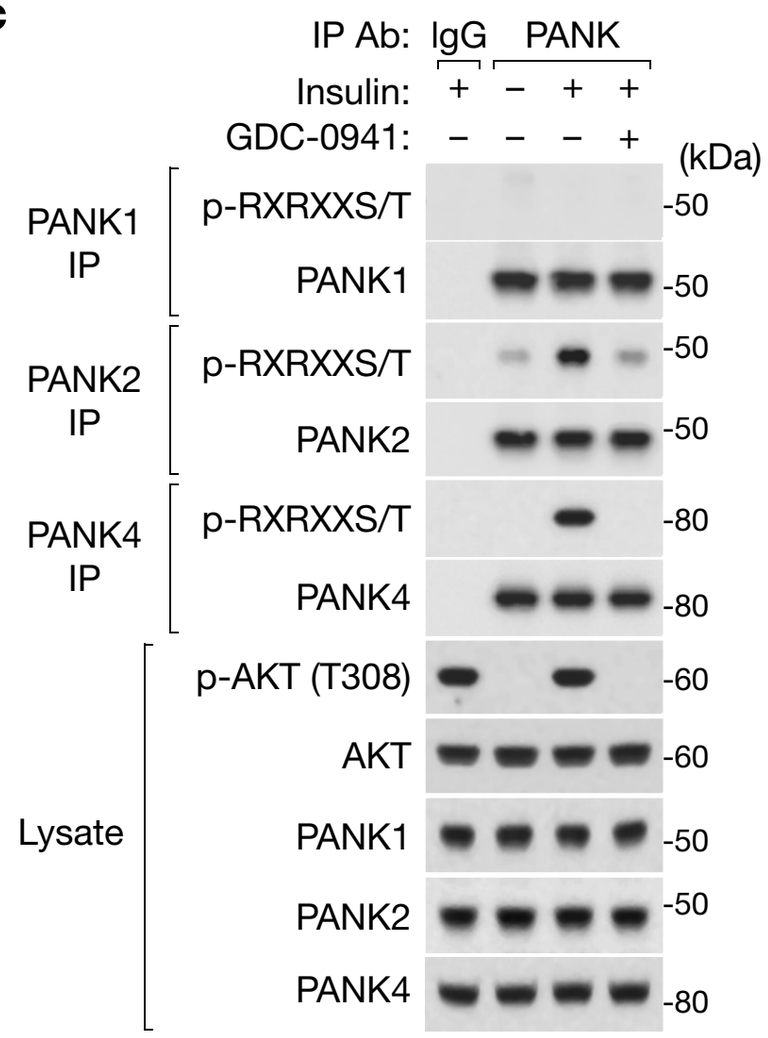
c



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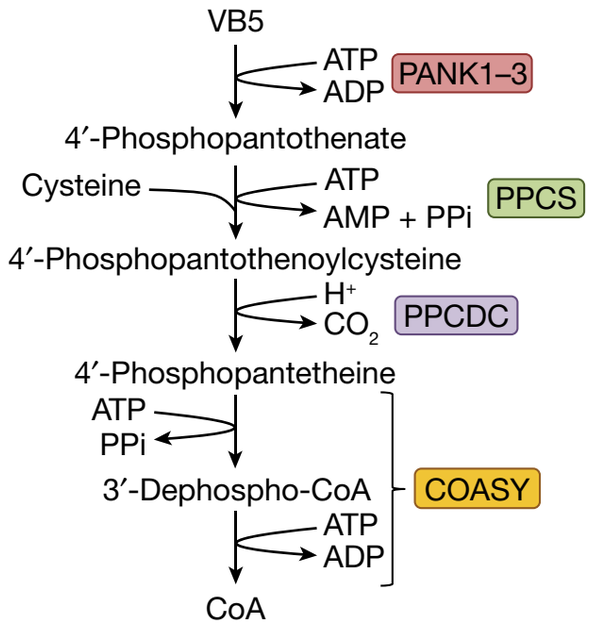

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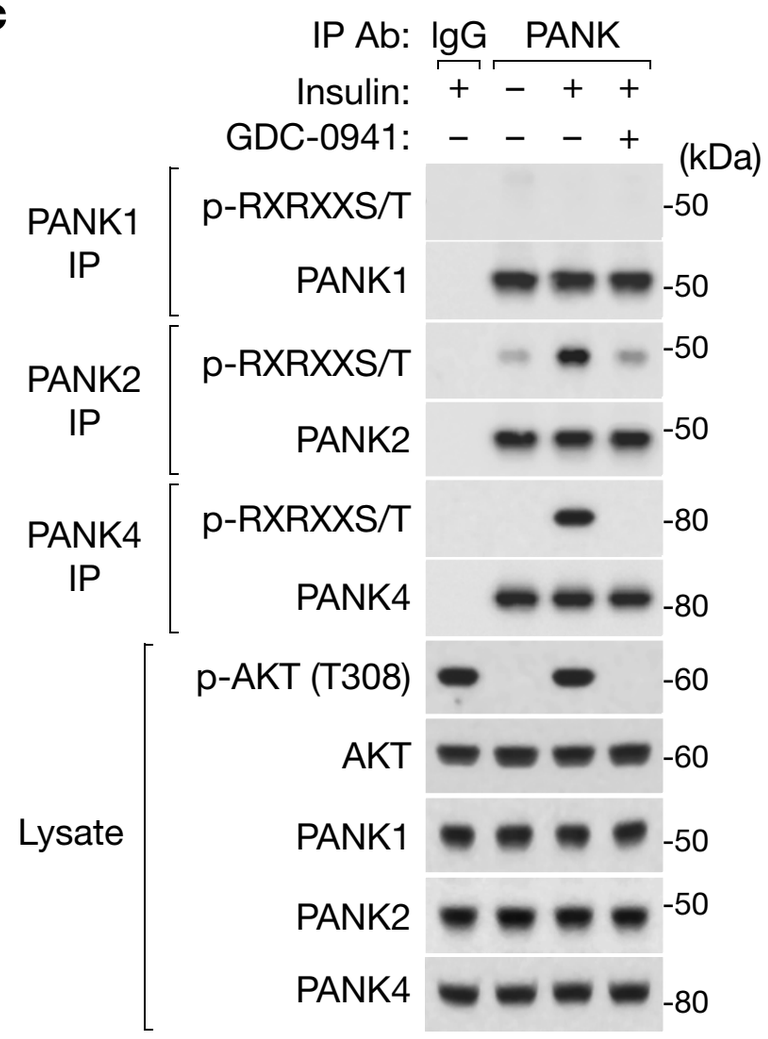

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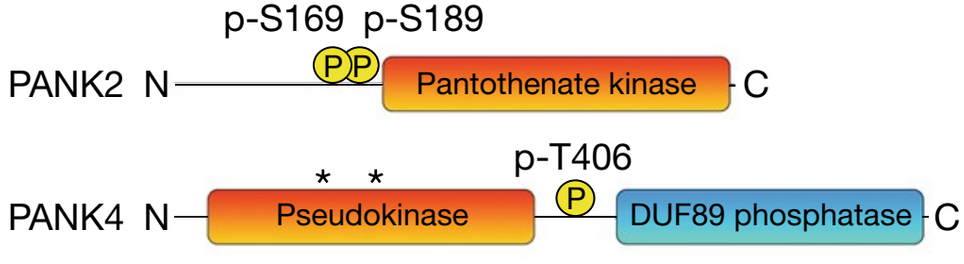
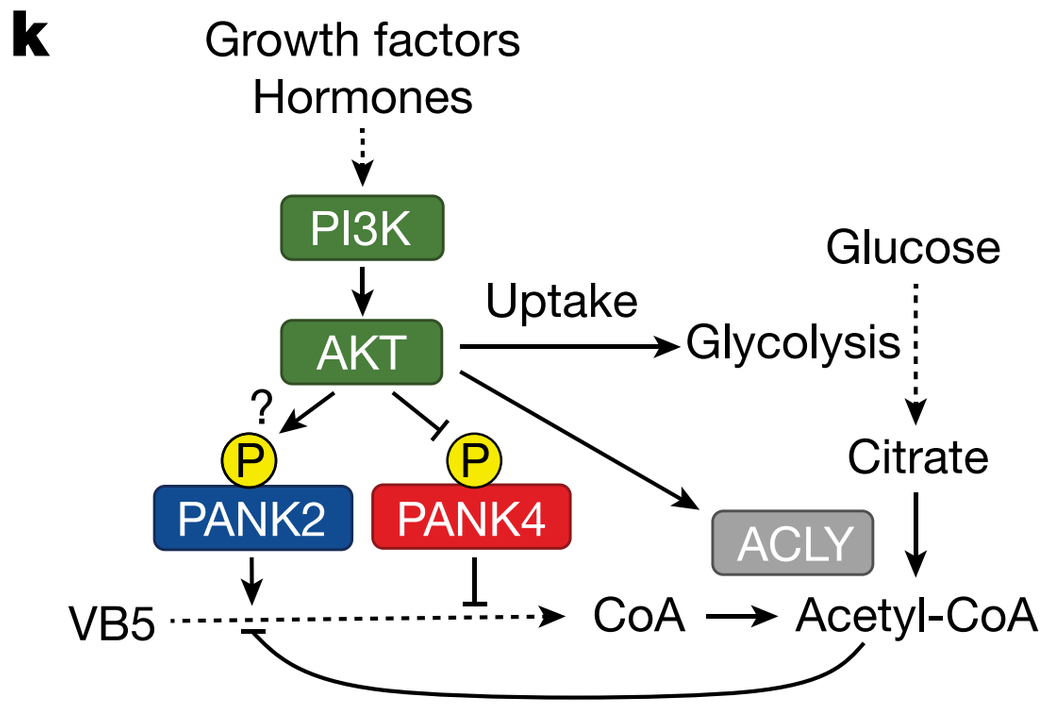


PI3K drives the de novo synthesis of coenzyme A from vitamin B5



Dibble et al, ***Nature****, 2022*

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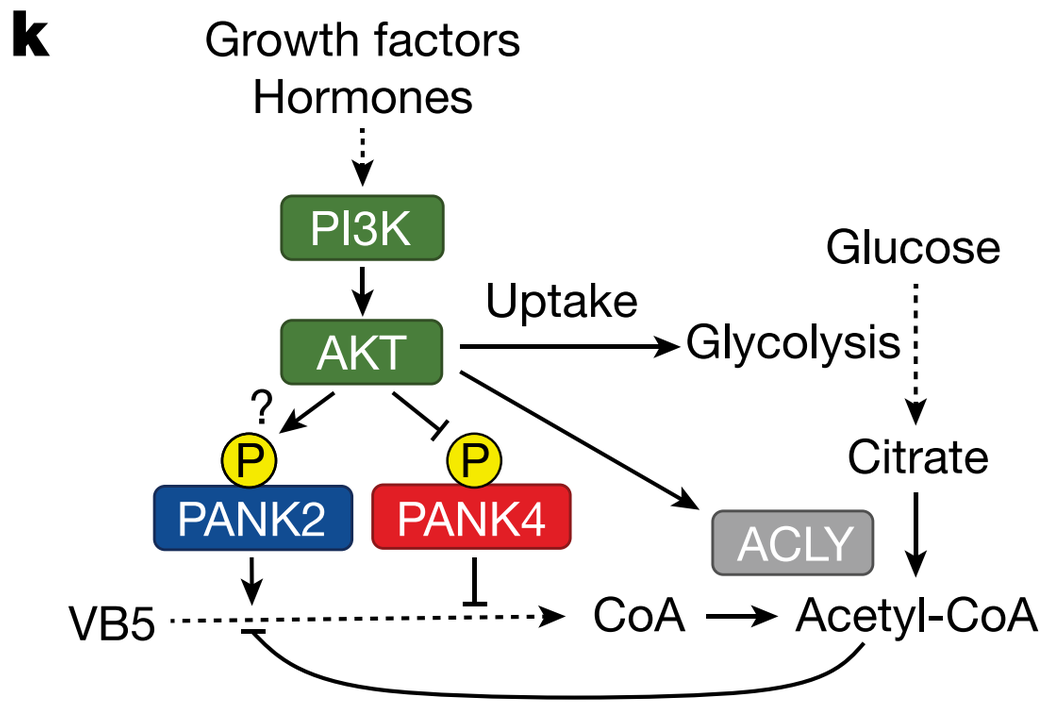


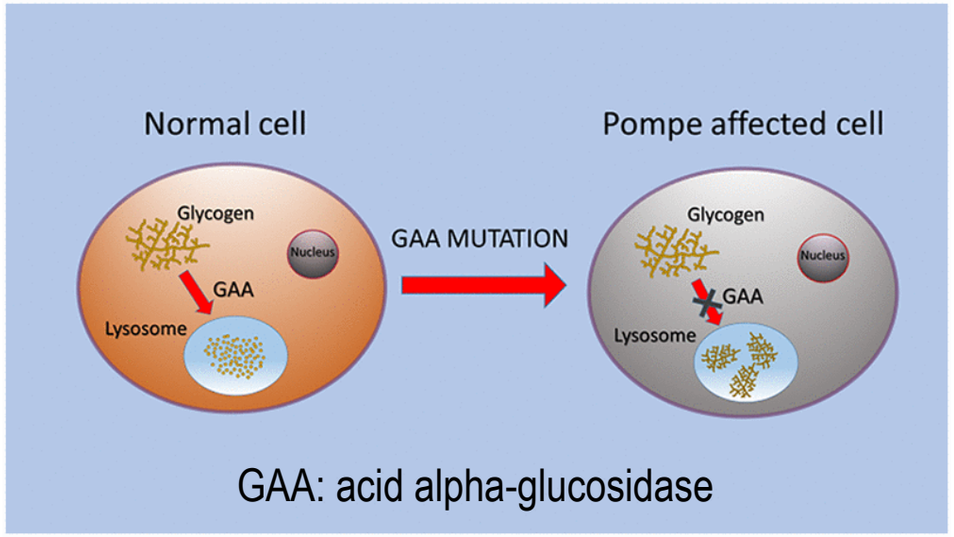
New layers of metabolic regulation are being constantly discovered

Different signaling pathways converge to the same metabolic goal

Dibble et al, ***Nature****, 2022*

Inborn errors of metabolism (IEM)

- Genetic (loss of function)
- Almost all are autosomal or X-linked recessive
- Large class of congenital disorders. Individually rare, but collectively affect ca. 1:1500
- Multi-organ system dysfunction –organs with prominent roles in metabolic regulation (e.g. liver) or high metabolic demand (brain, muscle) are often involved.
- Progressive
- Some are treatable



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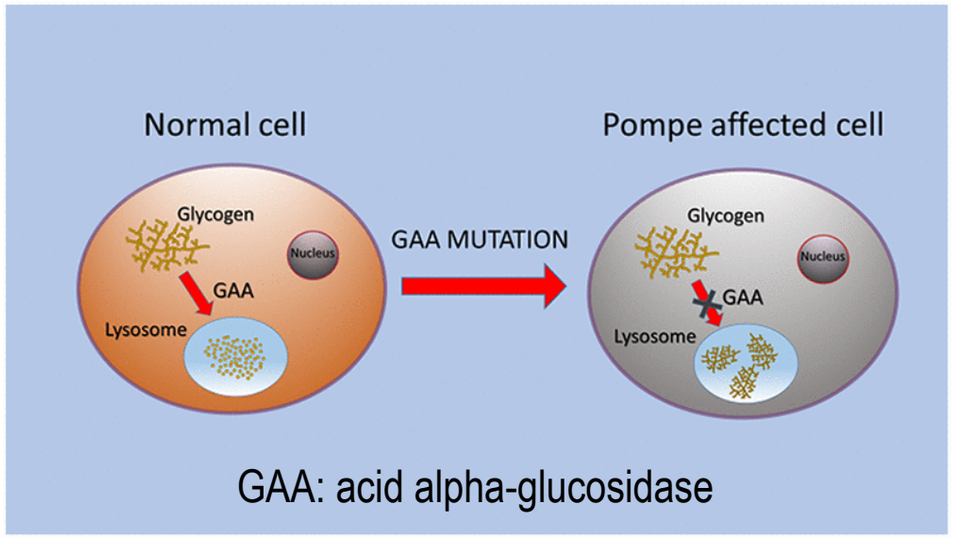
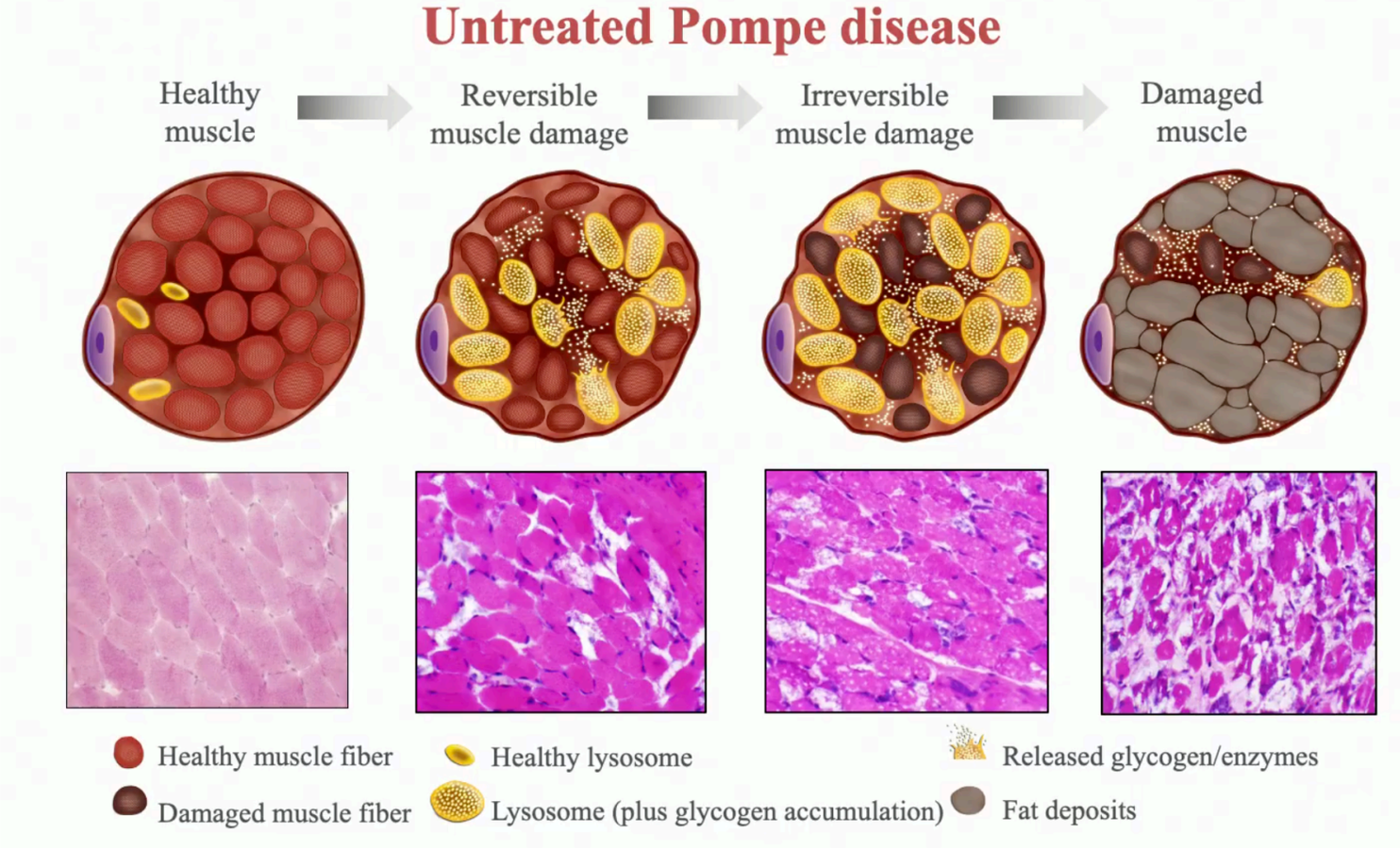
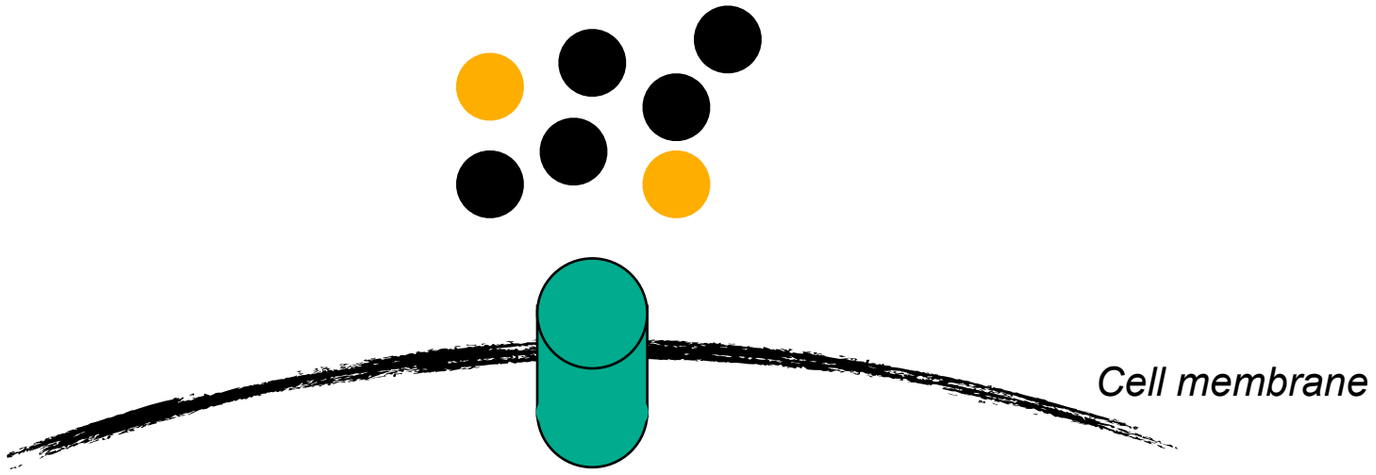




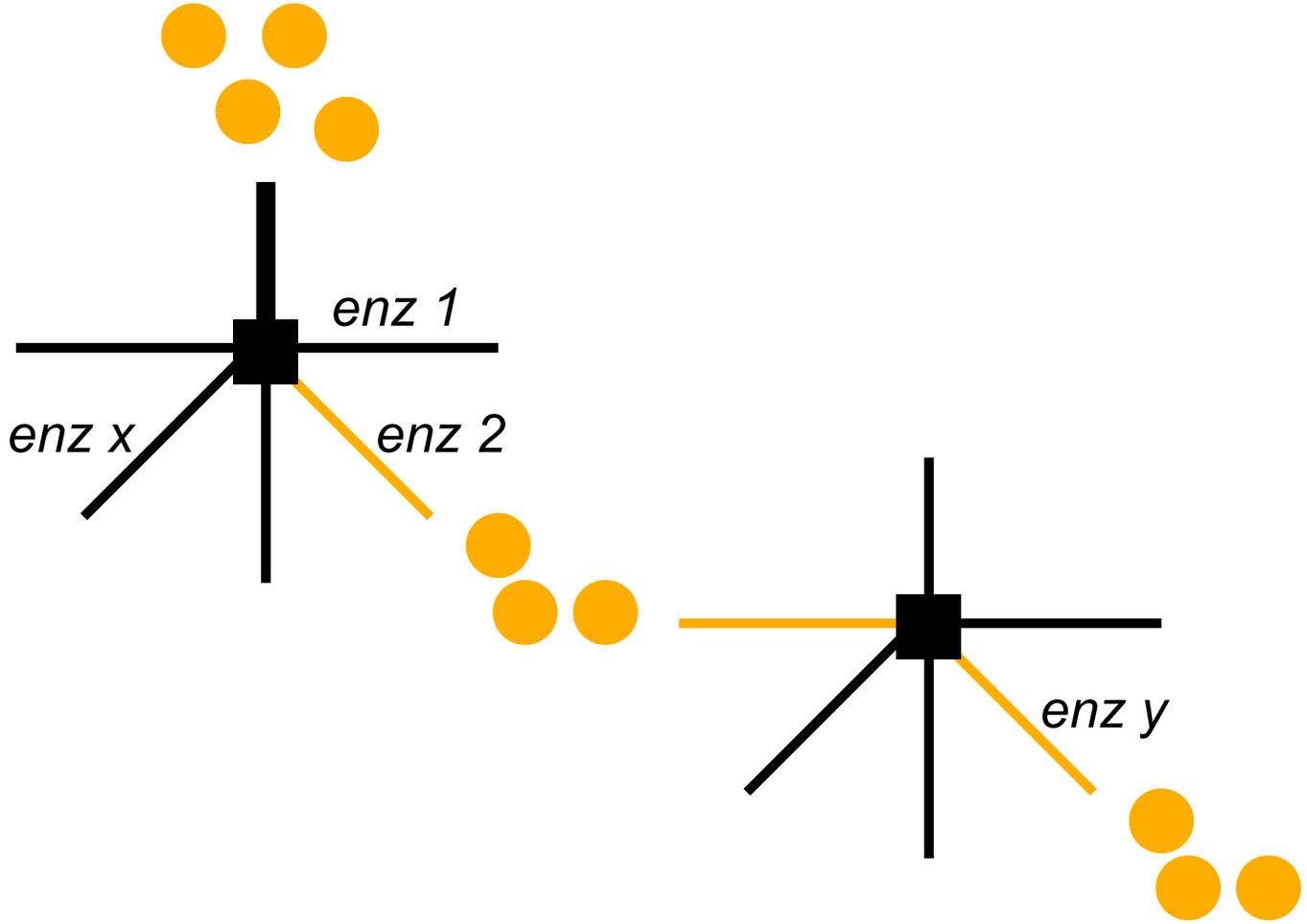
Multi-level regulation of intracellular metabolism

Nutrient availability

Nutrient uptake



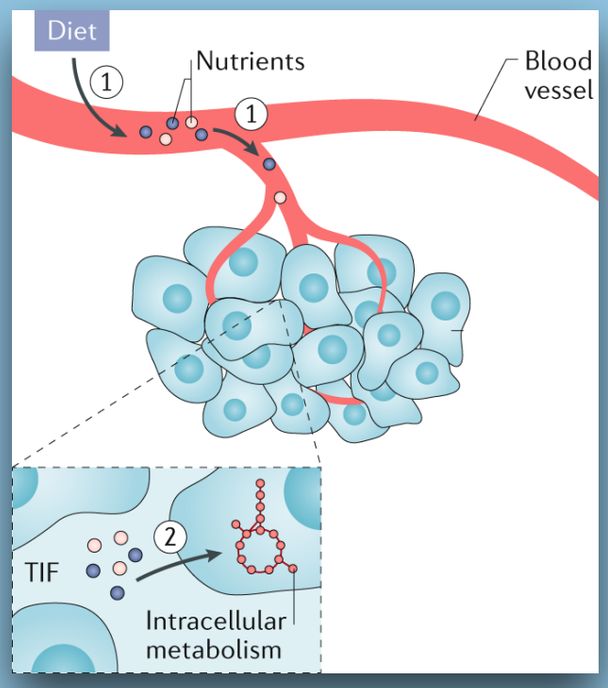
Nutrient channeling (wiring)



Tissue metabolism dictates nutrient availability

1

Dietary intake dictates local abundance of metabolites in peripheral tissues



SYSTEMIC/TISSUE RELATIONSHIP

Tissue metabolism dictates nutrient availability

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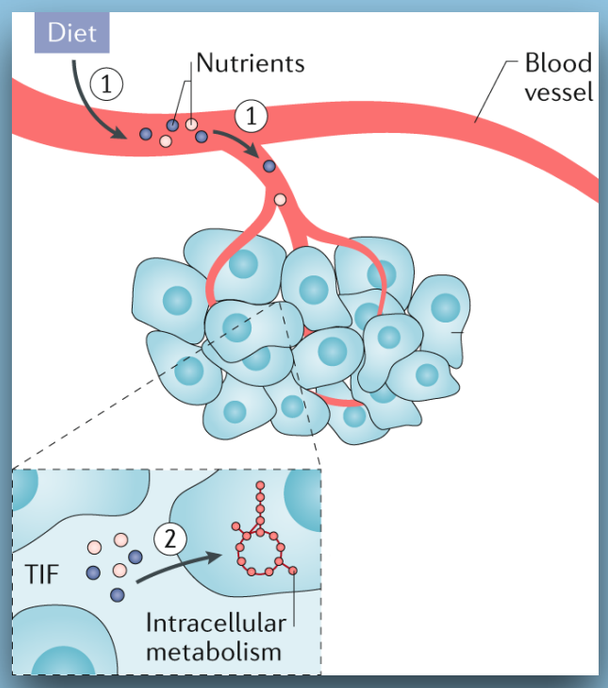
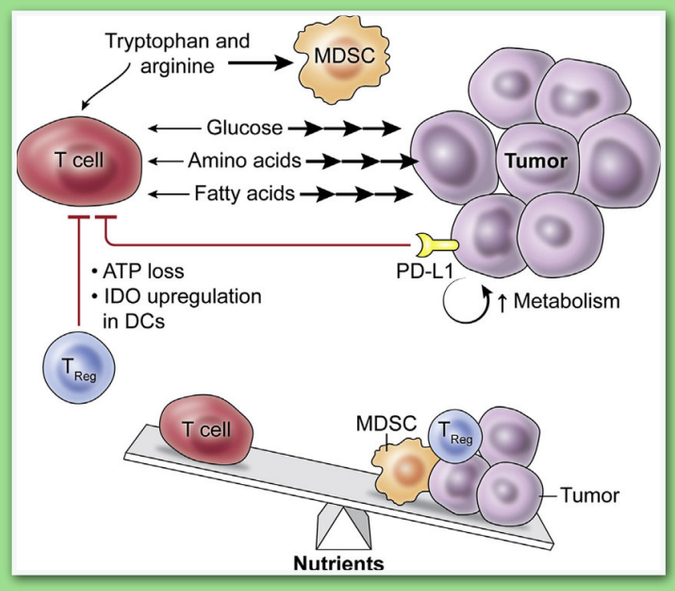


SYSTEMIC/TISSUE RELATIONSHIP

2

Different cell types often compete for the same nutrients.

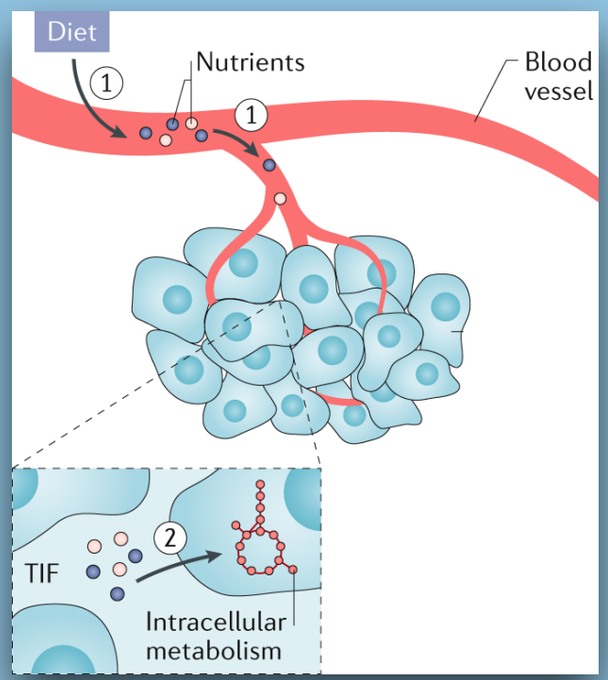


METABOLIC COMPETITION

Tissue metabolism dictates nutrient availability

1

Dietary intake dictates local abundance of metabolites in peripheral tissues



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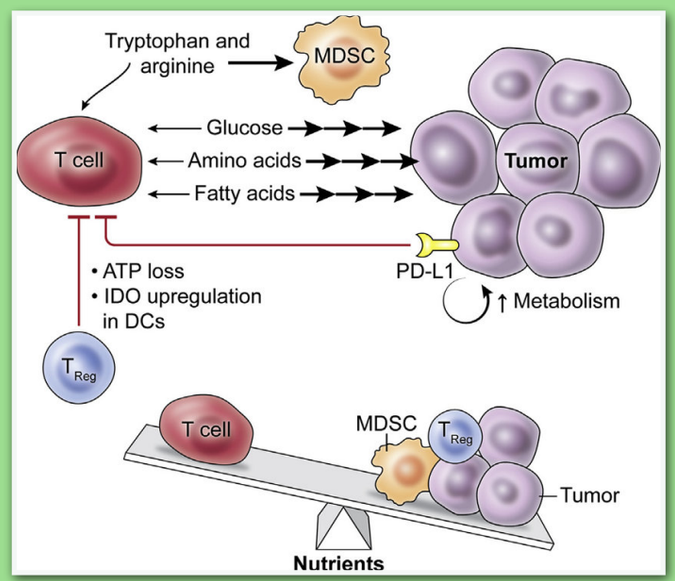
2

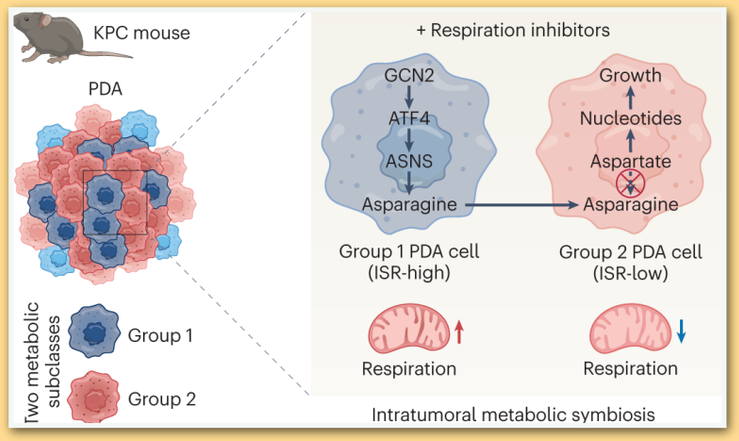
Different cell types often compete for the same nutrients.



METABOLIC COMPETITION

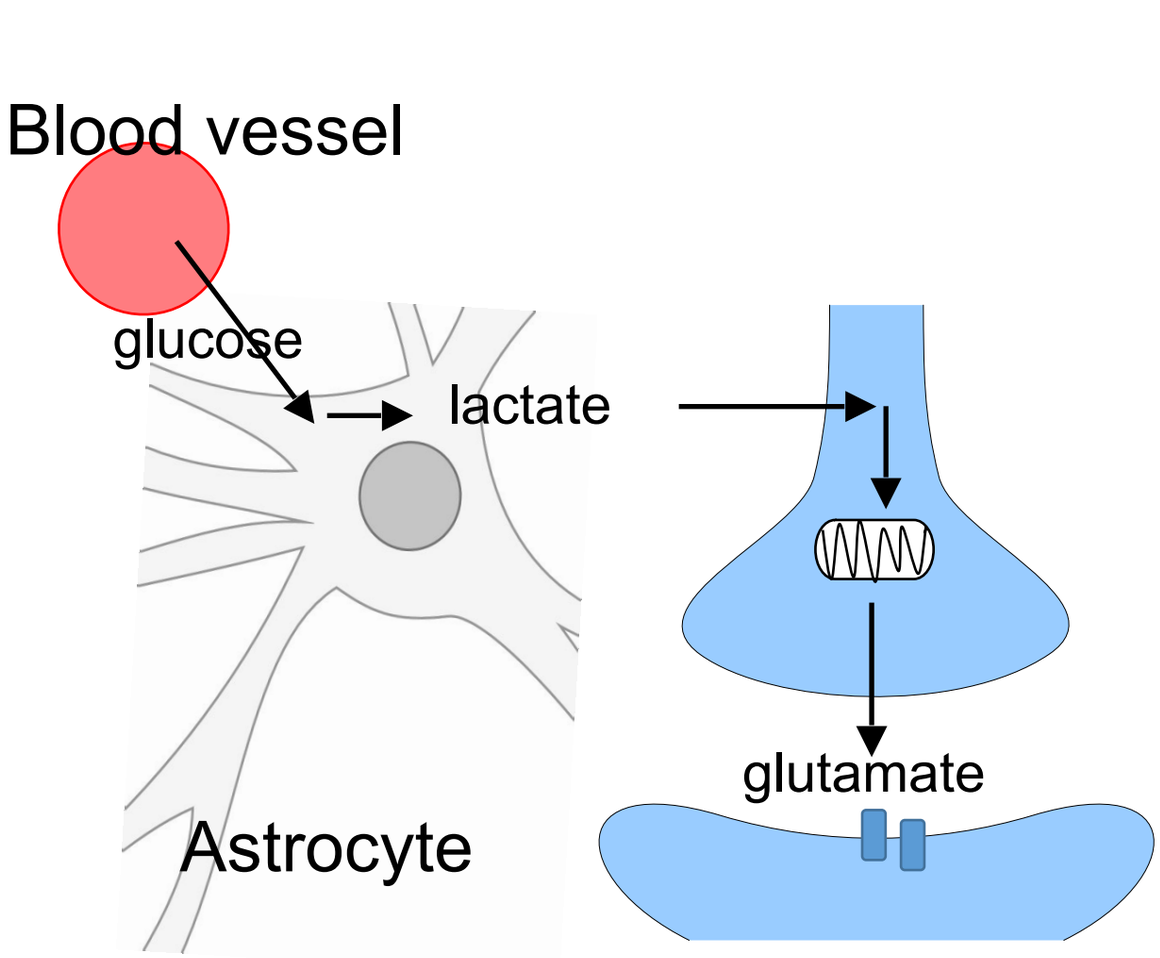
3

Nutrients can be provided by a different cell type in the tissue

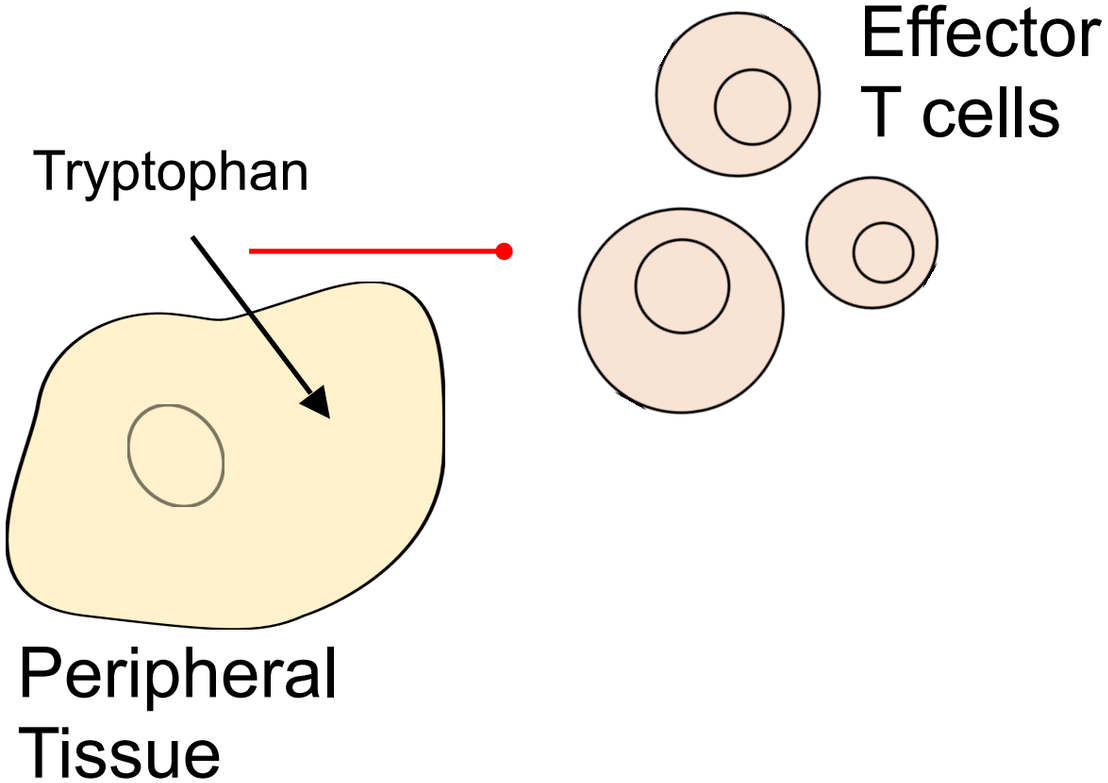


METABOLIC SYMBIOSIS

Metabolic Interactions

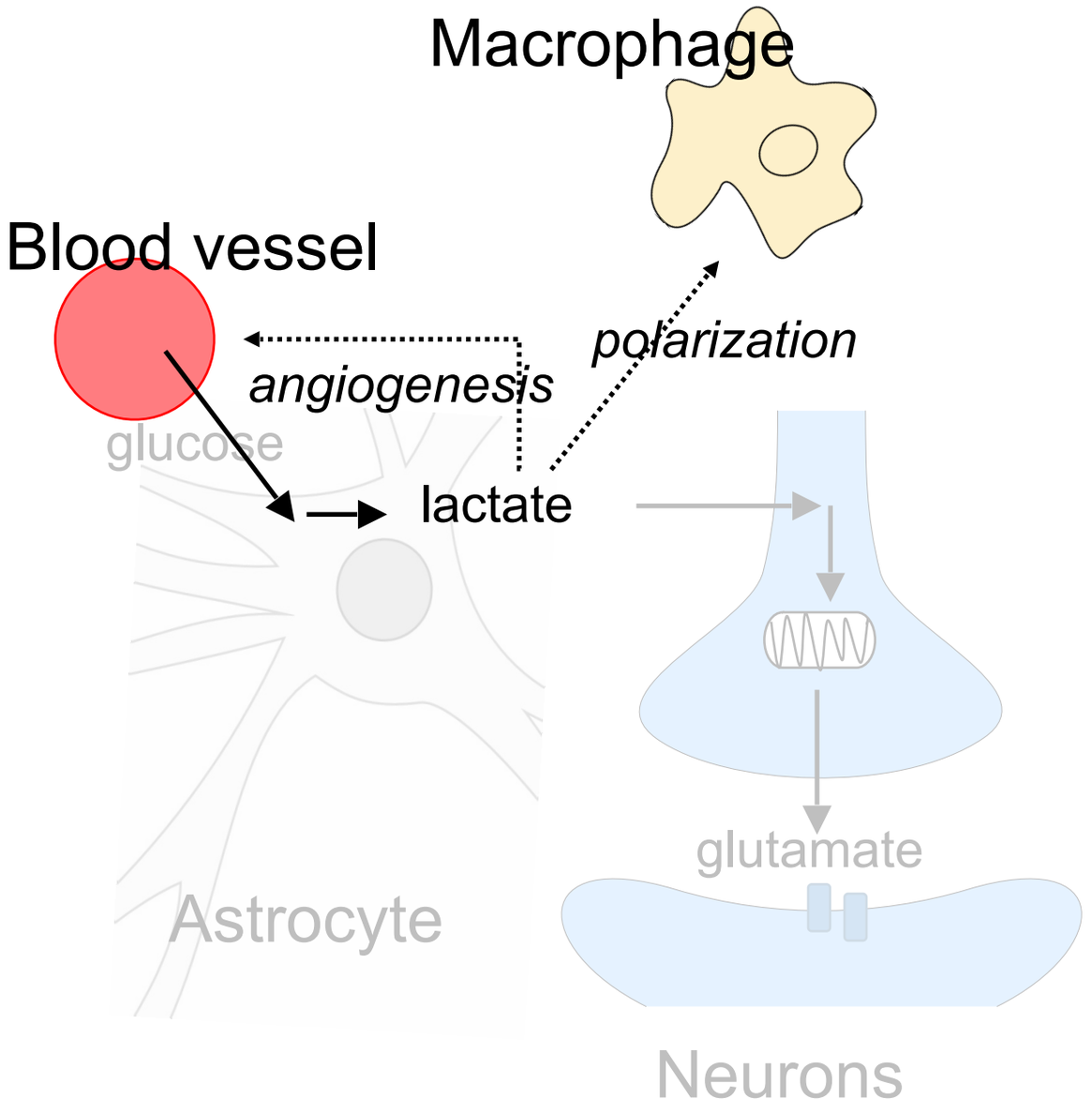


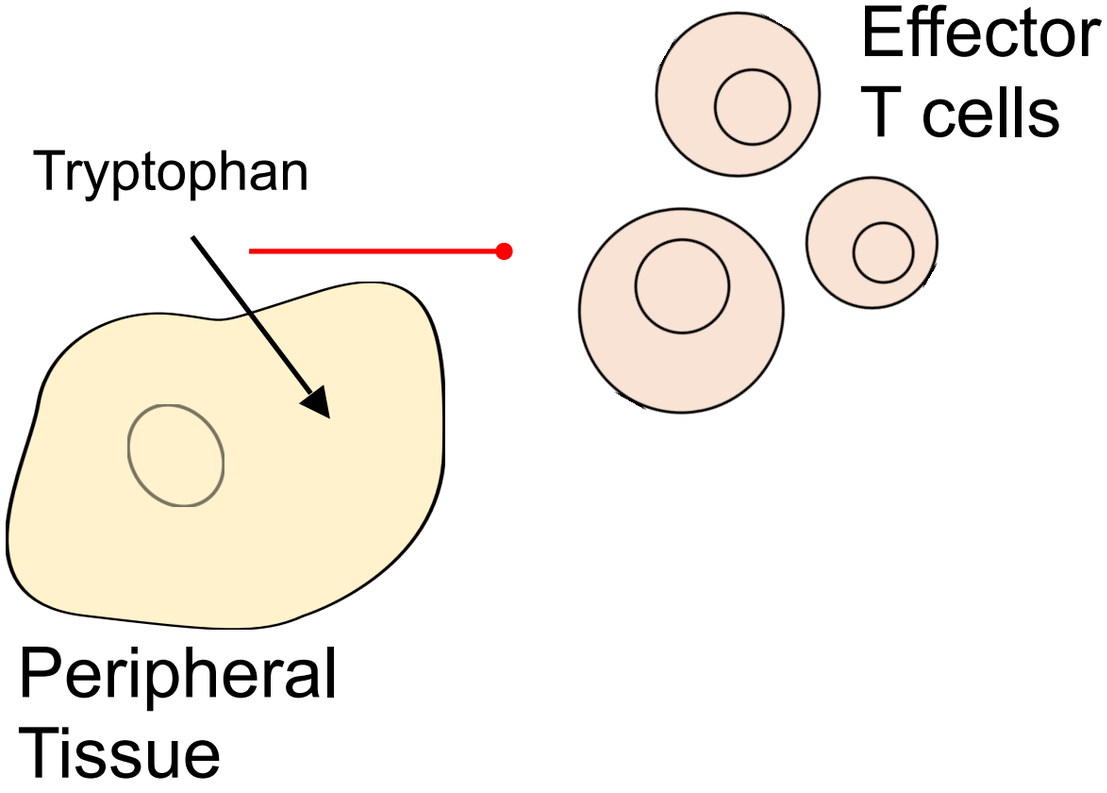
COOPERATIVE



COMPETITIVE

Metabolic Interactions

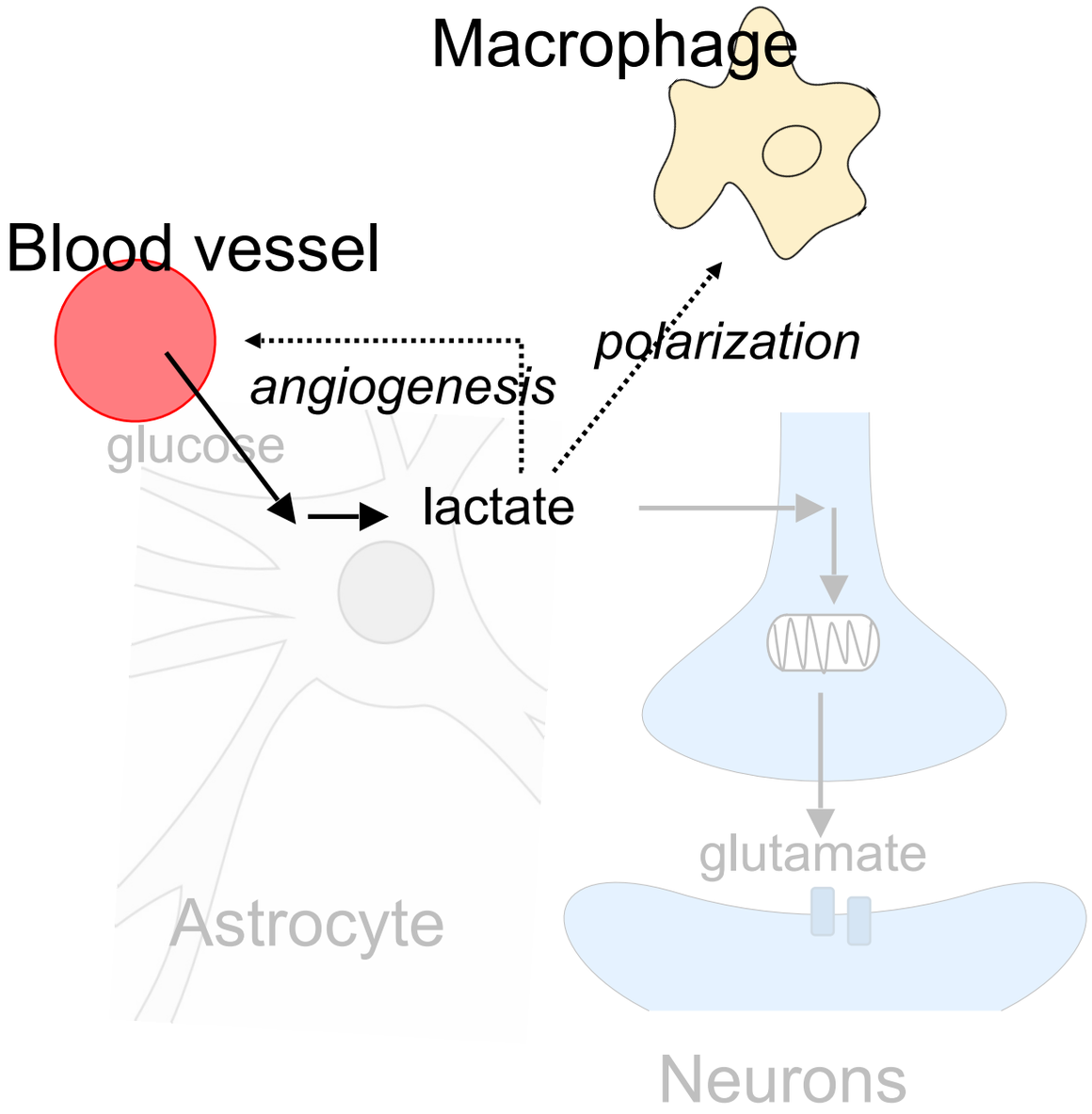


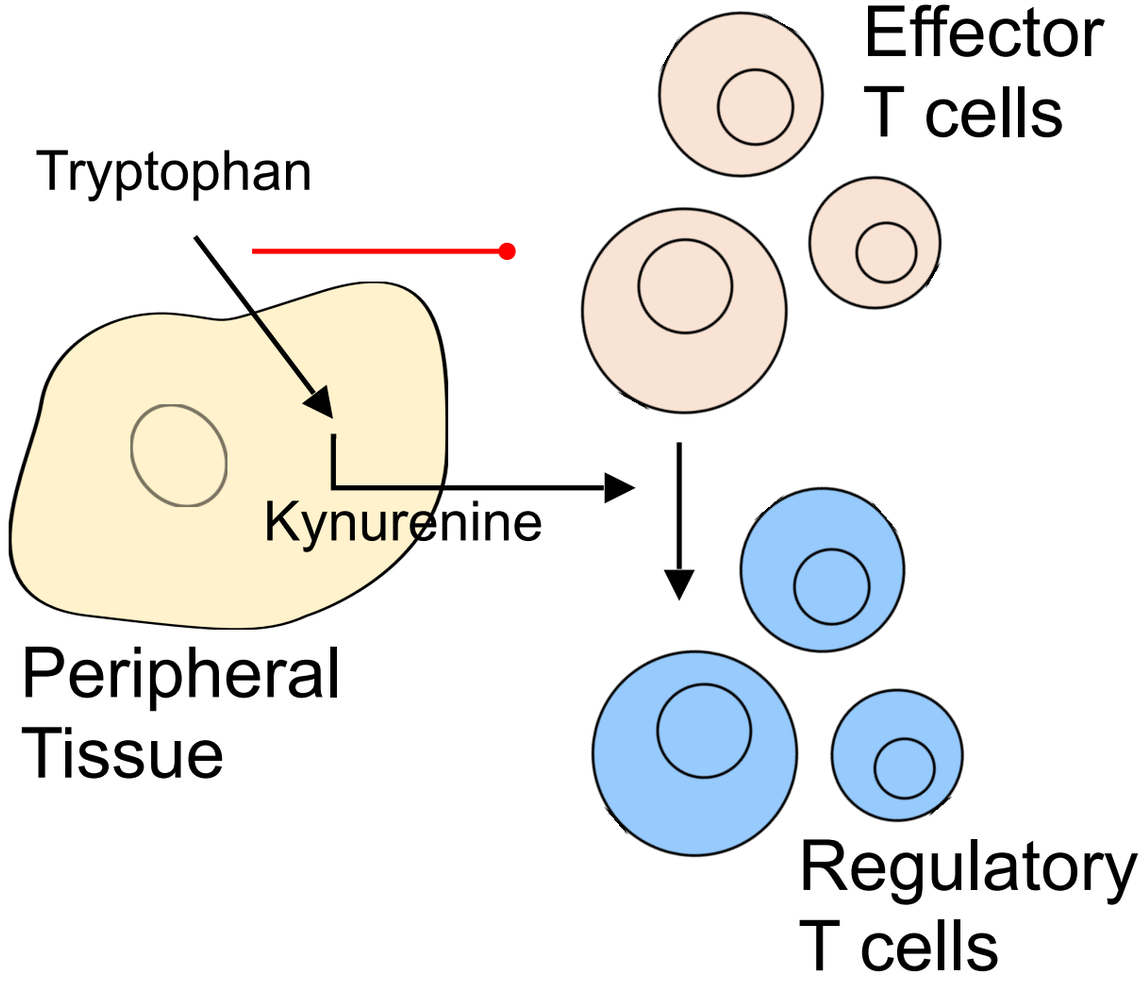


COOPERATIVE

COMPETITIVE

Metabolic Interactions





COOPERATIVE

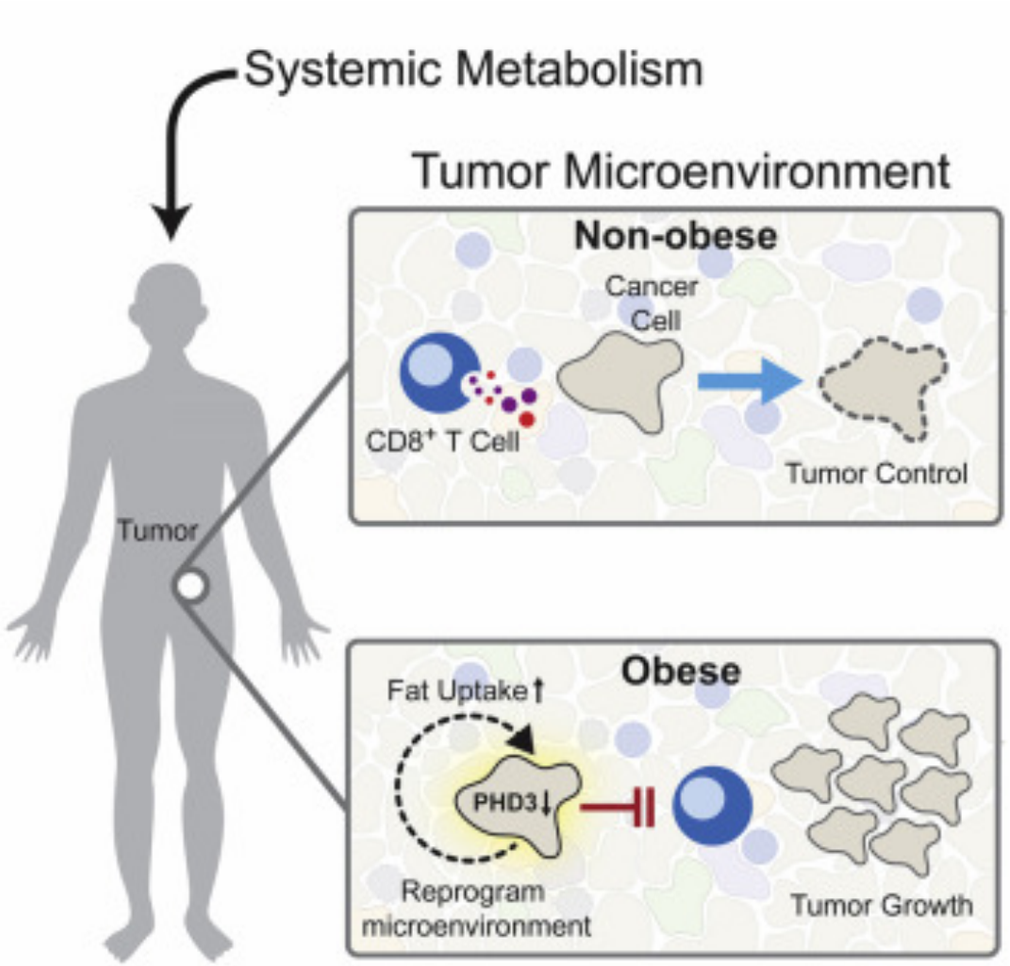
COMPETITIVE

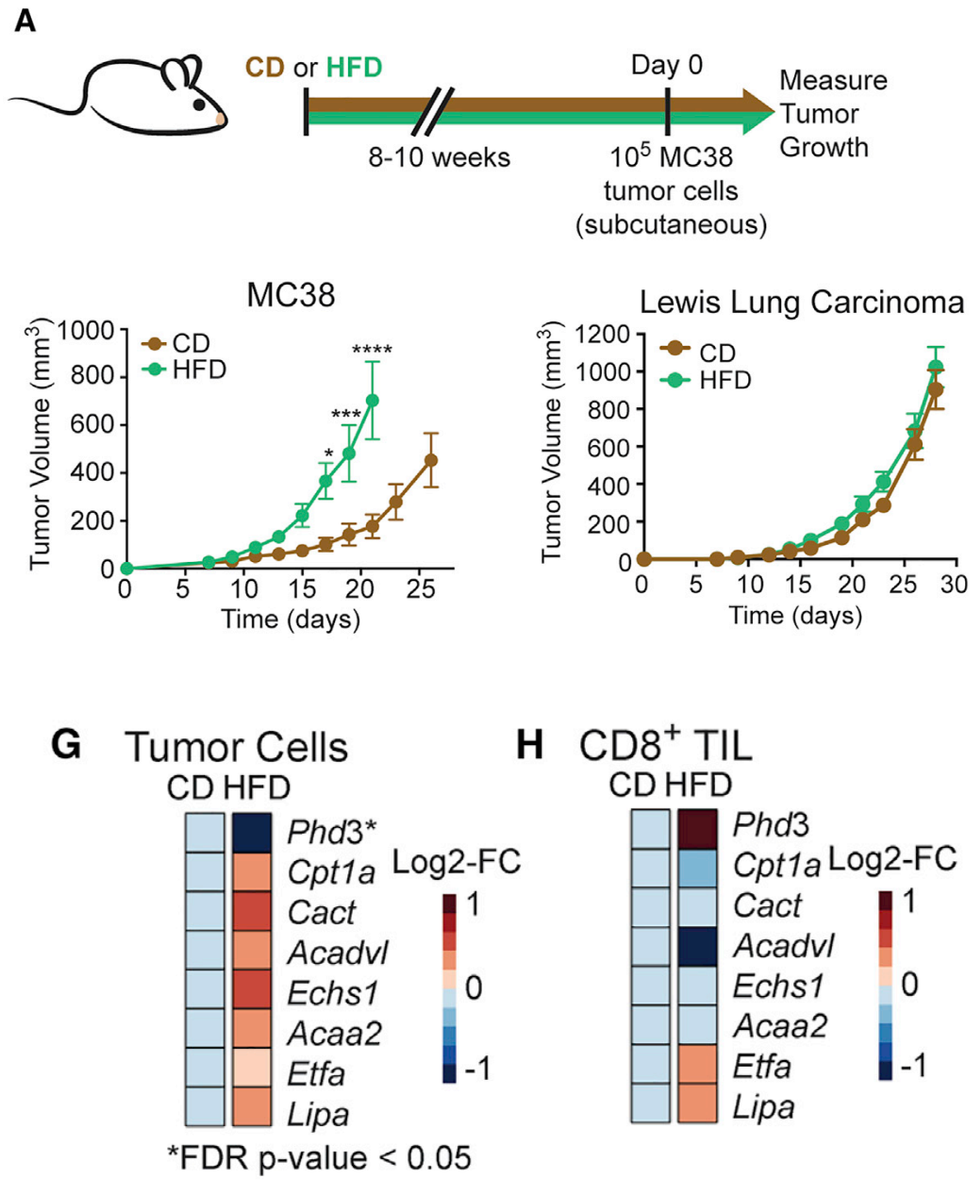
CellPress

Cell

Article

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





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

CONCLUSIONS (2)

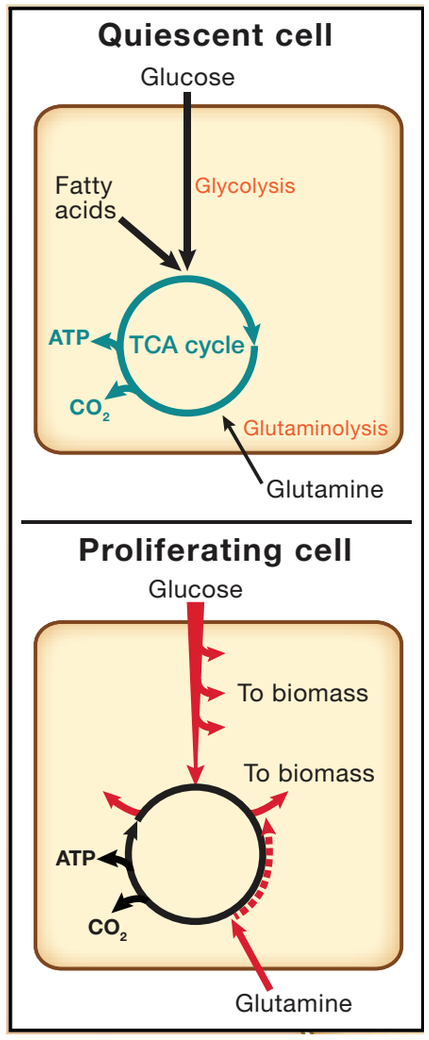
Local nutrient availability is dictated cell-cell interplay

Nutrient competition is a physiological feedback mechanism

Nutrient cooperation is a physiological mechanism of adaptation

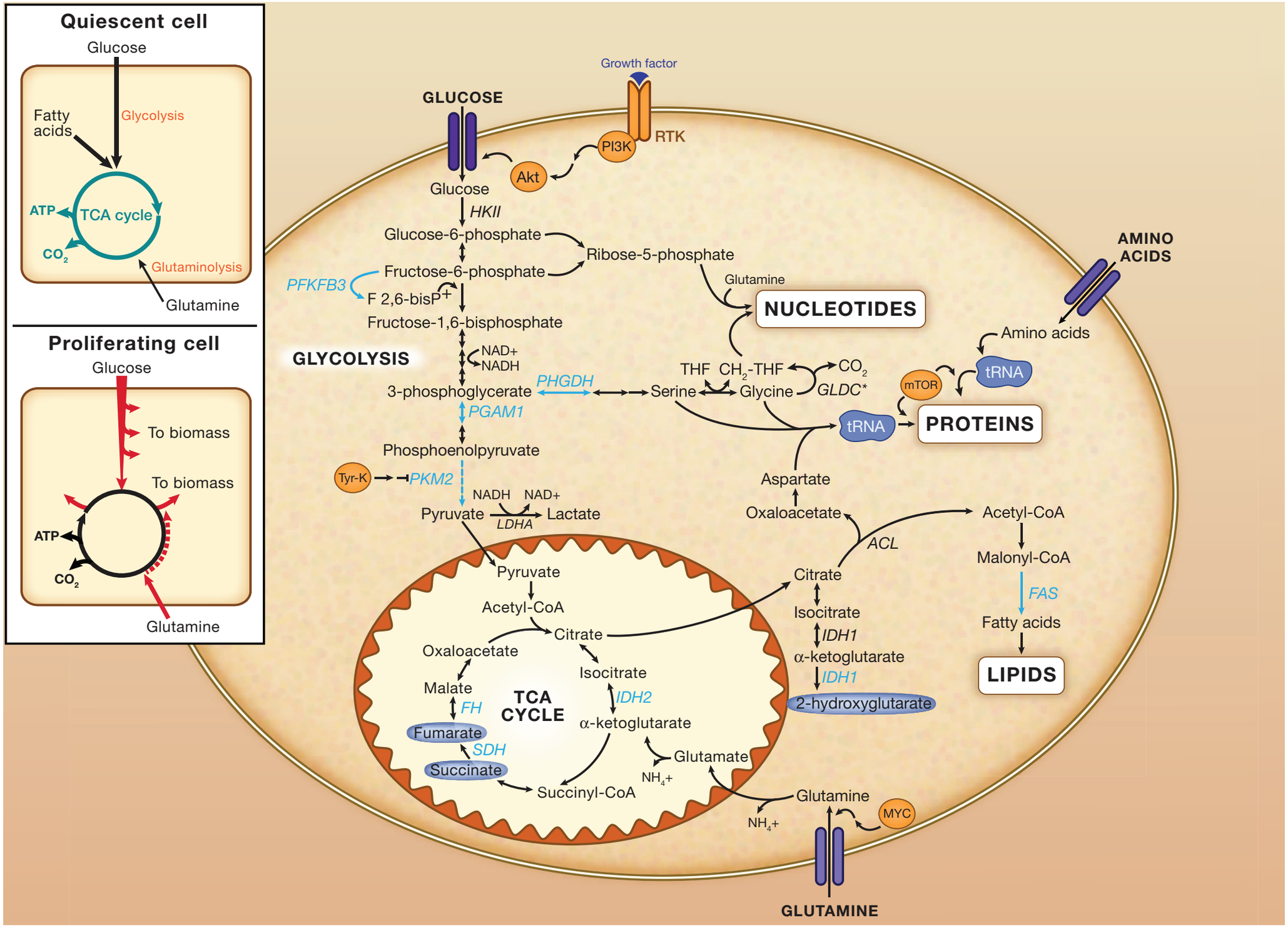
Local nutrient availability is different across different tissues and changes according to multiple systemic inputs

Proliferation presents metabolic challenges



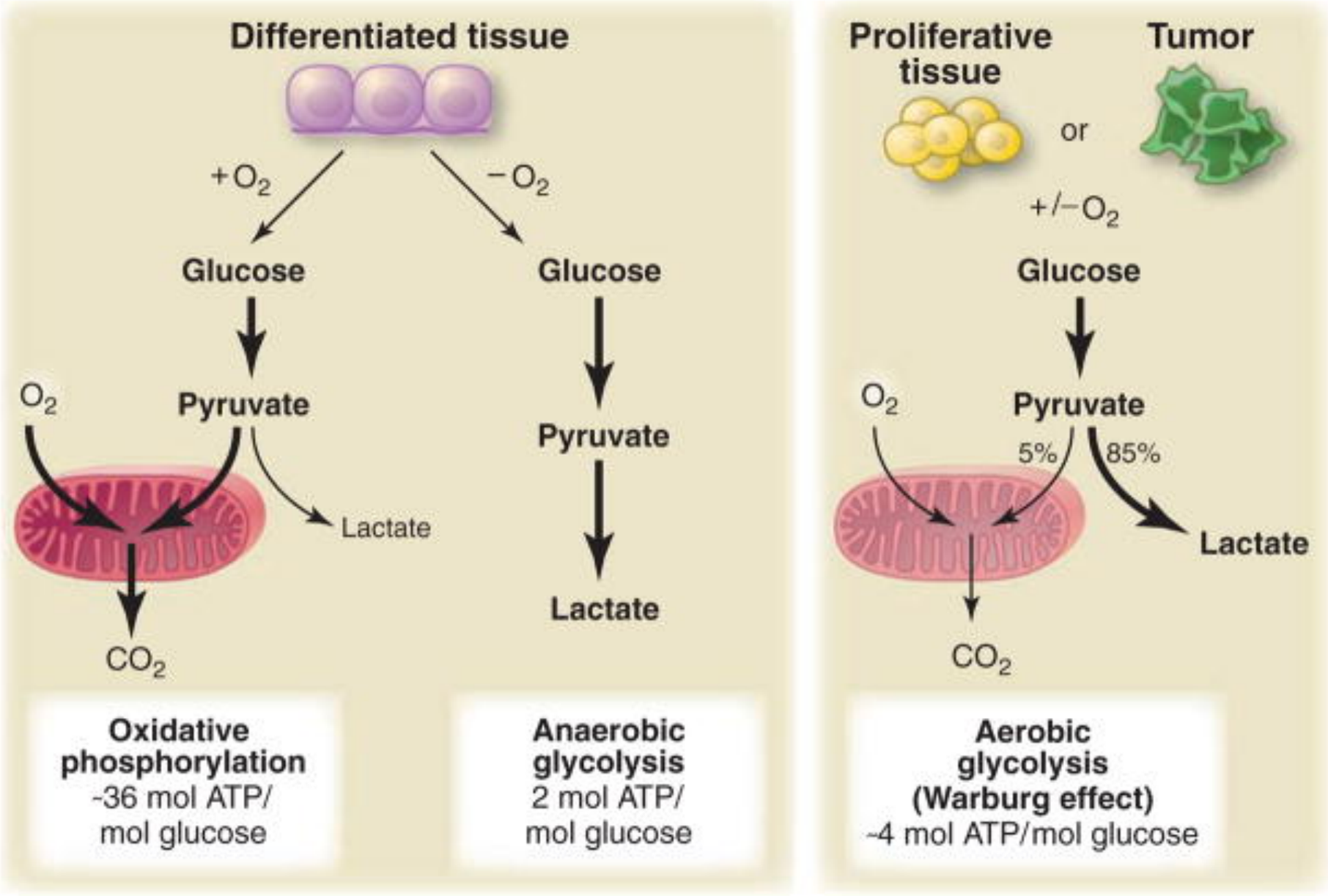
Finley LY, Thompson CB, ***Cell****, 2012*

Proliferation presents metabolic challenges



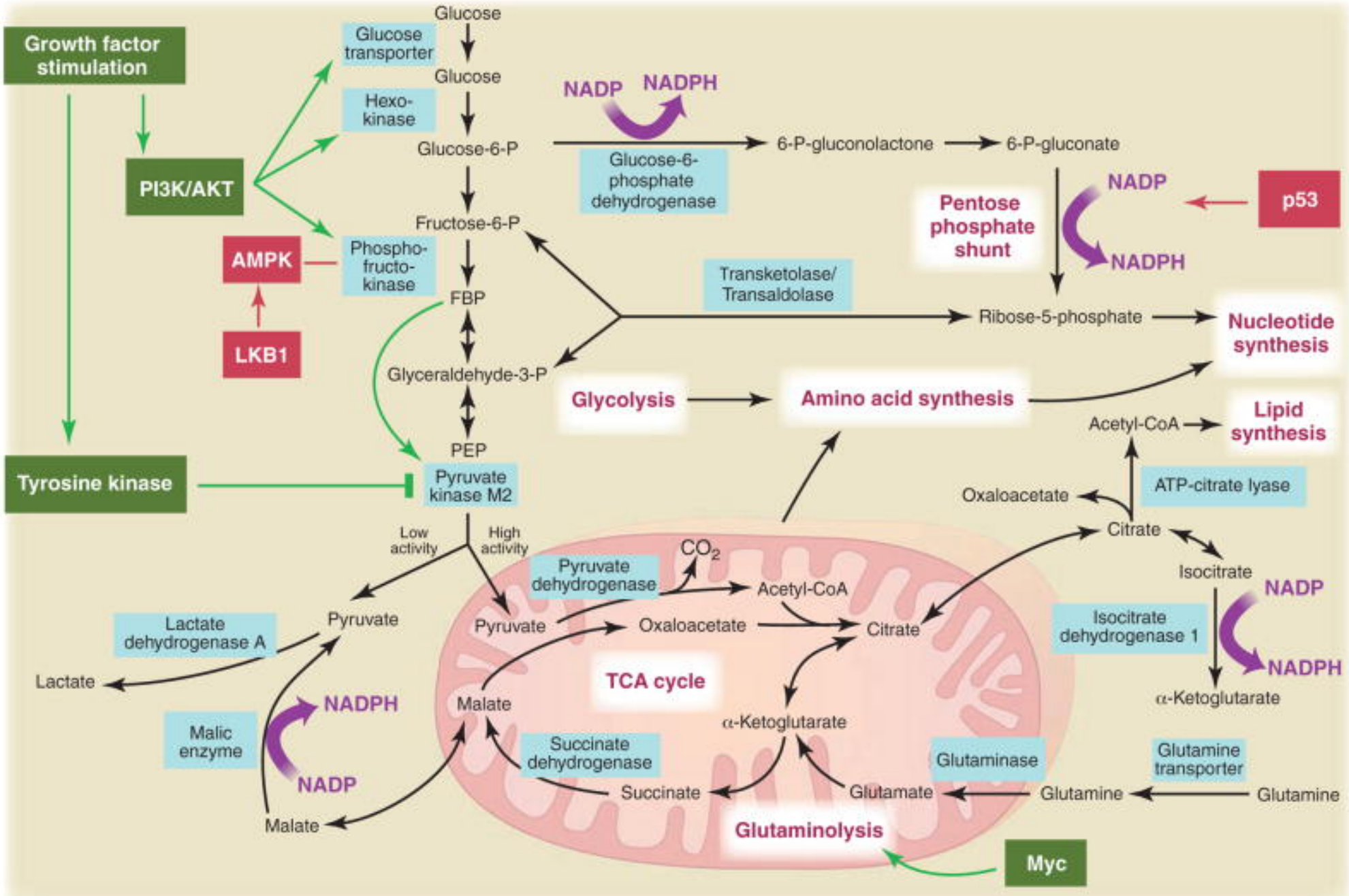
Finley LY, Thompson CB, ***Cell****, 2012*

Proliferating cells have increased demand for glycolytic intermediates



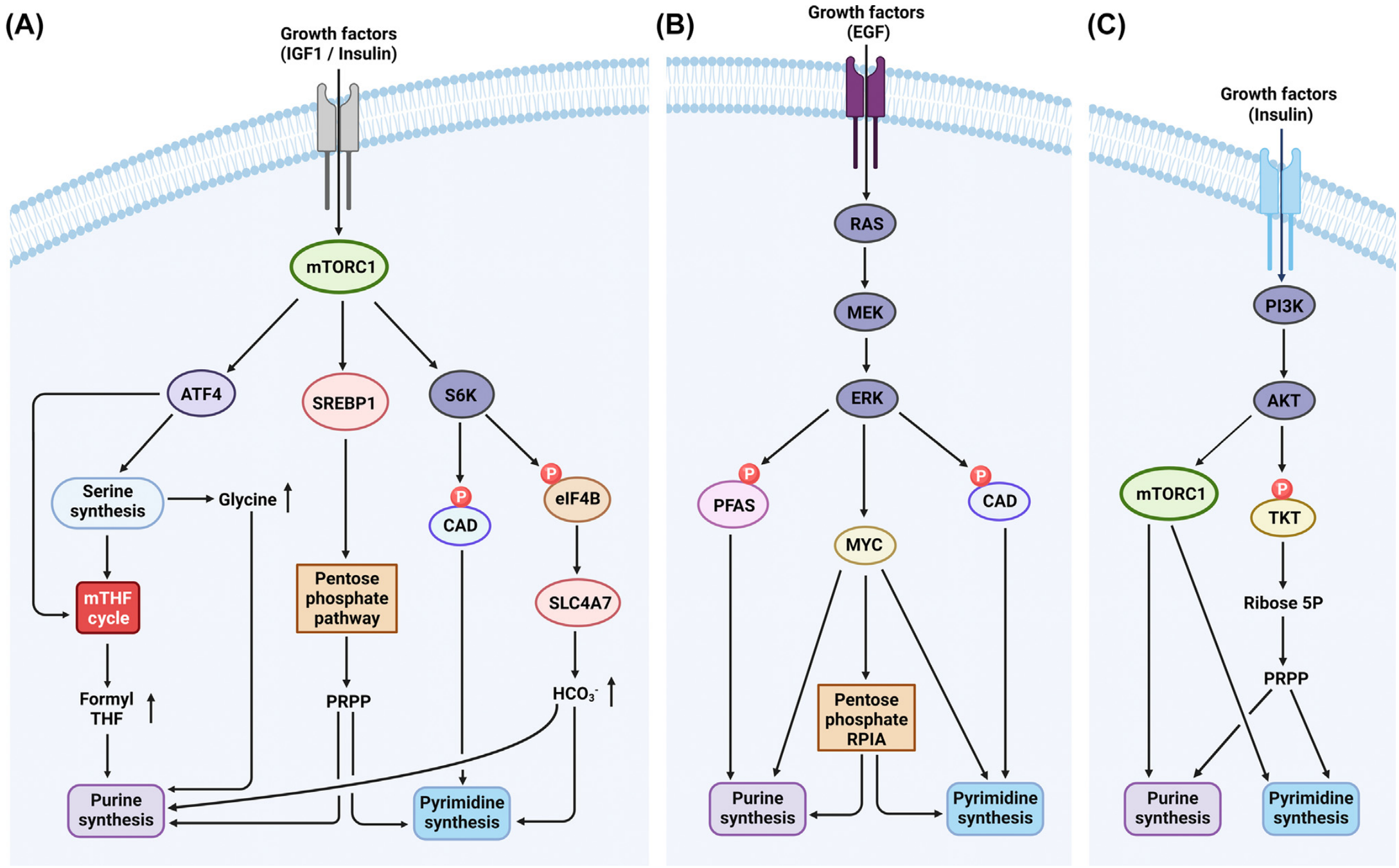
Vander Heiden et al, ***Science****, 2009*

Proliferating cells have increased demand for glycolytic intermediates

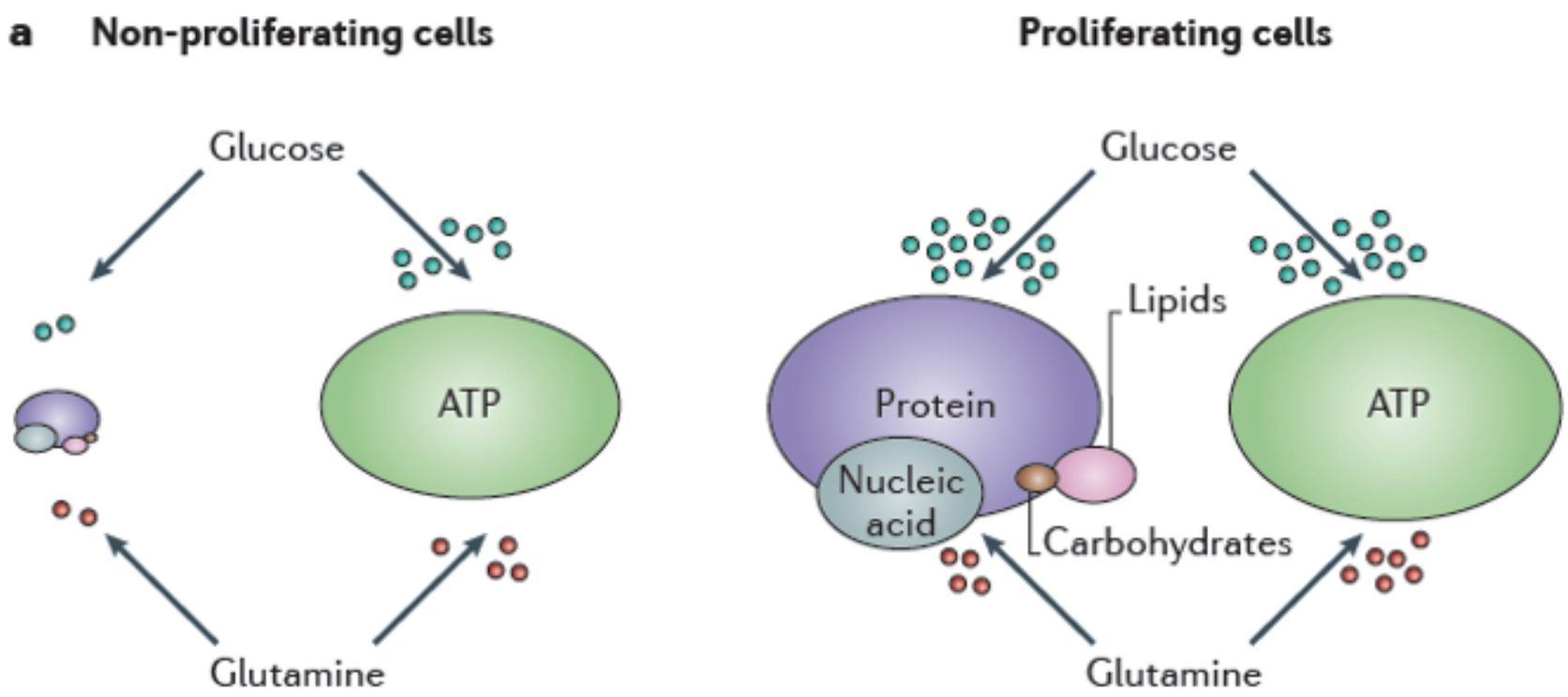


Vander Heiden et al, ***Science****, 2009*

Proliferating cells need nucleotides



Proliferating cells have increased demand for glycolytic intermediates



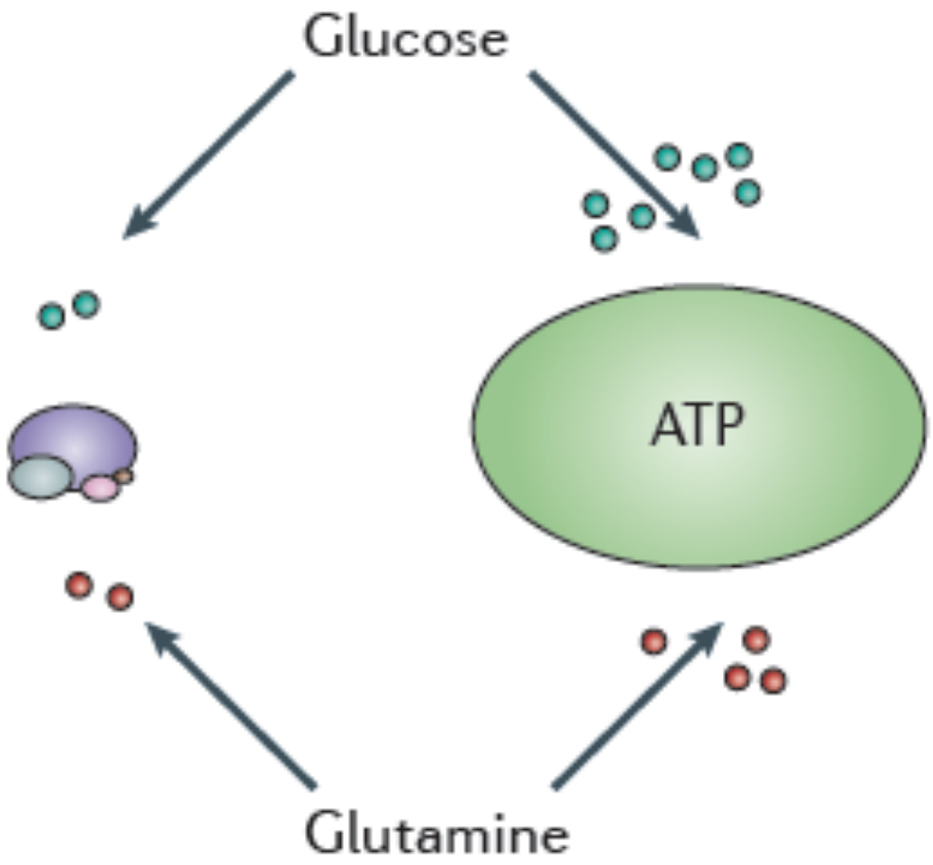
Post-mitotic differentiated cells focus on efficient oxidative metabolism to extract the maximum amount of ATP from nutrients -> ‘manning the pumps’ (ion channels) and executing specialized functions

Proliferating cells (development, immune system, cancer) rewire metabolism to support the biomass accumulation required for cell division; this funnels intermediates through all of the biosynthetic hubs we discussed earlier

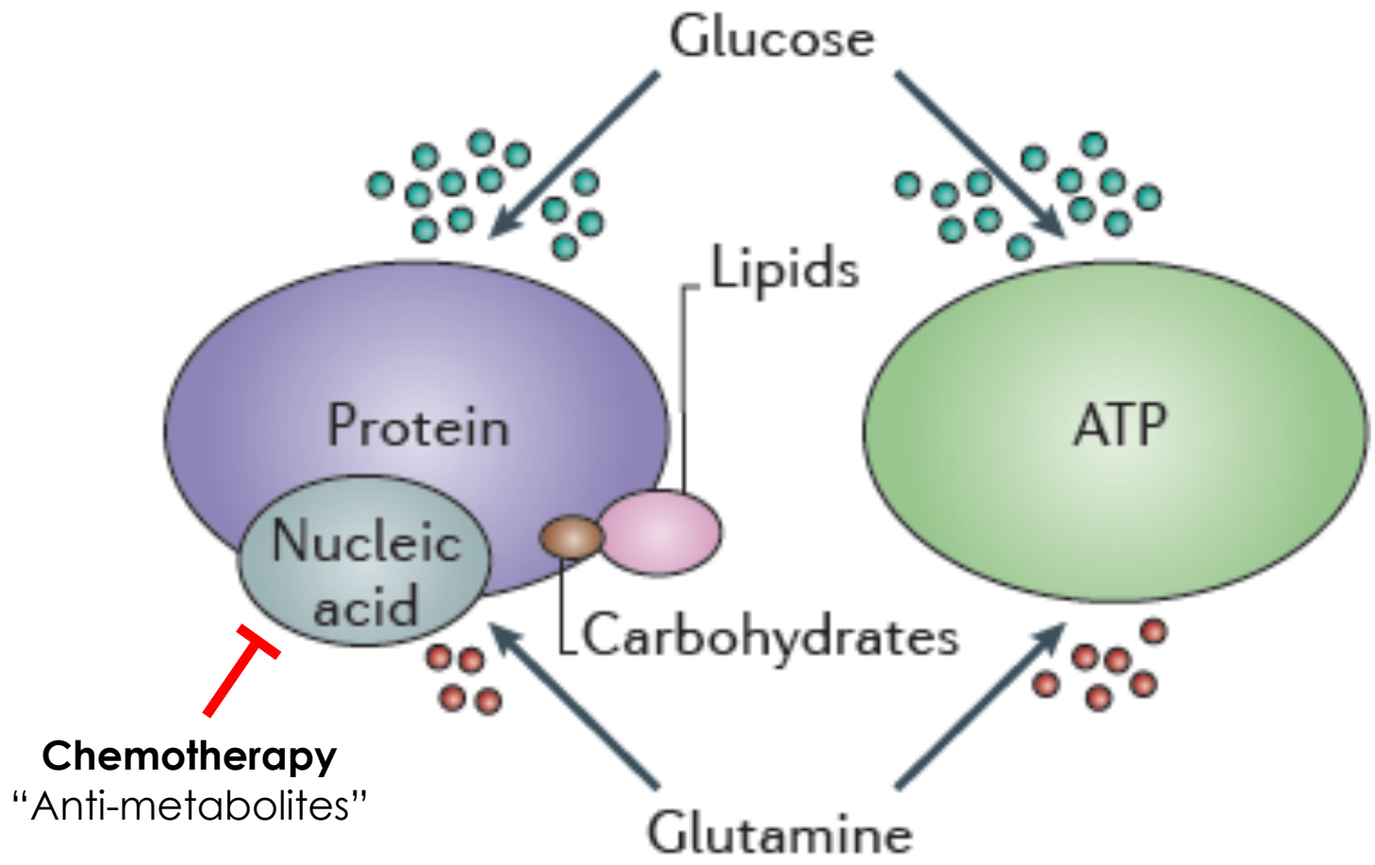
Proliferating cells have increased demand for reducing equivalents

(support anapldrotic reactions and regeneration antioxidants)

Non-proliferating Cells



Proliferating Cells



Chemotherapy
"Anti-metabolites"

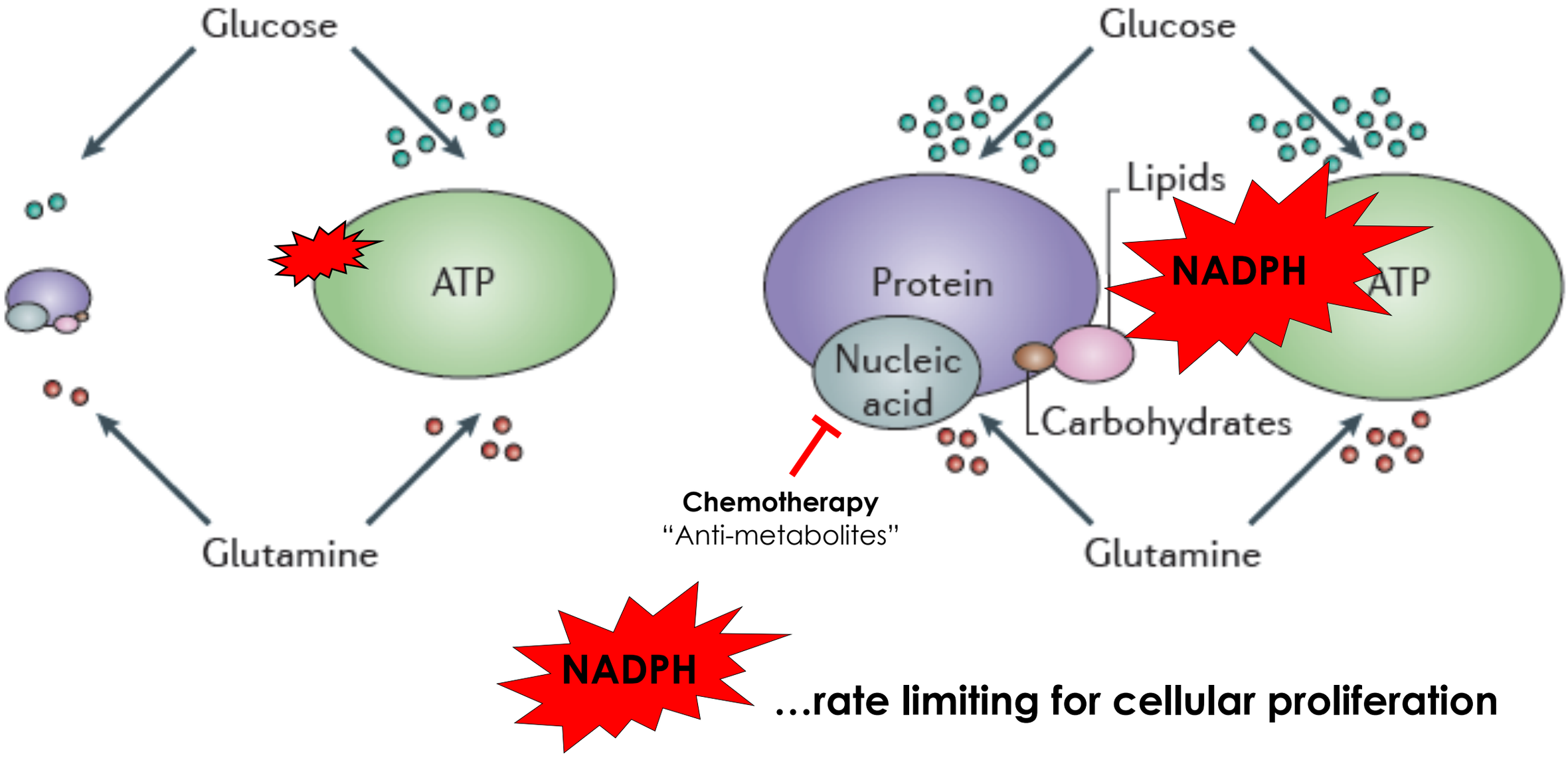
Adapted from: Vander Heiden M. ***Nat Rev Drug Disc*** 2011

Proliferating cells have increased demand for reducing equivalents

(support anapldrotic reactions and regeneration antioxidants)

Non-proliferating Cells

Proliferating Cells



NADPH **…rate limiting for cellular proliferation**

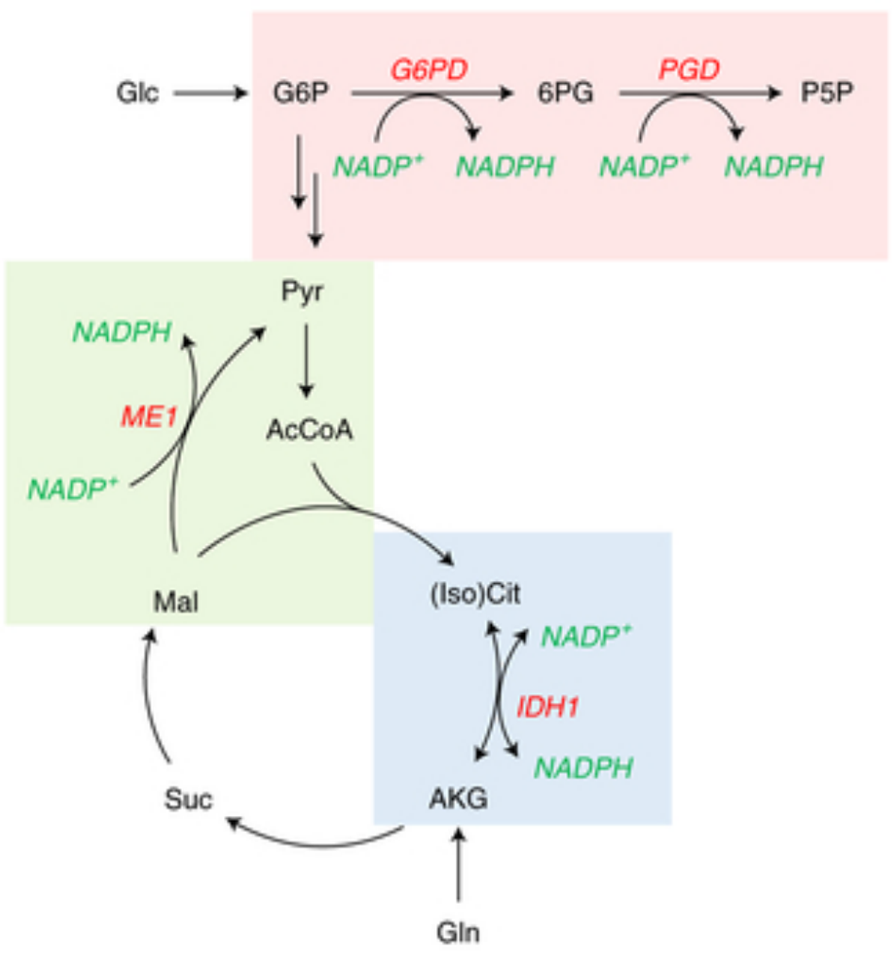
Adapted from: Vander Heiden M. ***Nat Rev Drug Disc*** 2011

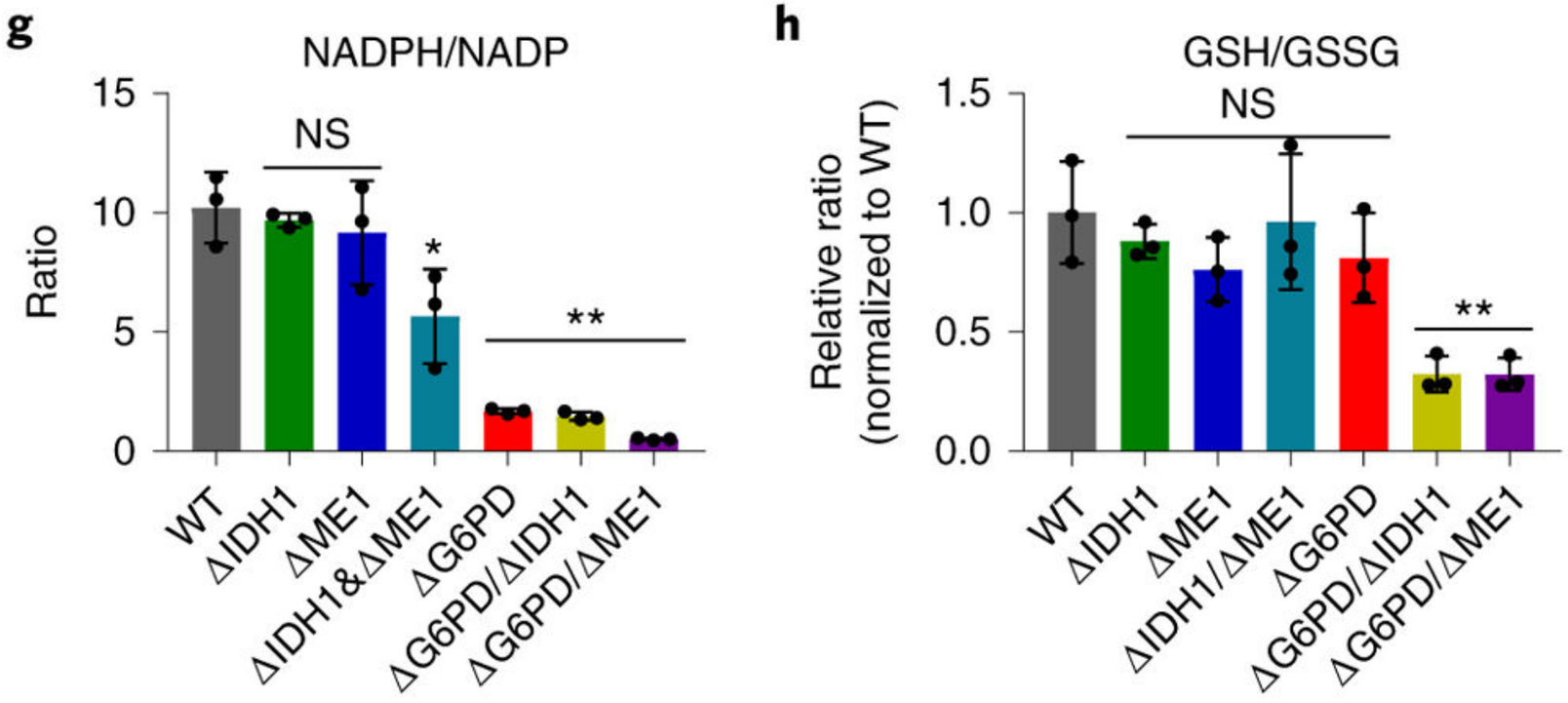
The cofactor NADPH provides high-energy electrons for antioxidant defense and reductive biosynthesis.

Consumption and production of NADPH is compartmentalized, with cytosolic NADPH used by enzymes including fatty acid synthase, ribonucleotide reductase, thioredoxin reductase, and glutathione reductase.

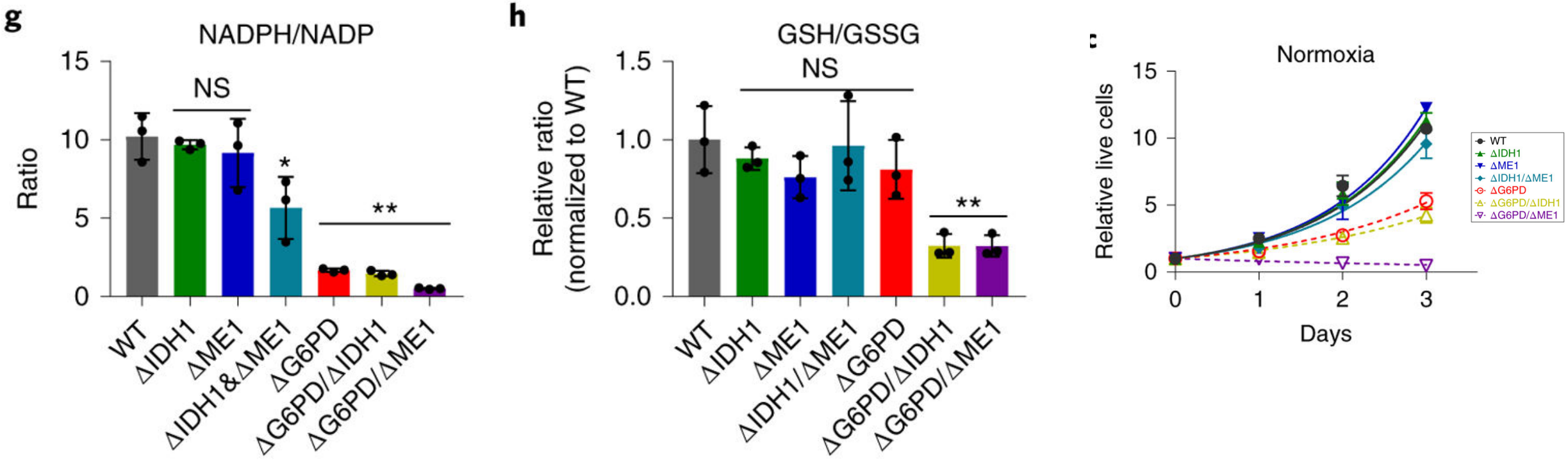
Regeneration of cytosolic NADPH from NADP occurs by three well-validated routes (each ubiquitously expressed in mammals):

- malic enzyme 1 (**ME1**),
- isocitrate dehydrogenase 1 (**IDH1**),
- the oxidative pentose phosphate pathway (**oxPPP**).

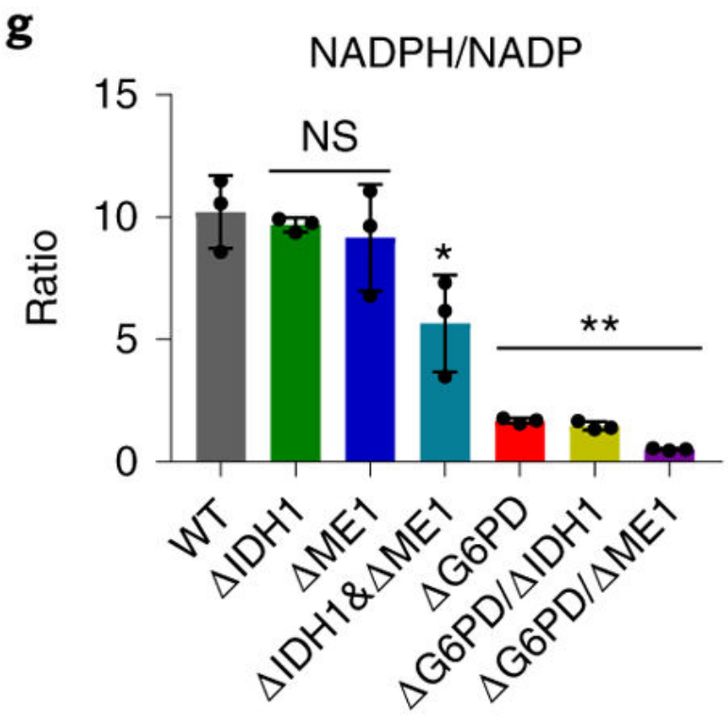


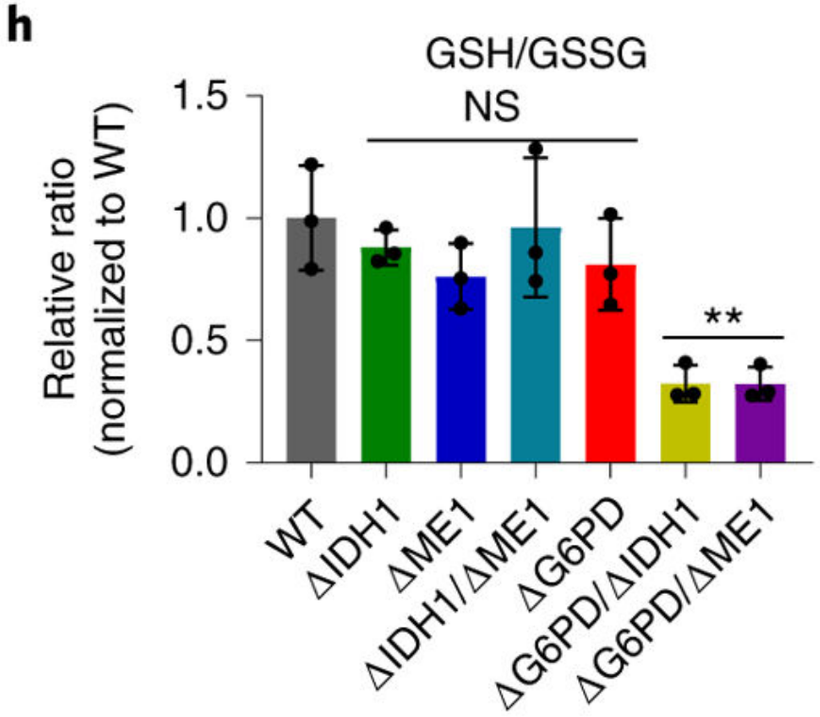


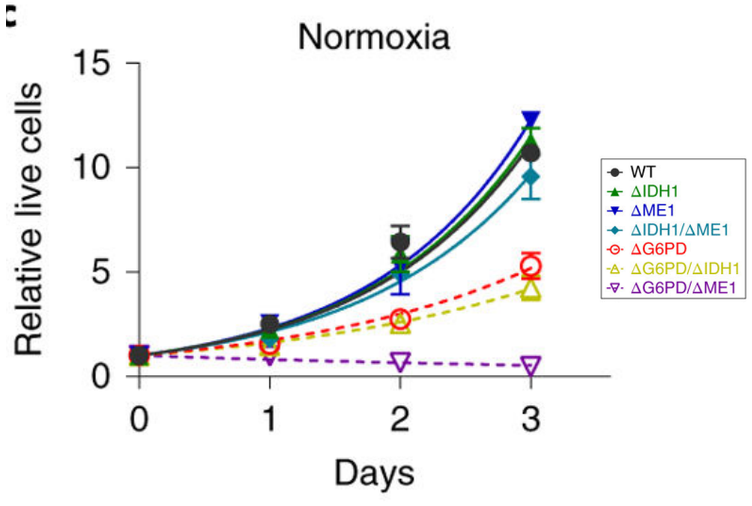
Chen et al, ***Nat Metab****, 2019*

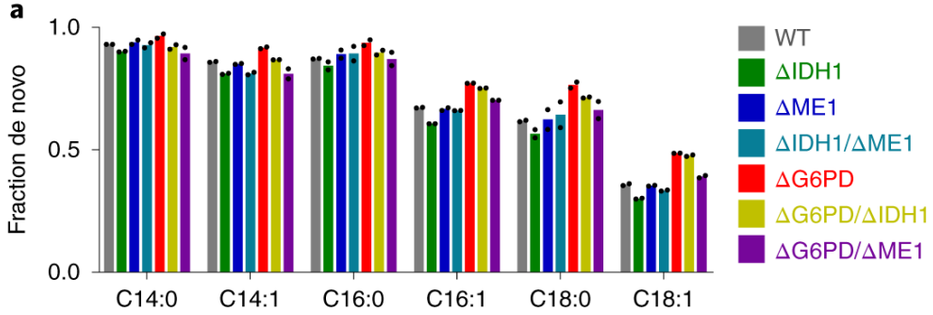


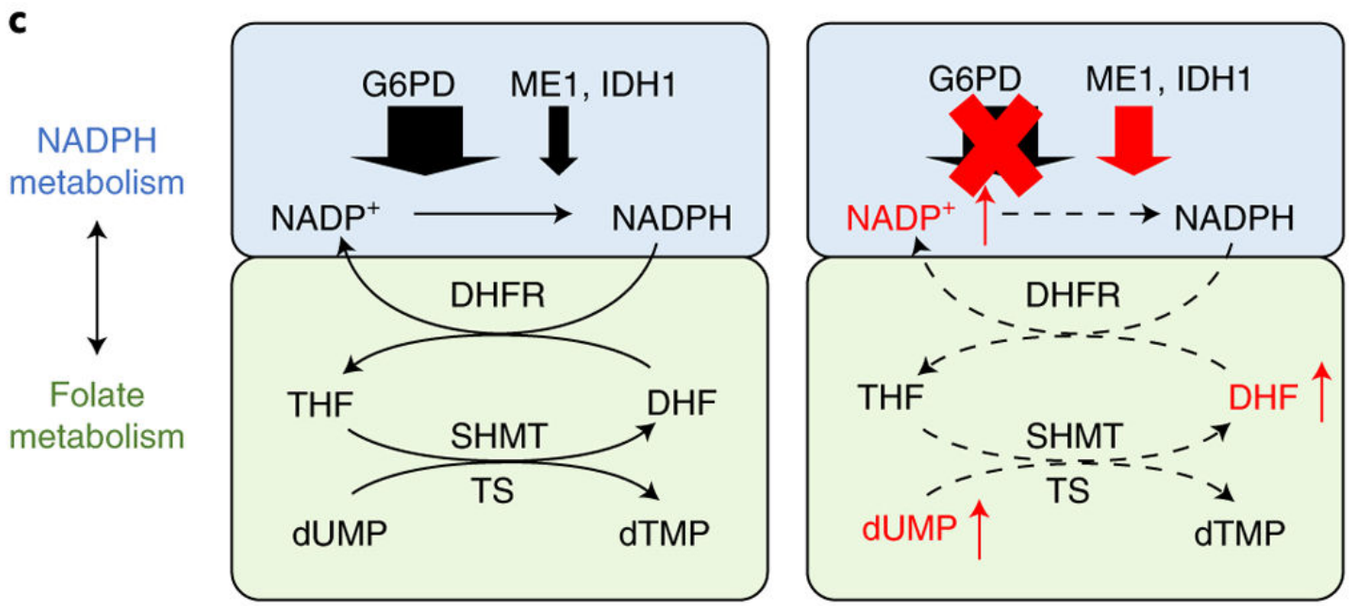
Chen et al, ***Nat Metab****, 2019*



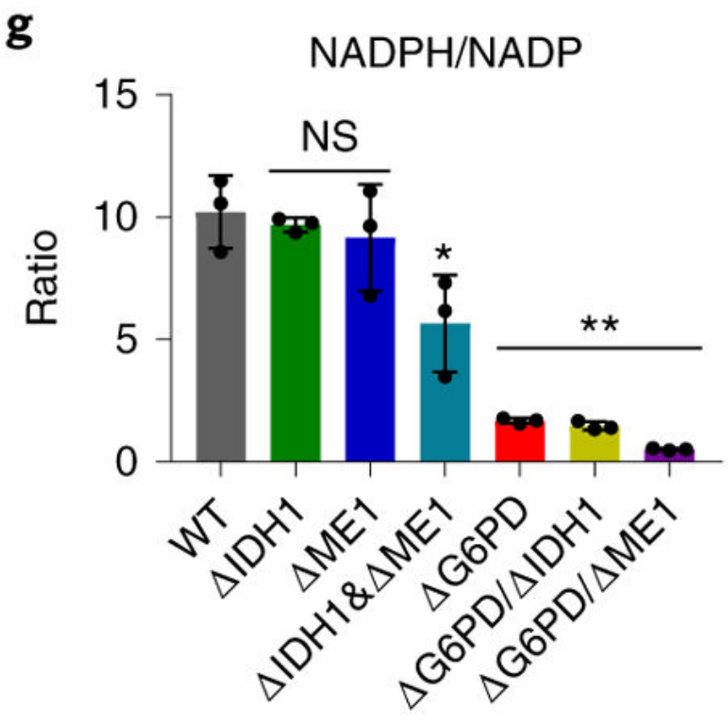


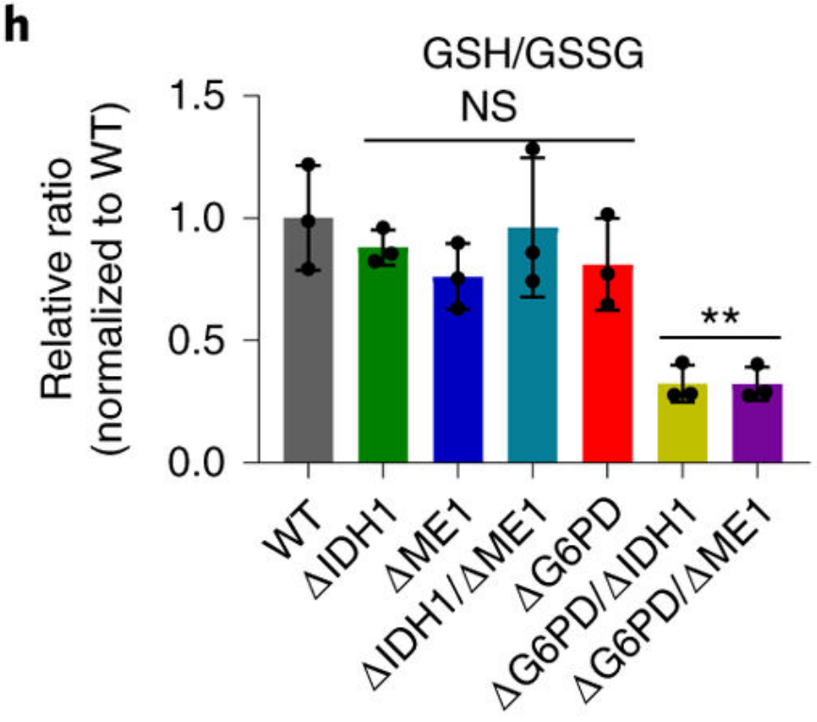


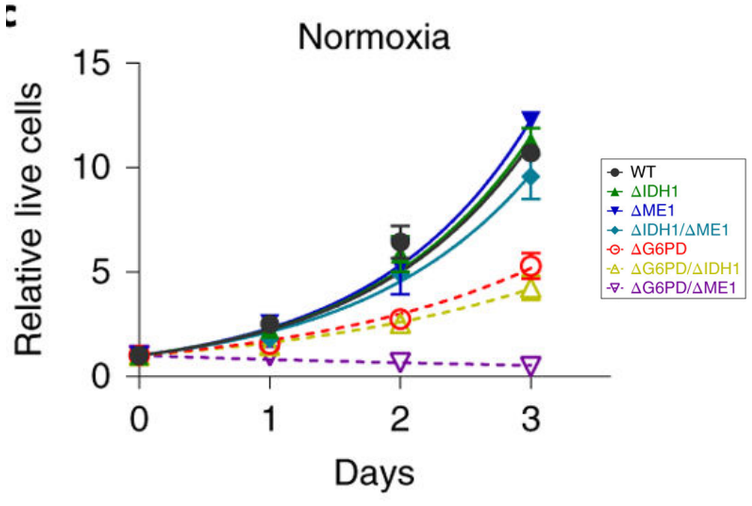


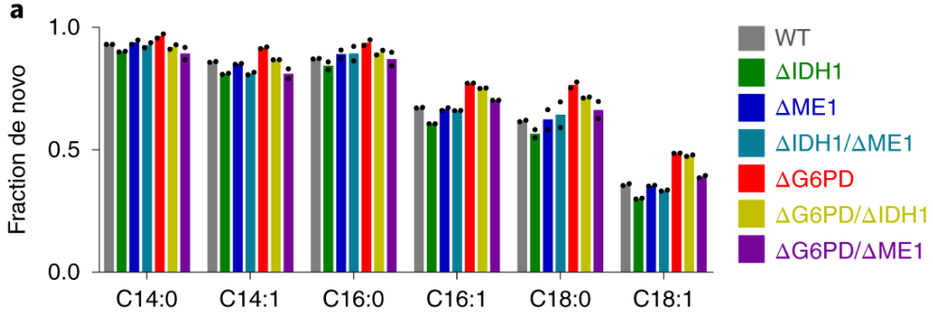


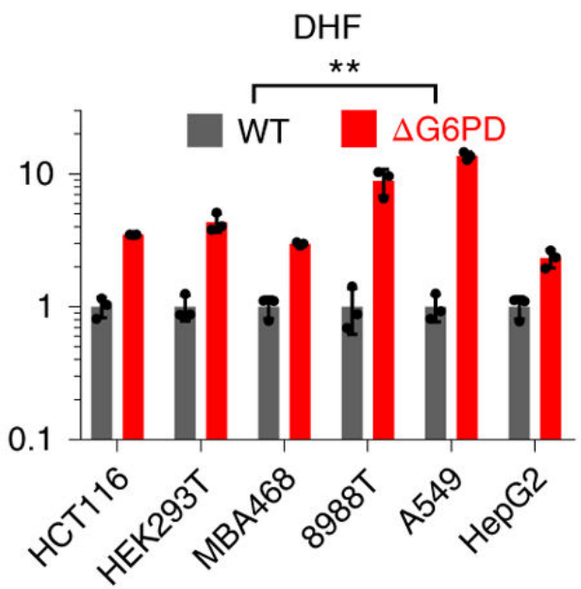
*Chen et al, **Nat Metab**, 2019*

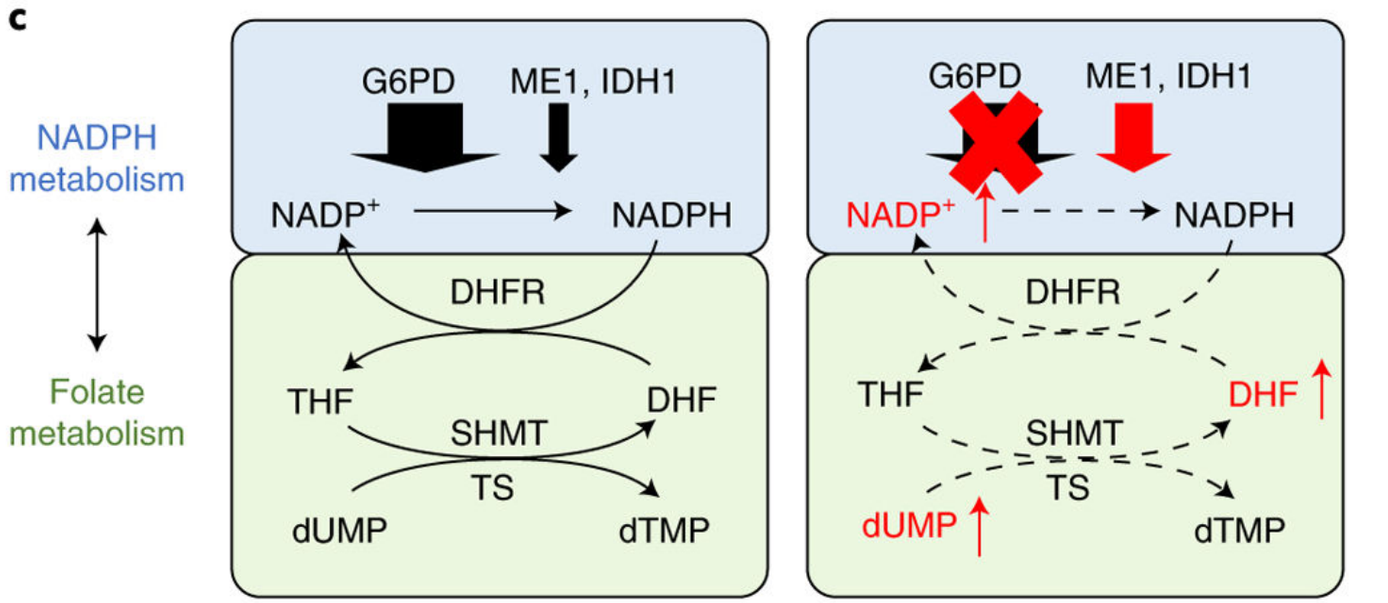






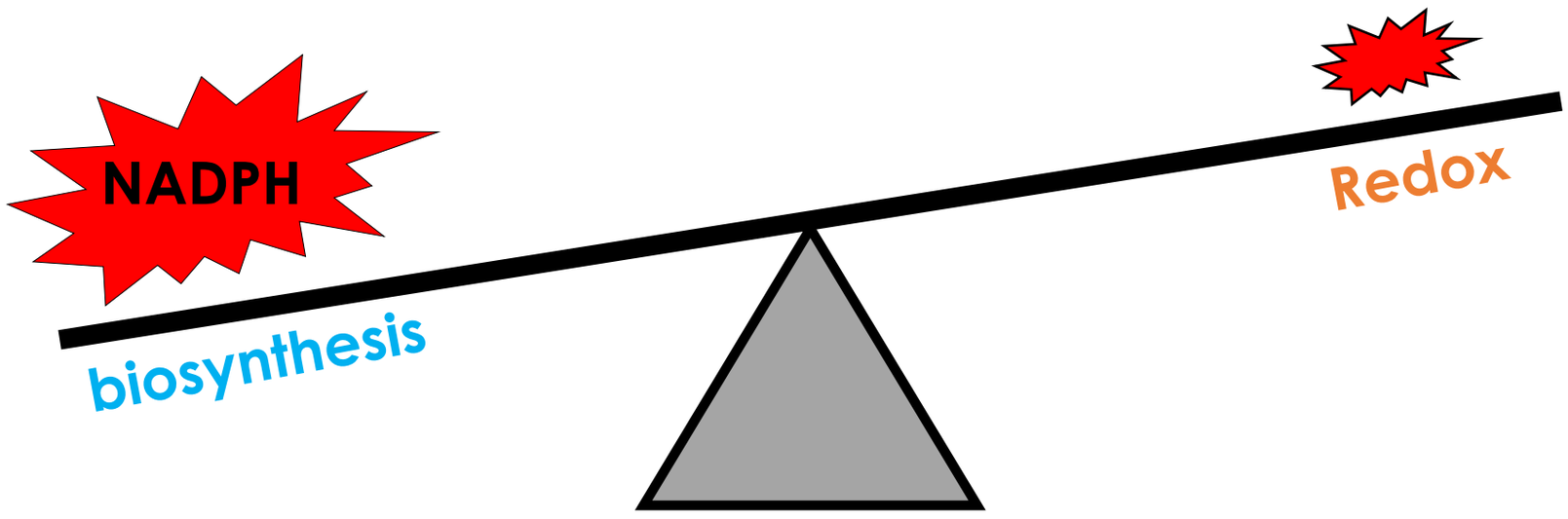






Chen et al, ***Nat Metab****, 2019*

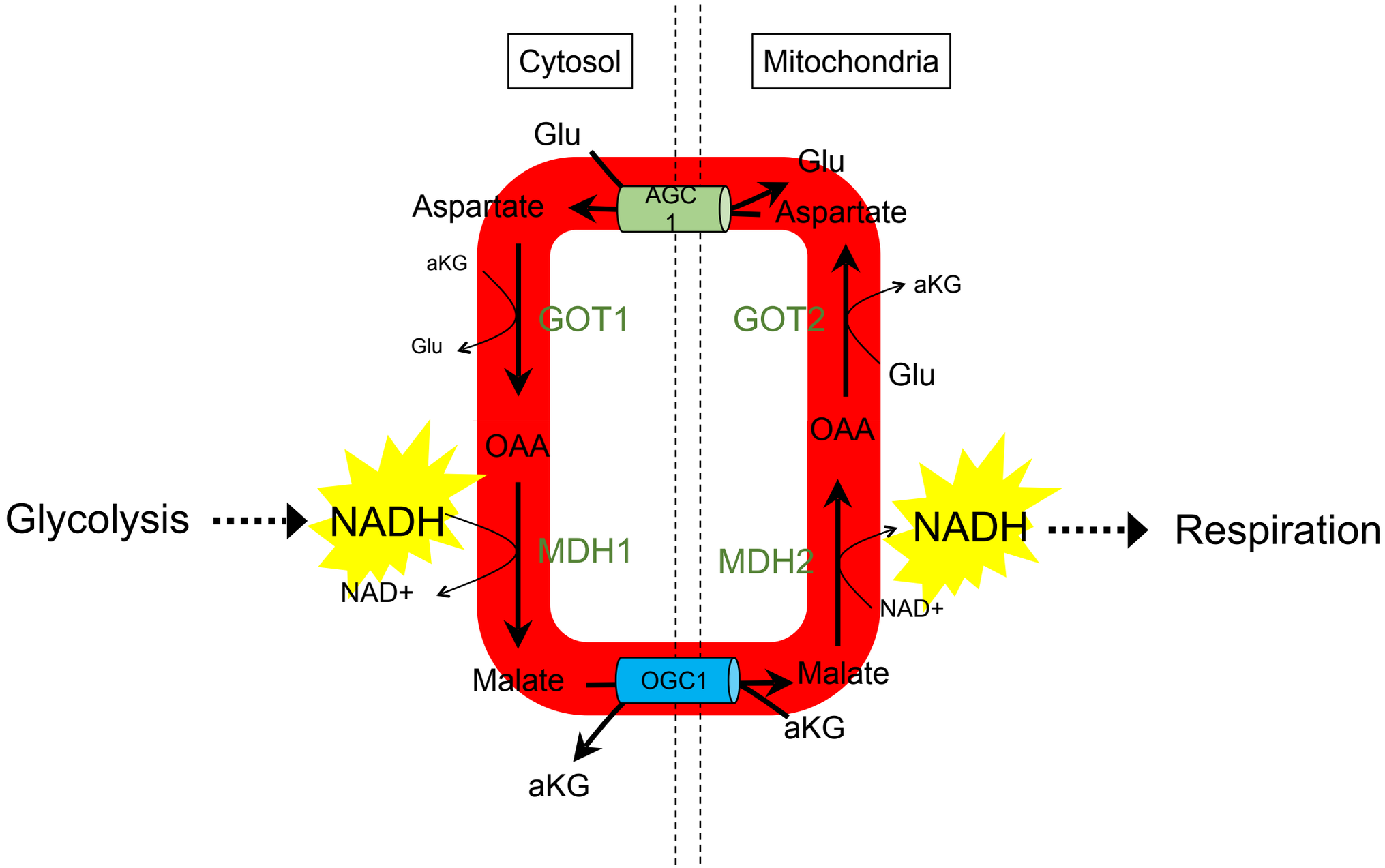
NADPH is Devoted to Support Growth…



…Opening Vulnerabilities in Redox Targeting

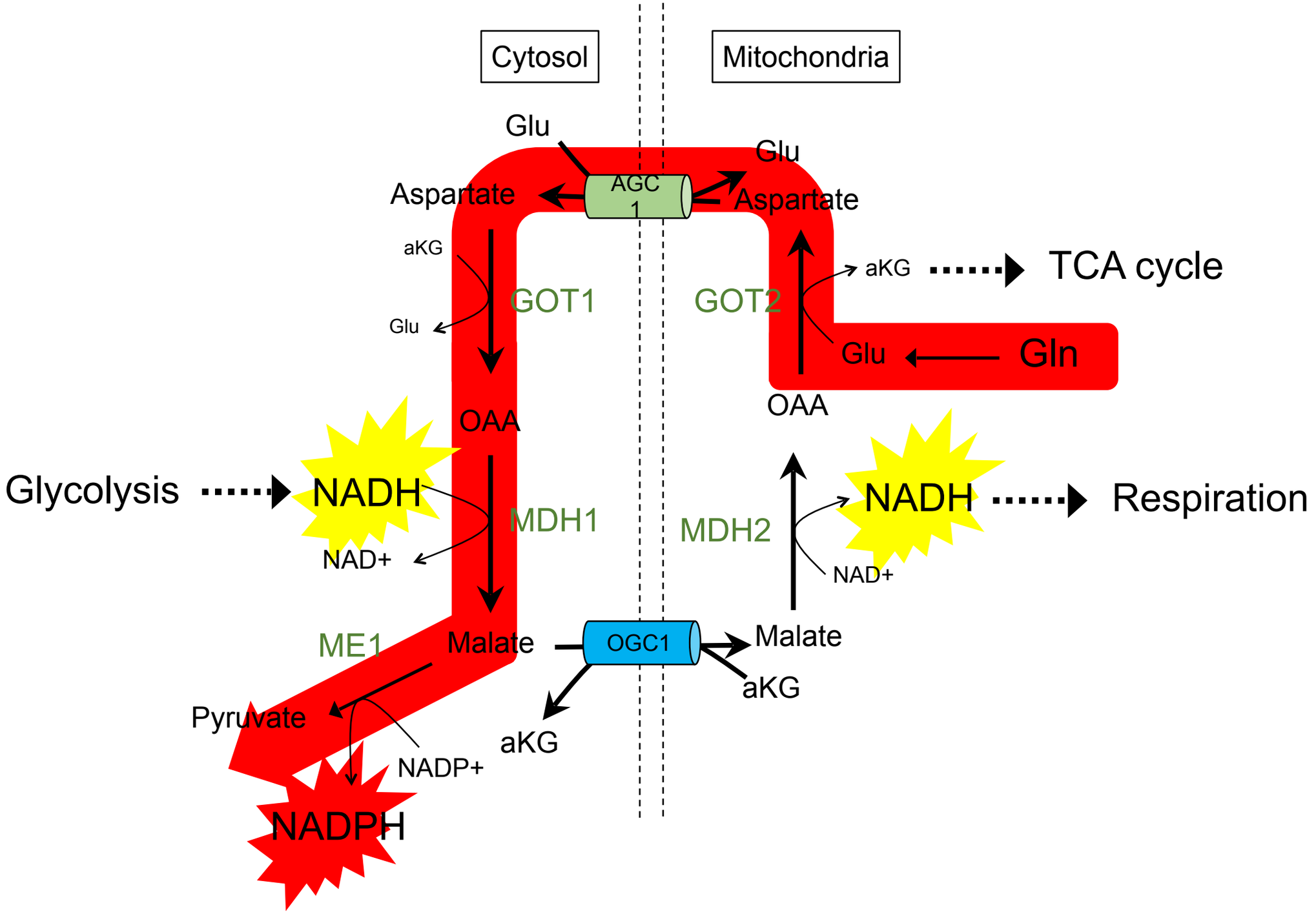
Lyssiotis CA, et al. ***Cell Cycle*** 2013

Energy Metabolism in Normal Cells



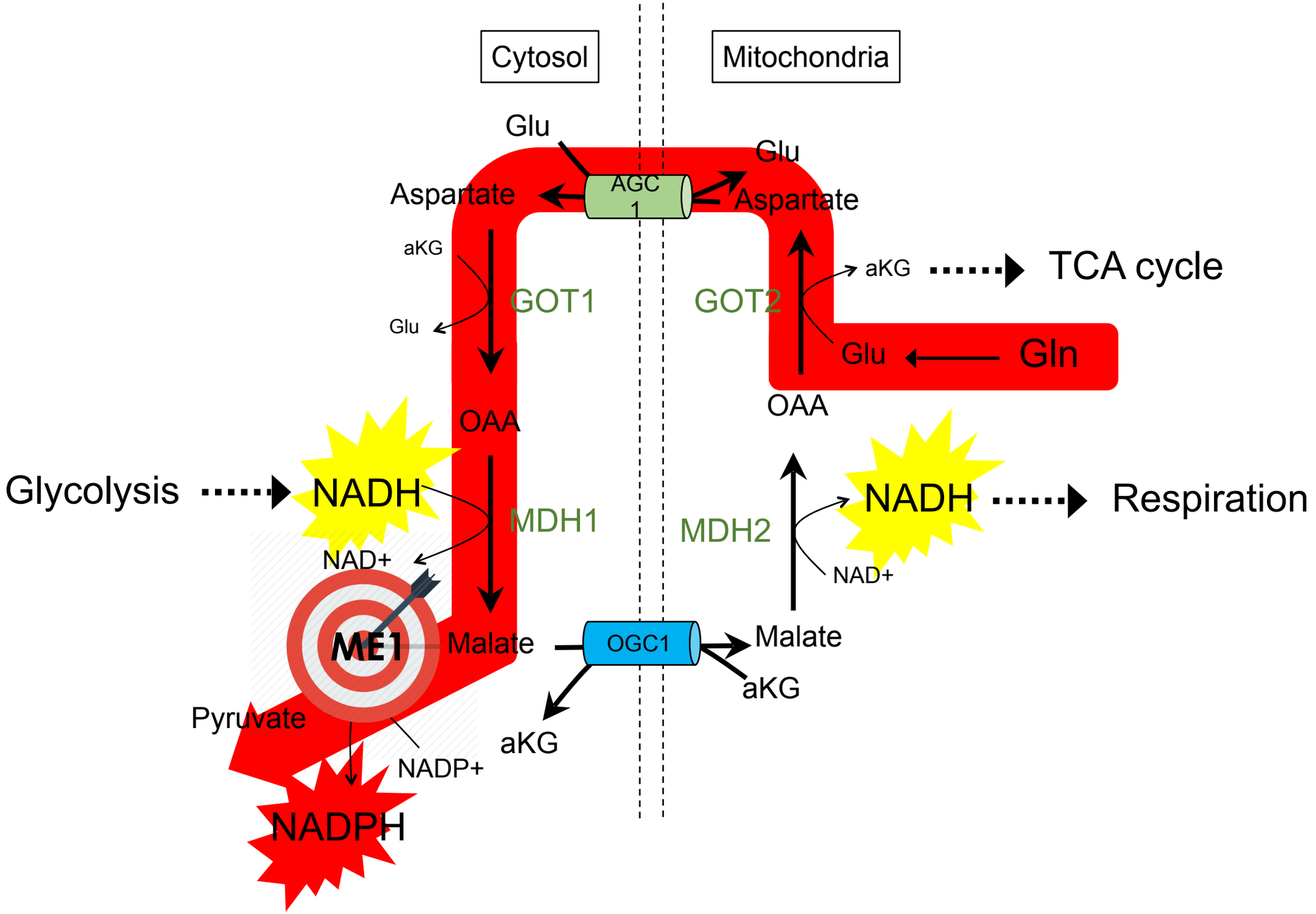
Lyssiotis CA, et al. ***Cell Cycle*** 2013

Oncogene (Kras)-mediated Rewiring of Pancreatic Cancer Metabolism



Son J, Lyssiotis CA, et al. ***Nature*** 2013

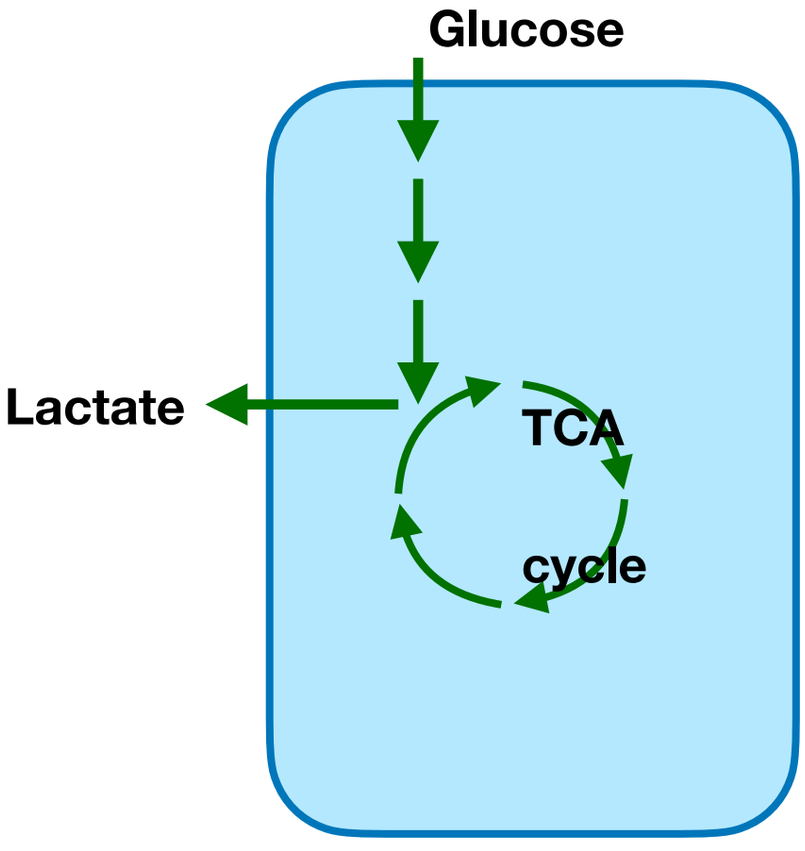
Oncogene (Kras)-mediated Rewiring of Pancreatic Cancer Metabolism



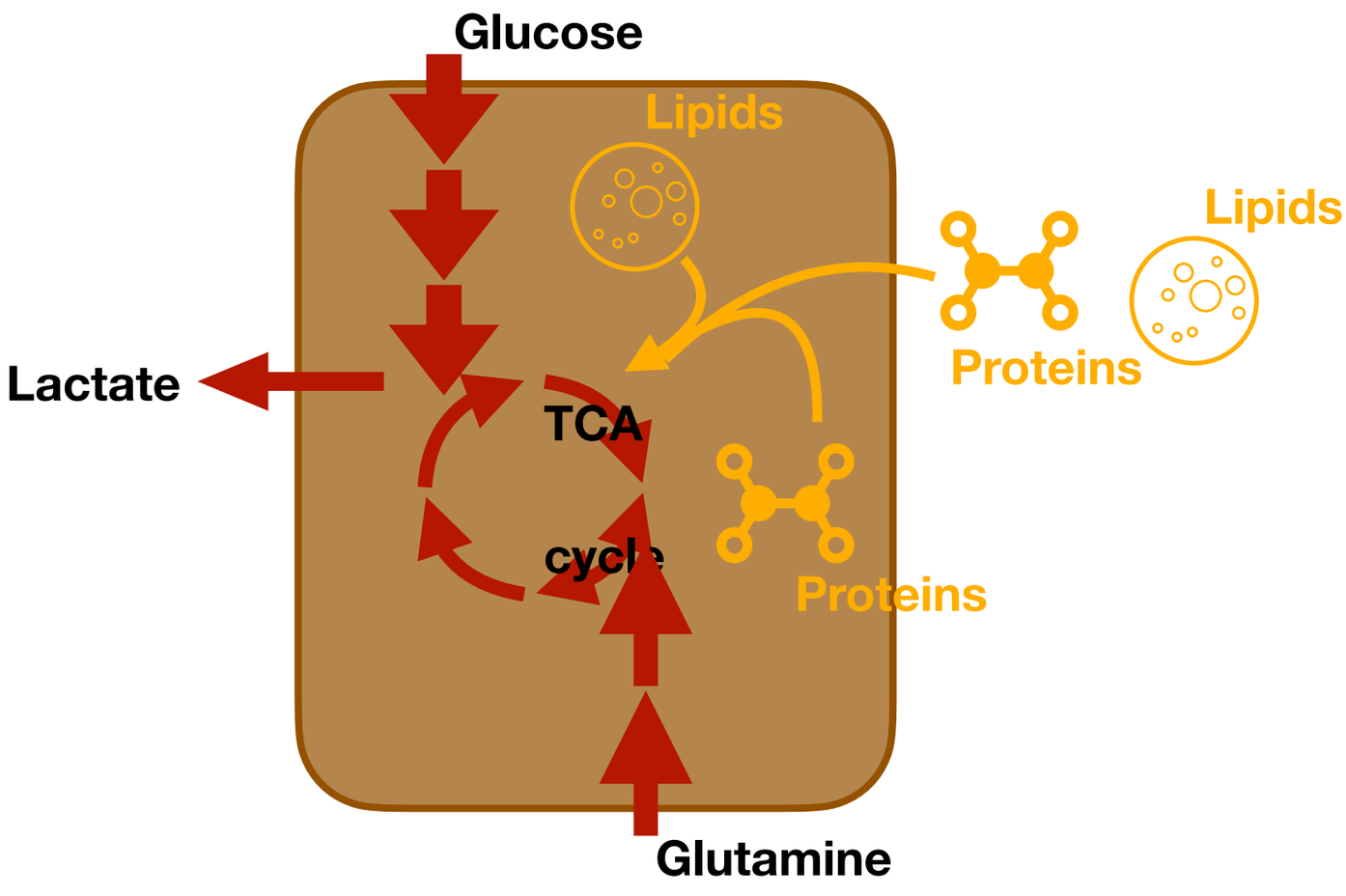
Son J, Lyssiotis CA, et al. ***Nature*** 2013

Proliferating cells enable anaplerosis from non-canonical carbon sources

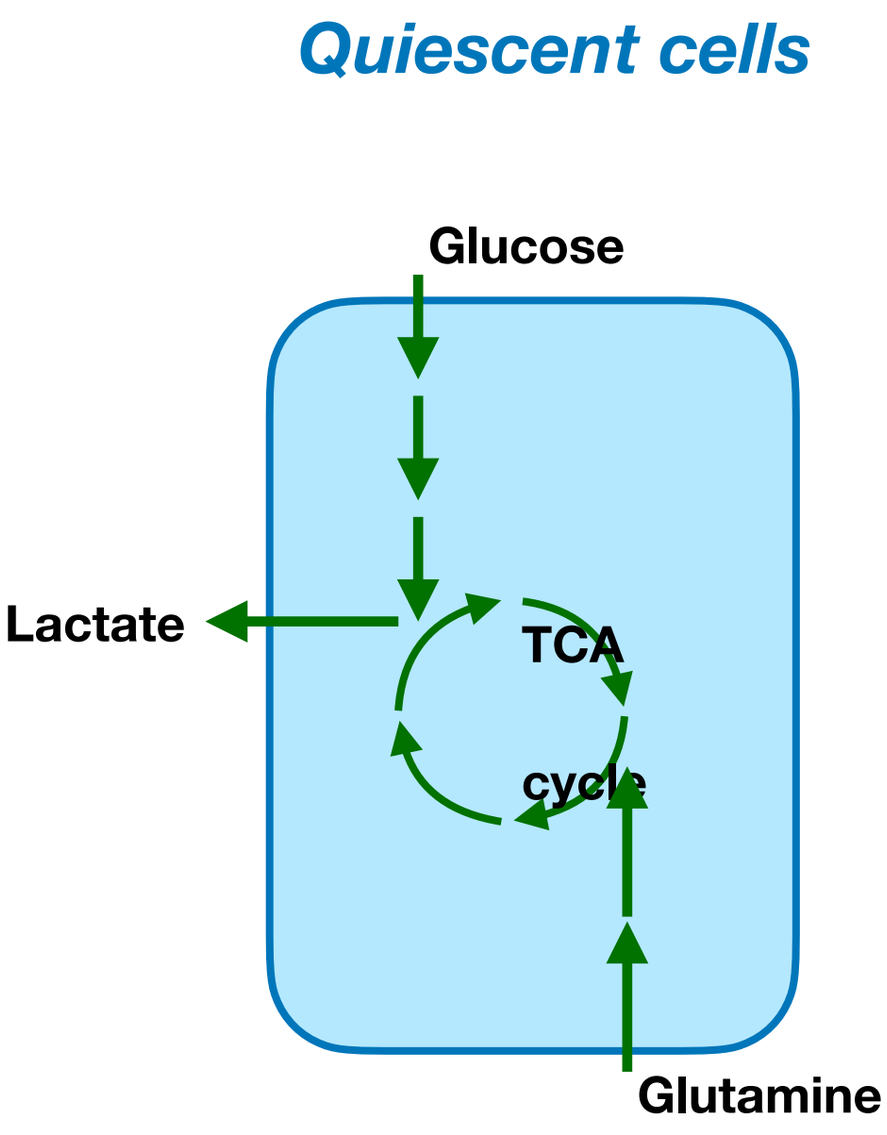
Quiescent cells

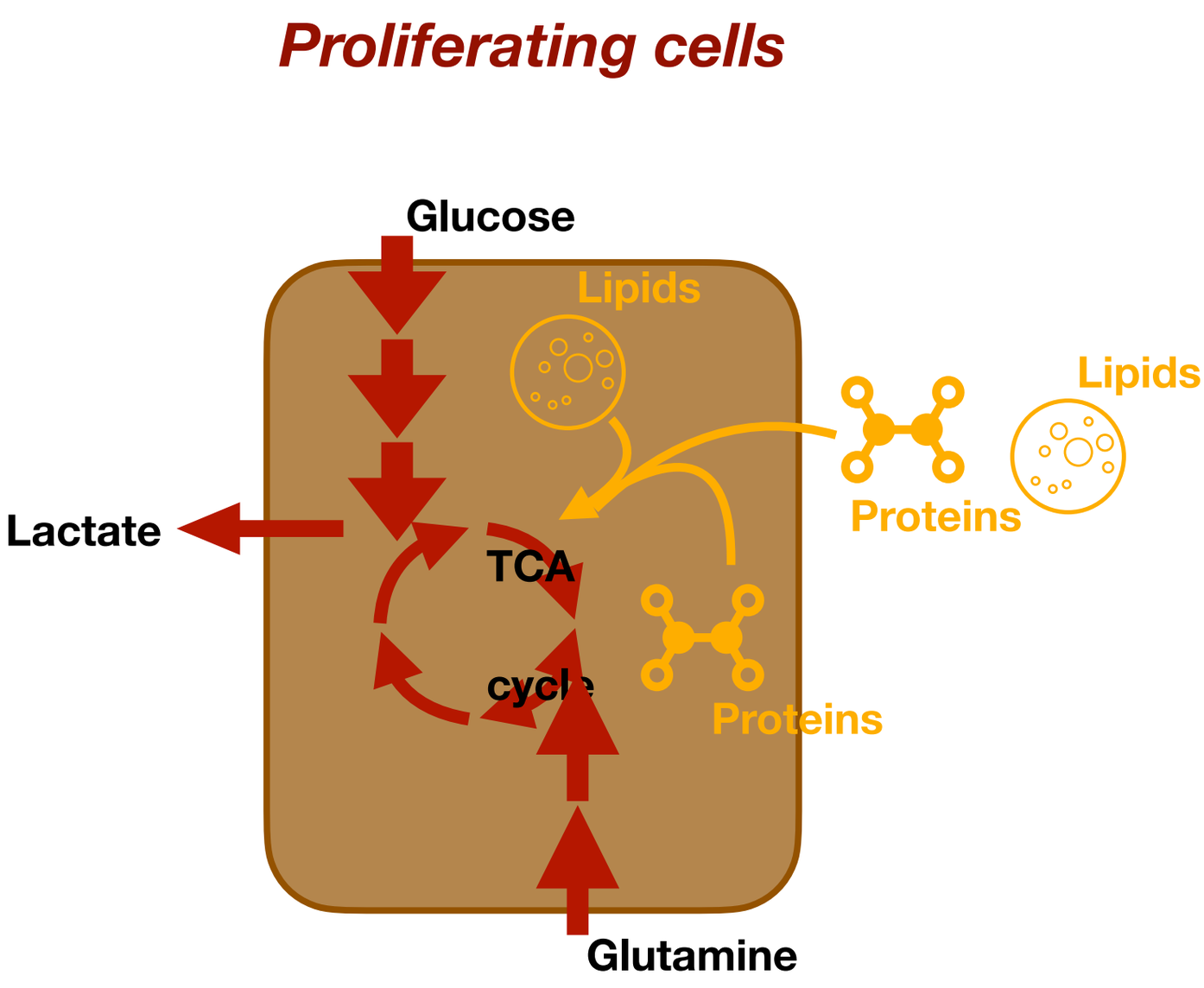


Proliferating cells

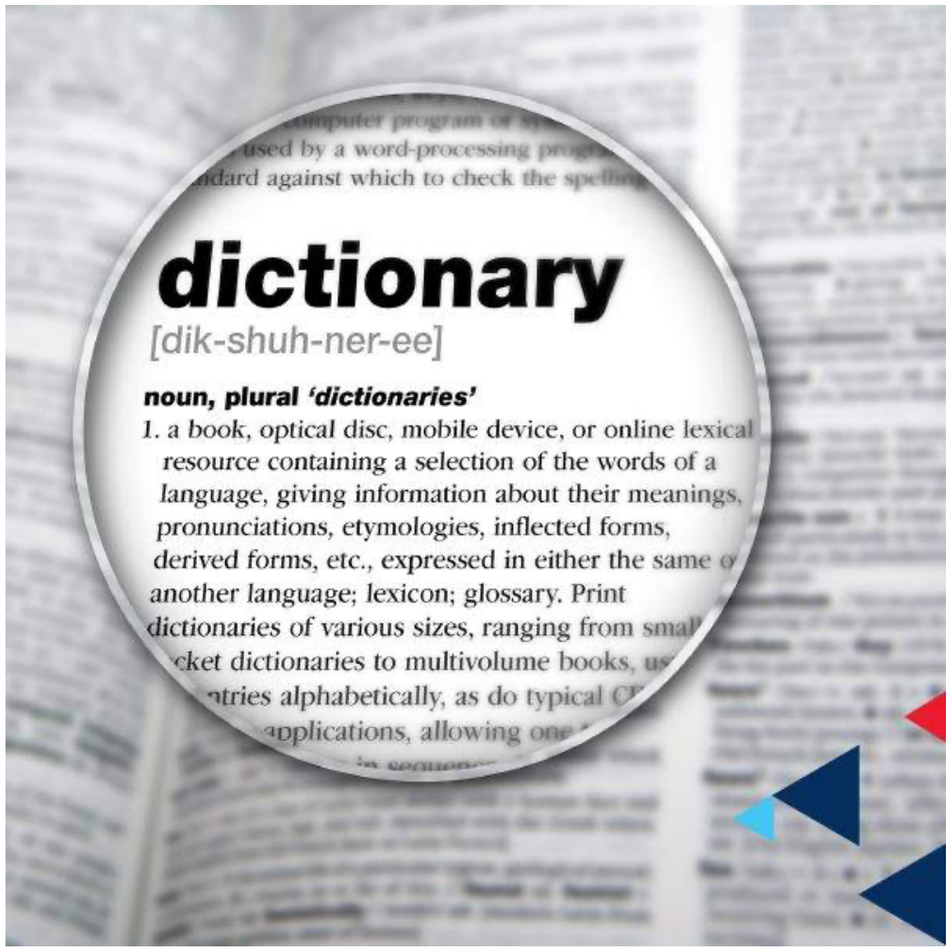


Proliferating cells enable anaplerosis from non-canonical carbon sources





ANAPLEROSIS vs CATAPLEROSIS

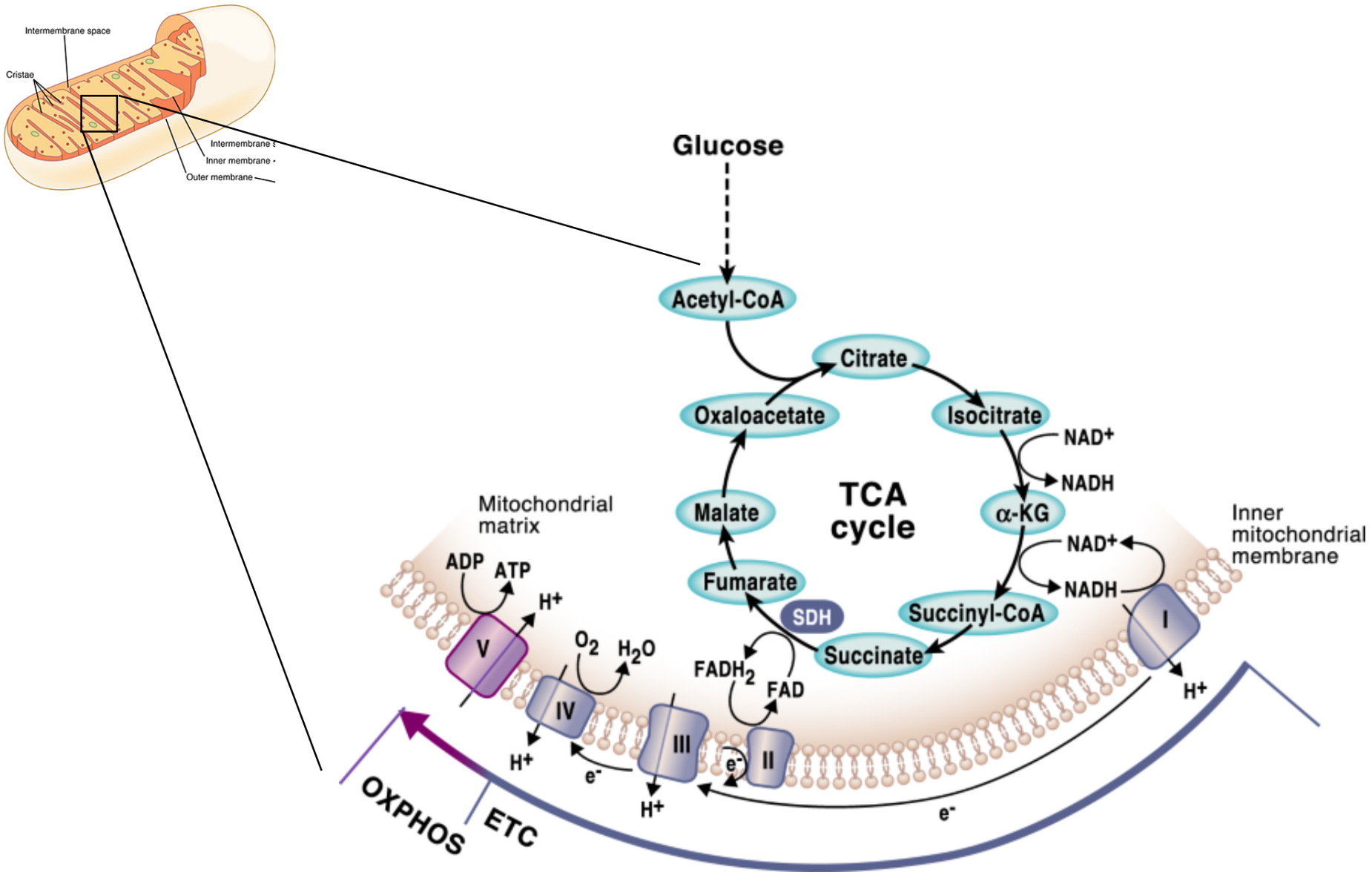


<u>Anaplerosis</u> is a series of enzymatic reactions in which metabolic intermediates enter the TCA cycle from the cytosol

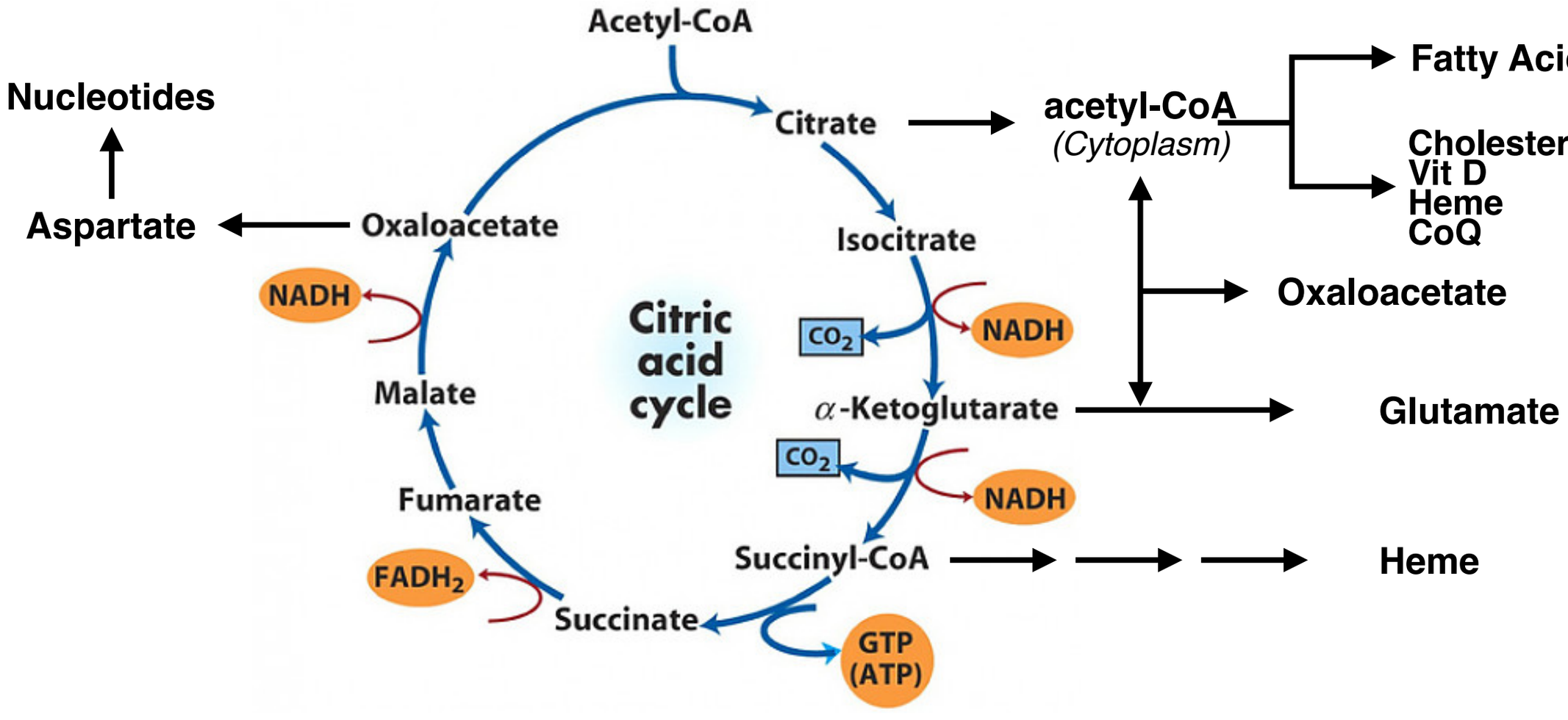
<u>Cataplerosis</u> is the opposite. A process where intermediates leave the TCA cycle (and mitochondria)

It implies if a C atom (CO_2) replenishes or not the TCA cycle

Mitochondria couple pyruvate oxidation, electron transport and oxidative phosphorylation

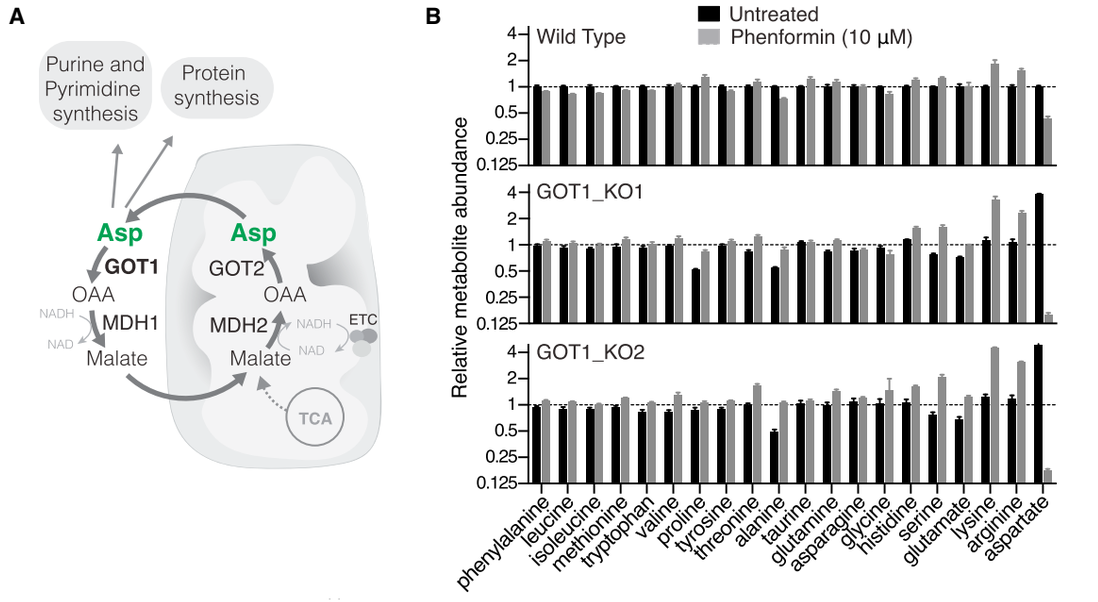


The TCA cycle at the crossroad of catabolism and anabolism



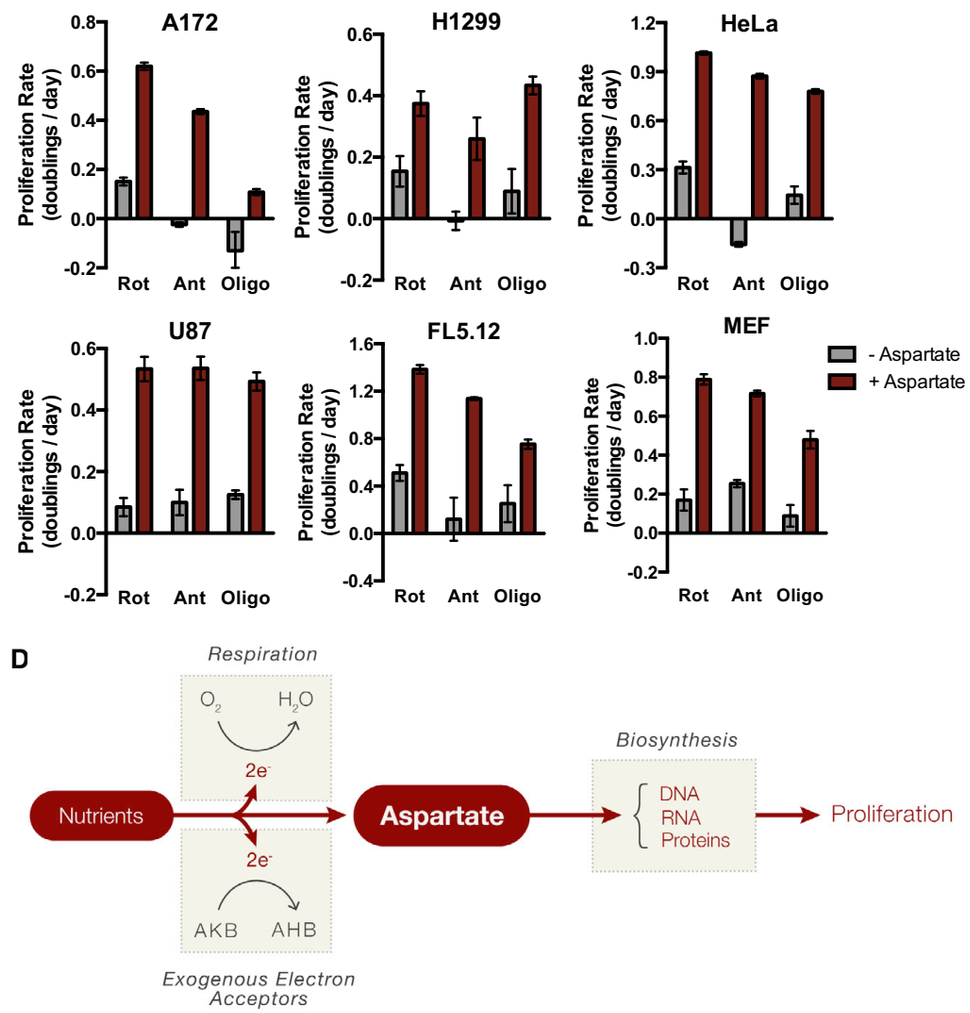
Cell

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



Cell

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



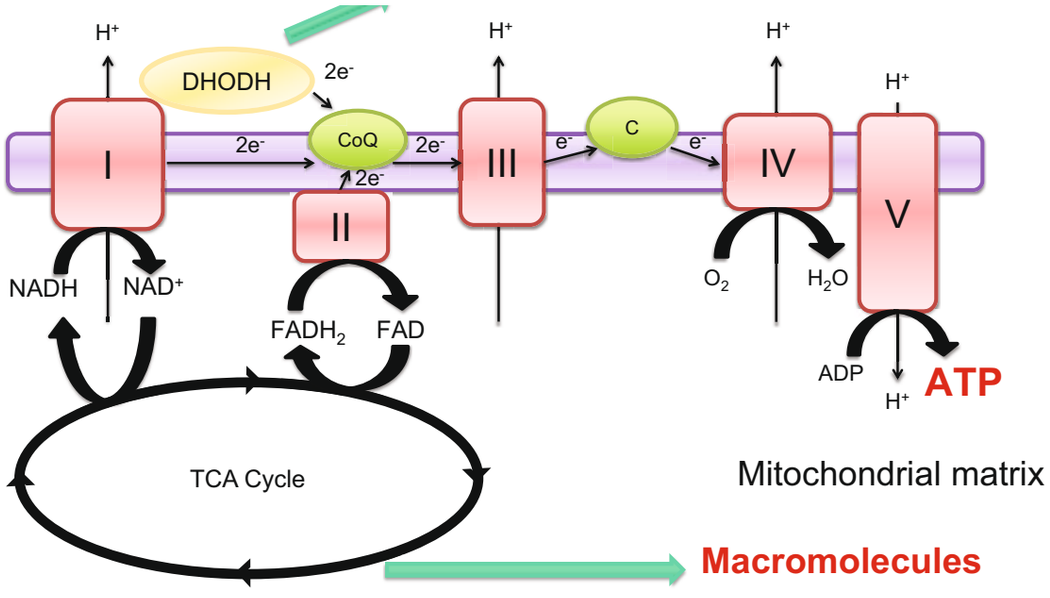
Aspartate is a precursor for nucleotide synthesis and is indispensable for cell proliferation. Moreover, the malate–aspartate shuttle plays a key role in redox balance, and a deficit in aspartate can lead to oxidative stress. It is now recognized that aspartate biosynthesis is largely governed by mitochondrial metabolism, including respiration and glutaminolysis in cancer cells.

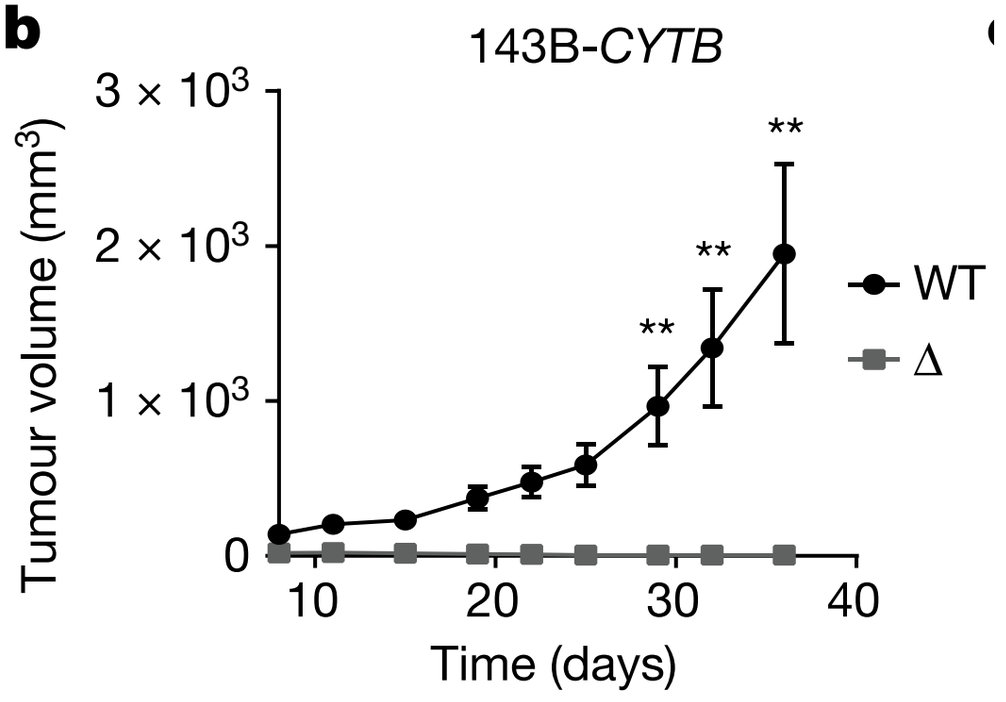
Birsoy et al, ***Cell****, 2015*
Sullivan et al, ***Cell****, 2015*

In vitro

In vivo??

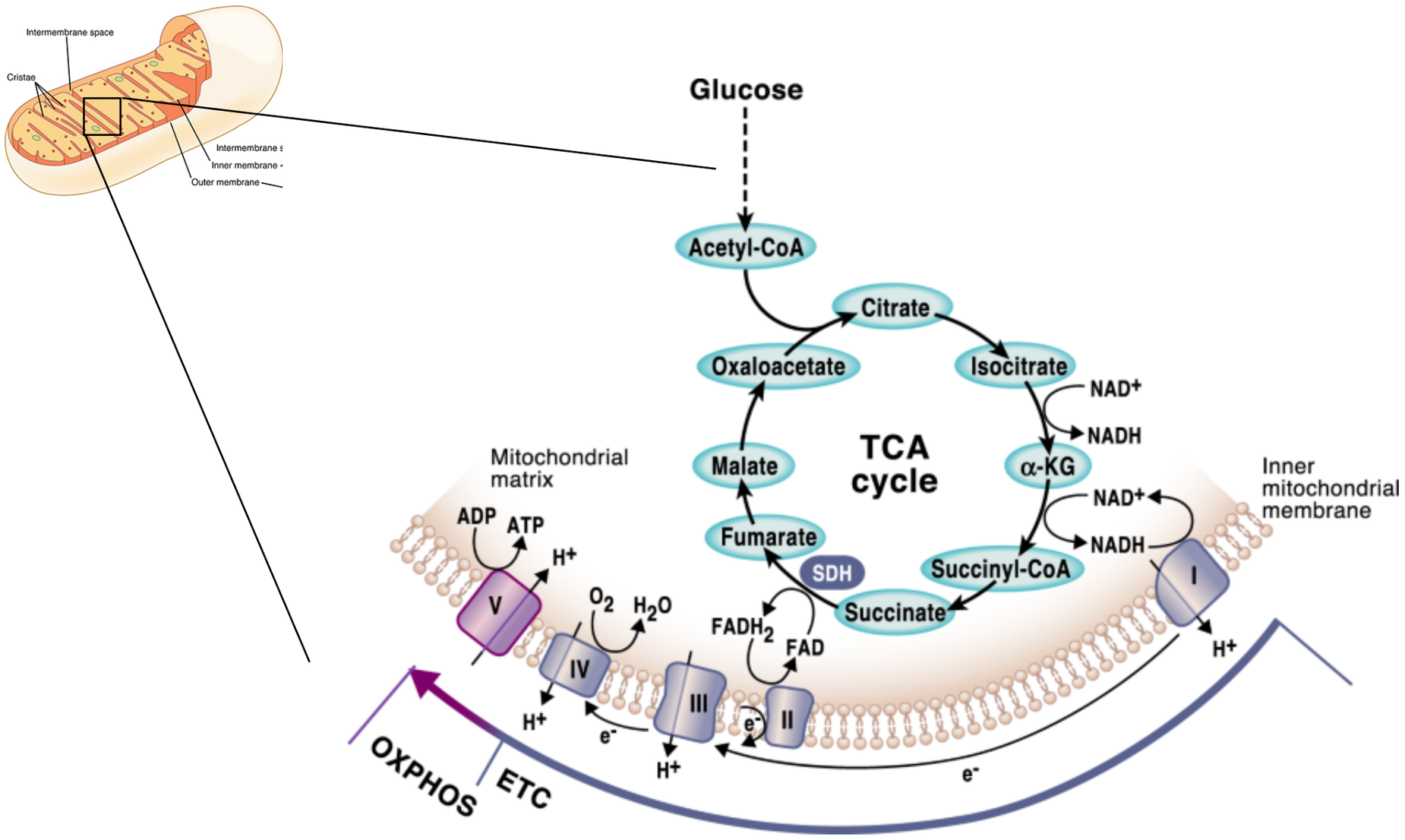
Targeting mitochondrial genes impairs tumor growth



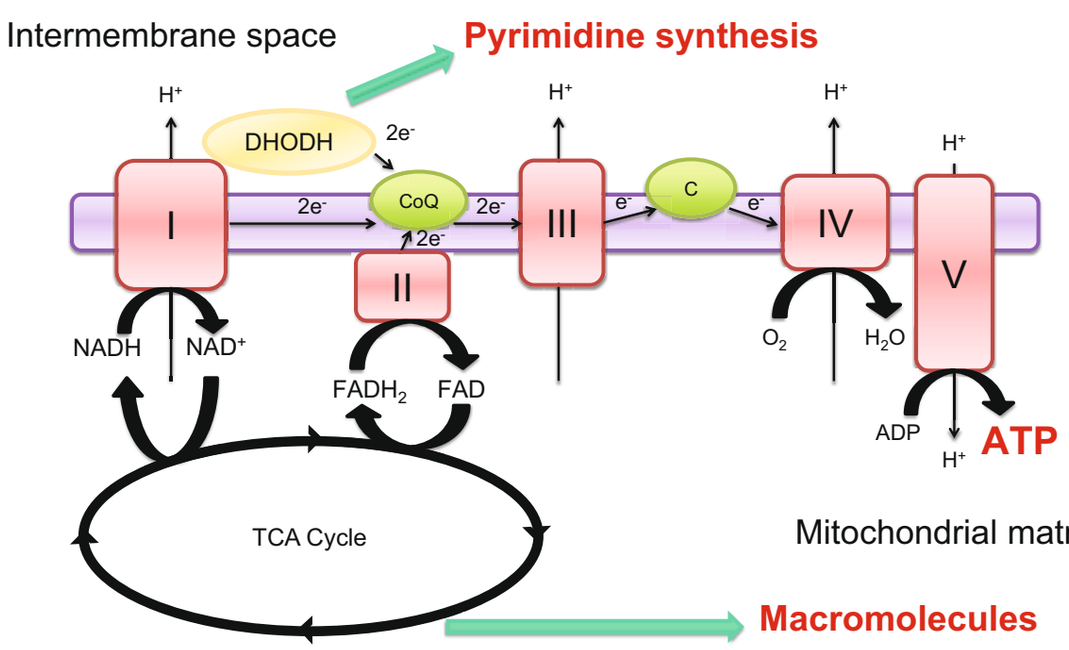


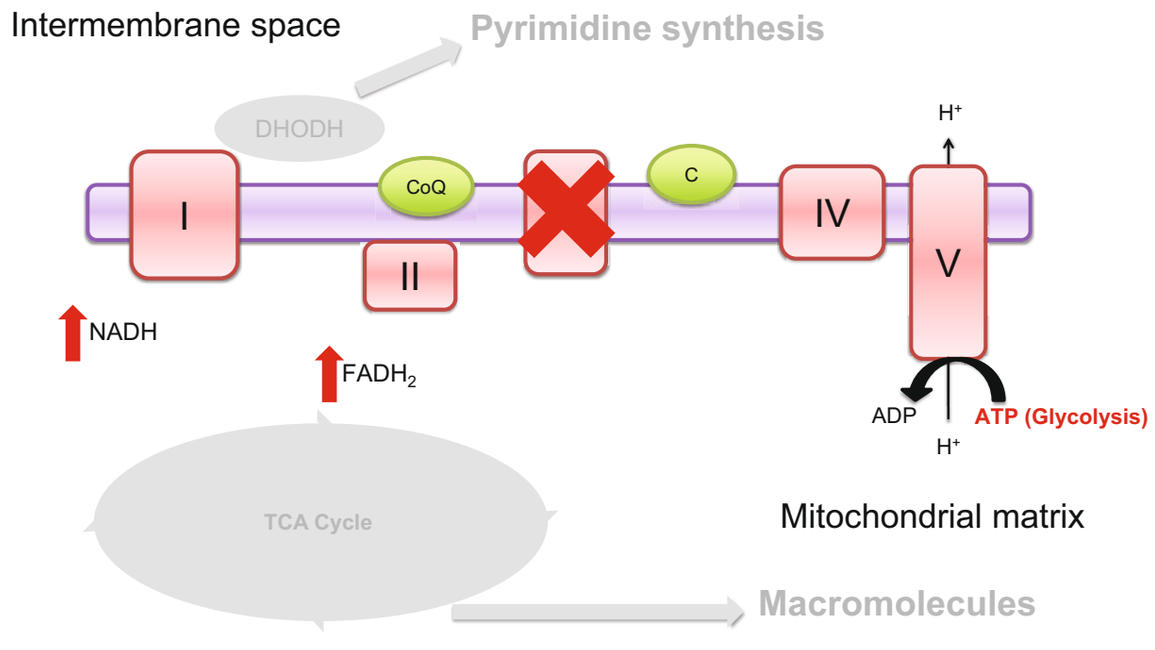
Martinez-Reyes et al, ***Nature****, 2020*

Mitochondria couple pyruvate oxidation, electron transport and oxidative phosphorylation



Targeting mitochondrial genes impairs tumor growth



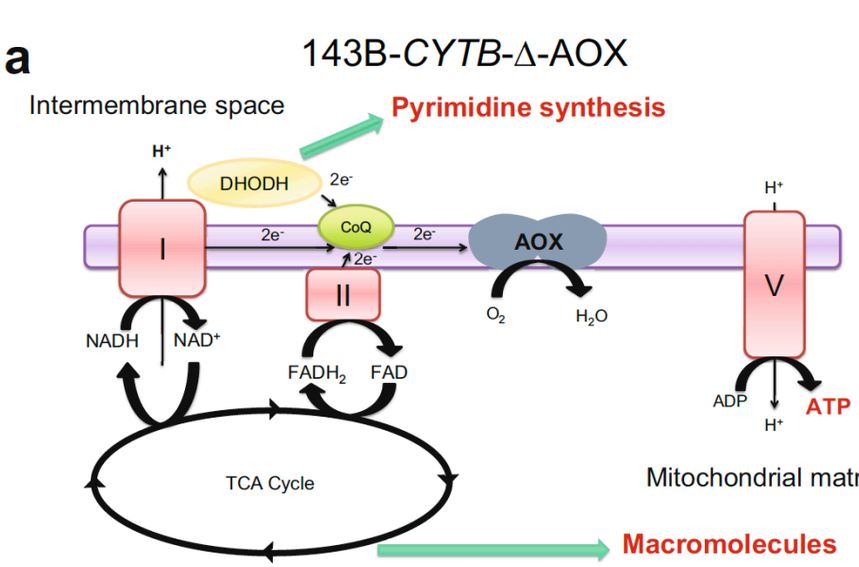


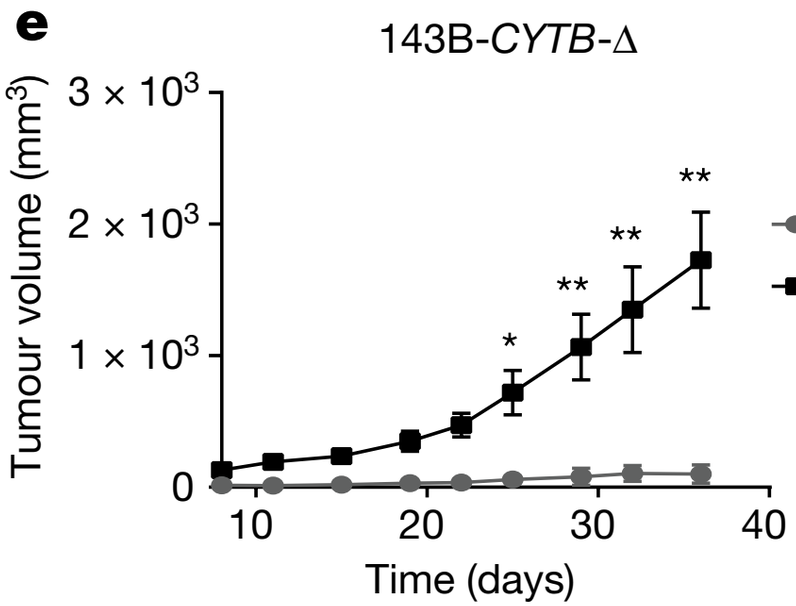
Complex III deficiency suppresses:

- *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

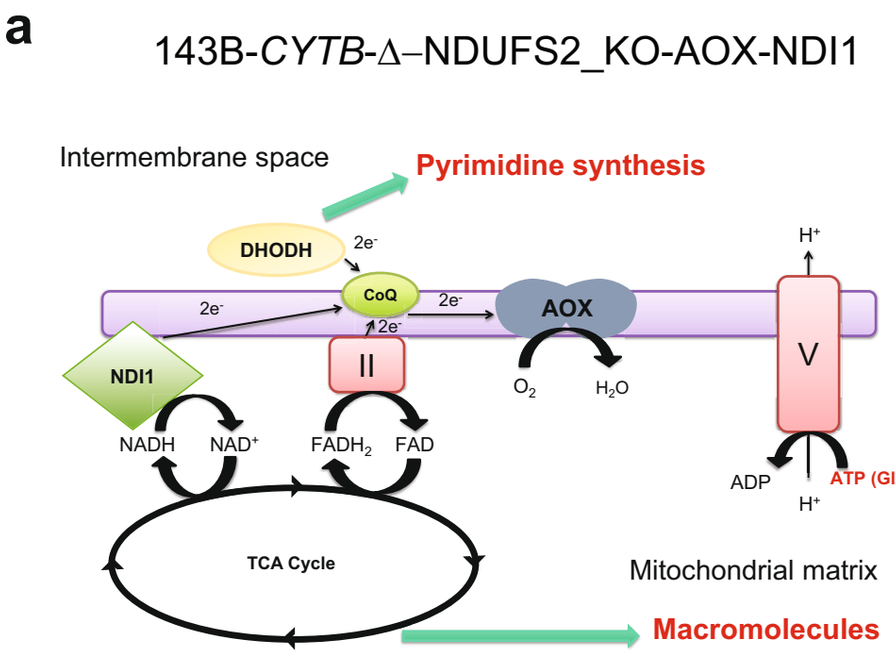


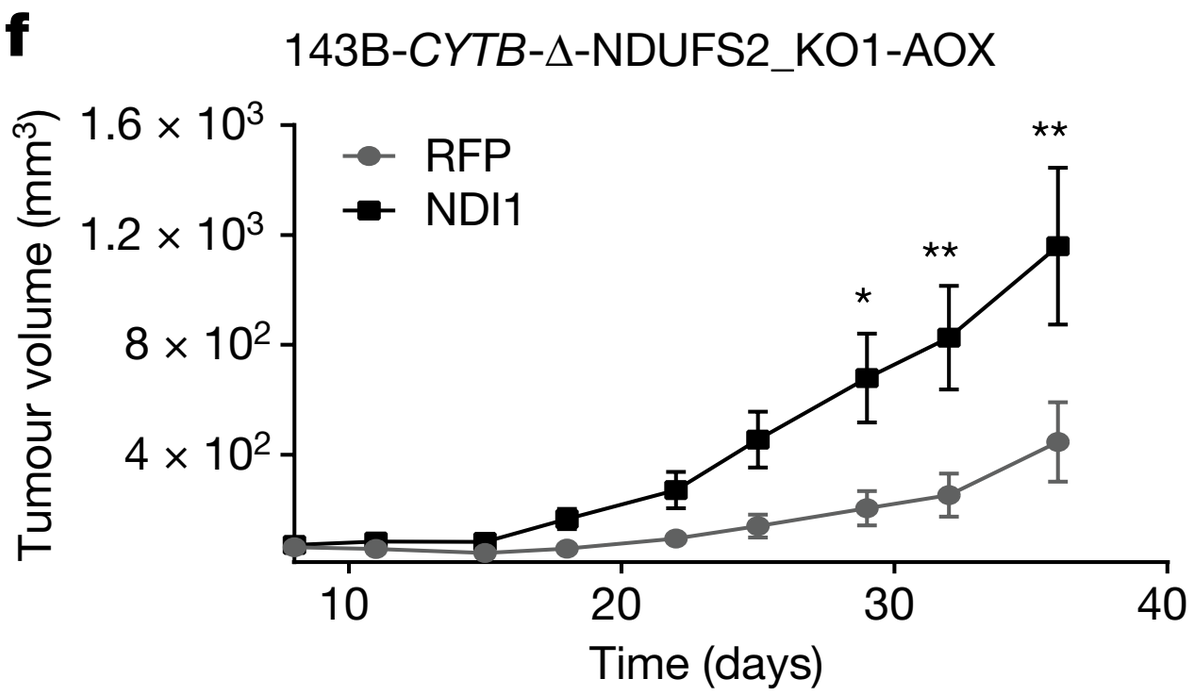


AOX expression (in C3-KO tumors) re-establish fully functional C1-C2 activity, only modestly rescues proton pumping, ATP synthesis

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

Mitochondrial ATP production is NOT essential for tumor growth





CoQ oxidation and TCA cycle are most important for tumor growth

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

CONCLUSIONS (3)

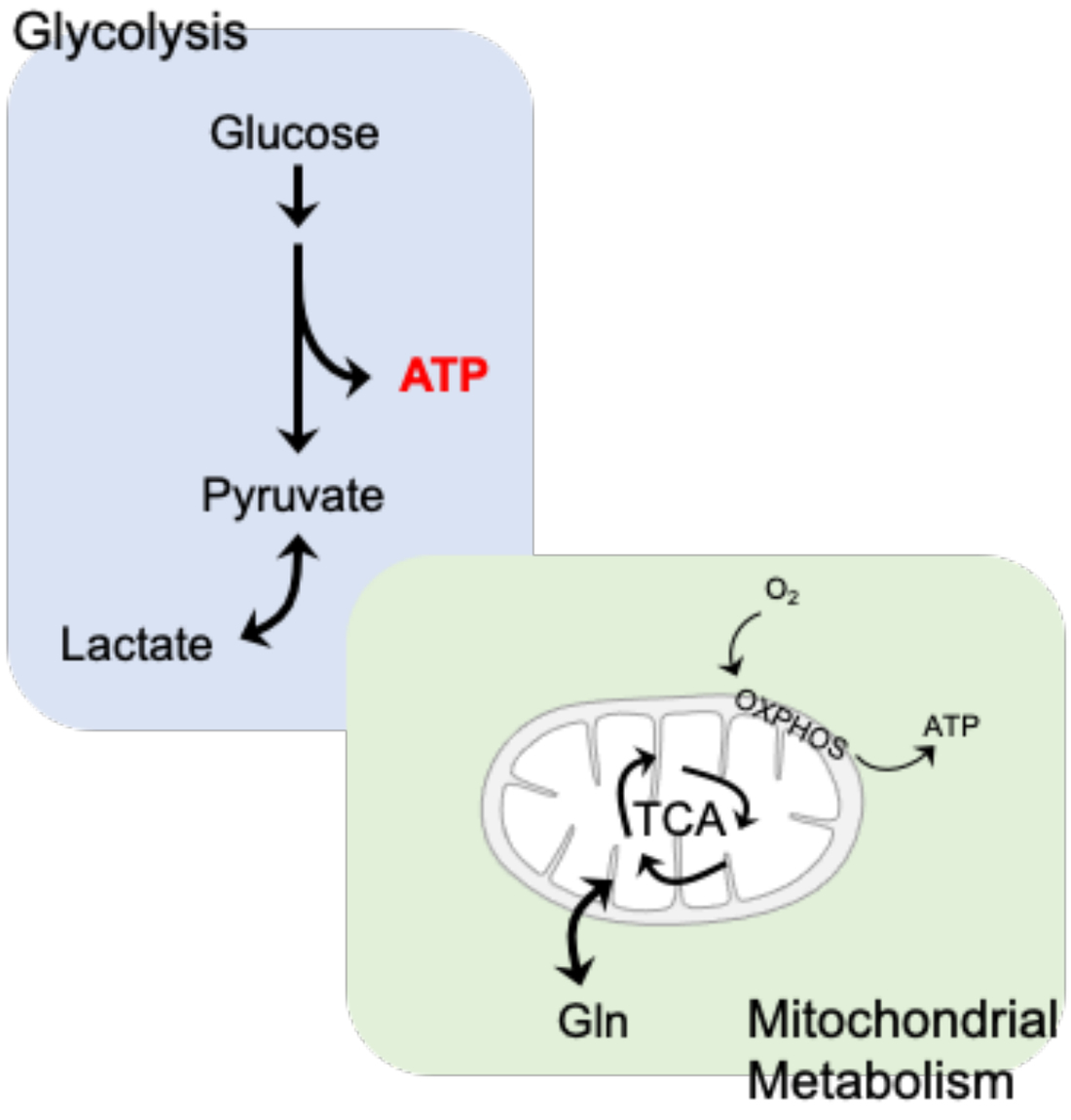
Proliferating cells have distinct metabolic demands

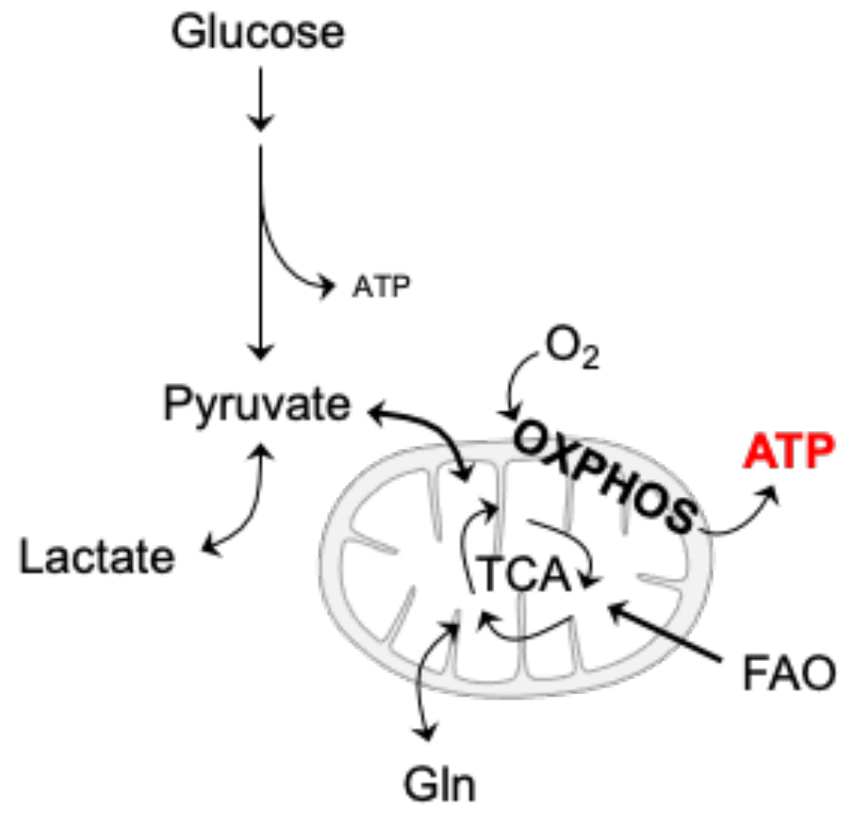
Metabolism influences proliferation

Critical: lipids and nucleotides. Biosynthesis requires NADPH.

Despite being highly glycolytic, proliferating cells need mitochondria

In Vitro and *In Vivo* Metabolism





Critical differences in metabolism observed *in vitro* and *in vivo*

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AKA: metabolism is context-dependent
AKA-bis: studying metabolism is challenging

Critical differences in metabolism observed *in vitro* and *in vivo*

Cell culture (plates)

Animals

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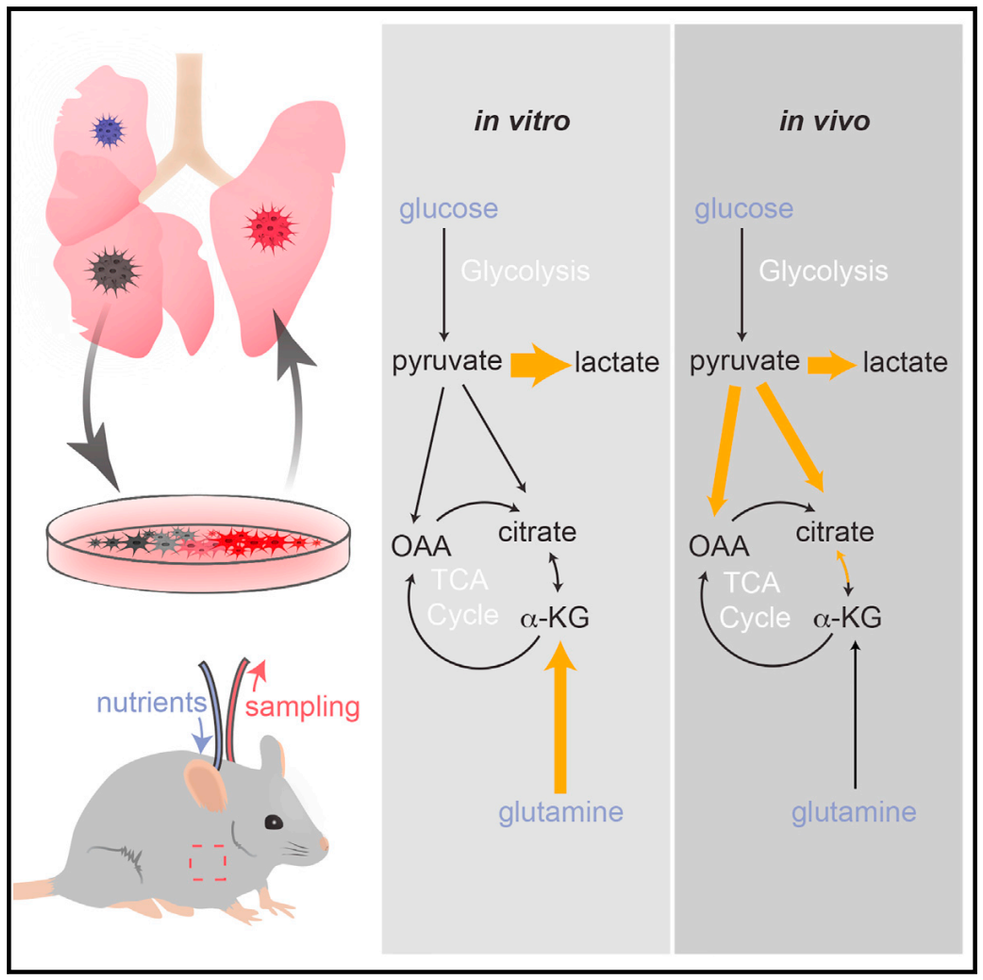
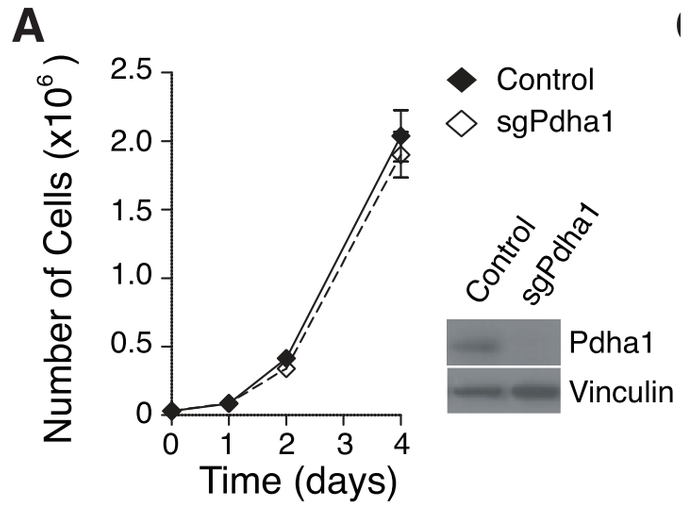
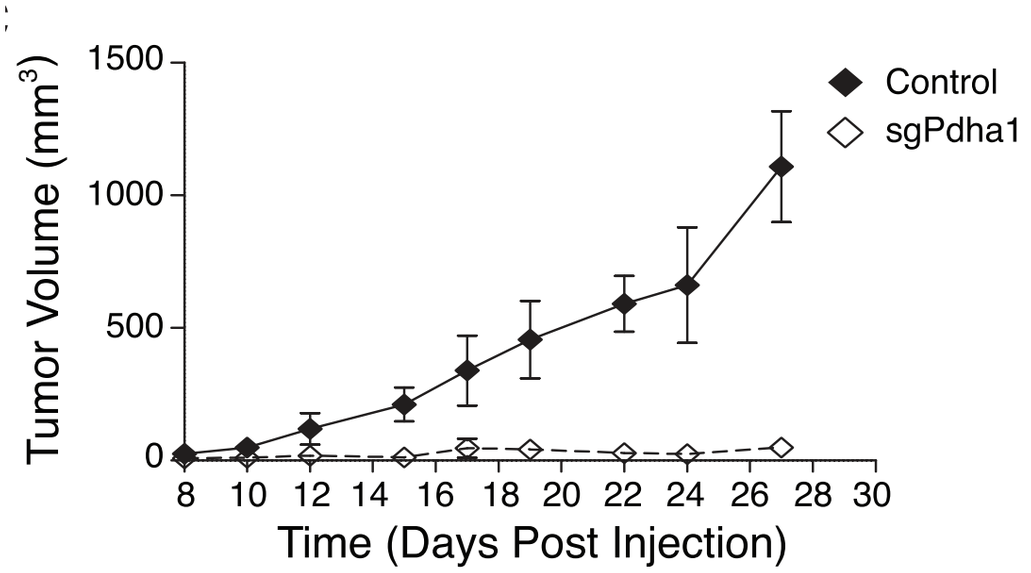






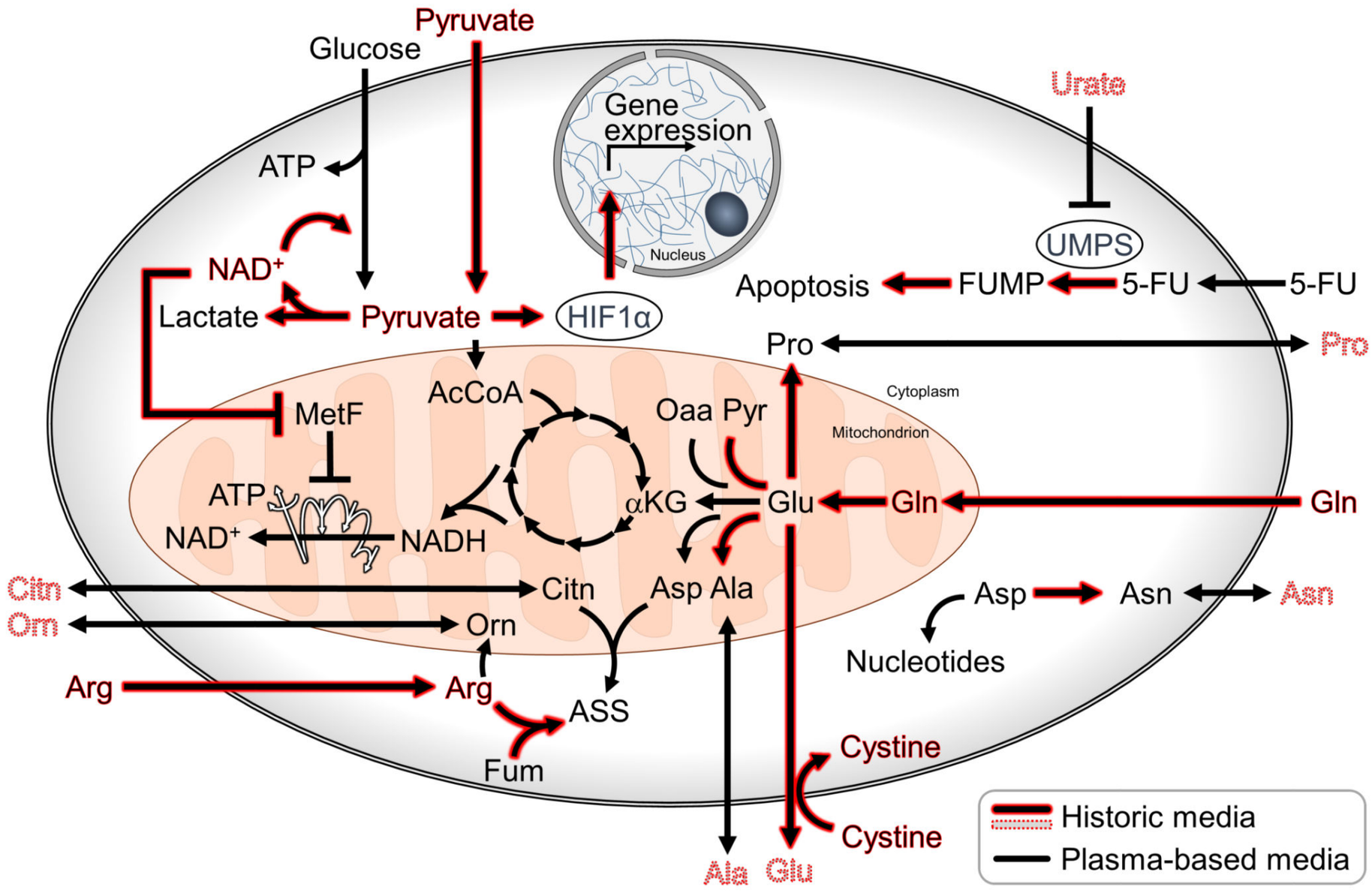
Davidson et al, ***Cell Metab****, 2016*

Cell culture media composition is extremely different from plasma

	Human plasma	Plasmax™	HPLM	MEM	IMDM	DMEM	DMEM/F-12	F-12	RPMI 1640
Proteinogenic Amino Acids									
L-Alanine	230 - 510 [13]	510	430	NA	281	NA	50	100	NA
L-Arginine	13 - 64 [13]	64	110	597	399	398	699	1000	1149
L-Asparagine	45-130 [13]	41	50	NA	189	NA	50	100	379
L-Aspartic acid	0 - 6 [13]	6	20	NA	226	NA	50	100	150
L-Cysteine	23.2 - 43.8 [14]	33	40	NA	NA	NA	100	200	NA
L-Glutamate	32-140 [13]	98	80	NA	510	NA	50	100	136
L-Glutamine	420-720 [13]	650	550	2000	4000	4000	2500	1000	2055
Glycine	170 - 330 [13]	330	300	NA	400	400	250	100	133
L-Histidine	26 - 120 [13]	120	110	200	200	200	150	100	97
L-Isoleucine	42 - 100 [13]	140	70	397	802	802	416	31	382
L-Leucine	66 - 170 [13]	170	160	397	802	802	451	100	382
L-Lysine	150 - 220 [13]	220	200	399	798	798	499	199	219
L-Methionine	16 - 30 [13]	30	30	101	201	201	116	30	101
L-Phenylalanine	41 - 68 [13]	68	80	194	400	400	215	30	91
L-Proline	110-360 [13]	360	200	NA	348	NA	150	300	174
L-Serine	56 - 140 [13]	140	150	NA	400	400	250	100	286
L-Threonine	92 - 240 [13]	240	140	403	798	798	449	100	168
L-Tryptophan	44.8 - 64.2 [14]	78	60	49	78	78	44	10	25
L-Tyrosine	45 - 74 [13]	74	80	199	462	399	214	30	111
L-Valine	150 - 310 [13]	230	220	393	803	803	452	100	171
Non-proteinogenic Amino Acids									
α-Aminobutyrate	15 - 41 [13]	41	20	NA	NA	NA	NA	NA	NA
L-Citrulline	16 - 55 [13]	55	40	NA	NA	NA	NA	NA	NA
L-Cystine	30 - 65 [13]	65	100	99	292	201.3	100	NA	207.7
L-Homocysteine	6.1 - 12.1 [15]	9	NA	NA	NA	NA	NA	NA	NA
4-Hydroxy-L-proline	3 - 23 [16]	13	20	NA	NA	NA	NA	NA	152.7
L-Ornitine	27 - 80 [13]	80	70	NA	NA	NA	NA	NA	NA
L-Pyroglutamate	12.2 - 15.3 [17]	20	NA	NA	NA	NA	NA	NA	NA

*Ackermann & Tardito, **Trends in Cancer**, 2019*

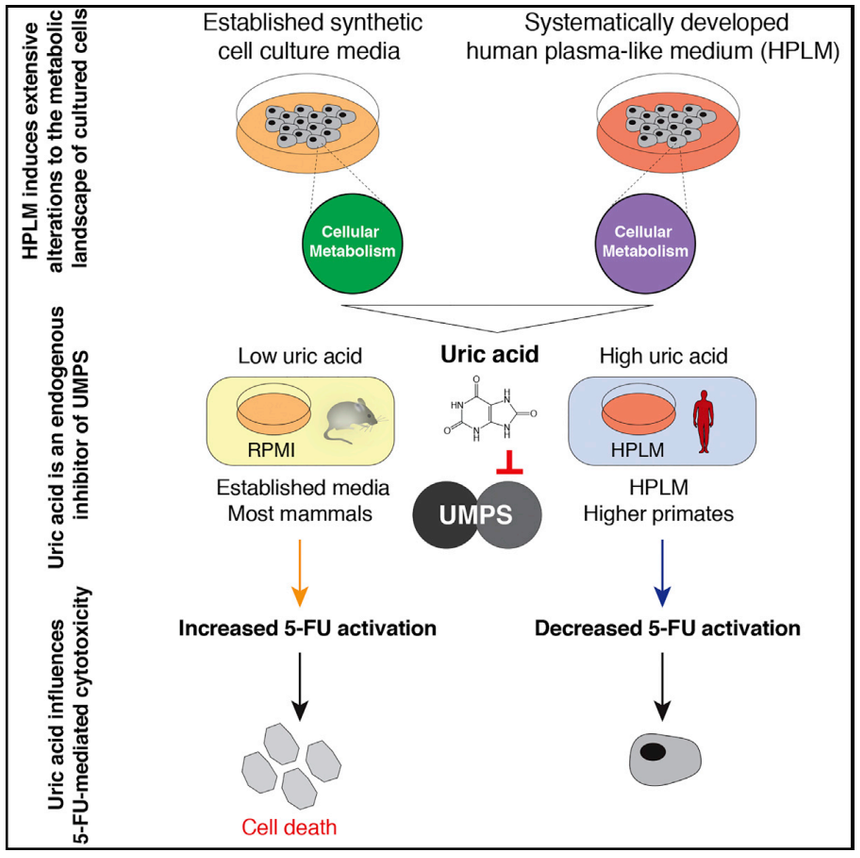
Cell culture media composition is extremely different from plasma

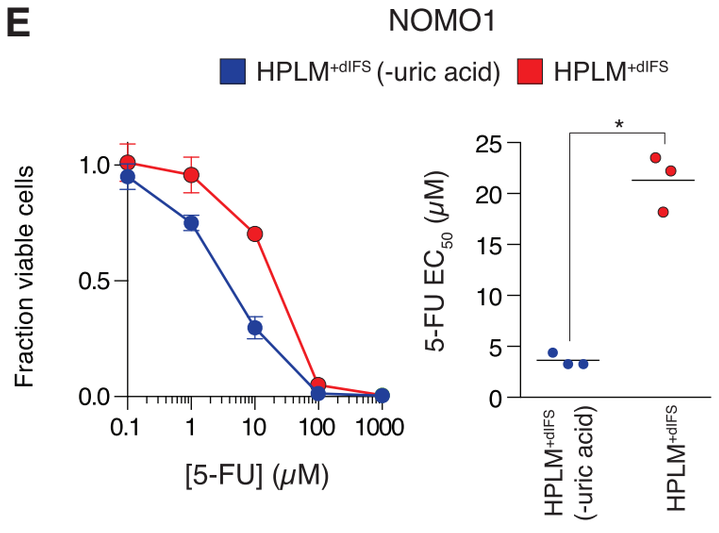


Ackermann & Tardito, ***Trends in Cancer****, 2019*

Physiologic Medium Rewires Cellular Metabolism and Reveals Uric Acid as an Endogenous Inhibitor of UMP Synthase

Jason R. Cantor,[1,2,3,4] Monther Abu-Remaileh,[1,2,3,4] Naama Kanarek,[1,2,3,4] Elizaveta Freinkman,[1] Xin Gao,[1,5] Abner Louissaint, Jr.,[6] Caroline A. Lewis,[1] and David M. Sabatini[1,2,3,4,7,*]





*Cantor et al, **Cell**, 2017*

Improving the metabolic fidelity of cancer models with a physiological cell culture medium

Johan Vande Voorde[1], Tobias Ackermann[1], Nadja Pfetzer[1], David Sumpton[1], Gillian Mackay[1], Gabriela Kalna[1], Colin Nixon[1], Karen Blyth[1,2], Eyal Gottlieb[1,3], Saverio Tardito[1,2]*

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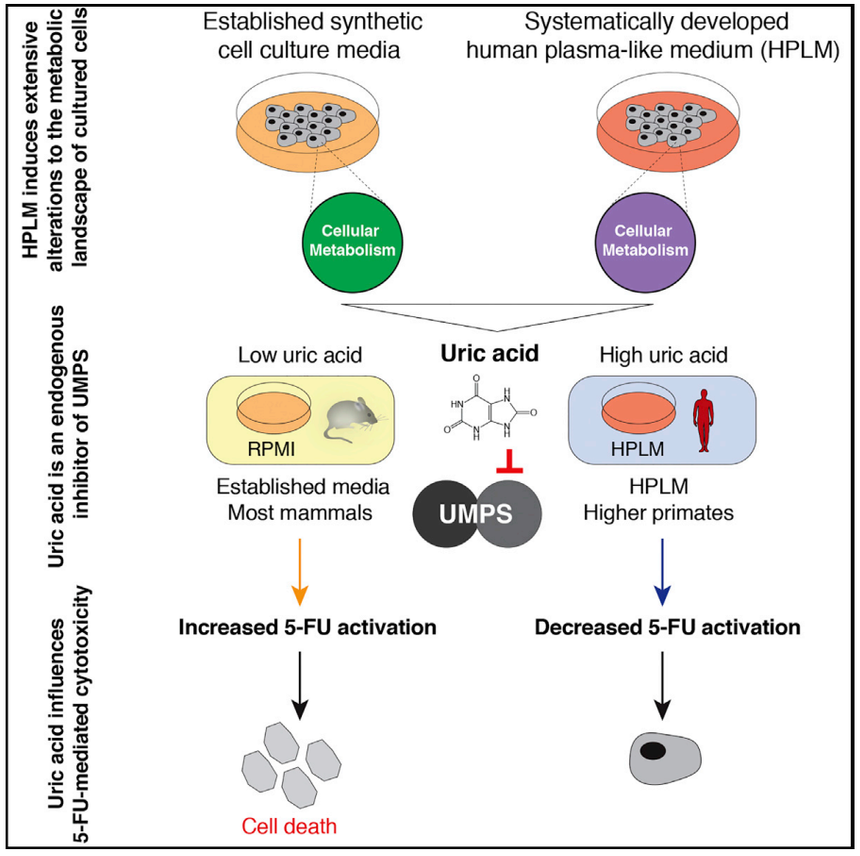

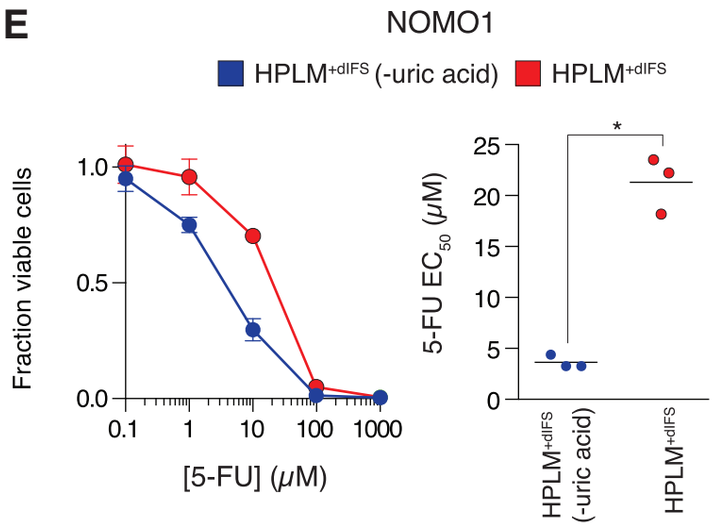

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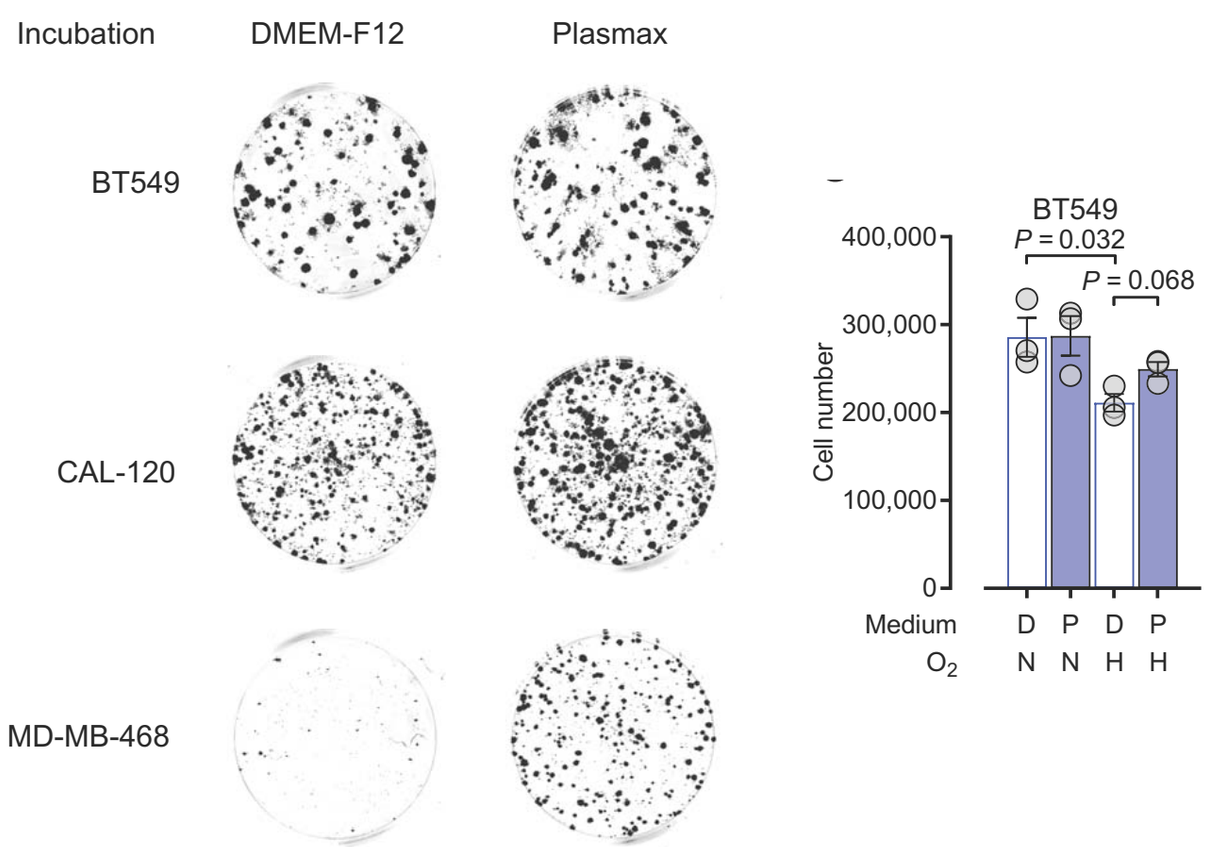

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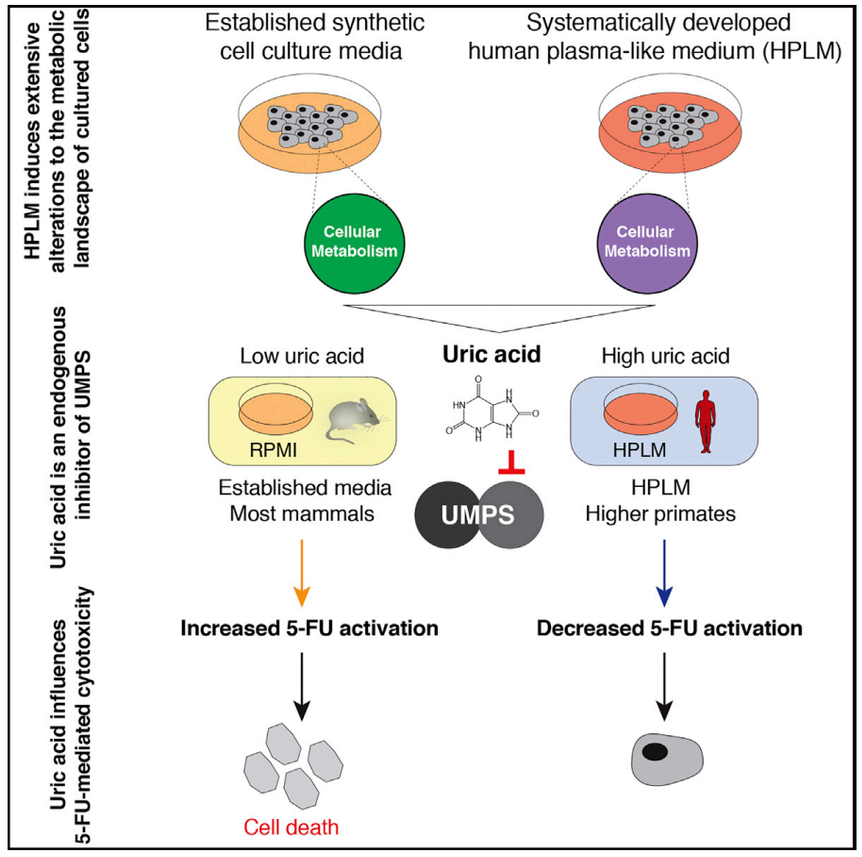

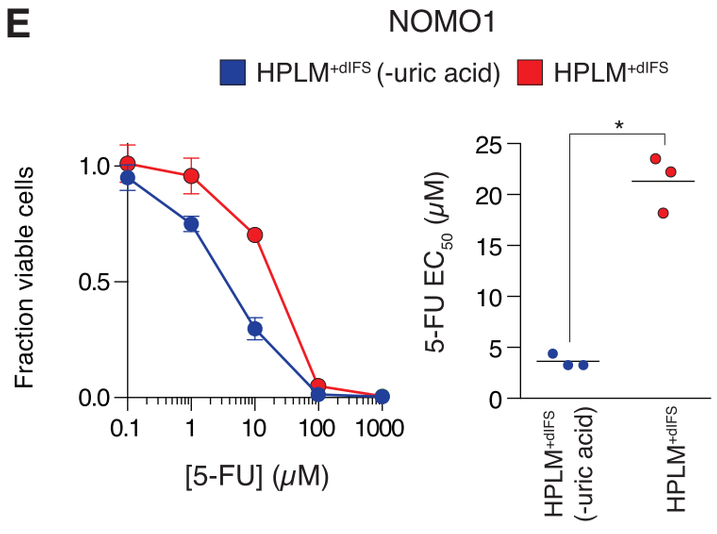

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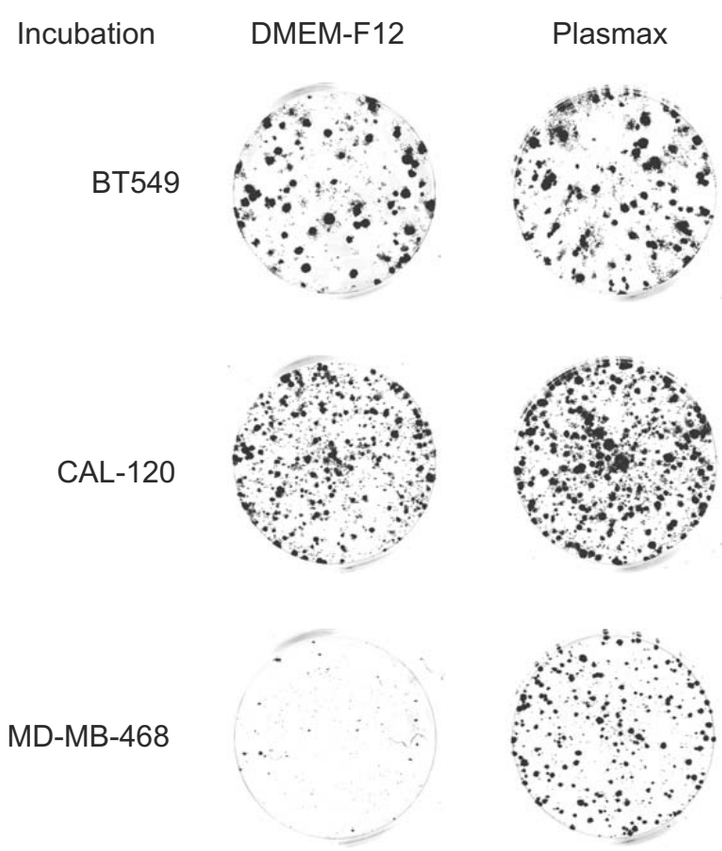

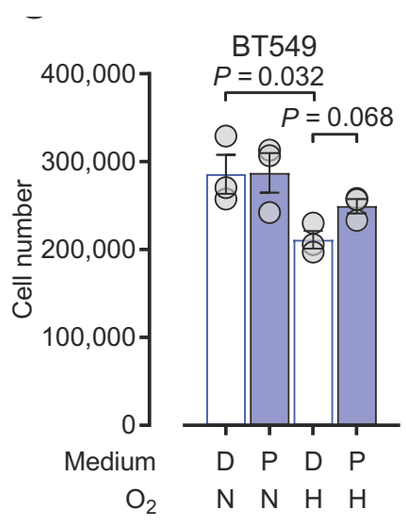

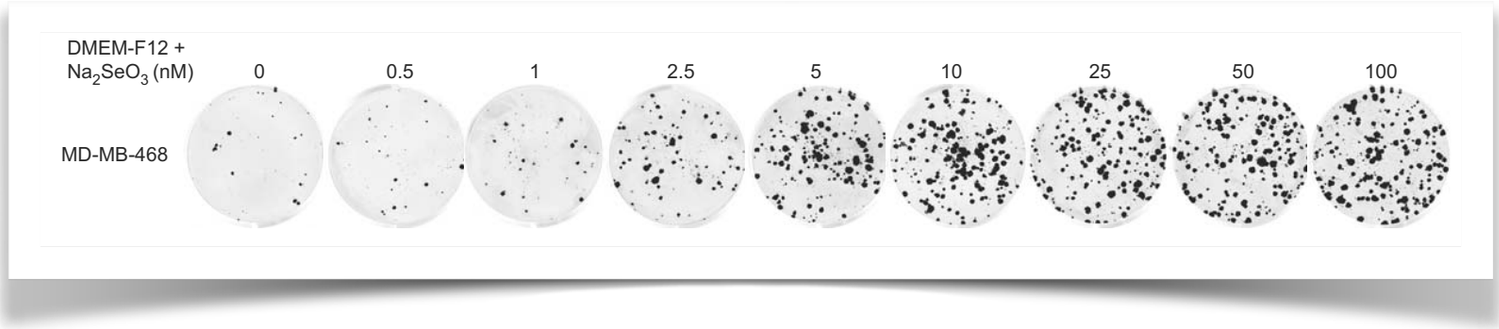

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*Vande Voorde et al, **Sci Adv**, 2019*

Metabolism is DYNAMIC.

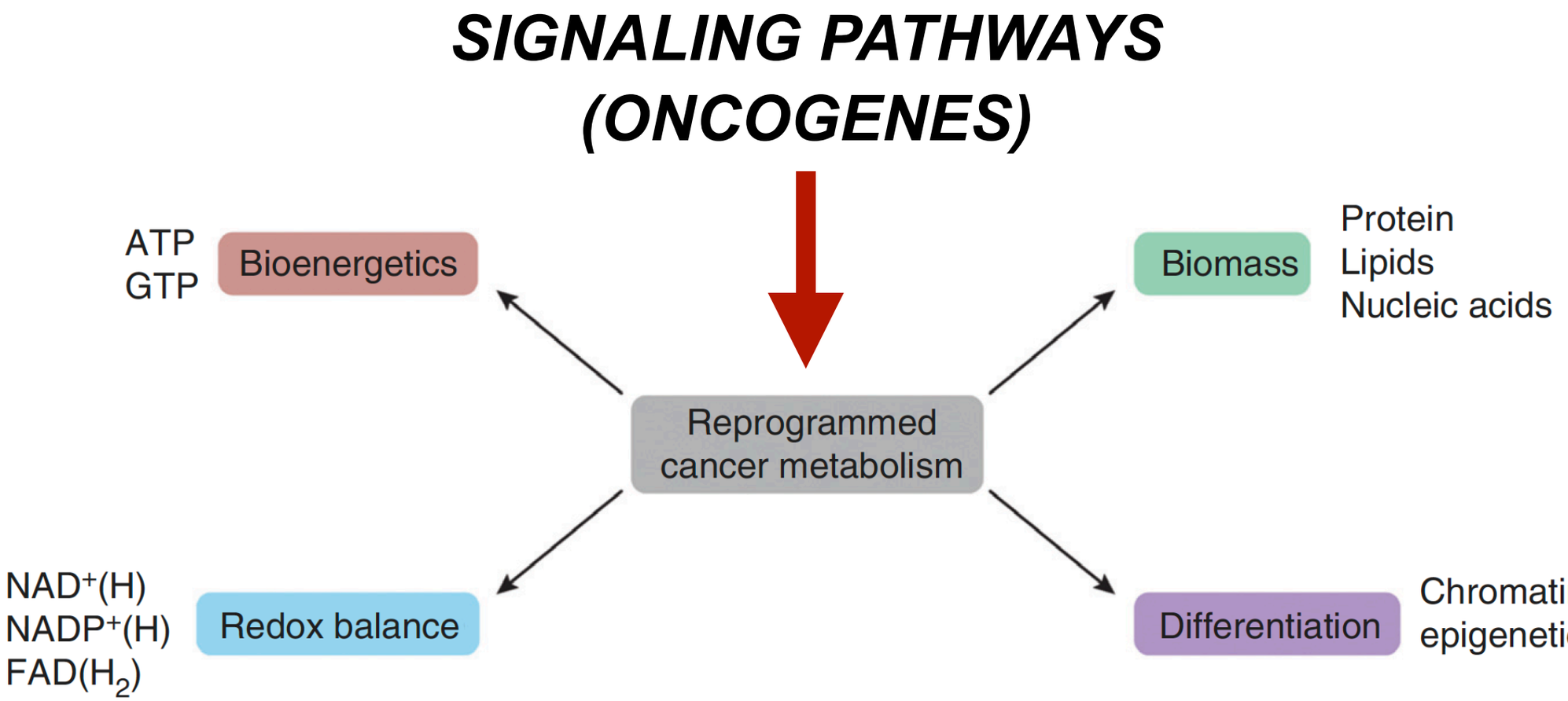
Cells need to reprogram their metabolism in order to:

- **Produce more biomass (cell division; cell growth)**
- **Produce more nucleotides (cell division; meiosis)**
- **Preserve energy (storage; response to nutrient scarcity)**
- **Cope with (oxidative) stress (replication and nutrient stress)**
- **Compartmentalize toxic metabolites (iron overload)**
- **Adapt to different environments (mobility, 3D growth)**
- **Secrete immunomodulatory molecules (immune response)**
- **Adjust availability of "signaling metabolites" (support signals)**
- **Support epigenetic rewiring (differentiation)**

…NOT to "produce" more energy

Cells reprogram their metabolism:

anabolic and catabolic pathways are rewired to tackle different needs



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