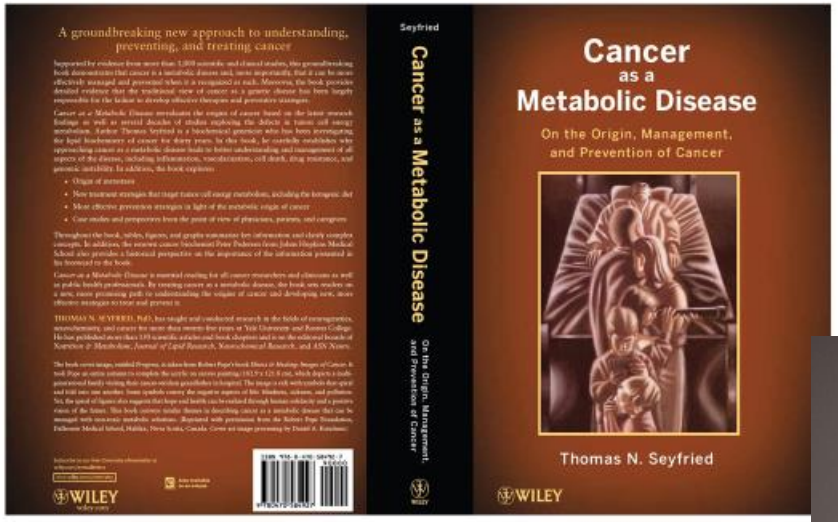
METABOLIC ALTERATIONS IN CANCER CELLS

Cancer: a metabolic disease?



METABOLIC CHARACTERISTICS OF CANCER CELLS

Increased GLYCOLYTIC ACTIVITY (Warburg Effect)

Increased production of LACTATE

Loss of PASTEUR'S EFFECT

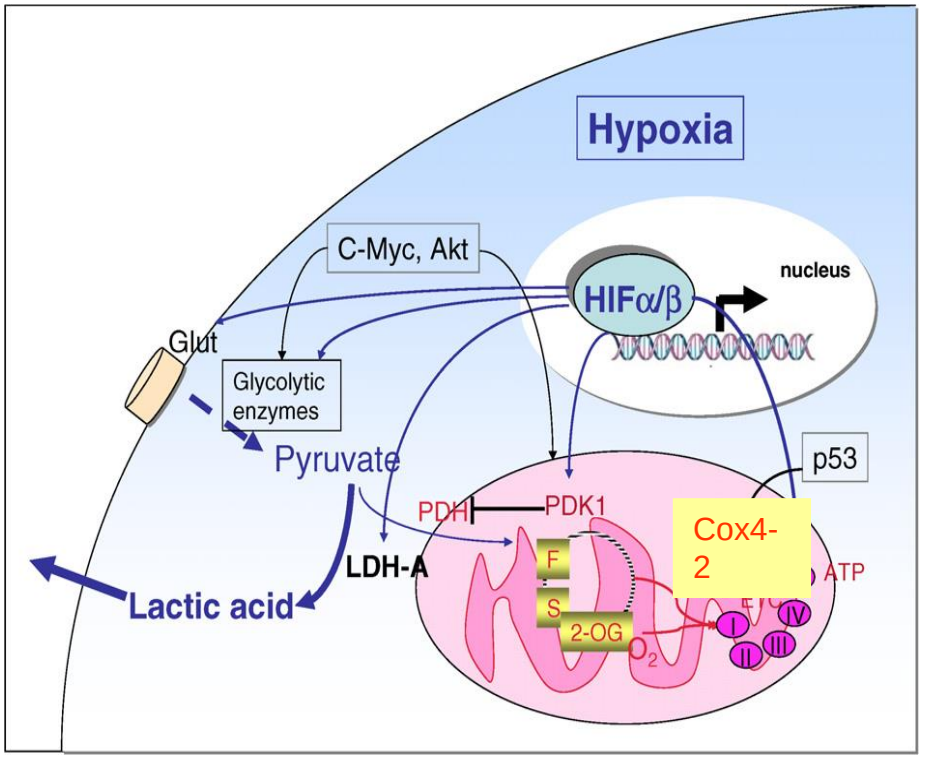
(Oxygen inhibition of glycolysis)

INCREASED CONSUMPTION of GLUTAMINE

INCREASED PROTEIN SYNTHESIS

DECREASED PROTEOLYSIS

DECREASED SYNTHESIS OF FATTY ACIDS (increased lipolysis from host adipose tissue)



ENERGETIC METABOLISM IN TUMOURS

- WARBURG EFFECT
- In the 1920s, Otto Warburg observed that tumor cells consume a large amount of glucose, much
- more than normal cells, and convert most of it to lactic acid. This phenomenon, now known as the
- ‘Warburg effect,’ is the foundation of one of the earliest general concepts of cancer: that a
- fundamental disturbance of cellular metabolic activity is at the root of tumor formation and growth.

Biography

Otto Heinrich Warburg:

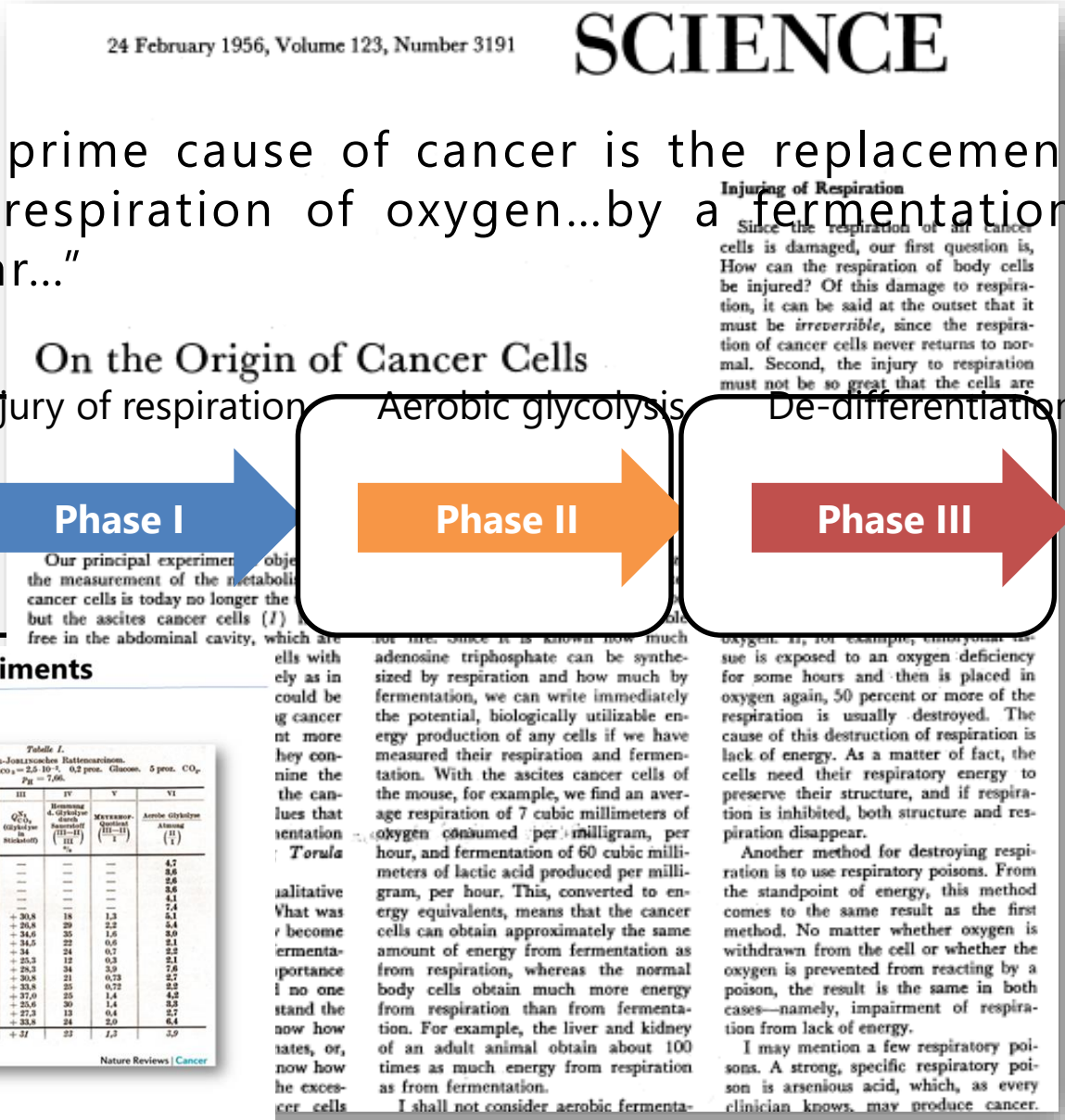
- Born-October 8, 1883 in Germany
- Died-August 1, 1970 in Berlin, Germany
- Son of physicist Emil Warburg
- Otto was a German physiologist and medical doctor.
- He won a Nobel prize in Physiology and Medicine for his Warburg effect in 1931.
- He was one of the twentieth century's leading biochemist

One of his Lectures…

- *"Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar… "* -- Dr. Otto H. Warburg in Lecture

The Warburg hypothesis

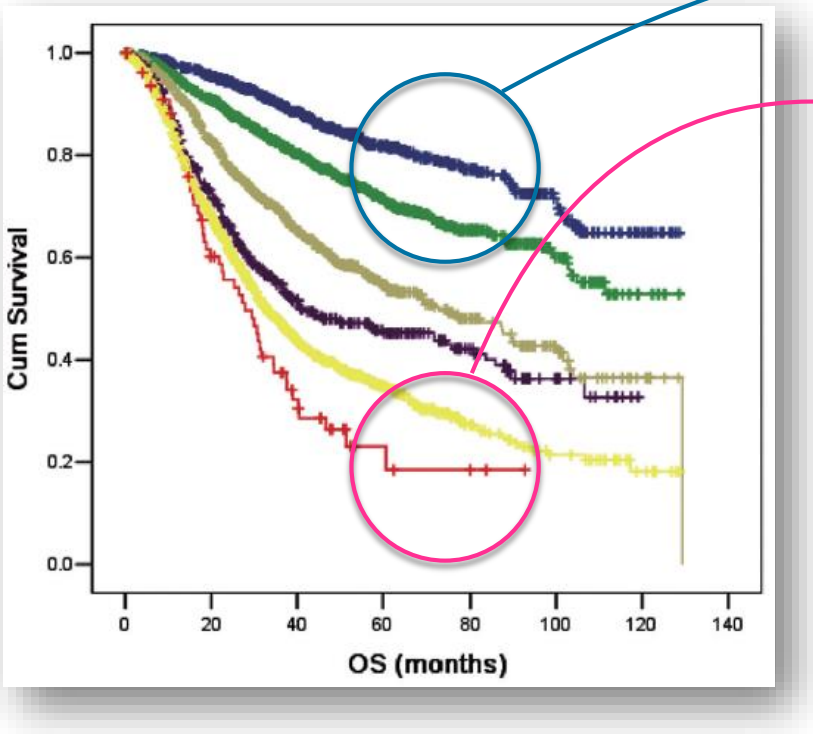
The prime cause of cancer is the replacement of the respiration of oxygen…by a fermentation of sugar…"



The Warburg Effect

- Pyruvate is an end-product of glycolysis, and is oxidized within the mitochondria.
- According to Warburg, cancer should be interpreted as a mitochondrial dysfunction.
- As a consequence, most cancer cells predominantly produce energy by a high rate of glycolysis followed by lactic acid fermentation in the cytosol, rather than by a comparatively low rate of glycolysis followed by oxidation of pyruvate in mitochondria like most normal cells. The latter process is aerobic. Tumour cells typically have glycolytic rates that are up to 200 times higher than those of their normal tissues of origin; this occurs even if oxygen is plentiful
- He postulated that this change in metabolism is the fundamental cause of cancer

Metabolism and patient outcome



Low Survival

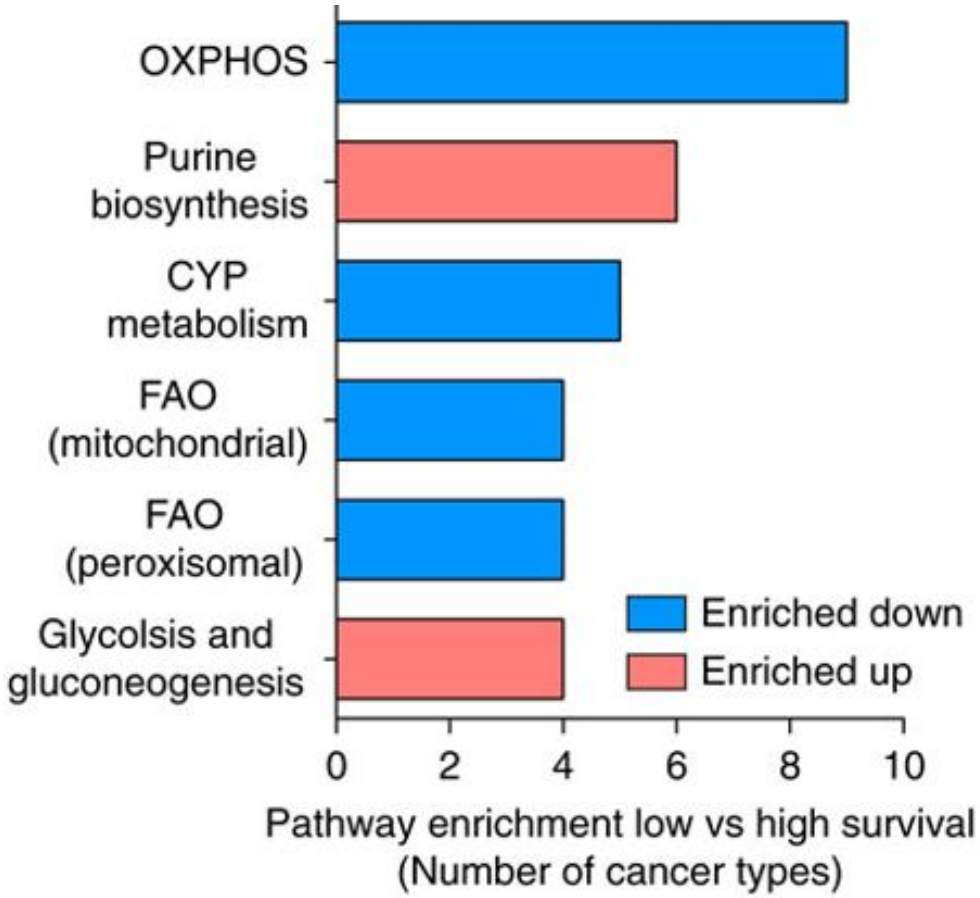
High Survival

Gene Set Enrichment Analysis

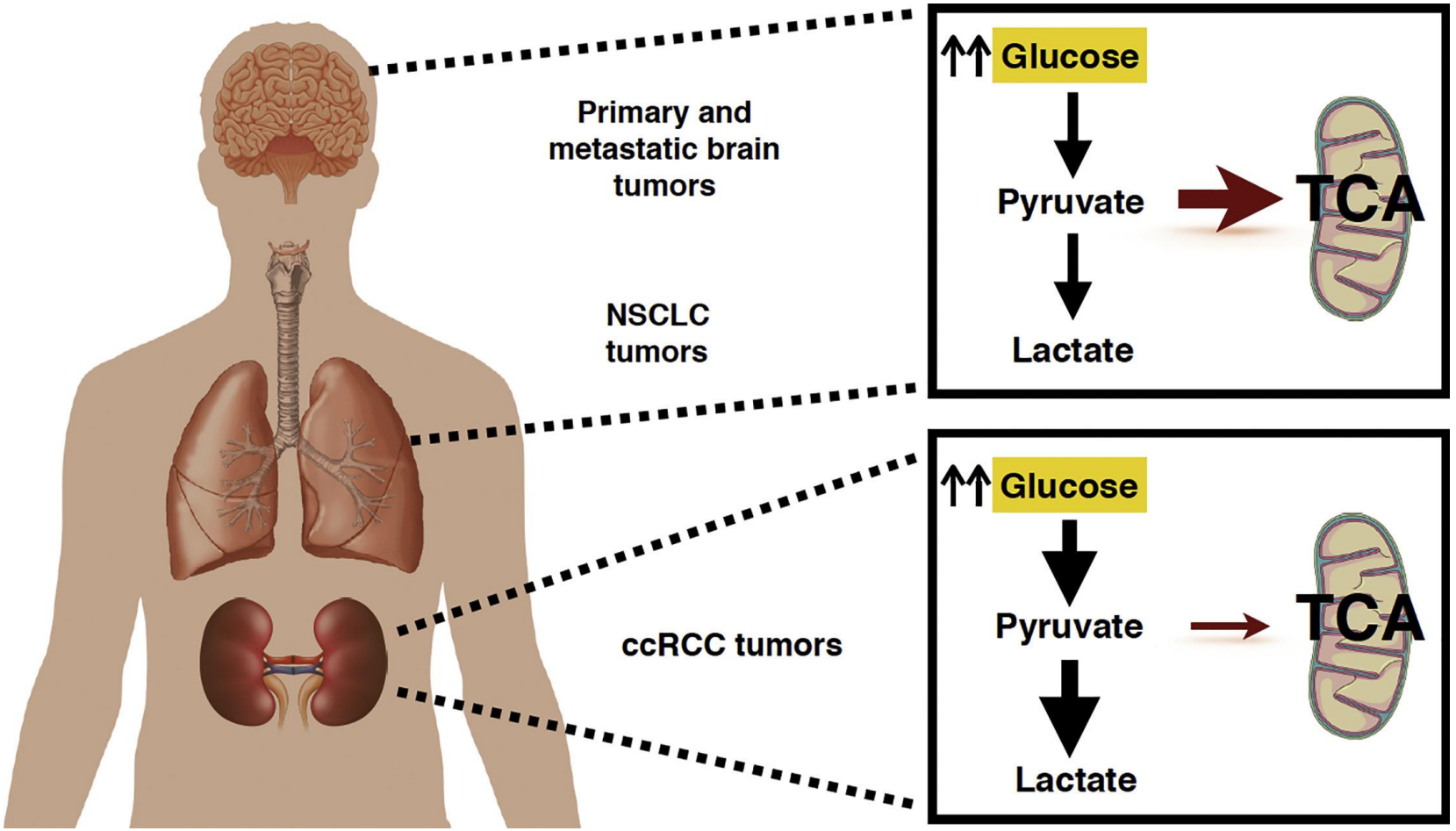
Metabolic Pathways linked to patient **survival**

Metabolism and patient outcome

OXPHOS is suppressed in low survival patients



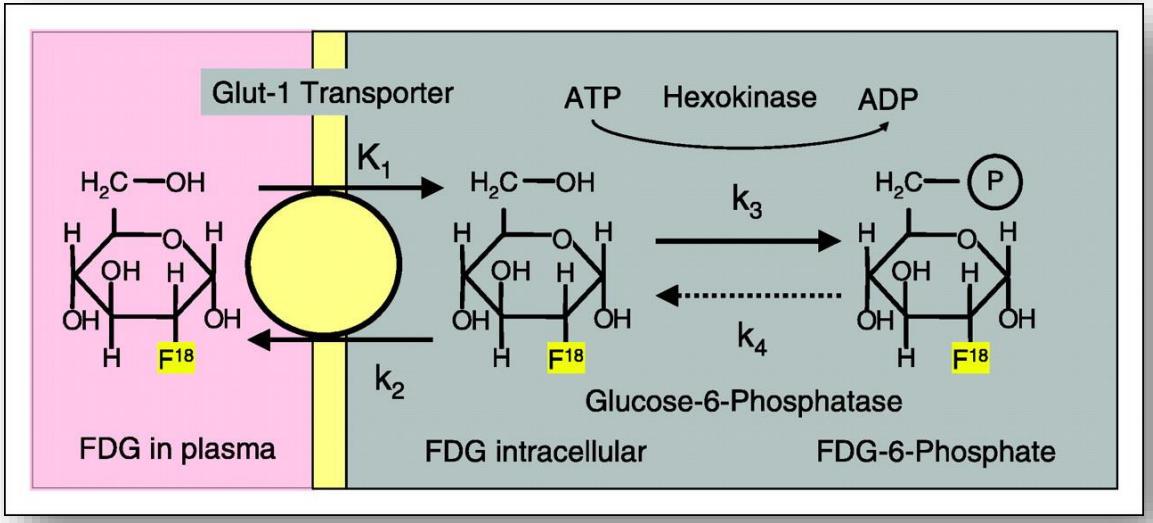
Evidence from *in vivo* experiments



Cell Metabolism Volume 28, Issue 5, (November 2018)

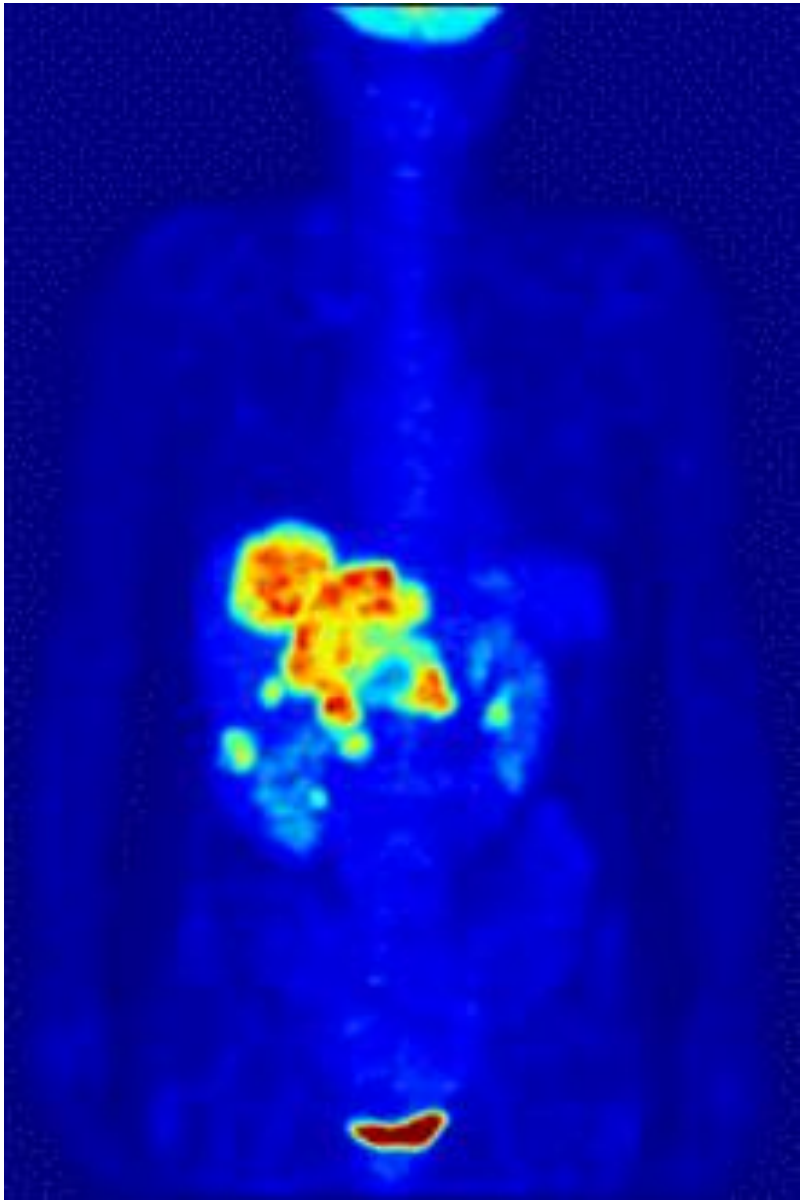
Aerobic glycolysis in cancer

detection of cancer exploiting glucose addiction



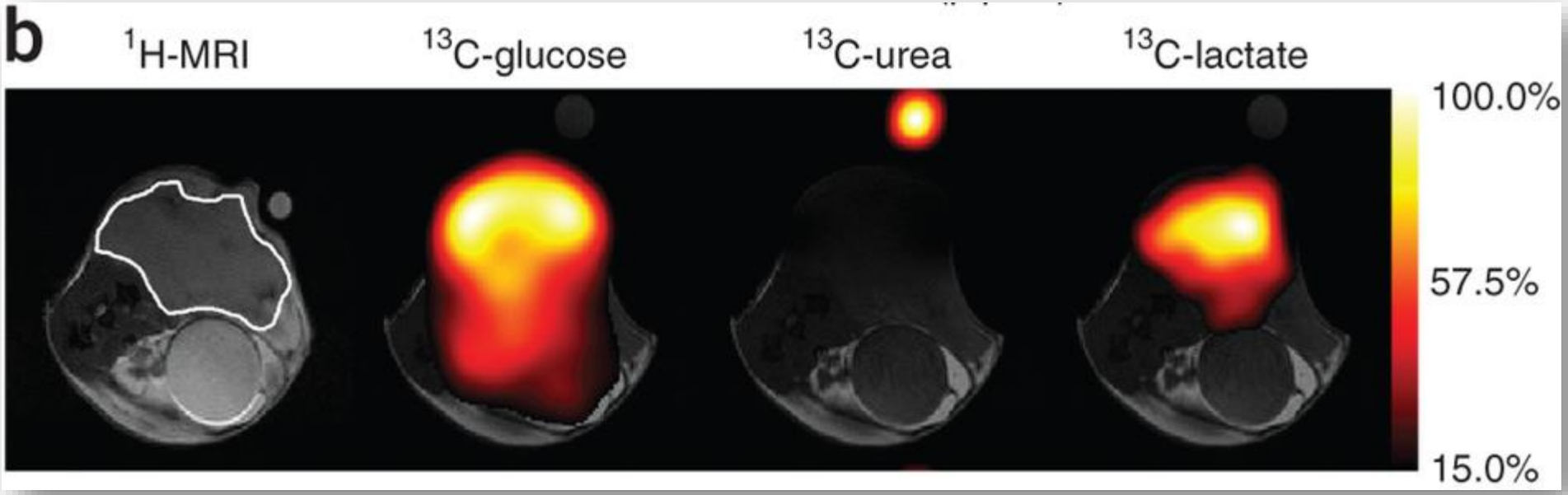
[^{18}F]flouro-2-deoxyglucose (FDG) Positron Emission Tomography (PET)

FDG-PET shows increase in glucose uptake in cancer



https://en.wikipedia.org/wiki/Positron_emission_tomography

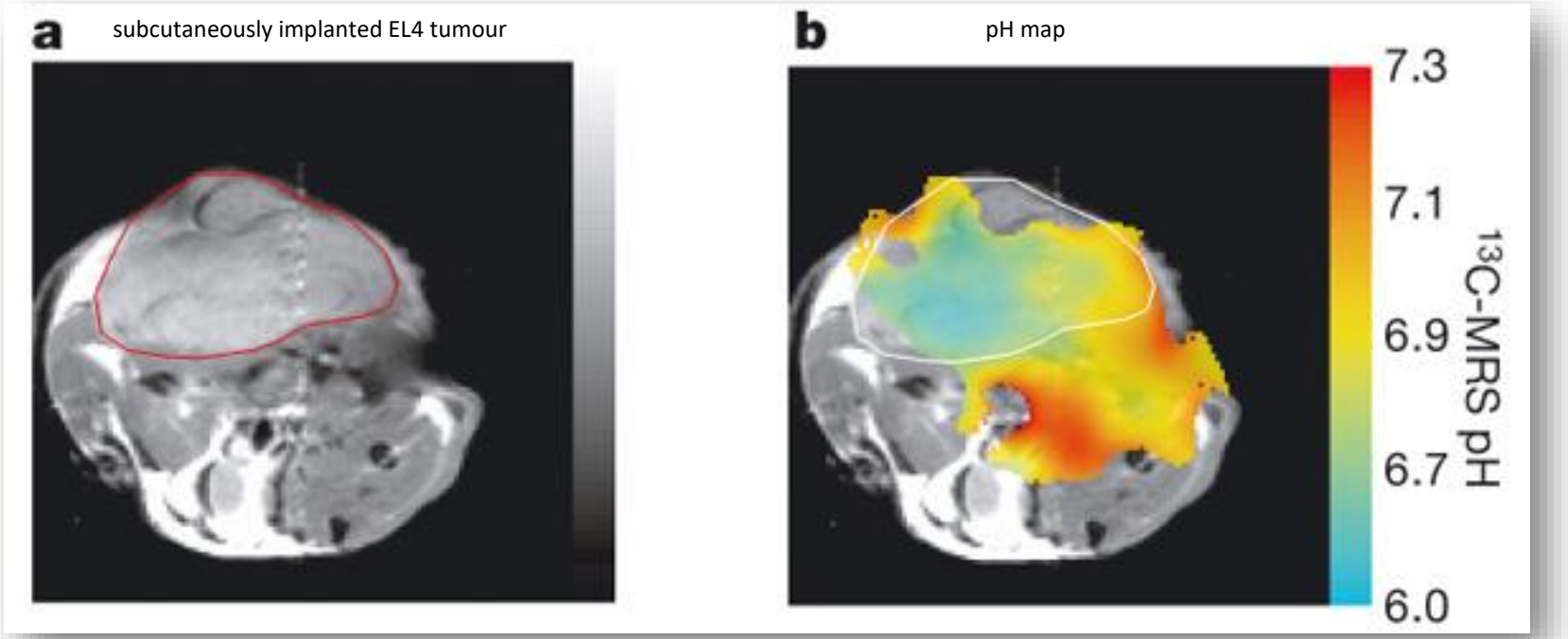
State-of-the-art imaging of cancer metabolism



Magnetic resonance imaging of tumor glycolysis using hyperpolarized ^{13}C-labeled glucose

Tiago B Rodrigues[1], Eva M Serrao[1], Brett W C Kennedy[2], De-En Hu[2], Mikko I Kettunen[1–3] & Kevin M Brindle[1–3]

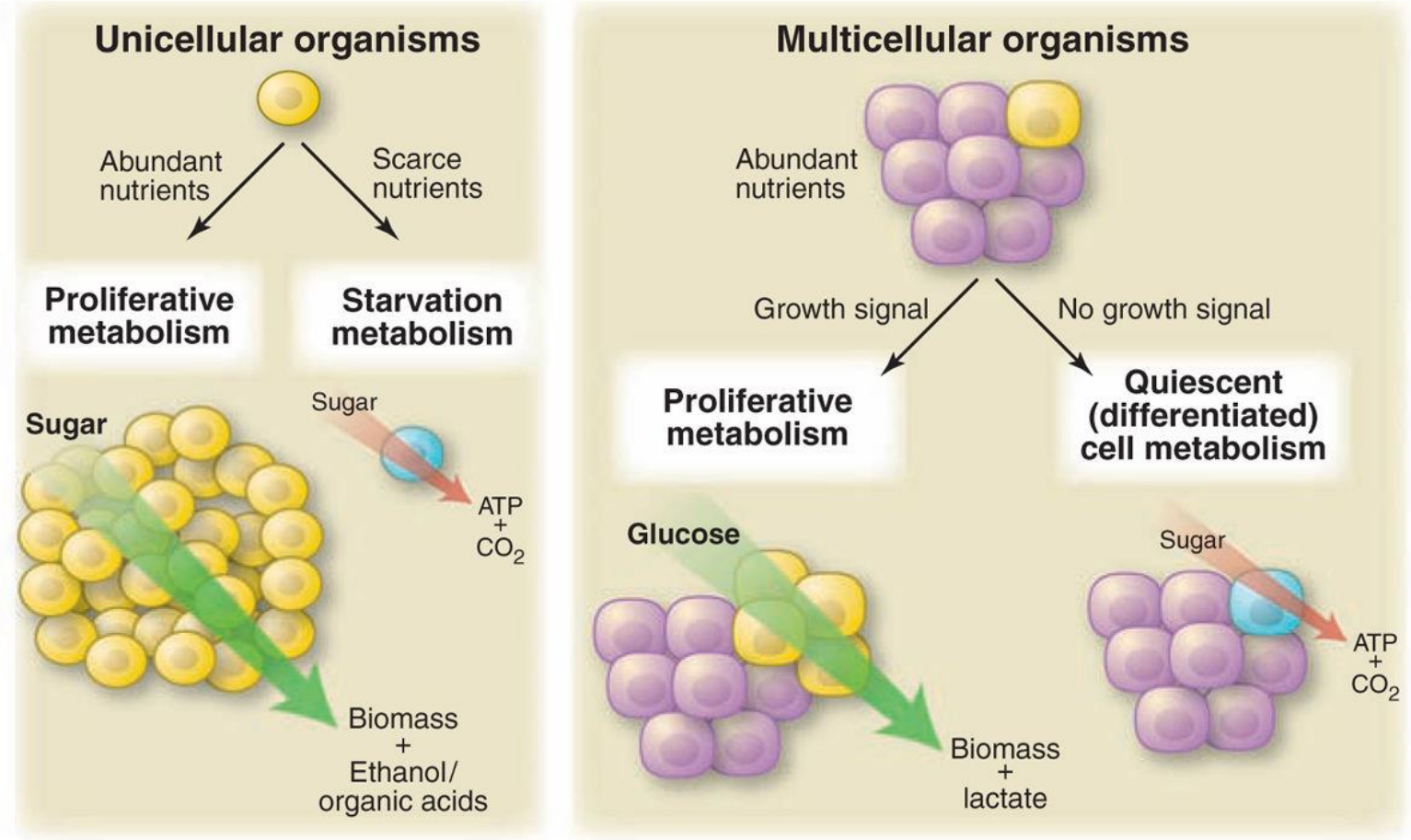
State-of-the-art imaging of cancer metabolism



Magnetic resonance imaging of pH *in vivo* using hyperpolarized ^{13}C-labelled bicarbonate

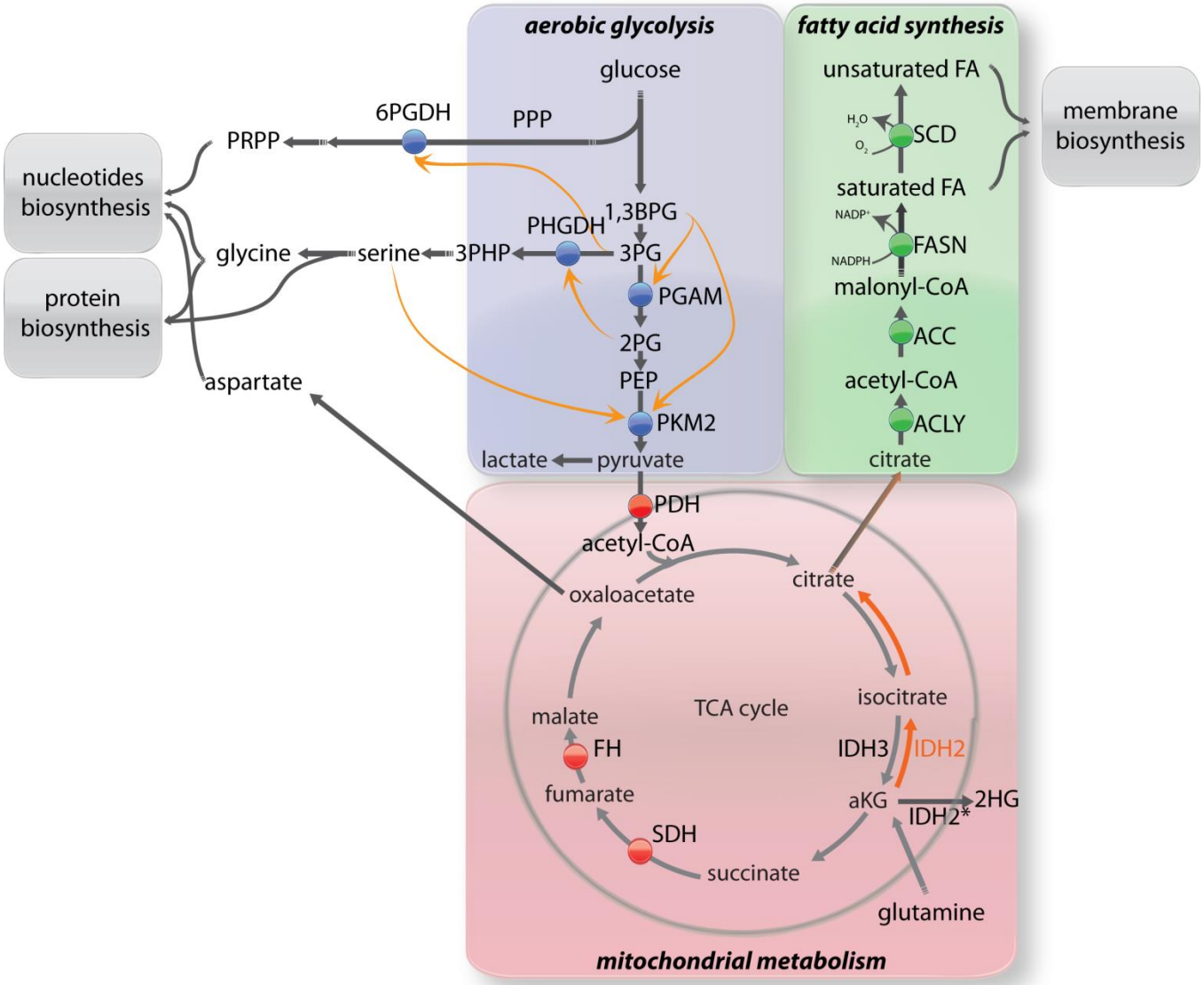
Ferdia A. Gallagher[1,2,3]*, Mikko I. Kettunen[1,2]*, Sam E. Day[1,2]†, De-En Hu[1,2], Jan Henrik Ardenkjær-Larsen[4], René in 't Zandt[5], Pernille R. Jensen[5], Magnus Karlsson[5], Klaes Golman[5], Mathilde H. Lerche[5] & Kevin M. Brindle[1,2]

there is an advantage to
oxidative metabolism during nutrient limitation
and to nonoxidative metabolism during cell proliferation

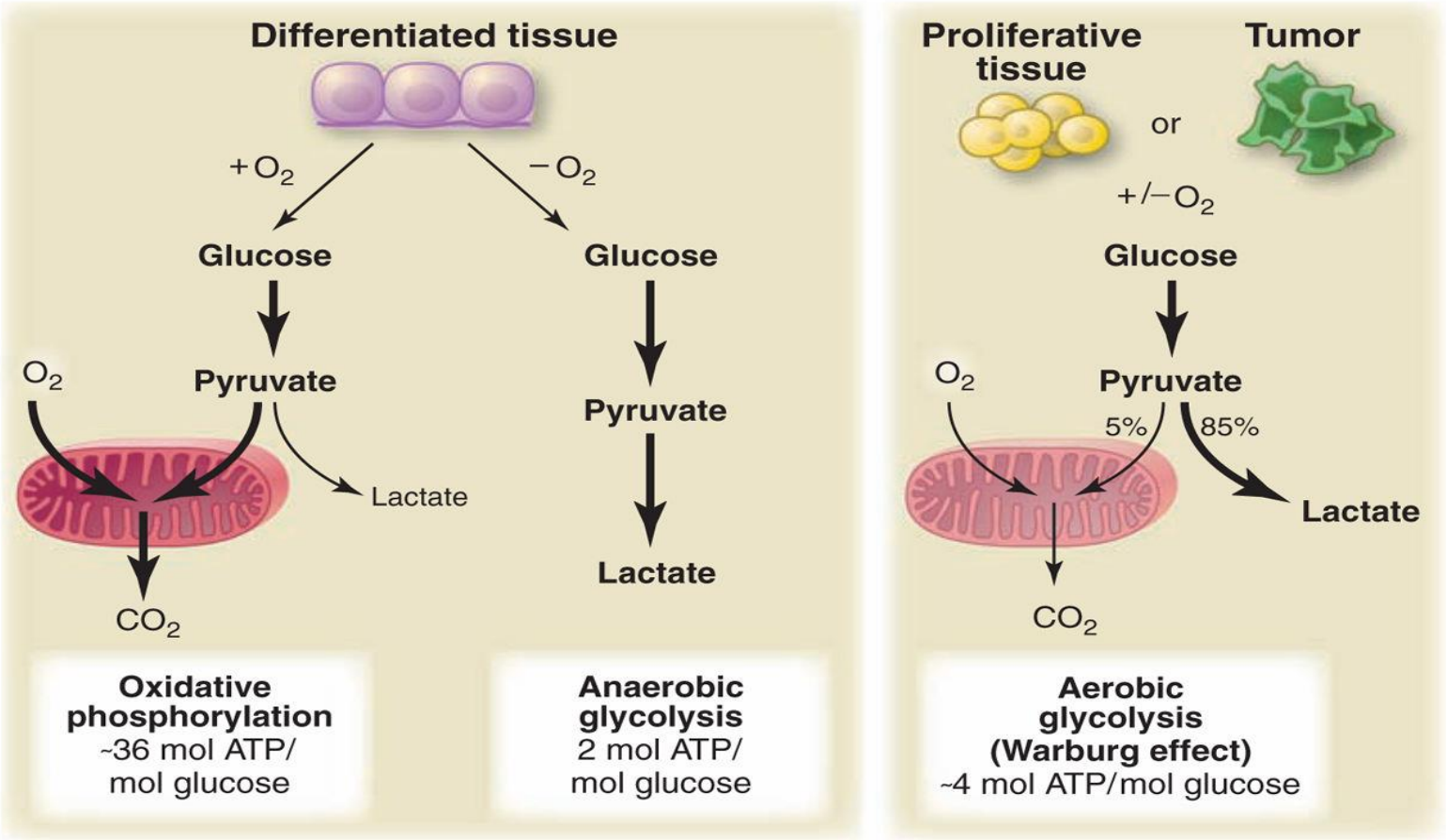


Aerobic glycolysis supports proliferation

providing substrates for neosynthesis

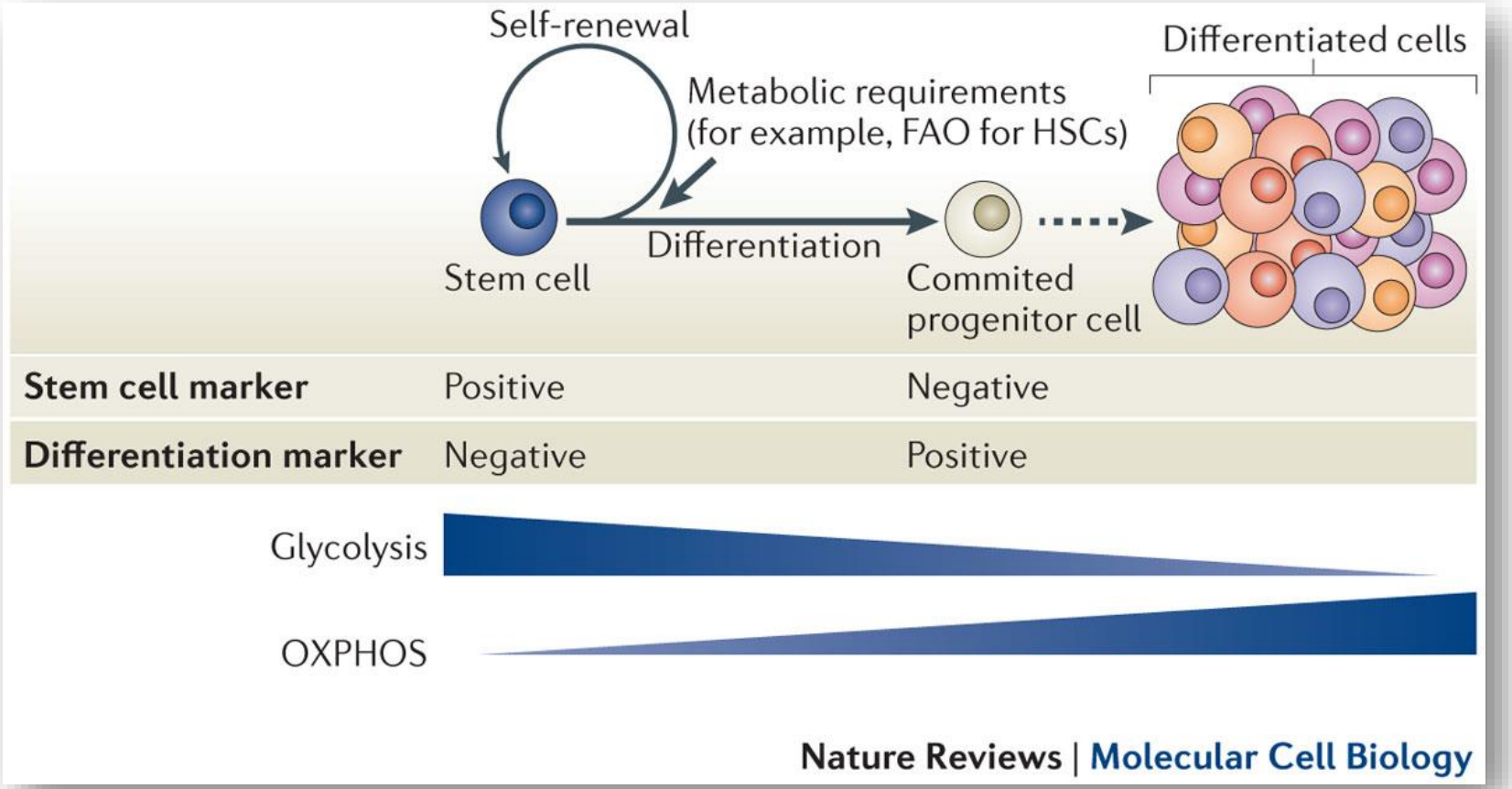


Schematic representation of the differences between oxidative phosphorylation, anaerobic glycolysis, and aerobic glycolysis (Warburg effect)

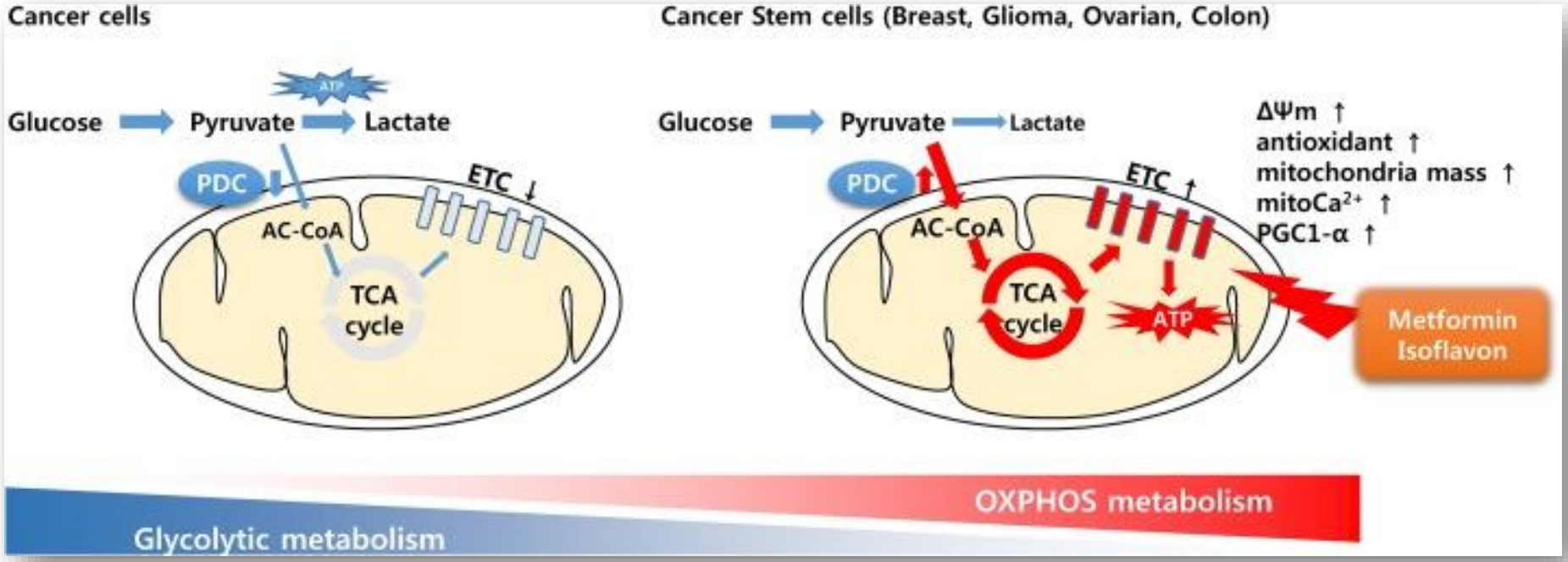


In proliferating cells, ~10% of the glucose is diverted into biosynthetic pathways upstream of pyruvate production. Cancer cells consume approx 200x glucose with respect to normal quiescent cells.

Aerobic glycolysis and "stemness"



Cancer stem cells and plasticity



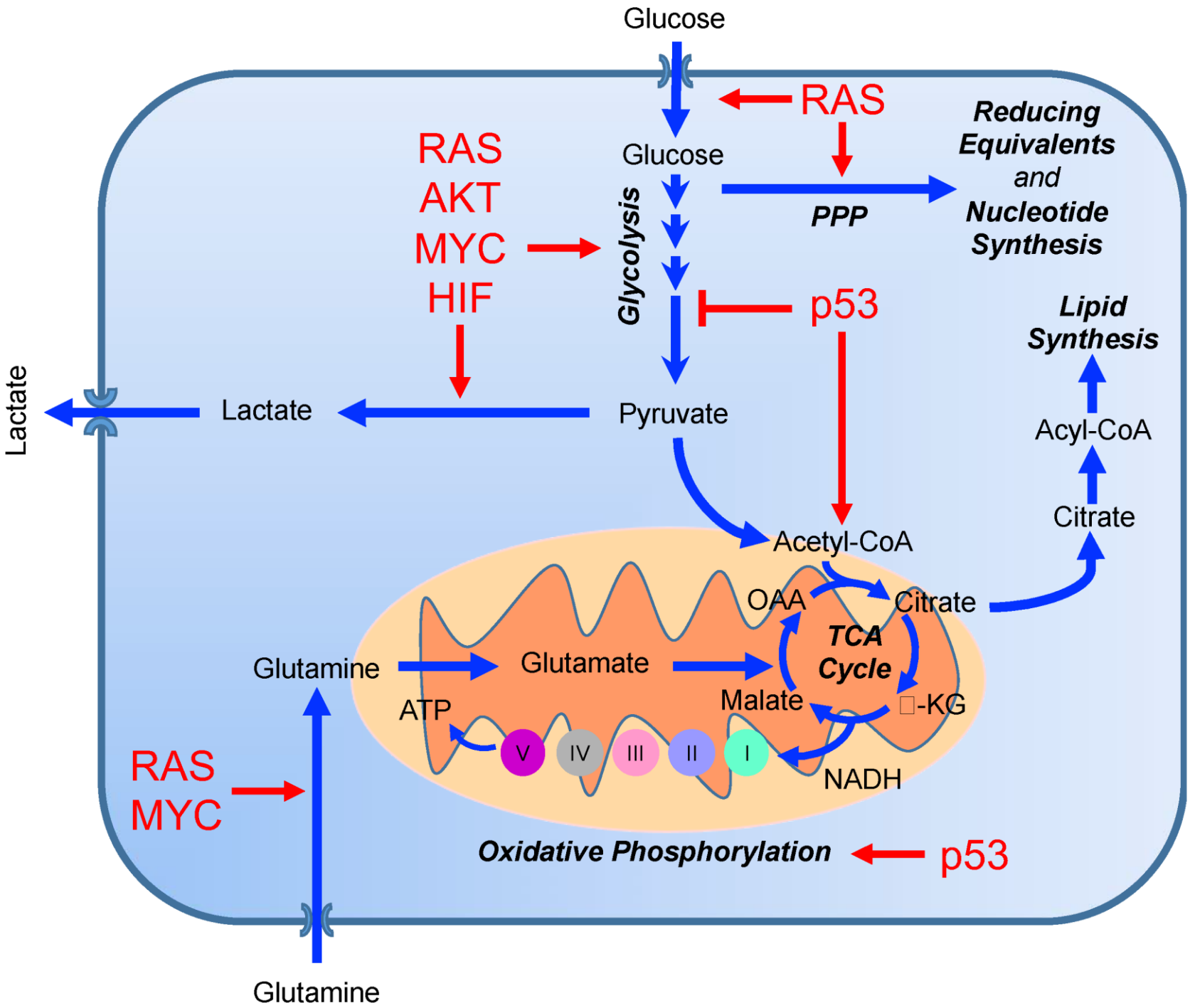
The Warburg effect describes the enhanced conversion of glucose to lactate by tumor cells, even in the presence of adequate oxygen.

Activation of the AKT oncogene results in increased glucose transportation and stimulation of HK2 activity, which enhances glycolytic rates.

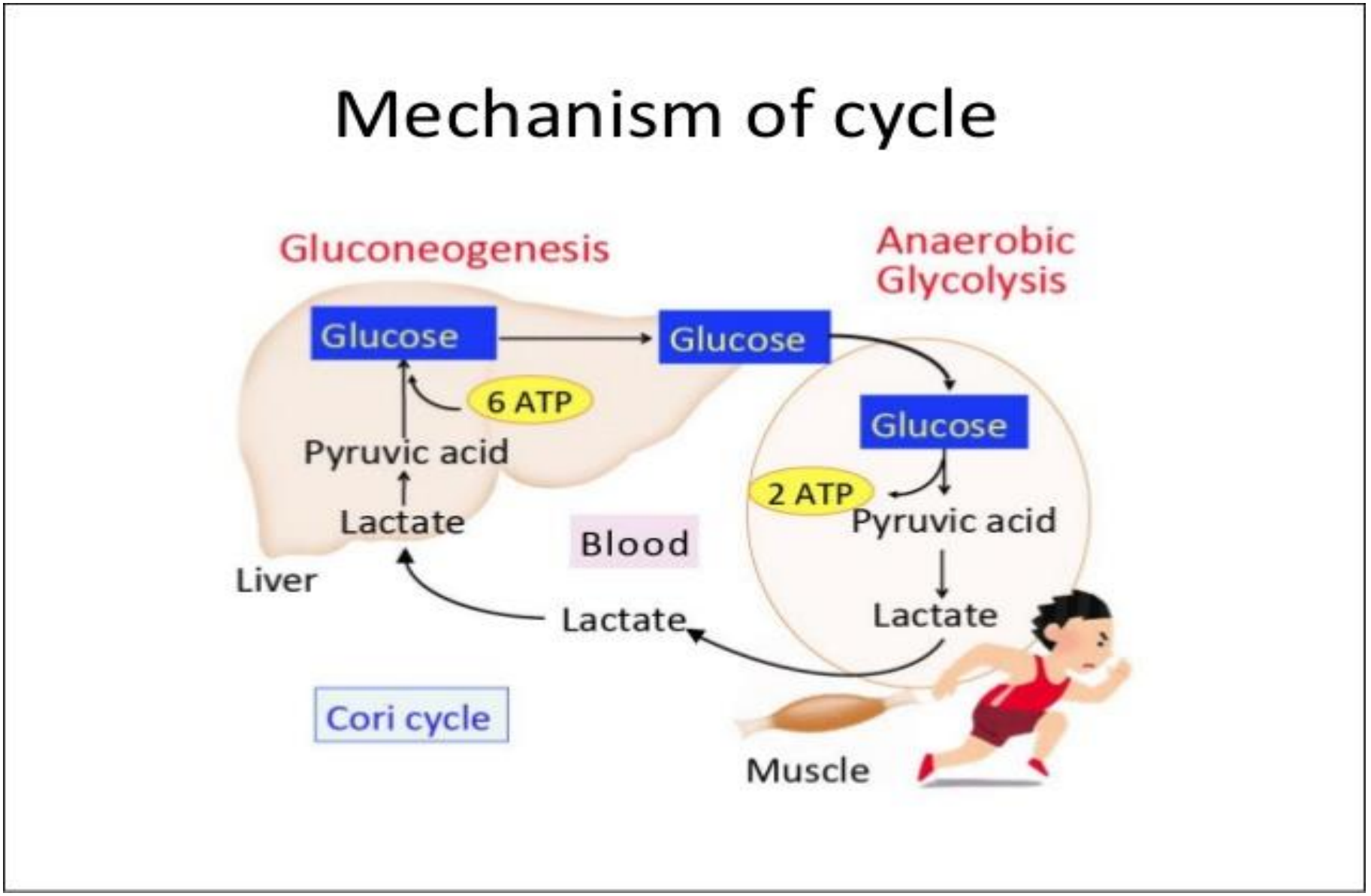
MYC oncogene activates glycolytic genes and mitochondrial biogenesis, which can result in ROS production. ROS could, in turn, cause mtDNA mutations that render mitochondria dysfunctional.

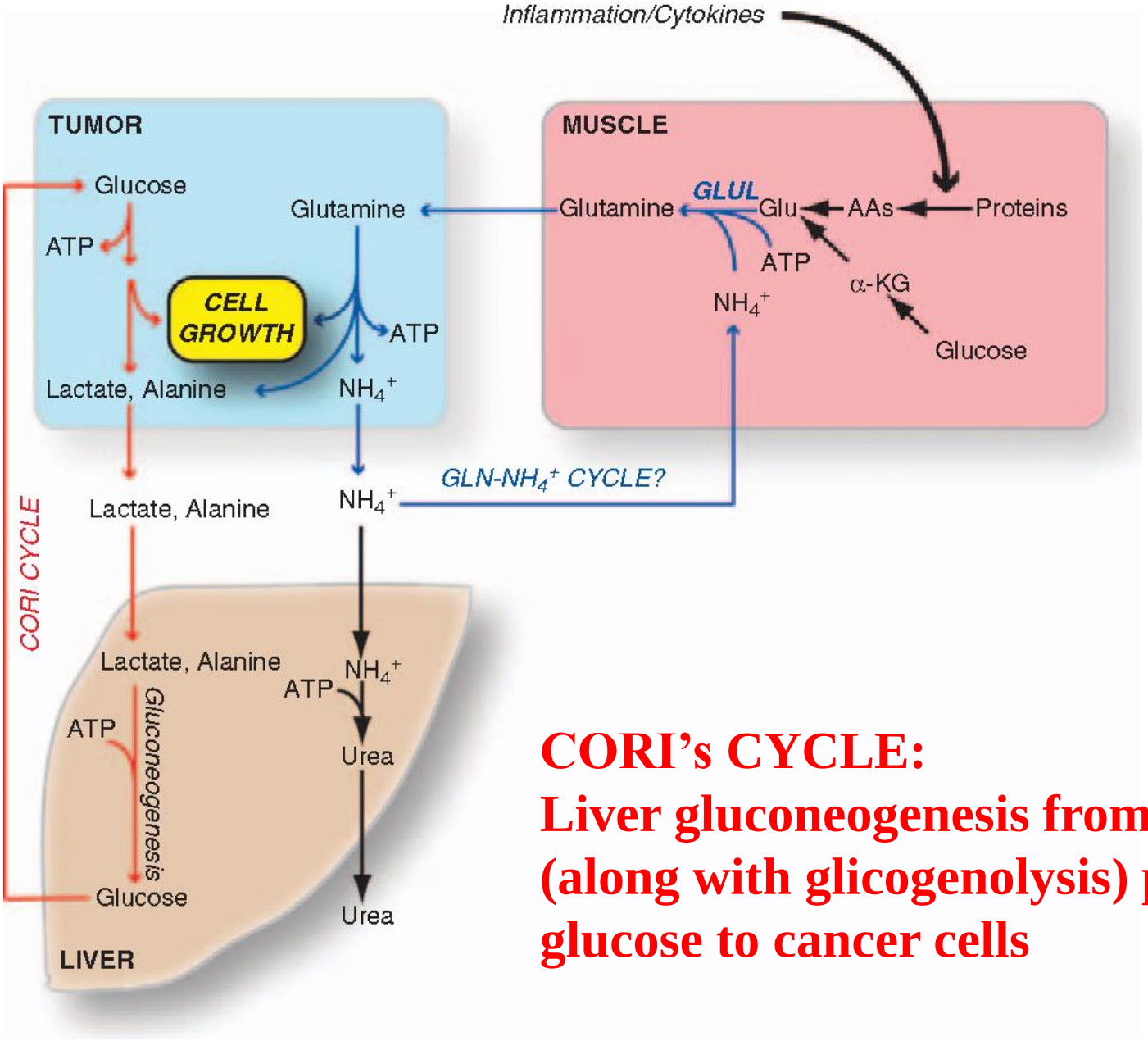
P53 stimulates respiration through activation of a component of the respiratory chain. HIF-1, increased by RAS, transactivates glycolytic genes as well as directly activates the PDK1 gene, which in turn inhibits PyruvateDH. (PDH catalyzes the conversion of pyruvate to acetyl-CoA, which enters the TCAcycle)

Inhibition of PDH by PDK1 attenuates mitochondrial function, resulting in the shunting of pyruvate to lactate.


Glucose
RAS
Glucose
RAS
AKT
MYC
HIF
Glycolysis
PPP
Reducing Equivalents and Nucleotide Synthesis
p53
Lipid Synthesis
Lactate
Lactate
Pyruvate
Acyl-CoA
Citrate
Acetyl-CoA
OAA
Citrate
TCA Cycle
Glutamine
Glutamate
Malate
-KG
ATP
V
IV
III
II
I
NADH
RAS
MYC
Oxidative Phosphorylation
p53
Glutamine

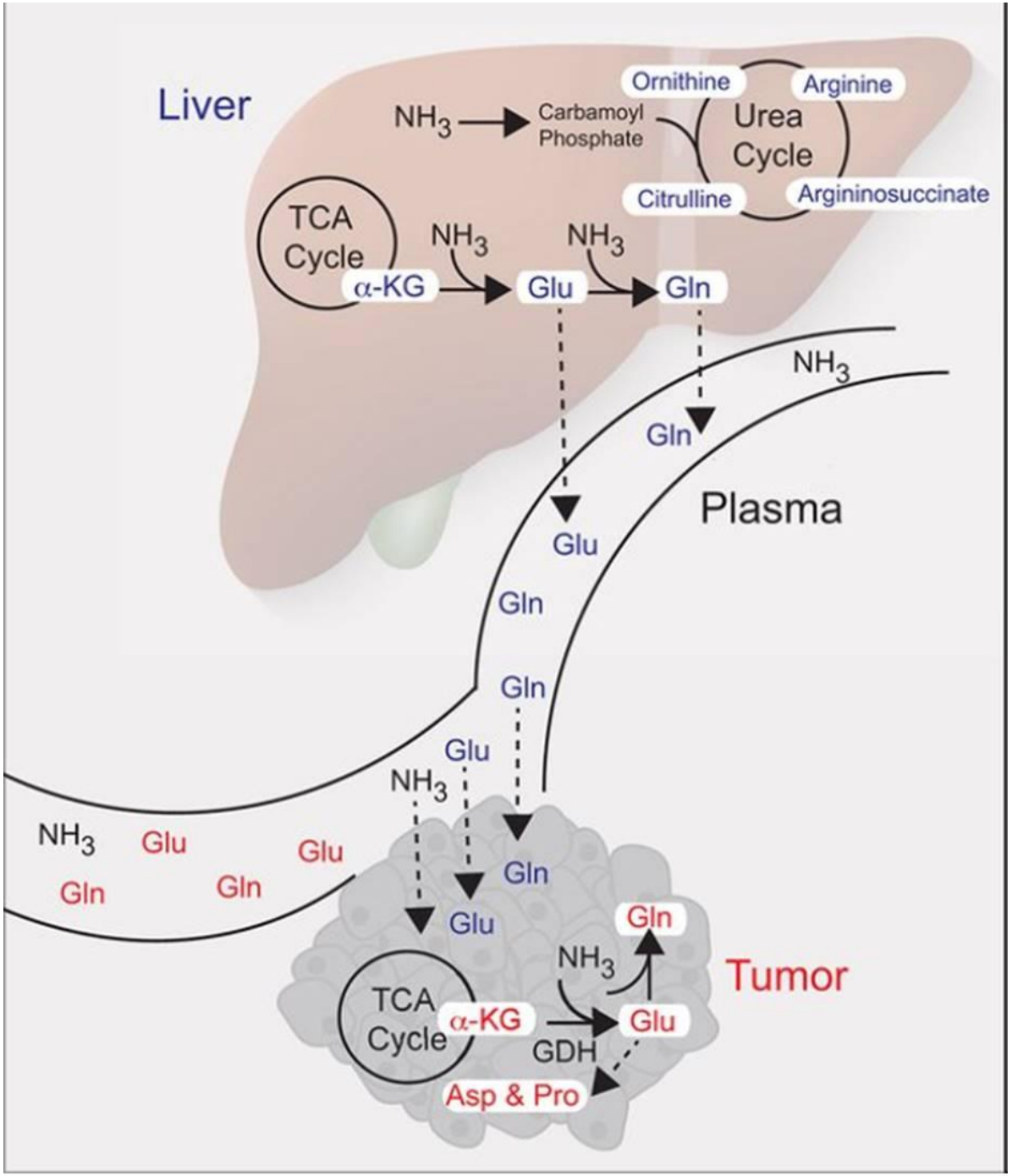
CYCLE OF CORI: lactate is used for gluconeogenesis in Liver to support glucose demand





CORI's CYCLE:
Liver gluconeogenesis from Lactate (along with glicogenolysis) provides glucose to cancer cells

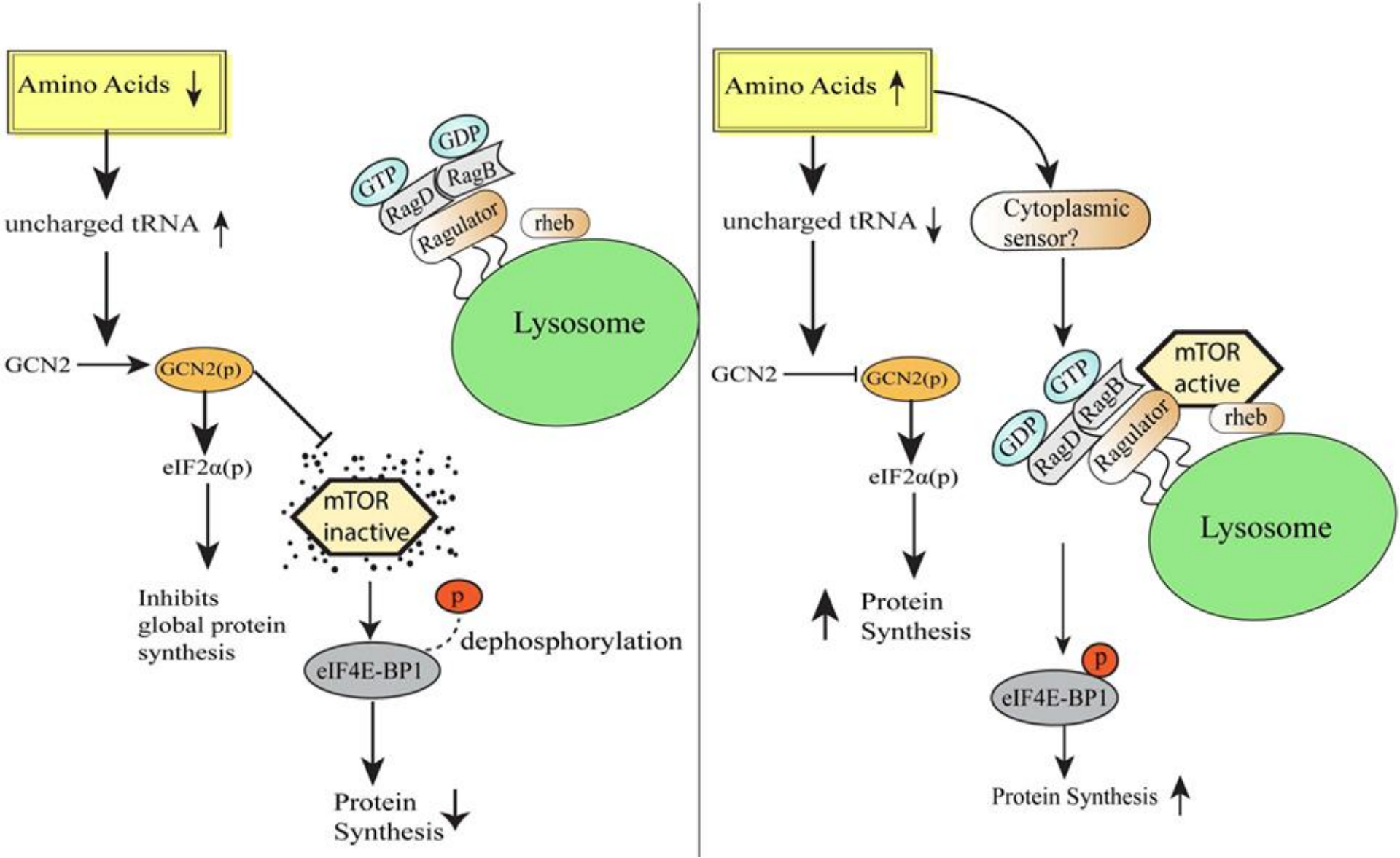
LIVER metabolism provides glutamine to cancer cells



Schematic of Systemic Ammonia Metabolism

Science. 2017

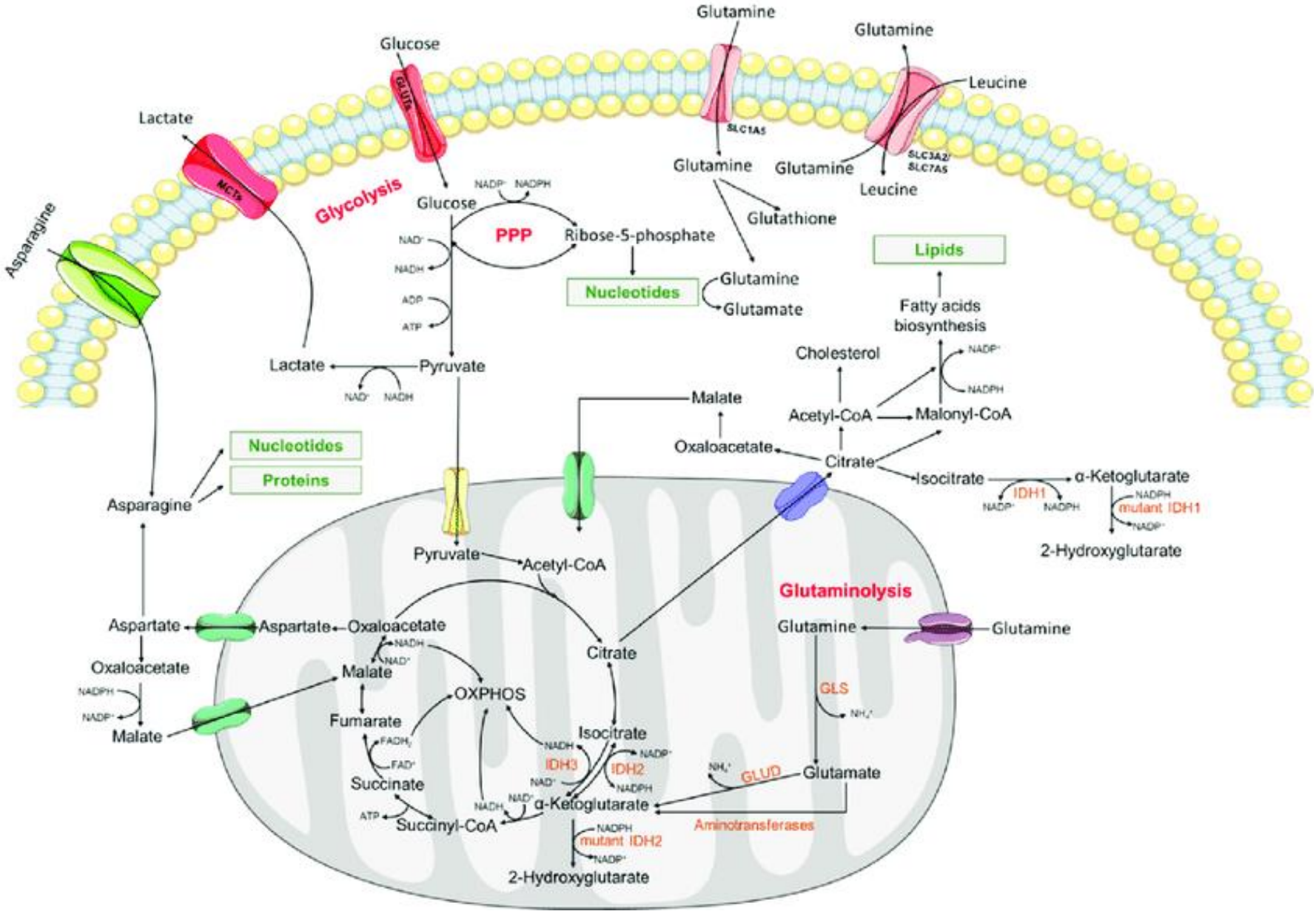
AMINOACID AVAILABILITY CONTROL PROTEIN SYNTHESIS

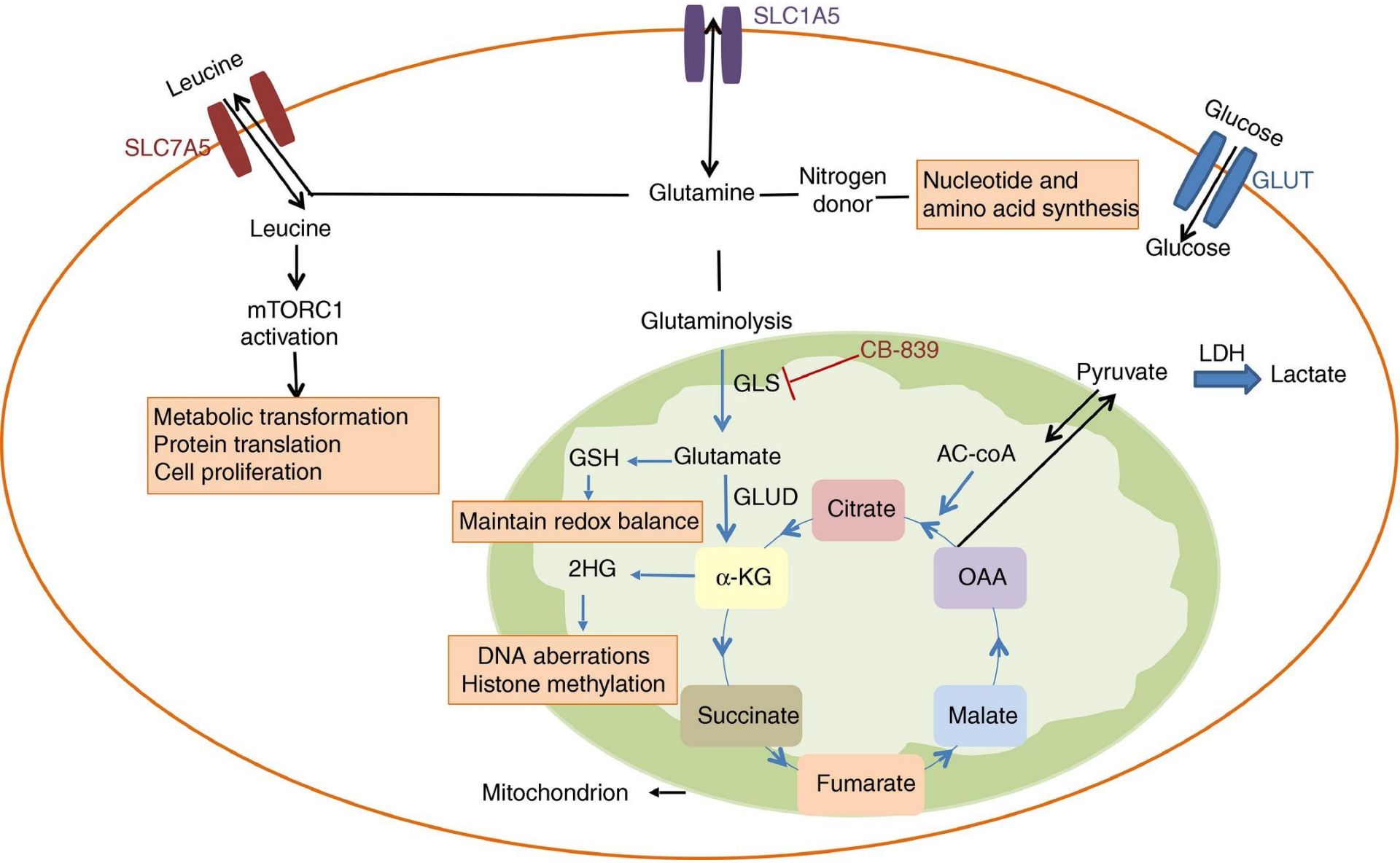


Essential vs. non-essential amino acids

Essential	Conditionally Non-Essential	Non-Essential
Histidine	Arginine	Alanine
Isoleucine	Asparagine	Asparatate
Leucine	Glutamine	Cysteine
Methionine	Glycine	Glutamate
Phenylalanine	Proline	
Threonine	Serine	
Tryptophan	Tyrosine	
Valine		
Lysine		

GLUTAMINE METABOLISM IN CANCER CELLS




SLC1A5
Leucine
SLC7A5
Glucose
GLUT
Glutamine
Nitrogen donor
Nucleotide and amino acid synthesis
Leucine
Glucose
mTORC1 activation
Glutaminolysis
CB-839
GLS
Pyruvate
LDH
Lactate
Metabolic transformation
Protein translation
Cell proliferation
GSH
Glutamate
AC-coA
GLUD
Citrate
Maintain redox balance
2HG
α-KG
OAA
DNA aberrations
Histone methylation
Succinate
Malate
Fumarate
Mitochondrion

The FEBS Journal

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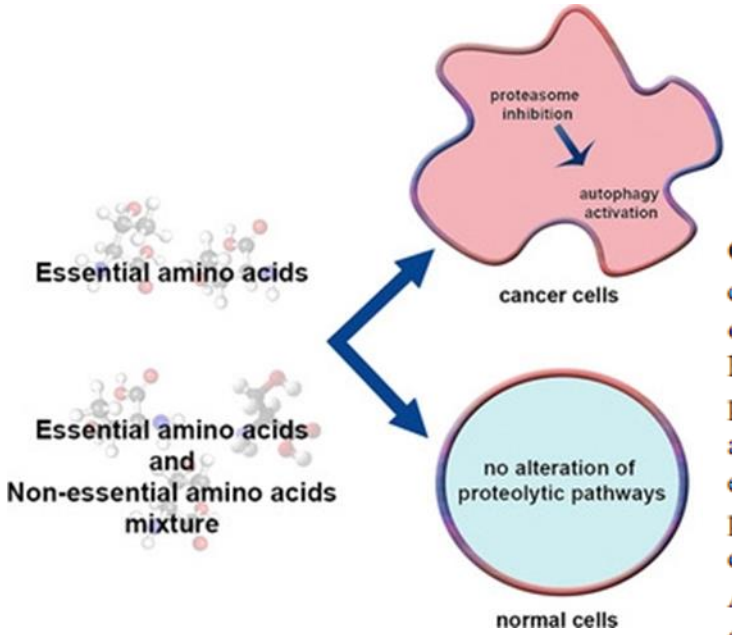
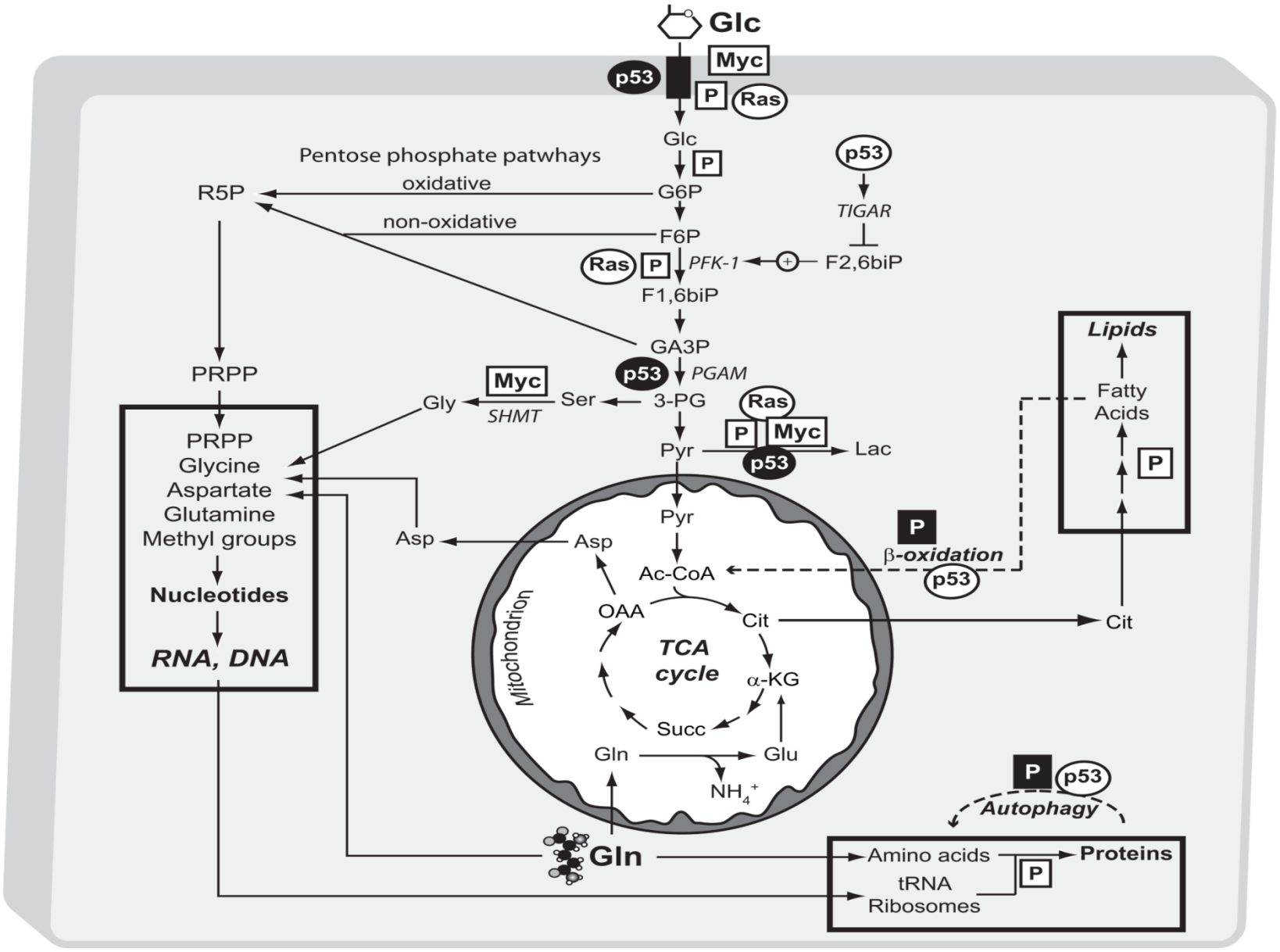
science publishing by scientists

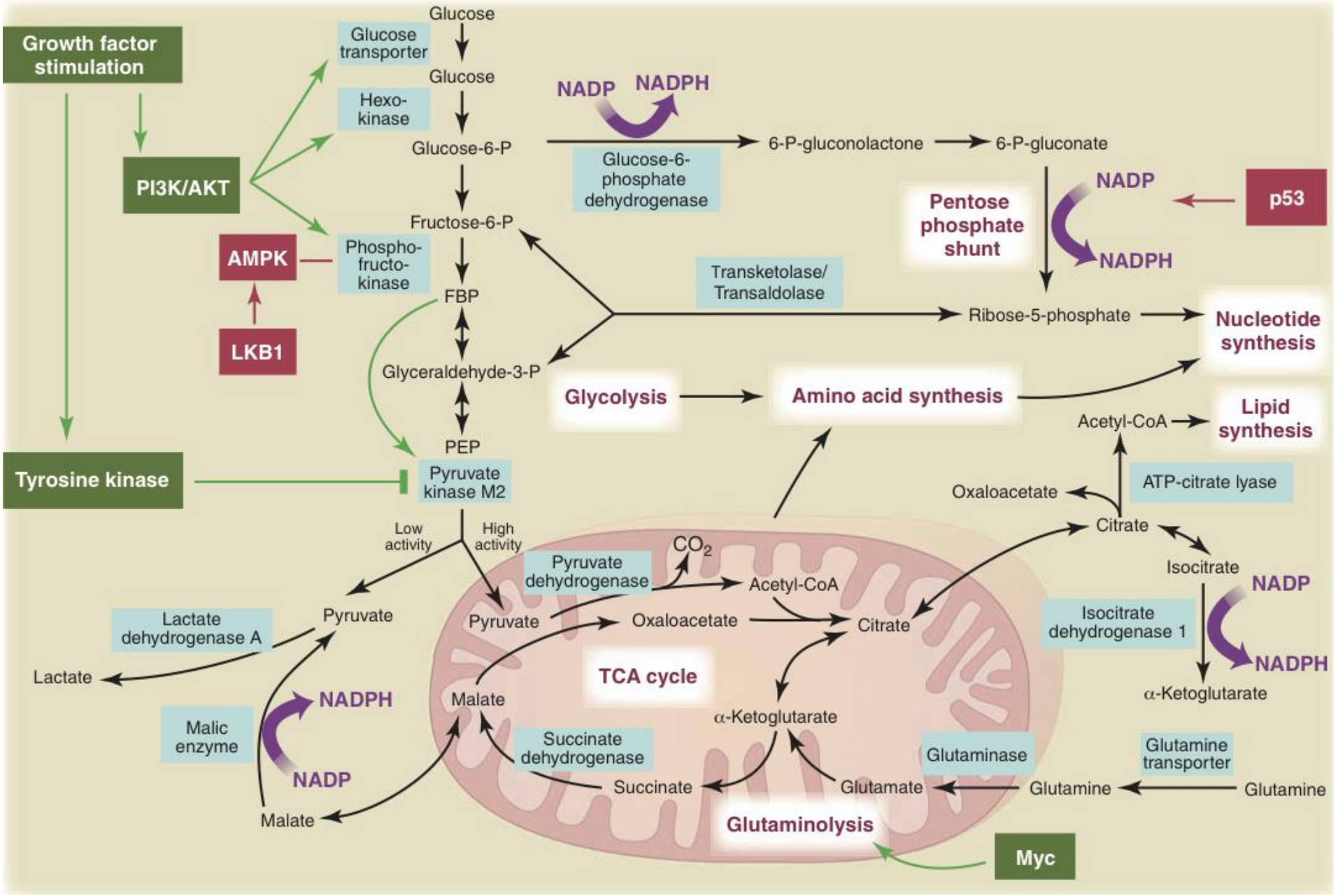
Essential amino acid mixtures drive cancer cells to apoptosis through proteasome inhibition and autophagy activation



Cancer cells require both energy and material to survive and duplicate in a competitive environment. Nutrients, such as amino acids (AAs), are not only a caloric source, but can also modulate cell metabolism and modify hormone homeostasis. Our hypothesis is that the environmental messages provided by AAs rule the dynamics of cancer cell life or death, and the alteration of the balance between essential amino acids (EAAs) and non-essential amino acids (NEAAs) (lower and higher than 50%, respectively) present in nutrients may represent a key instrument to alter environment-dependent messages, thus mastering cancer cells destiny. In this study, two AA mixtures, one exclusively consisting of EAAs and the other consisting of 85% EAAs and 15% NEAAs, were tested to explore their effects on the viability of both normal and cancer cell lines and to clarify the molecular mechanisms involved. Both mixtures exerted a cell-dependent anti-proliferative, cytotoxic effect involving the inhibition of proteasome activity and the consequent activation of autophagy and apoptosis. These results, besides further validating the notion of the peculiar interdependence and extensive crosstalk between the ubiquitin–proteasome system (UPS) and autophagy, indicate that variation in the ratio of EAAs and NEAAs can deeply influence cancer cell survival. Consequently, customization of dietary ratios among EAAs and NEAAs by specific AA mixtures may represent a promising anticancer strategy able to selectively induce death of cancer cells through the induction of apoptosis *via* both UPS inhibition and autophagy activation.

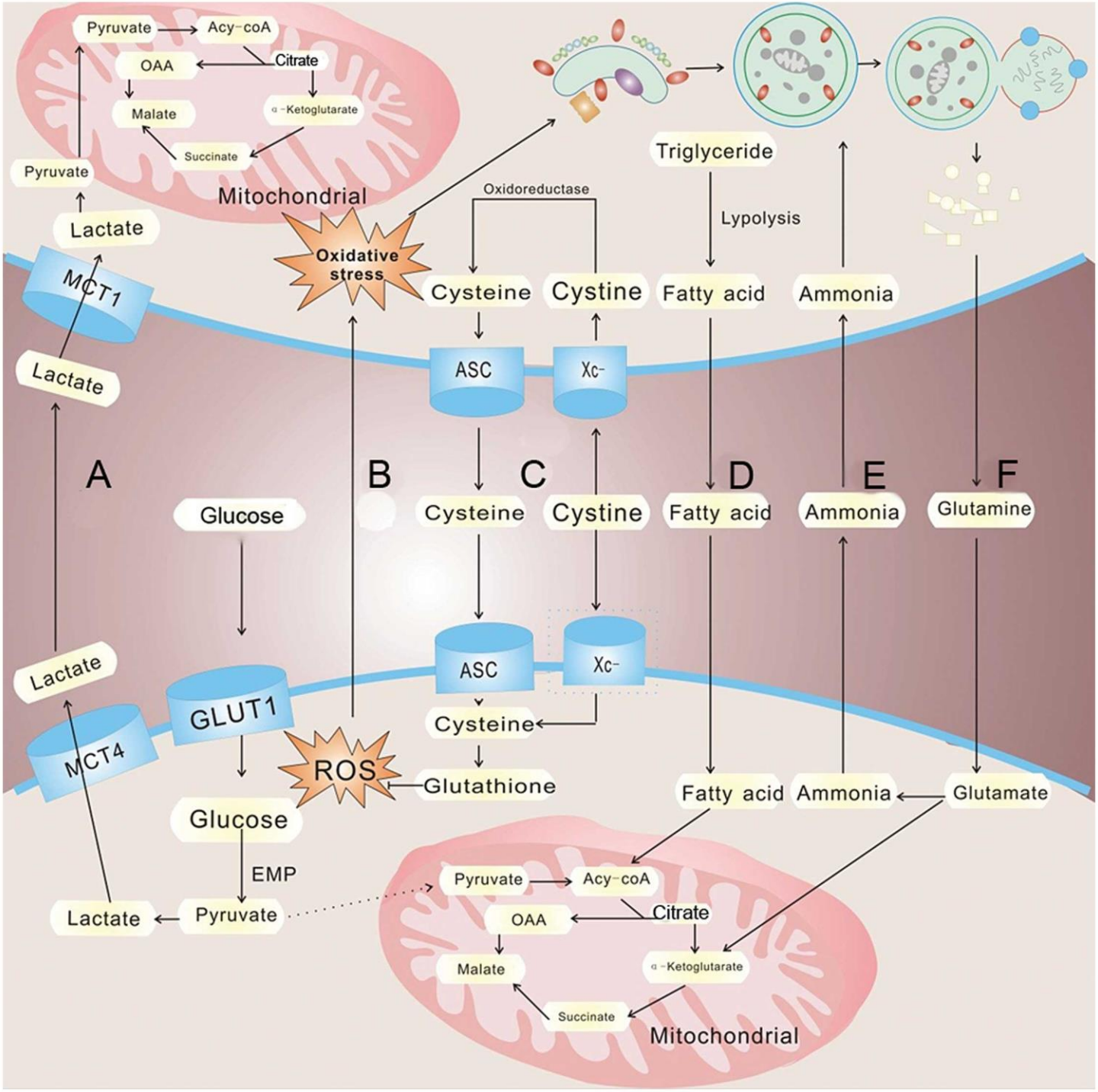
Tumor suppressors and proto-oncogenes regulate the metabolic pathways involved in tumor growth

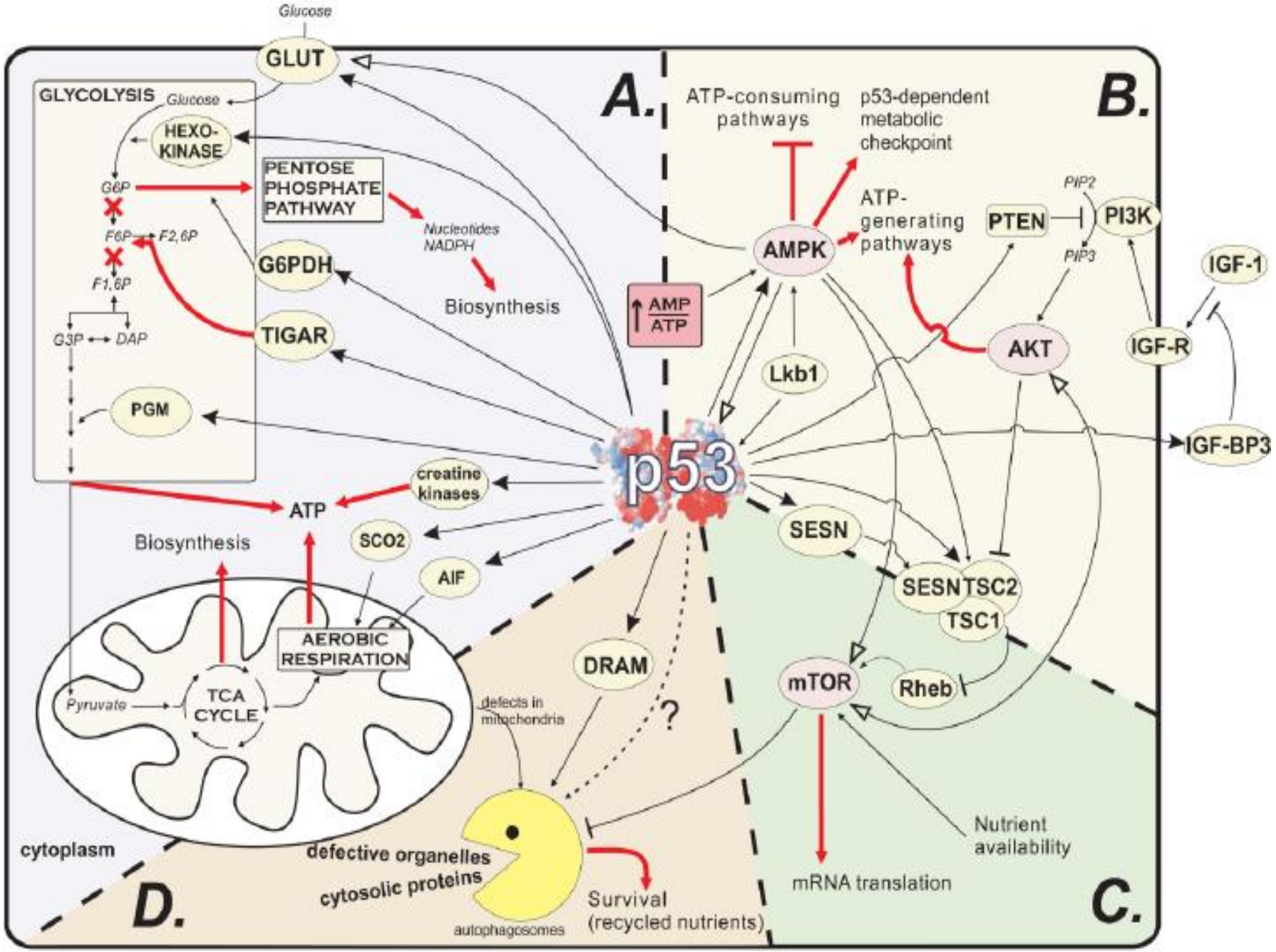



Growth factor stimulation
PI3K/AKT
Tyrosine kinase
Glucose
Glucose transporter
Glucose
Hexo-kinase
Glucose-6-P
Fructose-6-P
AMPK
Phospho-fructo-kinase
LKB1
FBP
Glyceraldehyde-3-P
PEP
Pyruvate kinase M2
Low activity
High activity
Pyruvate
Lactate dehydrogenase A
Lactate
Malic enzyme
NADPH
NADP
Malate
NADP
NADPH
Glucose-6-phosphate dehydrogenase
6-P-gluconolactone
6-P-gluconate
Pentose phosphate shunt
NADP
NADPH
p53
Transketolase/ Transaldolase
Ribose-5-phosphate
Nucleotide synthesis
Glycolysis
Amino acid synthesis
Acetyl-CoA
Lipid synthesis
ATP-citrate lyase
Oxaloacetate
Citrate
Isocitrate
NADP
Isocitrate dehydrogenase 1
NADPH
α-Ketoglutarate
Glutamine transporter
Glutamine
Glutamine
Glutaminase
Glutamate
Glutaminolysis
Myc
Succinate dehydrogenase
Succinate
α-Ketoglutarate
TCA cycle
Malate
Pyruvate
Pyruvate dehydrogenase
CO_2
Acetyl-CoA
Oxaloacetate
Citrate

METABOLIC CROSS-TALK BETWEEN CANCER CELLS AND CANCER ASSOCIATED FIBROBLASTS

Rol of the tumor microenvironment in the regulation of cancer cell metabolism. (A) Tumor cells, under hypoxic conditions, secrete lactate via MCT4. In response, cancer-associated fibroblasts (CAFs) and oxygenated tumor cells take up the tumor-extruded lactate. (B) Cancer cells induce ROS production in CAFs, leading to the onset of stromal oxidative stress, which in turn, drives autophagy and provides recycled nutrients via catabolism and aerobic glycolysis to feed the appetite of adjacent cancer cells. (c) Tumor stromal cells are able to take up cystine, convert it to the amino acid cysteine, and then secrete it. Tumor cells then use cysteine to produce glutathione, resulting in increased ROS resistance and survival. (D) Adipocytes provide tumor cells with fatty acids supplying the energy needs of rapid tumor growth. (E) Glutamine can be hydrolyzed as ammonia in tumor cells and reused by CAFs. (F) CAFs secrete glutamine into the tumor microenvironment to meet the glutamine needs of the cancer cells. MCT4, monocarboxylate transporter 4; GLUT1: Glucose transporter 1; ASC: Neutral amino acid transporter A; XC-: Cystine/glutamate transporter; ROS: Reactive Oxygen Species; OAA: Oxaloacetate.


Pyruvate
Acy-coA
OAA
Citrate
Malate
α-Ketoglutarate
Succinate
Mitochondrial
Pyruvate
Lactate
MCT1
Lactate
Oxidative stress
Oxidoreductase
Triglyceride
Lypolysis
Cysteine
Cystine
Fatty acid
Ammonia
ASC
Xc-
A
B
C
D
E
F
Glucose
Cysteine
Cystine
Fatty acid
Ammonia
Glutamine
Lactate
GLUT1
MCT4
ASC
Xc-
Cysteine
ROS
Glutathione
Fatty acid
Ammonia
Glutamate
Glucose
EMP
Lactate
Pyruvate
Pyruvate
Acy-coA
OAA
Citrate
Malate
α-Ketoglutarate
Succinate
Mitochondrial


Glucose
GLUT
A.
B.
GLYCOLYSIS
Glucose
HEXO-KINASE
G6P
PENTOSE PHOSPHATE PATHWAY
Nucleotides NADPH
Biosynthesis
F6P
F2,6P
G6PDH
F1,6P
G3P
DAP
TIGAR
PGM
ATP-consuming pathways
p53-dependent metabolic checkpoint
AMPK
ATP-generating pathways
AMP/ATP
Lkb1
PIP2
PIP3
PTEN
PI3K
IGF-1
IGF-R
AKT
IGF-BP3
p53
creatine kinases
ATP
Biosynthesis
SCO2
AIF
SESN
SESN
TSC2
TSC1
AEROBIC RESPIRATION
Pyruvate
TCA CYCLE
DRAM
defects in mitochondria
?
mTOR
Rheb
Nutrient availability
mRNA translation
cytoplasm
defective organelles
cytosolic proteins
autophagosomes
Survival (recycled nutrients)
D.
C.

“The prime cause of cancer is the replacement of the respiration of oxygen ... in normal body cells by fermentation of sugar”

Otto Warburg 1956

Tumor cells derive nearly all of their fatty acids from de novo synthesis

Sidney Weinhouse 1953

remember citrate lyase?

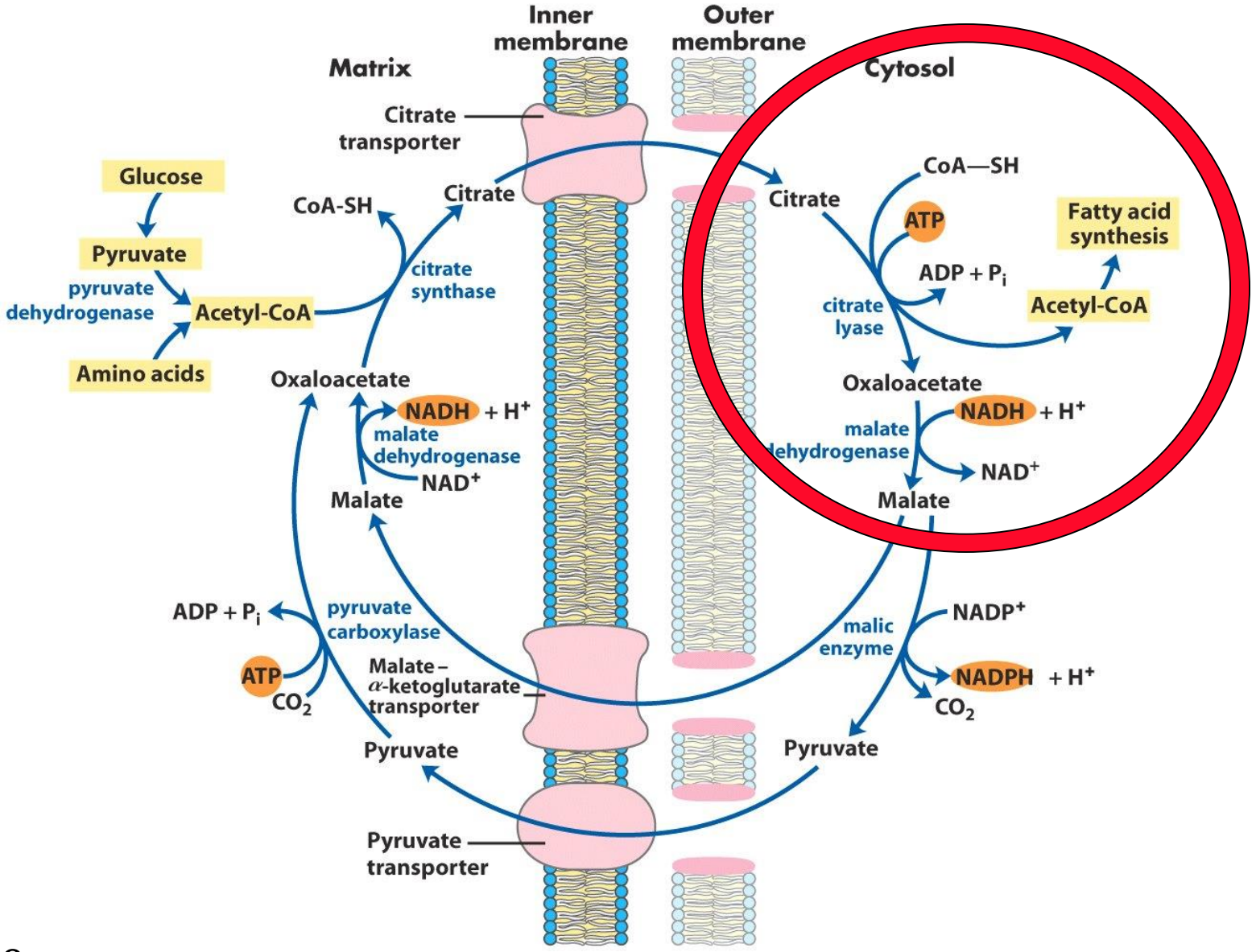
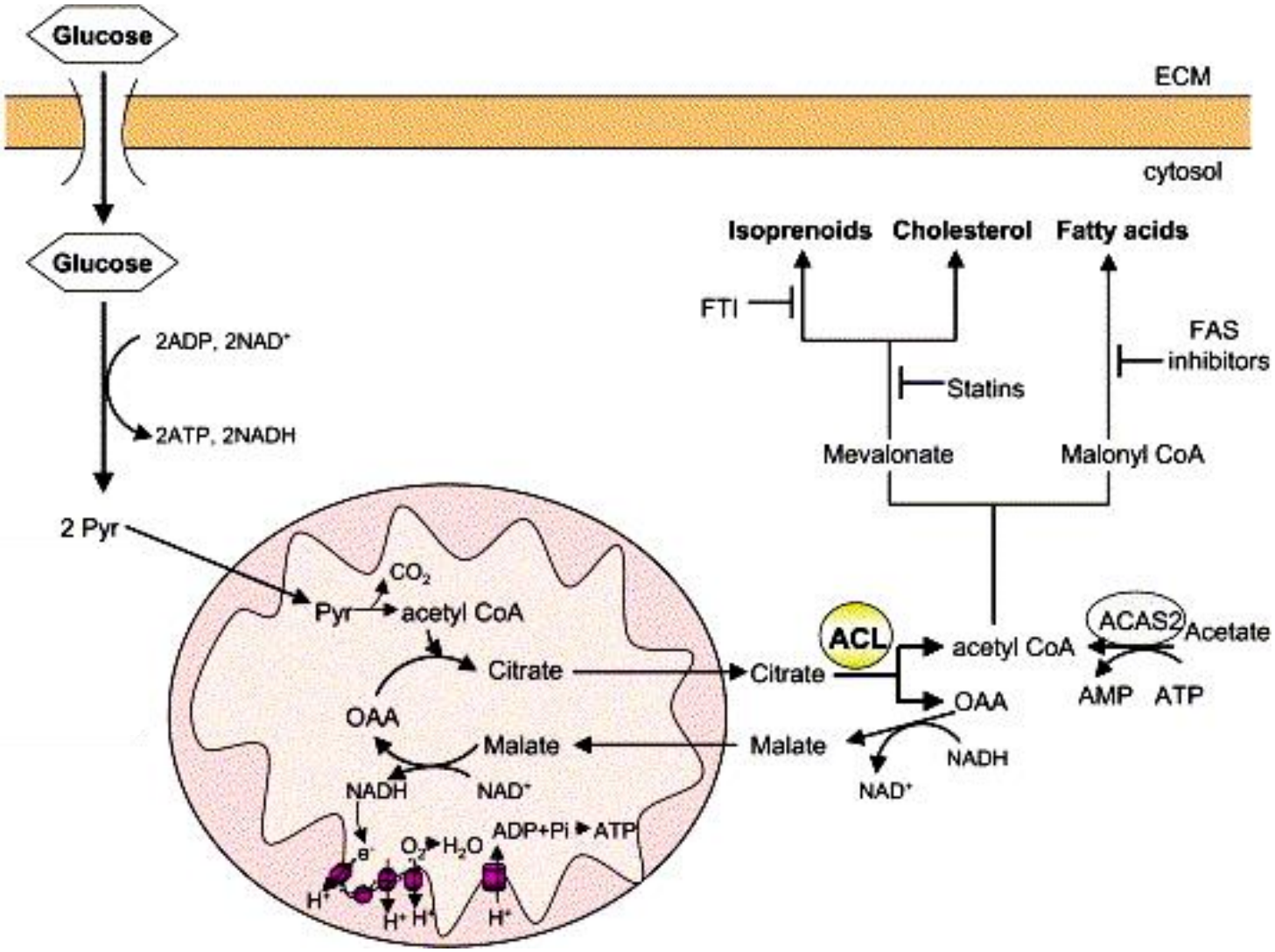
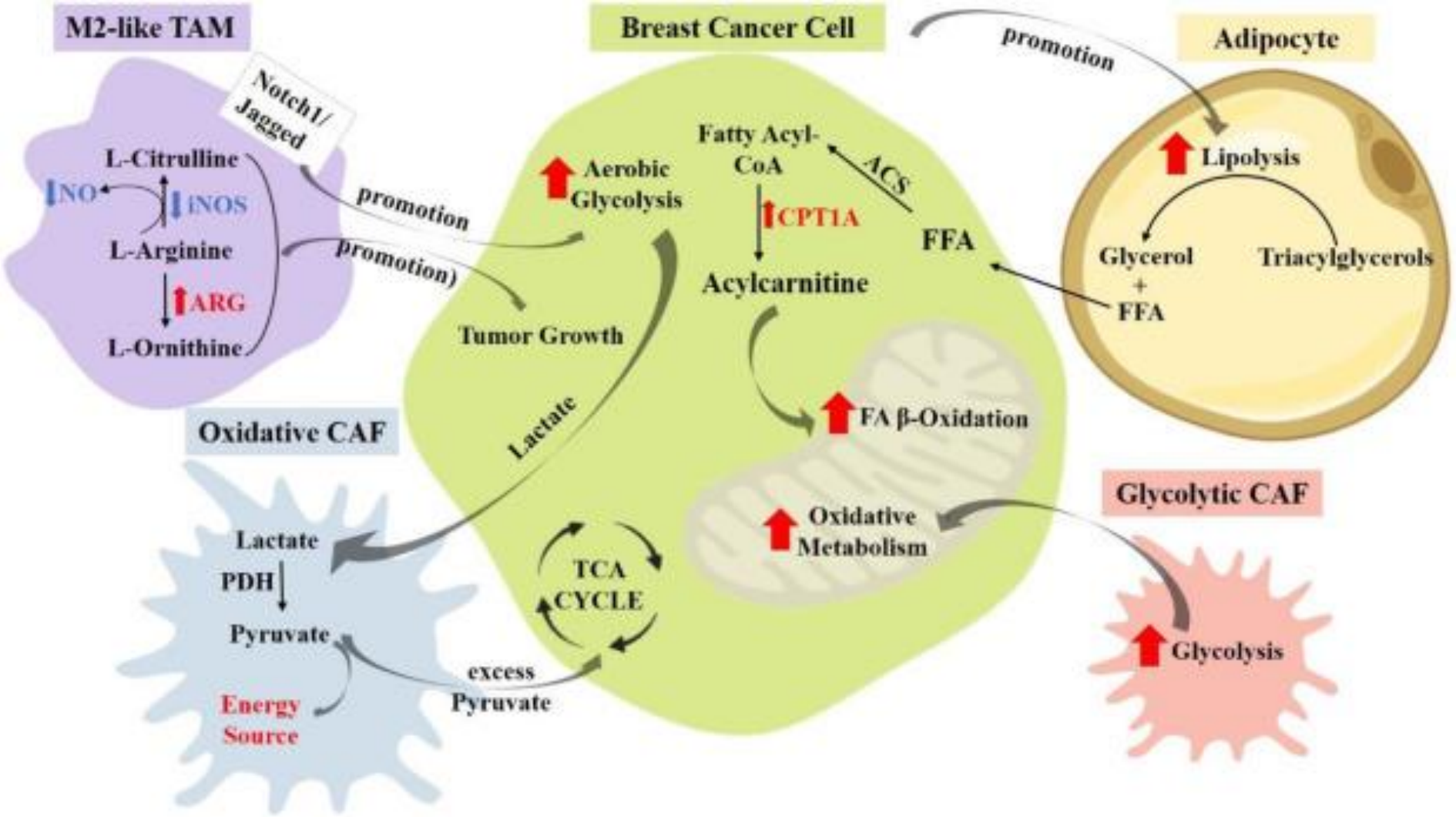


fig 21-10

FA synthesis is reduced in glycolytic tumor cells




M2-like TAM
Notch1/
Jagged
L-Citrulline
NO
iNOS
L-Arginine
ARG
L-Ornithine
promotion
promotion)
Breast Cancer Cell
Aerobic
Glycolysis
Fatty Acyl-
CoA
ACS
CPT1A
Acylcarnitine
FFA
Tumor Growth
Lactate
FA β-Oxidation
Oxidative
Metabolism
TCA
CYCLE
promotion
Adipocyte
Lipolysis
Glycerol
+
FFA
Triacylglycerols
Oxidative CAF
Lactate
PDH
Pyruvate
Energy
Source
excess
Pyruvate
Glycolytic CAF
Glycolysis

IDH and GLS inhibitors are in clinic

nature biotechnology

Altmetric: 16 Citations: 8 More detail »

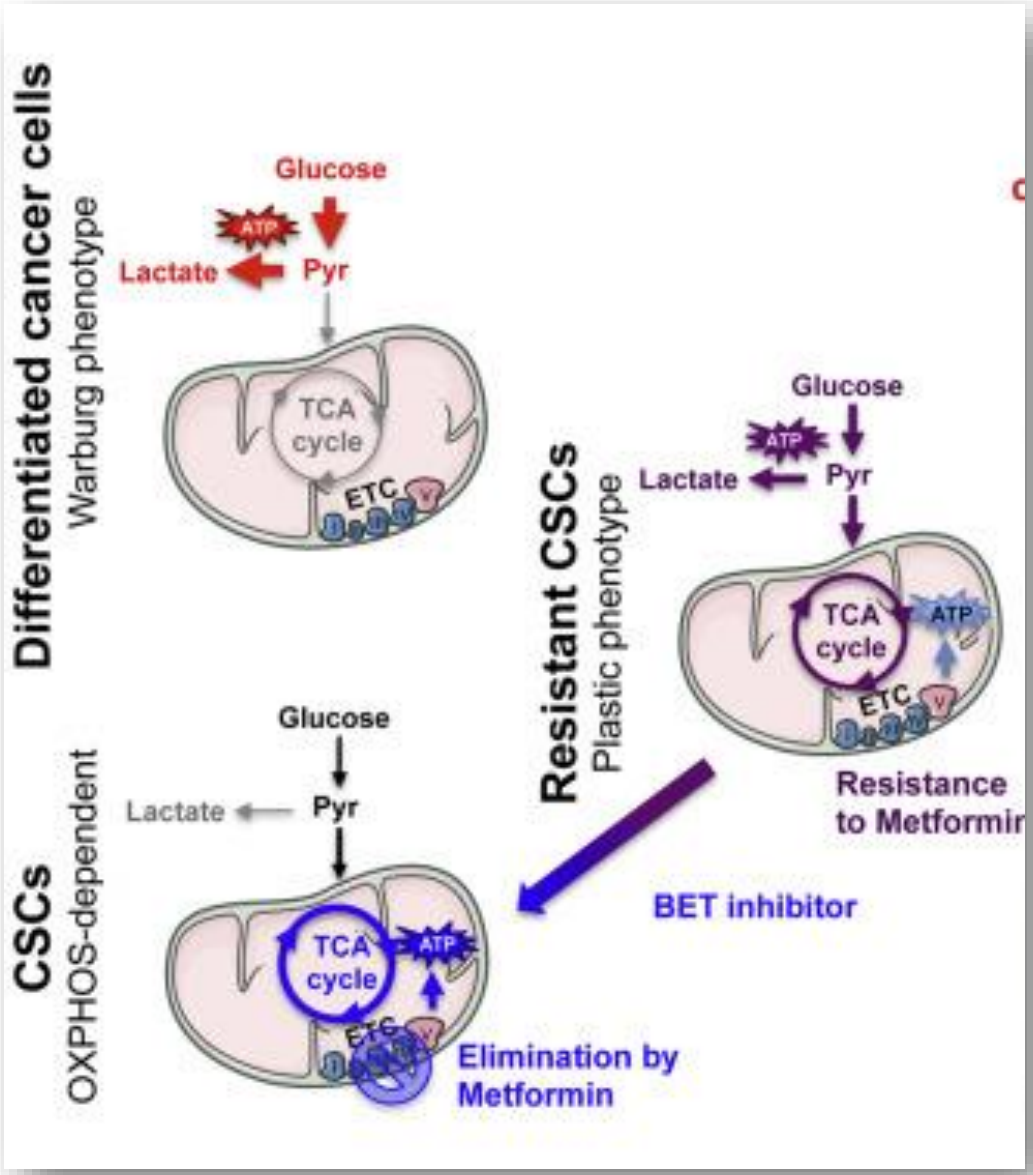
News

Cancer anabolic metabolism inhibitors move into clinic

Ken Garber

Company/location	Agent	Target	Indications	Status
Agios & Celgene	AG-221, AG-120, AG-881	IDH1 and IDH2	AML, MDS, solid tumors	Phase 3
Polaris Group/San Diego	ADI-PEG 20	Pegylated arginine deiminase	Hepatocellular carcinoma (HCC), others	Phase 3 in HCC missed primary endpoint
Cornerstone Pharmaceuticals/Cranbury, New Jersey	CPI-613	Pyruvate dehydrogenase	AML, MDS, solid tumors	Phase 2
Calithera Biosciences	CB-839	Glutaminase 1	RCC, breast cancer	Phase 1/2
3-V Biosciences	TVB-2640	Fatty acid synthase	Ovarian, breast, lung	Phase 2 pending
Novartis/Basel	IDH305	IDH1	Advanced cancers	Phase 1
Forma Therapeutics/Watertown, Massachusetts	FT-2102	IDH1	AML, MDS	Phase 1
Bayer/Leverkusen, Germany	BAY-1436032	IDH1	Solid tumors	Phase 1
Advanced Cancer Therapeutics/Louisville, Kentucky	PFK-158	PFKFB3	Solid tumors	Phase 1
Aeglea BioTherapeutics/ Austin, Texas	AEB-1102	Modified human arginase	AML, MDS, solid tumors	Phase 1

Resistance through metabolic reprogramming



Conclusions

Metabolism of cancer cells is different from that of normal cells

Dysregulated metabolism can drive oncogenic processes

Altered metabolism offers a therapeutic window to target cancer cells

Key references & links

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