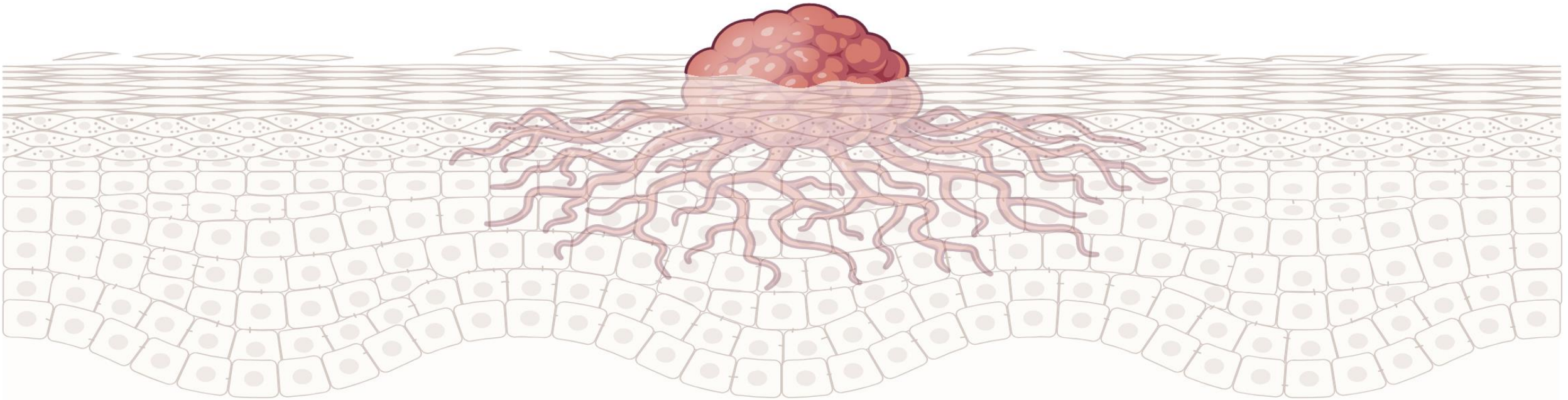
CANCER METABOLISM

PATHG4500 CANCER BIOLOGY

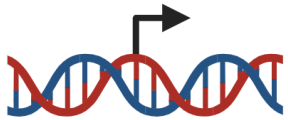
Lecture objectives

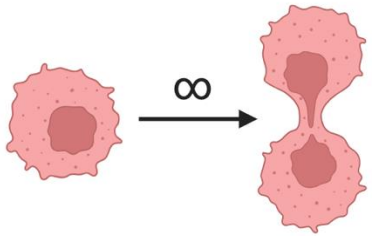
- Why do cancer cells rewire their metabolic programs?
- What are the functional consequences of these changes?
- Is there a therapeutic window for targeting cancer metabolism?

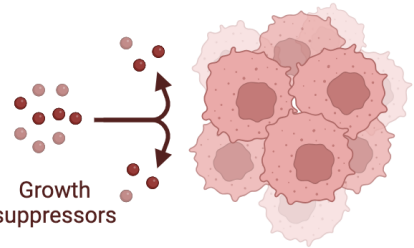
CANCER

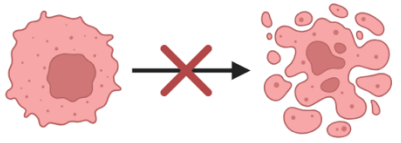


Sustained proliferative signaling	Enabling replicative immortality	Evading growth suppressors	Resisting cell death

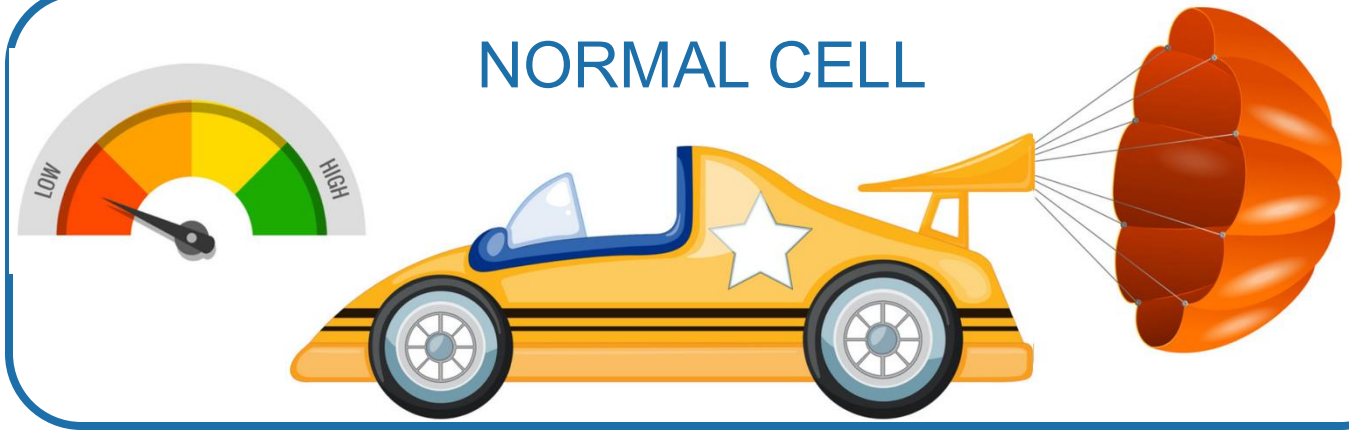




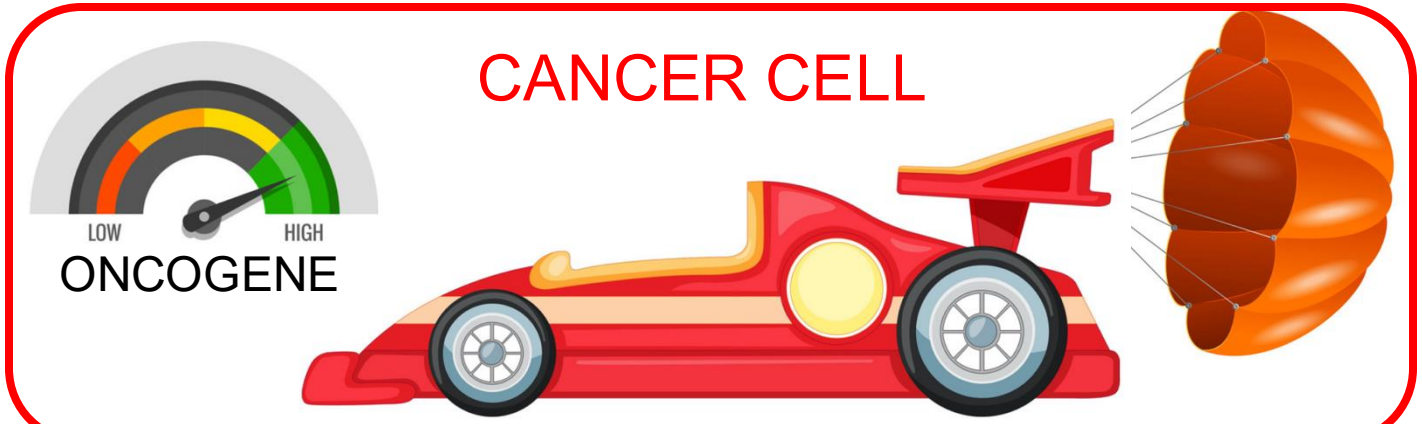




NORMAL CELL

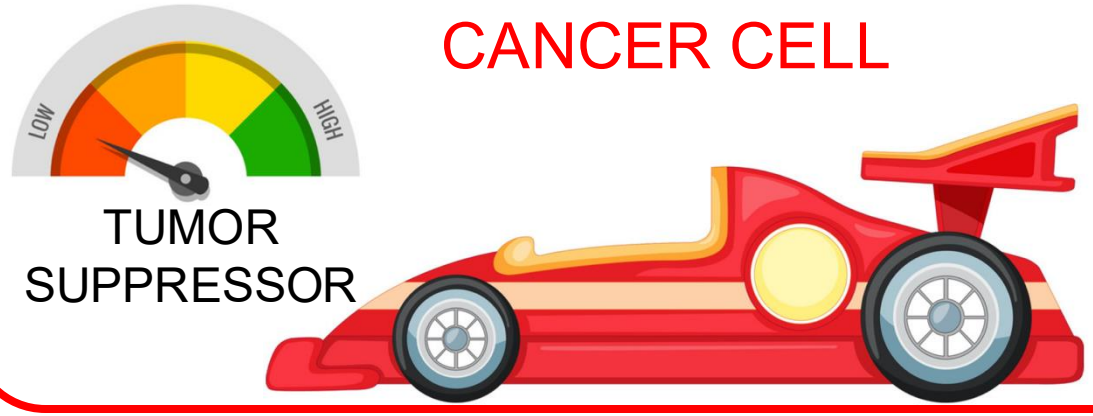


CANCER CELL



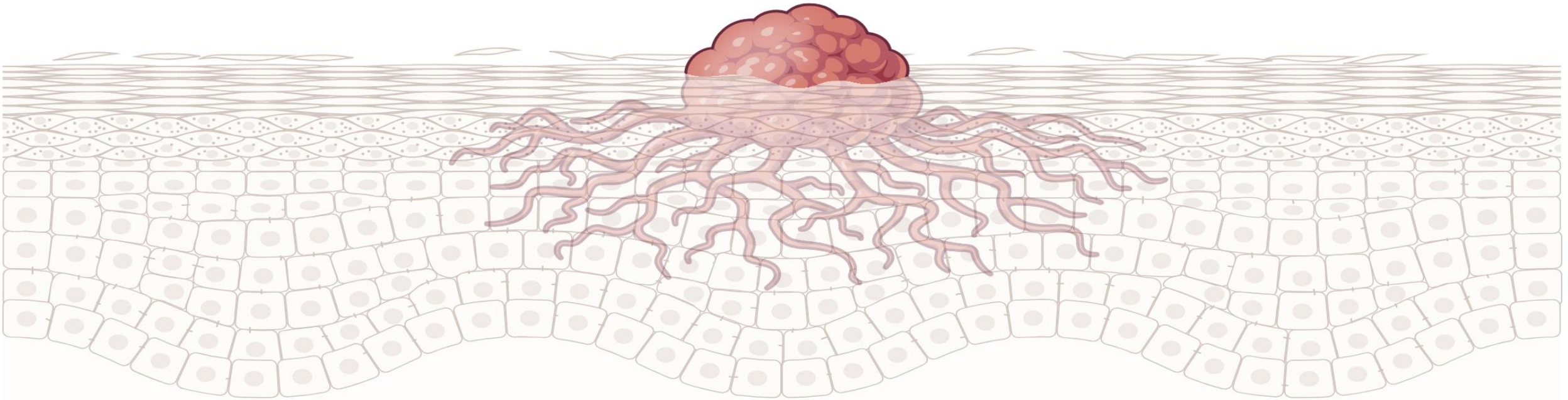
ONCOGENE

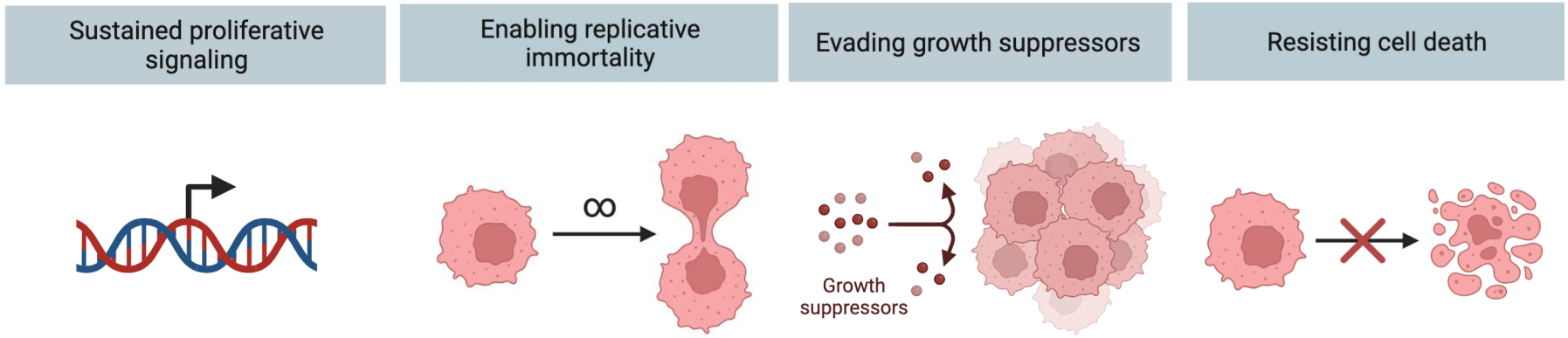
CANCER CELL



TUMOR SUPPRESSOR

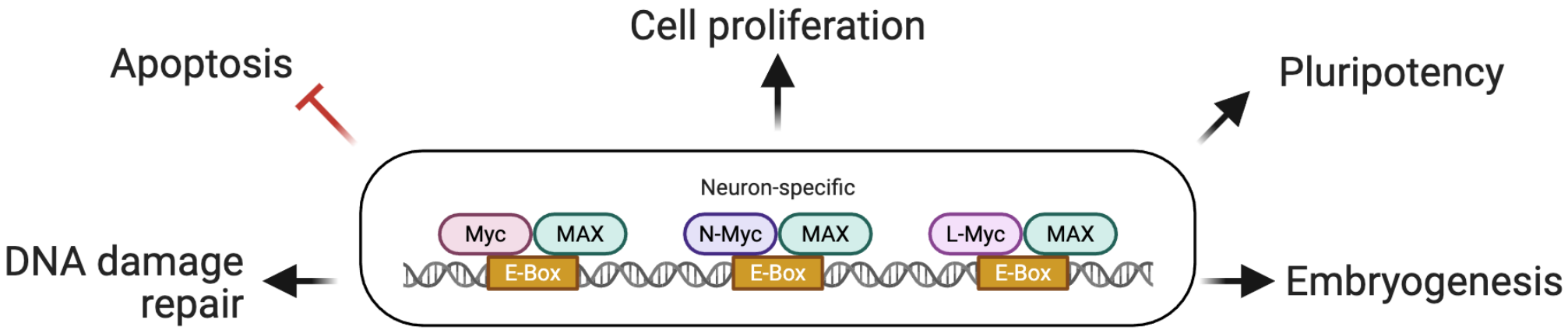
CANCER





Are these the key functions of oncogenes and tumor suppressor genes?

The gas pedal: Myc



Proc Natl Acad Sci U S A. 1997 Jun 24;94(13):6658–6663. doi: 10.1073/pnas.94.13.6658

c-Myc transactivation of *LDH-A*: Implications for tumor metabolism and growth

Hyunsuk Shim [*], Christine Dolde [†], Brian C Lewis [†], Chyi-Sun Wu [*], Gerard Dang [*], Richard A Jungmann [‡], Riccardo Dalla-Favera [§], Chi V Dang [*,†,¶,‖,**]

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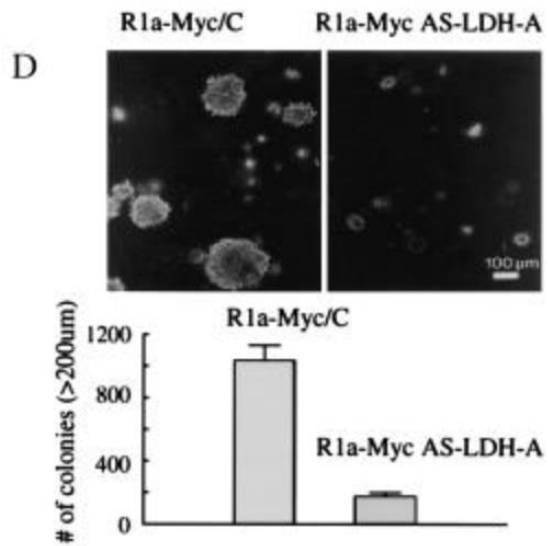
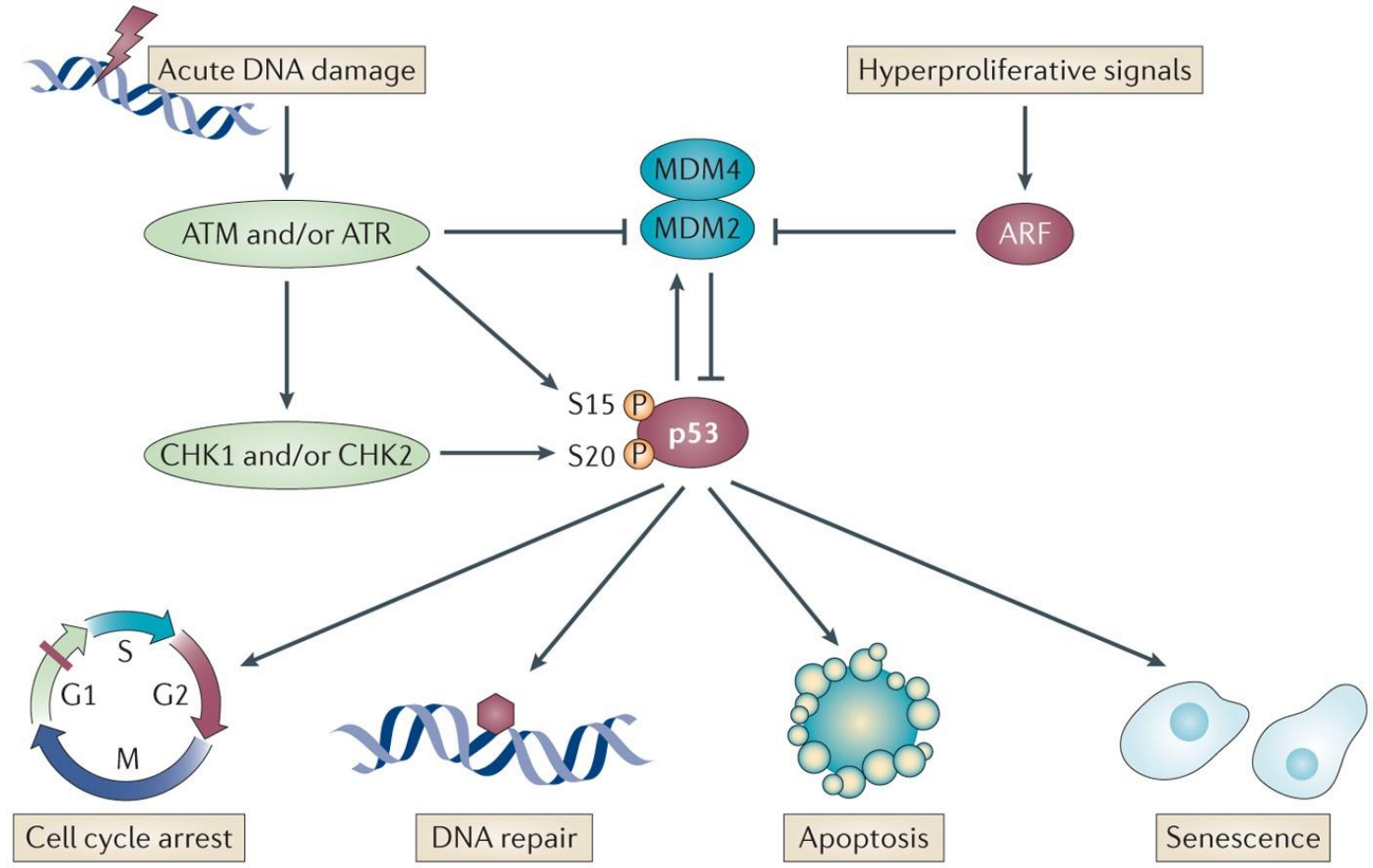
PMCID: PMC21214 PMID: 9192621



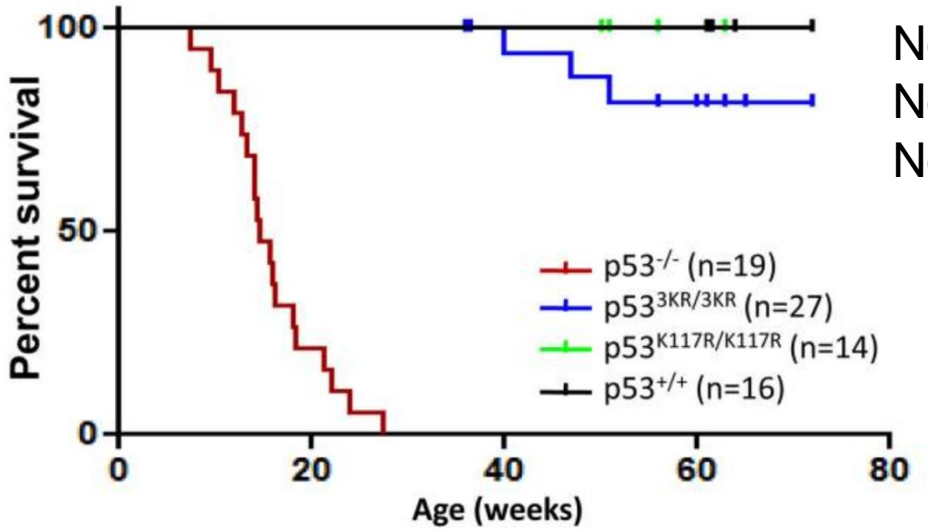
The brake: p53



Bieging et al, 2014

Tumor Suppression in the Absence of p53-Mediated Cell-Cycle Arrest, Apoptosis, and Senescence

Tongyuan Li,[1] Ning Kon,[1] Le Jiang,[1] Minjia Tan,[2] Thomas Ludwig,[1] Yingming Zhao,[2] Richard Baer,[1] and Wei Gu[1,*]
[1]Institute for Cancer Genetics, and Department of Pathology and Cell Biology, College of Physicians and Surgeons, Columbia University, 1130 St. Nicholas Avenue, New York, NY 10032, USA
[2]Ben May Department of Cancer Research, The University of Chicago, Chicago, IL 60637, USA
*Correspondence: wg8@columbia.edu
DOI 10.1016/j.cell.2012.04.026

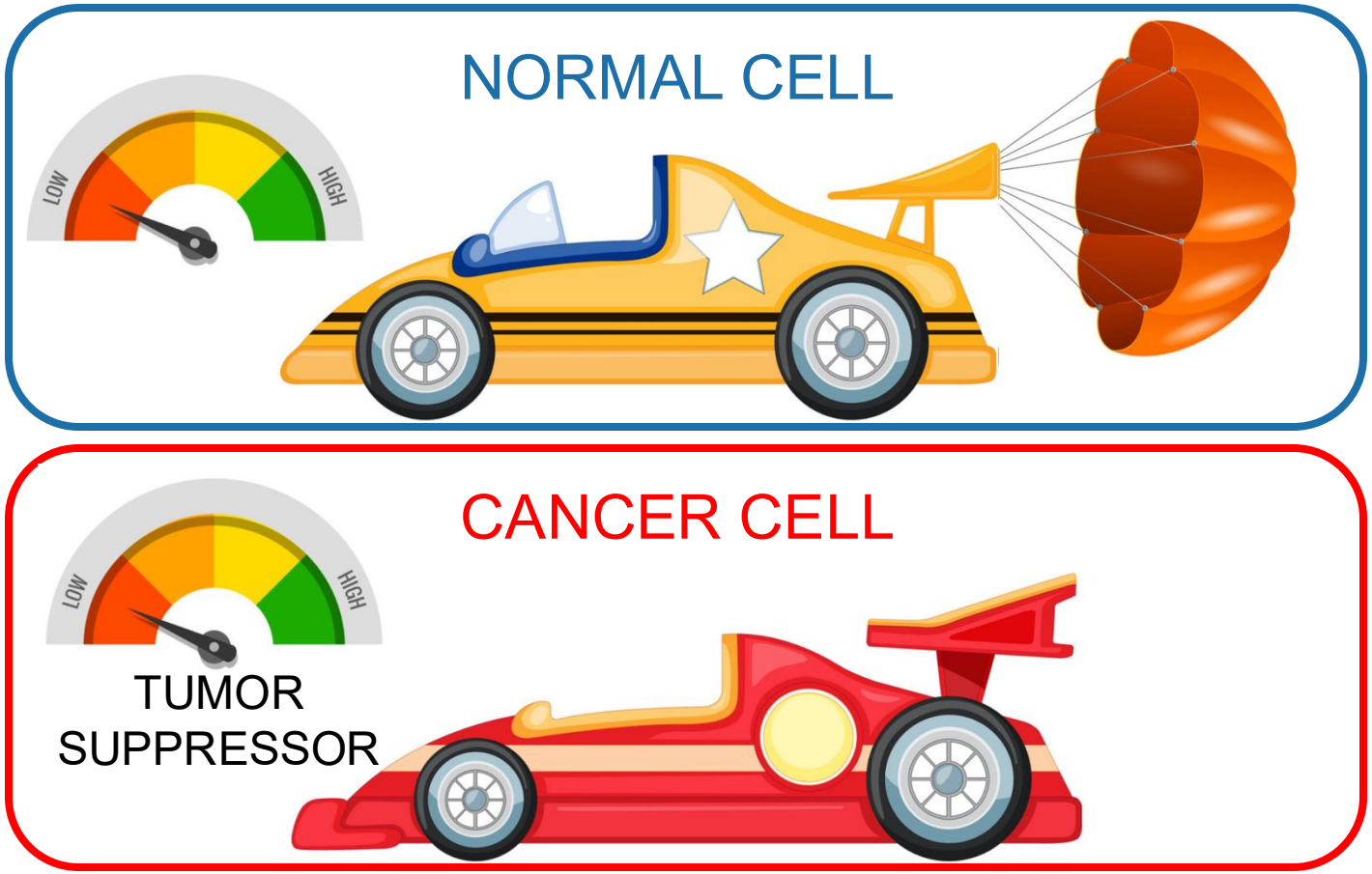


Not cell cycle arrest
Not apoptosis
Not senescence

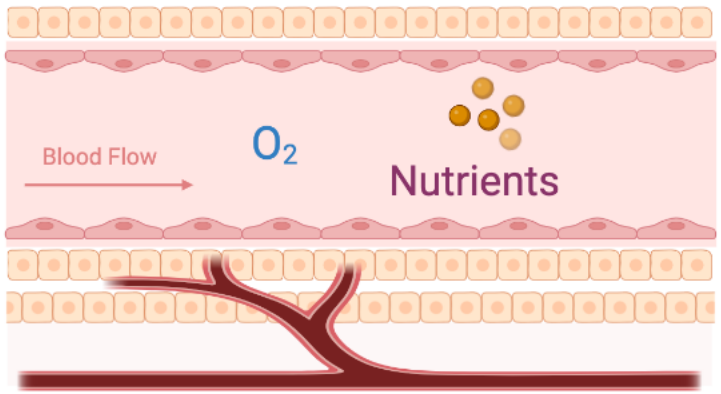
Retained ability to activate

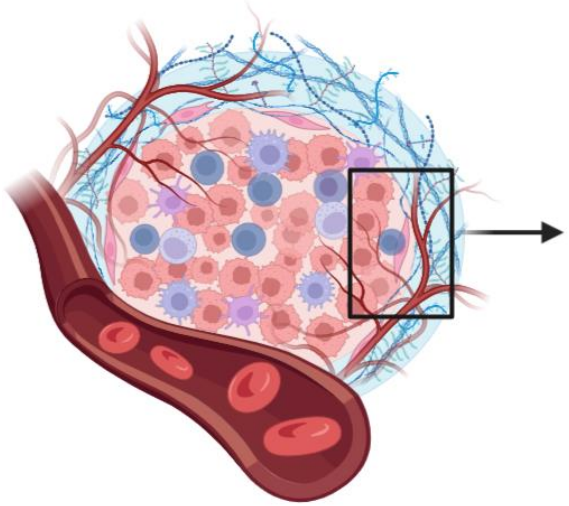
1. Gls2
2. Tigar
3. Glut3
4. GPX1

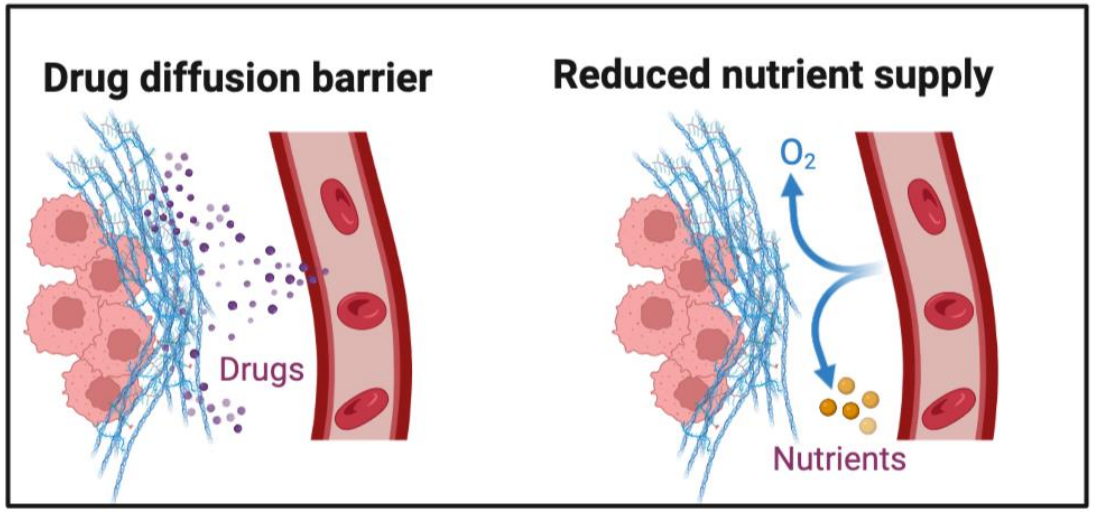
Oncogenes and tumor suppressor genes regulate how to use the fuel



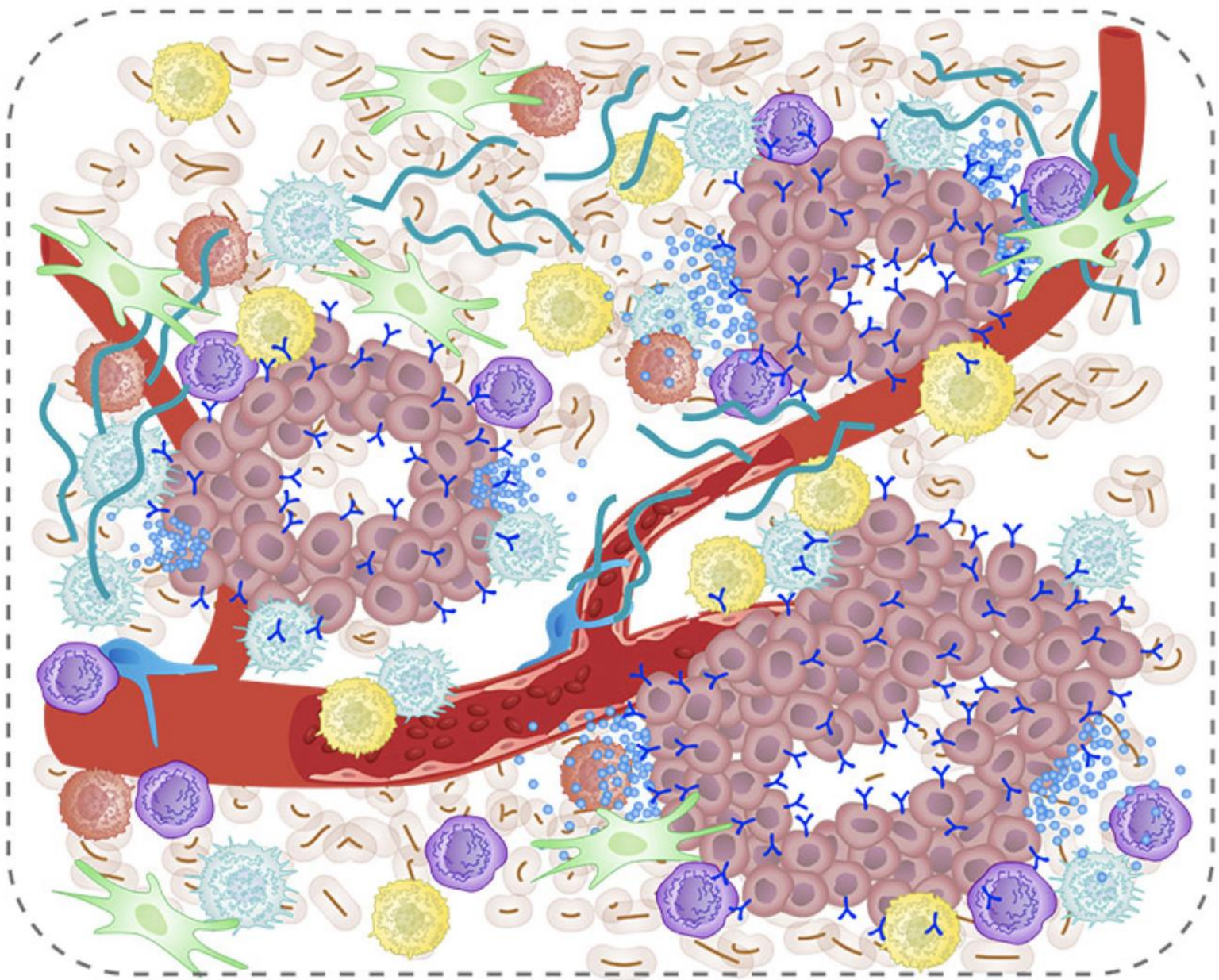
Why is fuel important and different for cancer?







The Tumor Microenvironment



Cancer cell

Vasculature

HA

Collagen

Macrophage

T-cell

Treg

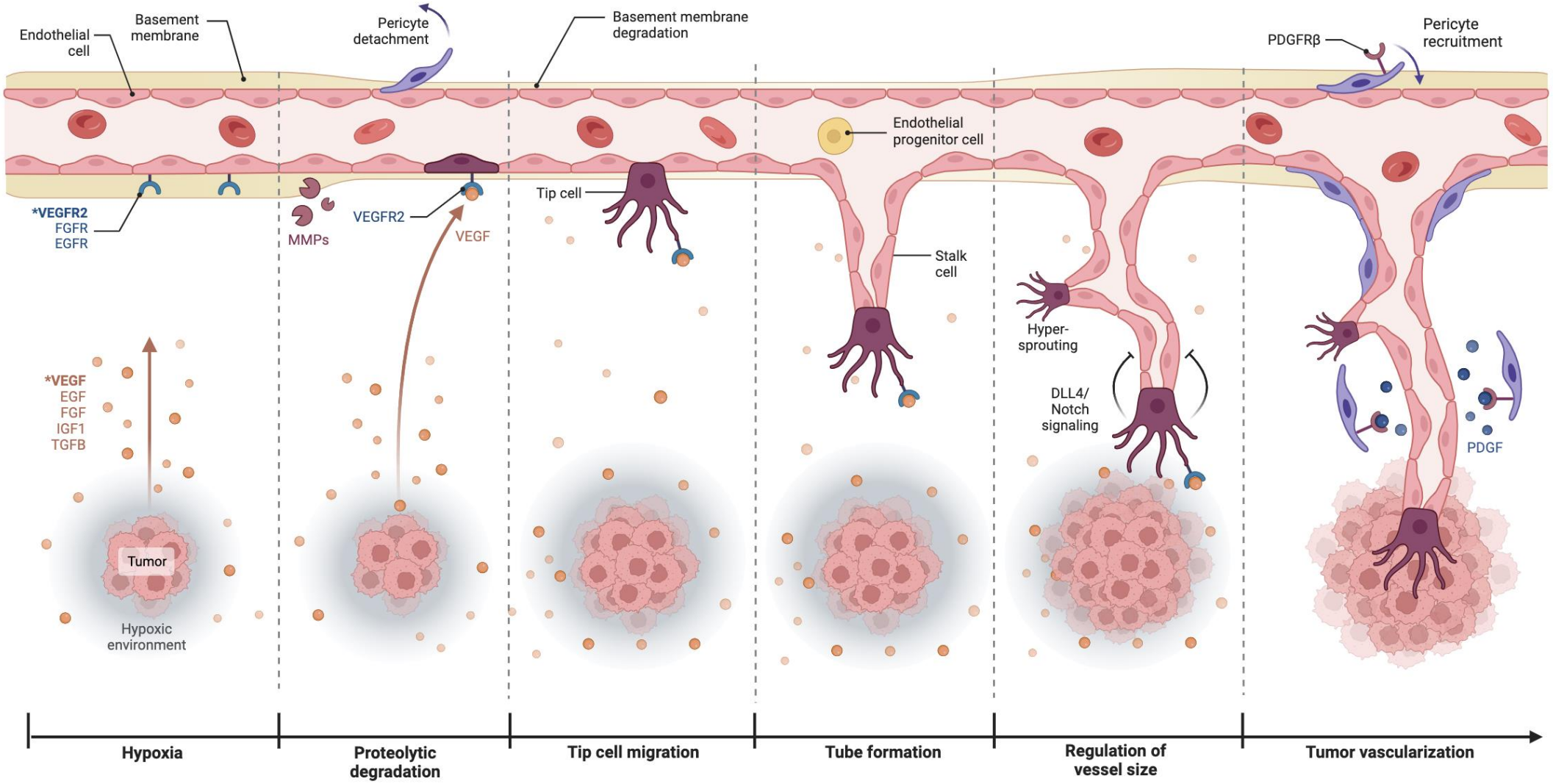
MDSC

Fibroblast

Adenosine

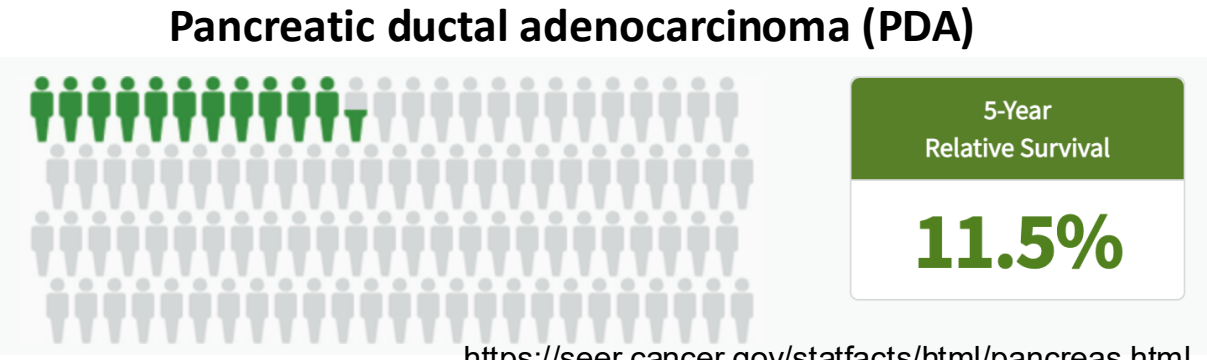
Molecular Receptors

ANGIOGENESIS

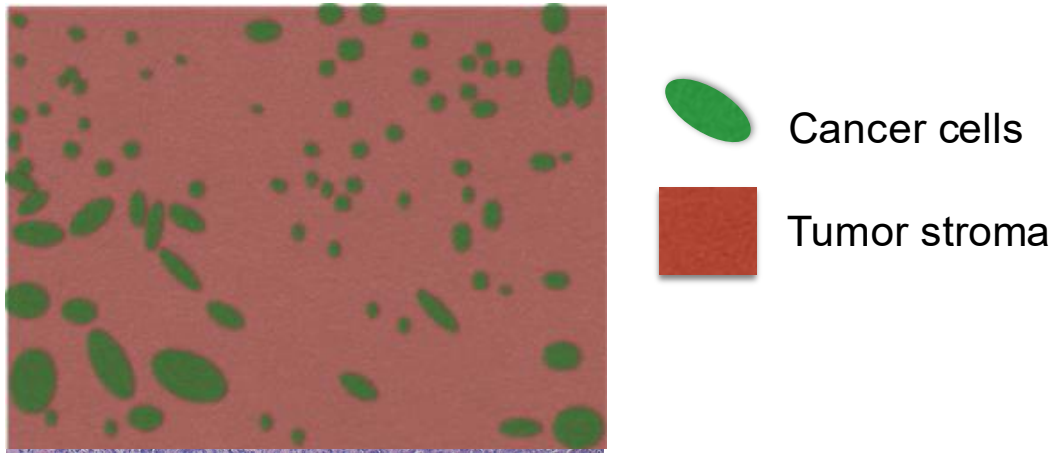


But angiogenesis does not occur in all cancers

Pancreatic ductal adenocarcinoma



https://seer.cancer.gov/statfacts/html/pancreas.html



Challenges

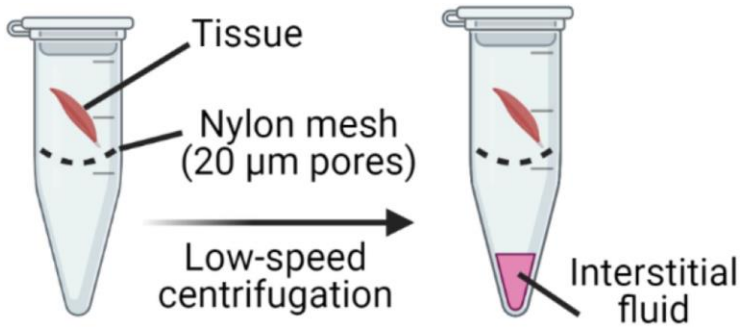
- Asymptomatic: Late Diagnosis
- Refractile to therapy
- Prone to metastasize
- Systemic deterioration

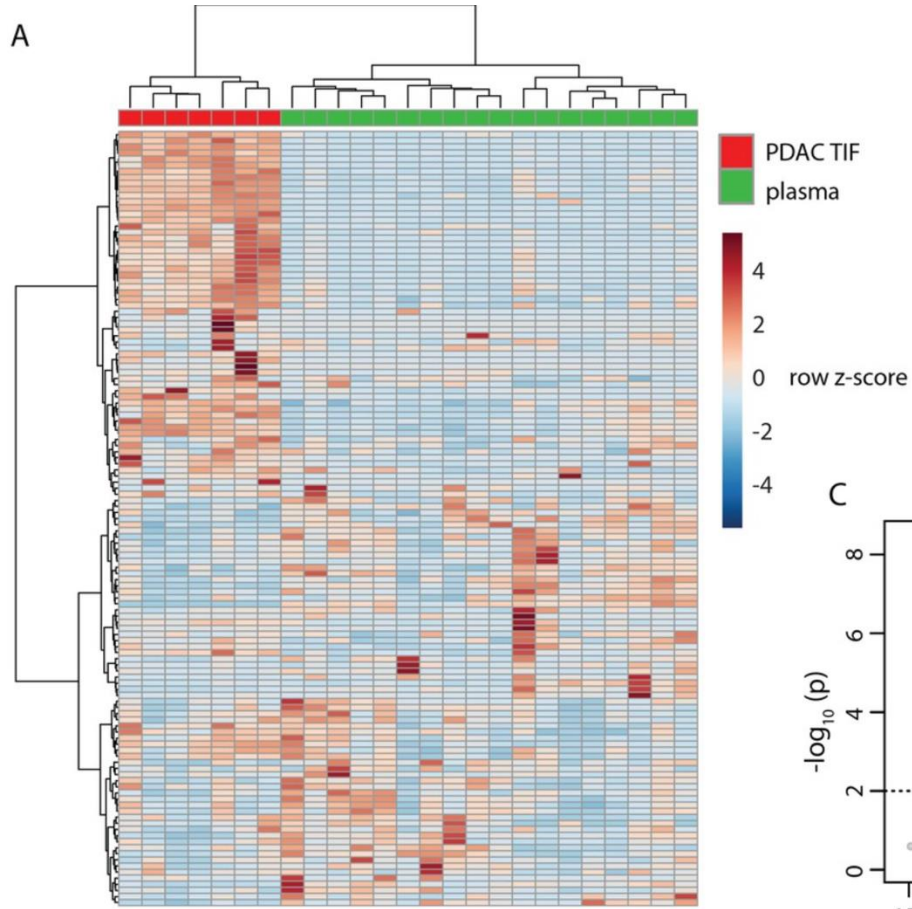
Hypovascularity necessitates cell intrinsic metabolic rewiring

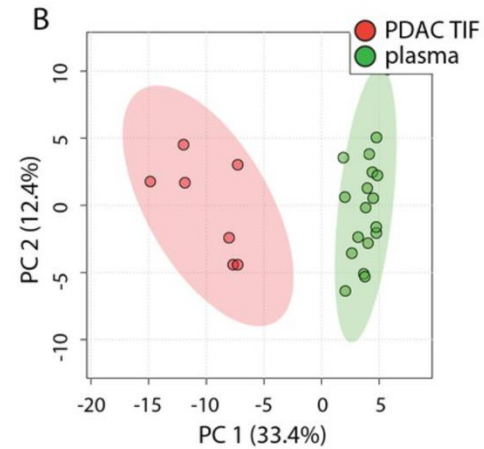
Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability

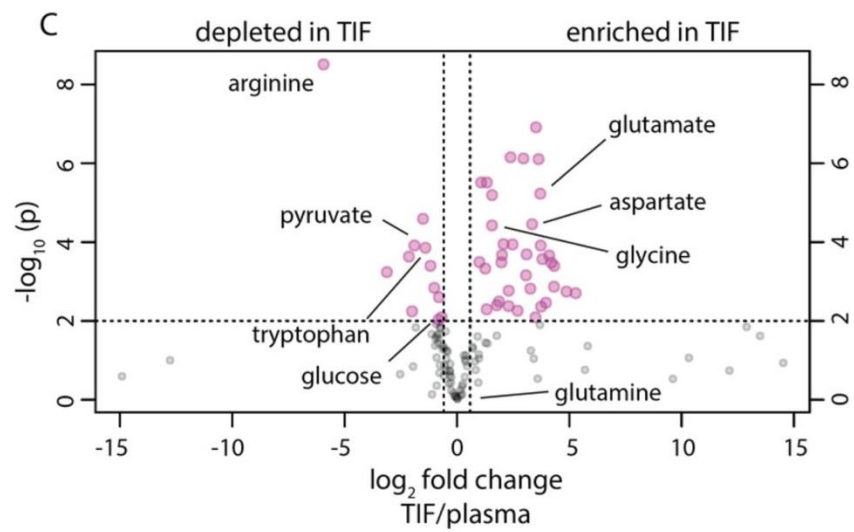
Mark R Sullivan, Laura V Danai, Caroline A Lewis, Sze Ham Chan, Dan Y Gui, Tenzin Kunchok, Emily A Dennstedt, Matthew G Vander Heiden, Alexander Muir

Massachusetts Institute of Technology, United States; University of Massachusetts, United States; Dana-Farber Cancer Institute, United States; University of Chicago, United States









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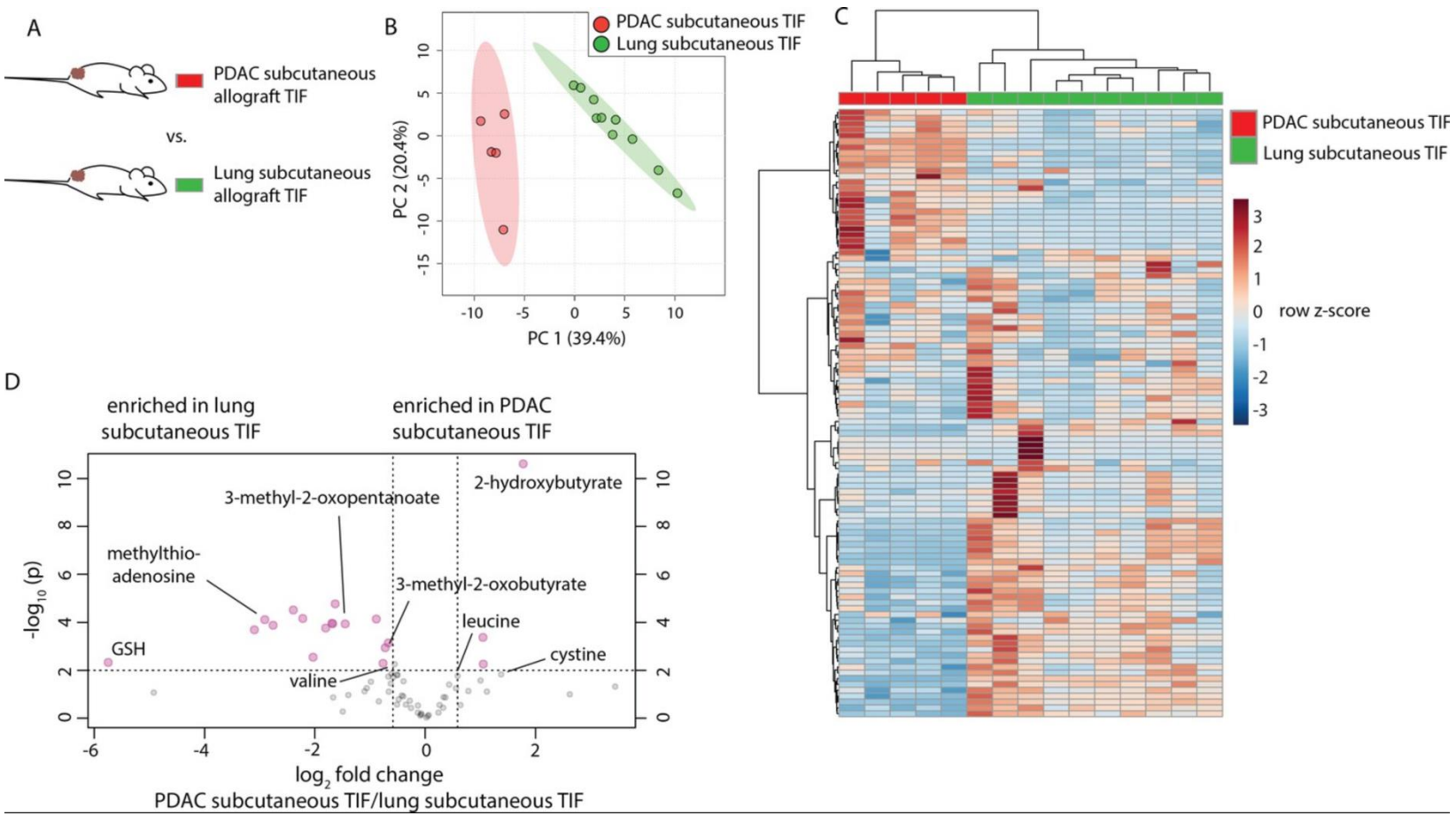
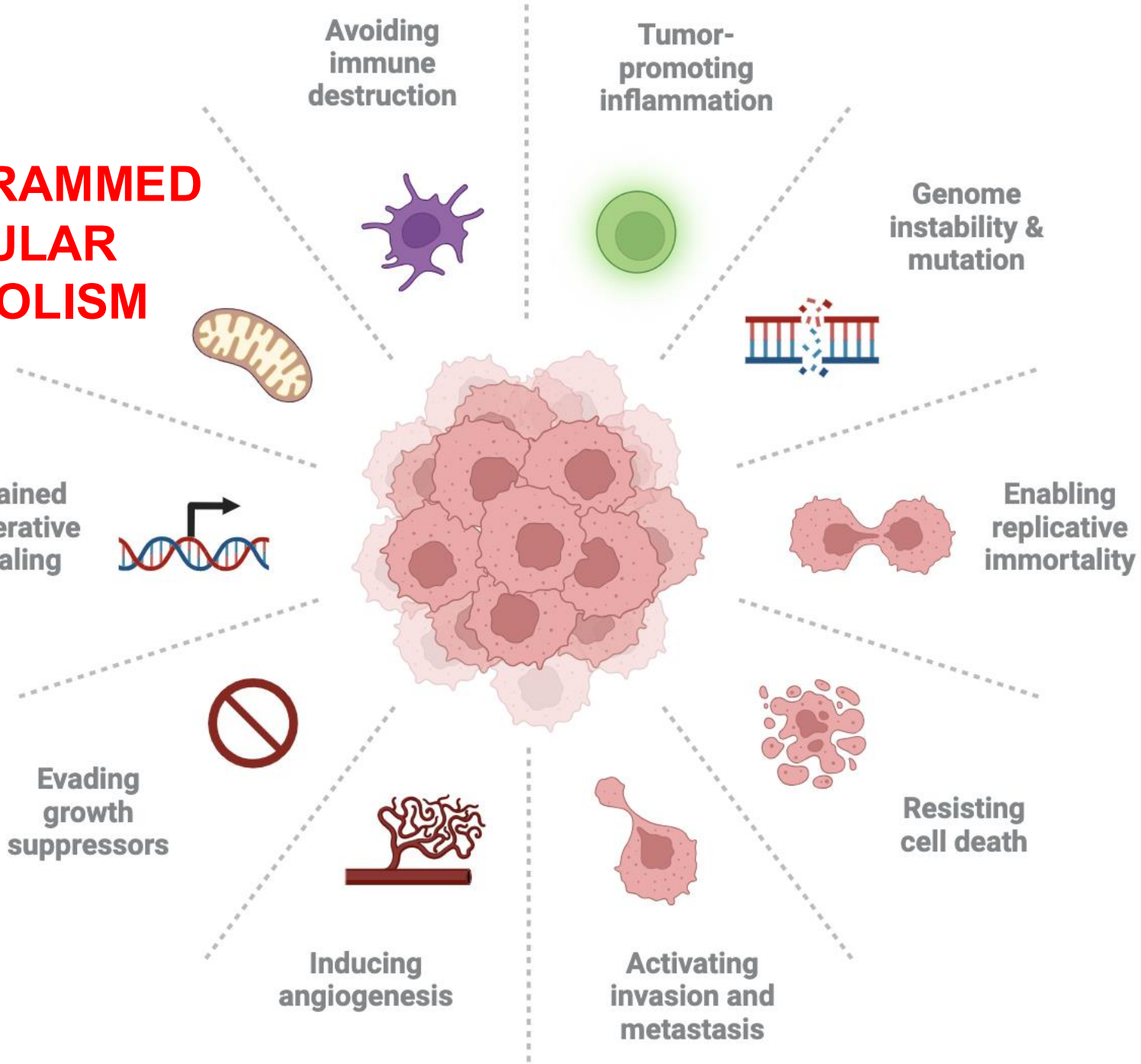
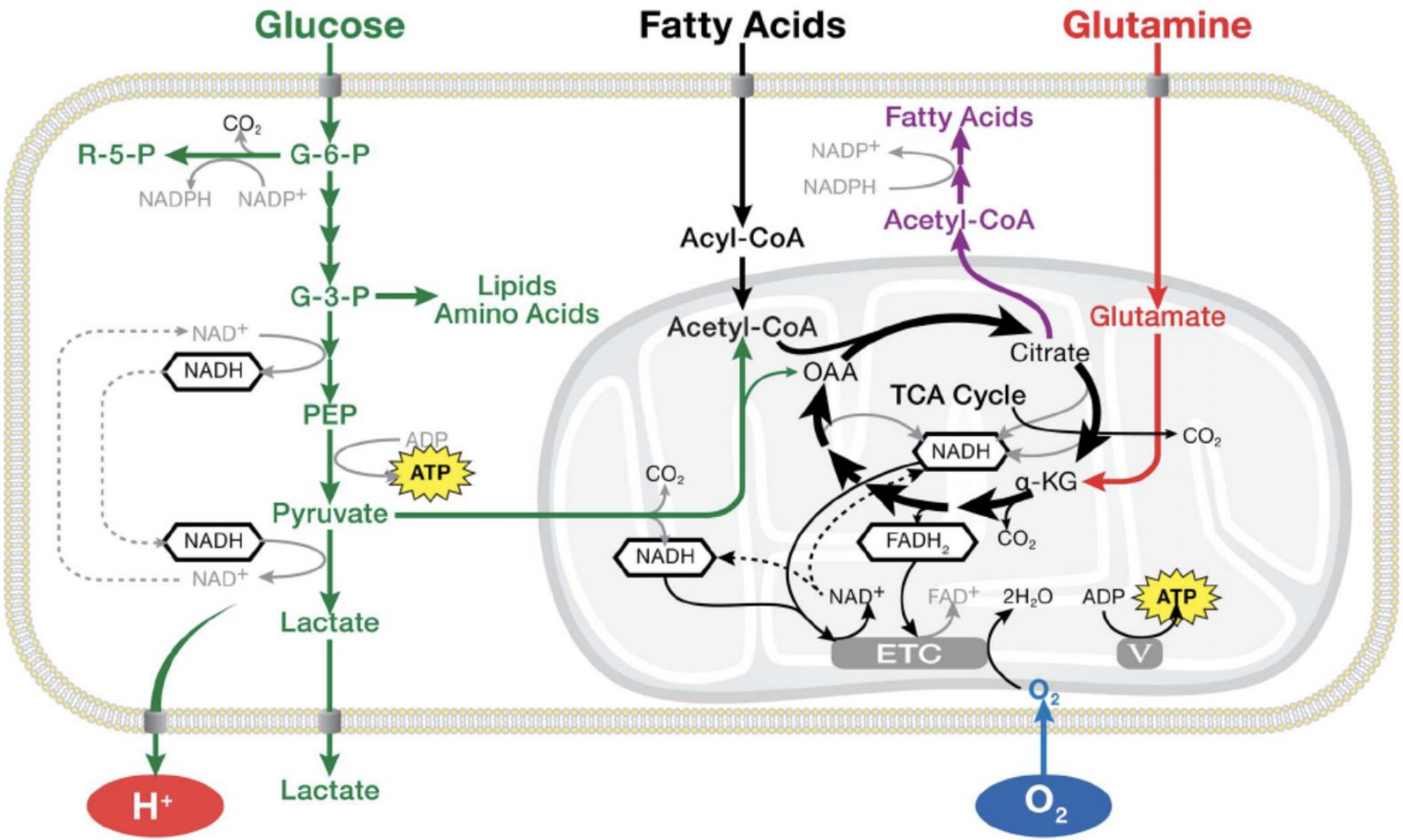


REPROGRAMMED CELLULAR METABOLISM



CELLULAR METABOLISM: A RECAP

Metabolic inputs



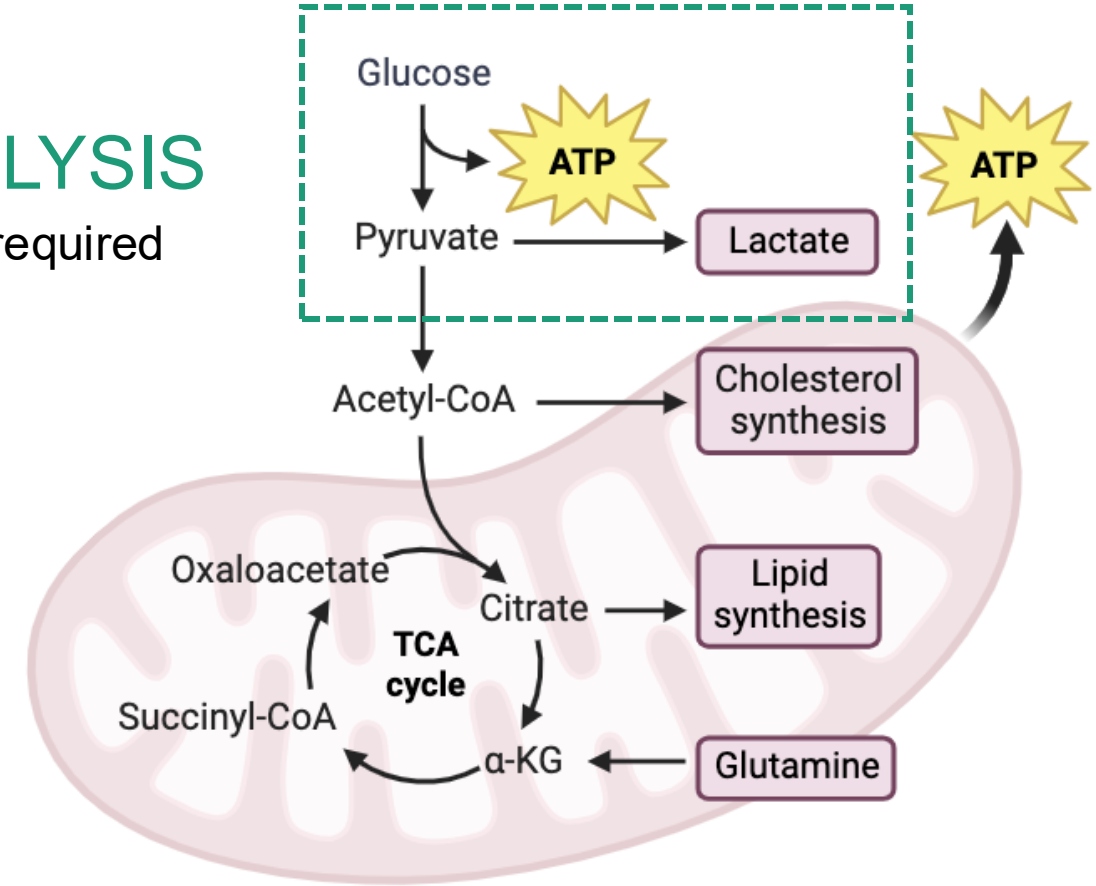
Glucose Metabolism

GLYCOLYSIS

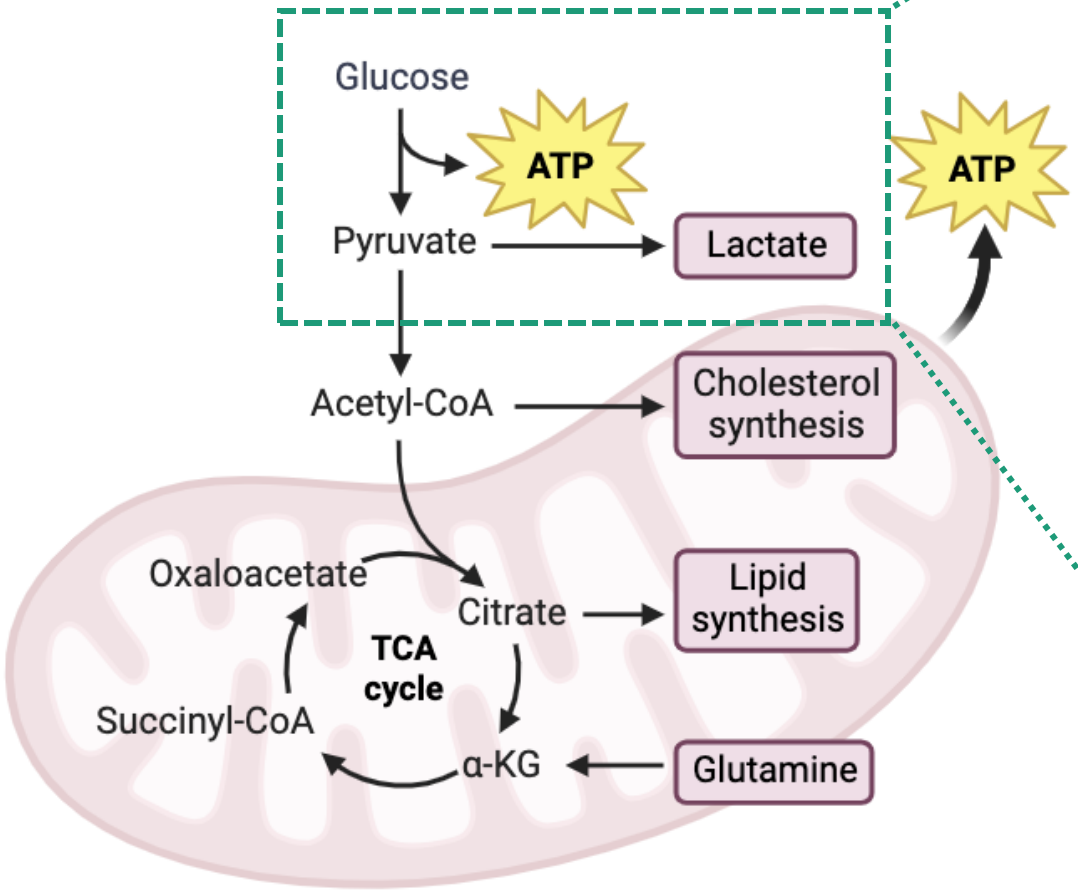
No oxygen required

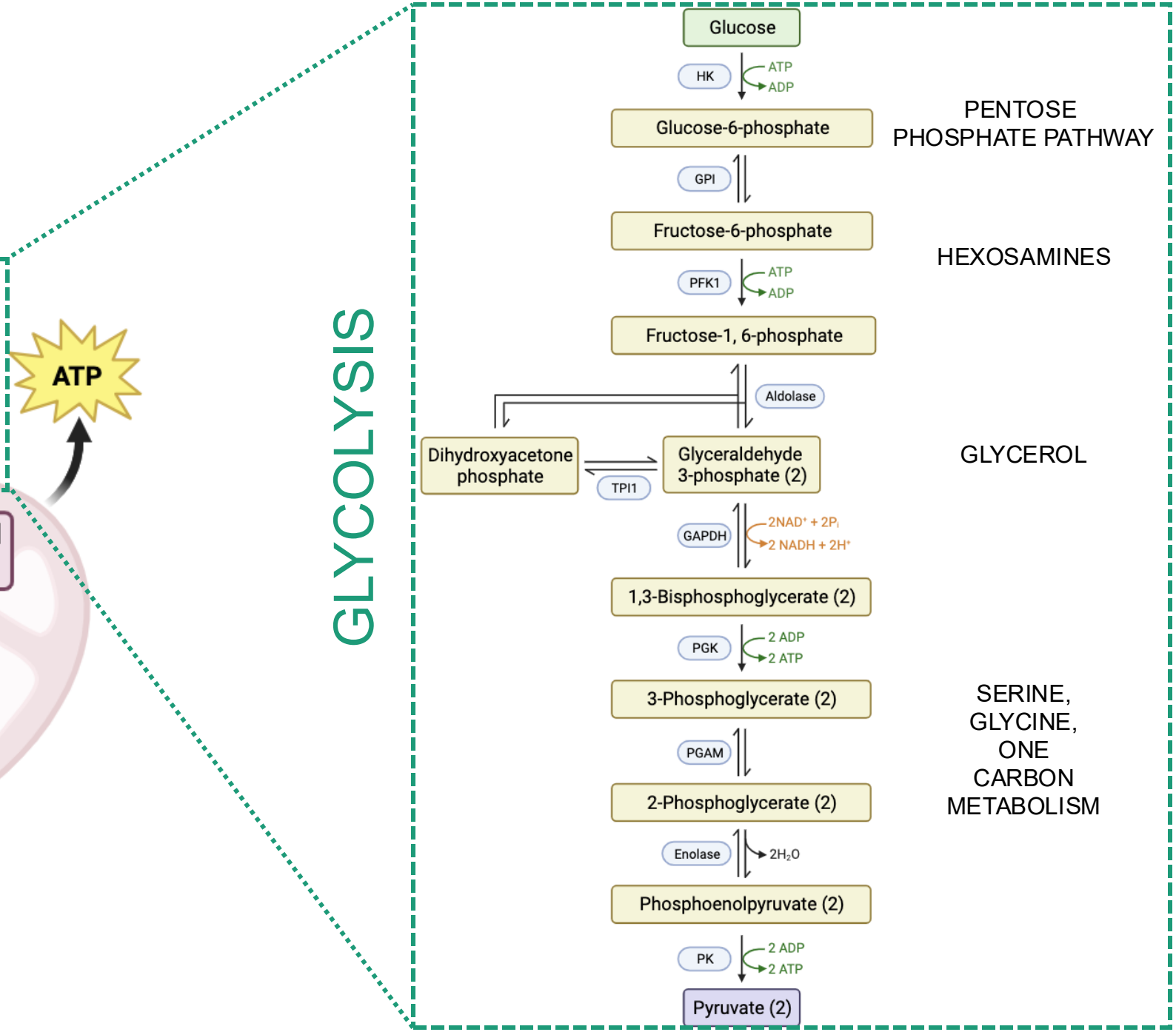
RESPIRATION

Oxygen required

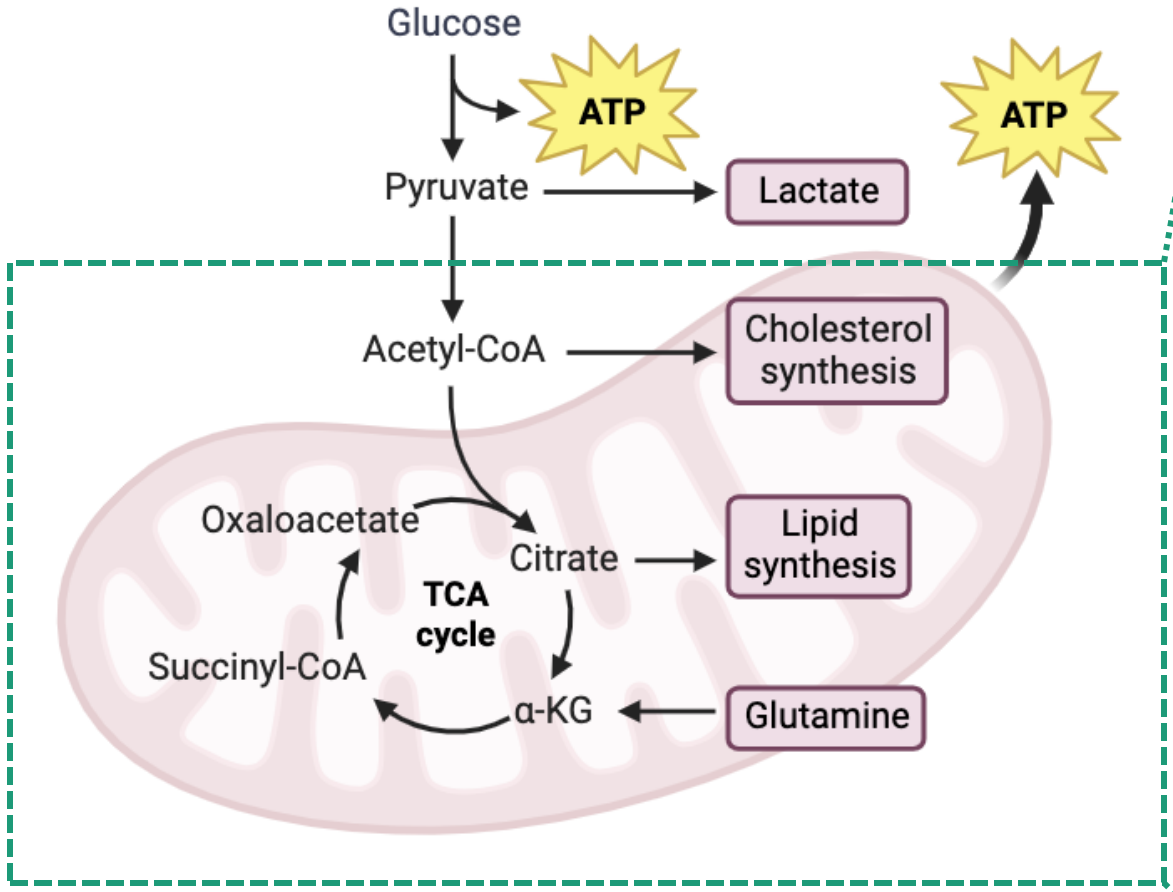


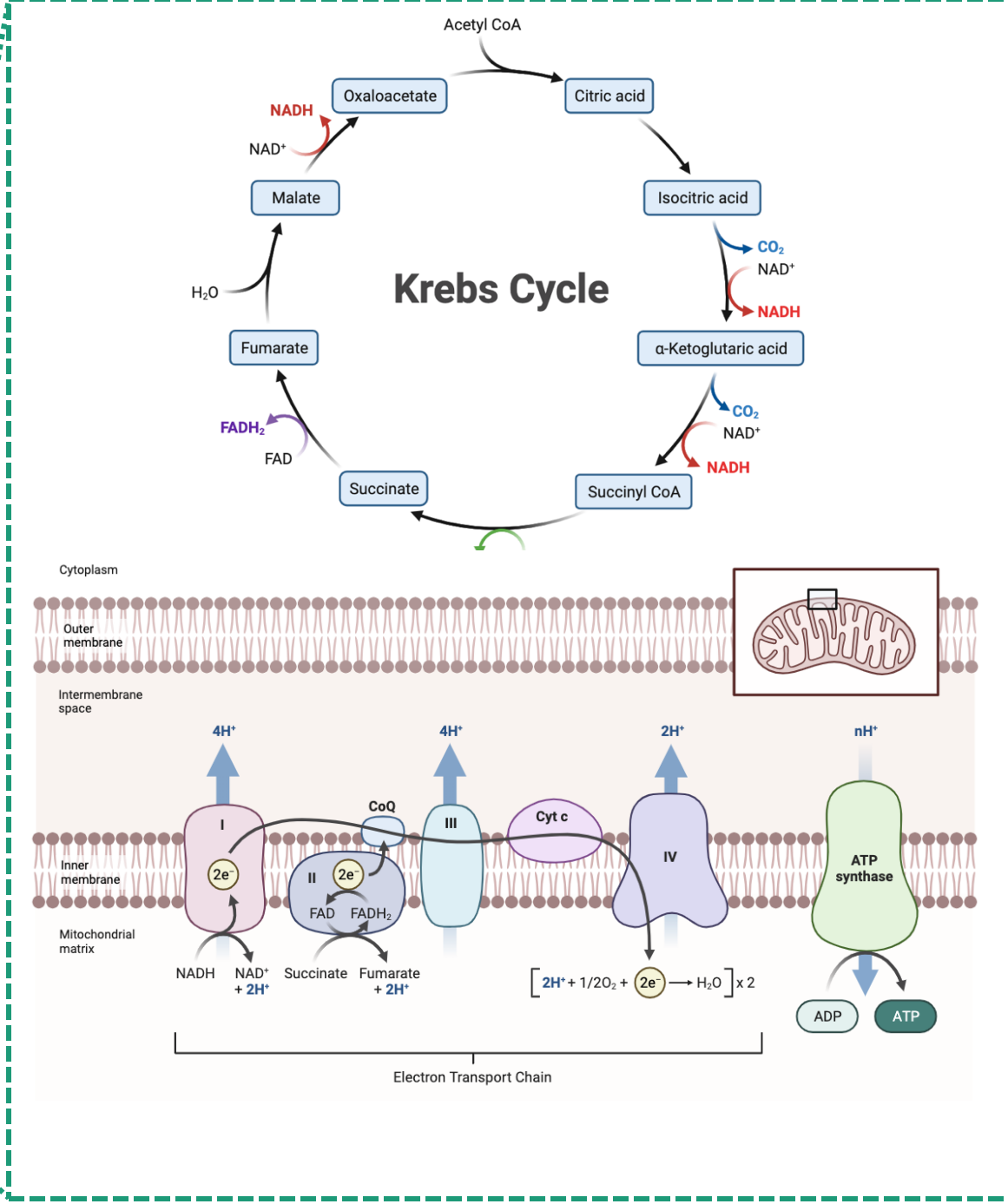
GLYCOLYSIS


Glucose
ATP
Pyruvate
Lactate
Acetyl-CoA
Cholesterol synthesis
Oxaloacetate
Citrate
Lipid synthesis
TCA cycle
Succinyl-CoA
α-KG
Glutamine

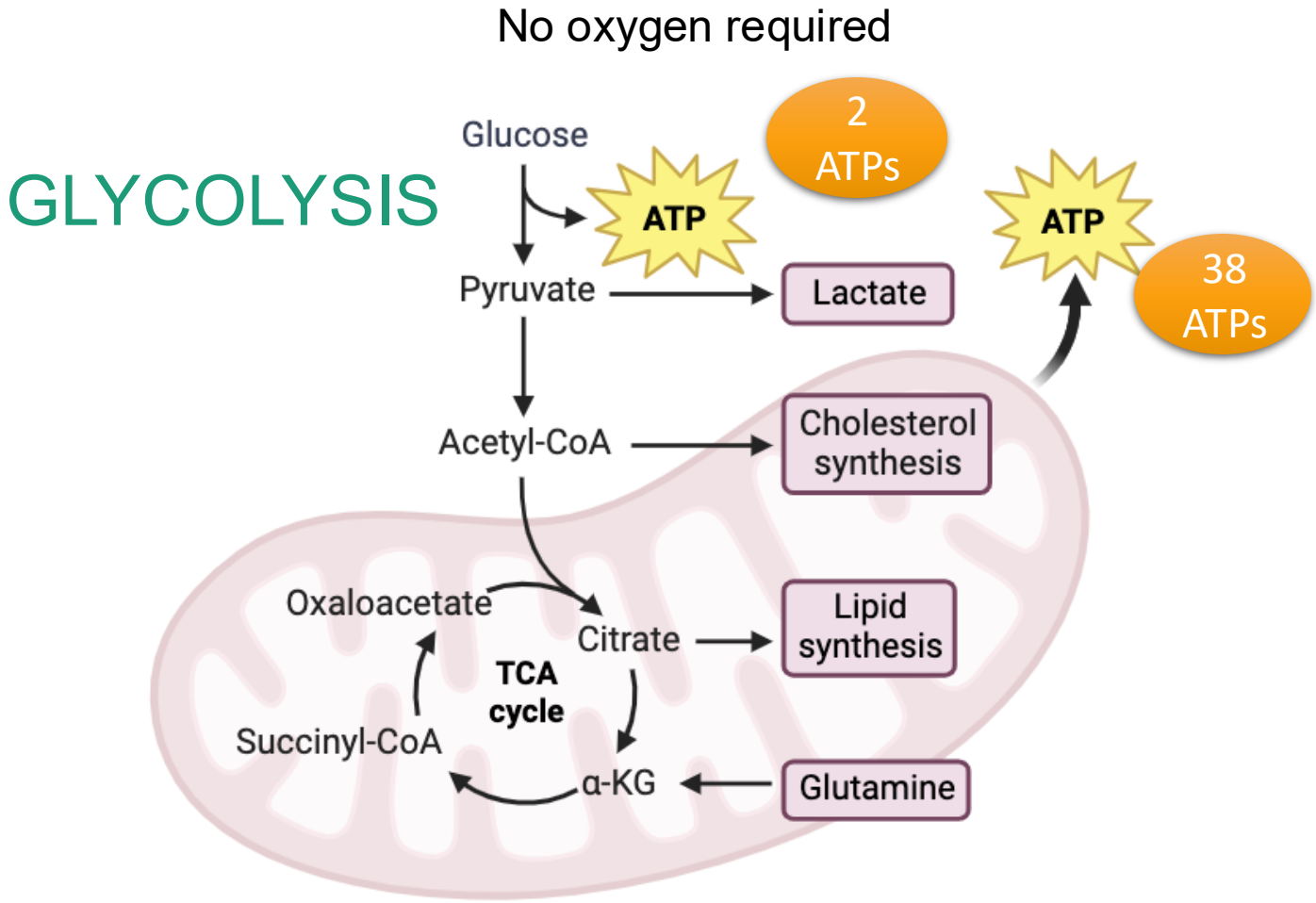

GLYCOLYSIS
Glucose
HK
ATP
ADP
Glucose-6-phosphate
GPI
Fructose-6-phosphate
PFK1
ATP
ADP
Fructose-1, 6-phosphate
Aldolase
Dihydroxyacetone phosphate
TPI1
Glyceraldehyde 3-phosphate (2)
GAPDH
2NAD+ + 2Pi
2 NADH + 2H+
1,3-Bisphosphoglycerate (2)
PGK
2 ADP
2 ATP
3-Phosphoglycerate (2)
PGAM
2-Phosphoglycerate (2)
Enolase
2H2O
Phosphoenolpyruvate (2)
PK
2 ADP
2 ATP
Pyruvate (2)
PENTOSE PHOSPHATE PATHWAY
HEXOSAMINES
GLYCEROL
SERINE, GLYCINE, ONE CARBON METABOLISM

RESPIRATION

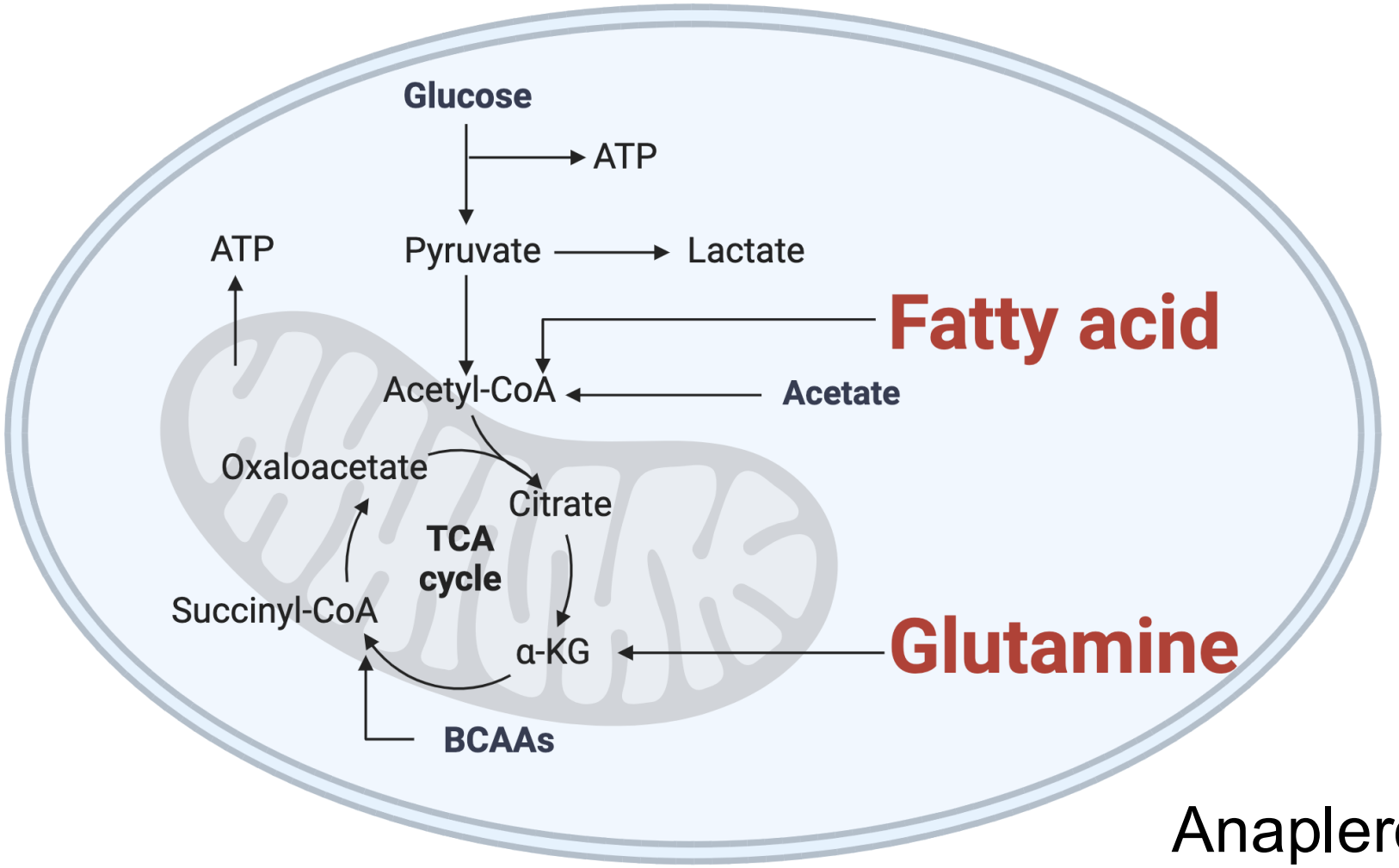




Glucose Metabolism

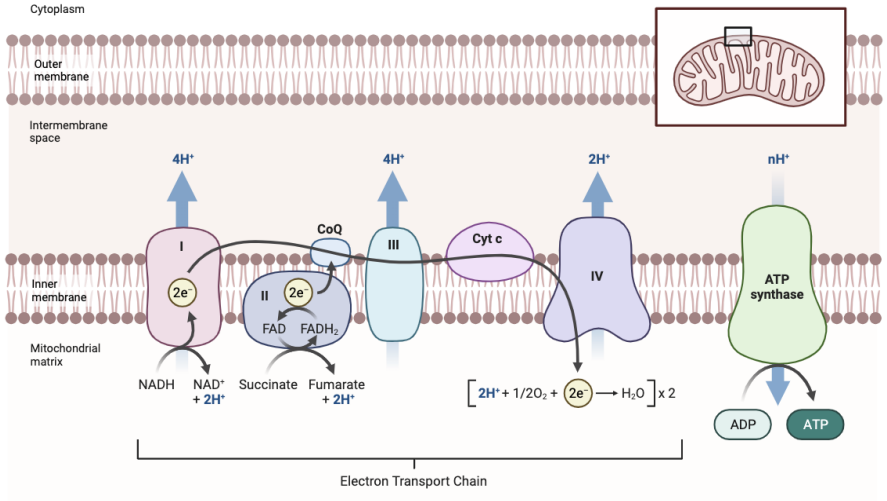


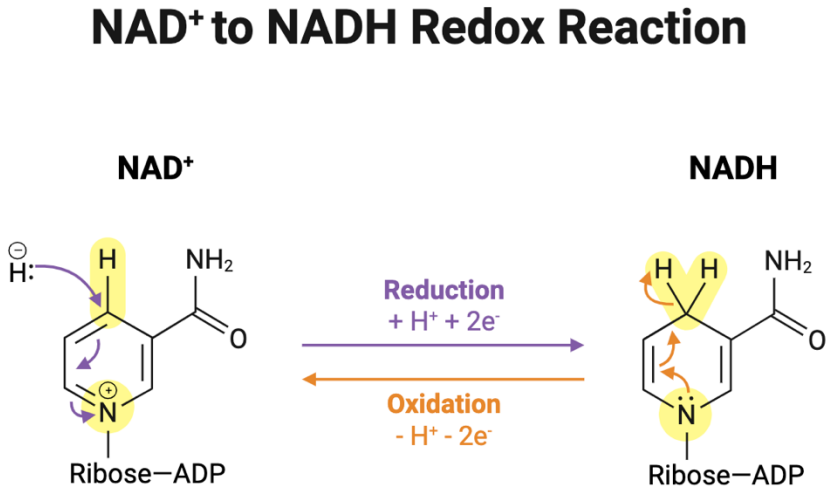
Fatty Acids and Glutamine

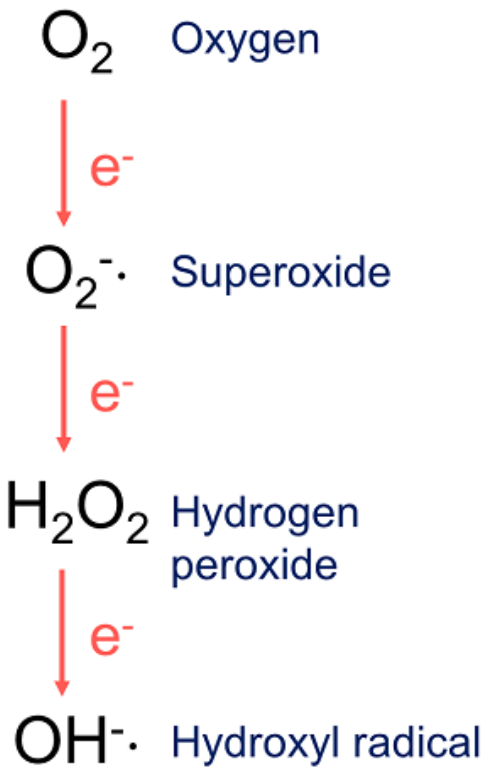


Anaplerosis

Metabolism is the flow of electrons



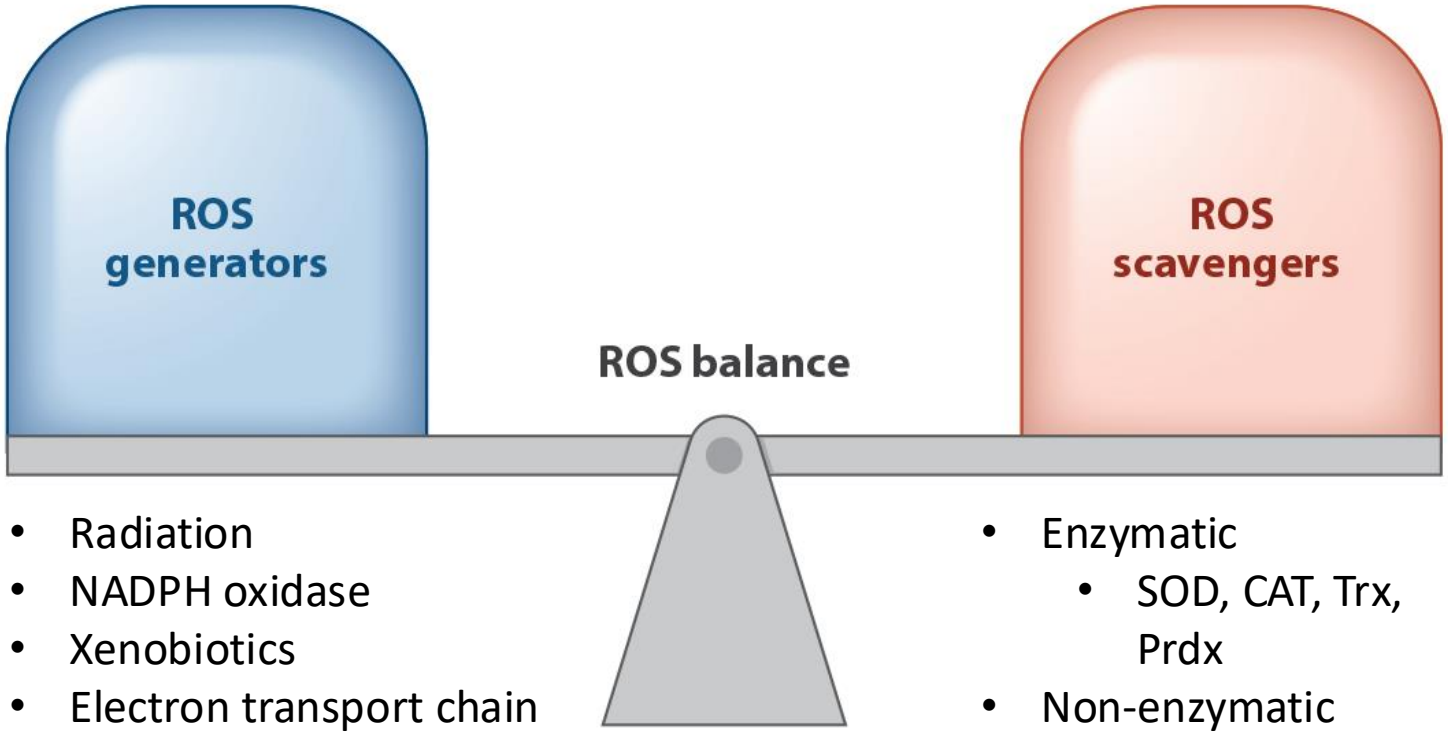




A significant fraction of metabolism concerns the flow of electrons

Reactive oxygen species (ROS)

Redox **homeostasis**



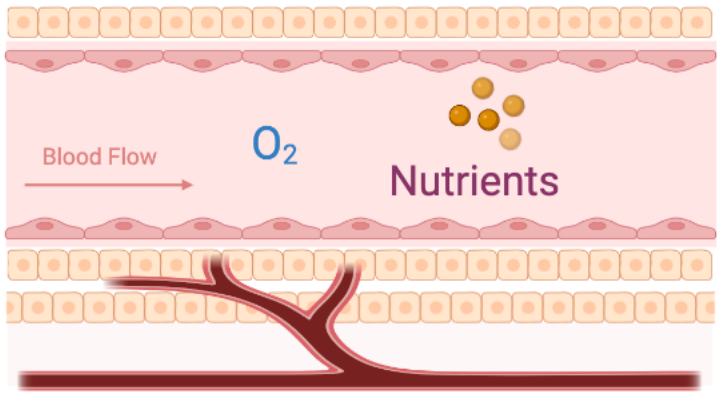
- Radiation
- NADPH oxidase
- Xenobiotics
- Electron transport chain
- Nitric oxide synthase

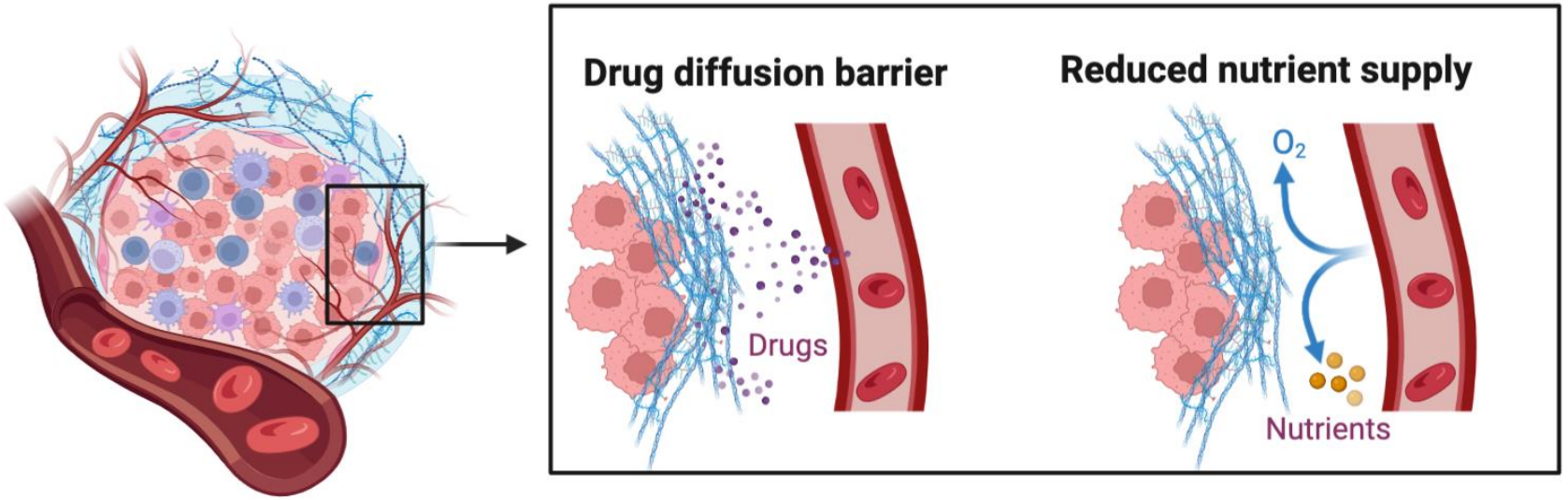
- Enzymatic
  - SOD, CAT, Trx, Prdx
- Non-enzymatic
  - Vit C, GSH, Vit E, Carotenoid

Chio and Tuveson, Trends in Molecular Medicine, 2017
Tonelli and Chio, Redox Signaling, 2018
Powers and Chio, Nature Cell Biology, 2022

WHAT HAPPENS IN CANCER?

Metabolic reprogramming is a hallmark of cancer





Cancer cell intrinsic and extrinsic adaptions

The goals of remodeling cancer metabolism

BIOMASS

ENERGY

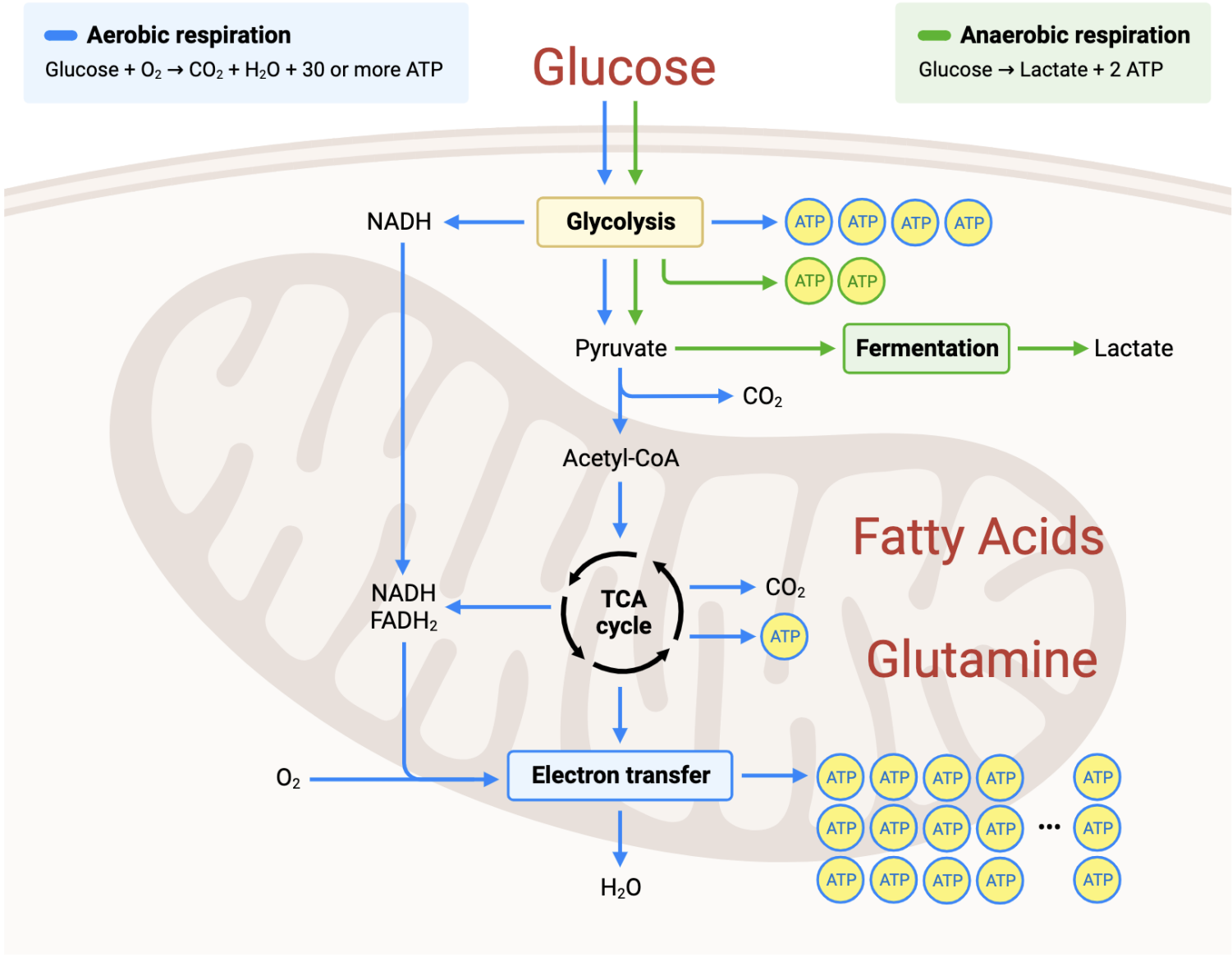
REDOX

- Affecting metabolite influx by conferring an increased ability to acquire necessary nutrients
- Shaping how nutrients are preferentially directed to metabolic pathways that contribute to cellular tumorigenic properties
- Exerting long-ranging effects on cellular fate, including alterations in the differentiation of cancer cells and cells within the TME

The 6 features of cancer metabolic reprogramming

- Deregulated uptake of glucose and amino acids
- Use of opportunistic modes of nutrient acquisition
- Use of glycolysis/TCA cycle intermediates for biosynthesis and NADPH production
- Increased demand for nitrogen
- Alterations in metabolite driven gene regulation
- Metabolic interactions with the TME

The Warburg effect: Rapid aerobic glycolysis



Cancer diagnostics: FDG PET

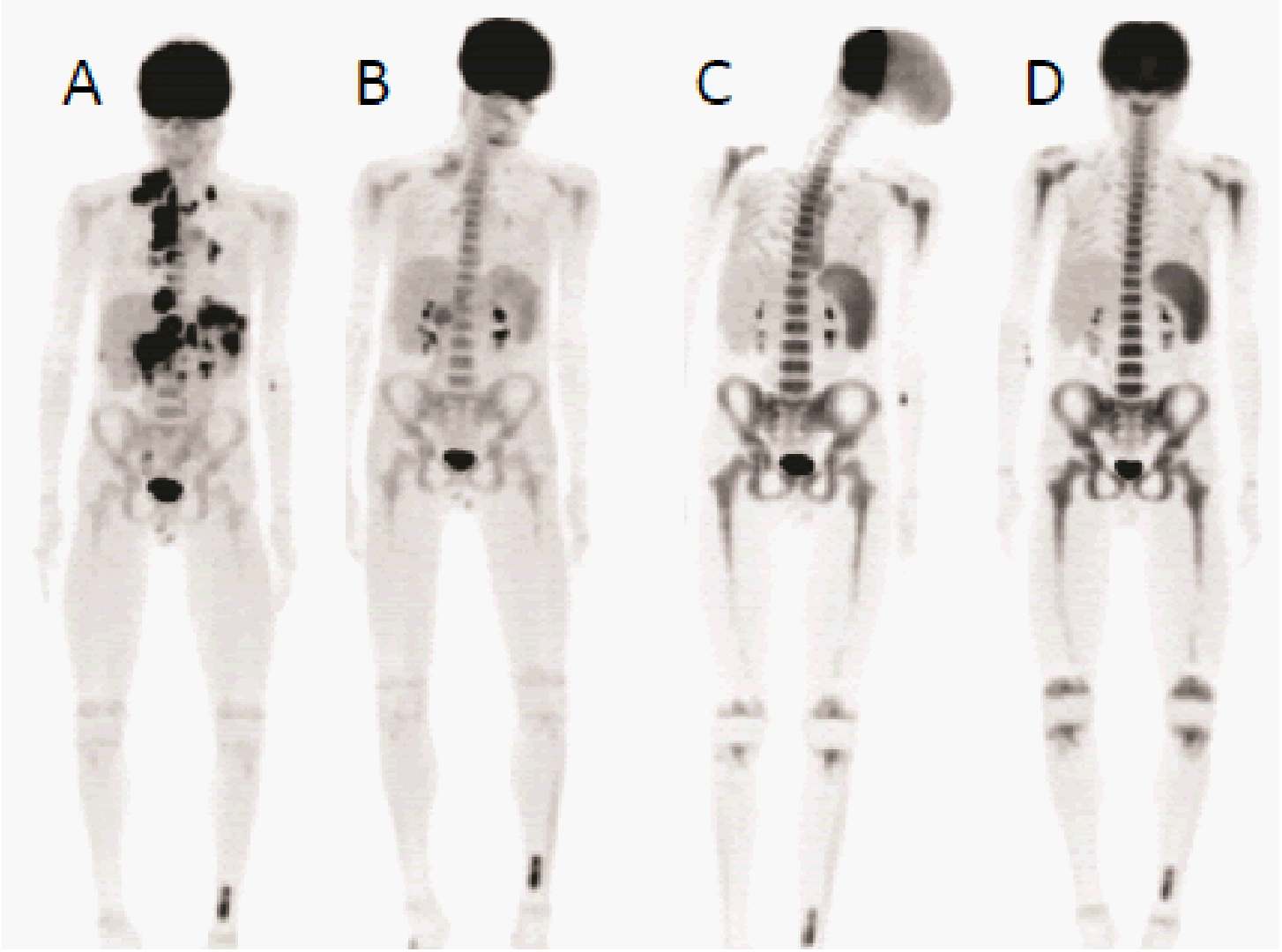


Figure 1: Legend for Sequential FDG PET-CT scans.

When non-essential becomes essential: Glutamine

- Harry Eagle 1950s
  - Optimal growth of cultured HeLa cells requires 10 -100 fold molar excess of glutamine in culture medium relative to other amino acids (Eagle 1955)

- Glutamine found to be most rapidly consumed amino acid by Ehrlich ascites carcinomas as well as by a number of hepatomas and carcinosarcomas proliferating in vivo (Marqez et al 1989, Sauer et al 1982).

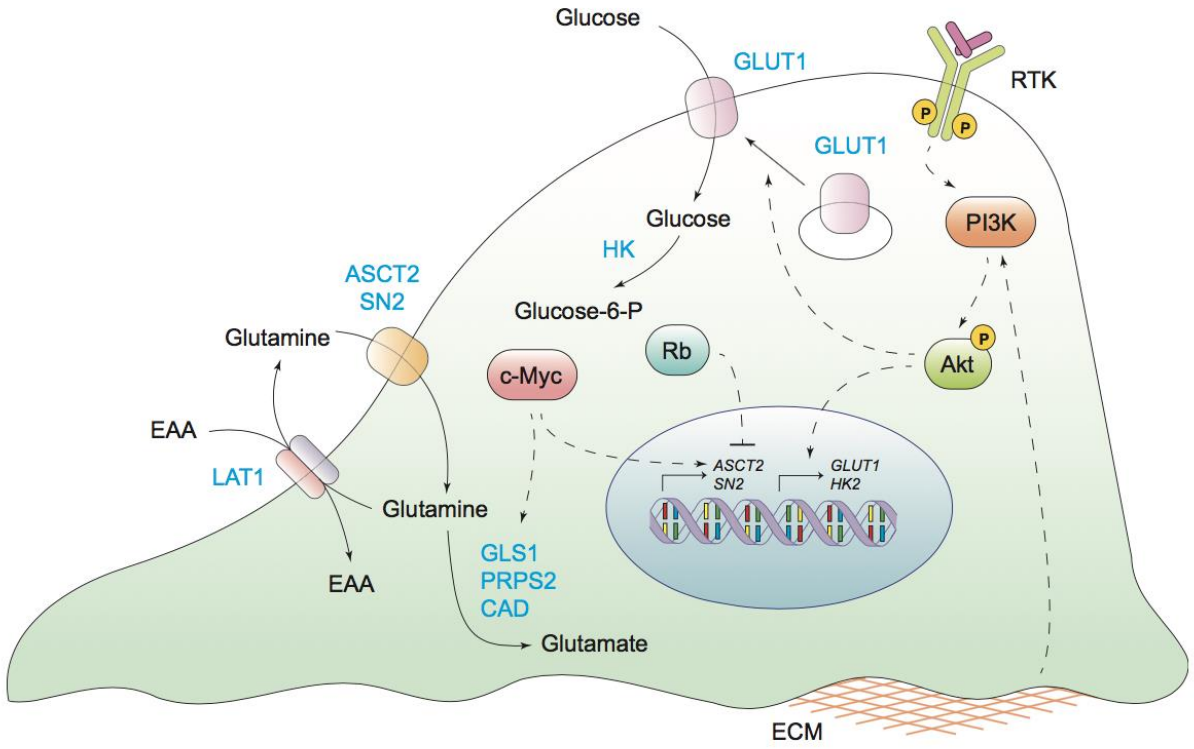
Why Glutamine?

- Contributes Carbon and nitrogen
  - Purine and pyrimidine nucleotides, glucose 6 phosphate, and nonessential aa

- Uptake of essential amino acids
  - Import of essential amino acid leucine is through the neutral amino acid antiporter LAT1 and this is coupled to simultaneous efflux of glutamine
  - In this manner, intracellular glutamine may facilitate the import of a broad range of LAT1 substrates, including leucine, isoleucine, valine, methionine, tyrosine, tryptophan and phenylalanine (Yanagida et al 2001).
  - 18F-glutamine recently employed to provide tumor information where 18F-fluoroglucose is not feasible eg tumors located in sites of heavy glucose utilization such as the brain.

Genetic mutations

- AKT: GLUT1
- Ras: GLUT1
- MYC: ASCT2 and GLS1
- System Xc: as glutamate accumulates it cannot exit through glutamine transport, and as it accumulates, promotes TCA cycle anaplerosis and stimulates uptake of cysteine by acting as an exchange substrate for the cysteine antiporter Xct.



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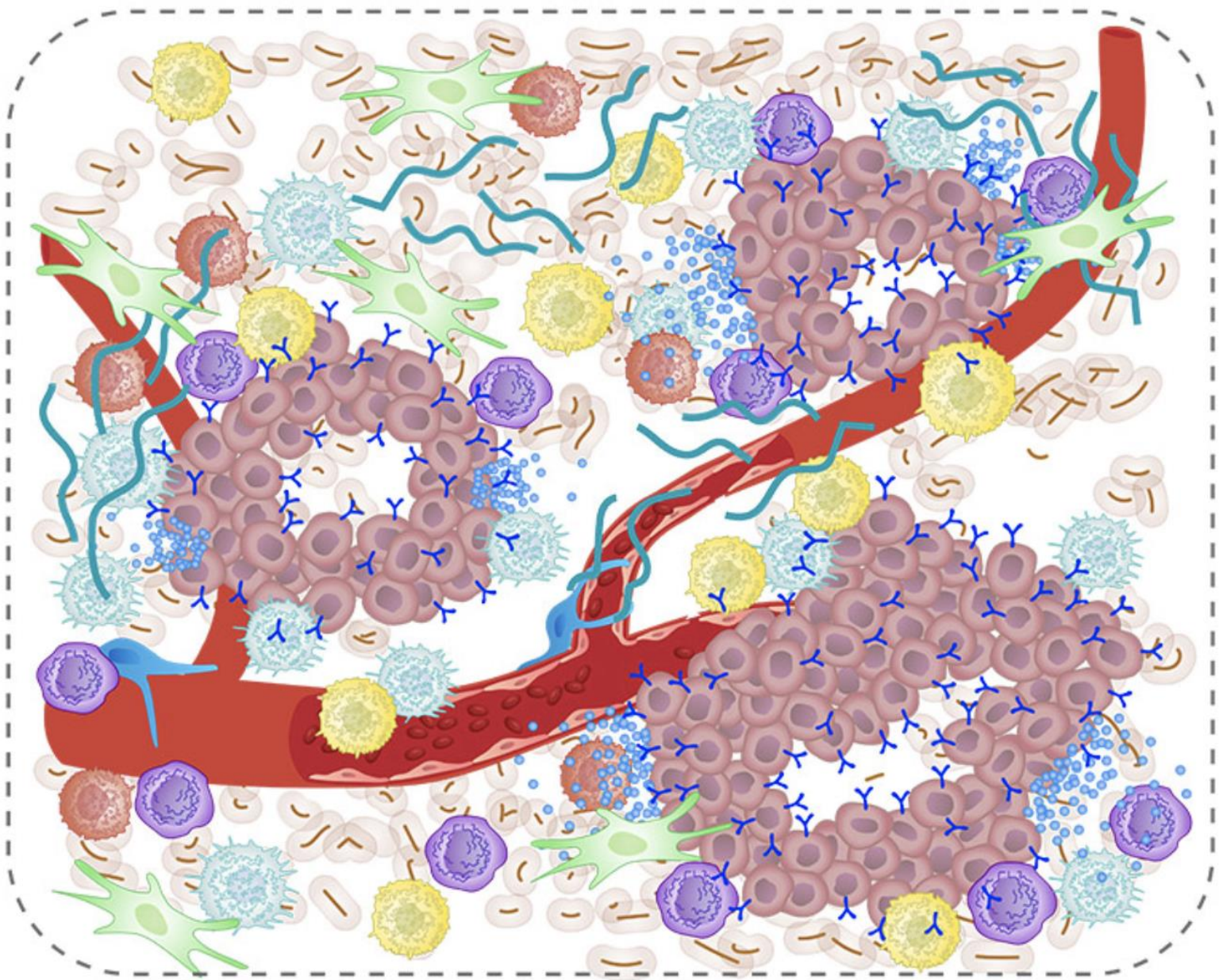
- Metabolic interactions with the TME

The Tumor Microenvironment



Cancer cell

Vasculature

HA

Collagen

Macrophage

T-cell

Treg

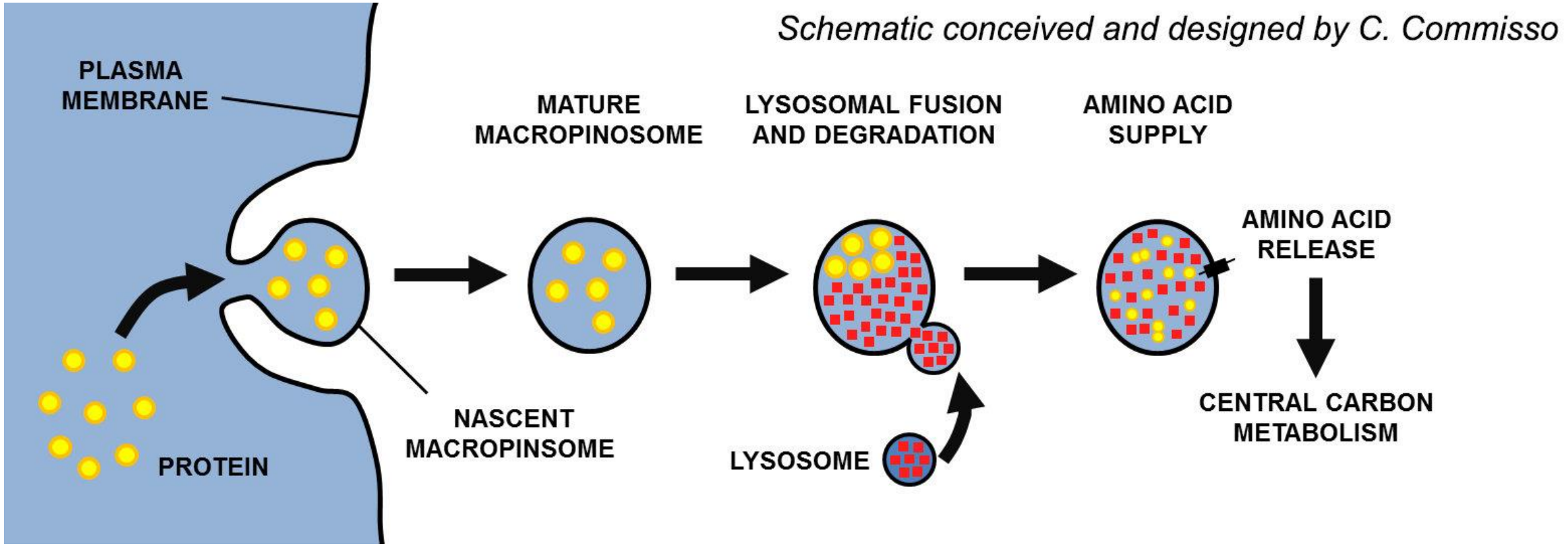
MDSC

Fibroblast

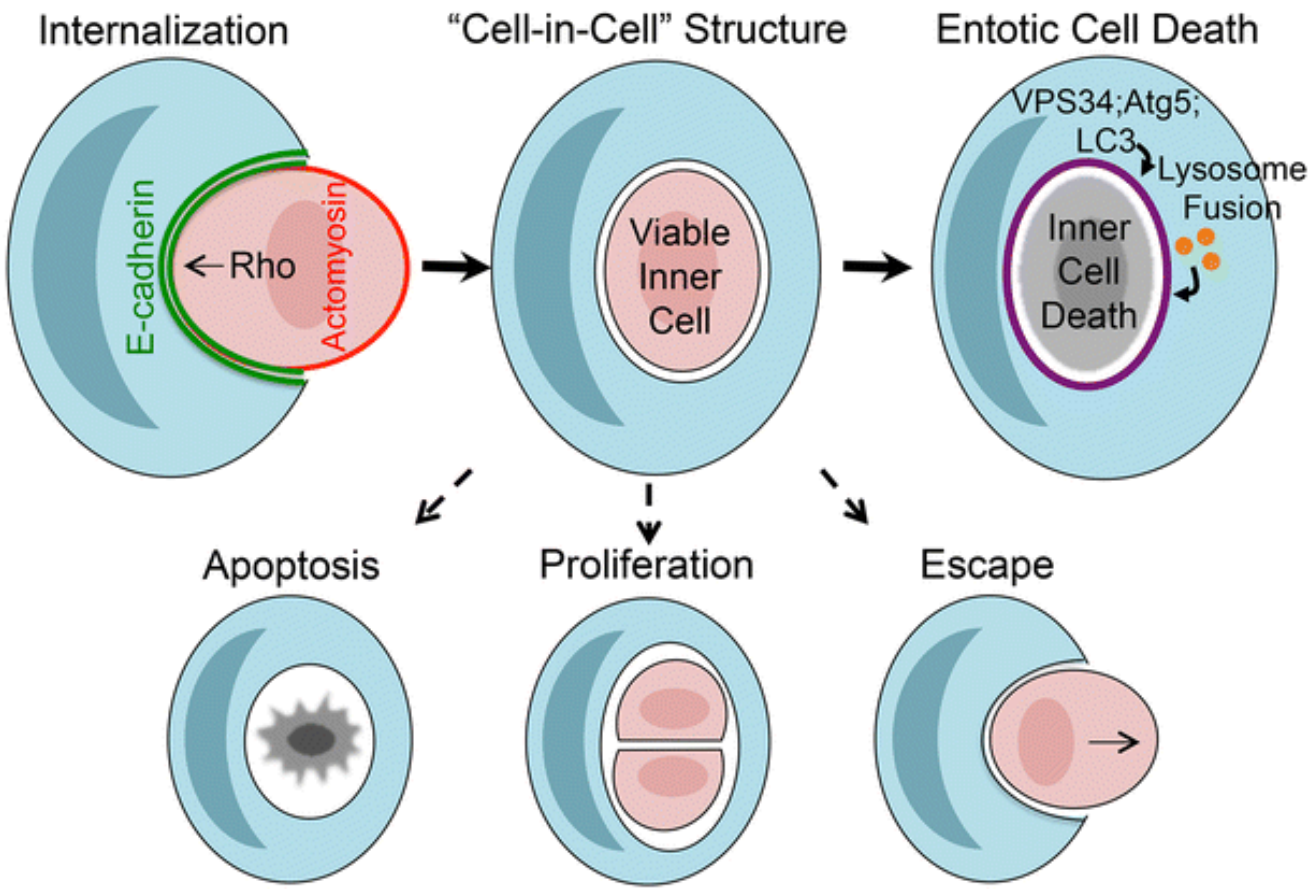
Adenosine

Molecular Receptors

Macropinocytosis: Extracellular protein scavenging



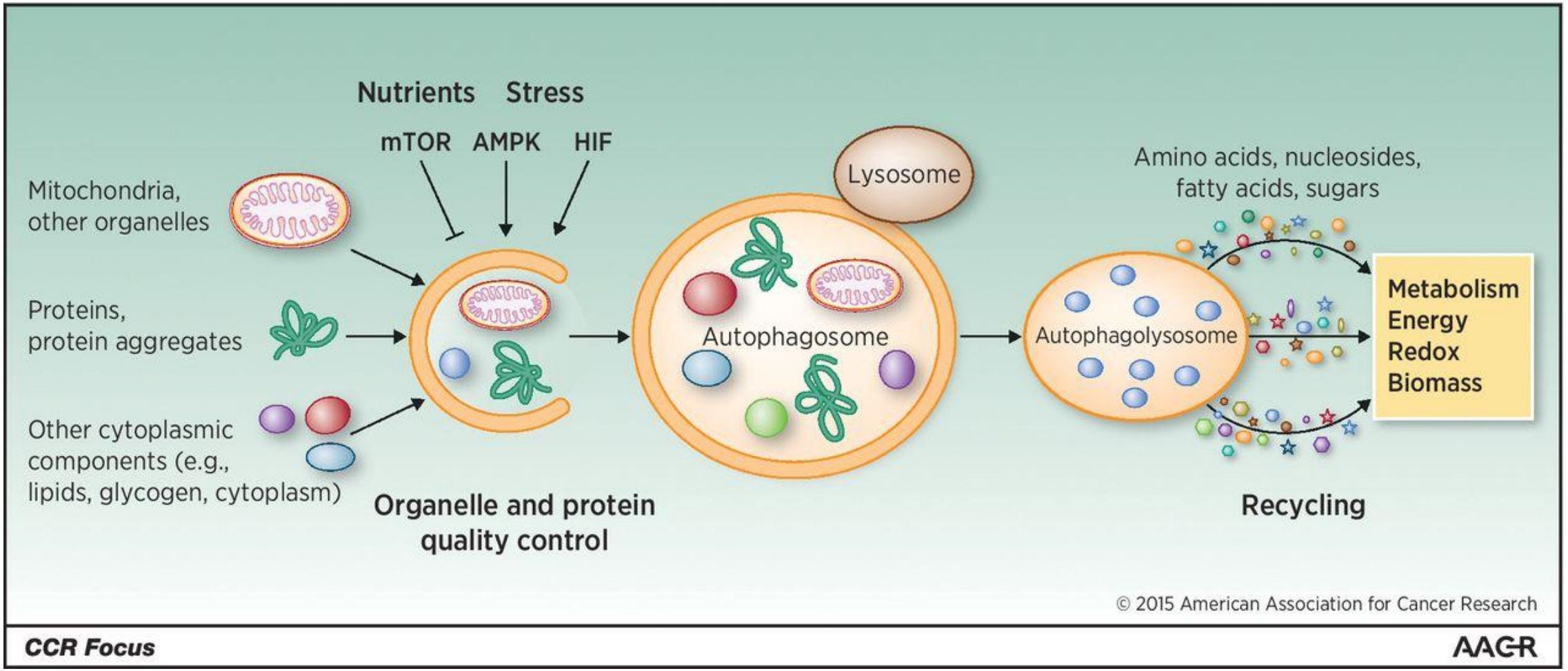
Entosis



- Engulfment and digestion of entire living cells
- KRAS mutant cells are more likely to perpetrate entosis than to be consumed in this process (Sun et al 2014)

Phagocytosis of apoptotic cellular corpses also supply amino acids to support cell survival and proliferation during conditions of amino acid deficits

Autophagy


Nutrients
Stress
mTOR
AMPK
HIF
Mitochondria, other organelles
Proteins, protein aggregates
Other cytoplasmic components (e.g., lipids, glycogen, cytoplasm)
Organelle and protein quality control
Lysosome
Autophagosome
Autophagolysosome
Amino acids, nucleosides, fatty acids, sugars
Metabolism
Energy
Redox
Biomass
Recycling
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CCR Focus
AACR

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- Deregulated uptake of glucose and amino acids
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- Use of glycolysis/TCA cycle intermediates for biosynthesis and NADPH production
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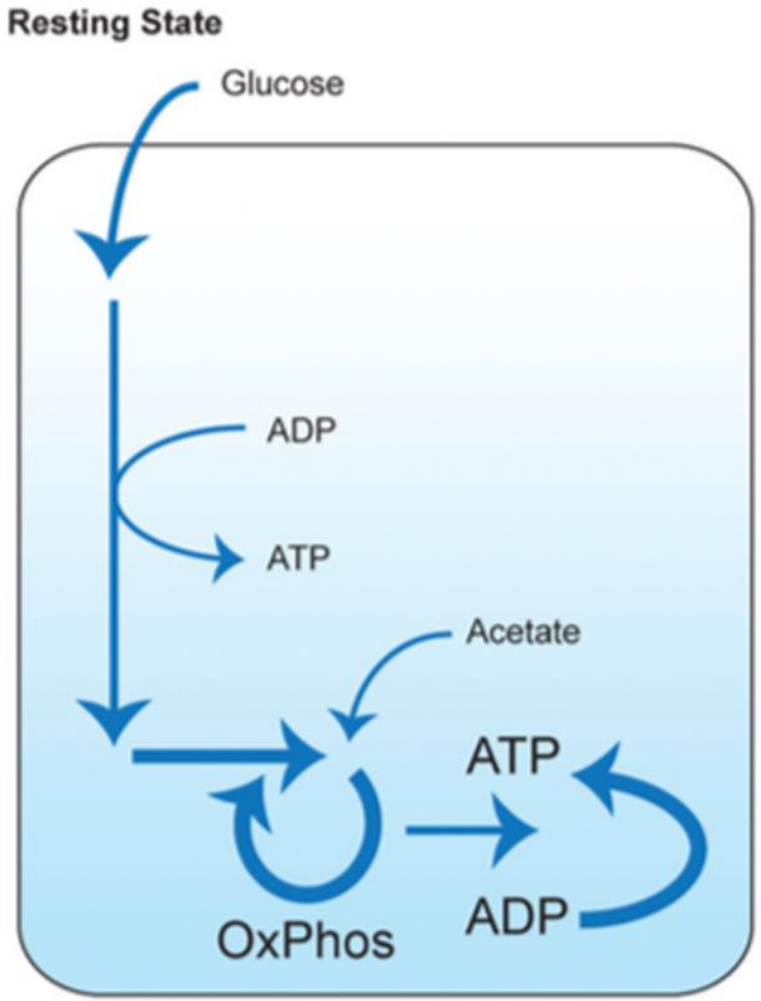
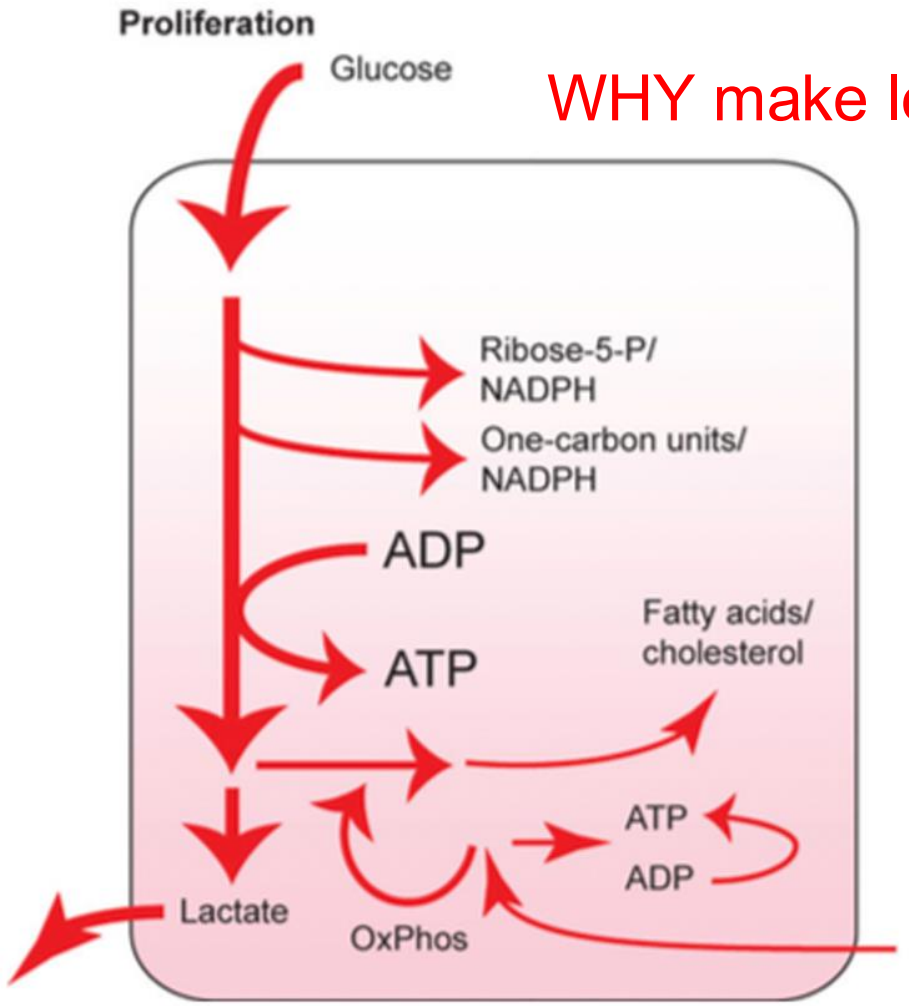
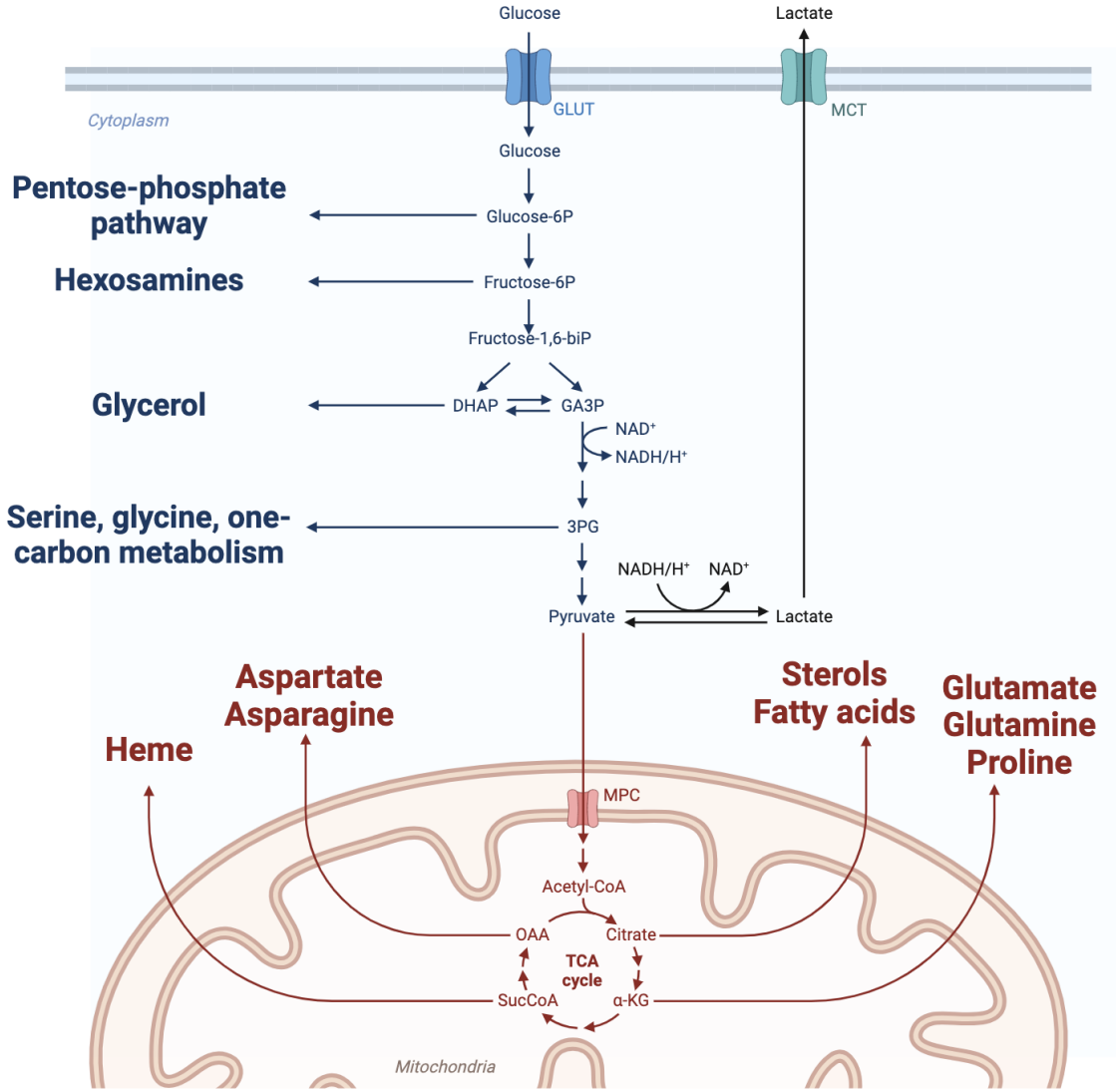
Use of glycolysis and TCA cycle intermediates for biosynthesis and NADPH production



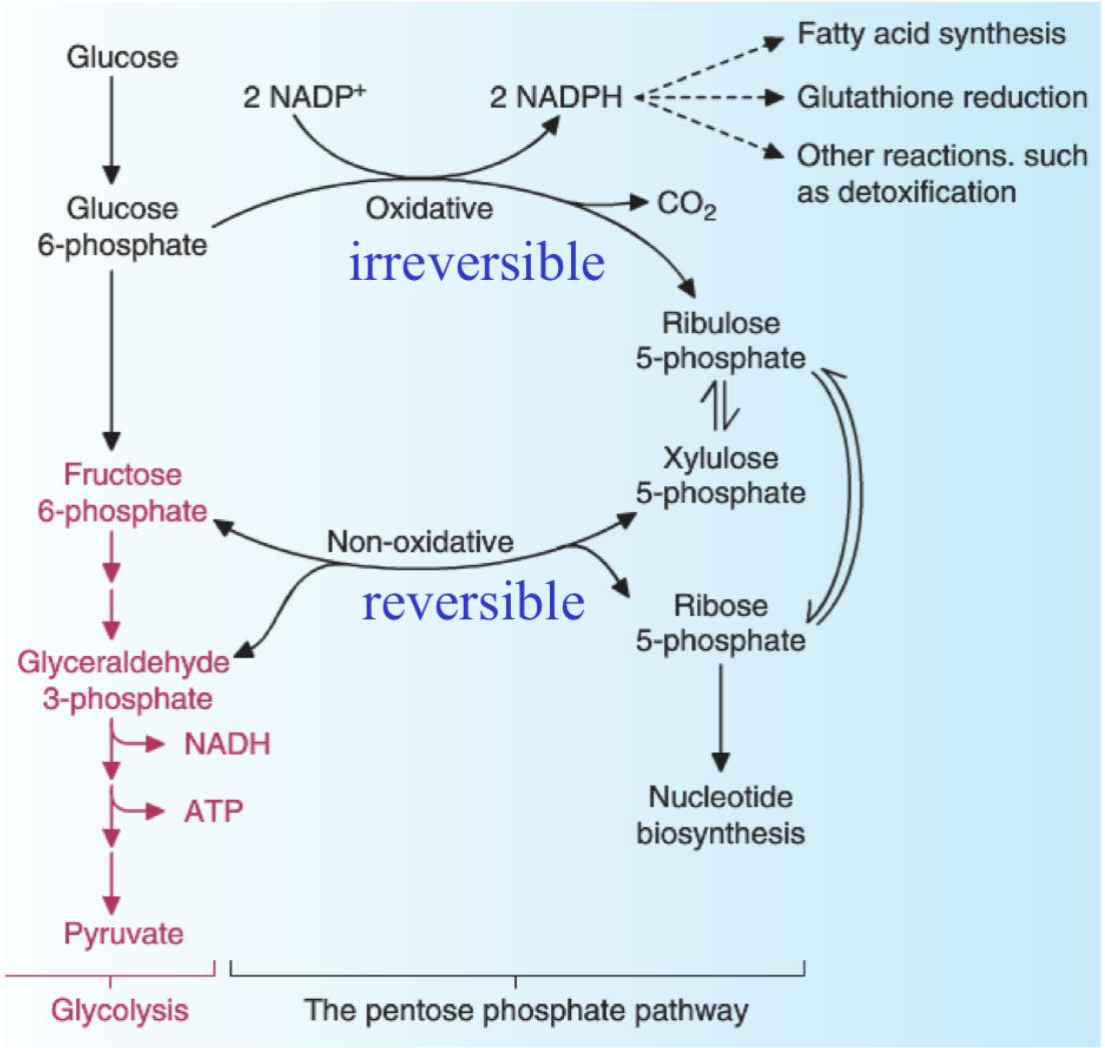


WHY make less ATP?

Glycolysis and TCA cycle intermediates: Biosynthesis and NADPH production



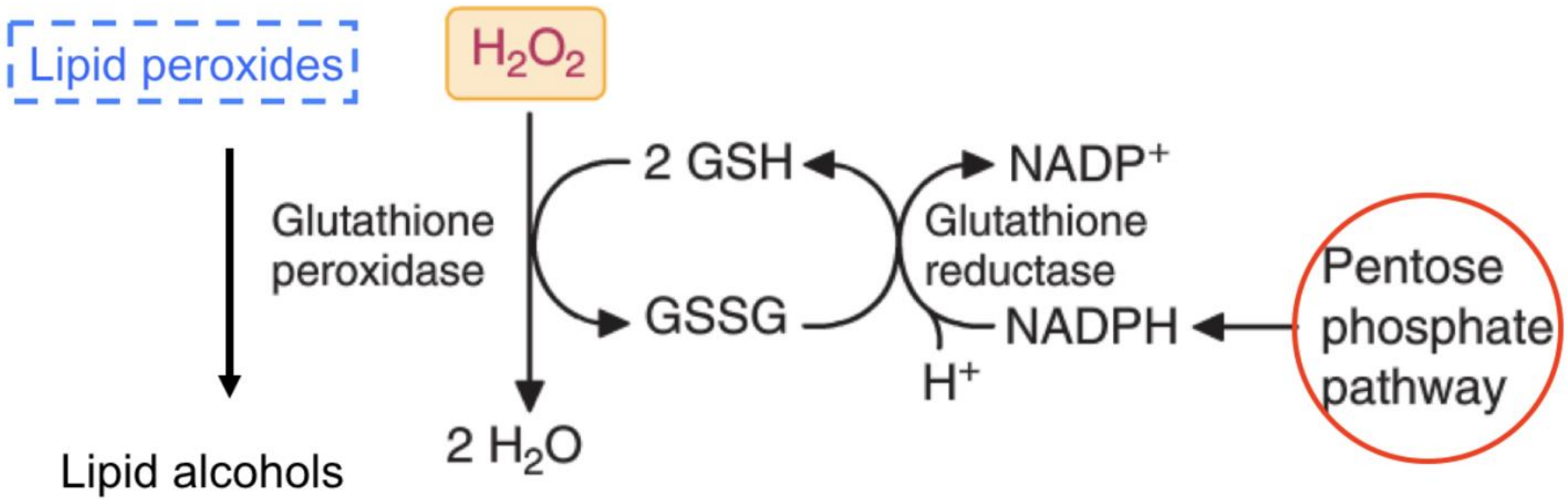
The Pentose Phosphate Pathway (PPP)



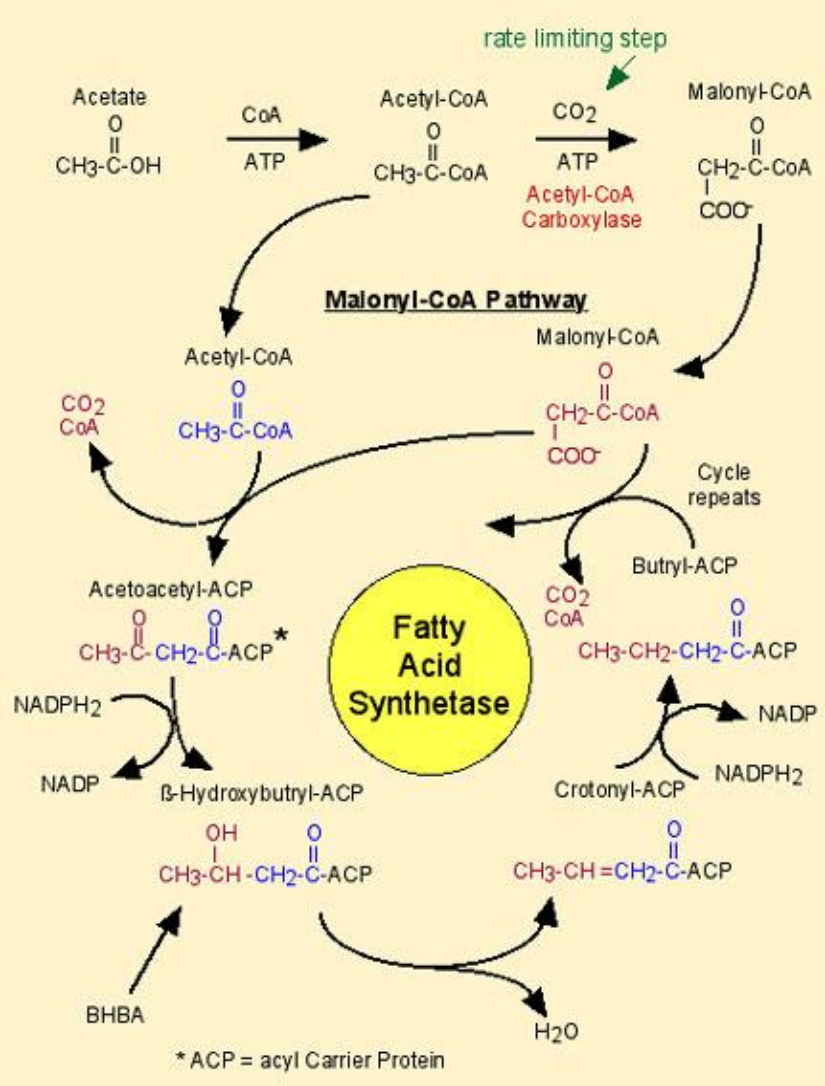
NAPDH

NUCLEOTIDES

NADPH: Protection from oxidative damage



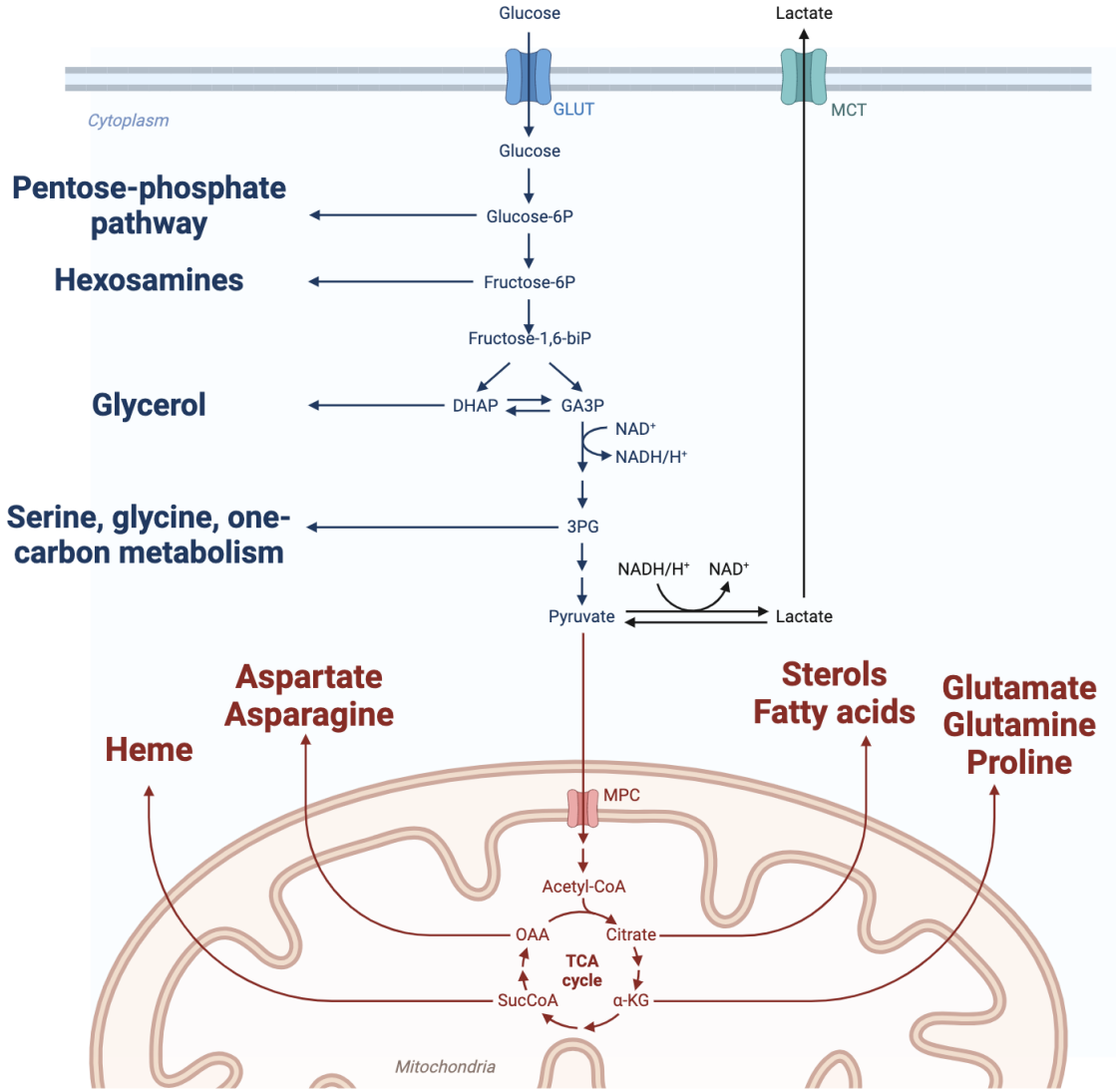
NAPDH: Fatty acid synthesis



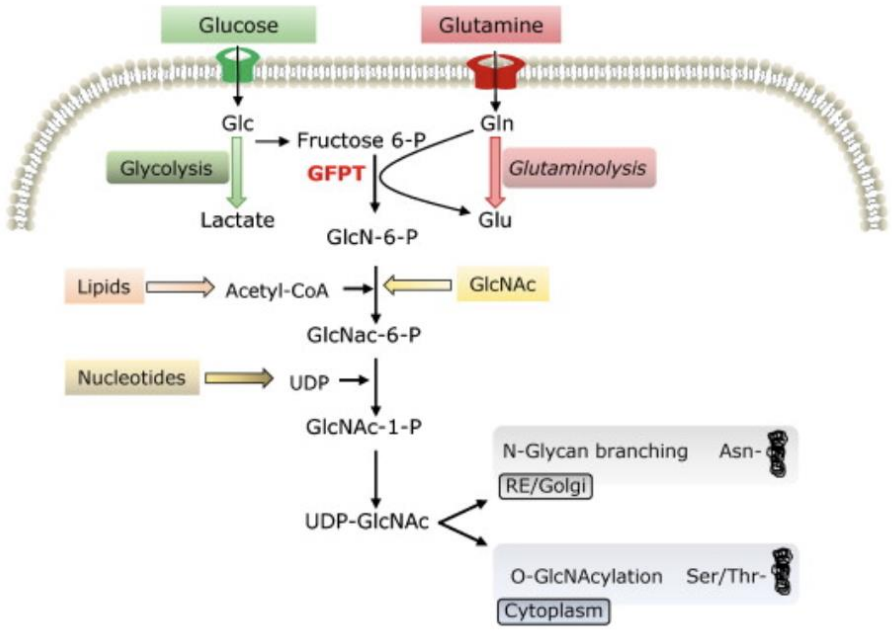
- De novo biosynthesis of fatty acids is low in normal adult tissues, but tumorigenesis is associated with a dramatic increase in lipid production (Li and Cheng 2014).

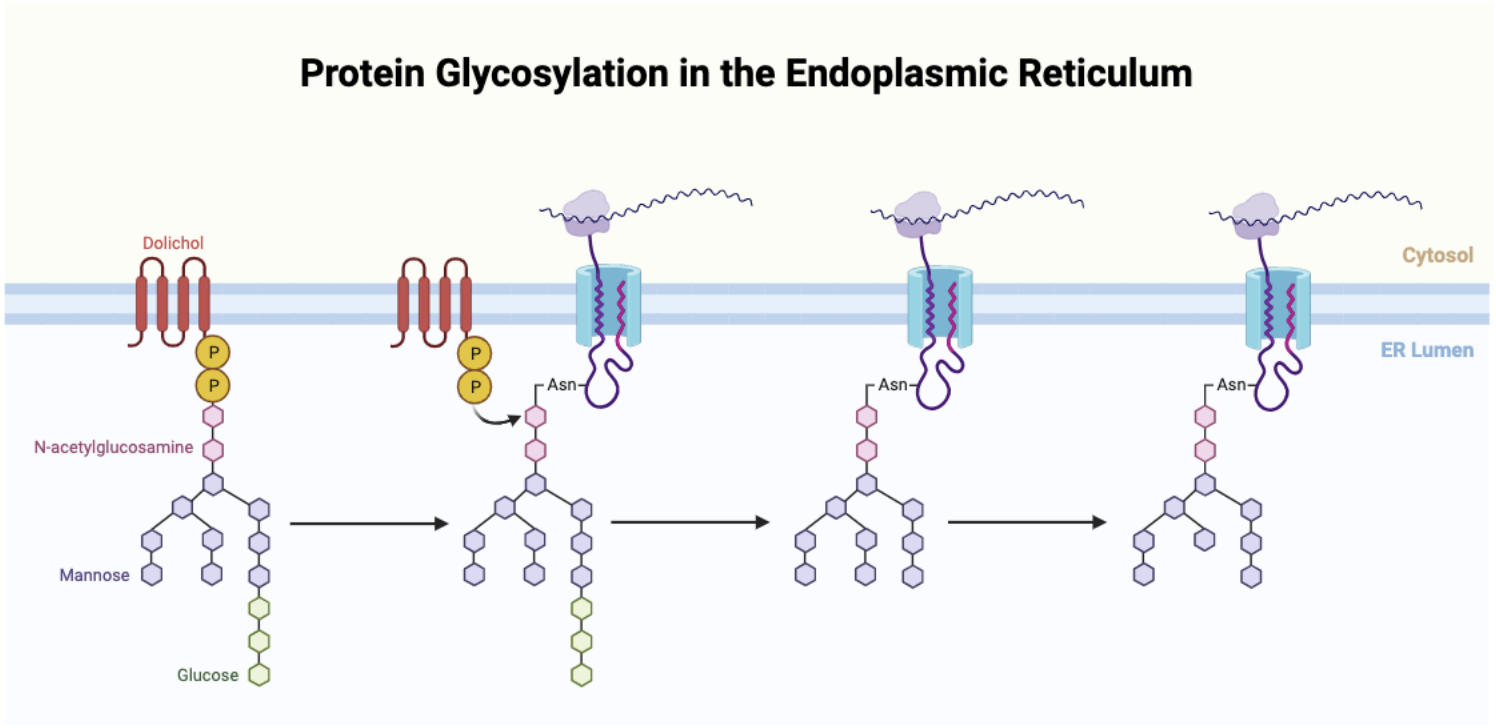
- Allows cells to alter their membrane composition in favor of oxidative damage-resistant saturated fatty acids as a means of adapting to oxidative stress (Rysman et al 2010).

Glycolysis and TCA cycle intermediates: Biosynthesis and NADPH production

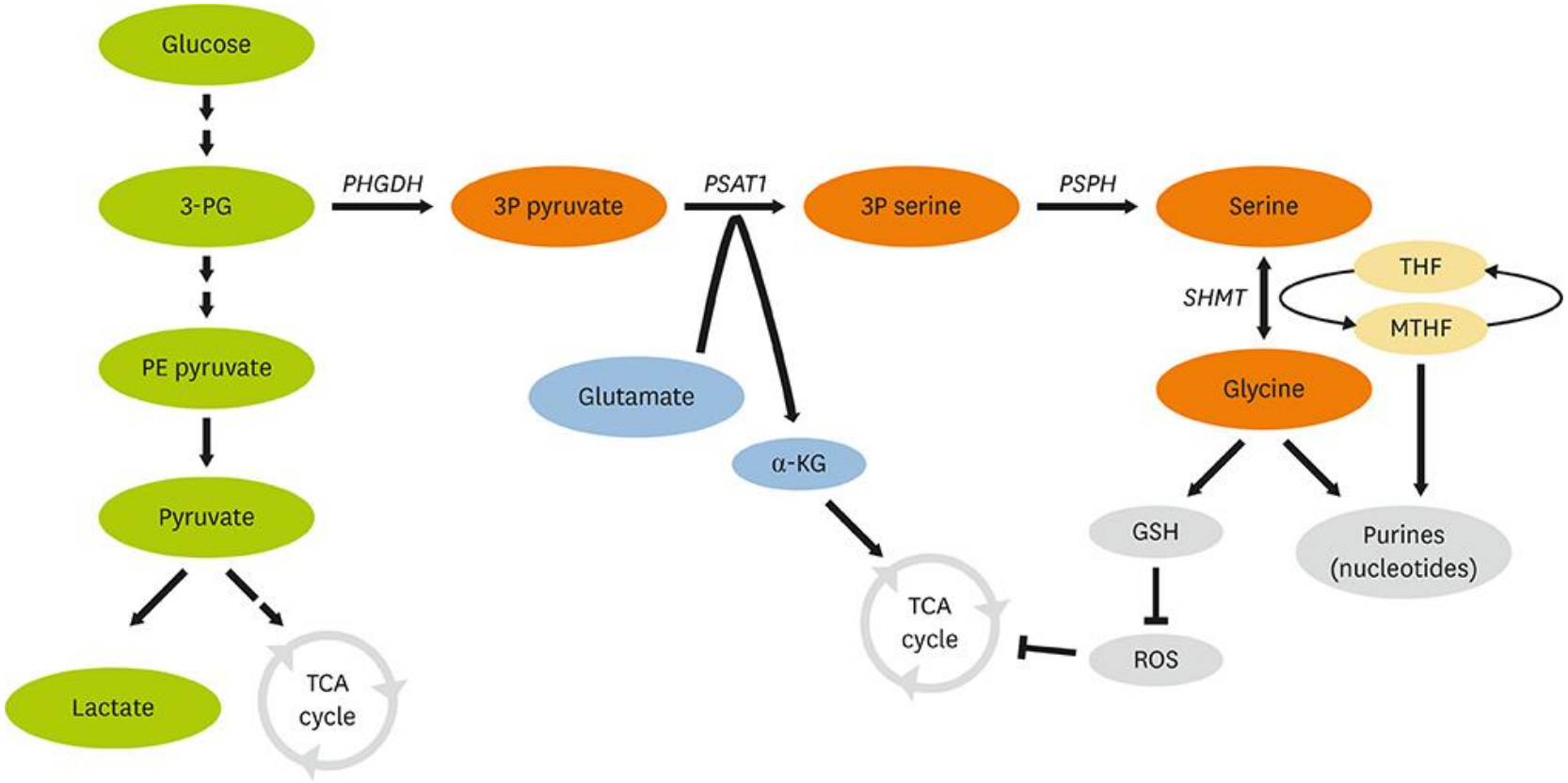


Hexosamine biosynthetic pathway

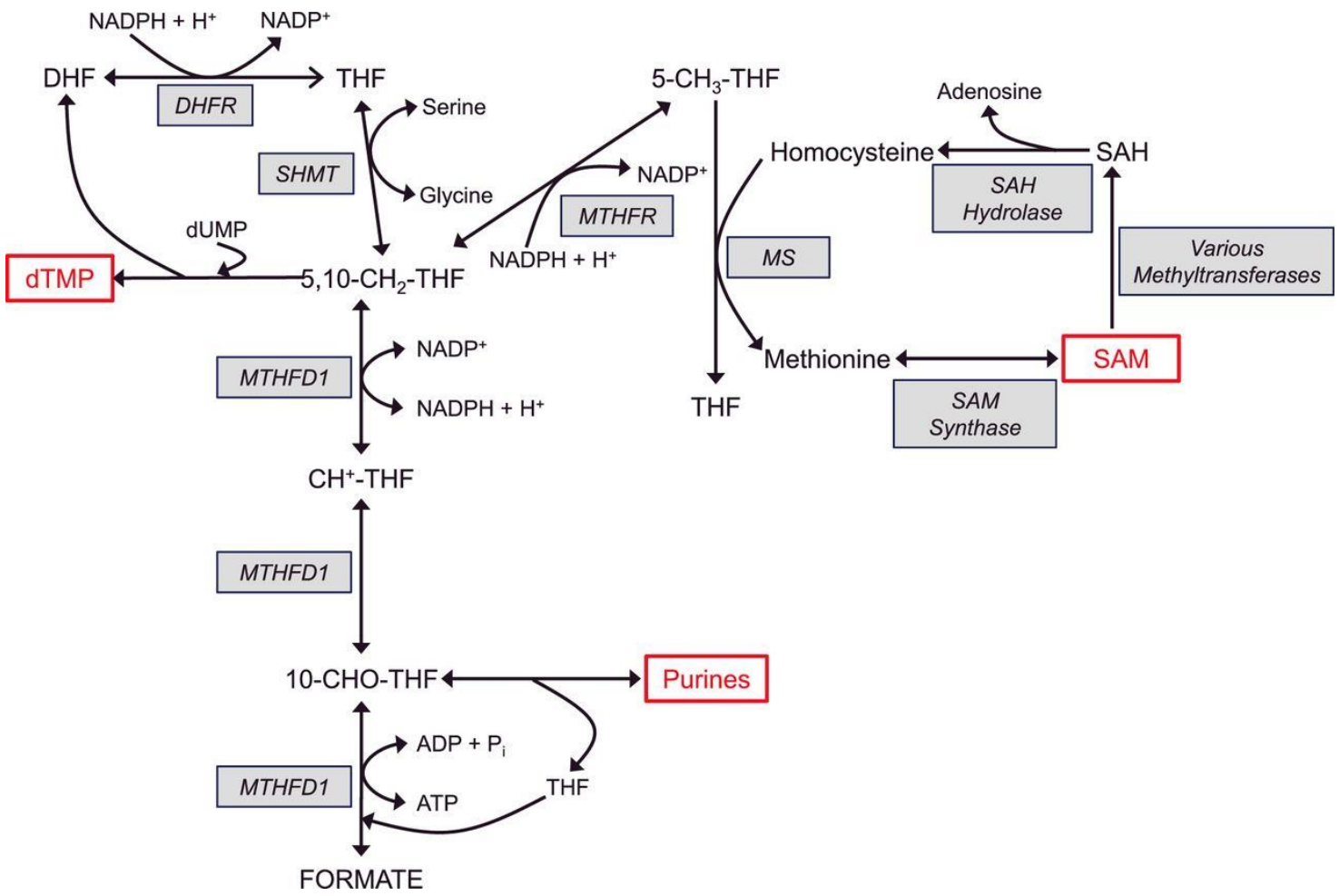




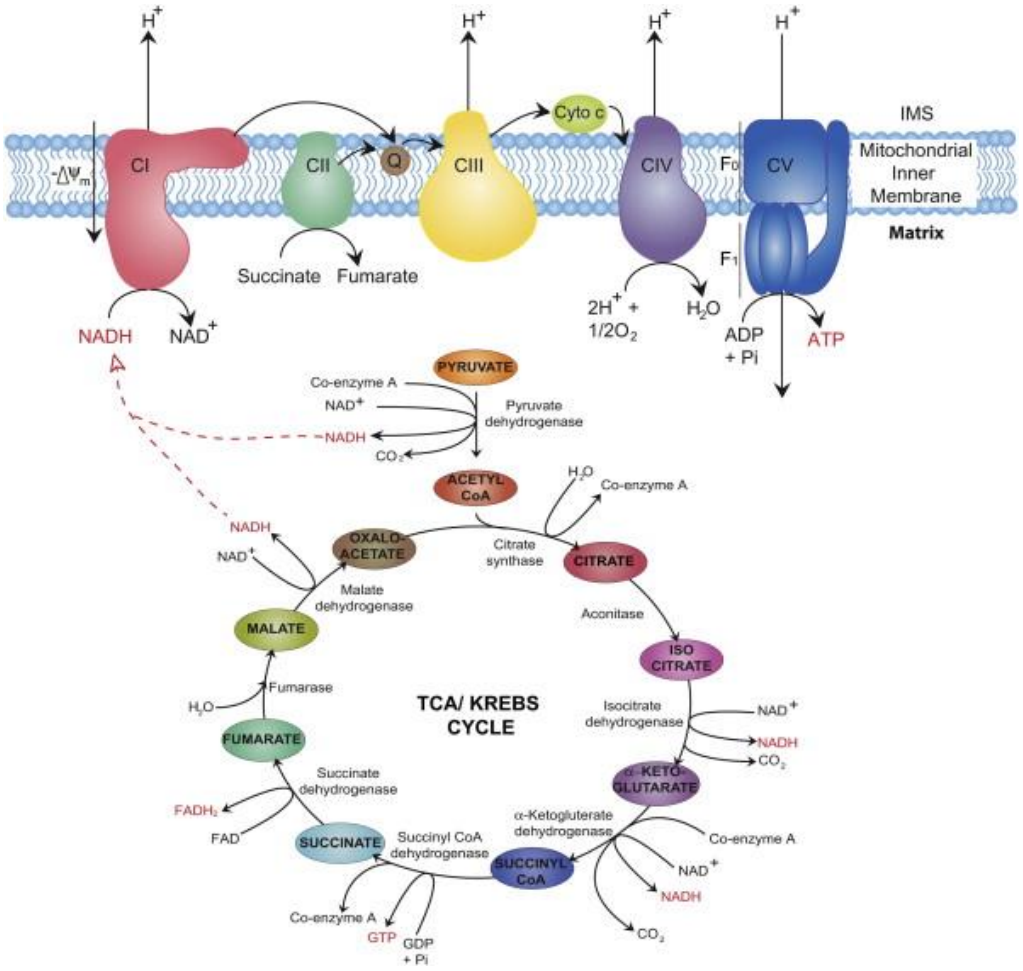
Serine Glycine Biosynthesis



Reduction of dihydrofolate to tetrahydrofolate catalyzed by DHFR generates NADPH



Avoid overloading the ETC



- Excess glycolytic flux that isn't used for biosynthesis is mainly converted to lactate. This process helps maintain enough NAD+ to keep glycolysis going and prevents an overload of NADH in the mitochondria, which could slow down the TCA cycle.

Genetic alterations

Enzyme	Status in tumors	Normal metabolic role	Additional role in cancer
Hexokinase 2 (HXK2)	Over-expressed	Glucose phosphorylation. Flux-controlling step of glycolysis.	Inhibition of apoptosis
Phosphofructokinase-2 (PFKFB3)	Over-expressed	Activation of phosphofructokinase-1. Glycolytic flux enhancement.	Not reported.
Pyruvate kinase M2 (PKM2)	Over-expressed	Production of pyruvate from phosphoenolpyruvate and ATP generation in glycolysis.	Accumulation of glycolytic intermediates for biosynthesis. Promotion of tumor cell proliferation
Glutaminase (GLS)	Overactive	Deamination of glutamine to glutamate.	Stimulation of lipid biosynthesis
Isocitrate dehydrogenase 1 and 2 (IDH)	Mutated	NADP-dependent decarboxylation of isocitrate to α-ketoglutarate.	Production of the oncometabolite 2-hydroxyglutarate
Succinate dehydrogenase (SDH)	Inactive	Succinate oxidation in Krebs cycle producing fumarate	Tumor suppressor
Fumarase (FH)	Inactive	Conversion of fumarate to malate in the Krebs cycle.	Tumor suppressor

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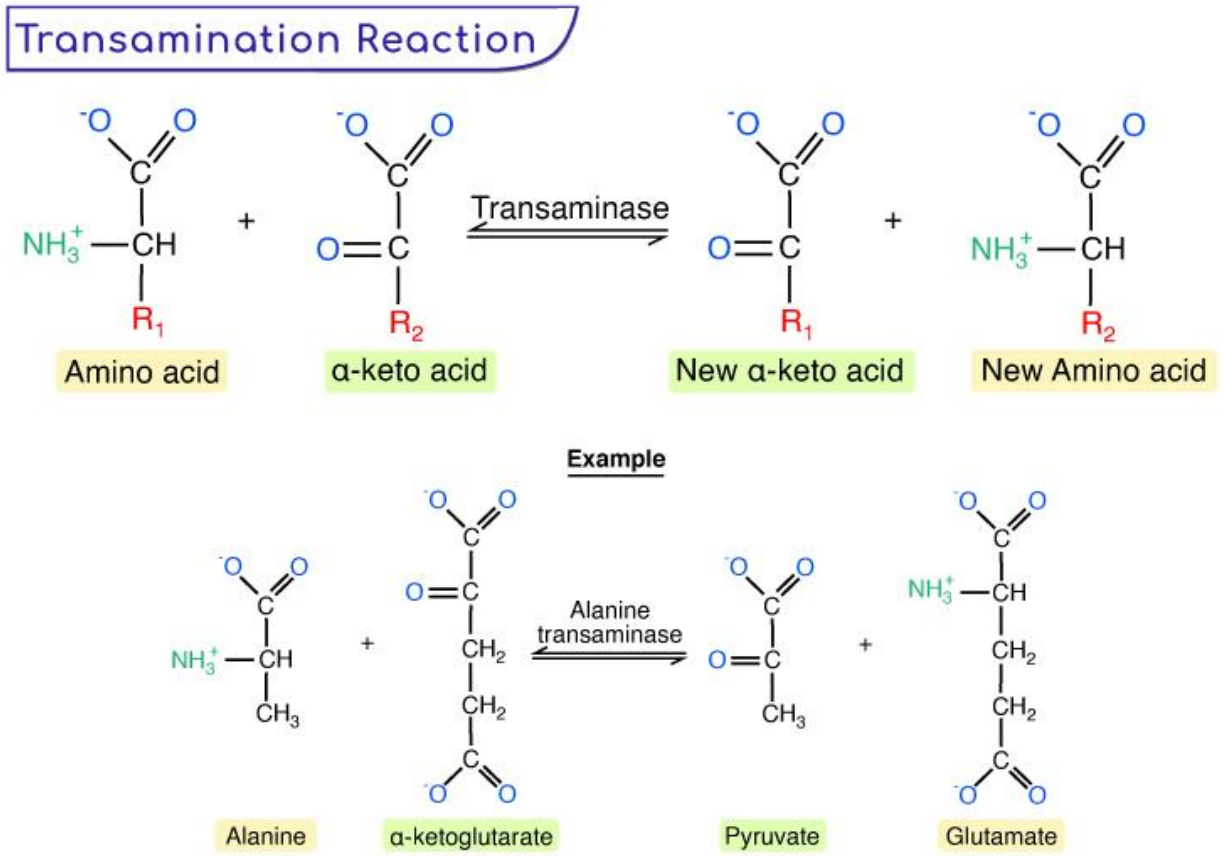
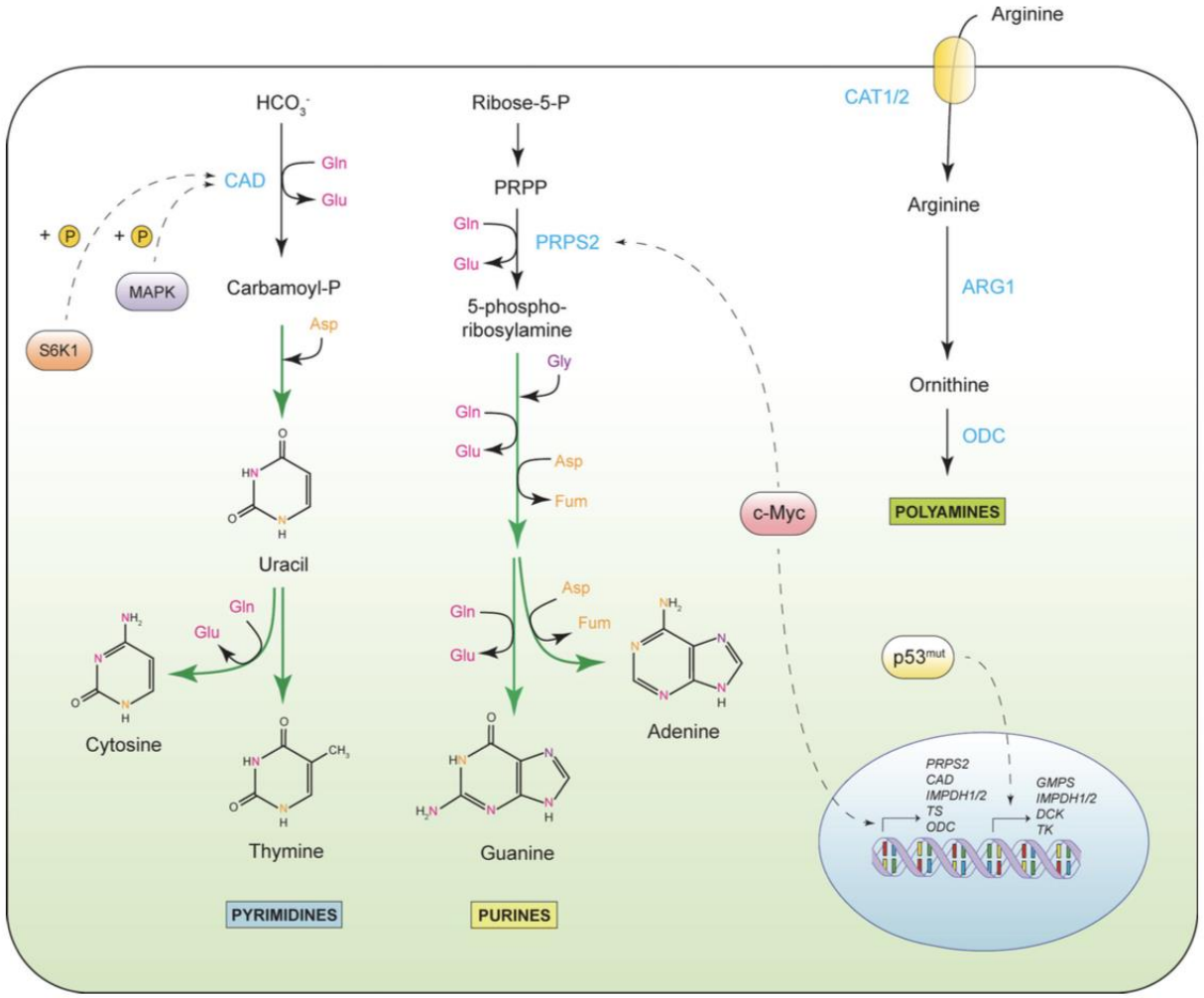
Glutamine



- In addition to its role in nucleotide biosynthesis, glutamine can be directly deamidated to glutamate by glutaminase.
- Glutamine-derived glutamate acts as a nitrogen donor for the synthesis of several nonessential amino acids through transamination.
- Conversely, the biosynthesis of asparagine from aspartate, catalyzed by asparagine synthetase (ASNS), uses the amide nitrogen from glutamine.

Arginine



Arginine provides a nitrogen source for synthesizing nucleotides, nonessential amino acids, and polyamines

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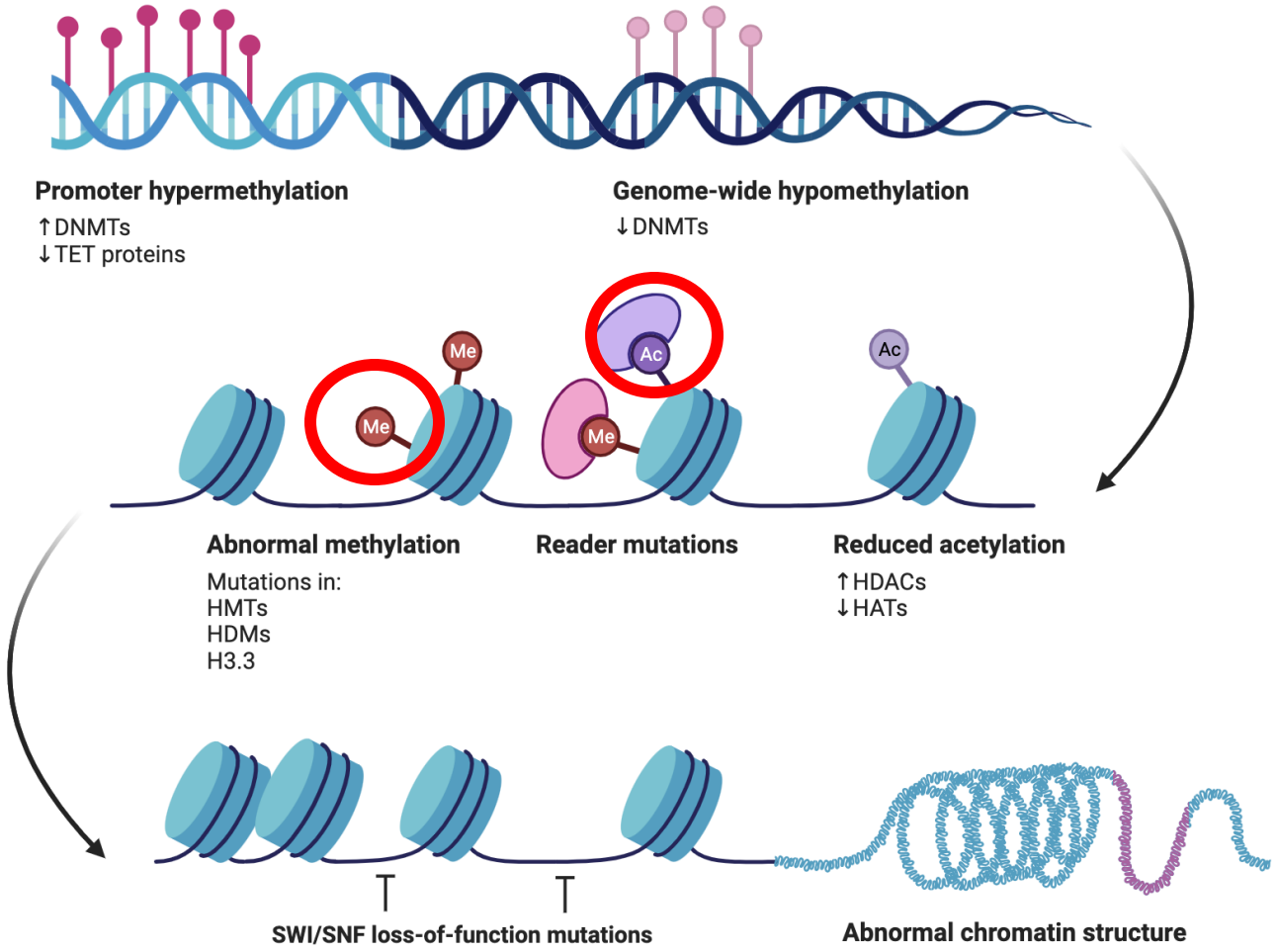
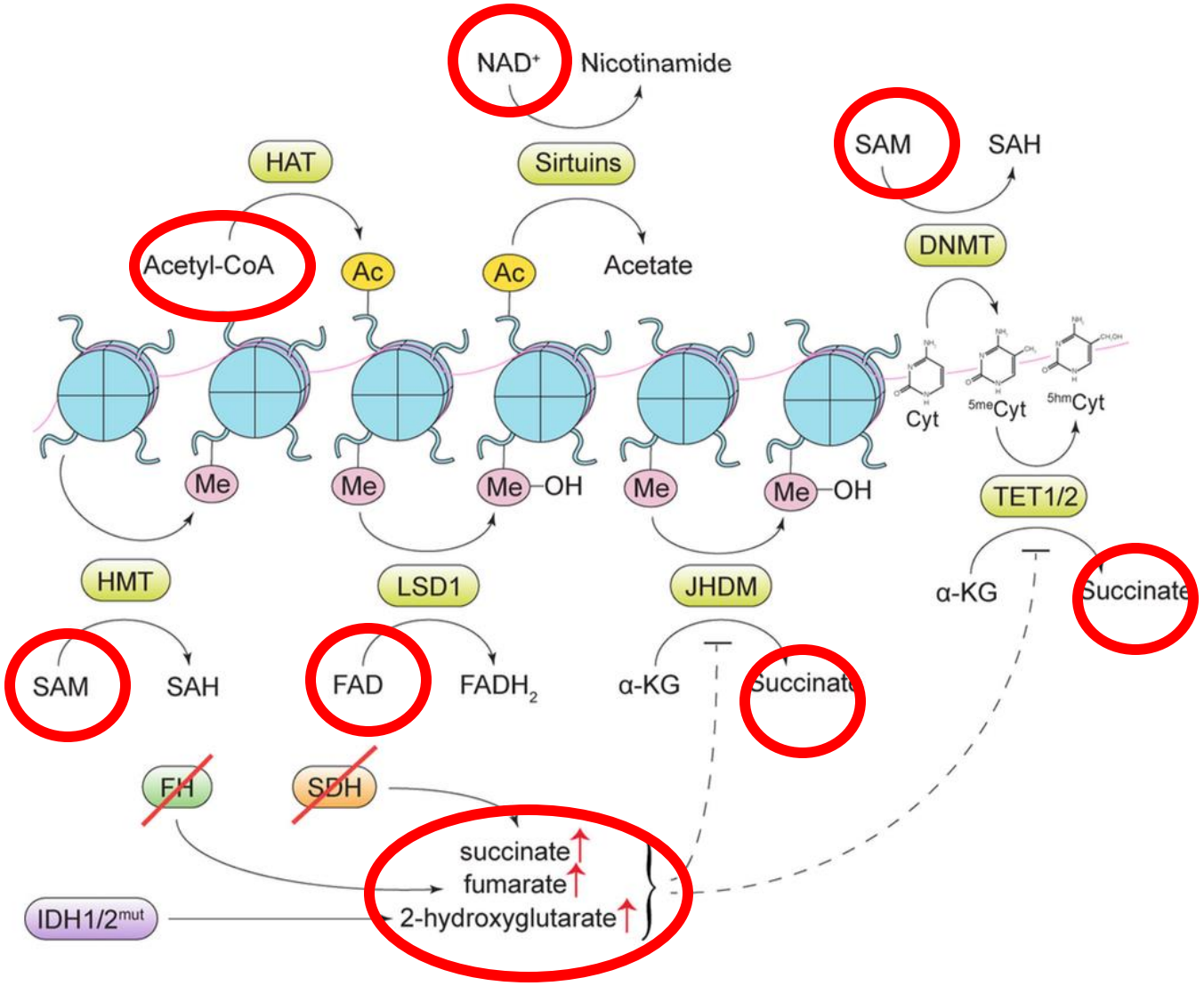
Epigenetics is …. metabolism?

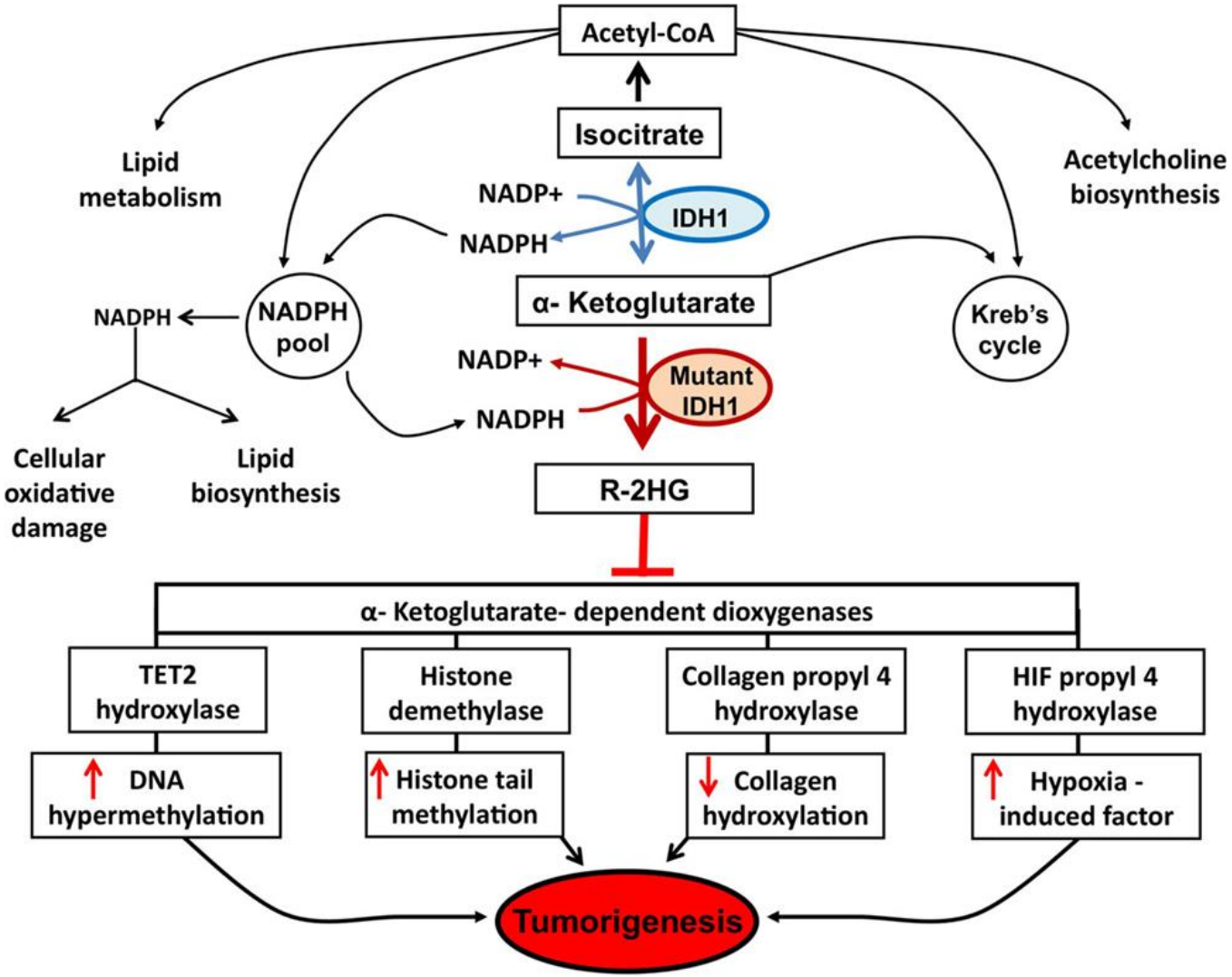


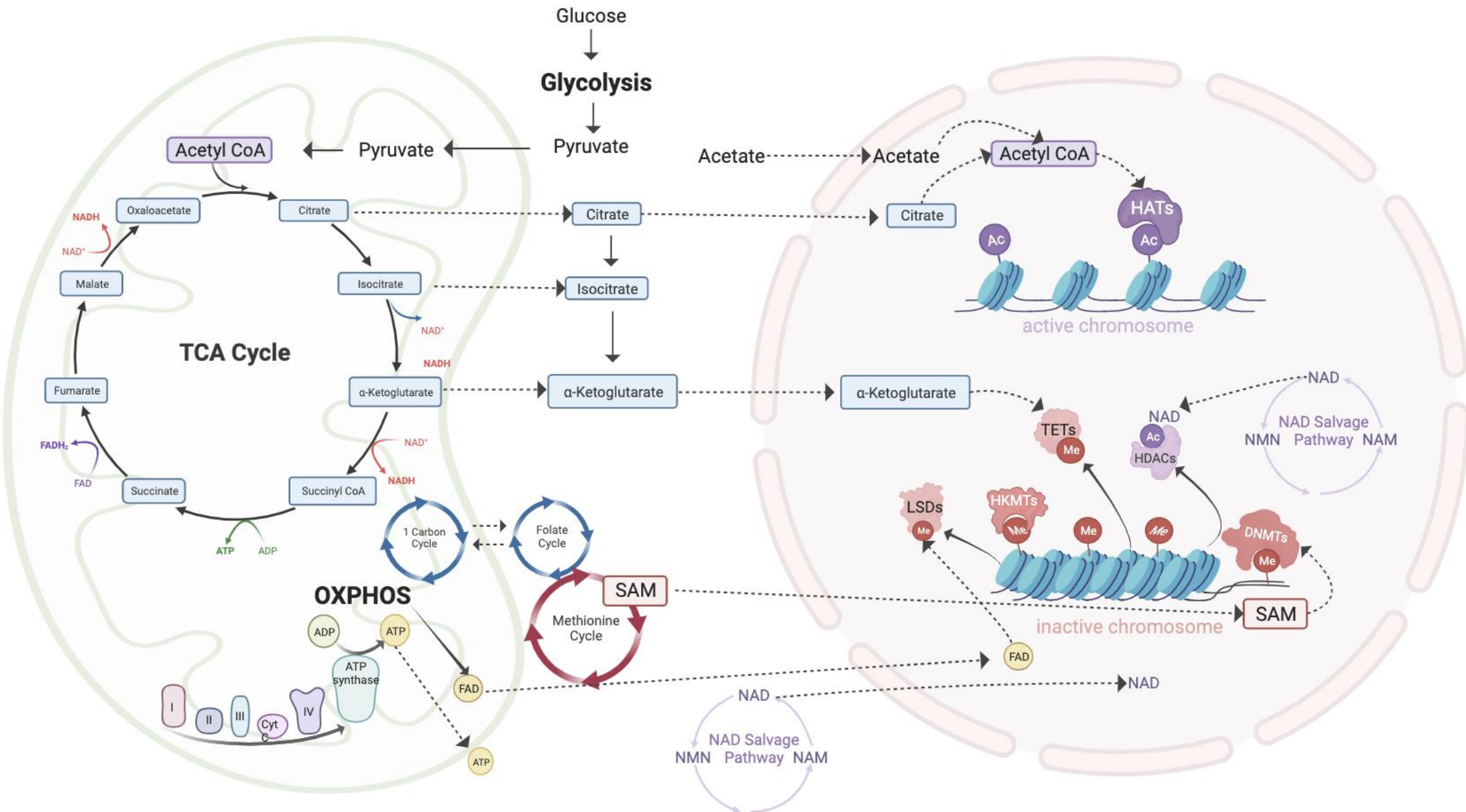
Alterations in metabolite-driven gene regulation



- Alpha-ketoglutarate-dependent dioxygenases include the TET family of DNA demethylases, Jumonji C family of histone demethylases, and a family of prolyl hydroxylase (PHD) enzymes, which, among other processes, regulate HIF1a levels in response to oxygen availability and oxidative stress.
- Alpha-ketoglutarate-dependent dioxygenases are prone to inhibition by their reaction product, succinate, as well as by fumarate, the downstream product of succinate degradation in the TCA cycle.

Oncometabolites: 2HG




Glucose
Glycolysis
Pyruvate
Pyruvate
Acetyl CoA
Pyruvate
Oxaloacetate
Citrate
NADH
NAD+
Malate
Isocitrate
NAD+
TCA Cycle
NADH
Fumarate
α-Ketoglutarate
NAD+
FADH2
FAD
NADH
Succinate
Succinyl CoA
ATP
ADP
1 Carbon Cycle
Folate Cycle
SAM
Methionine Cycle
OXPHOS
ADP
ATP
ATP synthase
I
II
III
Cyt C
IV
FAD
ATP
NAD
NAD Salvage
NMN Pathway NAM
Citrate
Isocitrate
α-Ketoglutarate
Acetate
Acetate
Acetyl CoA
Citrate
HATs
Ac
Ac
active chromosome
α-Ketoglutarate
NAD
NAD Salvage
NMN Pathway NAM
TETs
Me
NAD
Ac
HDACs
LSDs
Me
HKMTs
Me
Me
Me
DNMTs
Me
SAM
inactive chromosome
FAD
NAD

Moonlighting functions of metabolic enzymes and metabolites in cancer

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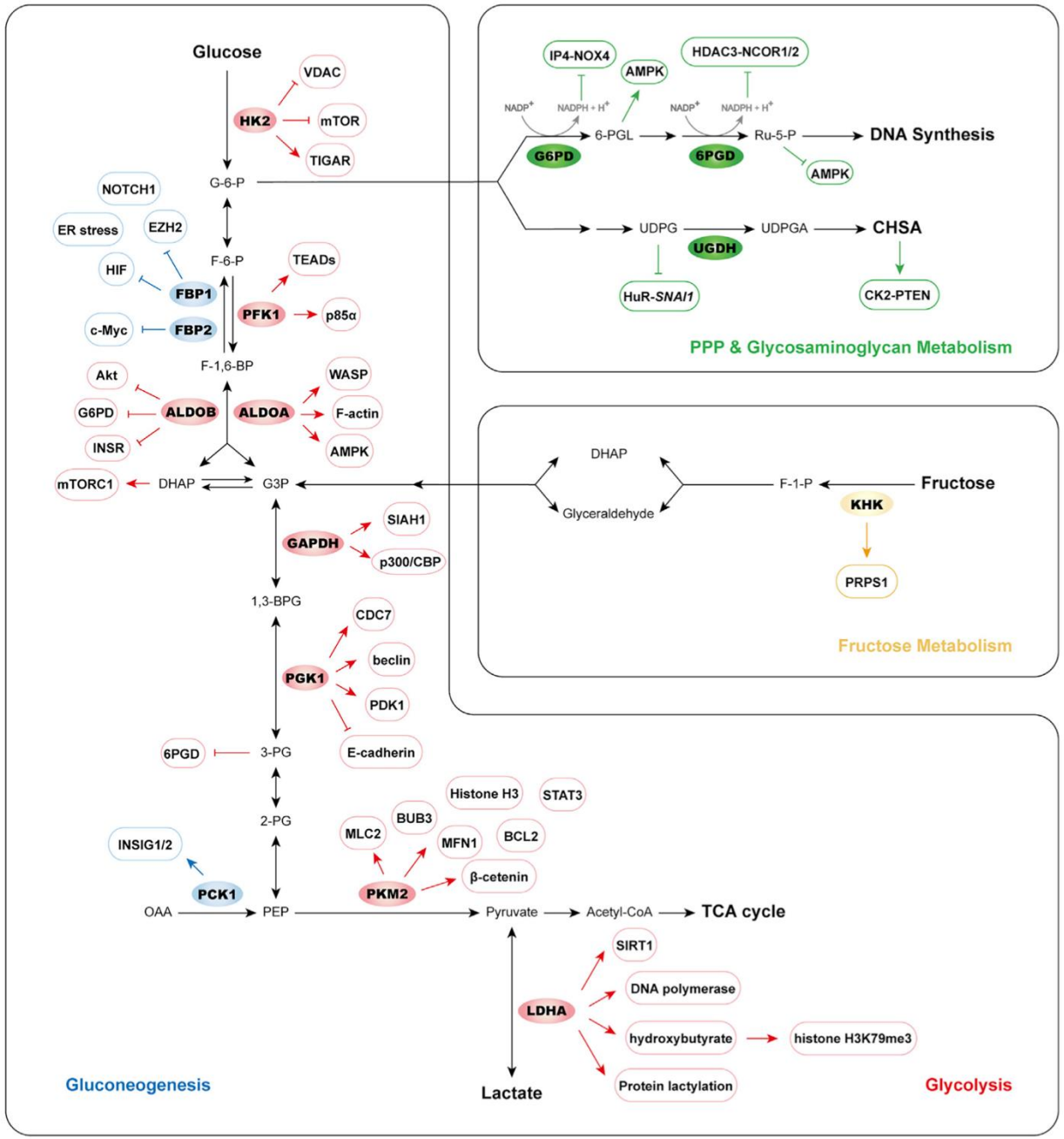
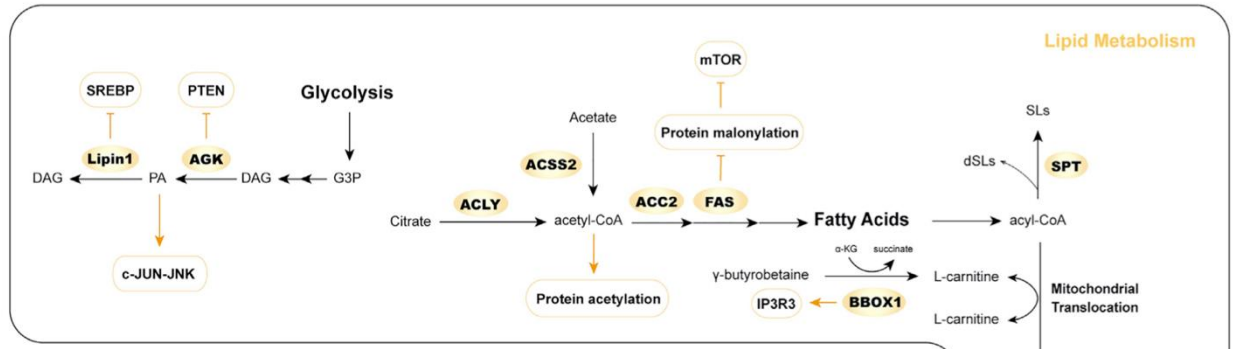
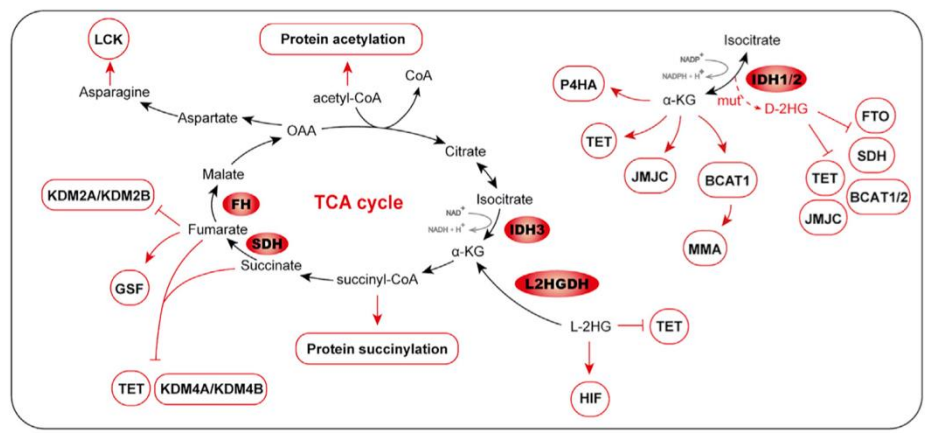
https://doi.org/10.1016/j.molcel.2021.08.031







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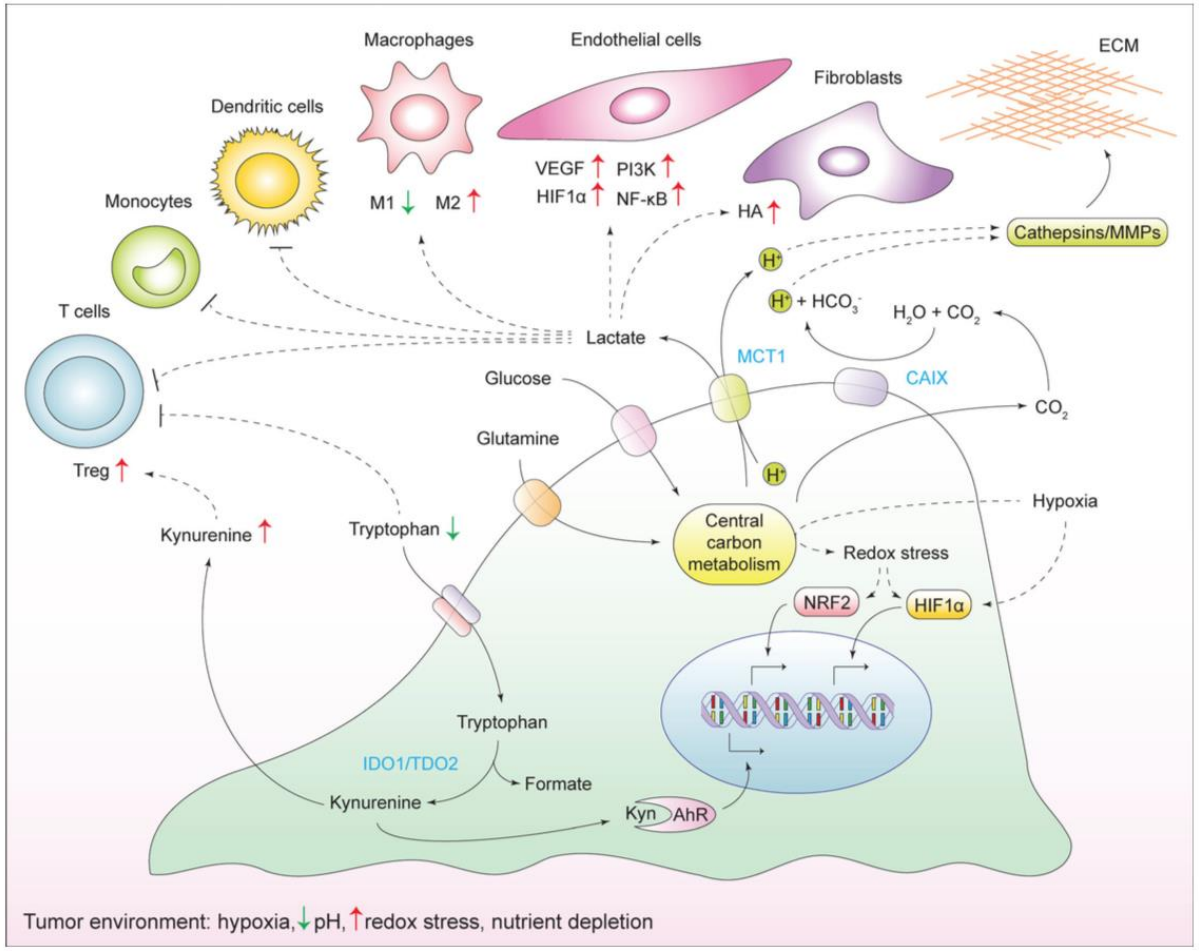
Metabolic interactions with the microenvironment



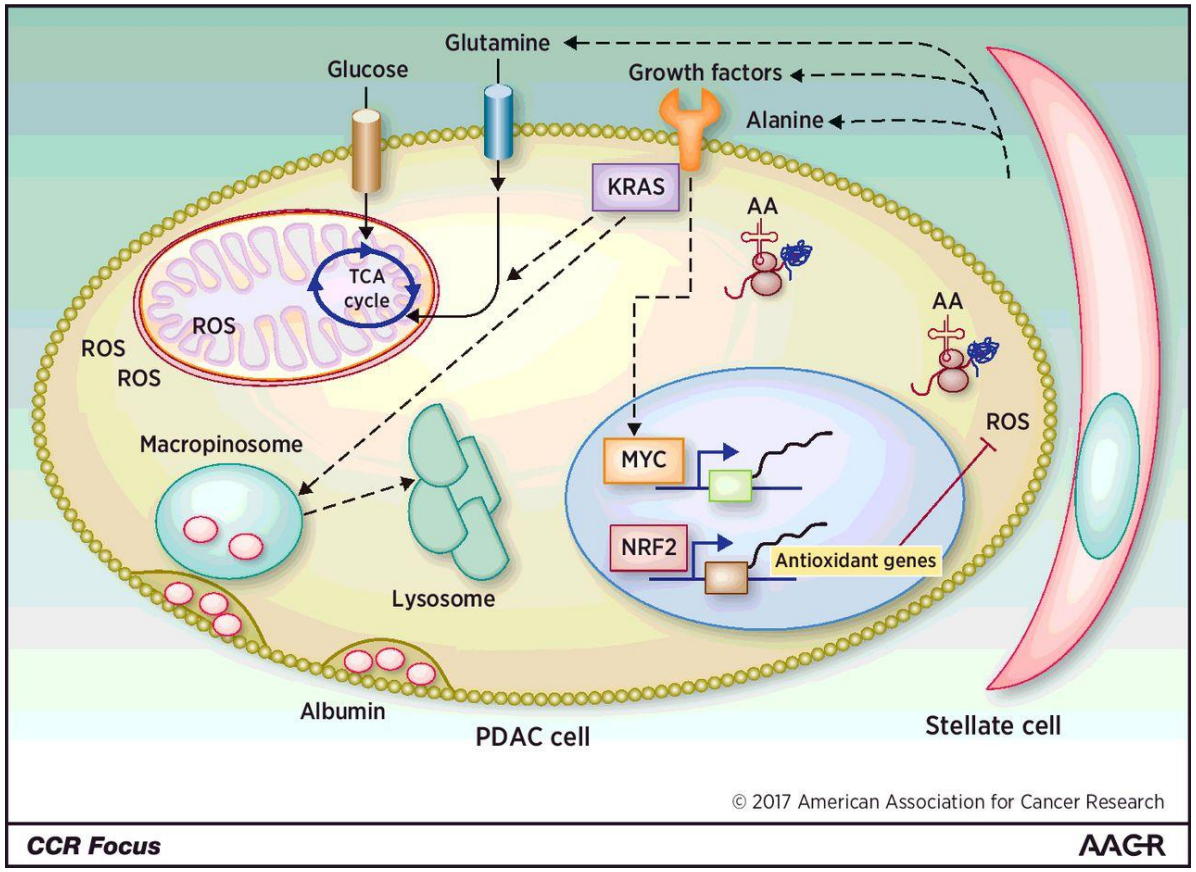
Lactate

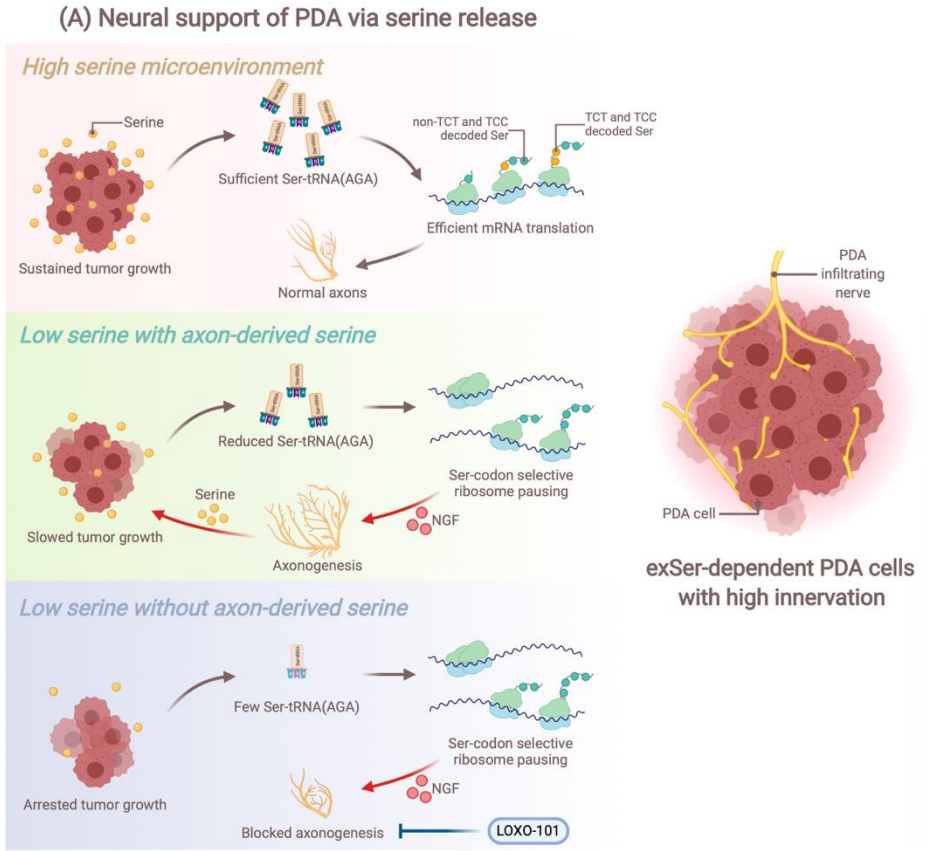
- Attenuates the activation of dendritic cells and T cells, as well as monocyte migration (Fischer et al 2007).
- Stimulates M2 polarization (Colegio et al 2014).
- Promotes angiogenesis (Sonveaux et al 2012).
- Increases acidification, leading to ECM degradation (Rotheberg et al 2013).

Metabolic interactions with the microenvironment

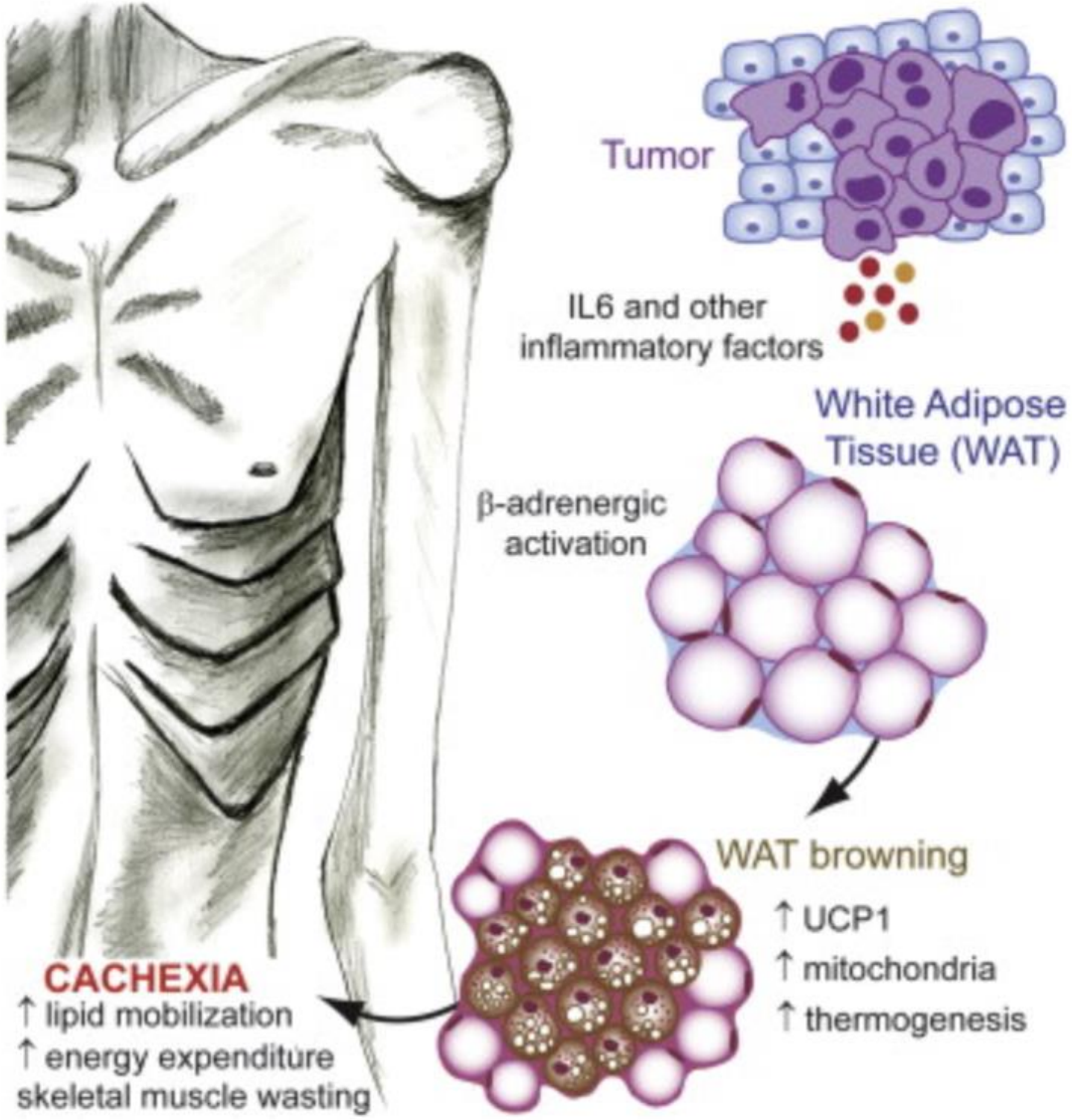
- Numerous solid tumor types overexpress tryptophan-degrading enzymes indoleamine 2,3-dioxygenase (IDO1) and tryptophan 2,3-dioxygenase (TDO2), which catalyze the conversion of an essential amino acid, tryptophan, into its derivative, kynurenine (Munn and Mellor, 2007).
- Tryptophan depletion triggers amino acid deprivation–induced apoptosis of effector T cells (Fallarino et al., 2002). Accumulated kynurenine acts as a ligand for the aryl hydrocarbon receptor (AhR) (Opitz et al., 2011).
- In an AhR-dependent manner, kynurenine promotes a Treg phenotype, further contributing to the suppression of antitumor immune responses (Fallarino et al., 2006).

Cellular crosstalk





Systemic crosstalk: Cachexia

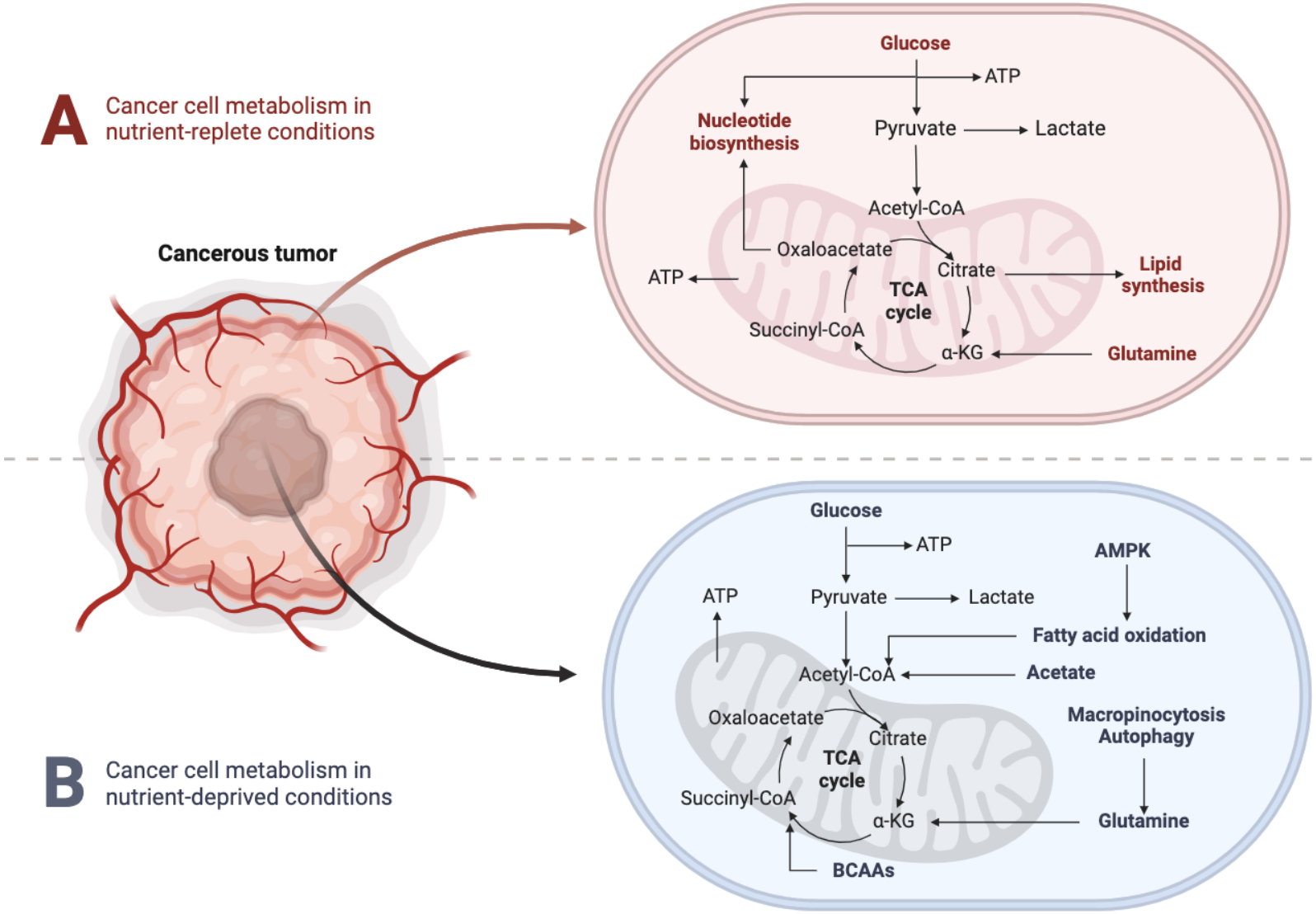


Cancer-associated cachexia

Vickie E. Baracos ✉, Lisa Martin, Murray Korc, Denis C. Guttridge & Kenneth C. H. Fearon

Nature Reviews Disease Primers **4**, Article number: 17105 (2018) | Cite this article

Key takeaways



PASSIVE RESPONSE

- Energy
- Biomass
- Redox Balance

ACTIVE REGULATION

- Regulation of gene expression
- Shaping the tumor microenvironment
- Remodeling the organism