What is the main role of catabolism in cellular metabolism?

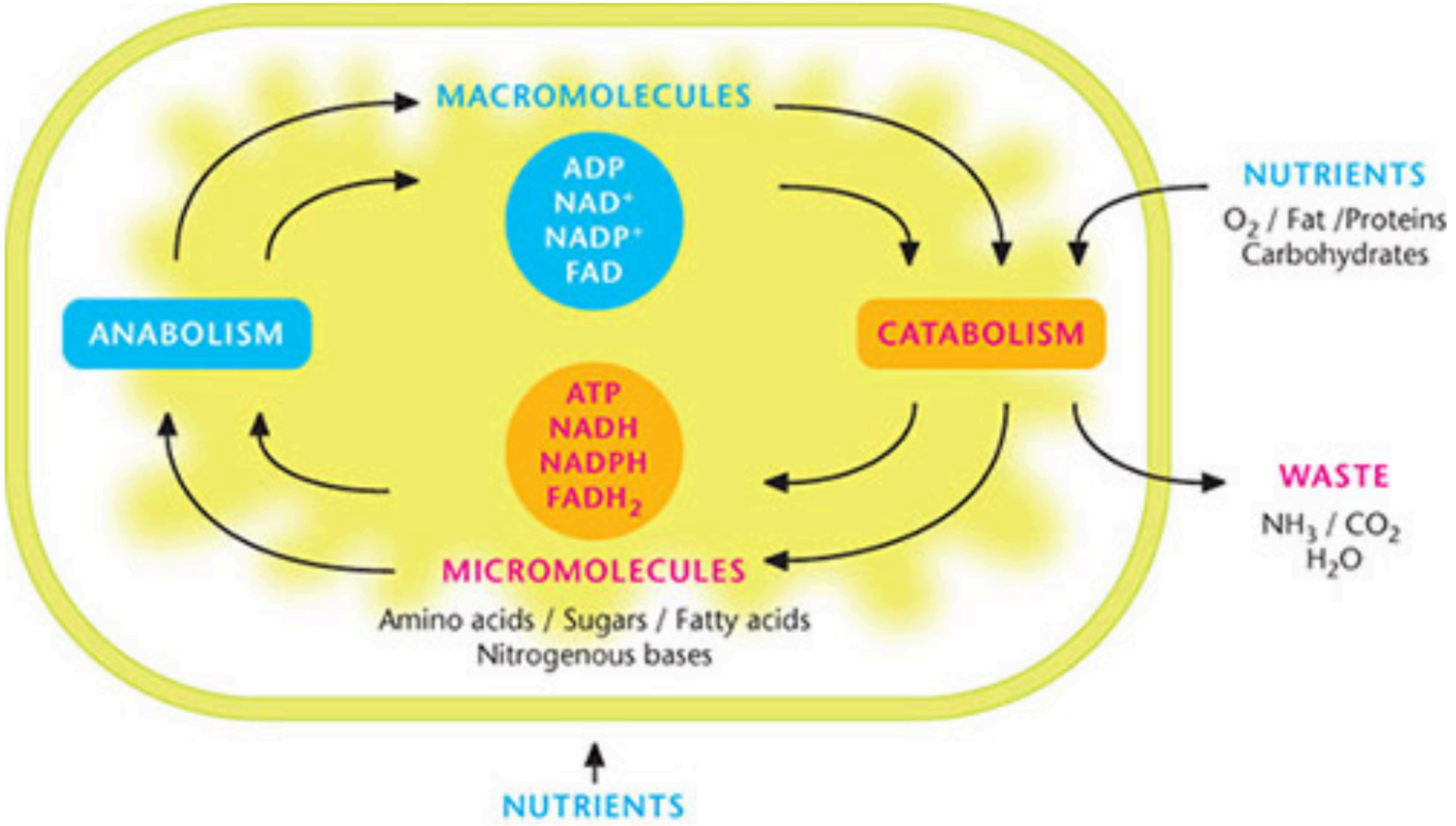
A. To build large molecules from small ones

B. To generate energy by breaking down nutrients

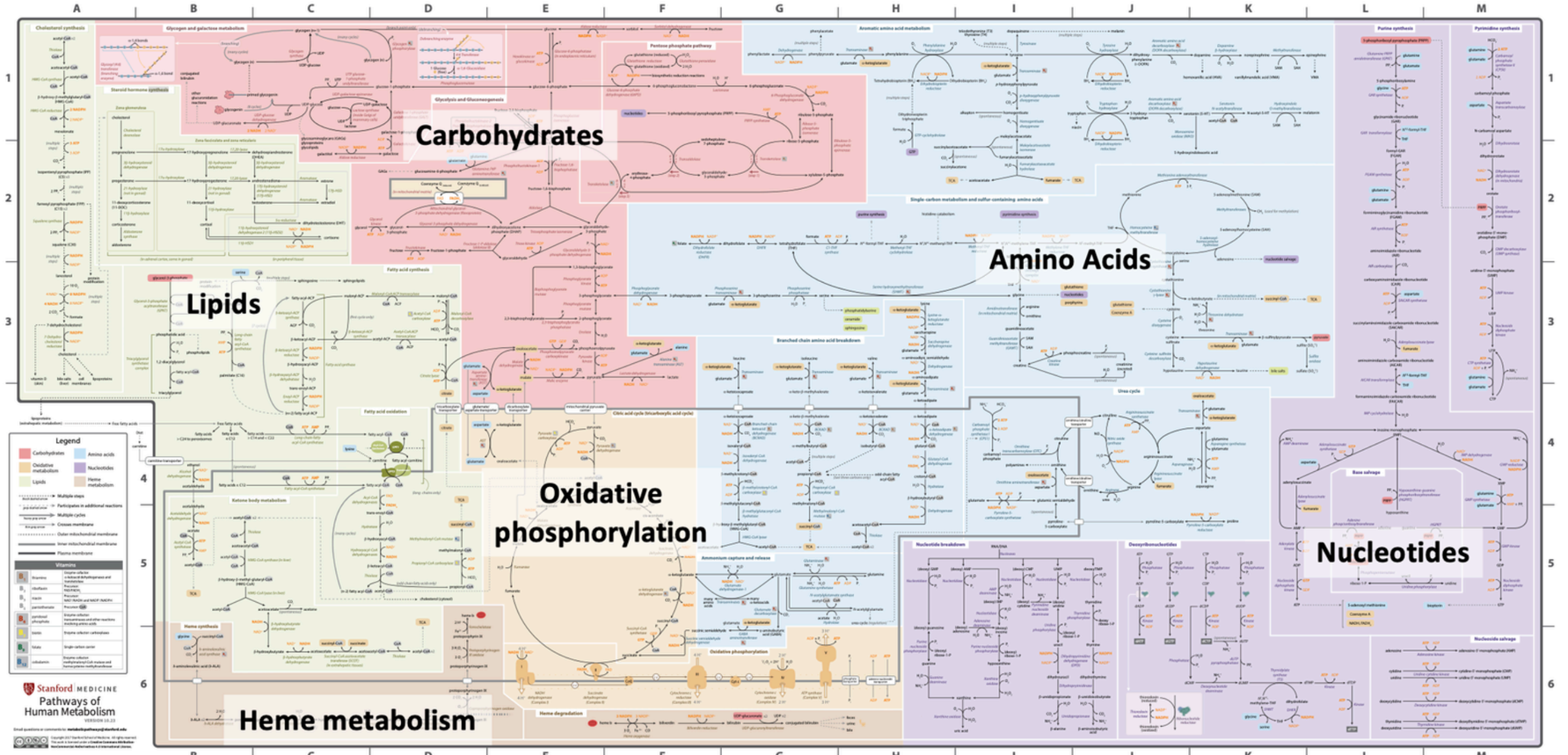
C.To transport nutrients into the cell

D.To remove waste from the cell

What is cellular metabolism?



Overview of major metabolic pathways in cells



Source: https://metabolicpathways.stanford.edu/

E.g. nucleotides are synthesised to build DNA, RNA, ATP (anabolic) and need to be degraded (catabolic) ; lipogenesis to build fatty acids from smaller molecules (anabolic) vs fatty acid b-oxidation into Acetyl-CoA for energy (catabolic)

What determines whether a cell sends pyruvate to fermentation or oxidative phosphorylation?

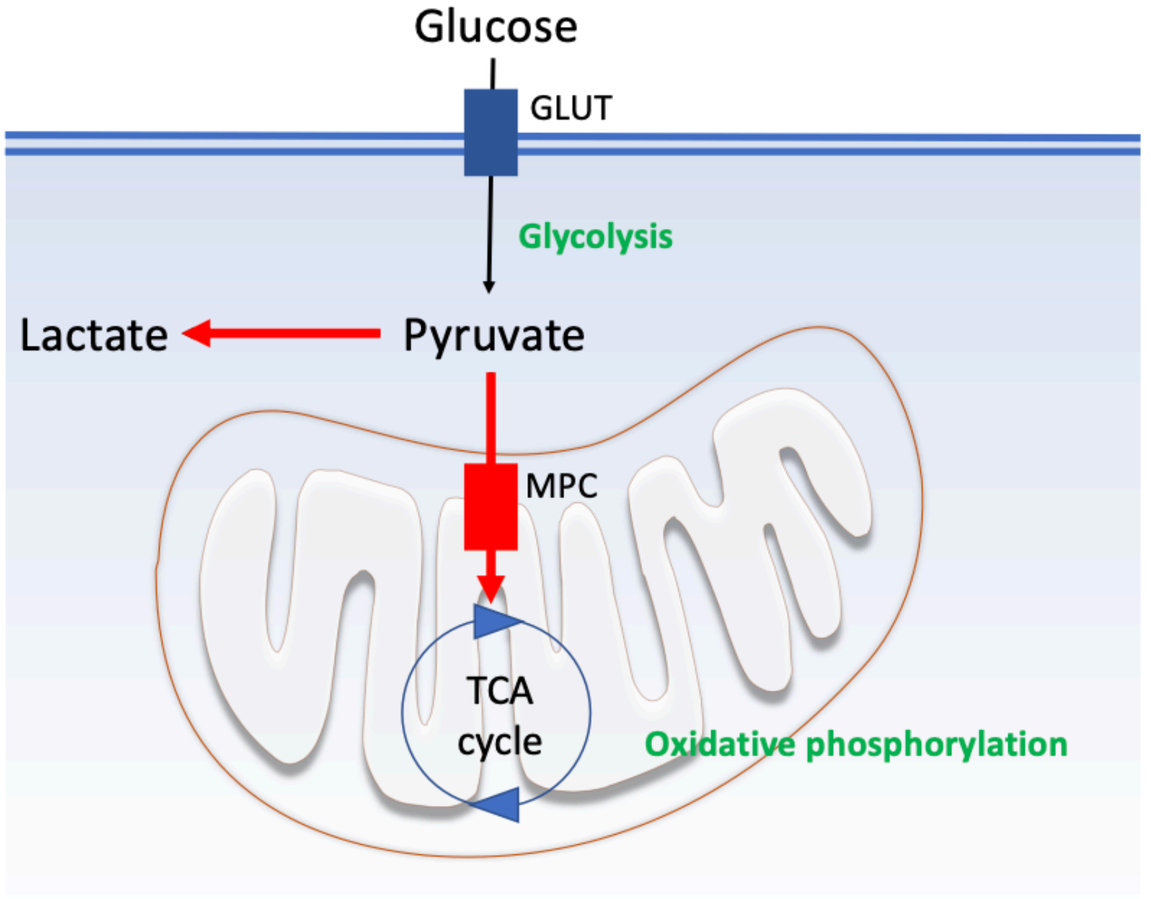
A. The amount of glucose available

B. Whether the mitochondria are active


C. The presence or absence of oxygen

D. The number of ATP already produced

Energy production through glucose fermentation versus oxidation



Glycolysis	Oxphos
2 molecules ATP	30 molecules ATP
Faster	Slower
NAD+ regenerated through lactate (fermentation)	NAD+ regenerated through electron transport chain (oxidation)
Anaerobic	Aerobic

Why are protons (H^+) pumped across the inner mitochondrial membrane during the electron transport chain?

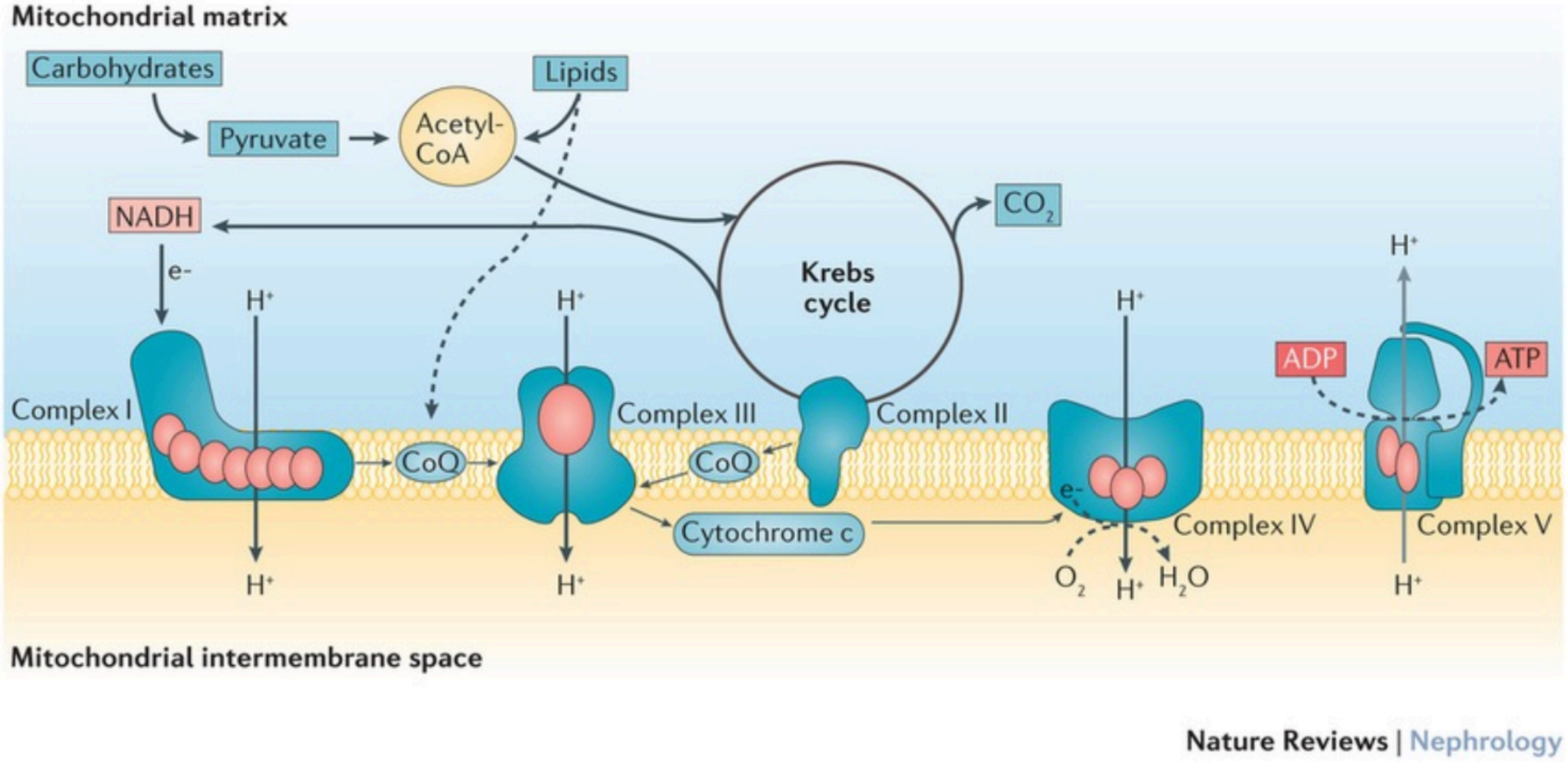
A. To break down glucose faster

B. To generate heat


C. To create a gradient that powers ATP production

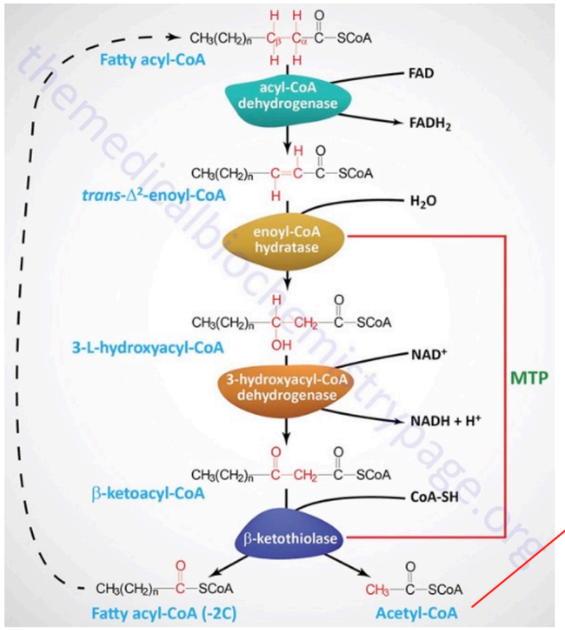
D. To activate oxygen for the Krebs cycle

Electron transport chain and oxidative phosphorylation

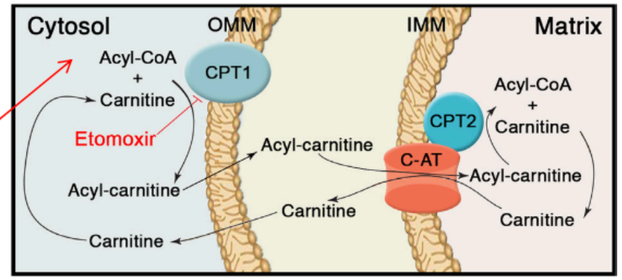


Emma F., et al., Nature Rev Neph, 2016

Fatty acid β-oxidation



Fatty acid oxidation produces **Acetyl-CoA** in the **cytosol**, which is imported by **CPT enzymes** into the **mitochondria** for oxidation



Nomura M. et. al., (2016) Nat. Immunol.

Just like glucose gets converted to Acetyl-CoA and enters the Krebs cycle, fatty acids also get broken down to make Acetyl-CoA - that Acetyl-CoA then enters the same TCA cycle and electron transport chain

Which TCA cycle product supports epigenetic gene regulation?

A. NADH for ATP generation in glycolysis

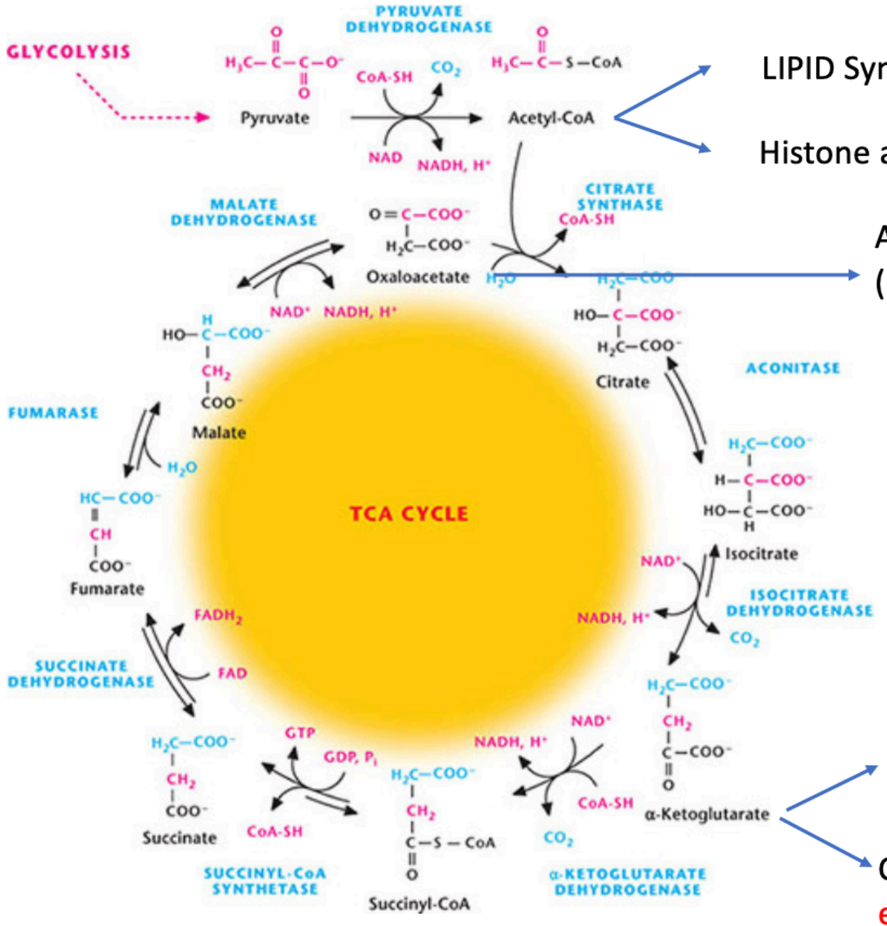
B. GTP for protein synthesis in mitochondria


C. a-KG acts as a cofactor for DNA methylation

D. Pyruvate for lactate synthesis only

The TCA cycle is a major producer of cellular **building blocks**

The TCA cycle produces:
- three NADH,
- one $FADH_2$
- one GTP



LIPID Synthesis

Histone acetylation-Epigenetics

Aspartate
(purine-Pyrimidine synthesis)

Glutamate—Glutamine
(adenosine-guanine synthesis)

Cofactors for DNMT enzymes
epigenetics

Chandel N., Navigating Metabolism 2014 (book)

How does acetyl-CoA influence gene expression?

A. It activates DNA polymerase to start replication

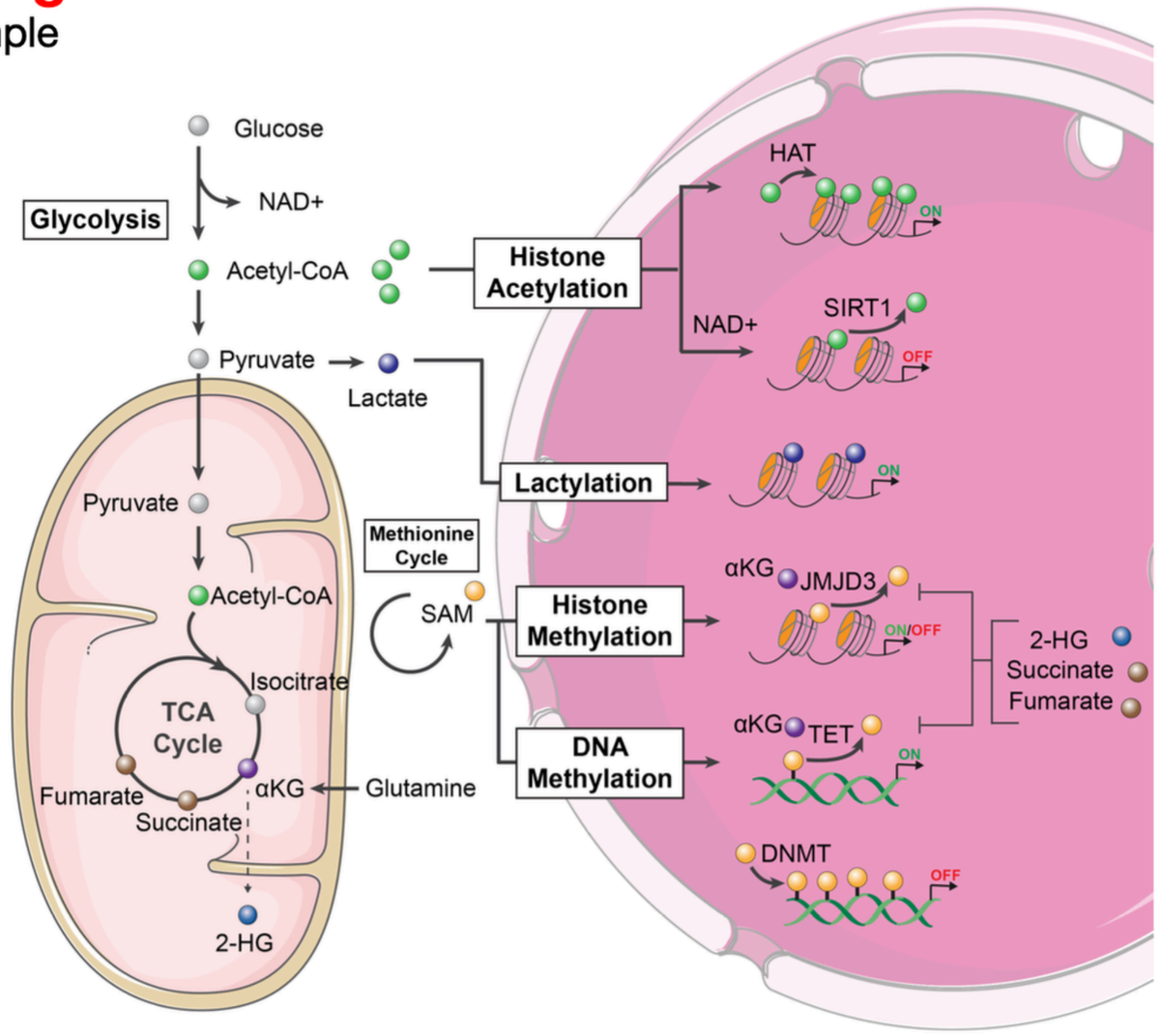
B. It donates acetyl groups to histones, loosening DNA

C. It blocks methylation of cytosines in DNA

D. It is used to generate ATP in the nucleus

Metabolism in **cellular signaling**

Regulation of gene expression as an example



Adapted from Franco *et al.*, Nature Metabolism 2020

What is a primary function of macrophages in the innate immune response?

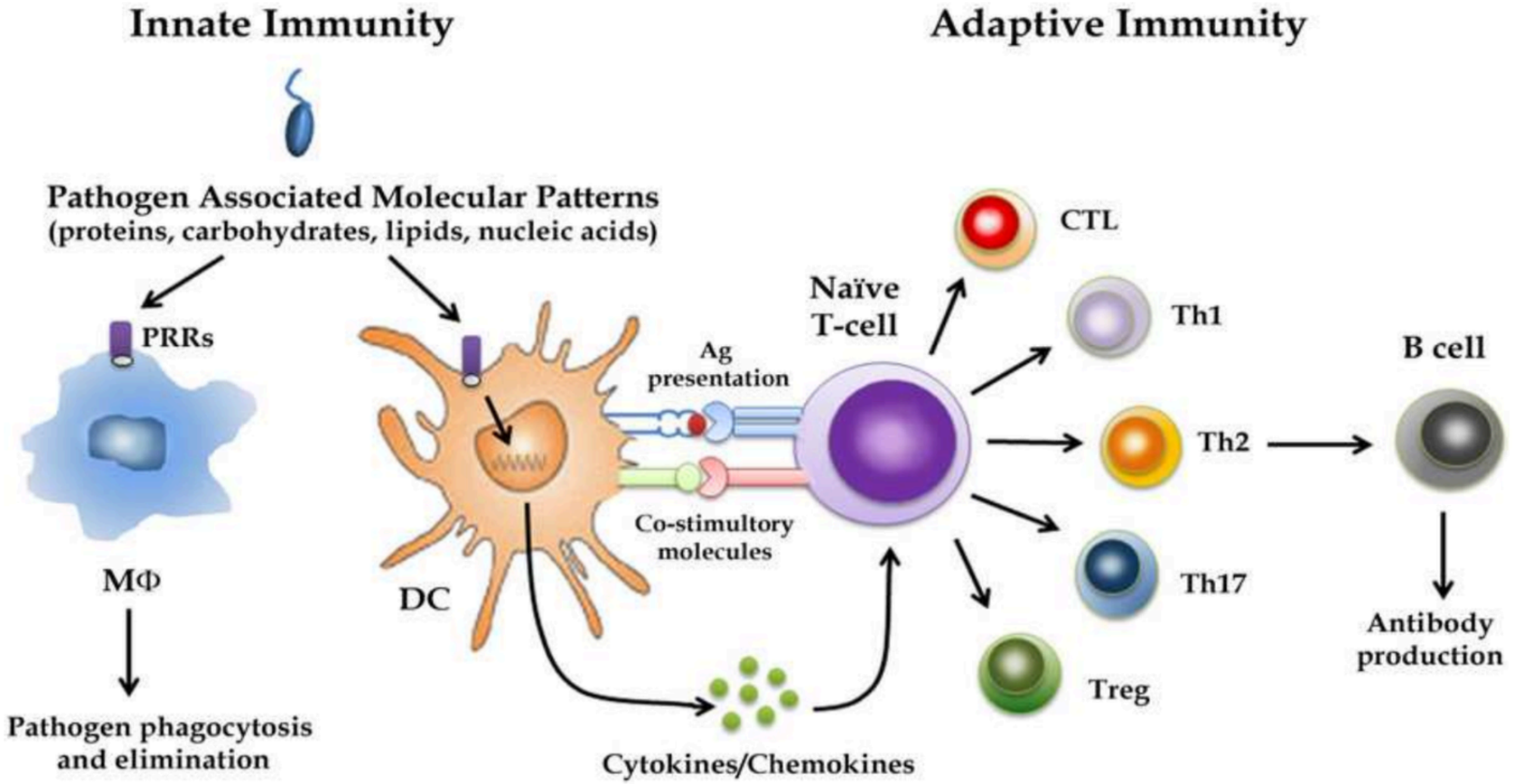
A. Producing antibodies

B. Presenting antigens to B cells

C. Phagocytosing pathogens and initiating inflammation

D. Activating cytotoxic T cells

Innate and adaptive immune response



Neves *et al*., IntechOpen, 2012

Which best describes M1 and M2 macrophage functions and metabolism?

A. M1 are anti-inflammatory & use fatty acids, M2 are pro-inflamm & glycolytic

B. M1 are pro-inflammatory & oxidative, M2 are anti-inflamm. & glycolytic

C. M1 are pro-inflammatory & glycolytic, M2 are anti-inflamm. & oxidative

D. M1 and M2 use same metabolism, function differs by surface markers

μακρός φαγεῖν-Big eaters

PRO-INFLAMMATORY **M1**

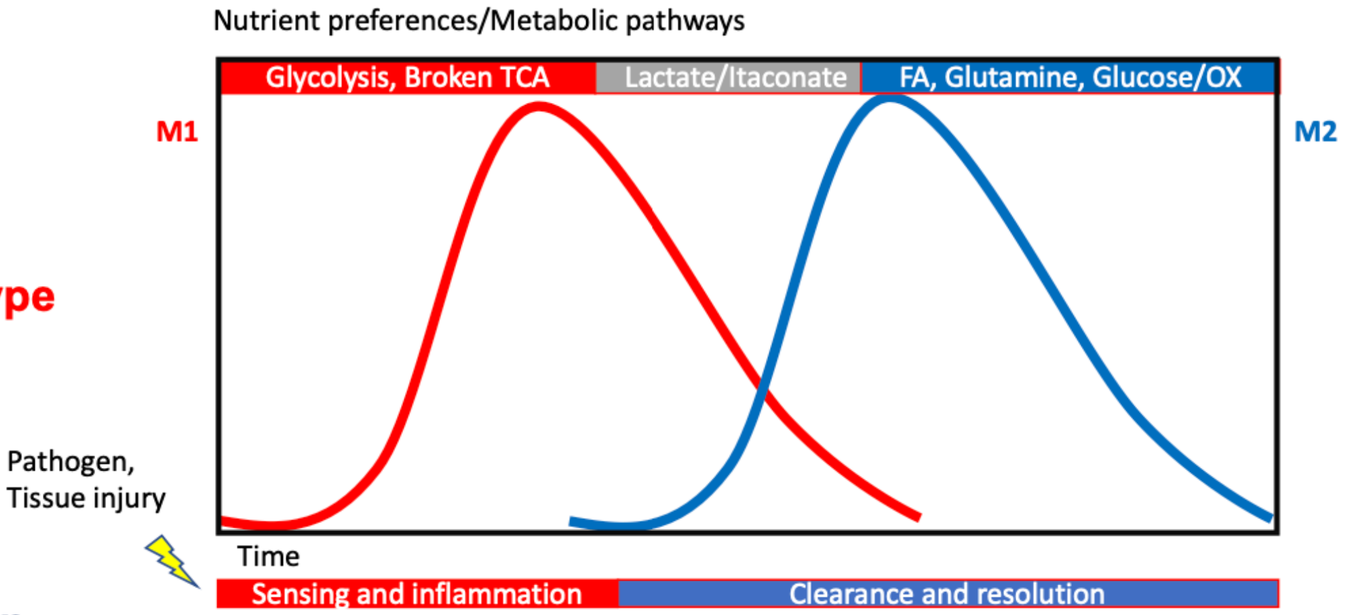
- **Bacteria**
- **Damaged/infected cells**

- **Antigen presentation**
- **Activation towards pro-inflammatory phenotype**

ANTI-INFLAMMATORY **M2**

- **Dead cells**
- **Debris**

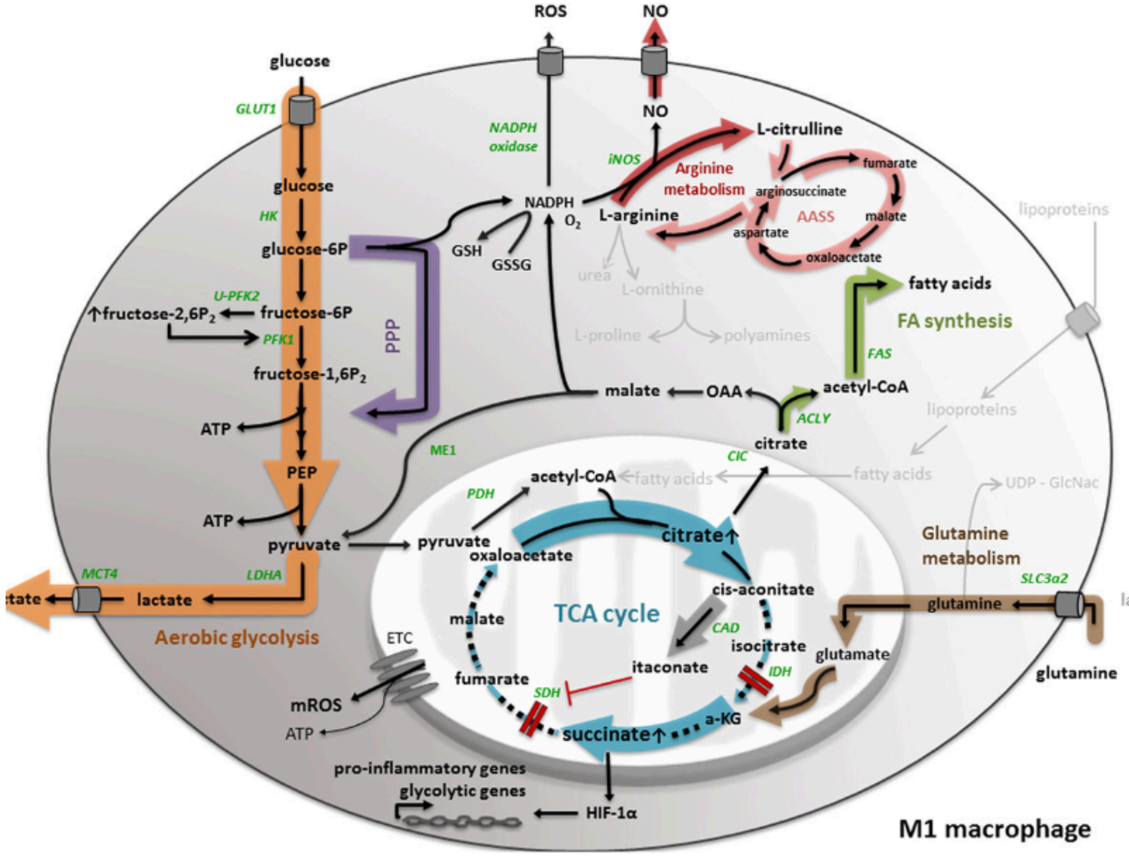
- **Resolution of inflammation**
- **Wound healing**

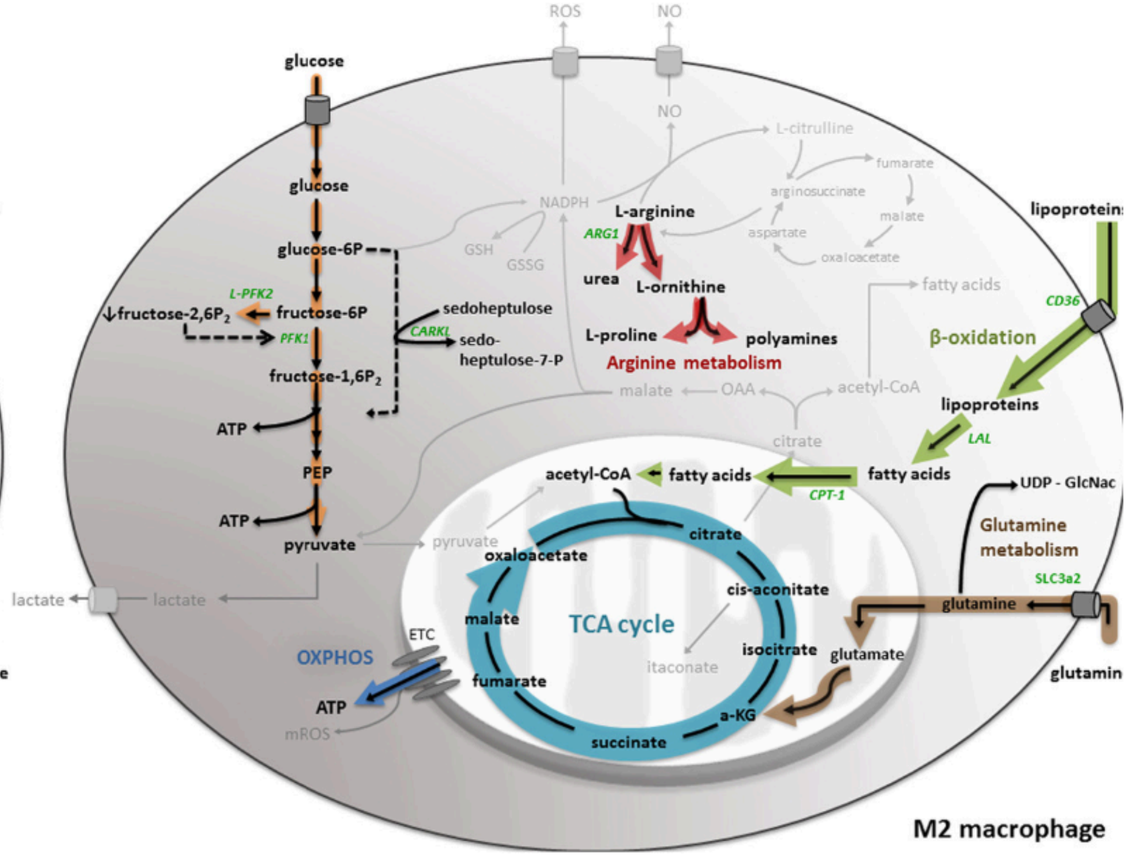


Macrophage polarization is accomplished by engagement of specific metabolic pathways

LPS, INFγ

IL4, IL13





Pro-inflammatory and immunosupportive

Anti-inflammatory and immunosuppressive

Geeraerts et al., Front in Imm, 2017

M1 macrophages, in comparison to M2 macrophages...

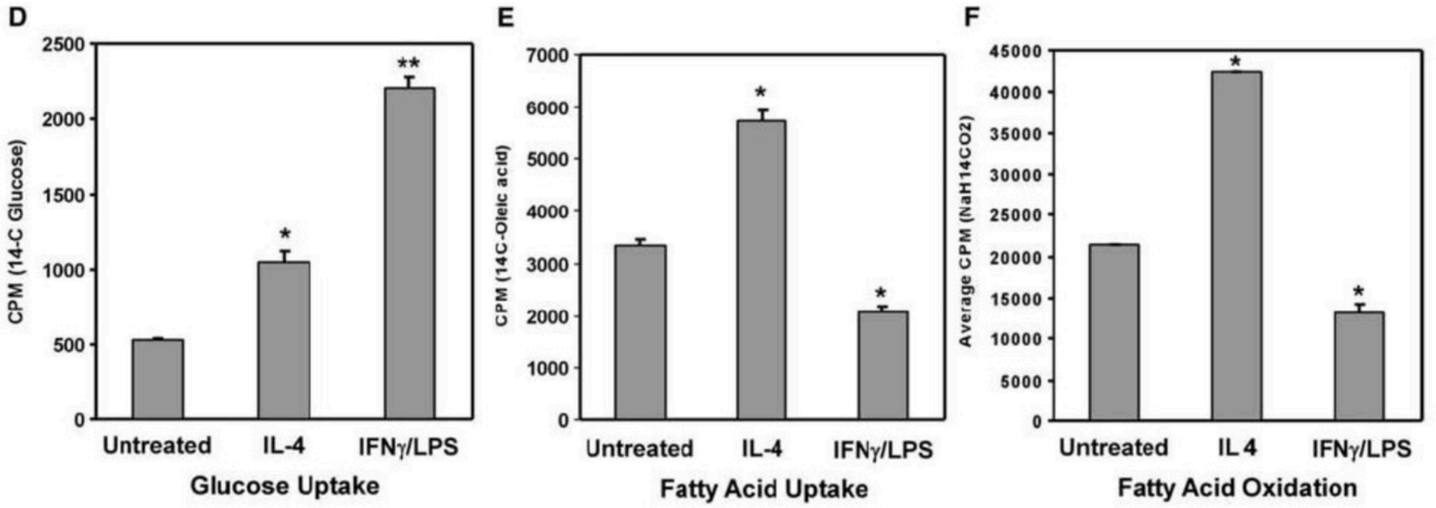
A. Take up more glucose

B. Take up more fatty acids

C. Take up more acetyl CoA

D. Oxidize more fatty acids

Metabolic preference in activated macrophages



Vats D. et. al., (2006) CeLl Metab.

Which of these statements is NOT correct?

A. Lactate is needed for M2 macrophage transformation

B. Lactyl-CoA binds to the tail of histones

C. Histone lactylation is a recently discovered epigenetic modification

D. Lactate is a product of OXPHOS in M1 macrophages

What is the role of lactate in macrophage gene regulation following activation?

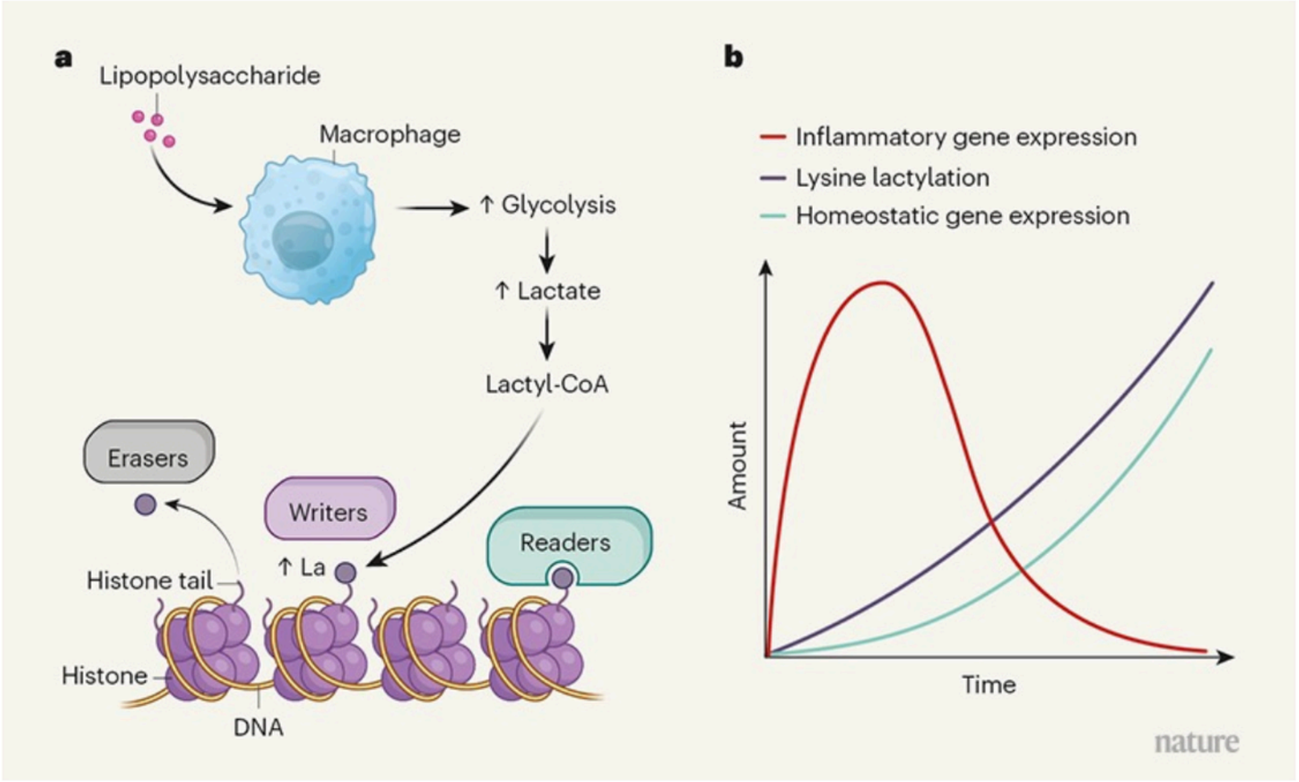
A. Lactate blocks glycolysis and promotes histone methylation

B. Lactate enhances oxidative phosphorylation in mitochondria

C. Lactate forms lactyl-CoA, promoting histone lactylation and gene expression

D. Lactate causes DNA methylation that suppresses inflammation

Histone lactylation, a new epigenetic modification



Izzo and Wellen, Nature 2019

Zhang et al., Nature 2019

Which of the following are required for full activation of a naïve T cell? (multiple answers)

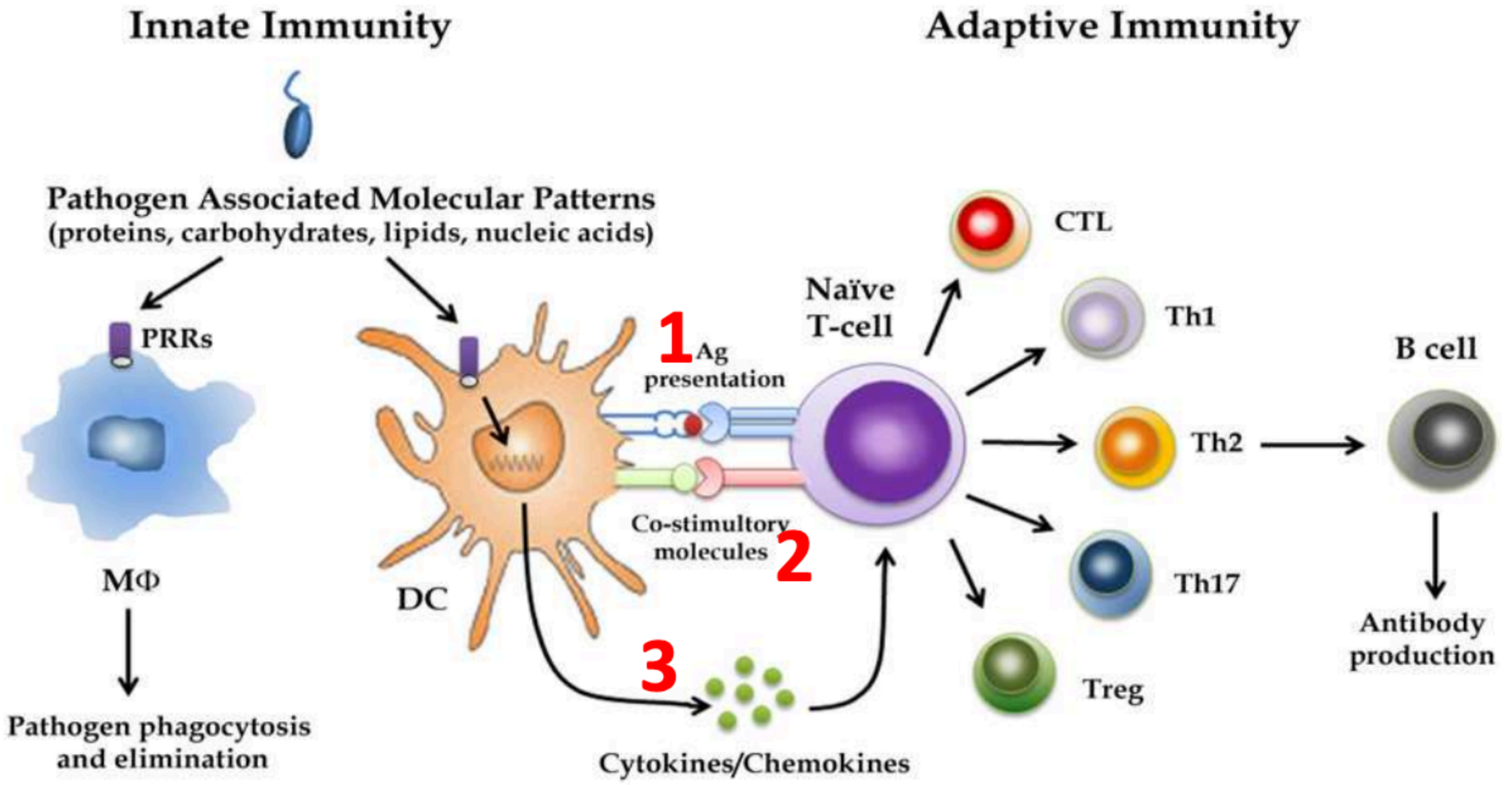
A. Recognition of antigen via the T cell receptor ✓

B. Binding of co-stimulatory molecules ✓

C. Exposure to cytokines ✓

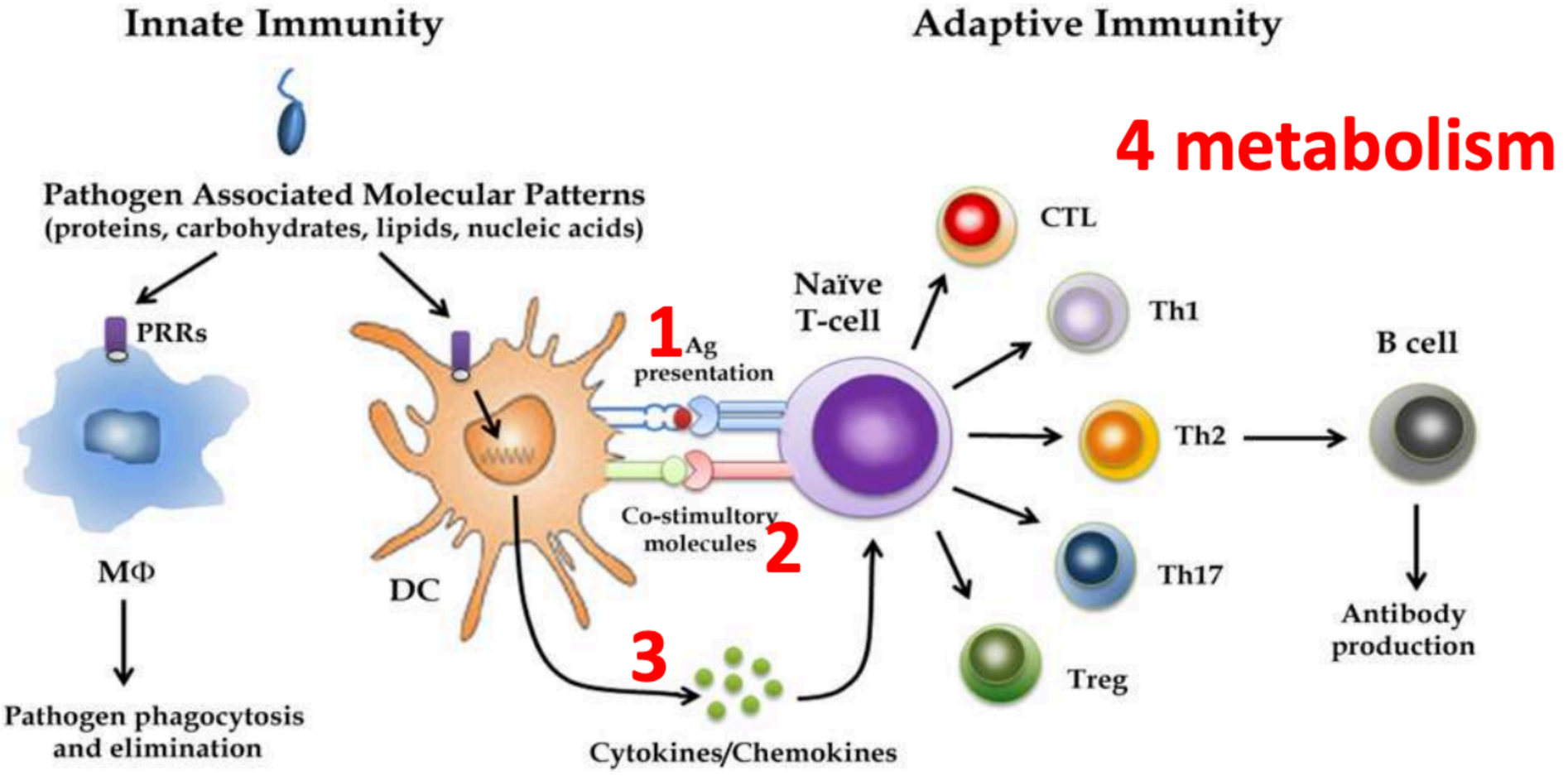
D. Production of antibodies

3 signals are required to fully activate a T cell



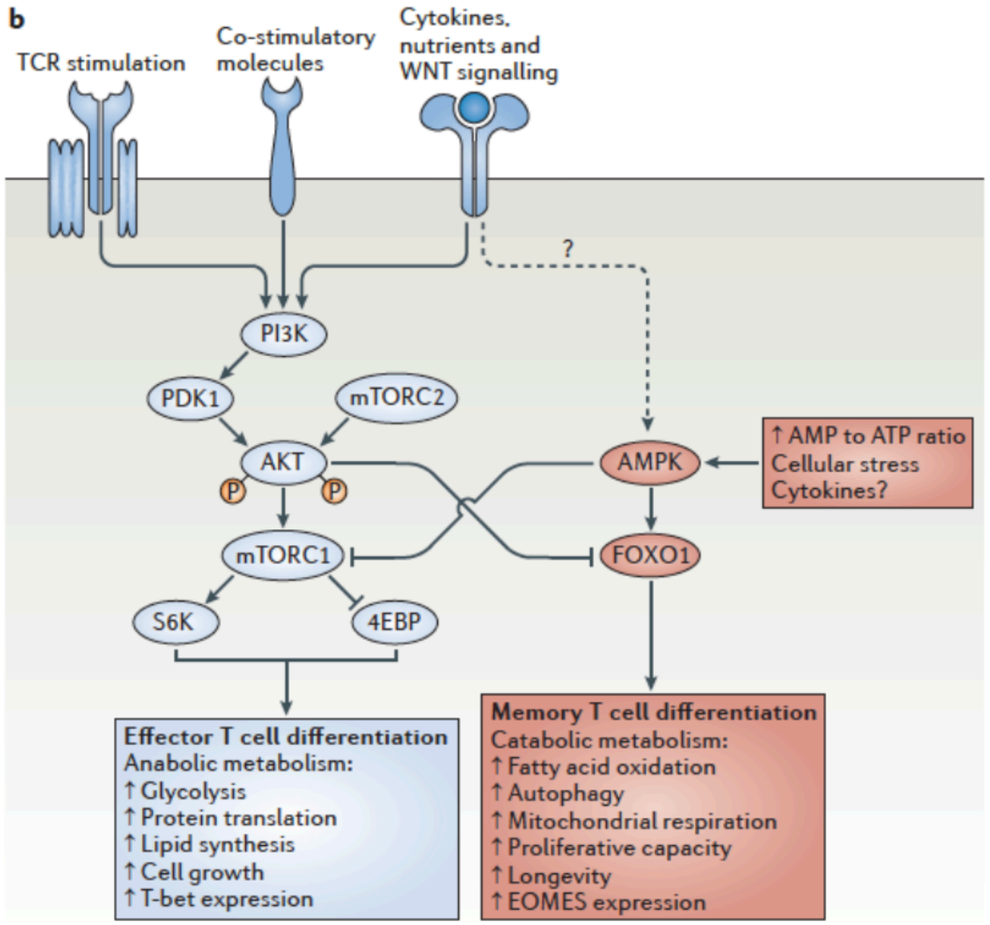
Neves *et al.*, IntechOpen, 2012

~~3~~ 4 signals are required to fully activate a T cell



Neves *et al.*, IntechOpen, 2012

Energy demands and supply change during acute and resolving phases



Cui W. et. al., (2012) Nat. Rev. Immunol.

Which signals can induce T cell exhaustion? (multiple options)

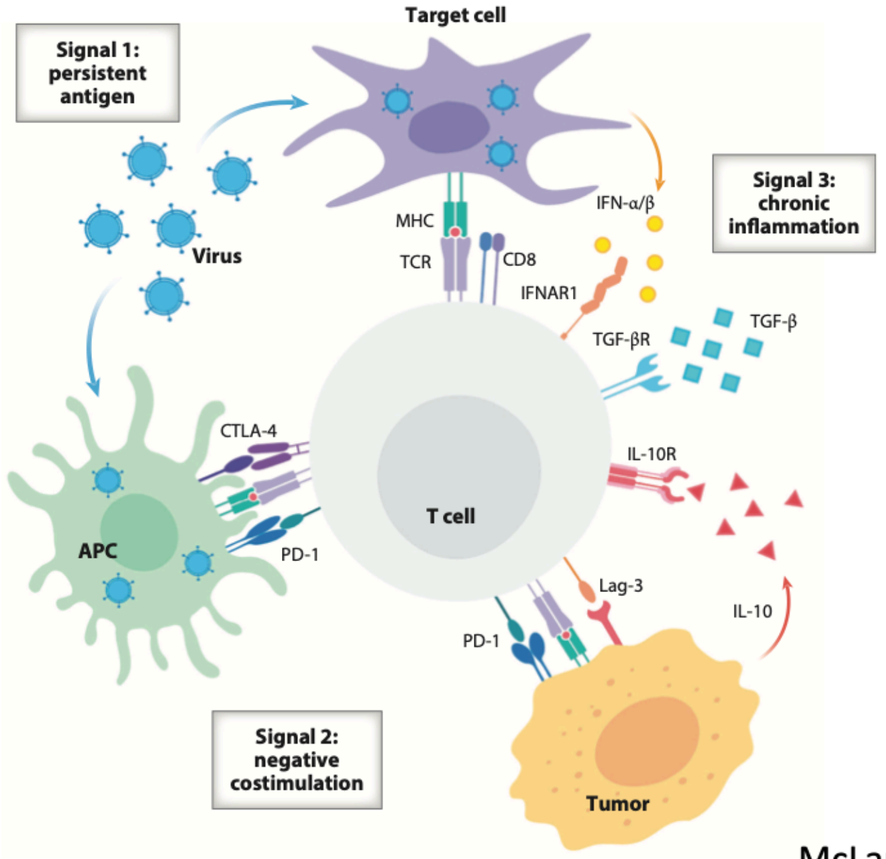
A. Persistent antigen ✓

B. Chronic inflammation ✓

C. Negative co-stimulation ✓

D. High nutrient availability

3 signals model to induce T cell exhaustion



McLane *et al.*, Annu. Rev. Immunol., 2019

Which inhibitory receptor contributes to metabolic suppression in exhausted T cells?

A. CD28

B. PD-1

C. IL-2R

D. TCR

Which therapy removes T cell inhibition to boost anti-tumor activity?

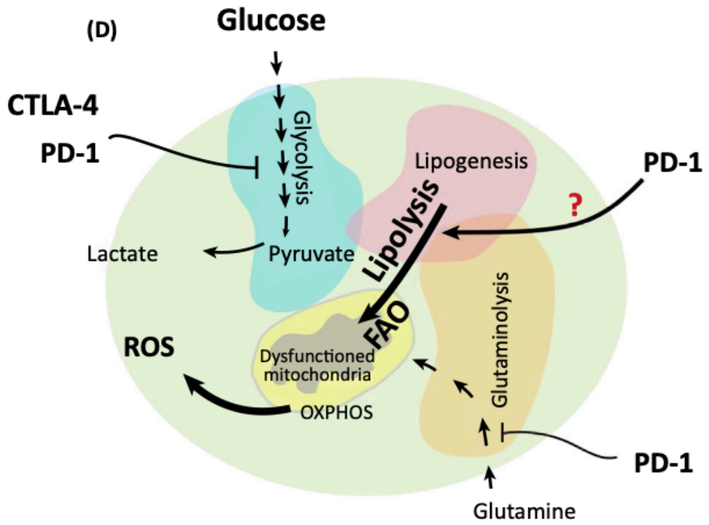
A. Tumor vaccines that stimulate antibody production

B. Engineered microbes presenting cancer antigens

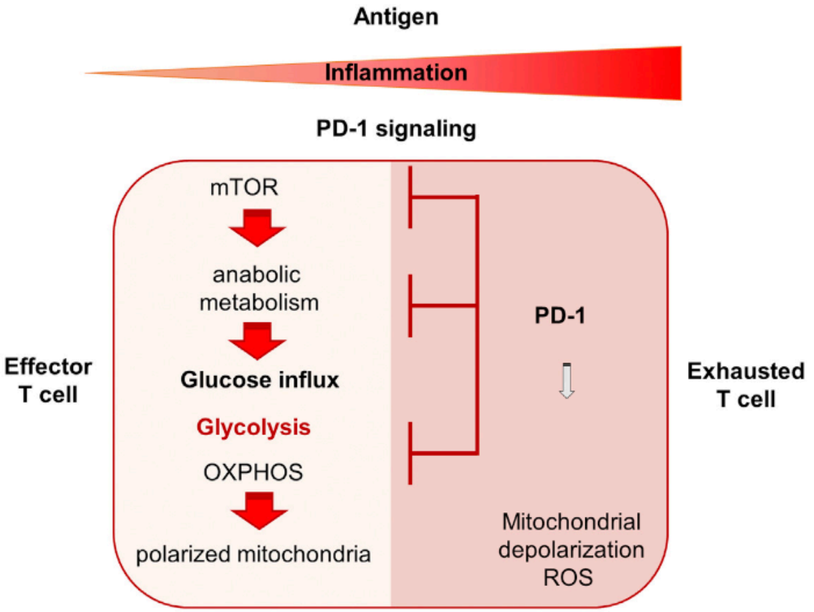
C. Antibodies that block CTLA-4 or PD-1 pathways

D. B cell-targeted monoclonal antibody treatments

Metabolism in exhaustion



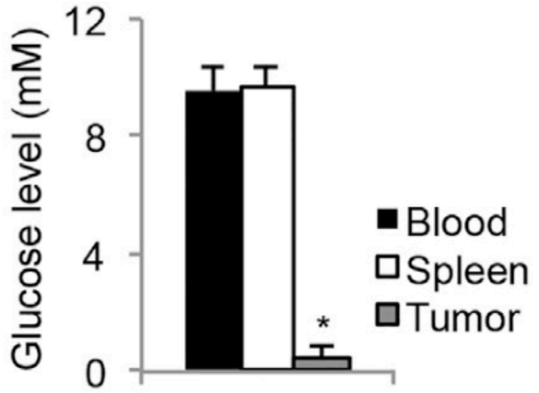
Zhang, Romero *et al.*, Trends Mol.Med. 2018



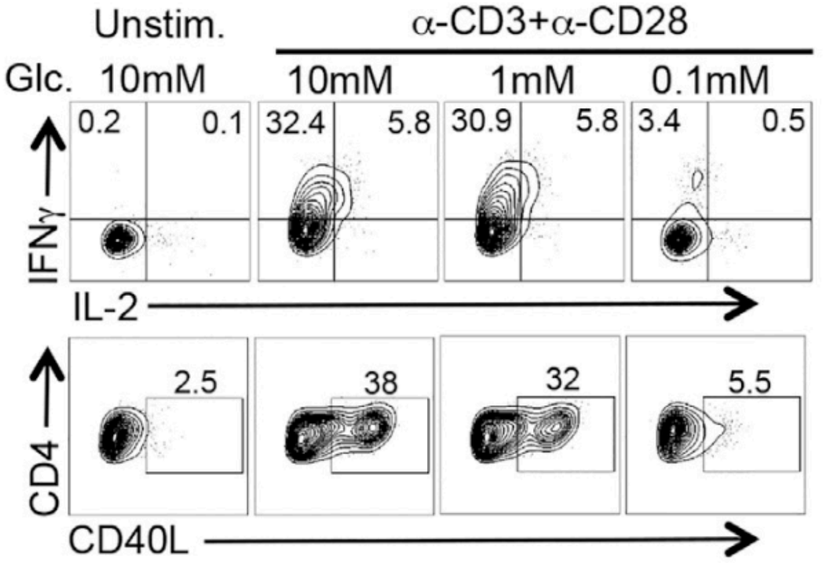
Bengsch *et al.*, Immunity 2016

Cancer cells steal glucose from T cells

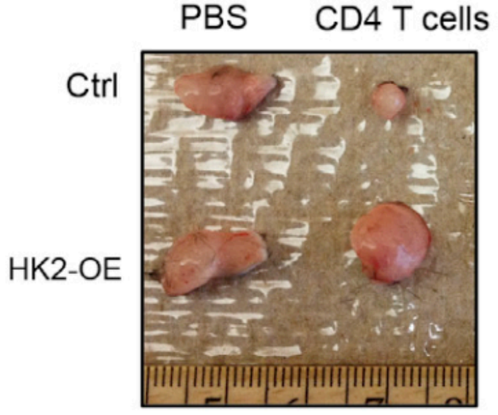
Glucose levels
are low in tumors



Glucose is required for
effector T cell function

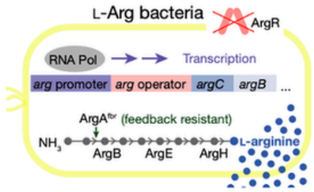


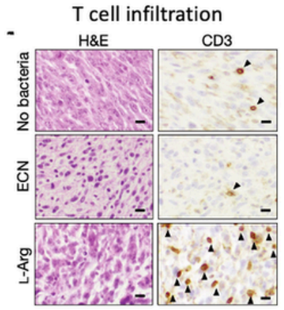
High glycolytic tumors
(hexokinase 2 overexpression, HK2-OE)
limit anti-tumor T cell function

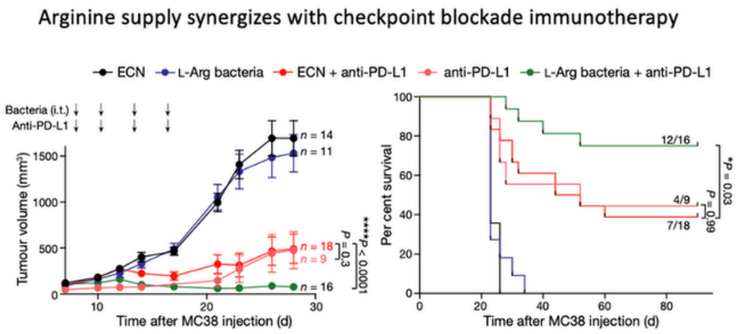


Ho *et al.*, Cell 2015

Immunotherapy is enhanced by nutrient supplementation through metabolically engineered bacteria

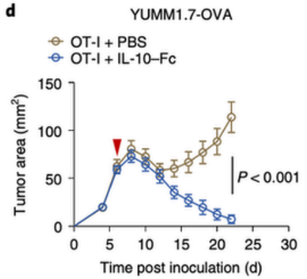


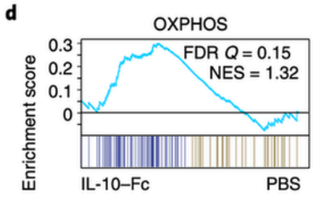


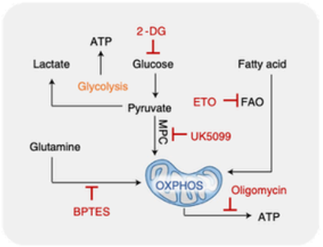


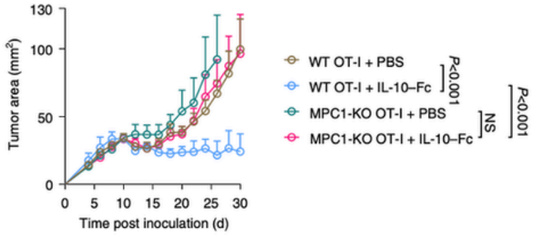
Canale *et al.*, 2021 Nature

Metabolic reprogramming of terminally exhausted CD8+ T cells by IL-10 enhances anti-tumor immunity









Guo, Xie et al., Nature Immunology 2021