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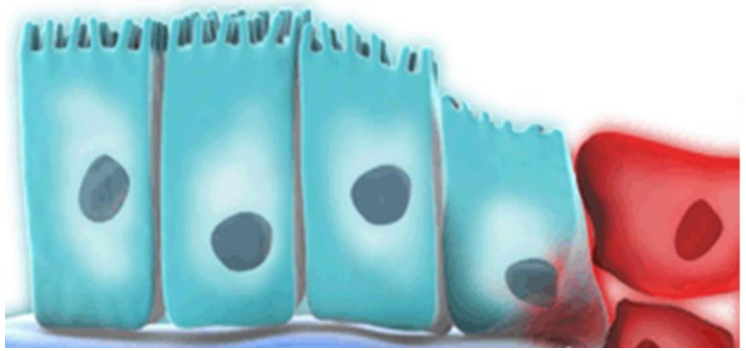


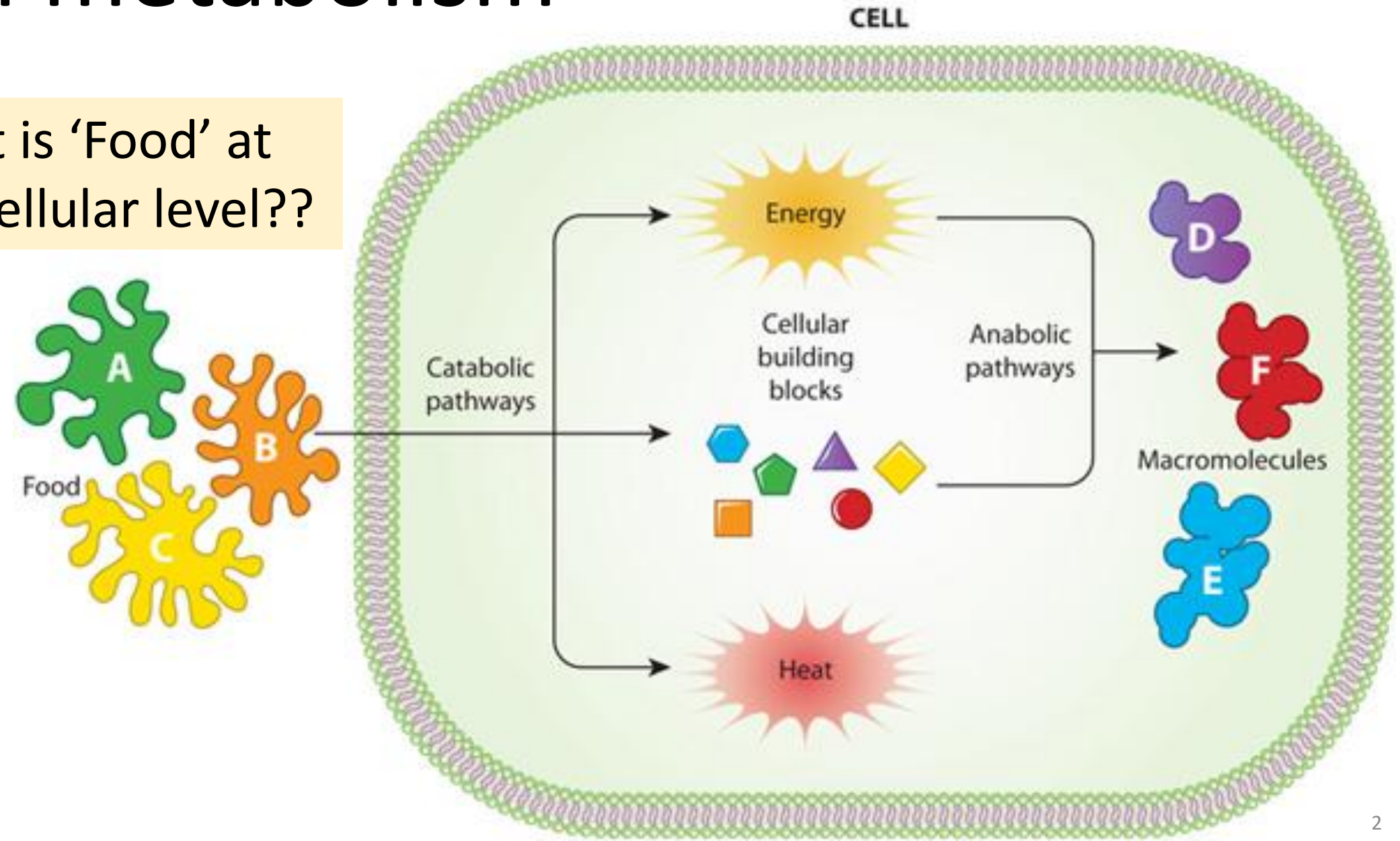
Oncobiology

Margarida Gama-Carvalho (DQB/FCUL) and Peter Jordan (INSA)

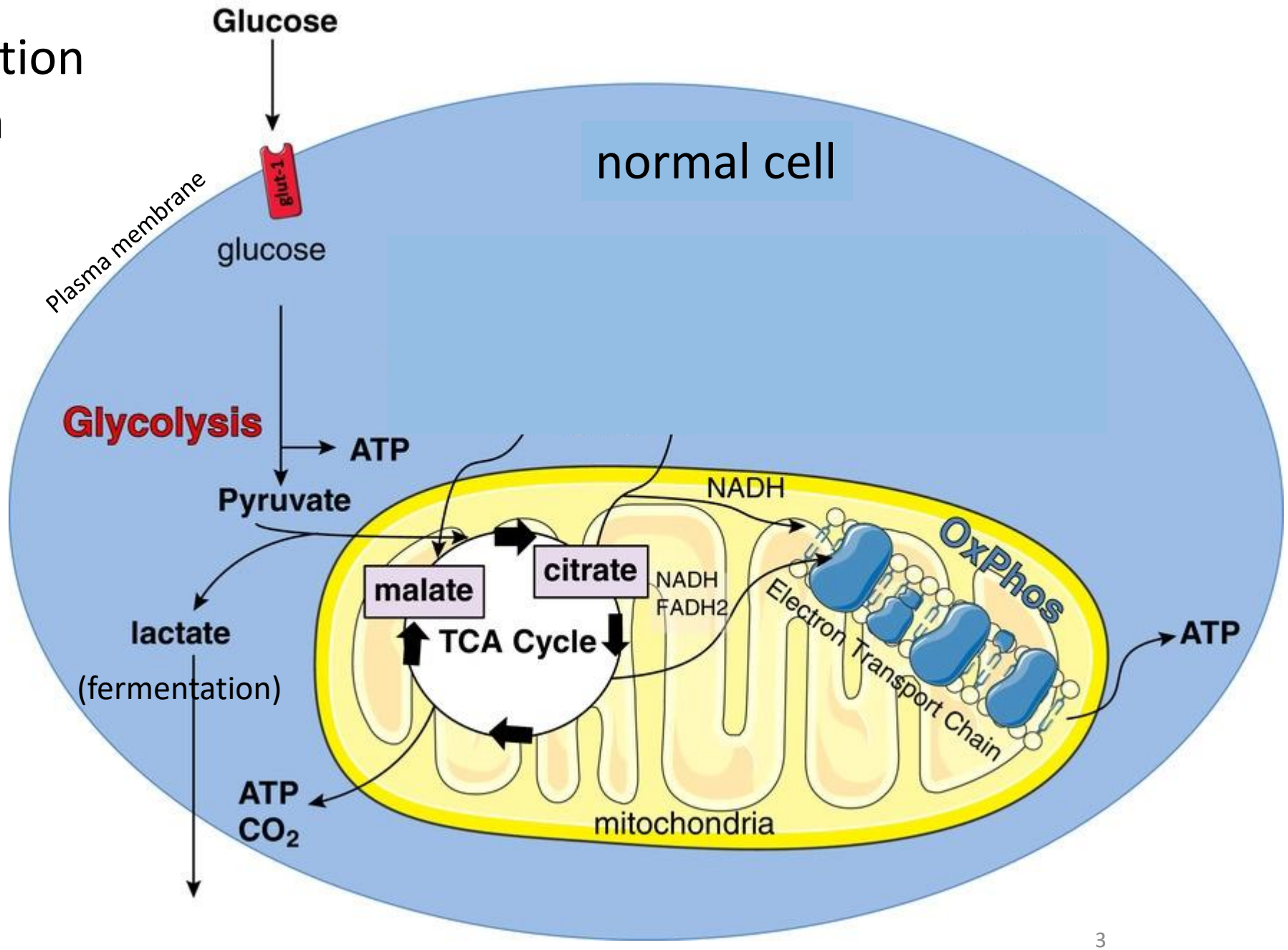
Cancer cell metabolism

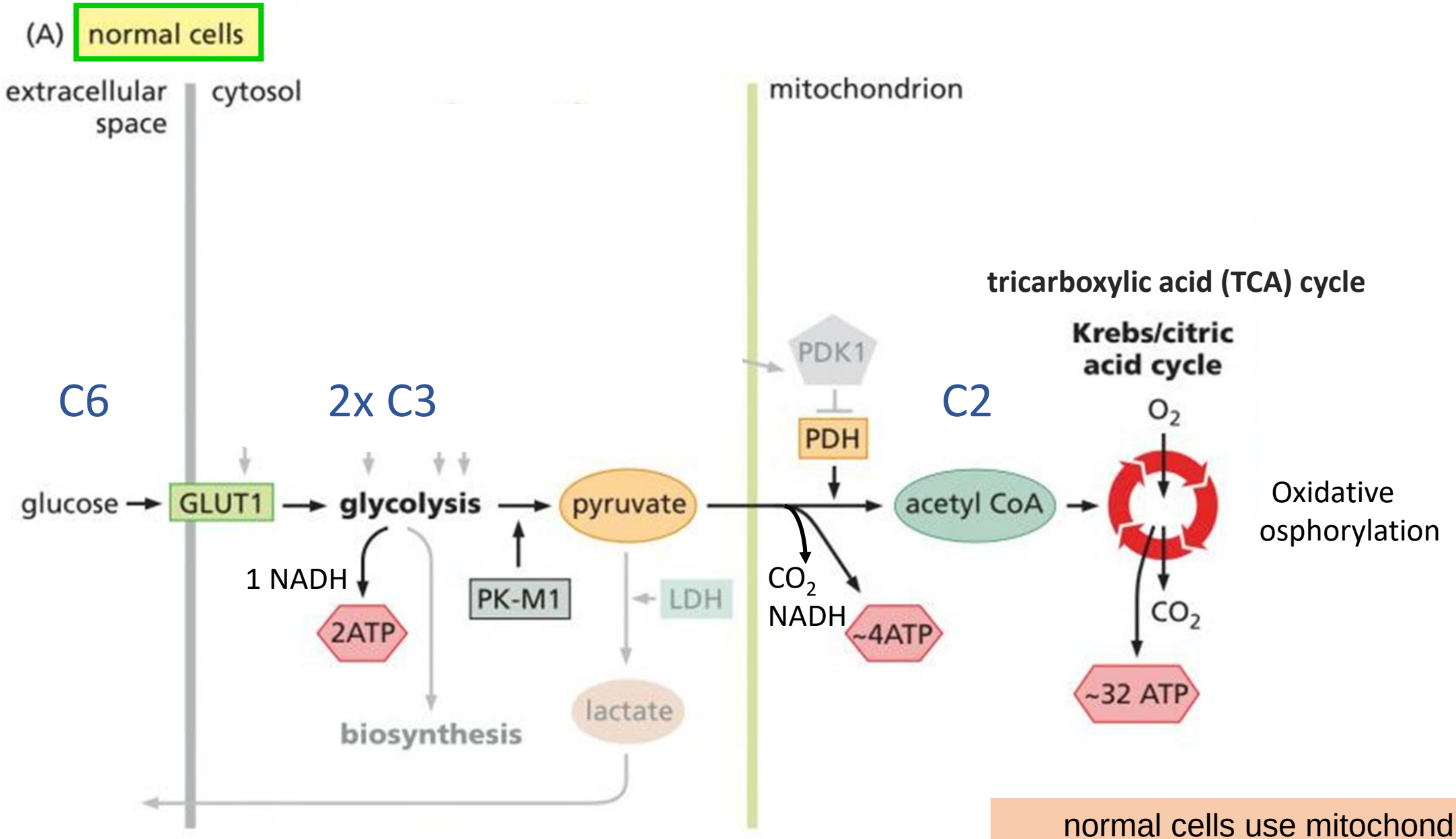
Cell metabolism

What is ‘Food’ at the cellular level??



Compartmentalization of metabolism

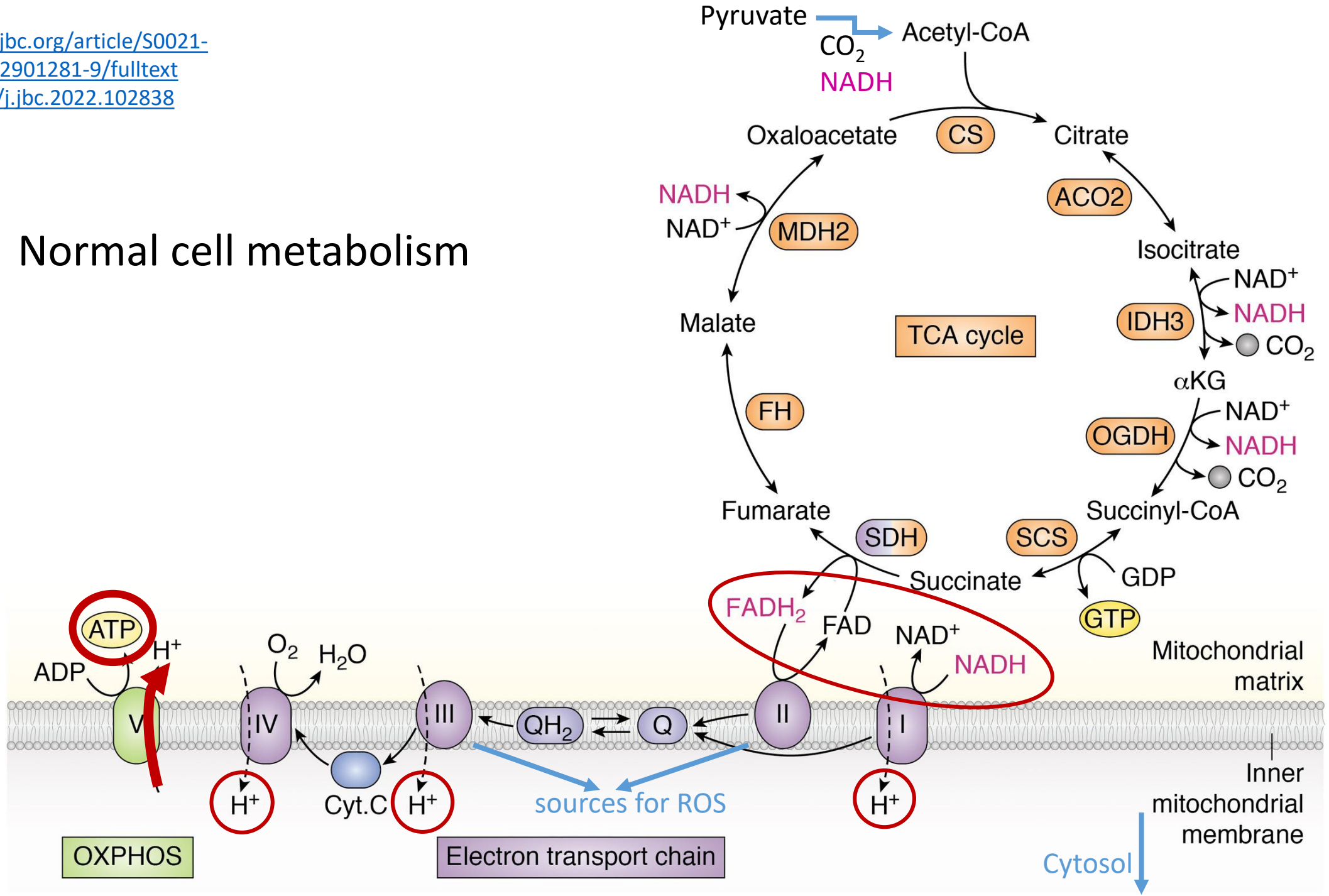




normal cells use mitochondrial oxidative phosphorylation (~36 ATP per glucose molecule)

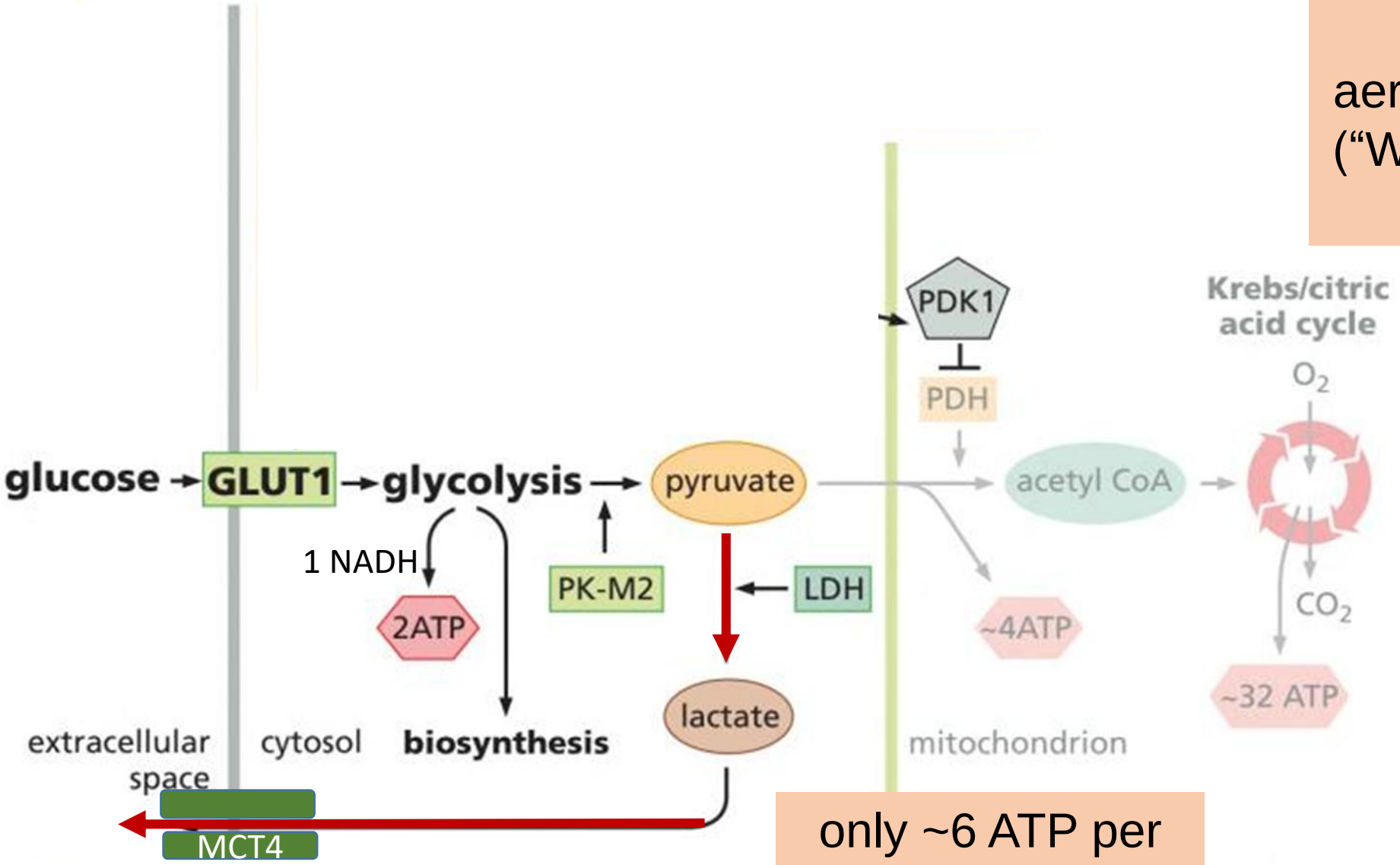
https://www.jbc.org/article/S0021-9258%2822%2901281-9/fulltext
DOI: 10.1016/j.jbc.2022.102838

Normal cell metabolism



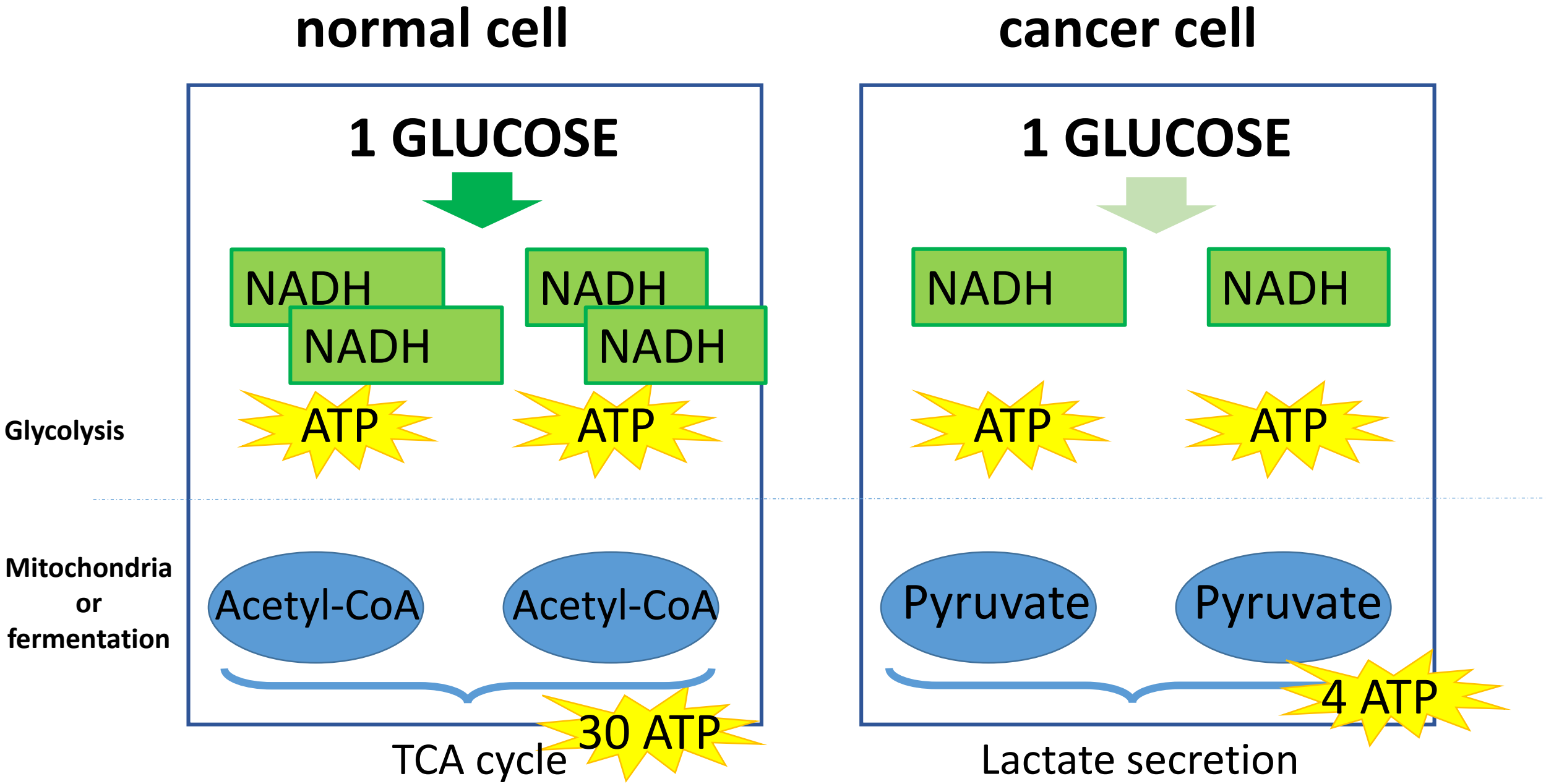
Cancer cells

cancer cells favour aerobic glycolysis ("Warburg effect"- 1925)



only ~6 ATP per glucose molecule

GLYCOLYSIS

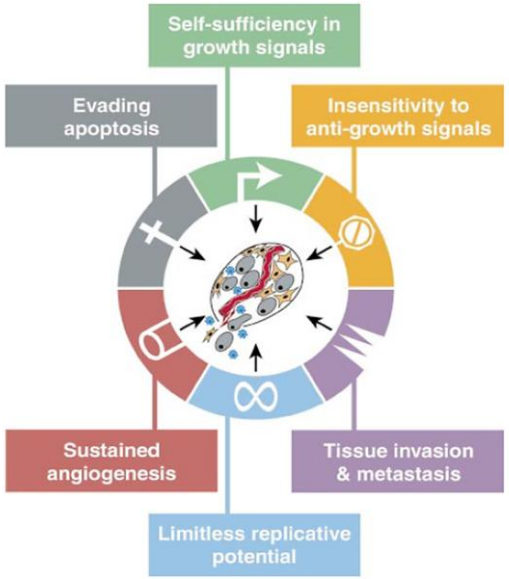

normal cell
cancer cell
1 GLUCOSE
1 GLUCOSE
NADH
NADH
NADH
NADH
NADH
NADH
ATP
ATP
ATP
ATP
Glycolysis
Mitochondria or fermentation
Acetyl-CoA
Acetyl-CoA
Pyruvate
Pyruvate
30 ATP
4 ATP
TCA cycle
Lactate secretion

Warburg effect:

Cancer cells prefer to use glycolysis for energy production,

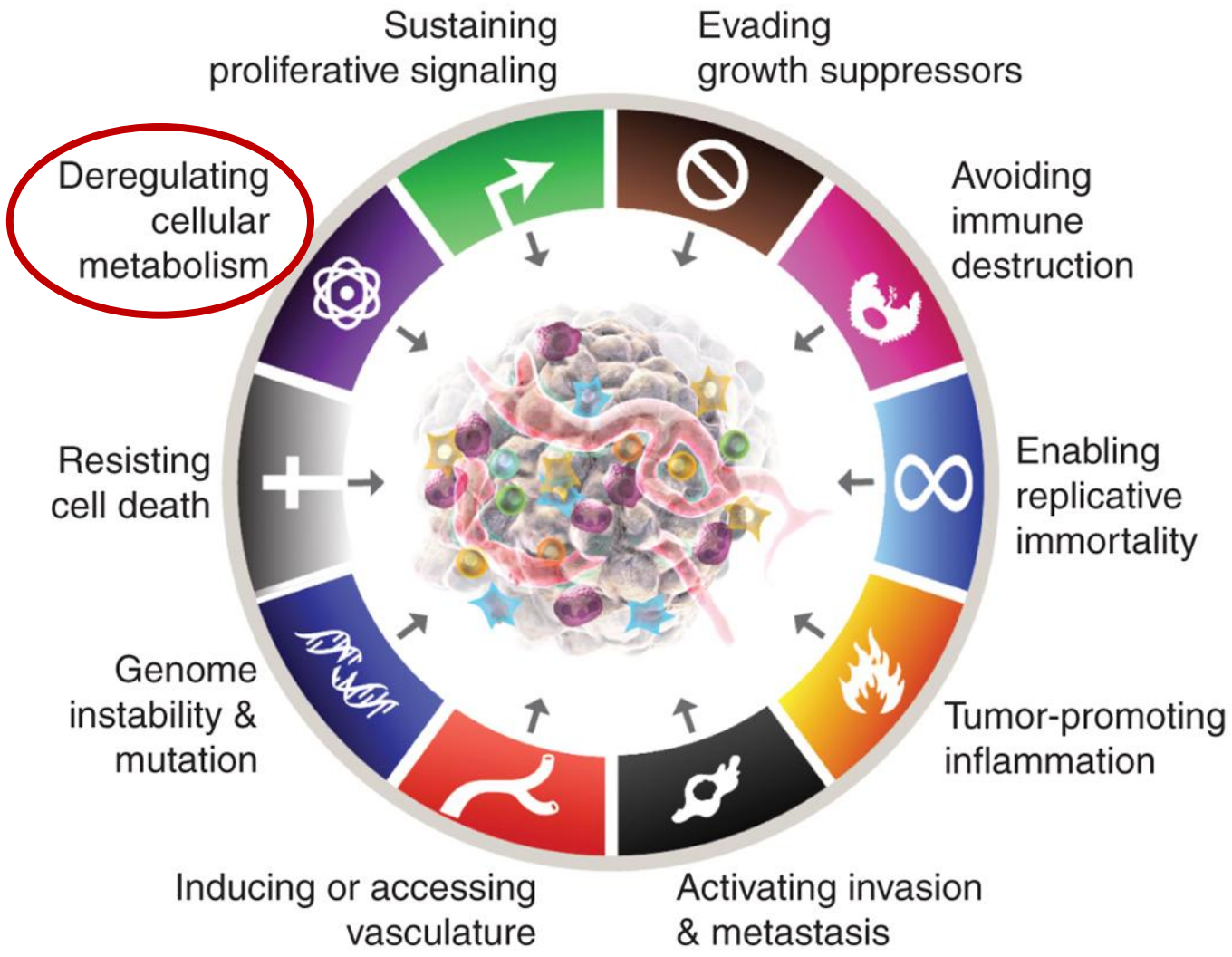
even when oxygen is available and mitochondrial respiration

would produce more ATP



Hanahan D, Weinberg RA (**2000**) , Cell 100, 57–70

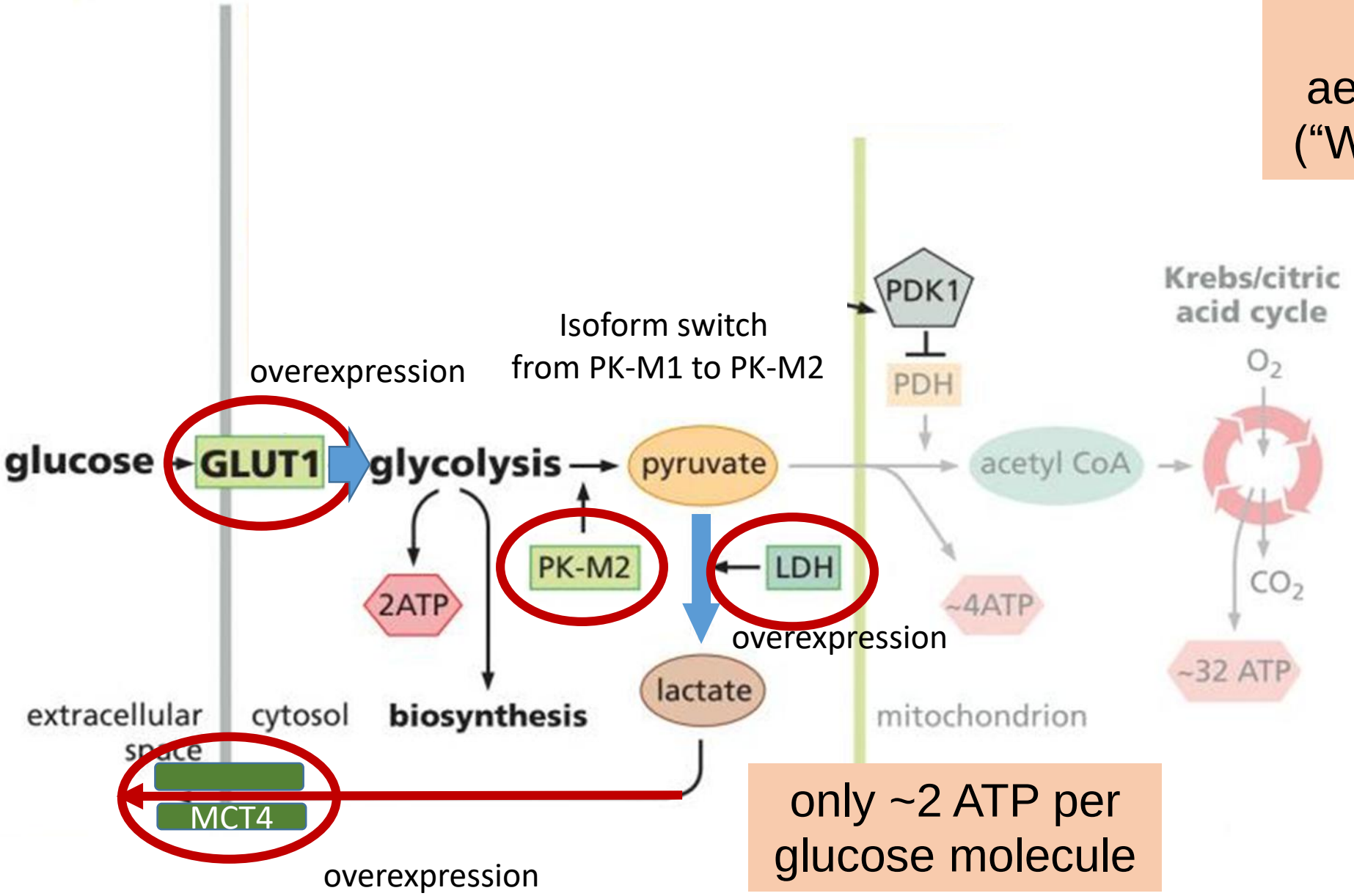
Revised *Hallmarks of Cancer*



Hanahan D, Weinberg RA (**2011**), Cell 144, 646-674.

Cancer cells

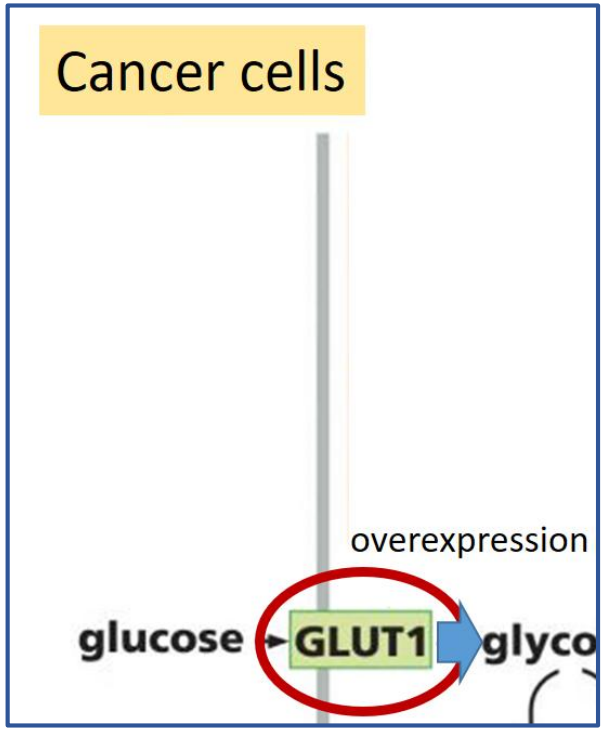
How do cancer cells favour aerobic glycolysis ("Warburg effect")?



only ~2 ATP per glucose molecule

Clinical relevance of cancer cell metabolism

1. Can leave a ‘footprint’ for diagnosis



Footprint: high glucose consumption

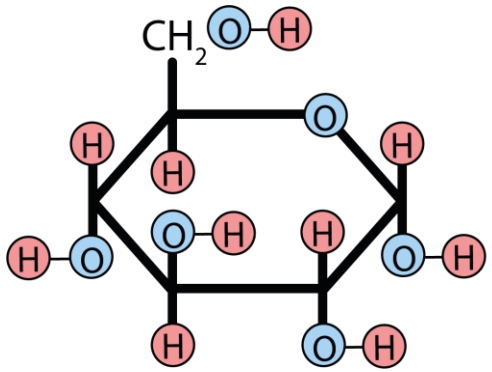
Brain, heart, kidneys, bladder

Diagnostic imaging by Positron emission tomography (PET-scan)

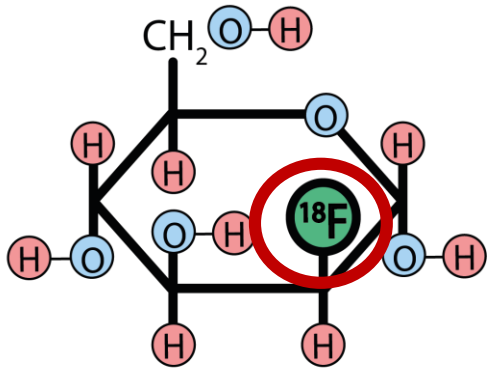
Intravenous application of radioactive 2-deoxy- (^{18}F) fluoro-D-glucose (FDG)

(technique available since 2000;

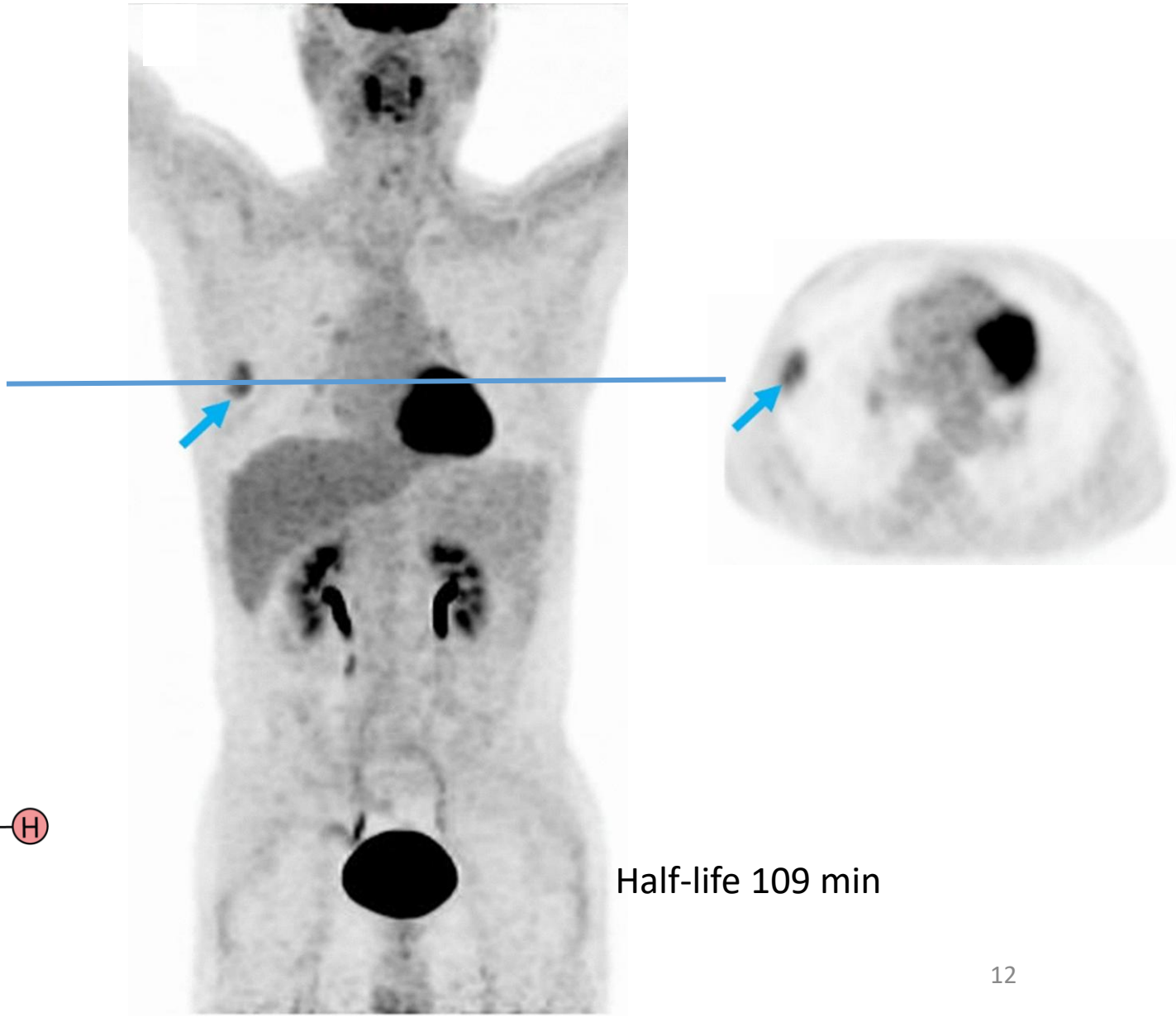
available since 2000;
revitalized research interest in cancer cell metabolism (see review "100 years of the Warburg effect: A cancer metabolism endeavor" doi: 10.1016/j.cell.2024.06.026)



Glucose

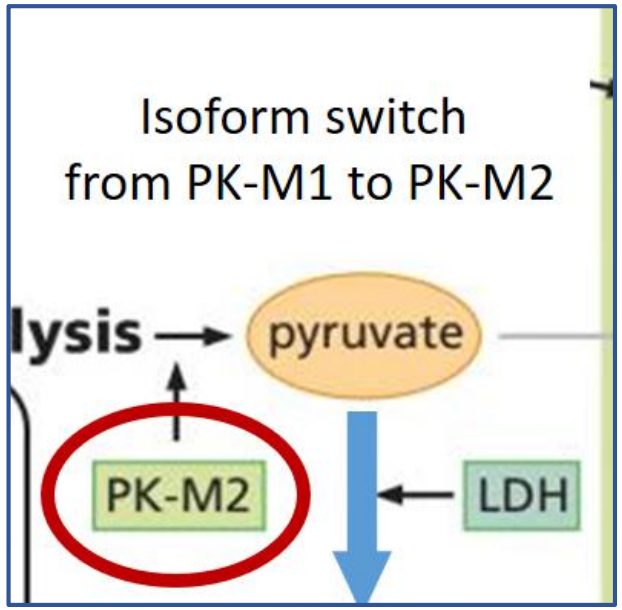


^{18}F - Glucose

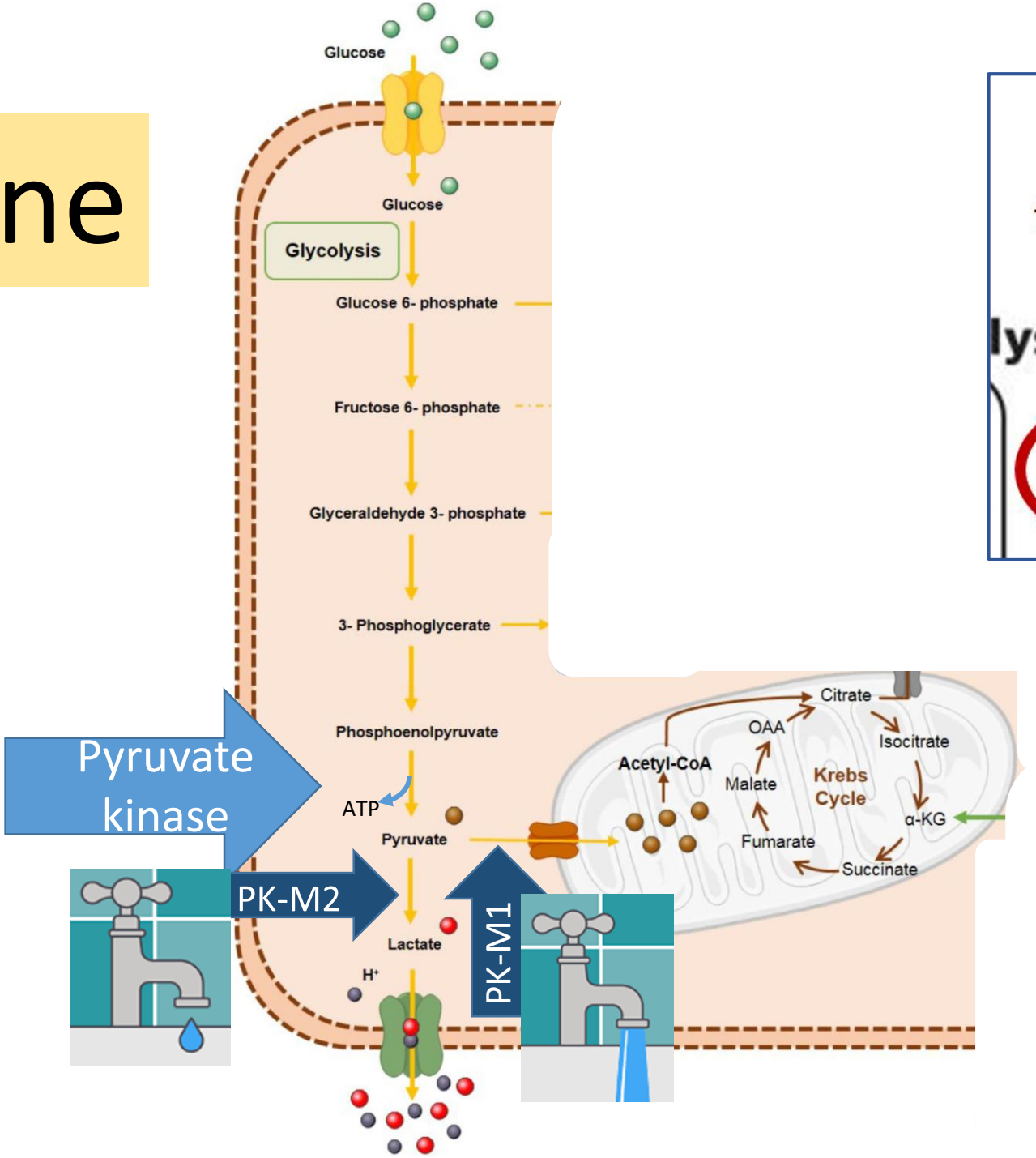


Half-life 109 min

PKM gene



PK-M2:
low affinity to its substrate PEP;
→ glycolytic intermediates above pyruvate accumulate

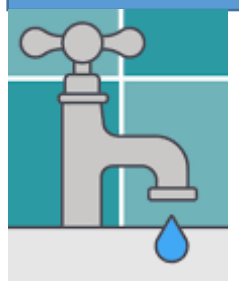


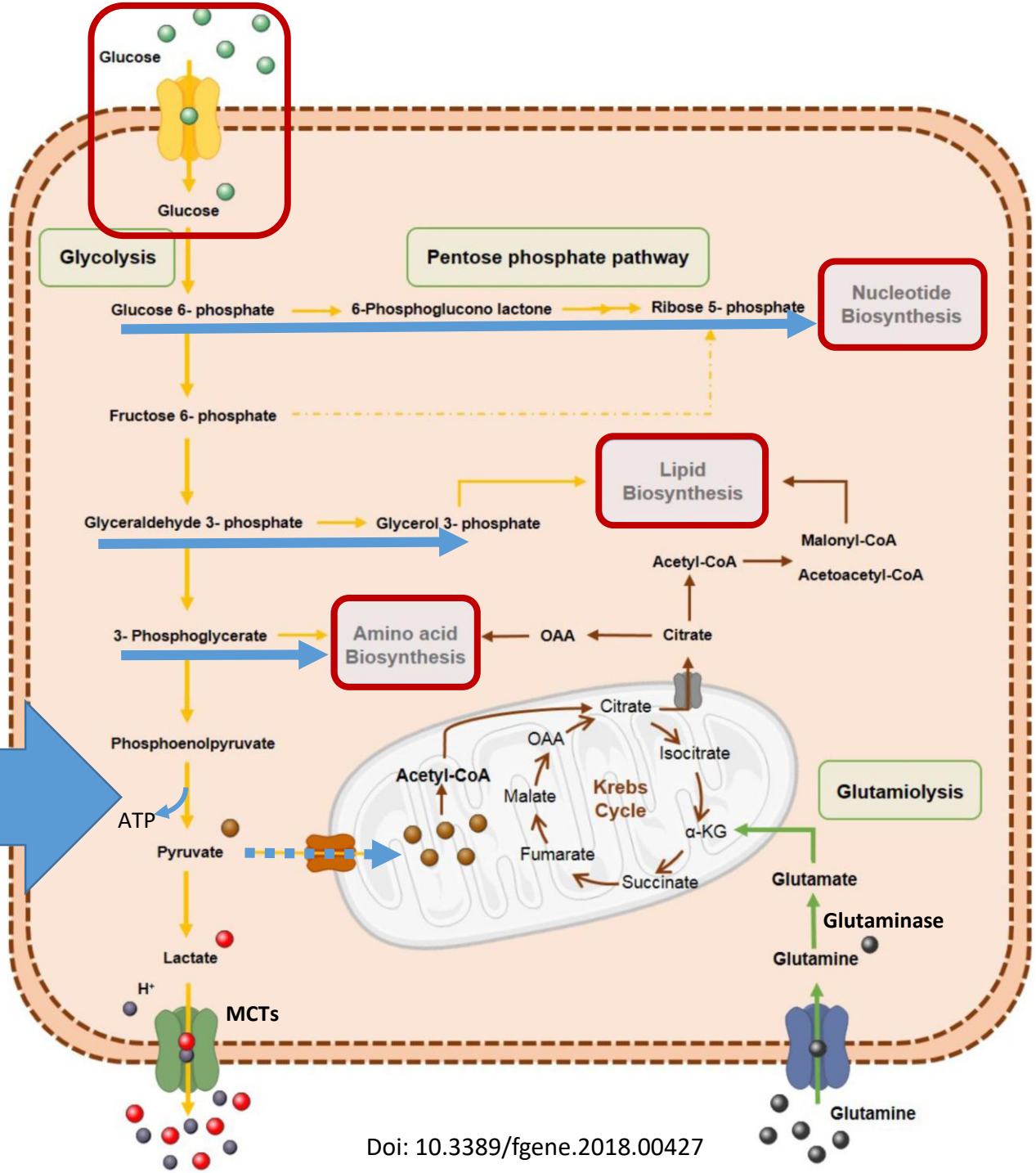
Cancer cells

Due to PK-M2 expression, the glycolytic intermediates above pyruvate accumulate

a) biosynthetic building blocks to sustain proliferation rate

PK-M2

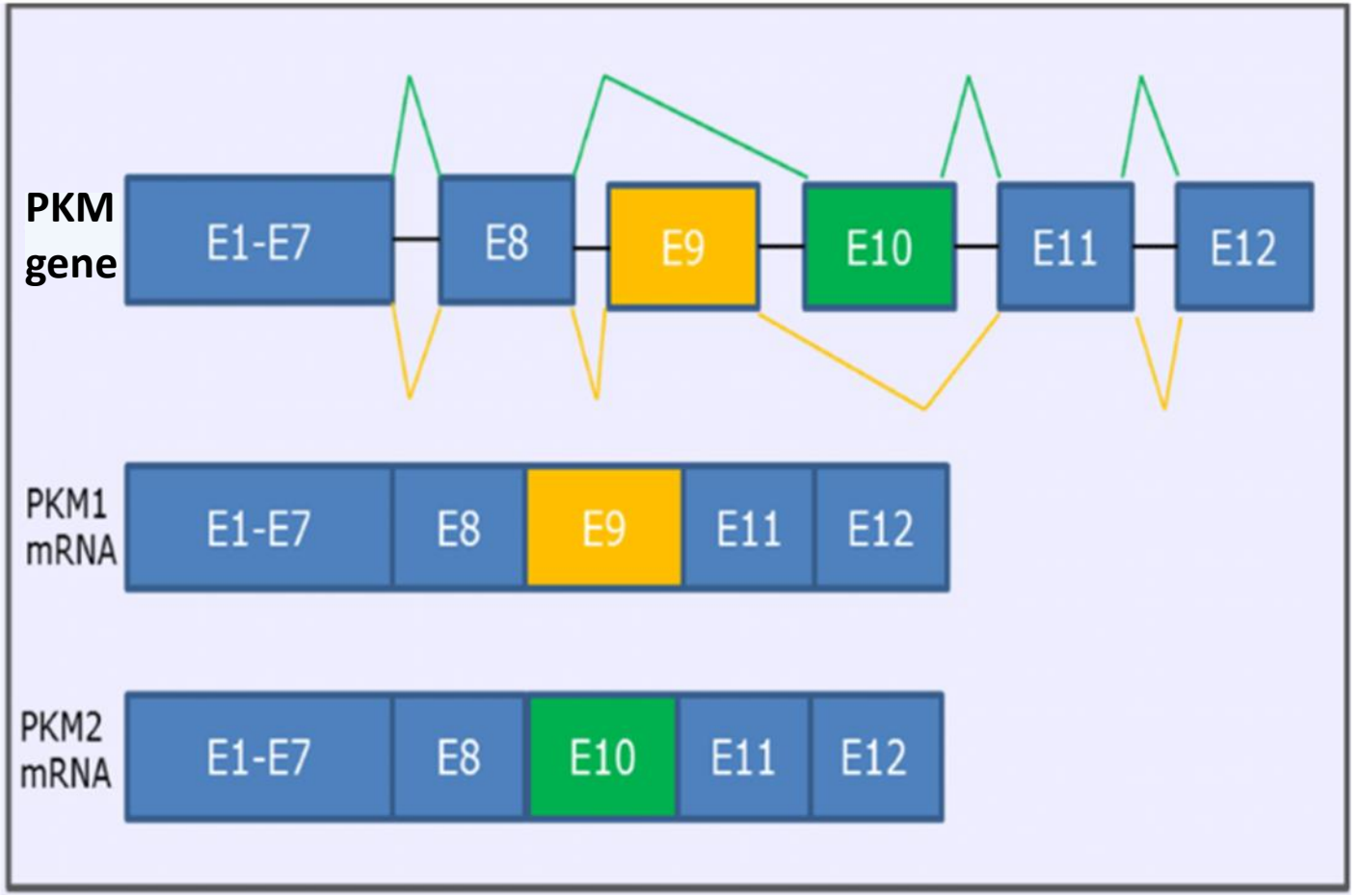




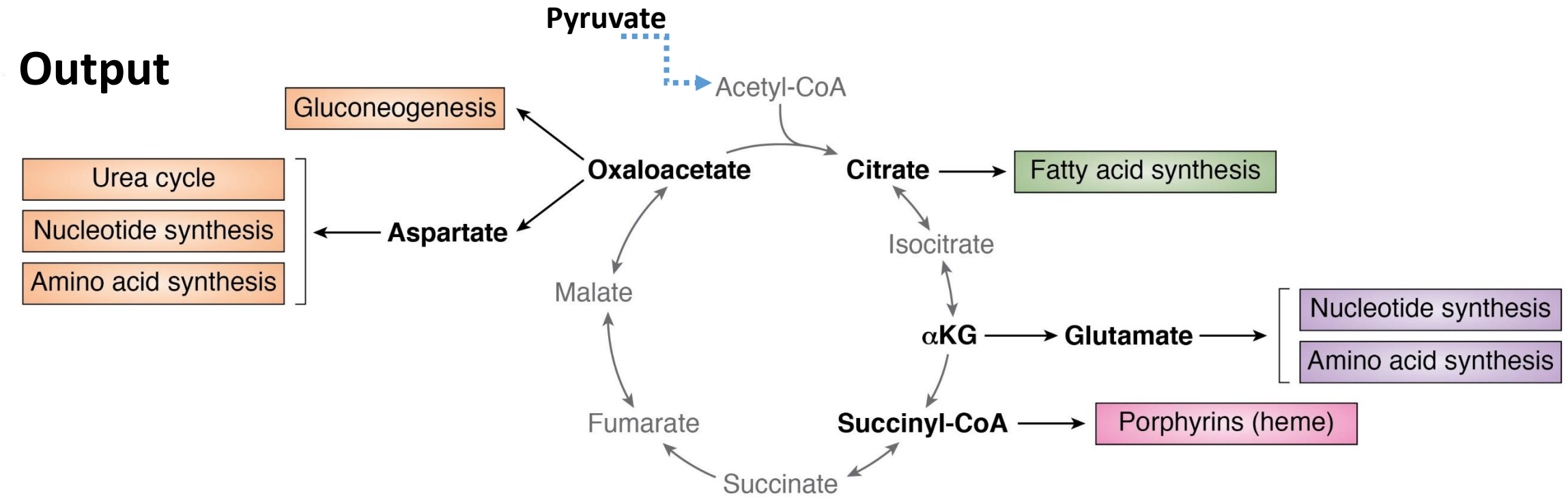
Doi: 10.3389/fgene.2018.00427

Alternative splicing of generates PKM isoforms in cancer cells

Mutually exclusive exons

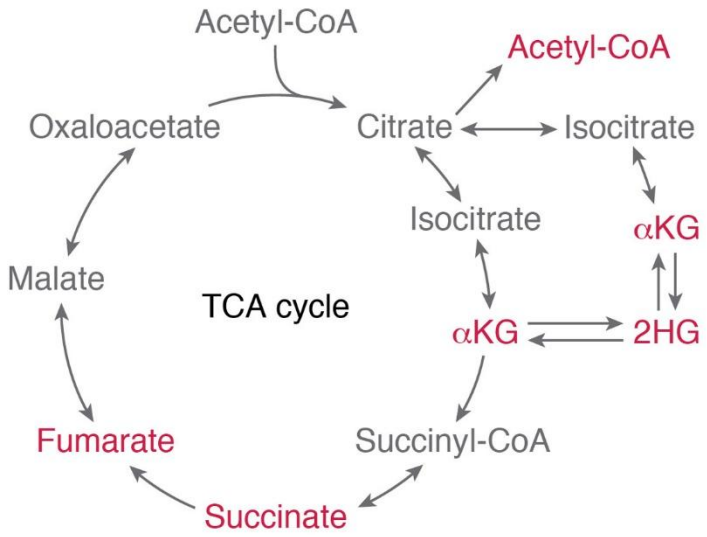


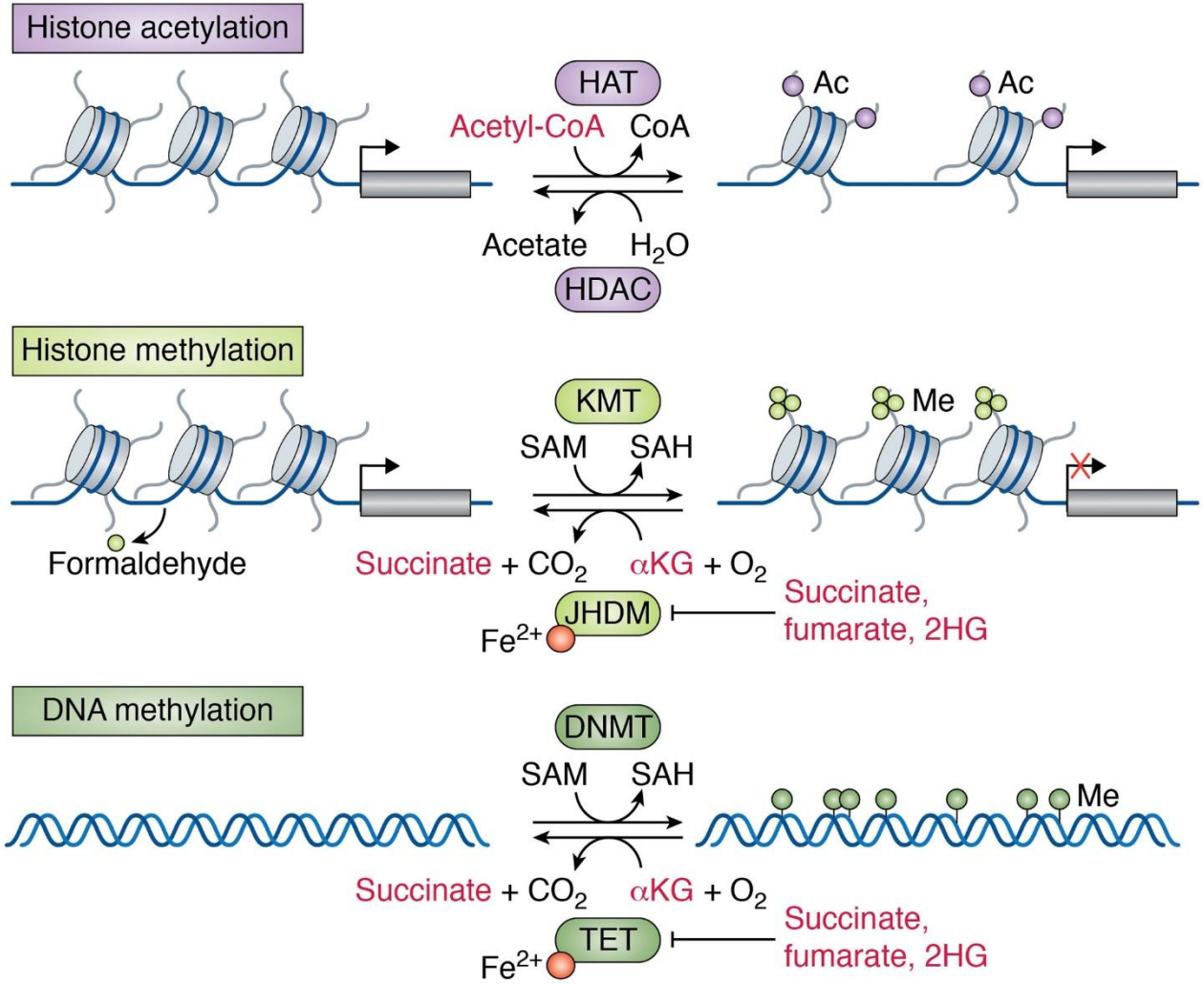
..Uuuups! Problem #1:
cells cannot do without the TCA because intermediates are wired to other metabolic processes



..Uuuups! Problem #2
cells cannot do without the TCA because intermediates are wired to other metabolic processes

TCA intermediates are required for epigenetic DNA modification reactions





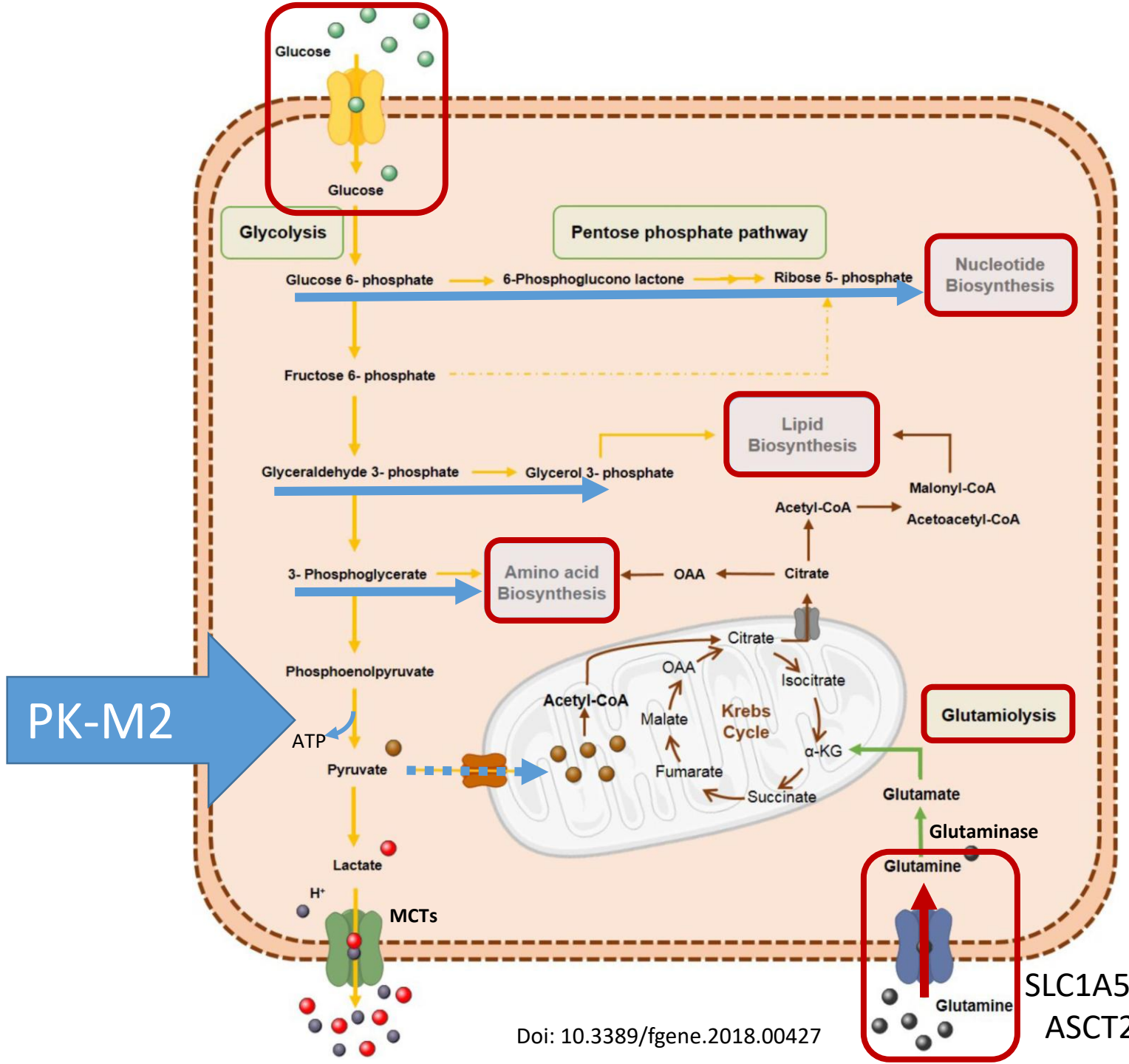
Cancer cells

Due to PK-M2 expression, the glycolytic intermediates above pyruvate accumulate

a) biosynthetic building blocks to sustain proliferation

b) Glutaminolysis to sustain the TCA

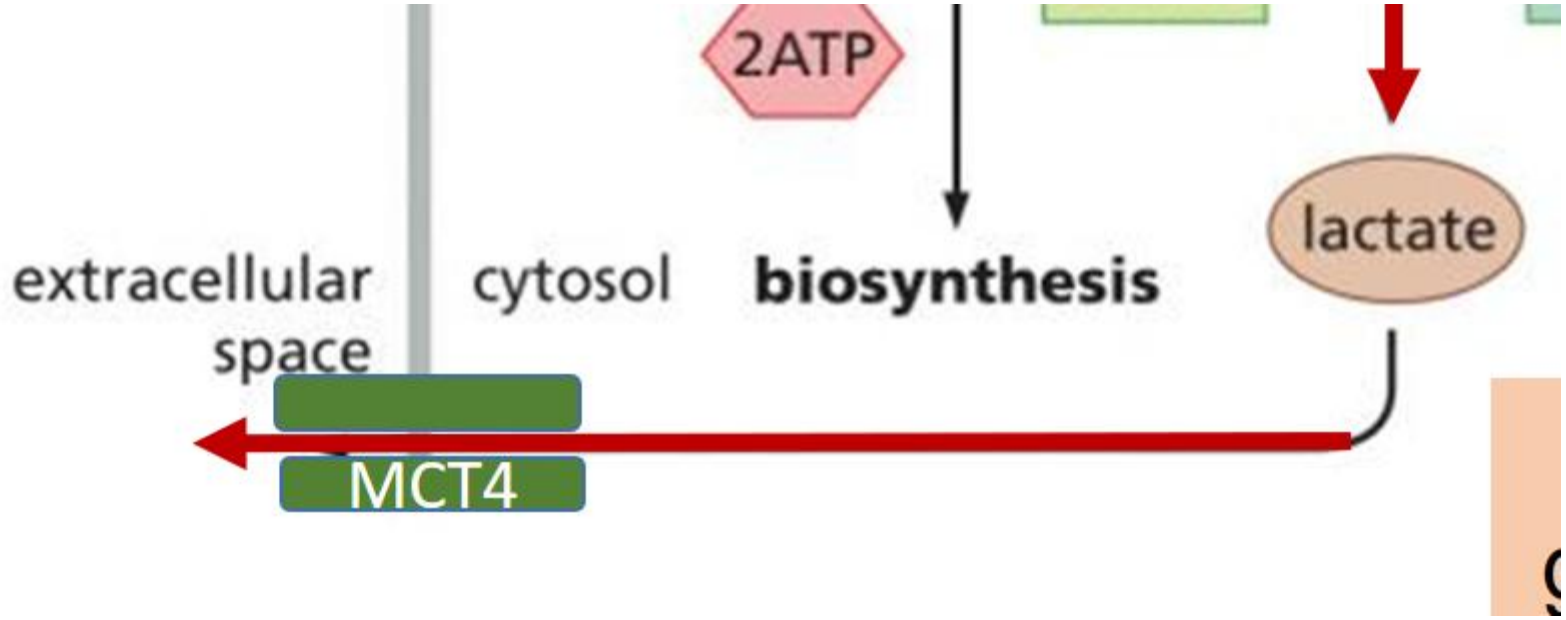
PK-M2

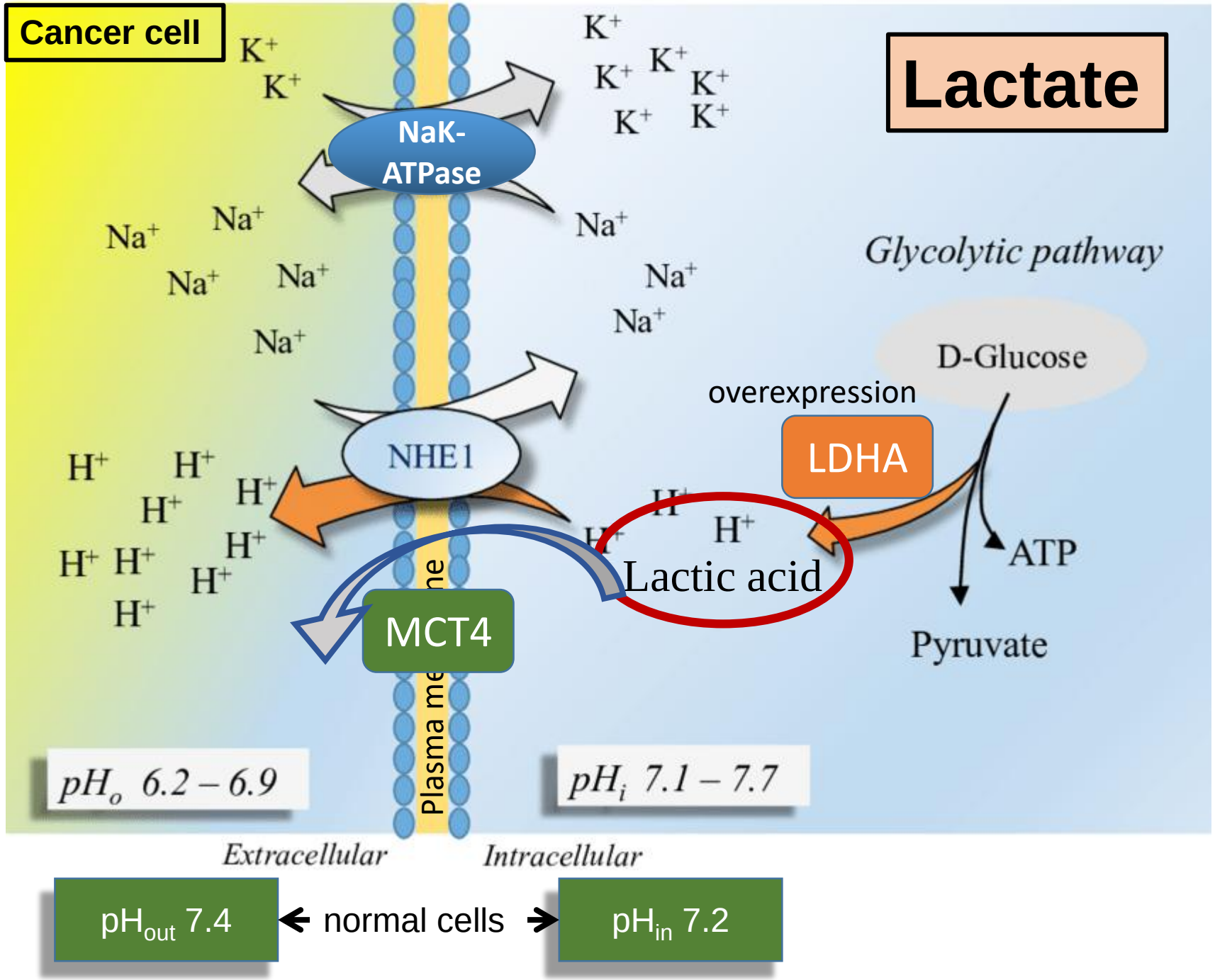


SLC1A5= ASCT2

Doi: 10.3389/fgene.2018.00427

besides GLUT1 and PK-M2…





A reversed pH gradient in cancer cells

- increased intracellular pH,
- decreased **extracellular pH** (more acidic relative to normal cells)

(sustained by a cation gradient created by the Na^+/K^+-ATPase)

acidic extracellular pH in the TME:
- promotes cell invasiveness,
- promotes angiogenesis,
- affects immune cell activity

Clinical relevance of cancer cell metabolism

Can leave a ‘footprint’ for diagnosis

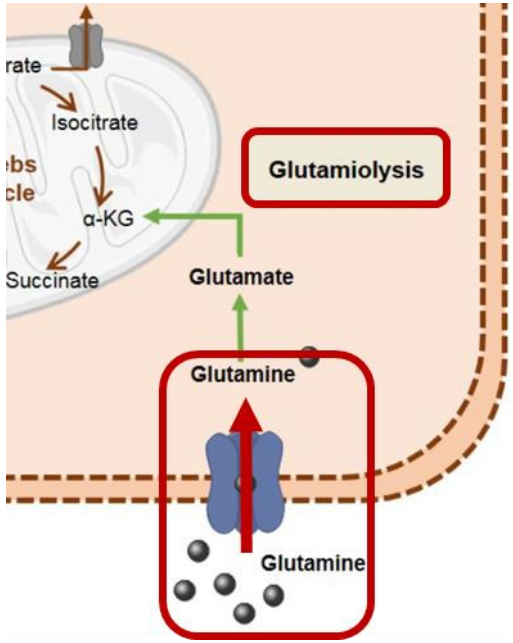
(Future) use of metabolomics for non-invasive tumour detection or choice of treatment strategies

May reveal tumour cell vulnerabilites and therapeutic approaches

Exploiting metabolic tumour cell vulnerabilites – part 1

Warburg-effect tumours:

Glutaminase inhibitors: reduce glutaminolysis pathway

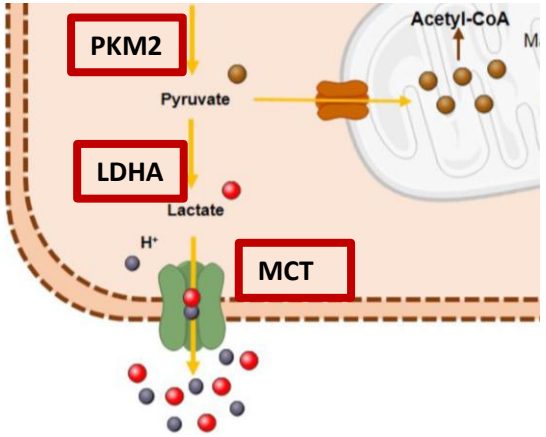


LDHA (lactate dehydrogenase A) inhibitors:

-> reduce lactate production

MCT (monocarboxylatetransporter) inhibitors:

-> reduce lactate export from cytoplasm

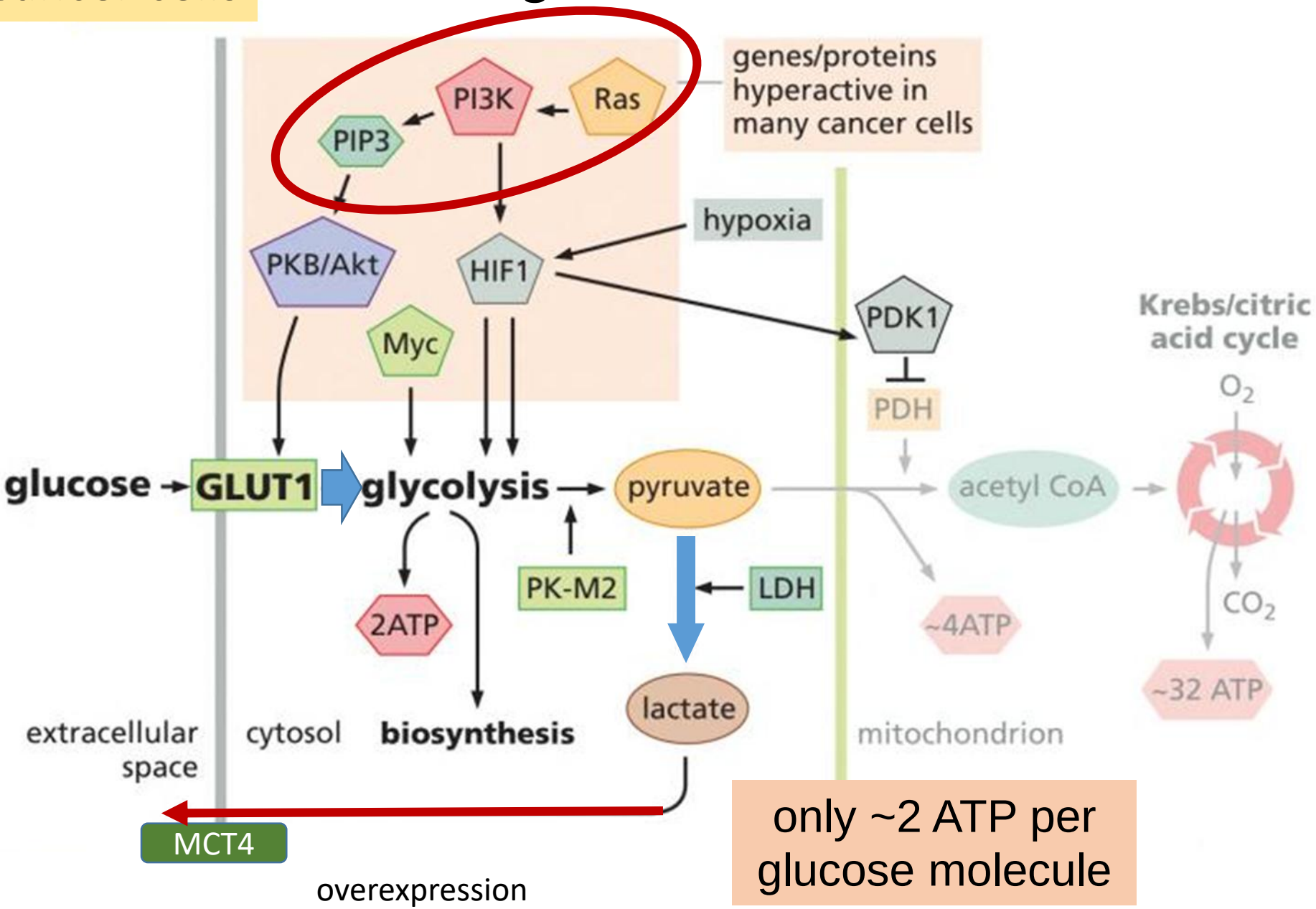


Why and how do cancer cells switch their metabolism?

Cancer cells

1. Oncogene activation

cancer cells favour aerobic glycolysis ("Warburg effect")



only ~2 ATP per glucose molecule

Predictive gene expression profile:

(Warburg-low, -moderate, or -high tumours)

Transcription factor-mediated increase in gene expression:

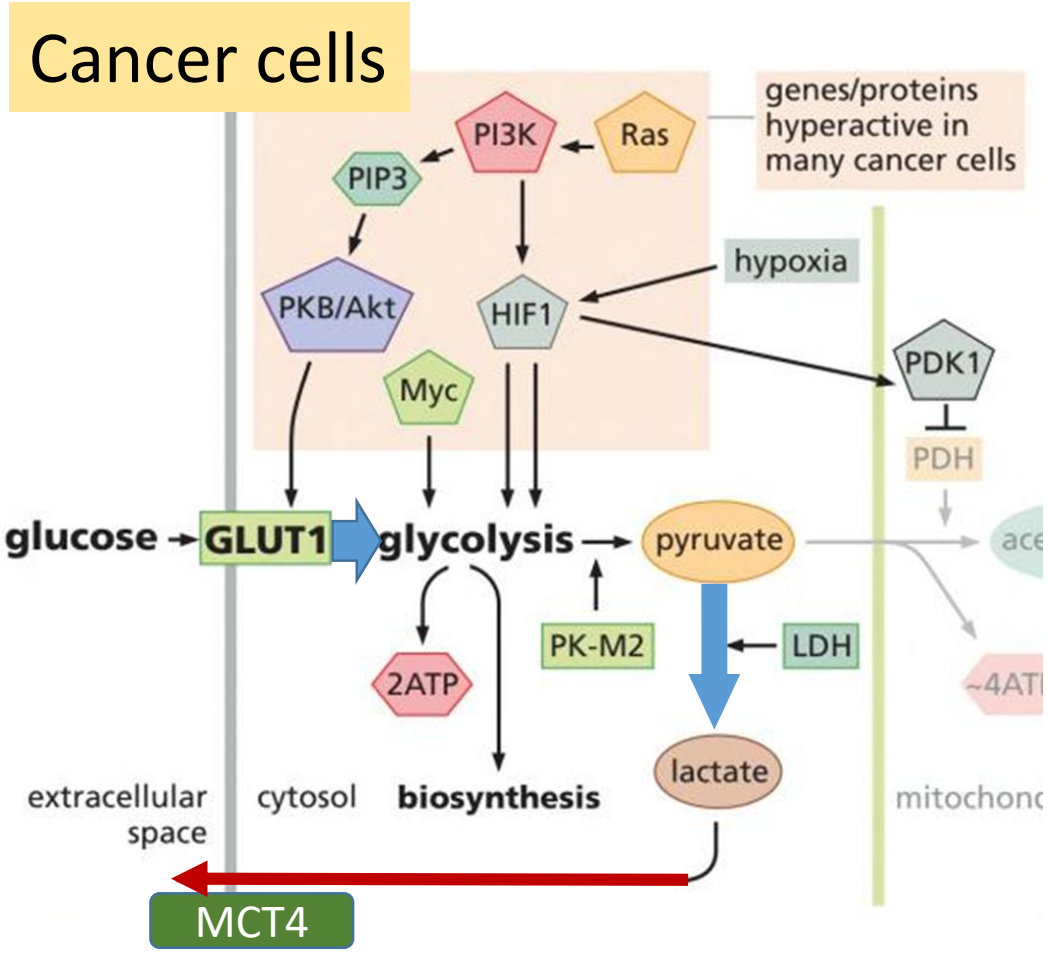
(1) upstream transcriptional regulators of the Warburg effect (**PTEN** ↓),

(2) glucose entrance pathway (**GLUT1** ↑),

(3) enhanced glycolysis (**PKM2** ↑),

(4) increased lactate production (**LDHA** ↑),

(5) enhanced lactate secretion (**MCT4** ↑).



J Pathol Clin Res. 2022, doi: 10.1002/cjp2.250

increased glucose levels characterize diabetes= cancer risk??

Yes, a life-style risk factor for several cancer types, such as pancreatic, liver, colon, breast, and endometrial cancer

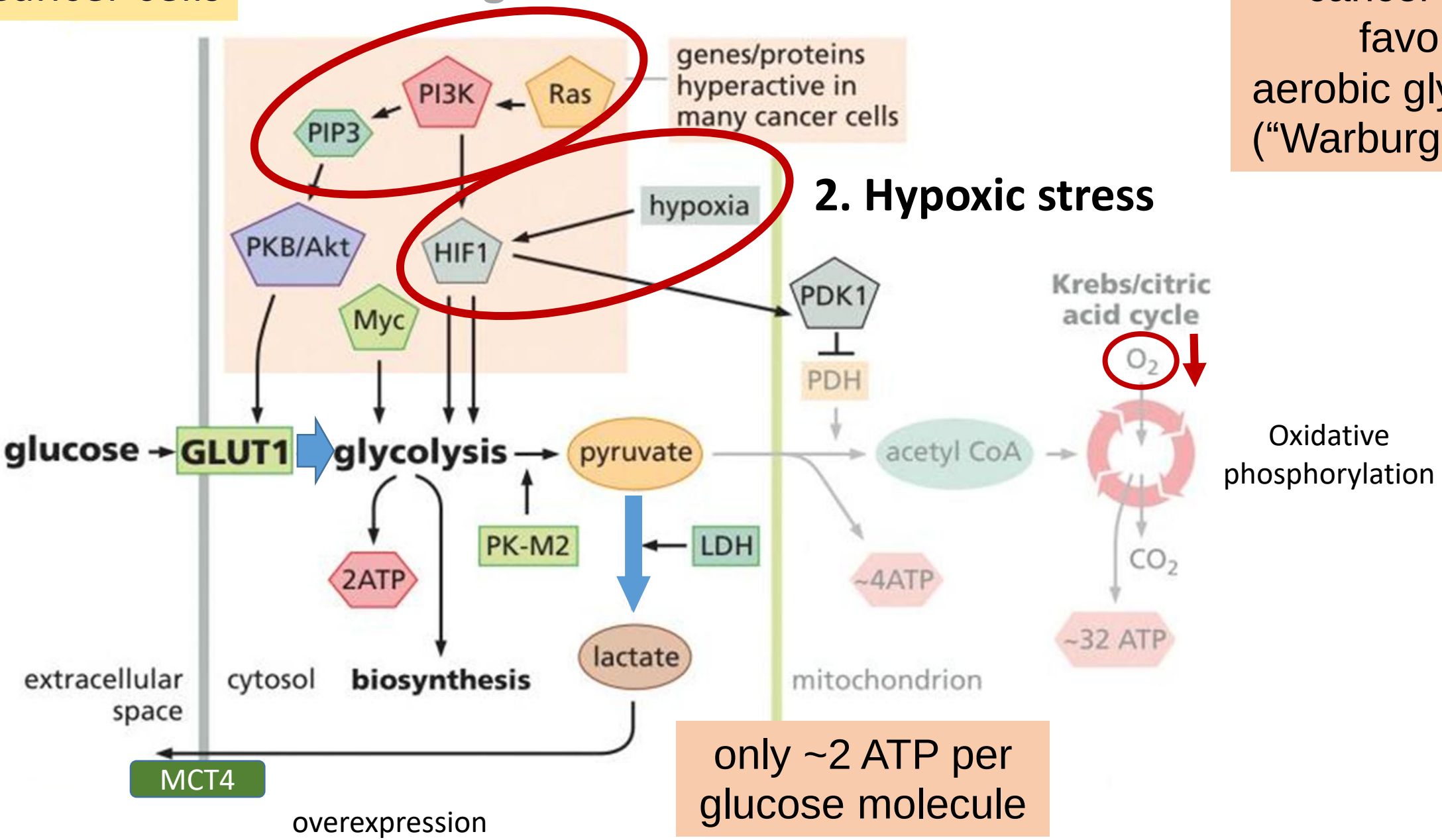
=

hyperglycemia + increased levels of circulating insulin

Cancer cells

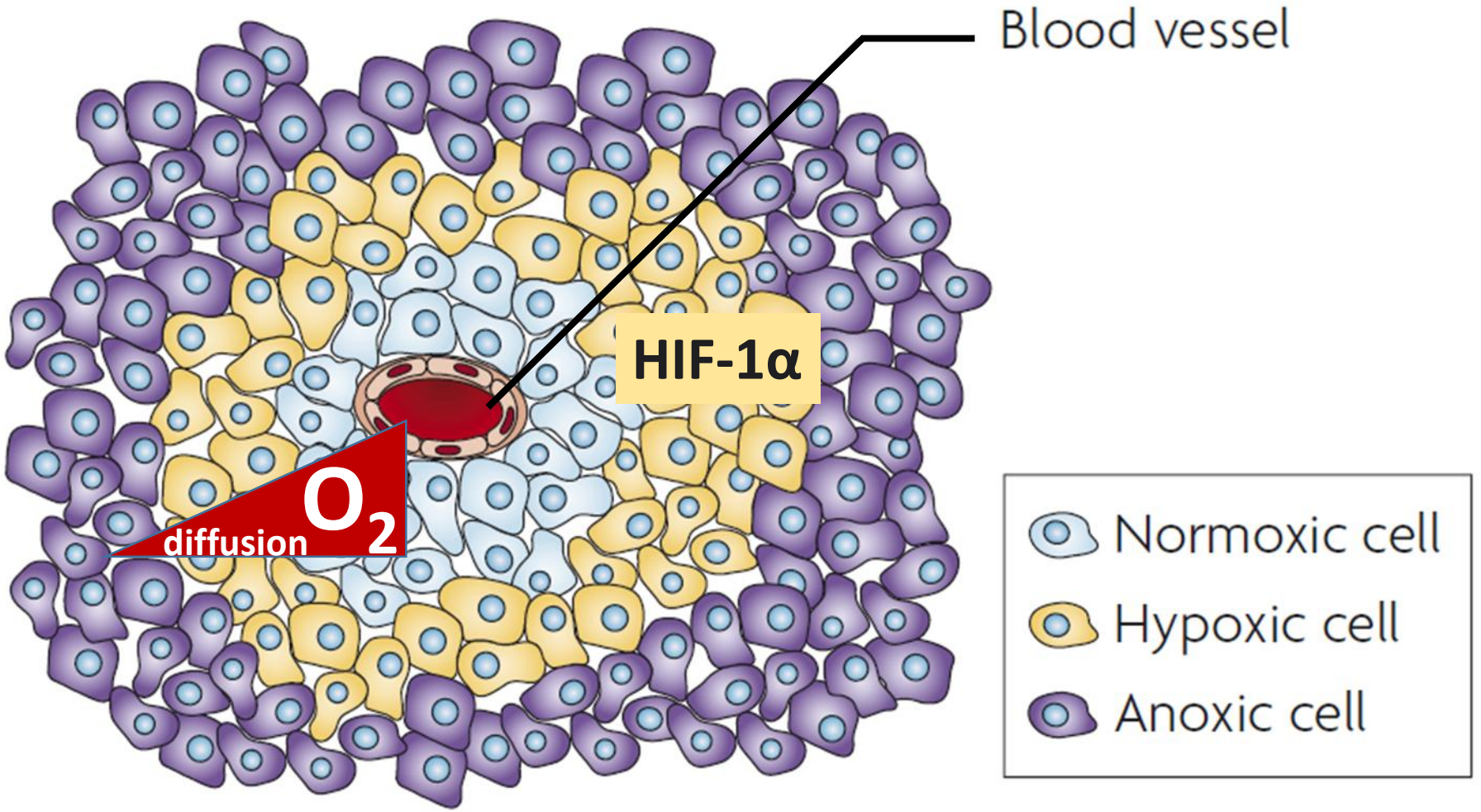
1. Oncogene activation

cancer cells favour aerobic glycolysis ("Warburg effect")



only ~2 ATP per glucose molecule

hypoxia



doi:10.1038/nrc2468

Target genes of hypoxia-induced factor (HIF-1α) that regulate glucose metabolism

HIF1α-stimulated target gene expression	Metabolic function
Glucose transporter GLUT1 or GLUT3	Glucose entry into the cell
Hexokinase2	1st glucose phosphorylation step
PGI, PFK1, aldolase, TPI, GAPDH, PGK, PGM, enolase, PK, PFKFB1	Glycolytic enzymes
LDHA	Conversion of pyruvate to lactate
MCT4	Removal of lactate from the cell
PDK1	Decreased conversion of pyruvate to acetyl-CoA for mitochondrial activity
VEGF	angiogenesis
erythropoietin	red blood cell production (erythropoiesis)

doi:10.1038/nrc2468

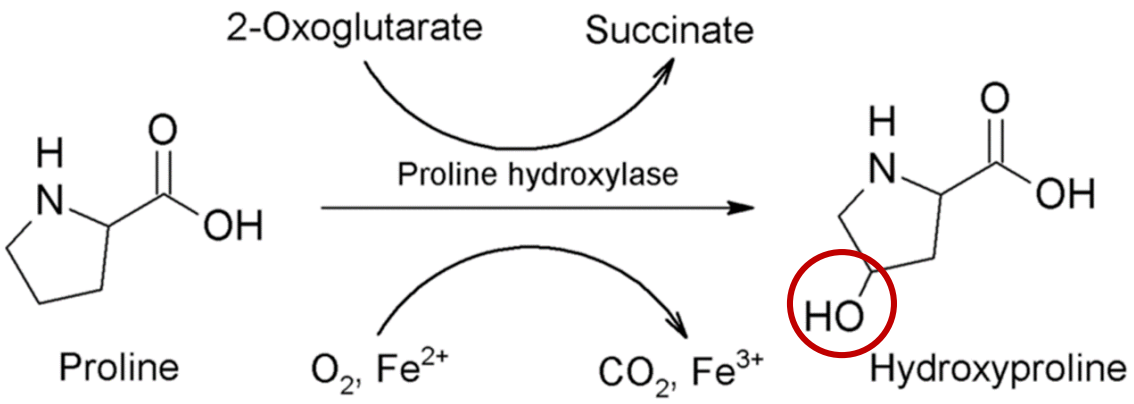
How is hypoxia sensed at the molecular level?

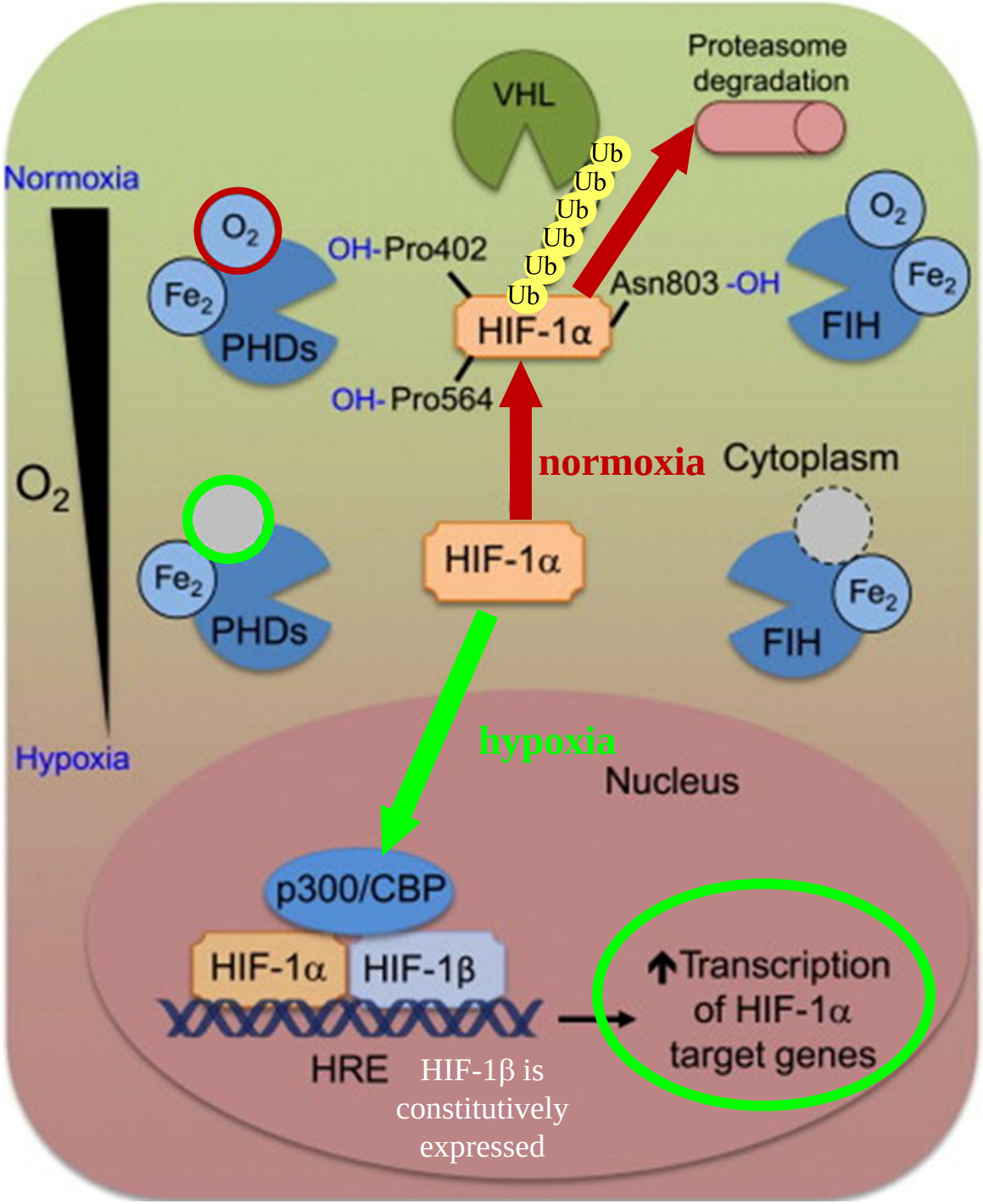
- Cytosolic **hypoxia-inducible factor** (HIF-1α) is unstable in well-oxygenated tissues due to constitutive ubiquitin-mediated degradation

- The signal for degradation is the oxygen-dependent hydroxylation of prolines 402 and 564 of human HIF-1α

- Prolyl hydroxylases have low-affinity to O_2 so that in low O_2, HIF-1α is no longer hydroxylated and thus not degraded

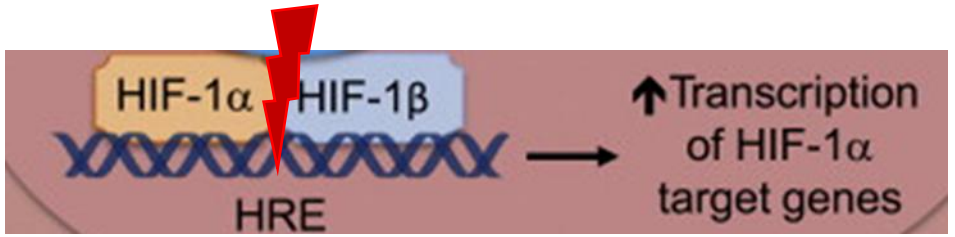
proline-hydroxylated HIF-1 is recognized by the E3-ubiquitin ligase *von-Hippel-Lindau* protein (VHL), a tumor suppressor gene





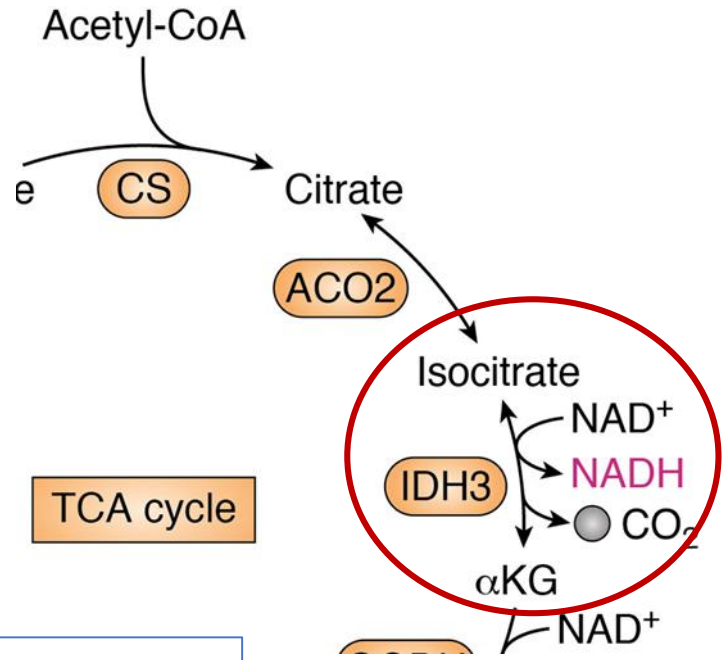
Exploiting metabolic tumour cell vulnerabilites – part 2

Warburg-effect tumours:
Glutaminase inhibitors: reduce glutaminolysis pathway
LDHA (lactate dehydrogenase A) inhibitors:
MCT inhibitors: reduce lacte export from cytoplasm



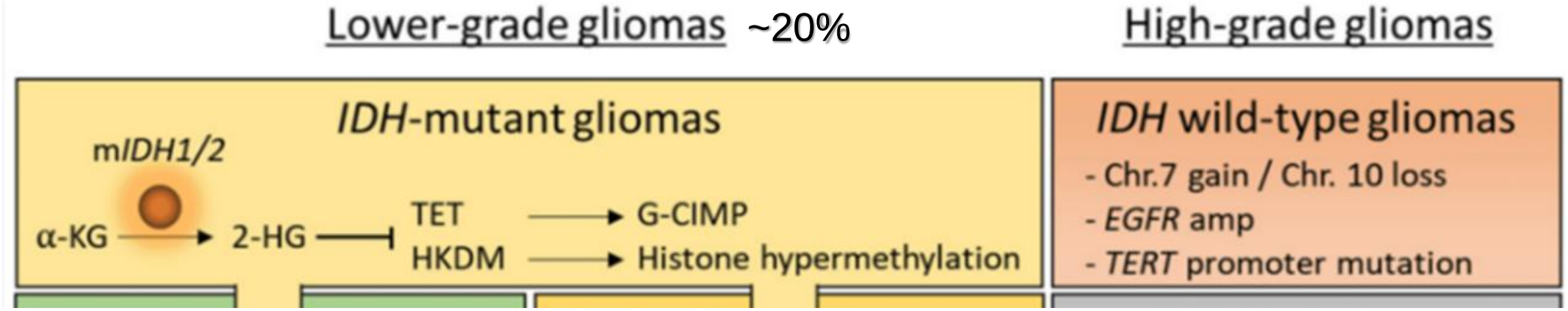
HIF-inhibitor Belzutifan (FDA-approved)

IDH1/2 missense mutation,
found in 80% brain tumours, 20% AML;
Decreases α-KG levels, required as co-factor for proline hydroxylase of HIF-1α and DNA demethylases (TSG promoter methylation)
-> inhibitors



Video animation - Nature editors https://www.youtube.com/watch?v=kYmLQP2M-qo

Metabolic changes due to IDH mutation help in stratifying glioma subtypes



Cancers 2019, 11(10), 1616; https://doi.org/10.3390/cancers11101616

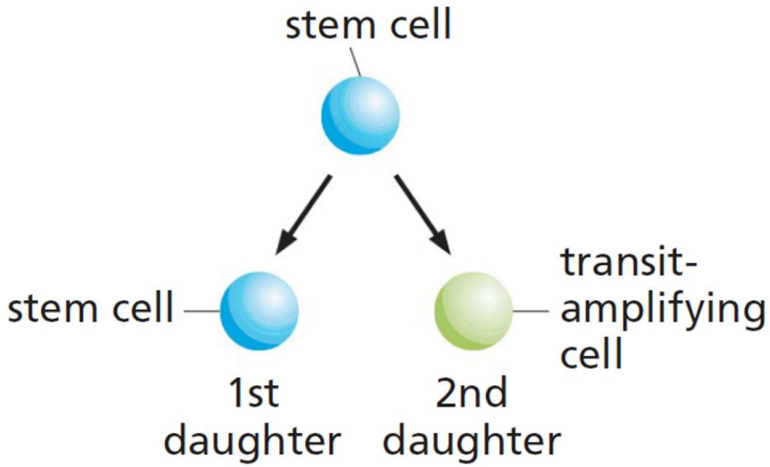
Is a switch in glucose metabolism unique to cancer cells??

…no, also utilized in:

- proliferating embryonic cells,
- adult stem cells
- activated immune cells

Stem cell properties

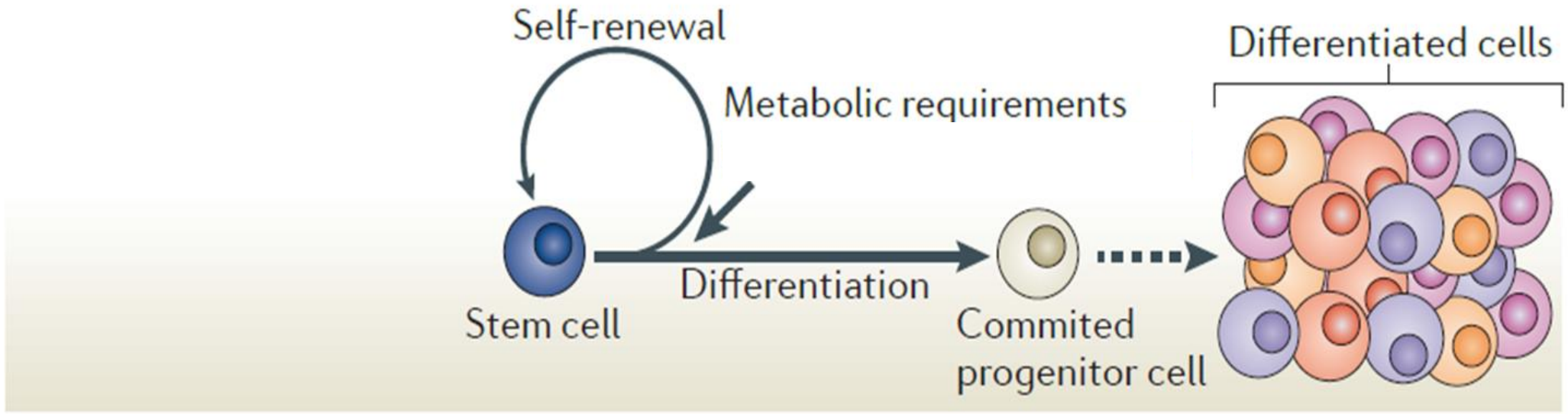
- A distinctive feature of stem cells is their capacity of self-renewal to maintain pluripotency
- Adult stem cells are undifferentiated reserve cells in various tissues that replenish dying cells or regenerate damaged tissues



Stem cell → **Transit amplifying cell** → **Differentiated cell**

pool of reserve cells → proliferation to increase cell number → accomplish function

glucose metabolism in stem cells



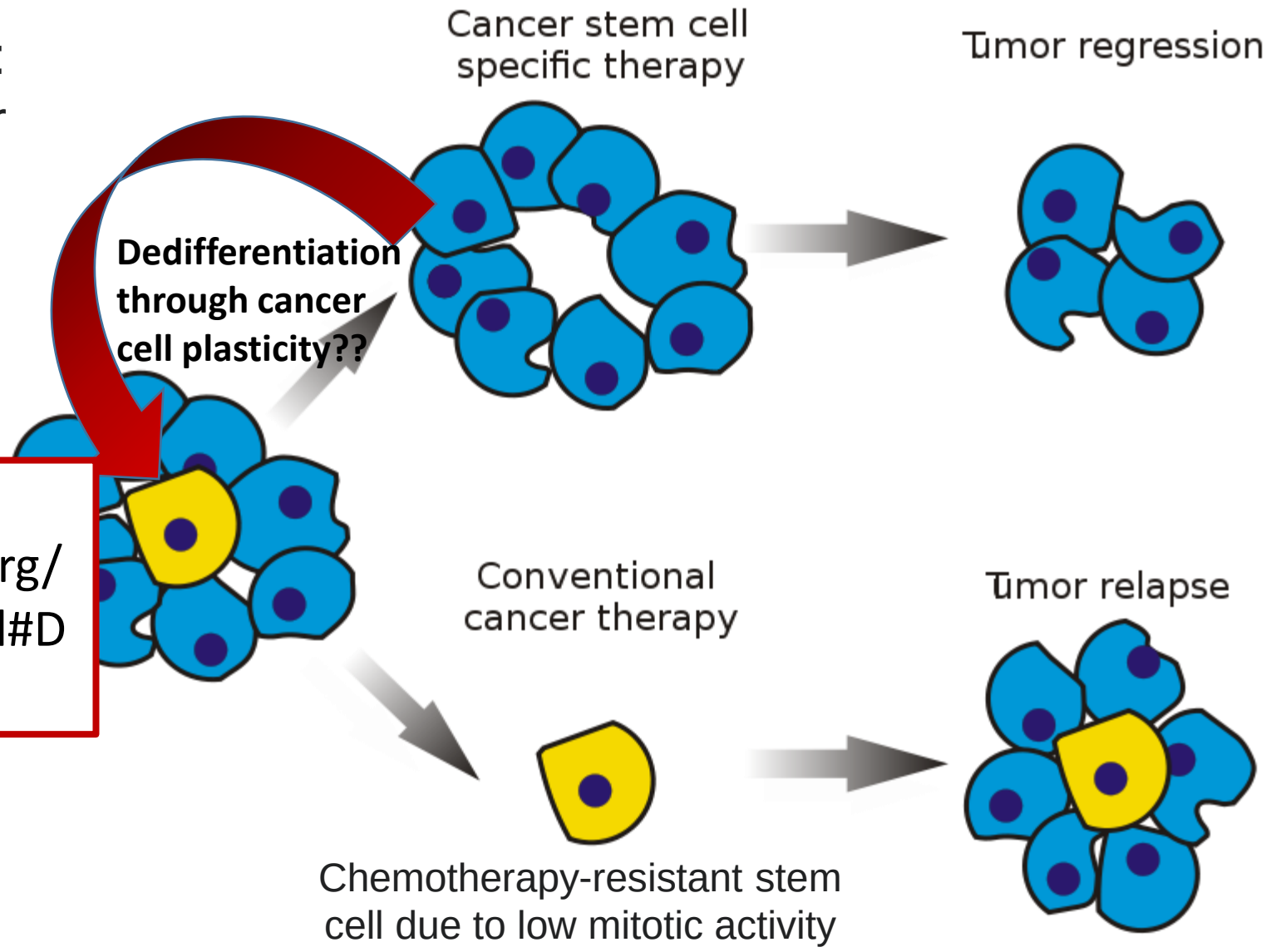
Stem cell marker	Positive	Negative
Differentiation marker	Negative	Positive

O_2 + ROS

(Hypoxia in stem cell niche promotes HSC maintenance)

doi:10.1038/nrm3772

Cancer stem cell model: a subpopulation of cancer stem cells sustains tumour growth and development



Check out the debate: https://en.wikipedia.org/wiki/Cancer_stem_cell#Debate

Lecture 9- Some take-home concepts

- **Many cancer cells rely on high glucose consumption, which is exploited in PET scan image diagnosis**
- **Many cancer cells show the Warburg effect: lack of mitochondrial pyruvate degradation to generate ATP through oxidative phosphorylation, but instead use of high glycolysis rate with secretion of lactate;**
- **High glycolysis rate provides monomers for macromolecule synthesis, and glutamine is used to maintain the citric acid cycle activity in mitochondria;**
- **The changes in metabolism are triggered by transcriptional activation of metabolic genes following oncogenic pathway activation (RAS or PI3K), or hypoxia-driven stabilization of transcription factor HIF-1α;**
- **The shift from oxidative phosphorylation to glycolysis is a metabolic adaptation observed normally in proliferating cells, e.g. in embryonic development, activated immune cells, and stem cells;**