Cancer Metabolism

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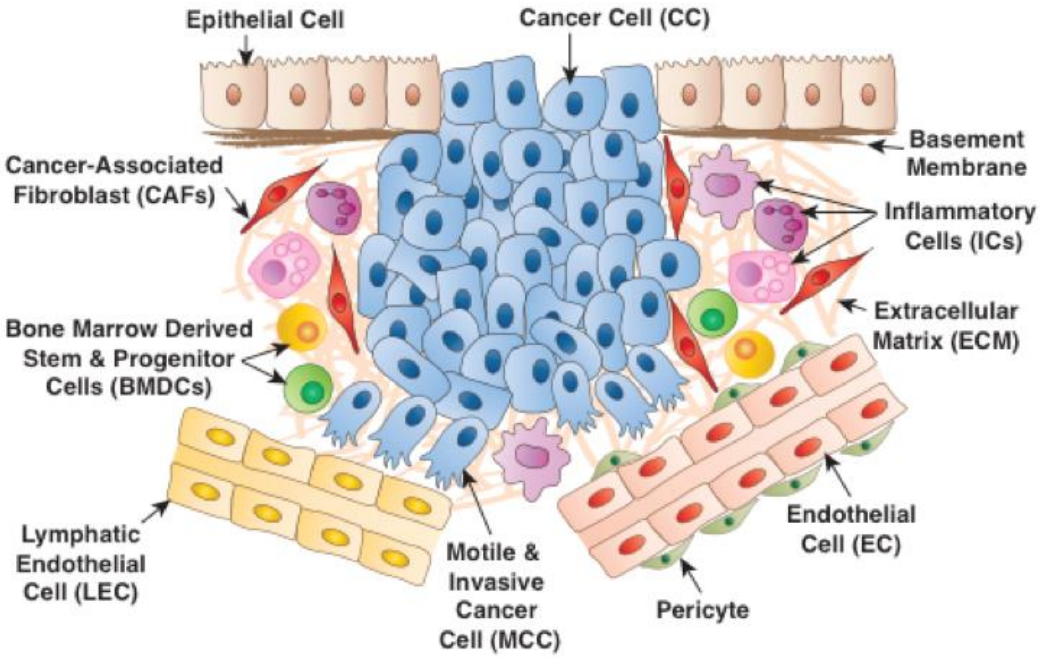
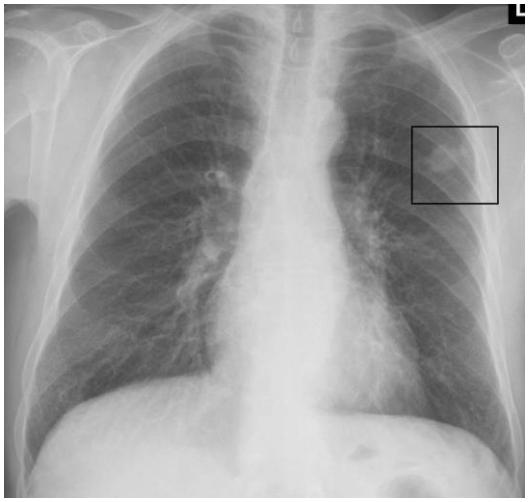
Introduction -- cancer

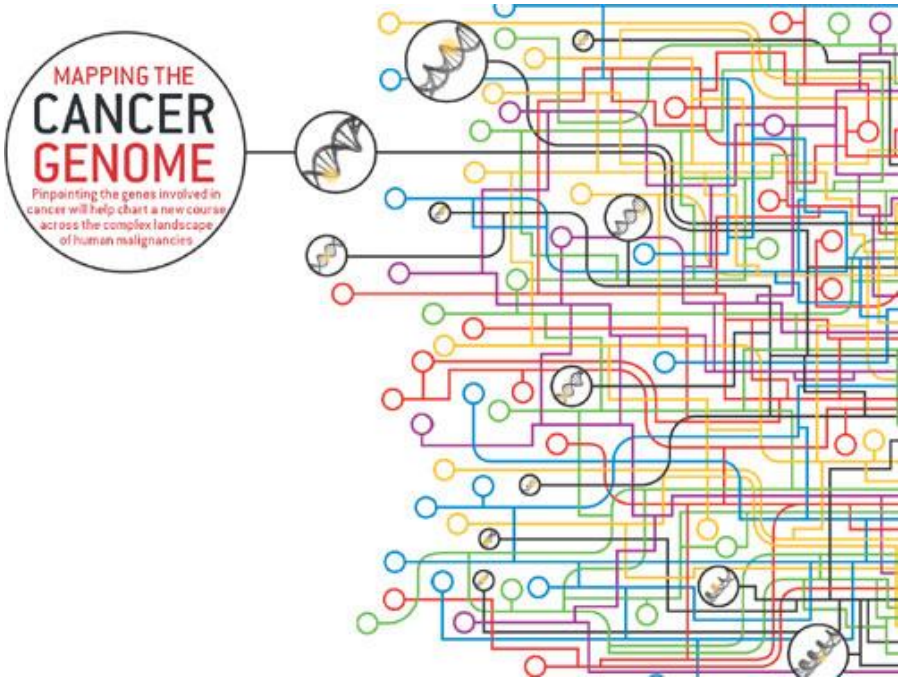




- Abnormal and uncontrolled growth of cells (neoplasia).
- Potential to invade and spread to other parts of the body (metastasis).

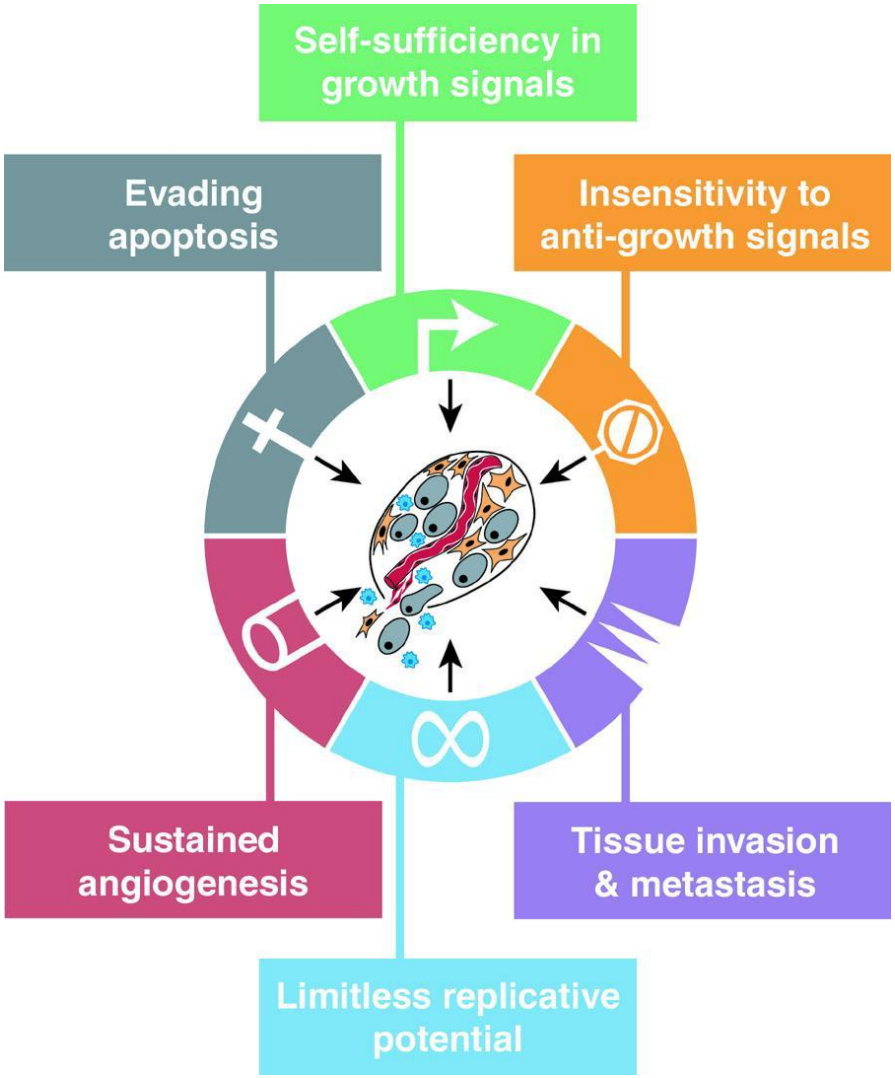
Our view of cancer – malignancy caused by genetic mutations

- Cancer is a disease involving dynamic changes in the genome.
  - Oncogenes – dominant gain-of-function mutations.
  - Tumor suppressors – recessive loss-of-function mutations.



Scientific American 18, 22 - 29 (2008)

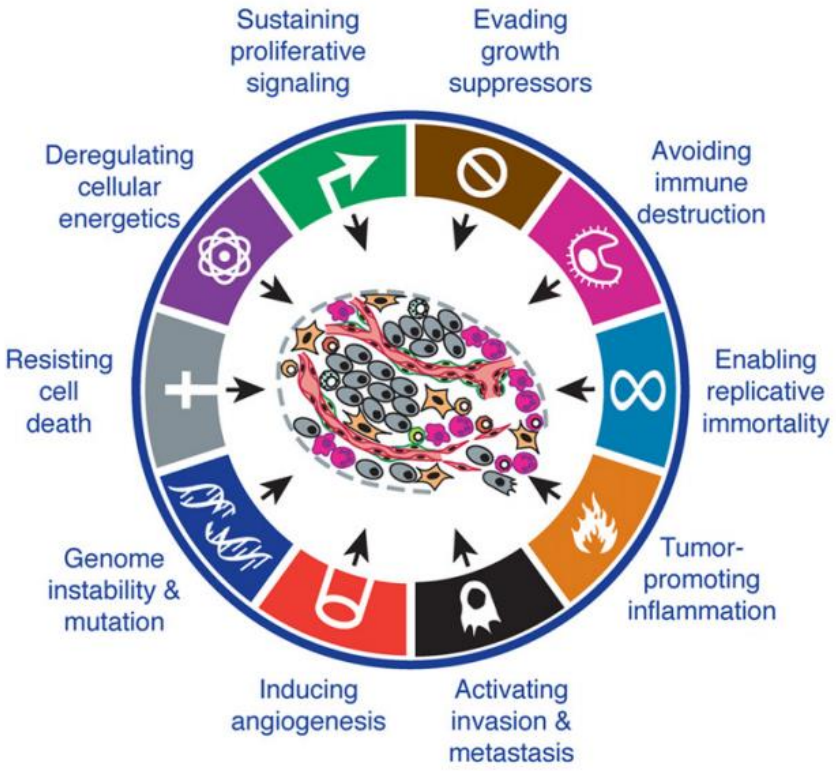
Genetic mutations endow the malignant capabilities of cancer



Hallmarks of cancer *Cell Volume 100, Issue 1, p57–70, 7 January 2000*

Hallmarks of cancer (2011)

- Updated in 2011 after a decade of research. New additions:
  - ➢Genome instability & mutation
  - ➢Tumor-promoting inflammation
  - ➢Reprogrammed energetic metabolism
  - ➢Avoiding immune destruction



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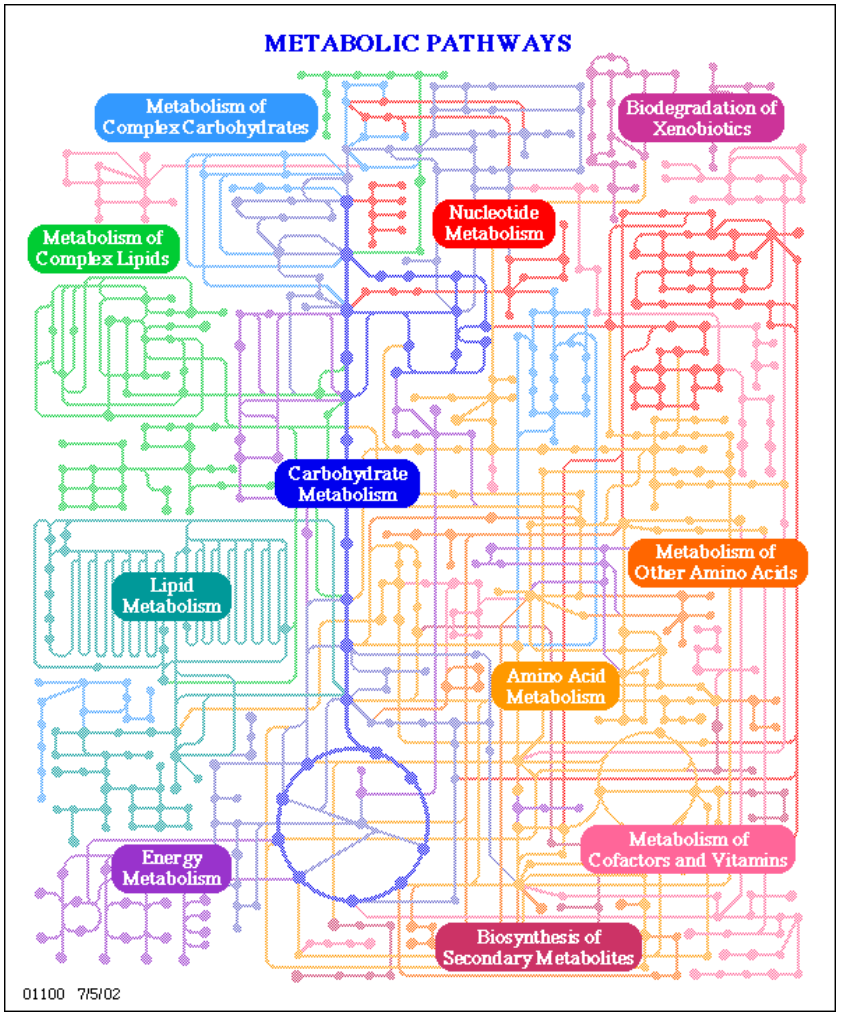
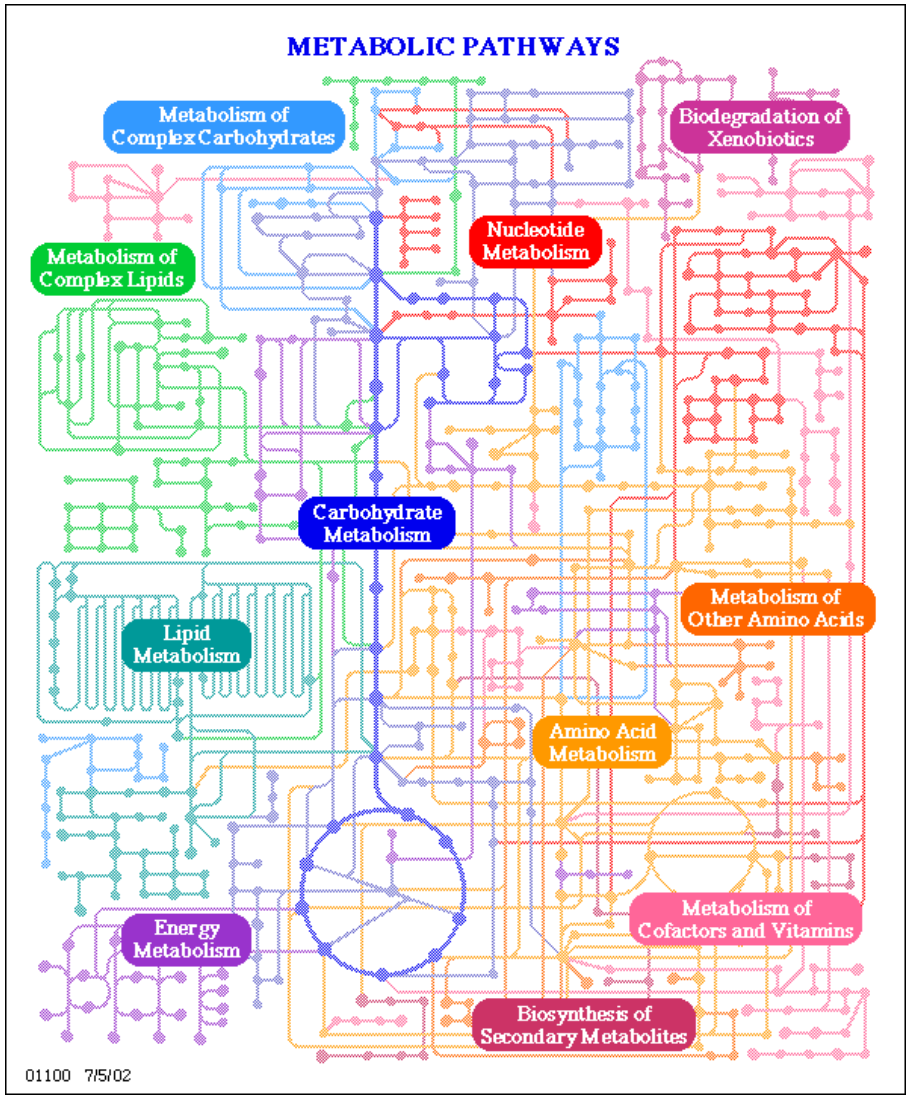


How important is metabolism to cancer?

- Cancer cells need energy (bioenegetics).
- Cancer cells need anabolism (biosynthesis).
- Cancer cells need catabolism (biodegradation).

How different is cancer metabolism from physiological metabolism?

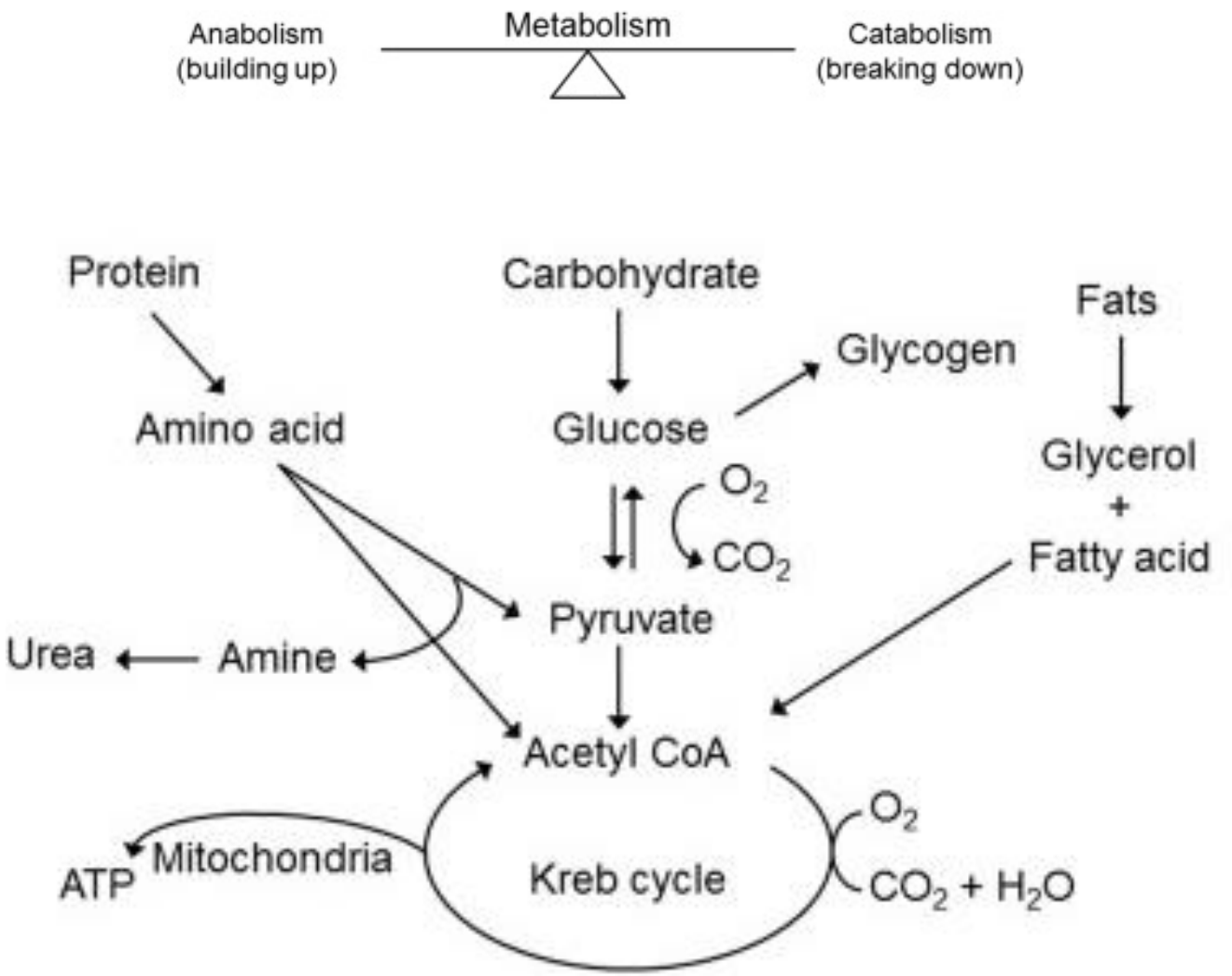


Reprograming of metabolic pathways in cancer cells:

- Energy
- Anabolism
- Catabolism

http://www.genome.jp/kegg-bin/show_pathway?map01100

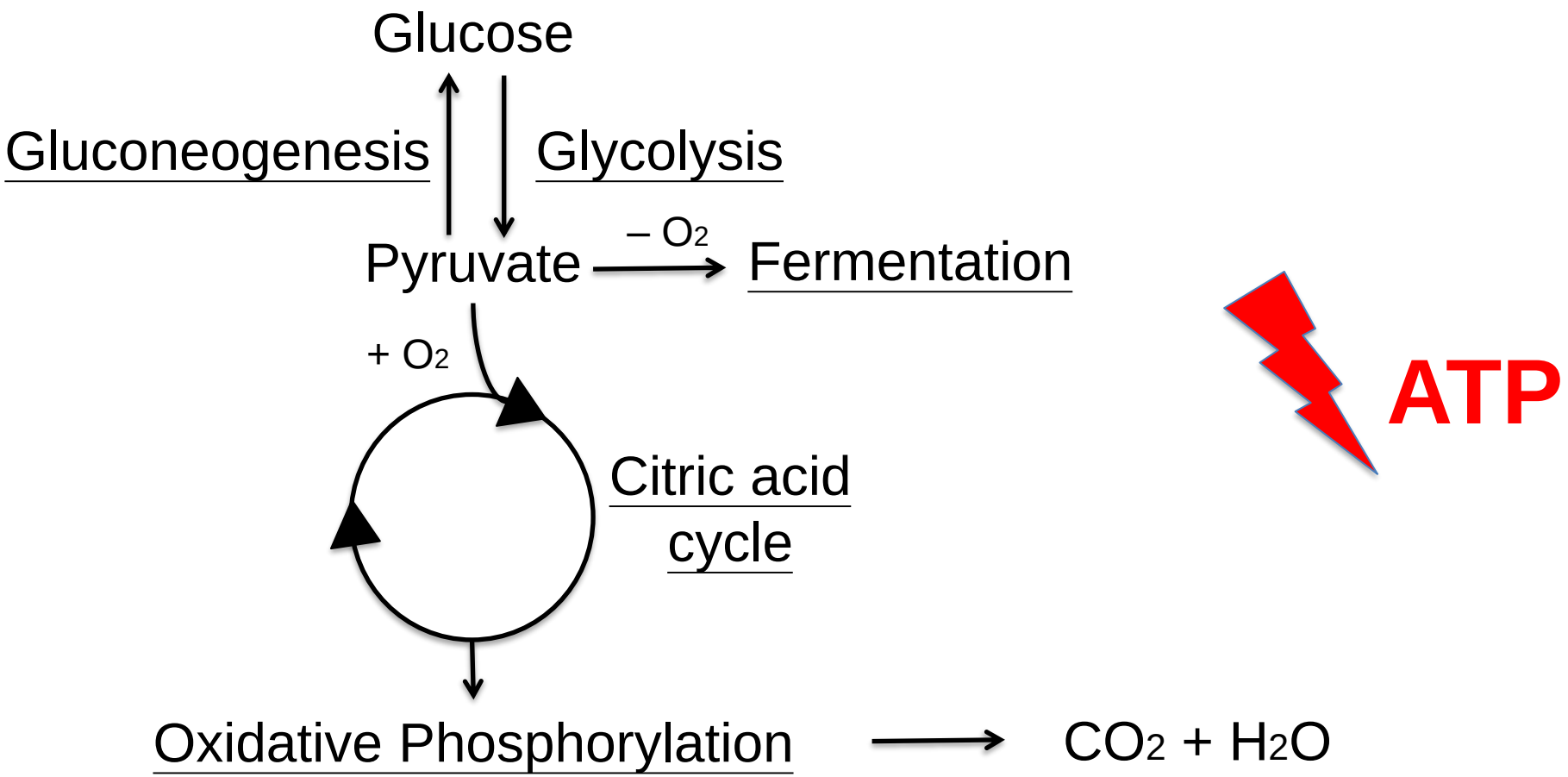
A simplified view



Summary of objectives I

- Cancer is uncontrolled abnormal cell growth.
- Genetic mutations underlie the malignant behaviors (hallmarks) of cancer.
- Reprogrammed metabolism is a hallmark of cancer.

Bioenergetics using glucose



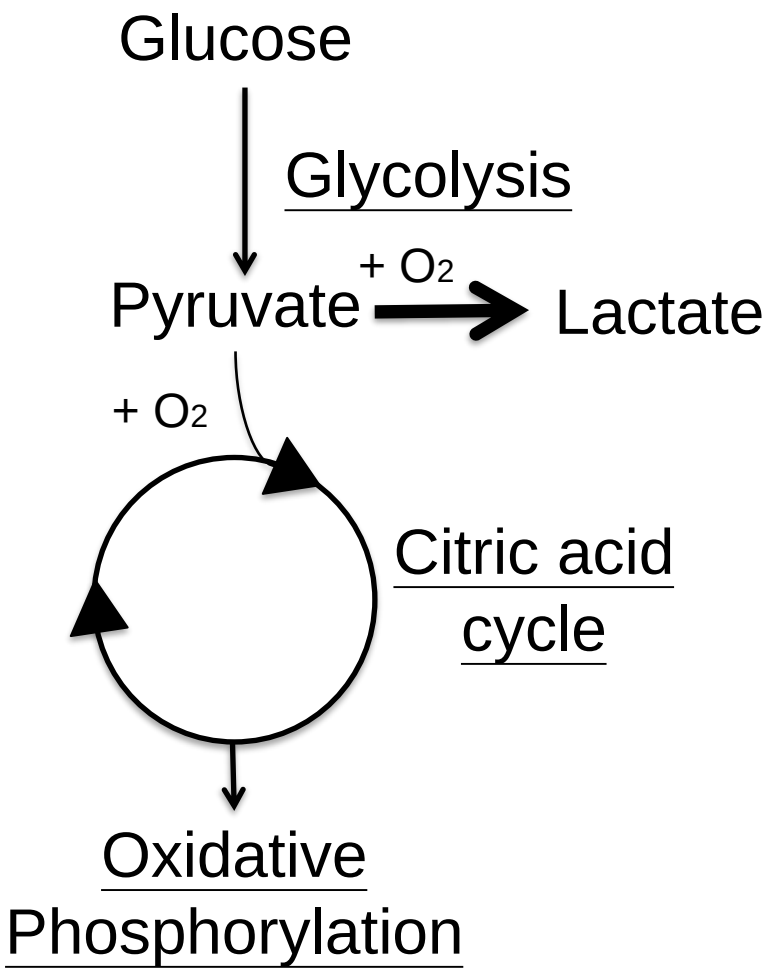
Warburg effect

Otto H. Warburg

“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.”

Warburg effect

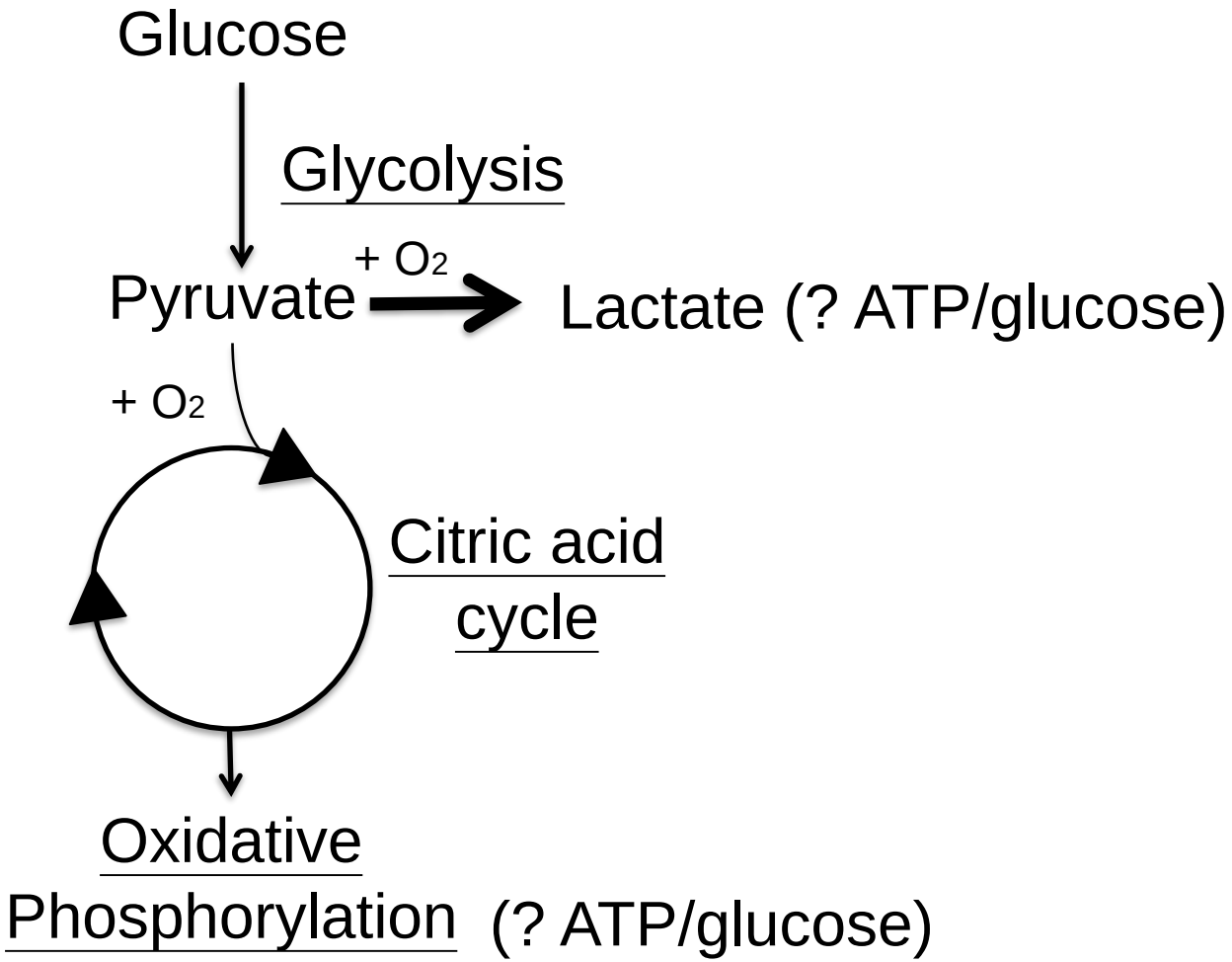
Otto H. Warburg



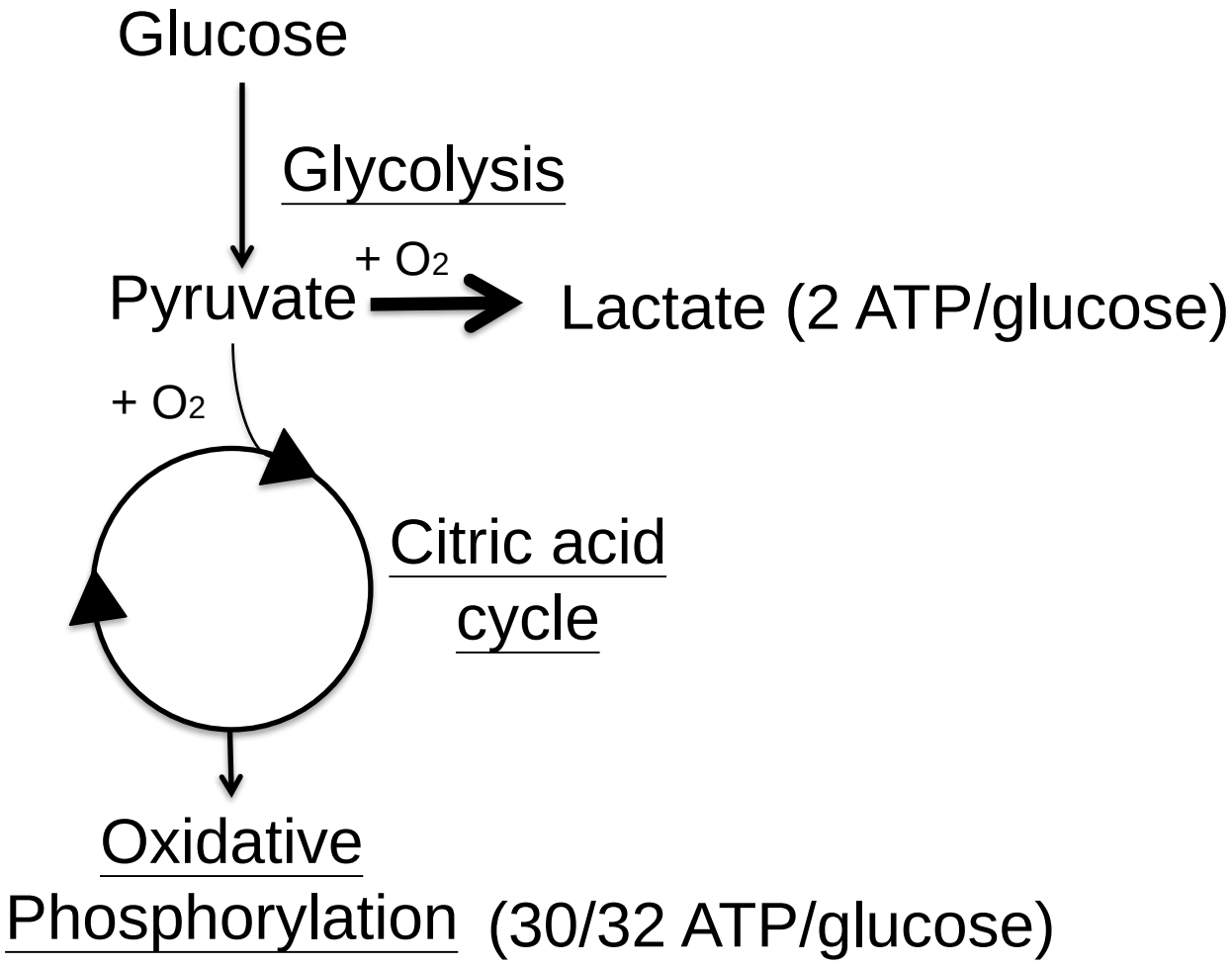
Even in the presence of O_2, cancer cells predominantly produce energy by glycolysis followed by lactate fermentation in cytosol, rather than by glycolysis followed by oxidation of pyruvate in mitochondria as in most normal cells.

The observation was made in the 1920s: under aerobic conditions, tumor tissues metabolize ~10-fold more glucose to lactate in a given time than normal tissues.

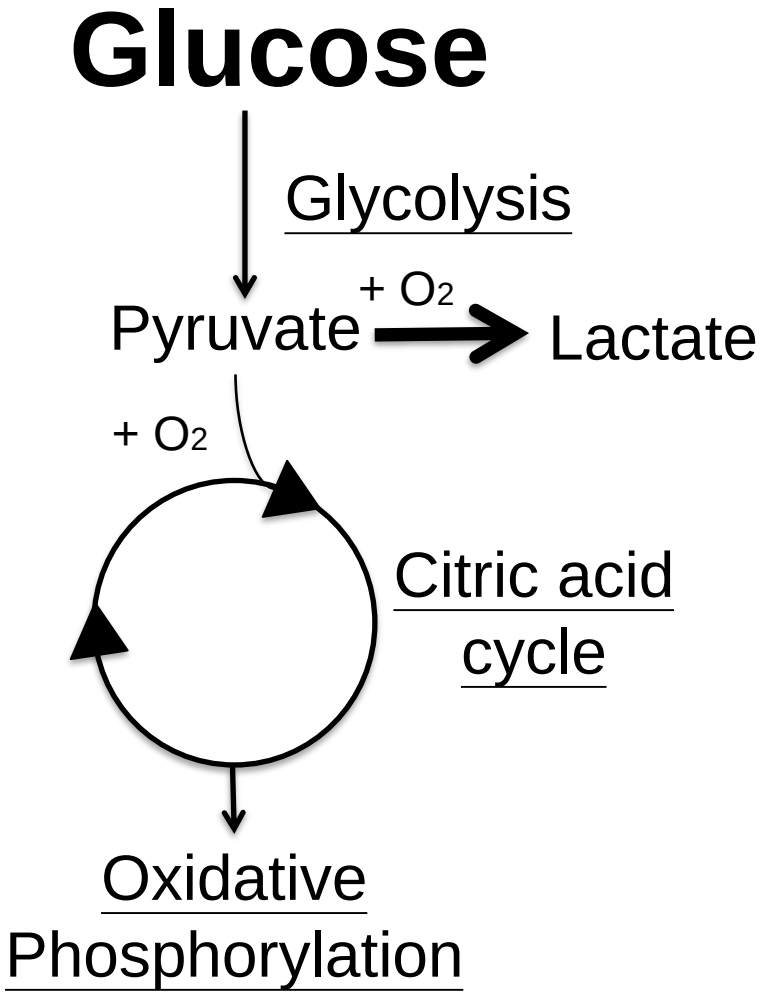
Is Warburg effect efficient?

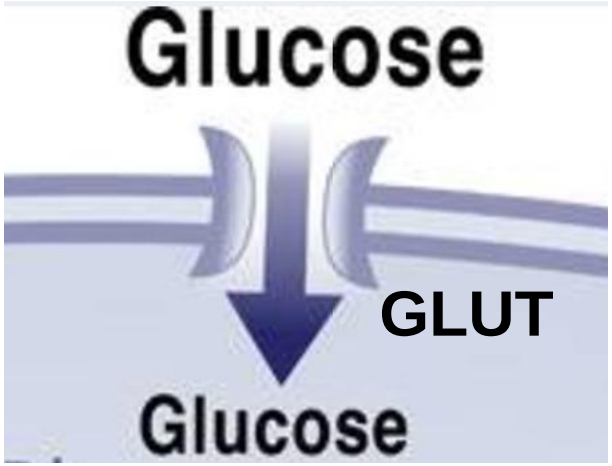


Is Warburg effect efficient?



Why cancer cells still use it?





Most cancer cells overexpress glucose transporter (GLUT) at cell surface to import **a lot of** glucose into the cytosol, so they can **afford** it.

Cancer cells need building blocks

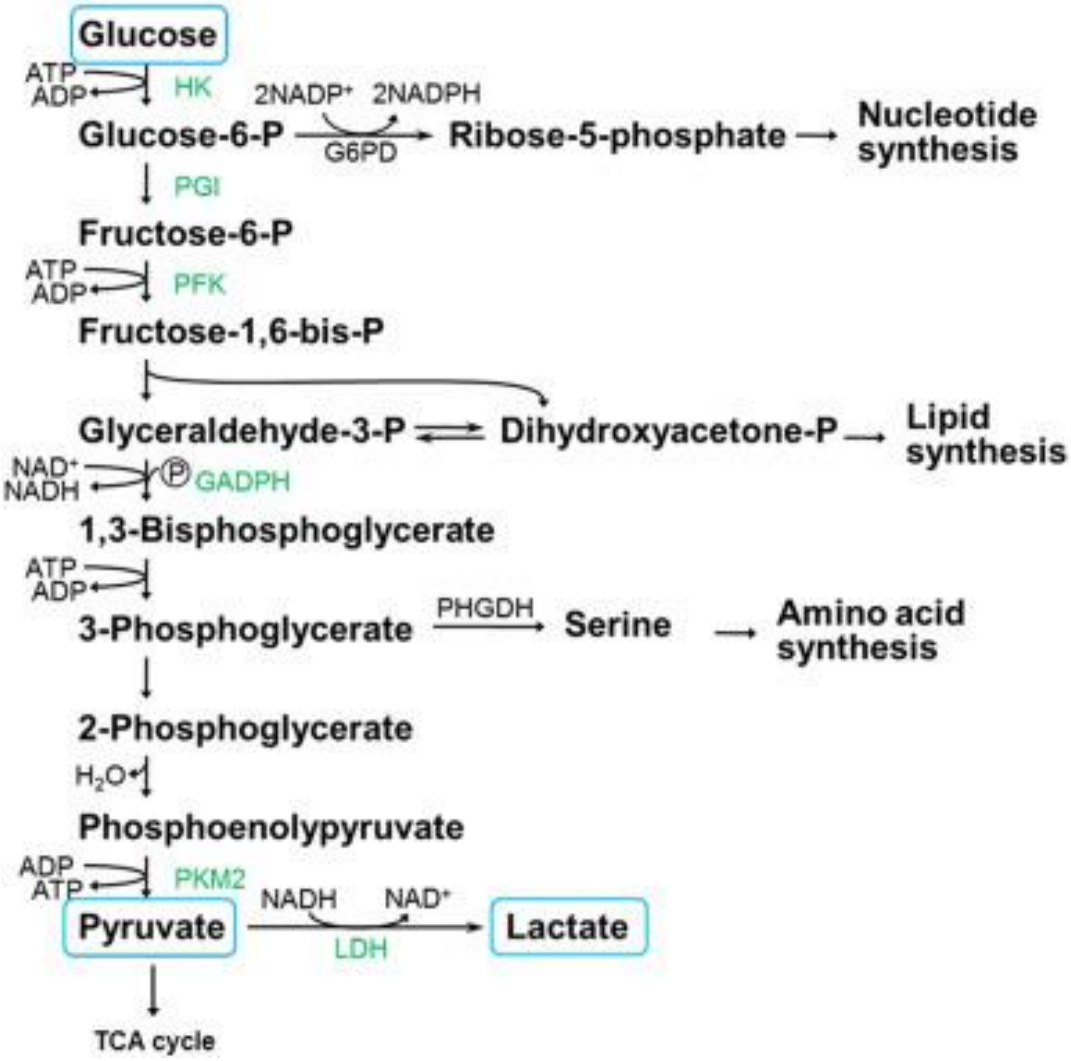
normal

cancer

- Sugars
- Proteins
- Lipids
- Nucleotides

The abnormal growth/proliferation of cancer cells need **more** building blocks, and need them to be there **fast**!

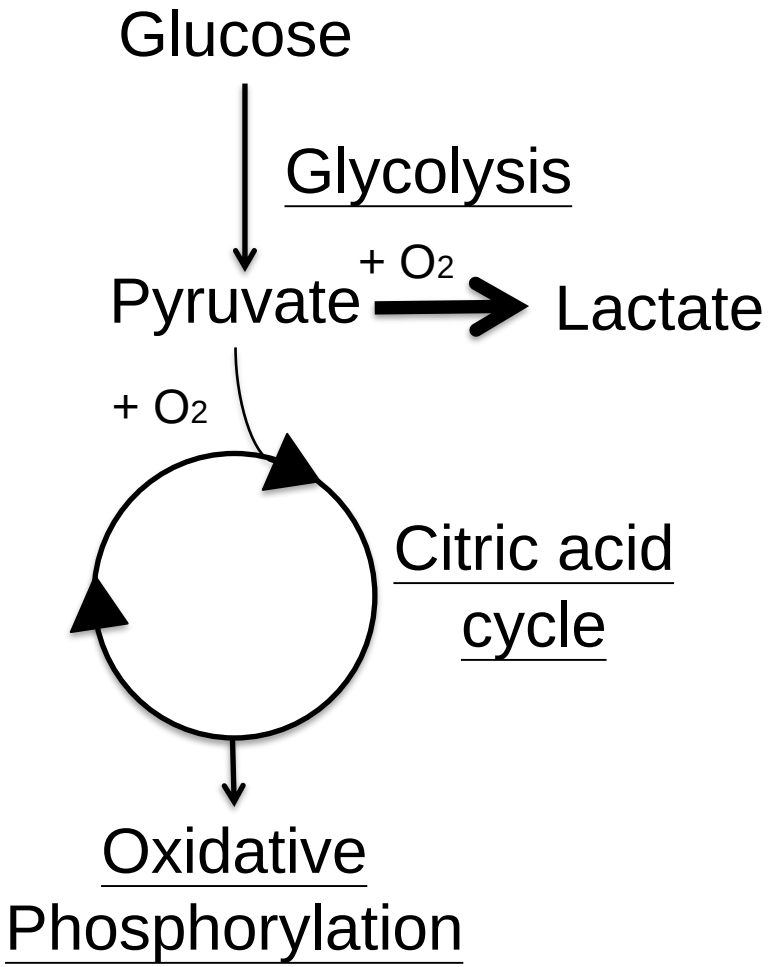
Warburg effect provides the blocks

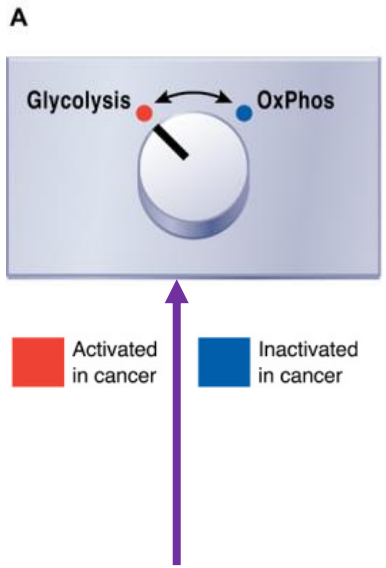


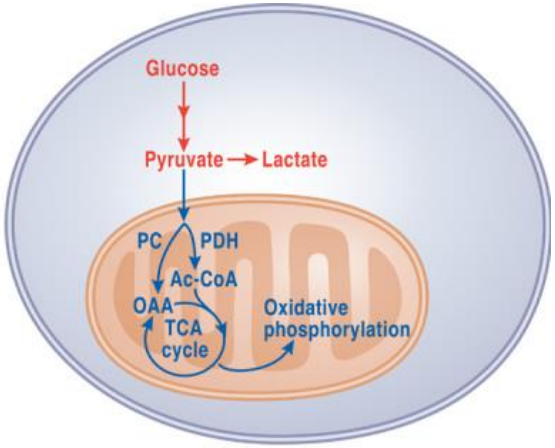
Summary of objectives II

- Cancer cells undergo a large amount of glycolysis-fermentation even with abundant supply of oxygen –Warburg effect.
- Through Warburg effect, cancer cells gain energy fast.
- Through Warburg effect, cancer cells gain a lot of building materials.

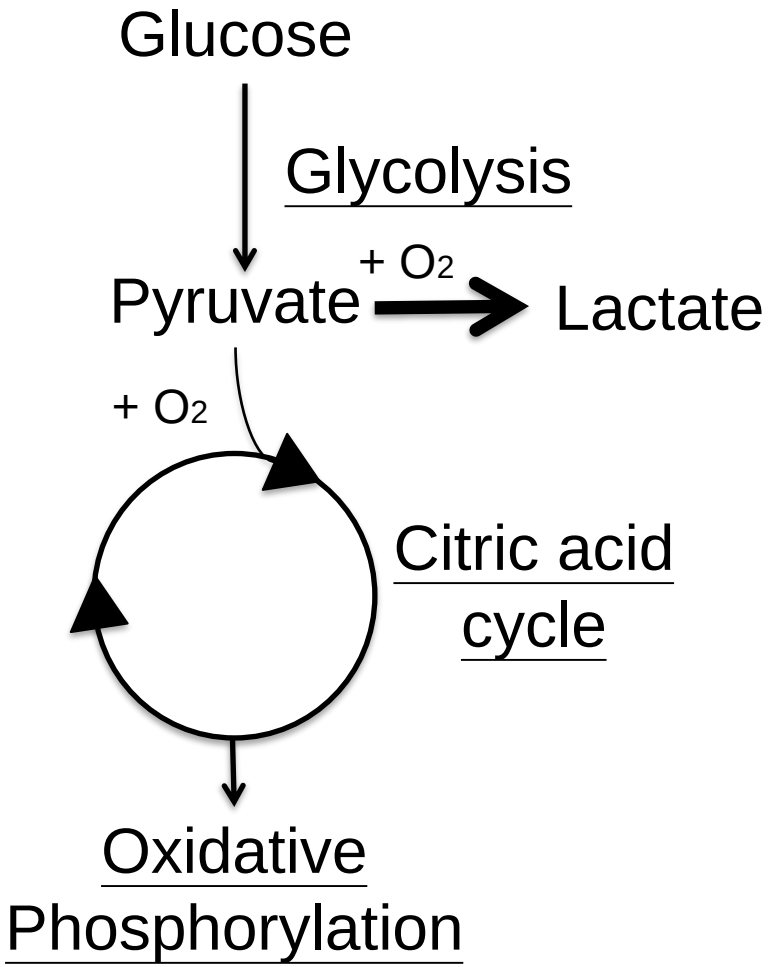
Do cancer cells shut down oxidative phosphorylation then?

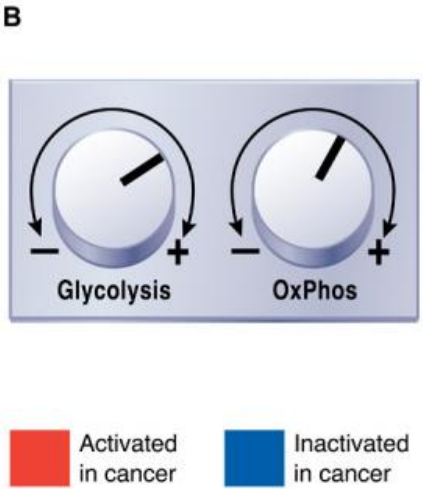


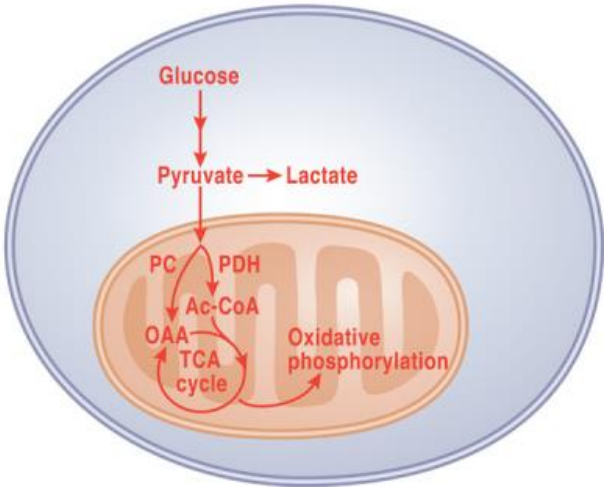




The answer is no



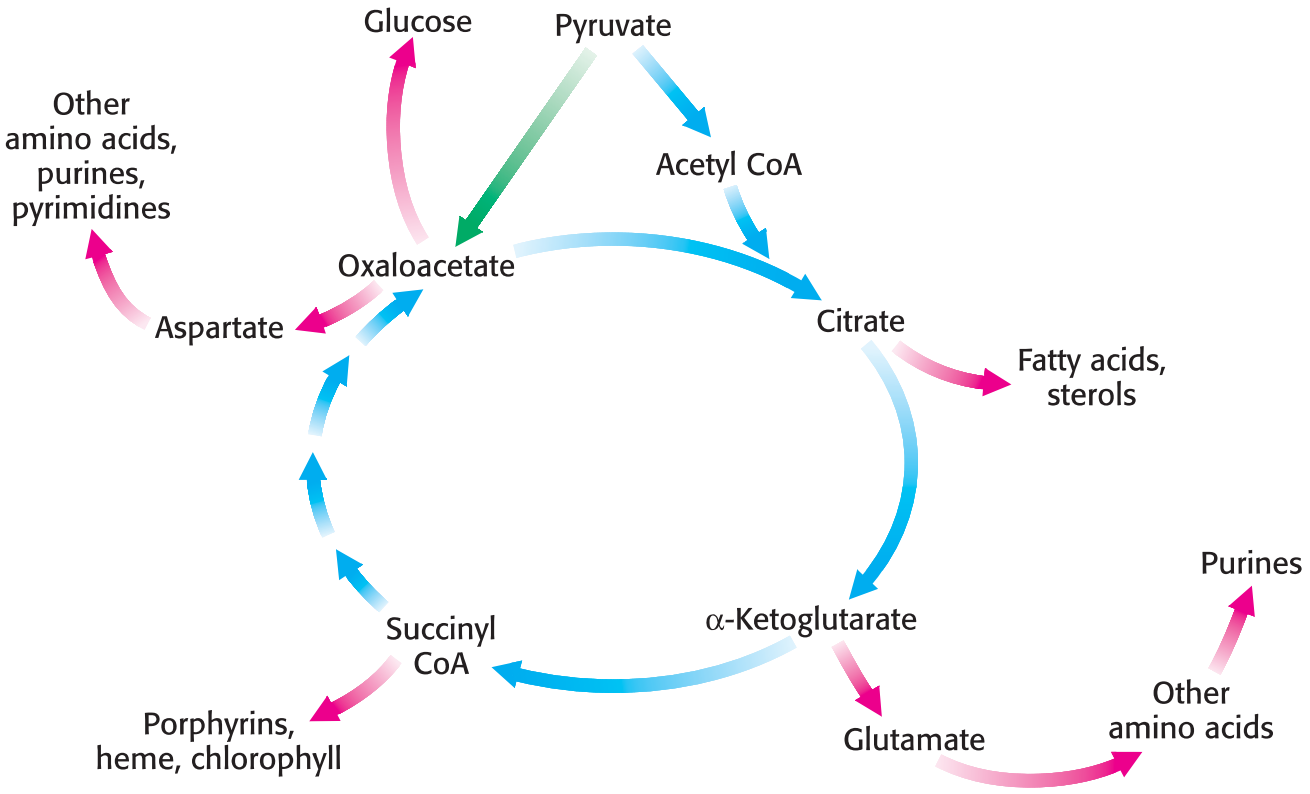




Cancer cells also have increased oxidative phosphorylation to generate ATP.

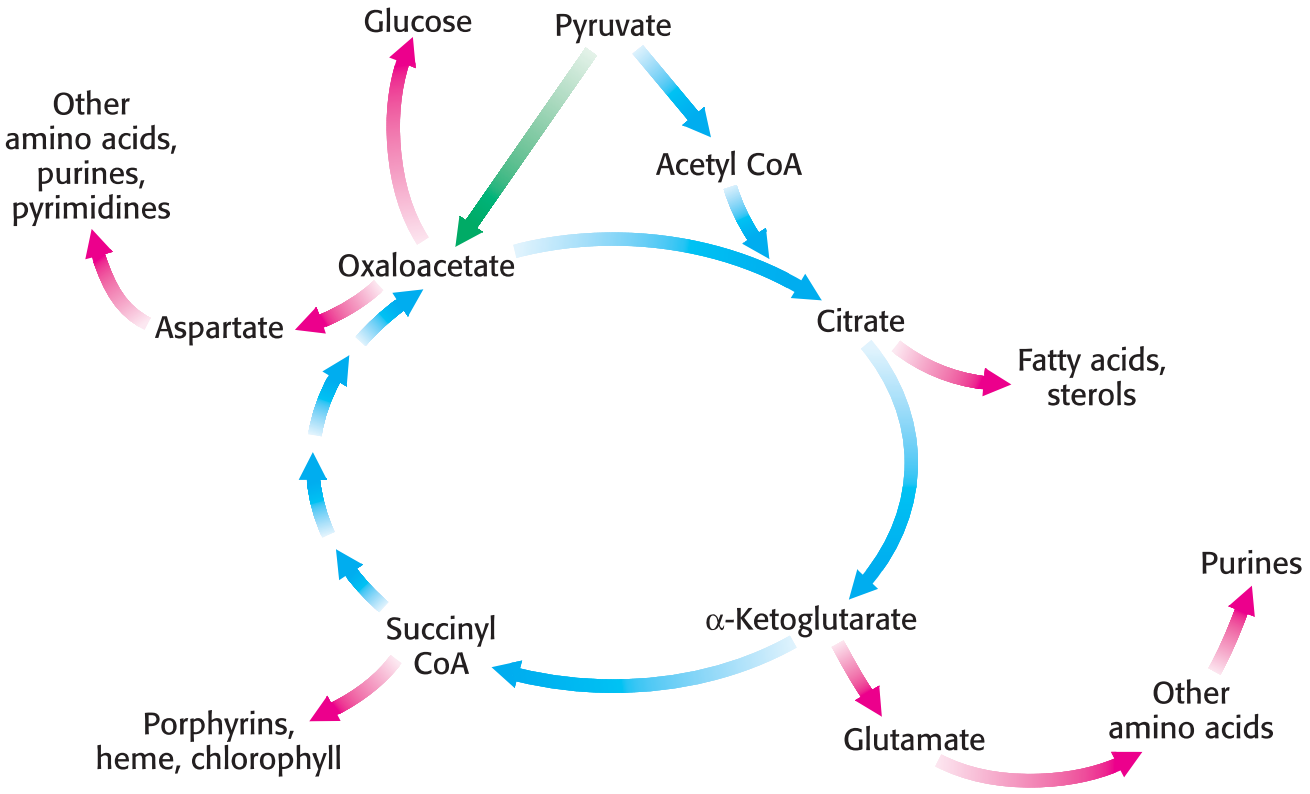
But what are the fuels if glucose is mainly used in the form of fermentation?

The anaplerotic citric acid cycle also provide cancer cells with building blocks



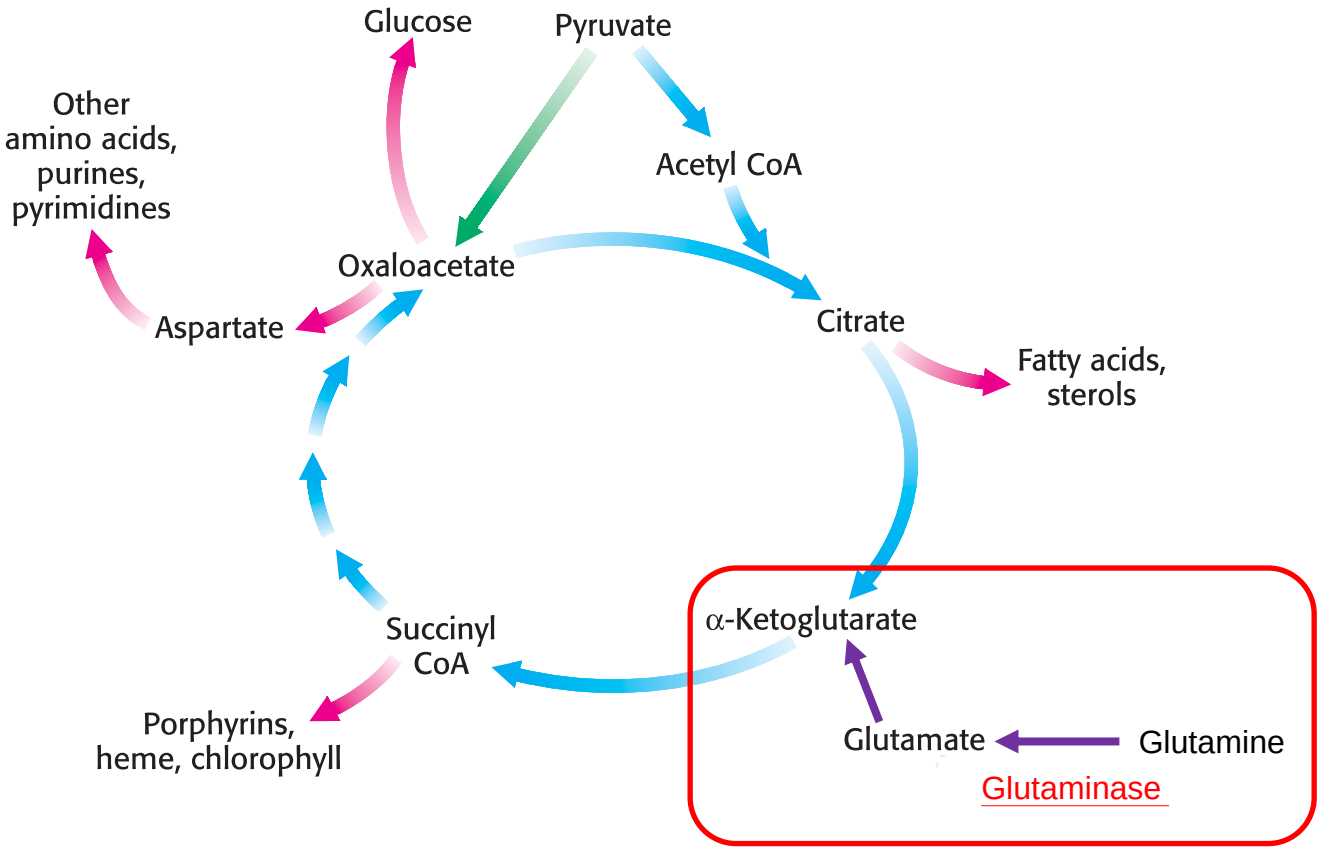
The citric acid cycle is not only a major degradative pathway for the generation of ATP, it also provides intermediates for biosynthesis.
= **Anaplerotic** (to fill up) **reactions**

The citric acid cycle is also a source of biosynthesis precursors



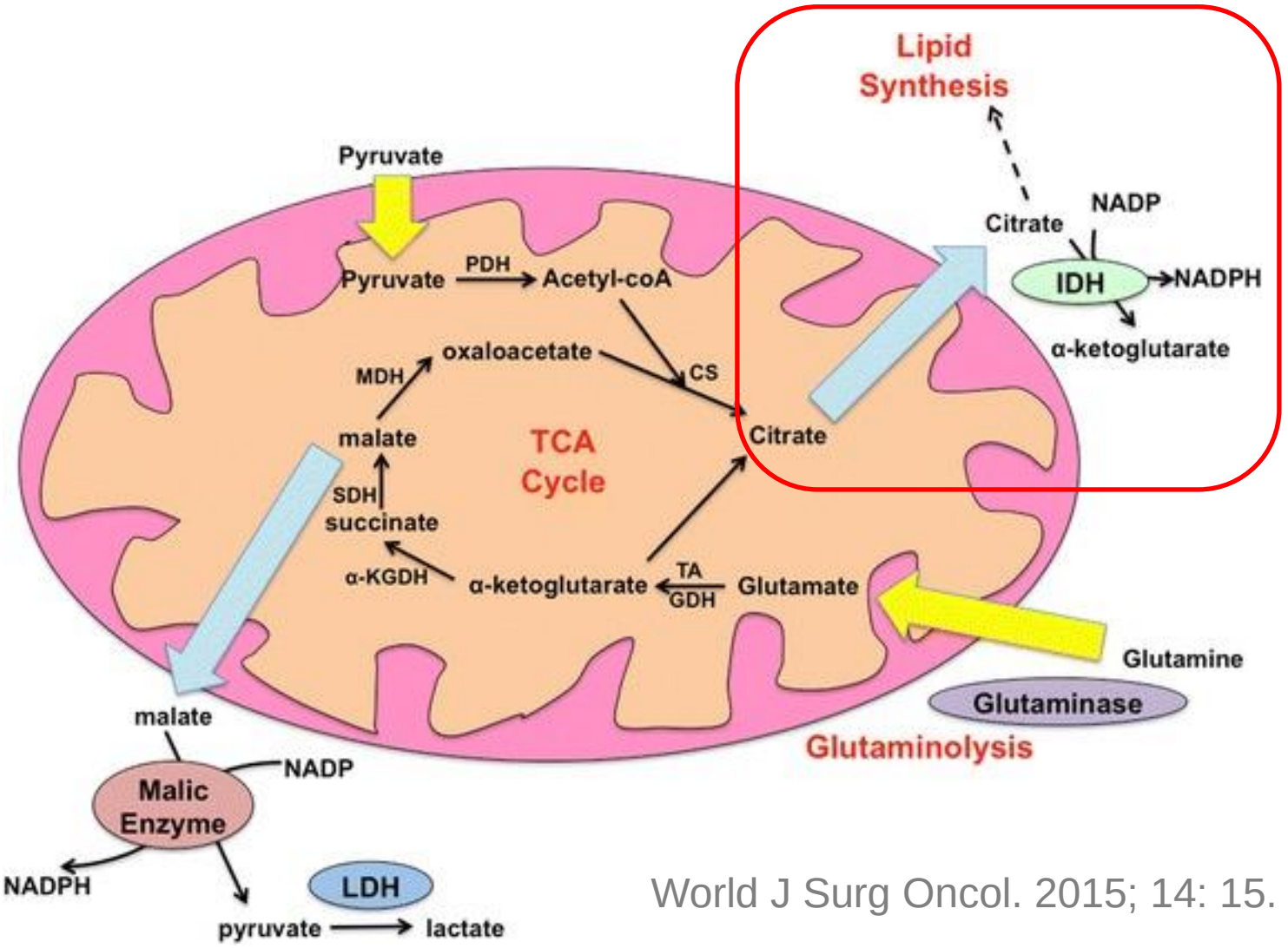
If pyruvate are mainly used for fermentation, how do cancer cells propel the citric acid cycle?

Cancer cells have high rates of glutaminolysis



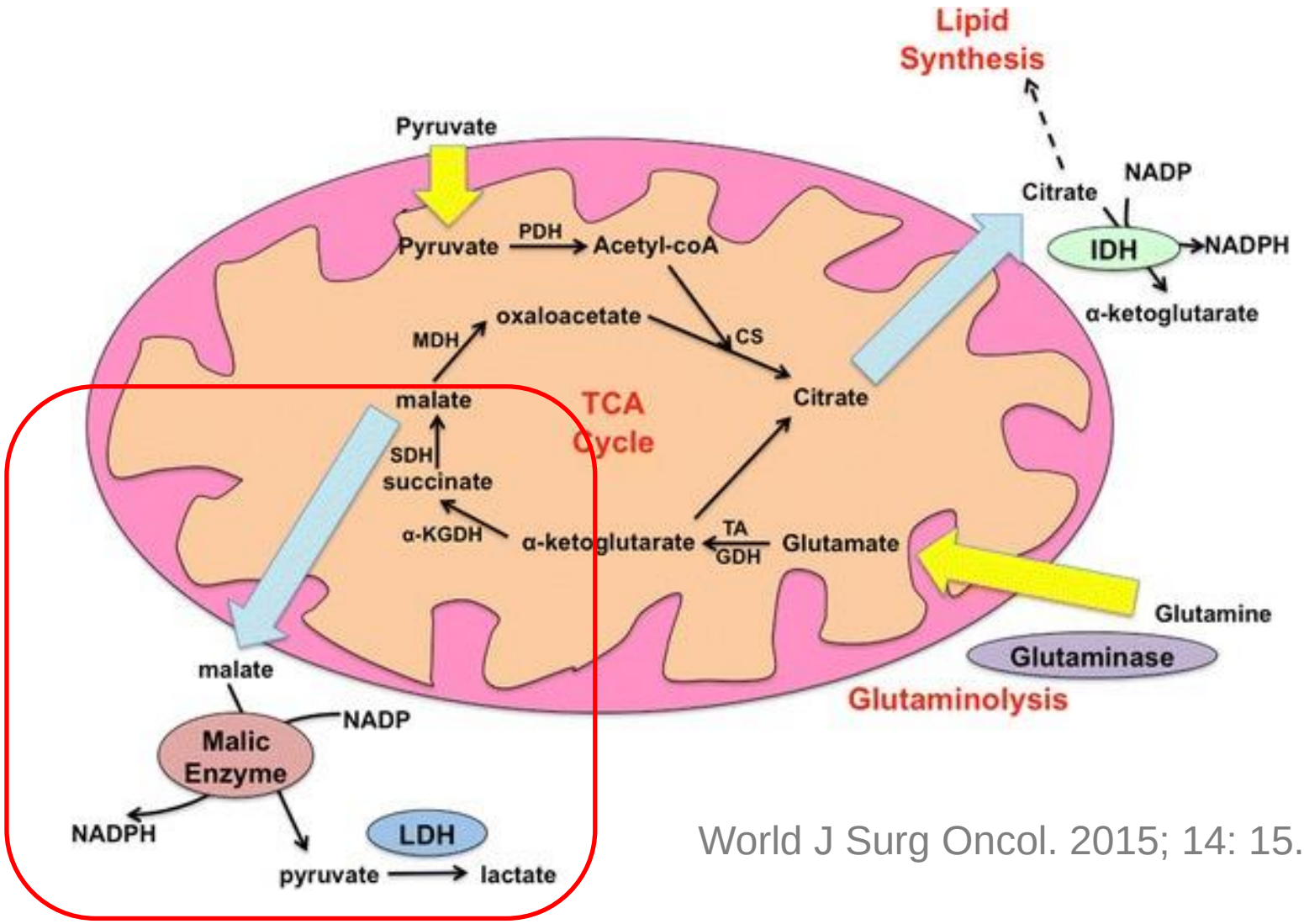
During glutaminolysis, glutamine is converted to glutamate by glutaminase, and glutamate is then transaminated into α-ketoglutarate, entering the citric acid cycle.

Examples of downstream reactions of glutaminolysis



World J Surg Oncol. 2015; 14: 15.

Examples of downstream reactions of glutaminolysis



World J Surg Oncol. 2015; 14: 15.

NADPH is actually an important molecule

- Co-factor for biosynthesis of macromolecules.
- Key reducing power in the antioxidant pathways.

Cancer cells have high levels of ROS

The transfer of four electrons leads to **safe** products (two molecules of H_2O), but partial reduction generates **hazardous** compounds (e.g. superoxide, hydroxyl radical $^{\bullet}OH$ and hydrogen peroxide are highly toxic to cells).

$$O_2 \xrightarrow{e^-} \underset{\text{superoxide}}{O_2^{\bullet -}} \xrightarrow{e^-} \underset{\text{peroxide}}{O_2^{2-}}$$

The cytochrome oxidase and other proteins that reduce O_2 have been designed not to release superoxide. However, a small amount of superoxide anion is unavoidably formed. Superoxide anion can be scavenged by superoxide dismutase:

$$O_2^{\bullet -} + O_2^{\bullet -} \xrightarrow[\text{superoxide dismutase}]{2H^+} H_2O_2 + O_2$$

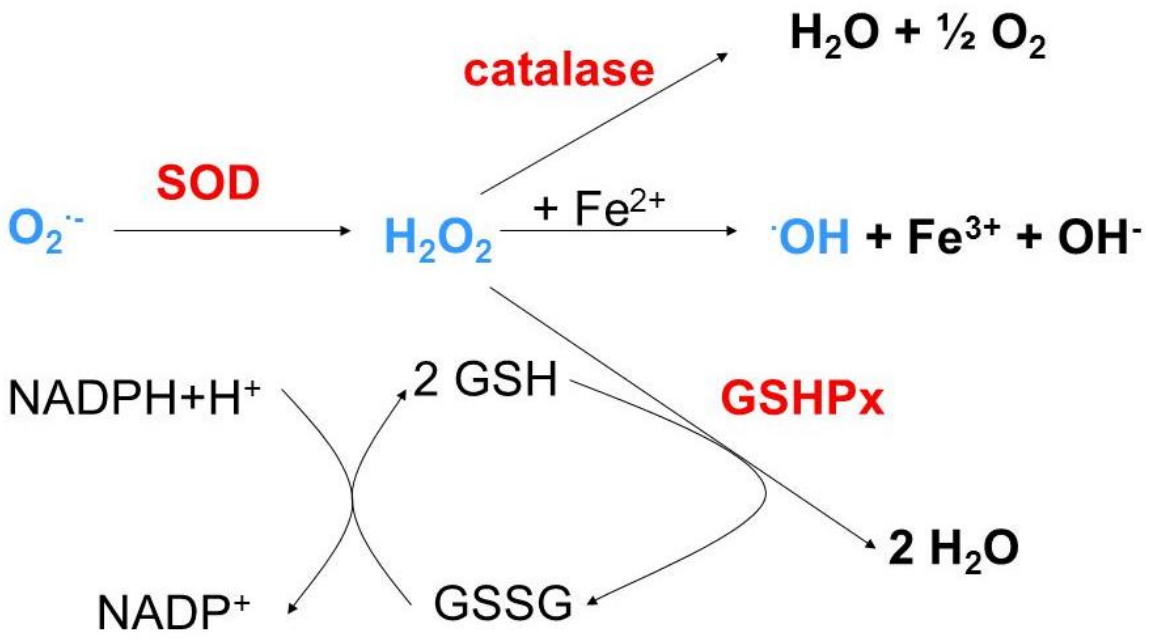
The hydrogen peroxide formed is scavenged by catalase:

$$H_2O_2 + H_2O_2 \xrightarrow{\text{catalase}} 2H_2O + O_2$$

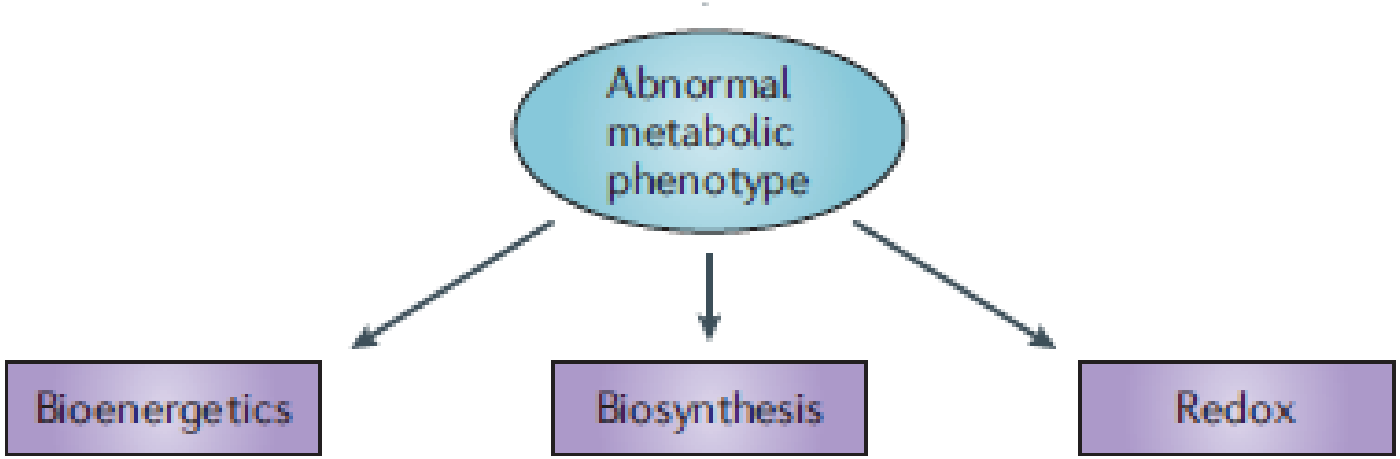
The free radicles **oxidize and cross-link** biomolecules they contact inside the cells. Therefore, the aging process of animals is partially because of the accumulating effect of the damage of ROS on cellular organelles.

NADPH is an important antioxidant molecule

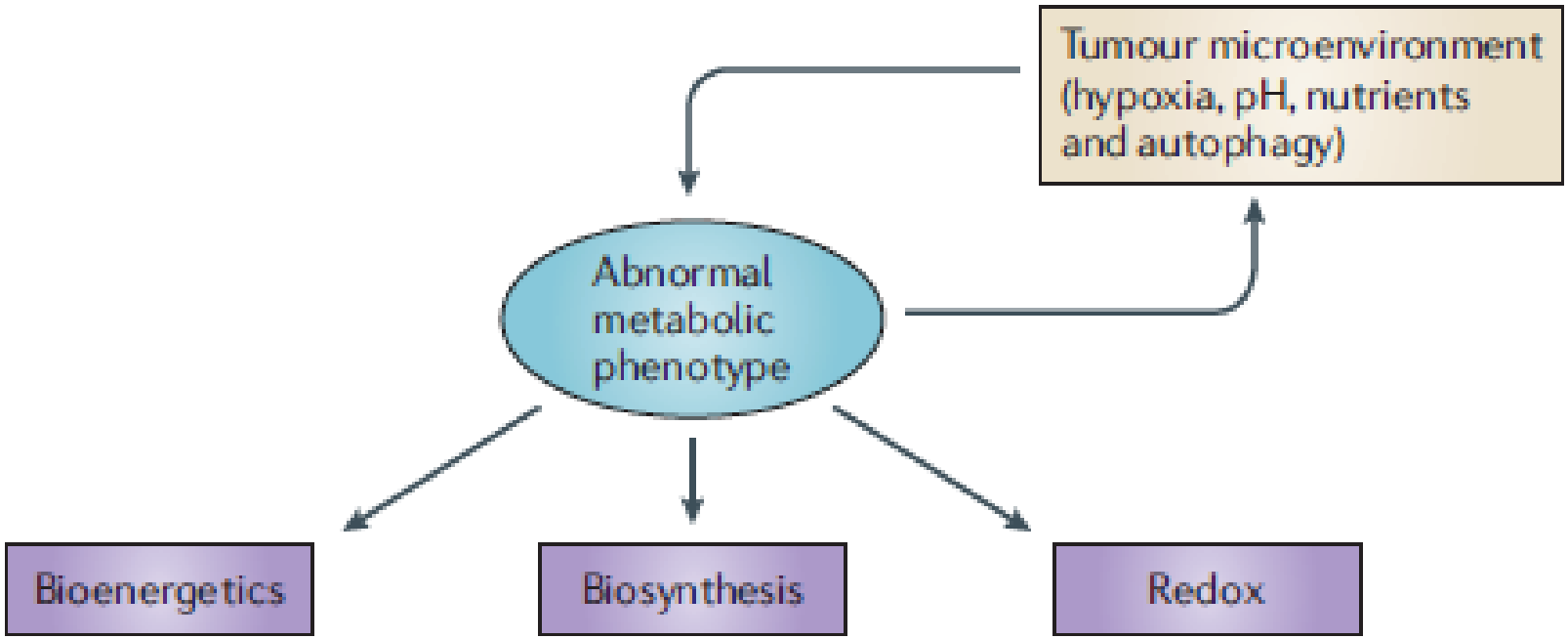
- Key reducing power in the antioxidant pathways.



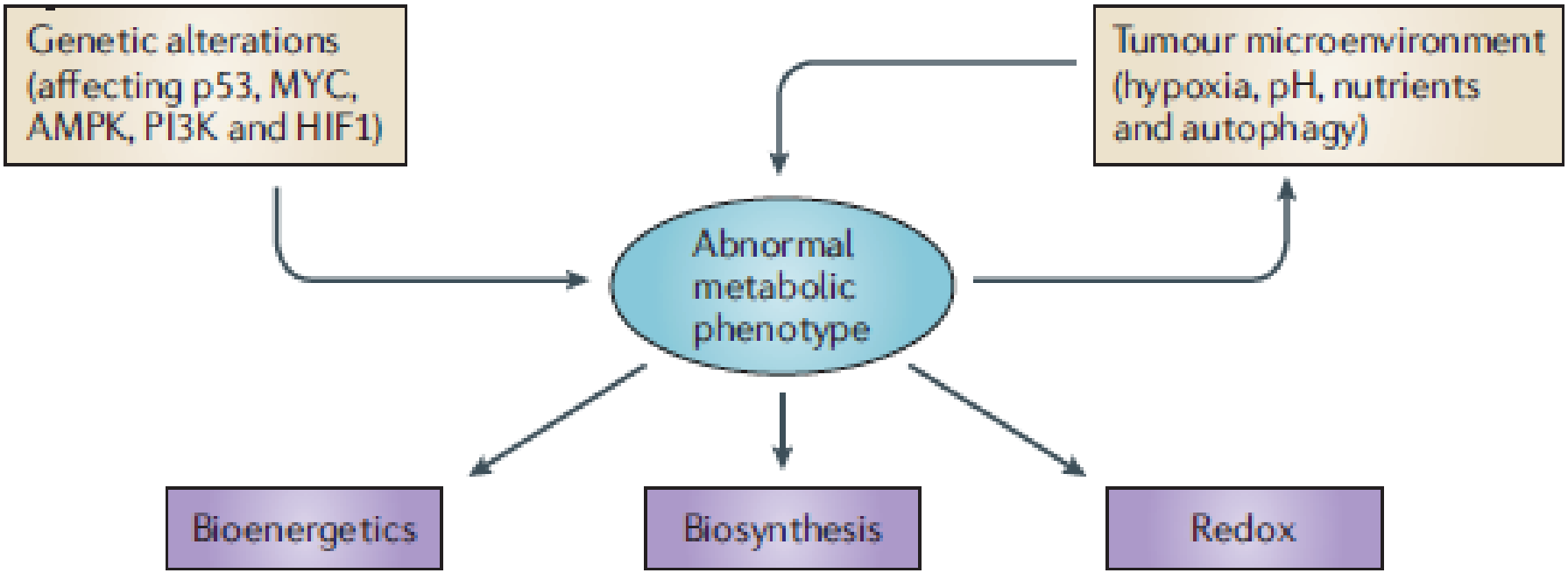
Summary


Abnormal
metabolic
phenotype
Bioenergetics
Biosynthesis
Redox

Cancer metabolism reflects the interaction between cancer cells and the microenvironment



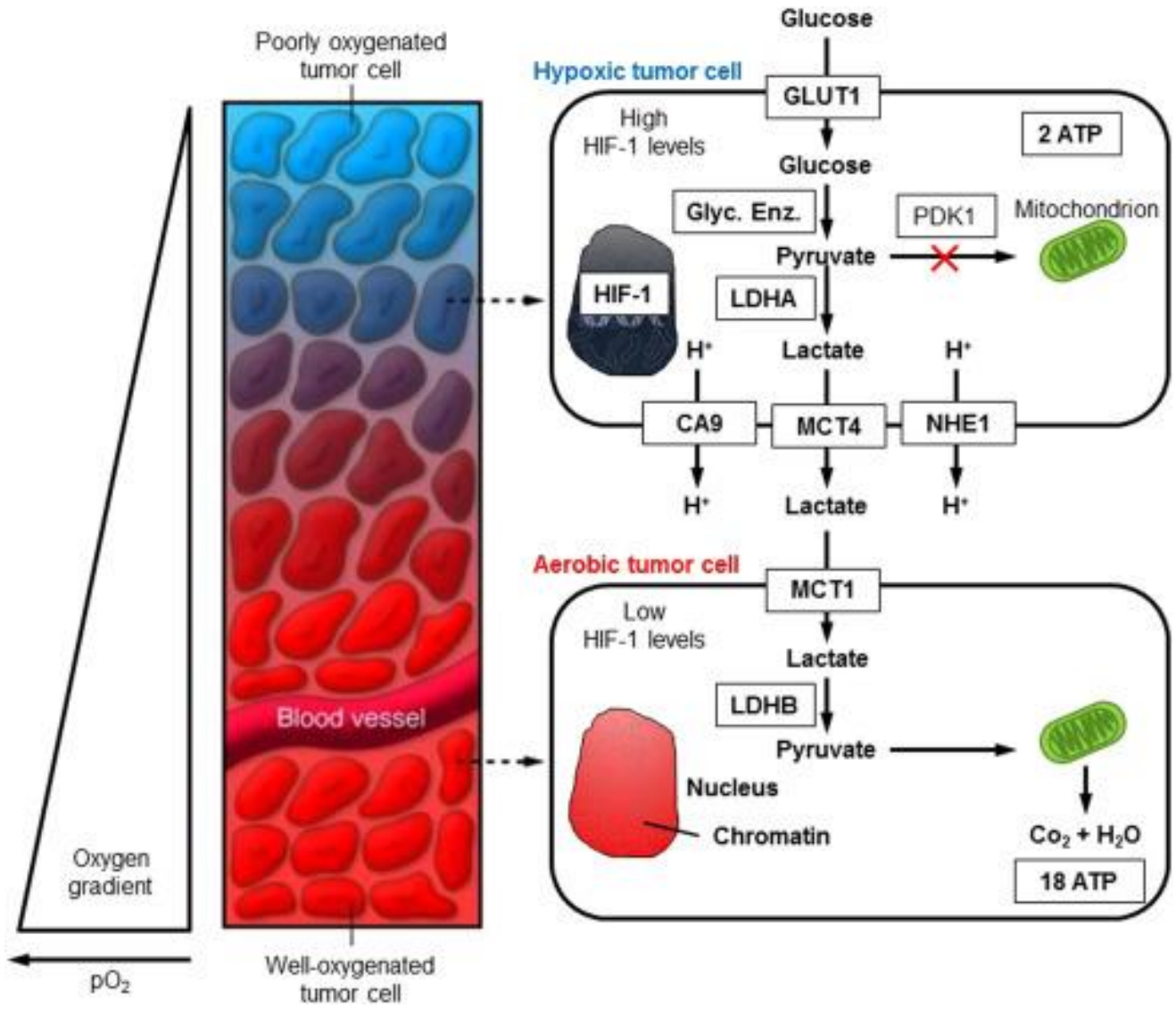
Aberrant signaling pathways regulate cancer metabolism



Summary of objectives III

- Cancer cells also upregulate the citric acid cycle.
- Glutaminolysis is an important driving power for citric acid cycle in cancer cells.
- NADPH is an important molecule.

The complexity of cancer metabolism

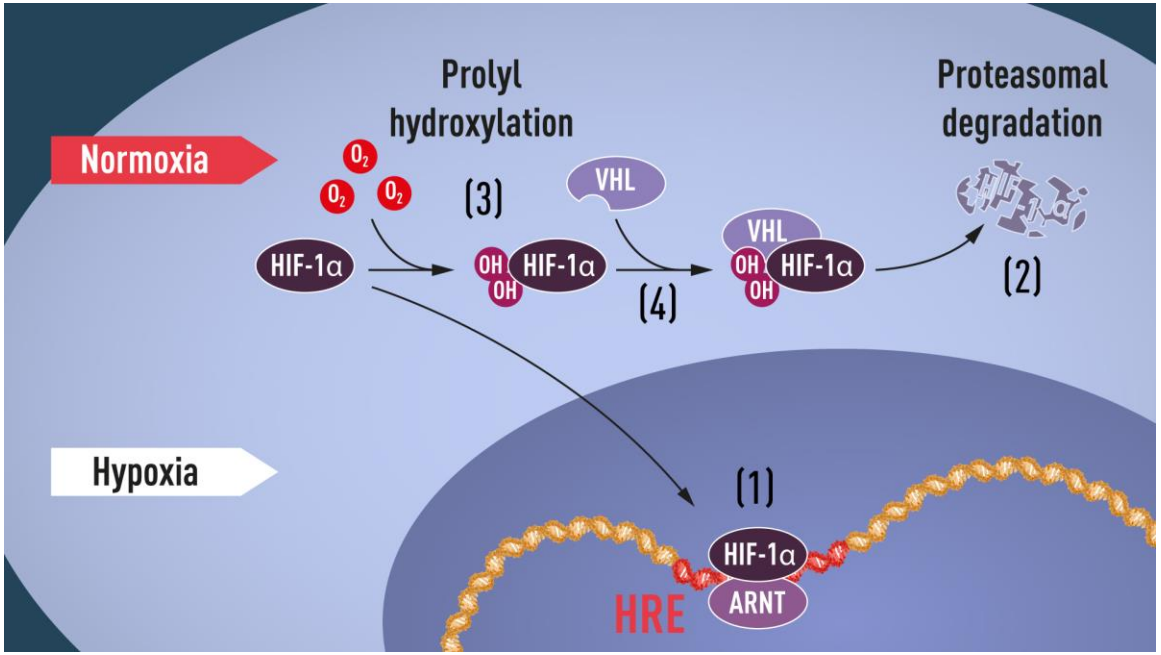


Sensing the availability of oxygen

HIF1-α as the cellular sensor of oxygen.

The target genes of HIF1-α include ones that promote angiogenesis.

For example:
Vascular endothelial growth factor (VEGF).



The fundamental research

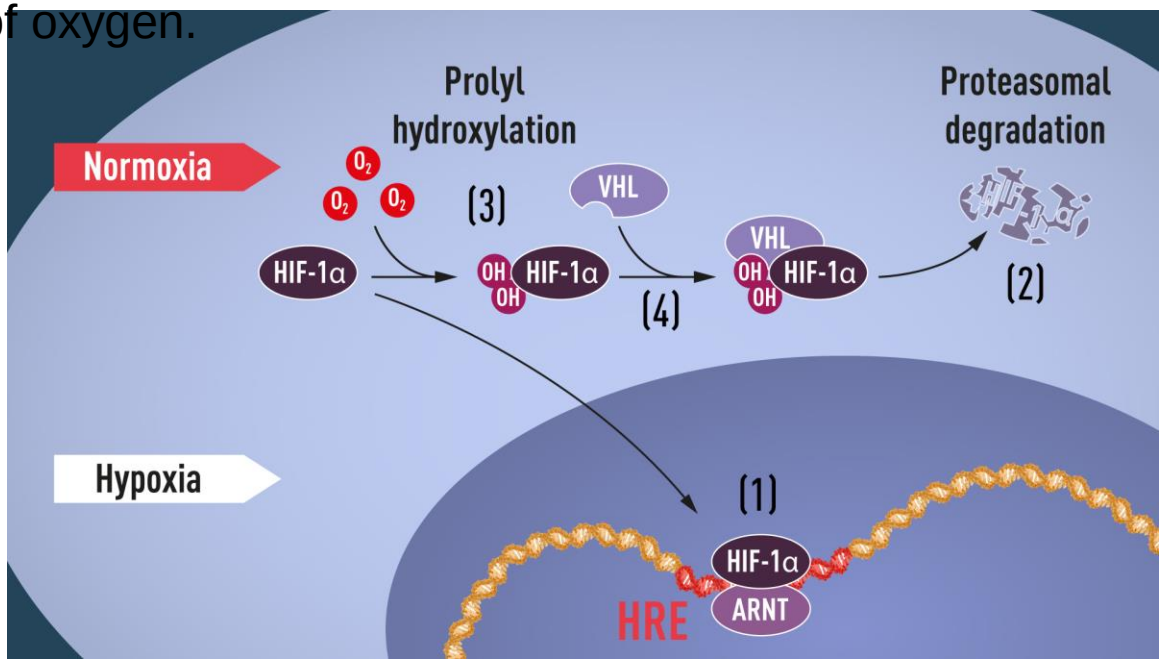
HIF1-α as the cellular sensor of oxygen.

William G. Kaelin Ill. Niklas Elmedhed. © Nobel Media.

Sir Peter J. Ratcliffe Ill. Niklas Elmedhed. © Nobel Media.

Gregg L. Semenza Ill. Niklas Elmedhed. © Nobel Media.

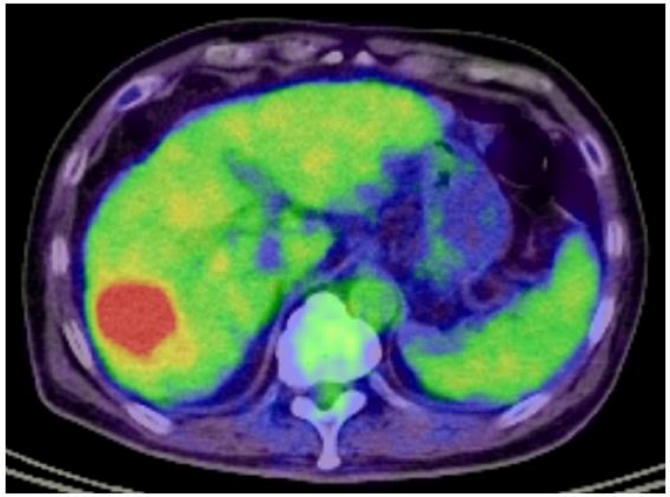
"for their discoveries of how cells sense and adapt to oxygen availability"



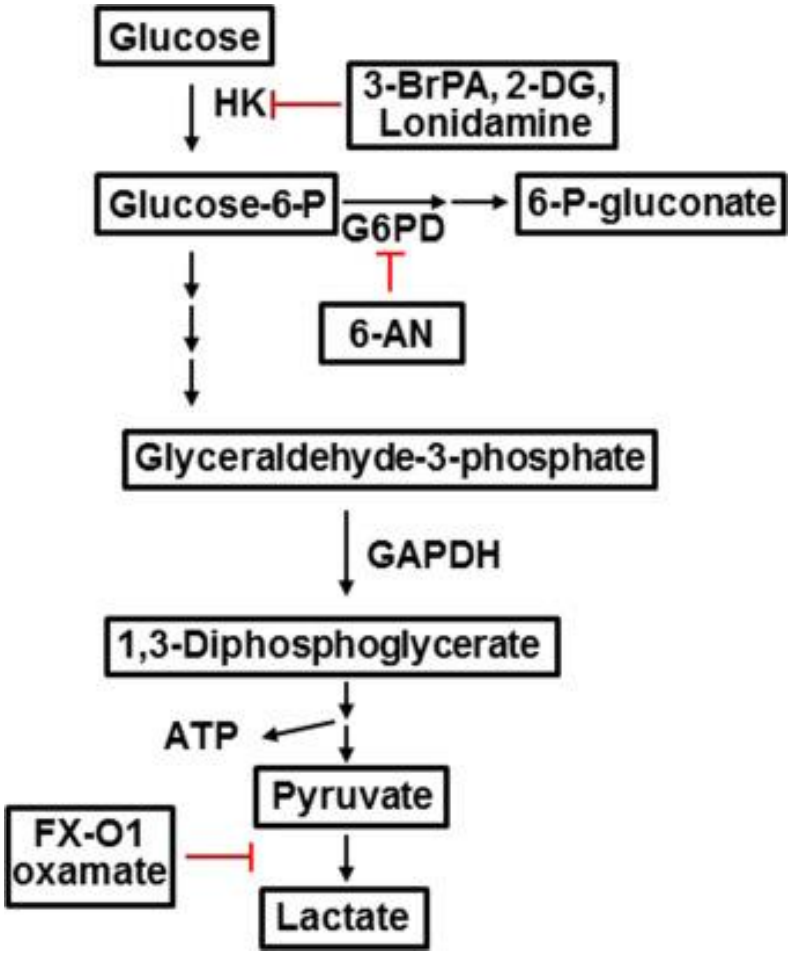
Cancer metabolism can also be utilized for diagnosis and monitoring

Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging

- A radioactive glucose analogue is used to detect regions of high glucose uptake.
- Highly effective for the identification and monitoring of many tumour types.



Targeting metabolism may help treat cancer



Summary of objectives IV

- Oxygen availability plays a primary role in the complex cancer metabolism.
- HIF1-α signaling is important in cancer metabolism.
- Diagnostics/therapeutics can be developed targeting cancer metabolism.

Focus of my contents

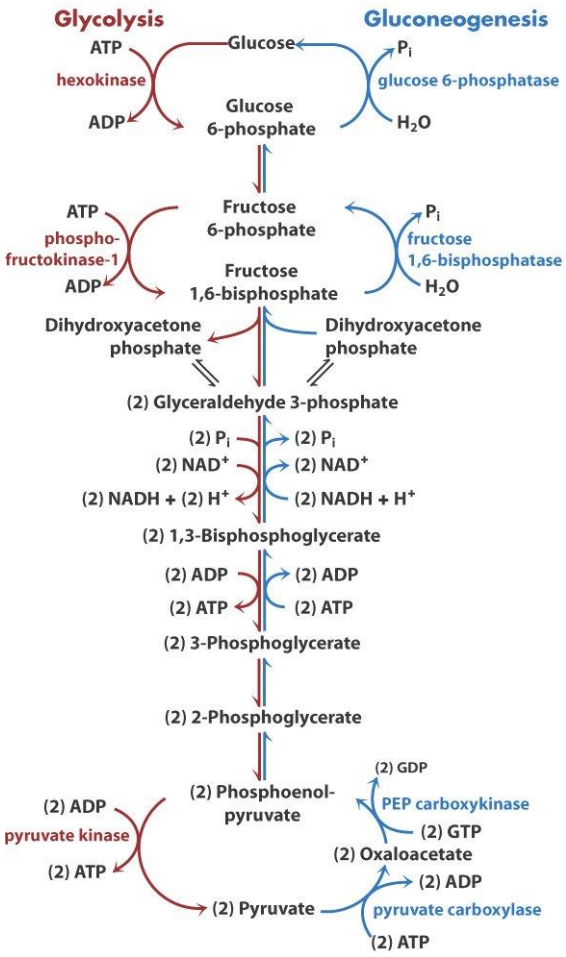
- Key features
- Regulation

Questions from students

I thought that the best regulation of some pathway is to inhibit the first reaction. However, we have a lot of enzymes that are regulated and located in the middle of the pathway. What will happen to the products of this enzymes? If inhibition of the enzyme located in the middle of the pathway occurred, the product will just proceed and finish cycle? Or it will be converted to something else?

Gluconeogenesis and glycolysis are similar but not identical

- The two processes are not identical pathways running in opposite directions.
- 7 out of 10 enzymatic reactions in gluconeogenesis are the reverse of glycolytic reactions.
- Remember that three reactions in glycolysis are irreversible in vivo and thus cannot be used in gluconeogenesis.



Step	*Reaction*	*Enzyme*
1	Glucose + ATP → glucose 6-phosphate + ADP + H^+	Hexokinase
3	Fructose 6-phosphate + ATP → fructose 1,6-bisphosphate + ADP + H^+	Phosphofructokinase
10	Phosphoenolpyruvate + ADP + H^+ → pyruvate + ATP	Pyruvate kinase

- Could you explain again why the body needs to make glucose when it is energetically expensive?

Comparing glycolysis and gluconeogenesis

Gluconeogenesis

2 Pyruvate + 2 NADH + 4 ATP + 2 GTP + 6 H_2O + 2 H^+

→ Glucose + 2 NAD^+ + 4 ADP + 2 GDP + 6 P_i

under intracellular condition

ΔG = -16 kJ/mol

Glycolysis

Glucose + 2 ADP + 2 NAD^+ + 2 P_i

→ 2 Pyruvate + 2 NADH + 2 ATP + 2 H_2O + 2 H^+

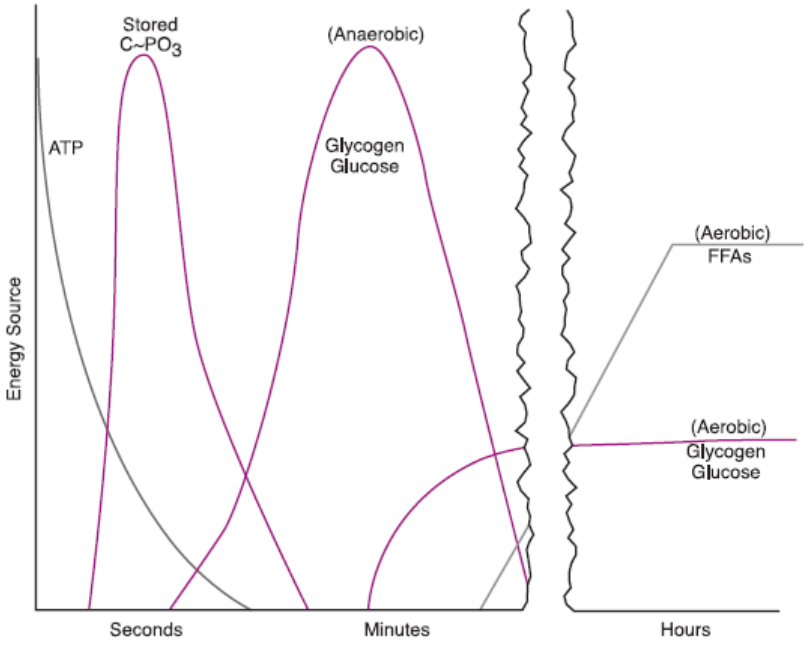
ΔG = -63 kJ/mol

It is necessary when the supply of glucose from the **glycogen** stores in muscles and the liver is low. It happens between meals, fasting and after vigorous exercise.

- Does normal metabolism happen during intensive exercising?

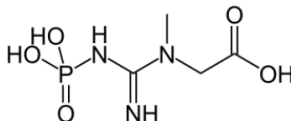
Exercise -- utilization of biofuels

- To generate energy, animals mobilize different types of biomolecules to provide the fuels for oxidation.
- The choice depends on the intensity and duration of exercise.



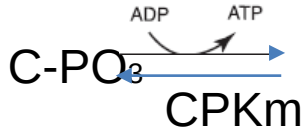
Creatine and creatine phosphate

- C-PO_3 facilitates the fast regeneration of ATP from ADP, with the function of creatine phosphokinase (CPKm).
- Muscle typically contains two to three times more C-PO_3 than ATP.
- As the aerobic phase is achieved, exercise can be continued for a longer period of time at a relatively constant, yet slower pace, supplied by high energy phosphates generated from oxidative phosphorylation.
- At times when the muscle is relaxed and demands for ATP are reduced. CPKm catalyzes the reverse reaction to form and store C-PO_3.



C-PO_3

C3PO



creatine

Thank you!