The Rest: Regenerating the C_4 Structure of Oxaloacetate

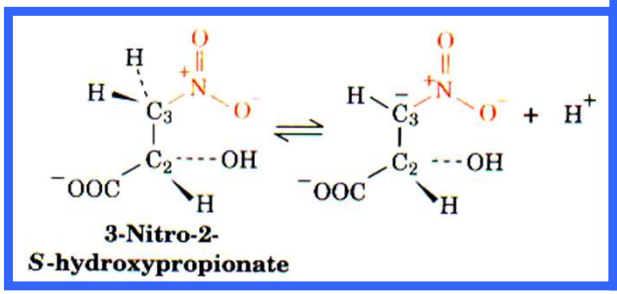
Oxidation of alcohols to aldehydes or ketones

⇒ Yields 3 ATPs in oxidative phosphorylation

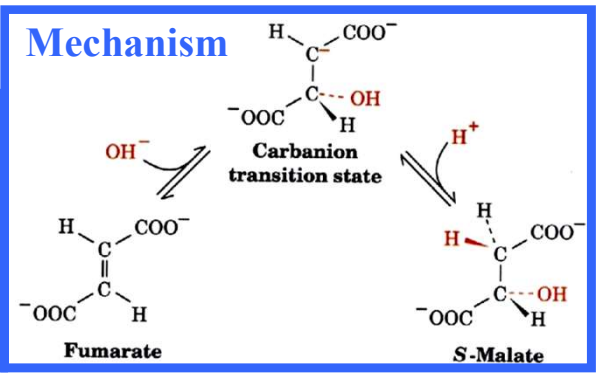
NADH + H^+

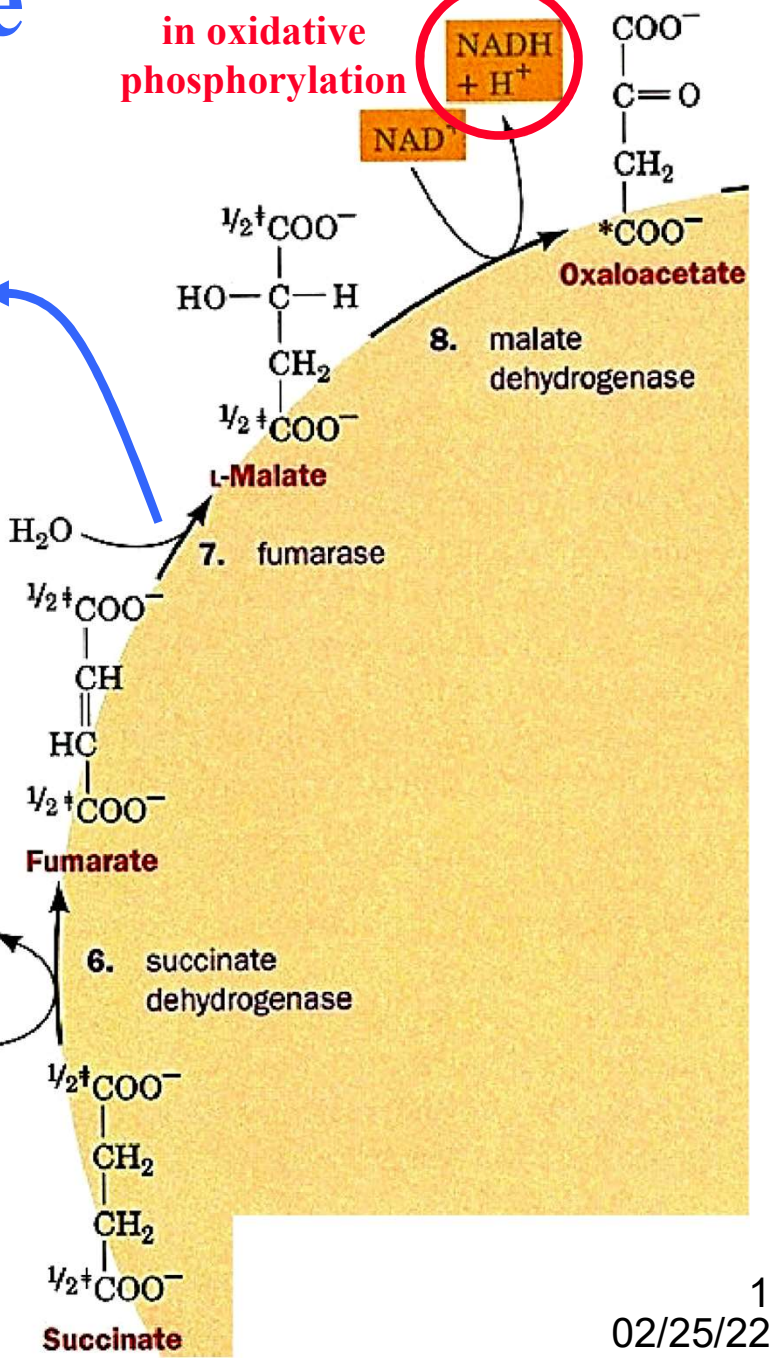
NAD$^+$

Evidence: Potent inhibitor



Mechanism

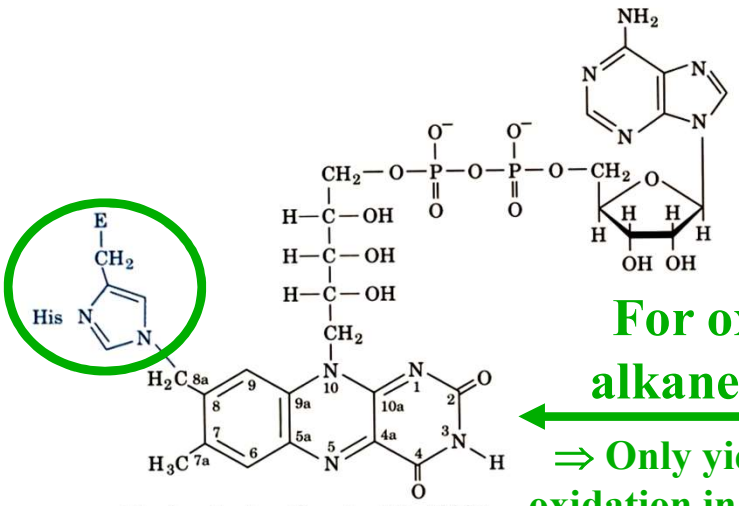




H_2O

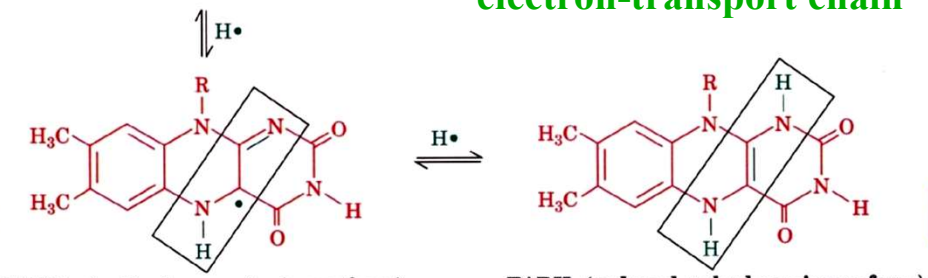
FADH$_2$

FAD



For oxidation of alkanes to alkenes

⇒ Only yields 2 ATPs upon oxidation in membrane-bound electron-transport chain

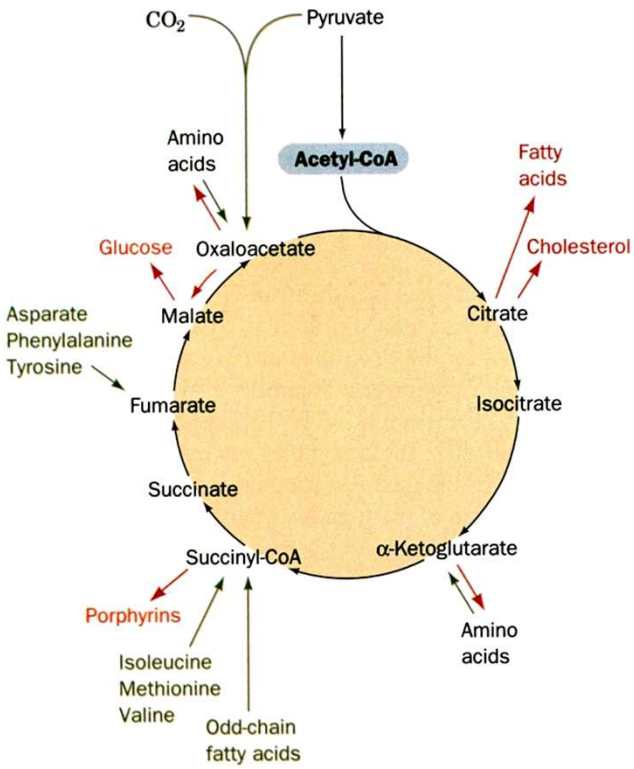


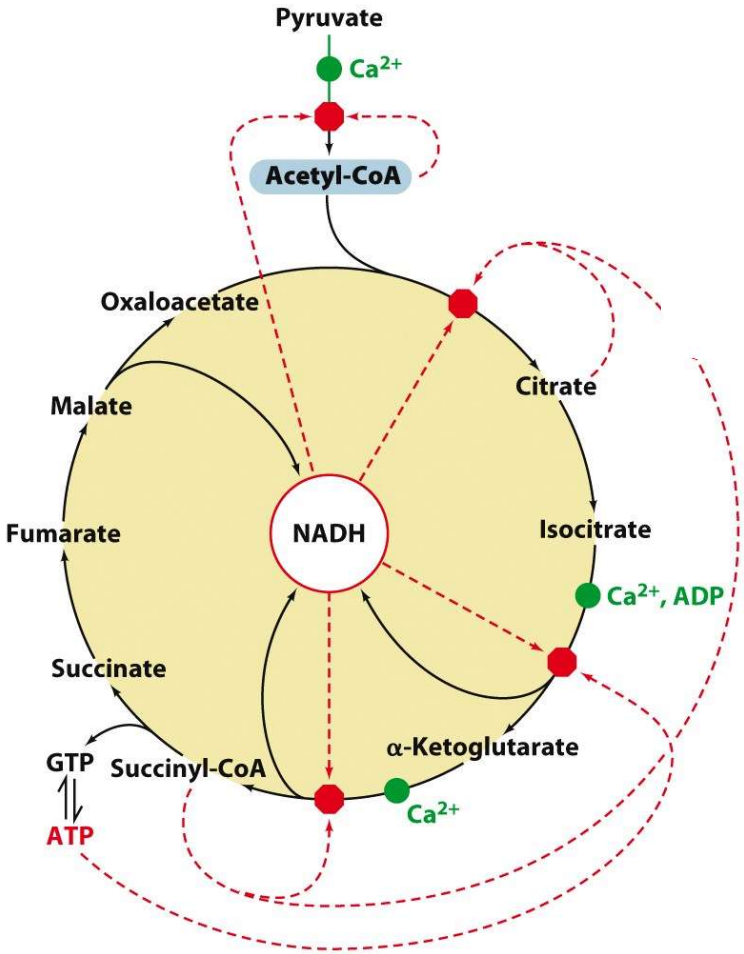
Rate-Limiting Steps, Regulation, Integration

TABLE 19-2. Standard Free Energy Changes ($\Delta G^{\circ\prime}$) and Physiological Free Energy Changes (ΔG) of Citric Acid Cycle Reactions

Reaction	Enzyme	$\Delta G^{\circ\prime}$ (kJ · mol^{-1})	ΔG (kJ · mol^{-1})
1	Citrate synthase	−31.5	Negative
2	Aconitase	~5	~0
3	Isocitrate dehydrogenase	−21	Negative
4	α-Ketoglutarate dehydrogenase multienzyme complex	−33	Negative
5	Succinyl-CoA synthetase	−2.1	~0
6	Succinate dehydrogenase	+6	~0
7	Fumarase	−3.4	~0
8	Malate dehydrogenase	+29.7	~0

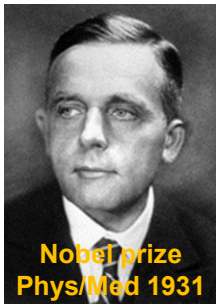
Far from equilibrium ⇒ most likely regulated





Regulation by
a. substrate availability (e.g., acetyl-CoA),
b. product inhibition (e.g., NADH),
c. inhibition by cycle intermediates (e.g., citrate, succinyl-CoA), and
d. allosteric control (e.g., Ca^{2+}, ADP)

The citric acid cycle is amphibolic = both catabolic and anabolic

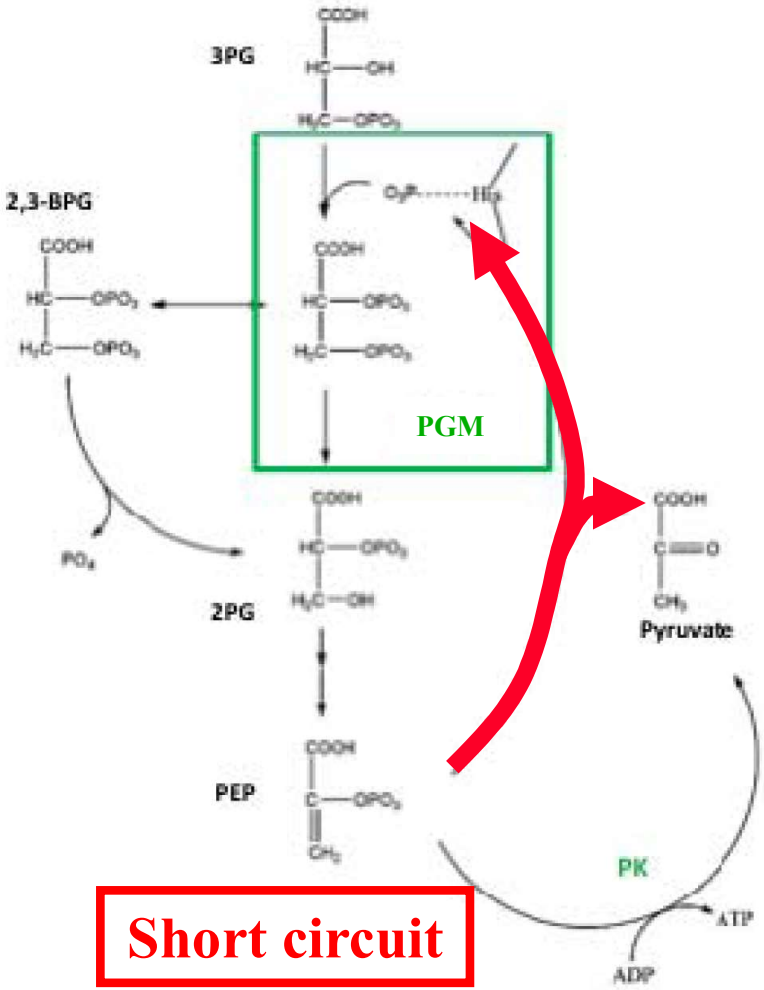


Otto Warburg explained: Cancer cells reprogram to skip the TCA Cycle

Evidence for an Alternative Glycolytic Pathway in Rapidly Proliferating Cells

Matthew G. Vander Heiden,[1,2,3]* Jason W. Locasale,[2,3] Kenneth D. Swanson,[2] Hadar Sharfi,[2] Greg J. Heffron,[4] Daniel Amador-Noguez,[5] Heather R. Christofk,[2] Gerhard Wagner,[4] Joshua D. Rabinowitz,[5] John M. Asara,[2] Lewis C. Cantley[2,3]†

1492 17 SEPTEMBER 2010 VOL 329 SCIENCE www.sciencemag.org



➢ **Warburg's Observation:** Cancer cells need a lot of anabolism and thus glycolysis to produce pyruvate as anabolic intermediate, but often have reduced pyruvate kinase (PK) activity – how?

➢ **Modern Answer:** In cancer cells PEP's phosphate transfers to phosphoglycerate mutase (PGM) where it eventually hydrolyses so that the cell avoids producing ATP from PEP, which would allosterically downregulate glycolysis!

One possibility for the Why

Overflow metabolism in *Escherichia coli* results from efficient proteome allocation

Markus Basan[1,2]*, Sheng Hui[1]*, Hiroyuki Okano[1,3], Zhongge Zhang[3], Yang Shen[3], James R. Williamson[4] & Terence Hwa[1,3,5]

Overflow metabolism refers to the seemingly wasteful strategy in which cells use fermentation instead of the more efficient respiration to generate energy, despite the availability of oxygen. Known as the Warburg effect in the context of cancer growth, this phenomenon occurs ubiquitously for fast-growing cells, including bacteria, fungi and mammalian cells, but its origin has remained unclear despite decades of research. Here we study metabolic overflow in *Escherichia coli*, and show that it is a global physiological response used to cope with changing proteomic demands of energy biogenesis and biomass synthesis under different growth conditions. A simple model of proteomic resource allocation can quantitatively account for all of the observed behaviours, and accurately predict responses to new perturbations. The key hypothesis of the model, that the proteome cost of energy biogenesis by respiration exceeds that by fermentation, is quantitatively confirmed by direct measurement of protein abundances via quantitative mass spectrometry.

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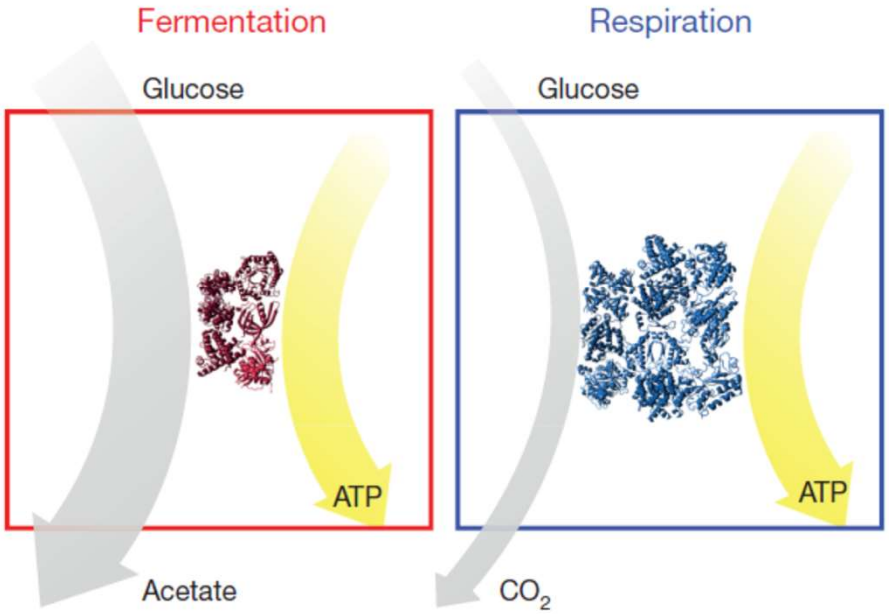
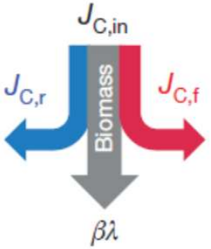
Model summary



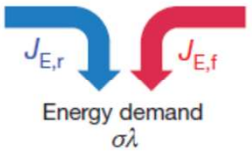
Carbon balance

$$J_{C,in} = \beta\lambda + J_{C,f} + J_{C,r}$$



Energy balance

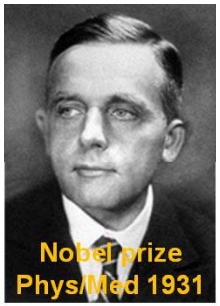
$$J_{E,f} + J_{E,r} = \sigma\lambda$$



Proteome balance

$$\phi_f + \phi_r = 1 - (\phi_0 + b\lambda)$$

em 451



But the Why is still controversial

TIBS 1211 No. of Pages 8 ARTICLE IN PRESS

Trends in Biochemical Sciences

Special Issue: Mitochondria & Metabolism

Opinion

The Warburg Effect: How Does it Benefit Cancer Cells?

Maria V. Liberti[1,2] and Jason W. Locasale[2,*]

Key Figure

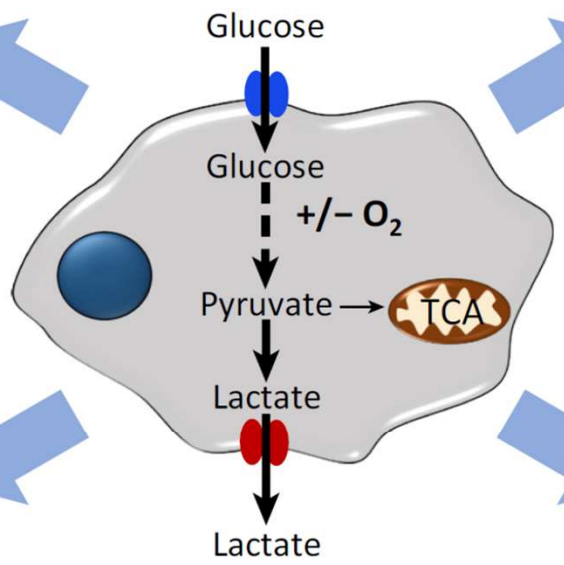
Summary of the Proposed Functions of the Warburg Effect

Rapid ATP synthesis

- **Proposal:** increases access to a limited energy source
- **Questions:**
  - Why are ATP demands not limiting for proliferation?
  - Why are there other mechanisms for rapid ATP synthesis?

Biosynthesis

- **Proposal:** promotes flux into biosynthetic pathways
- **Questions:**
  - Why is most glucose not retained?
  - Why does optimal biosynthesis not require aerobic glycolysis?



Function of the Warburg Effect?

Tumor microenvironment

- **Proposal**: enhances disruption of tissue architecture and immune cell evasion
- **Questions:**
  - Why do unicellular organisms and cultured cells use aerobic glycolysis?
  - Why do oncogenes induce the Warburg Effect cell intrinsically?

Cell signaling

- **Proposal**: allows for signal transduction through ROS and/or chromatin modulation
- **Questions**:
  - Why is the specificity unclear?
  - Why would metabolite levels be influenced by flux?

Trends in Biochemical Sciences

Figure 2. The Warburg Effect is defined as an increase in the rate of glucose uptake and preferential production of lactate, even in the presence of oxygen. Each of these functions has been hypothesized to be the function of the Warburg Effect. Abbreviations: ROS, reactive oxygen species; TCA, tricarboxylic acid cycle.

Chapter 21: What have we learned?

☺ **Priming the pump: The pyruvate dehydrogenase multienzyme complex and its dynamic mechanism**

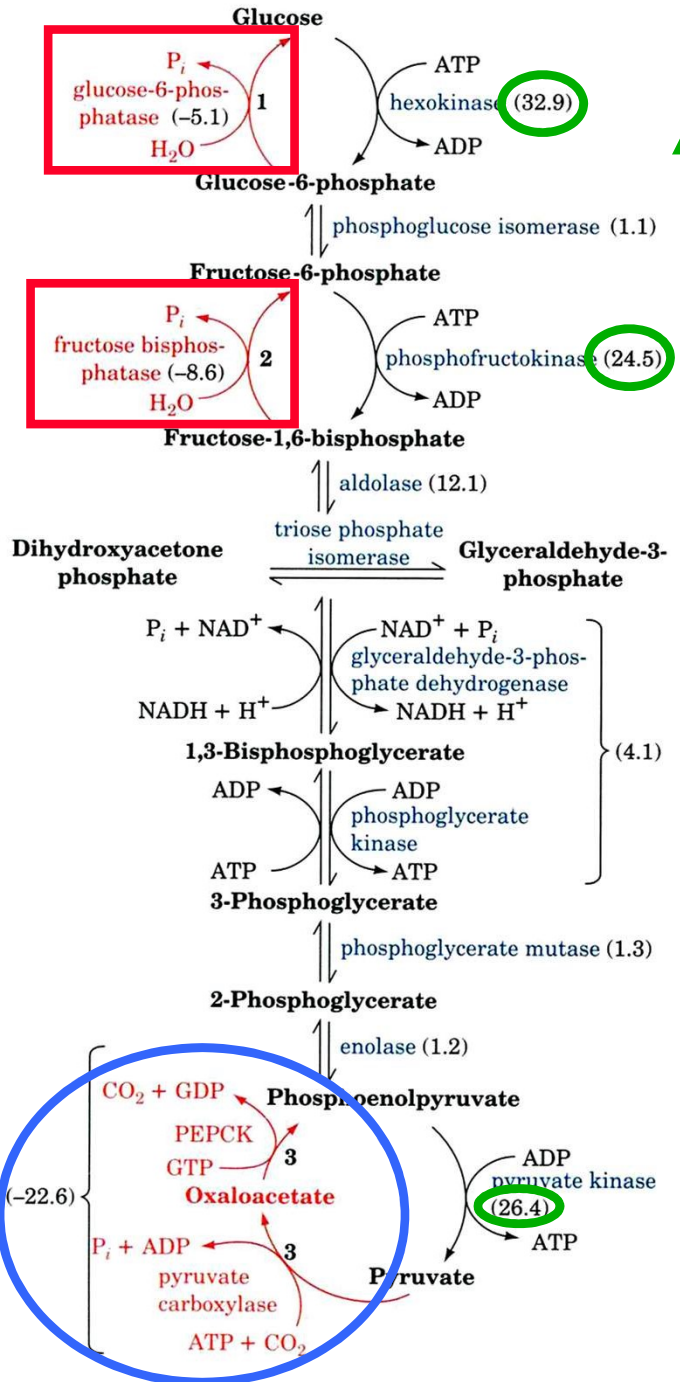
☺ **The citric acid (or TCA) cycle: The major players and their mechanisms (citrate synthase, aconitase, isocitrate dehydrogenase, succinyl-CoA synthetase, fumarase)**

☺ **Regulation and amphibolic nature of the citric acid cycle**

☺ **The Warburg effect in rapidly growing cells – still not fully resolved**

Gluconeogenesis: Making Glucose from Scratch

Voet & Voet, Chapter 23

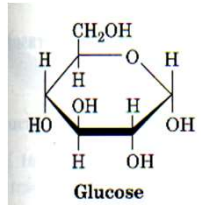


Gluconeogenesis is necessary to supply glucose after glycogen is used up when fasting (only 12-h supply in liver)

Most steps of glycolysis, when reversed, are endergonic, and three are real bone breakers (the irreversible steps of glycolysis)

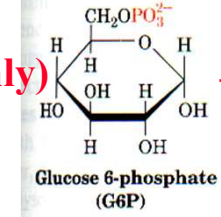
⇓

The easiest thing:
Hydrolyze a high-energy compound (at the expense of the ATP that was used to make it in the first place)

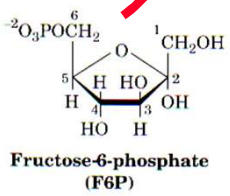


+ P_i

1: glucose-6-phosphatase (liver and kidney only) ΔG = - 5.1 kJ/mol

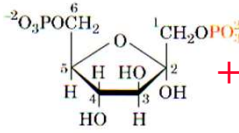


+H_2O



+ P_i

2: fructose-bisphosphatase ΔG = - 8.6 kJ/mol



+H_2O

Oxaloacetate: A Crucial Intermediate for Both Catabolic and Anabolic Pathways

Nearly all amino acids can be converted to oxaloacetate, but NOT leucine and lysine, or fatty acids (they yield only acetyl-CoA, which is not convertible in animals)