Other Carbohydrate Metabolic Pathways

CHEM 420 – Principles of Biochemistry
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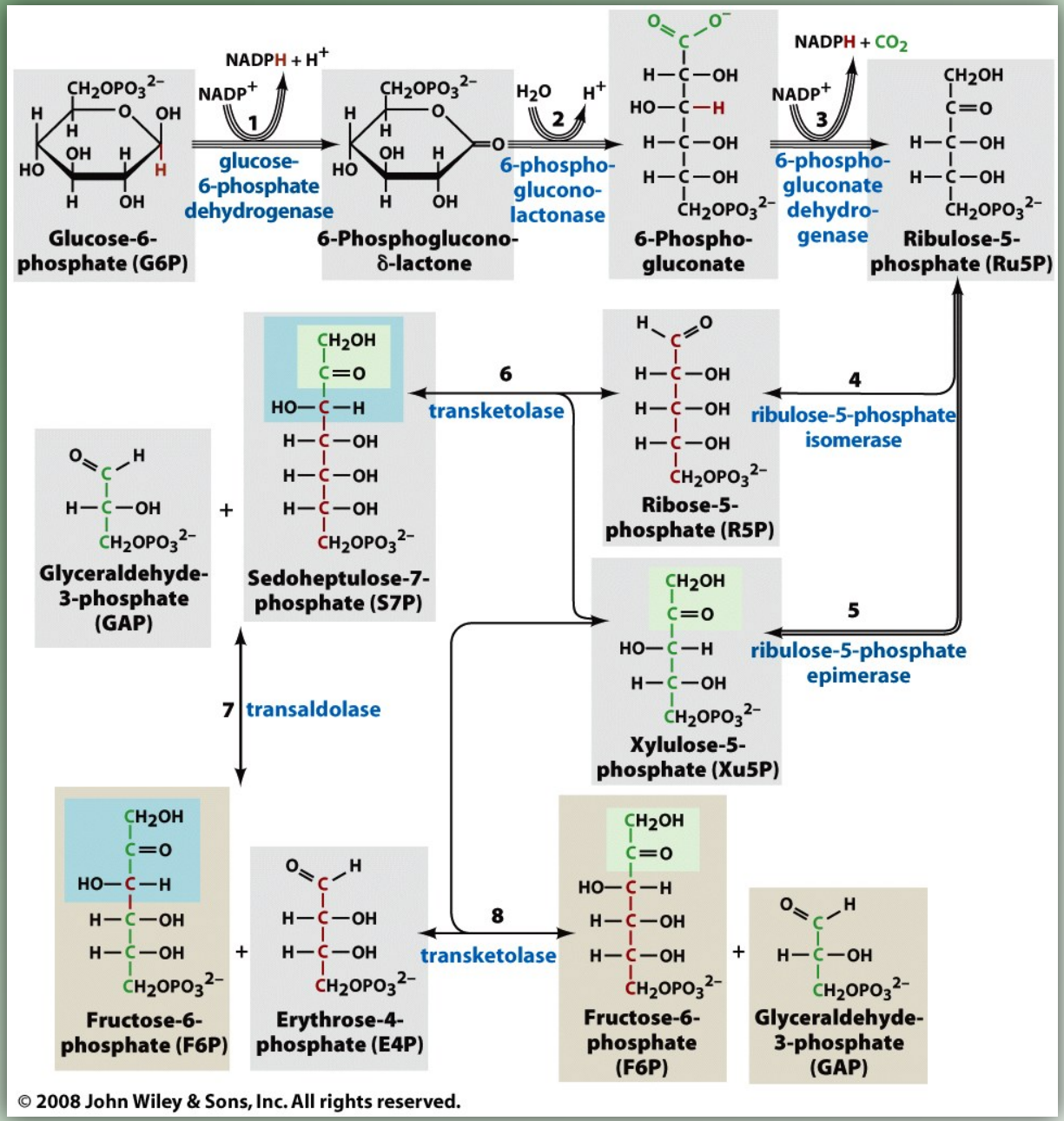
Chapter 23: Voet/Voet, *Biochemistry*, 2011
Fall 2015

November 11 & 13

Primary functions of the PPP

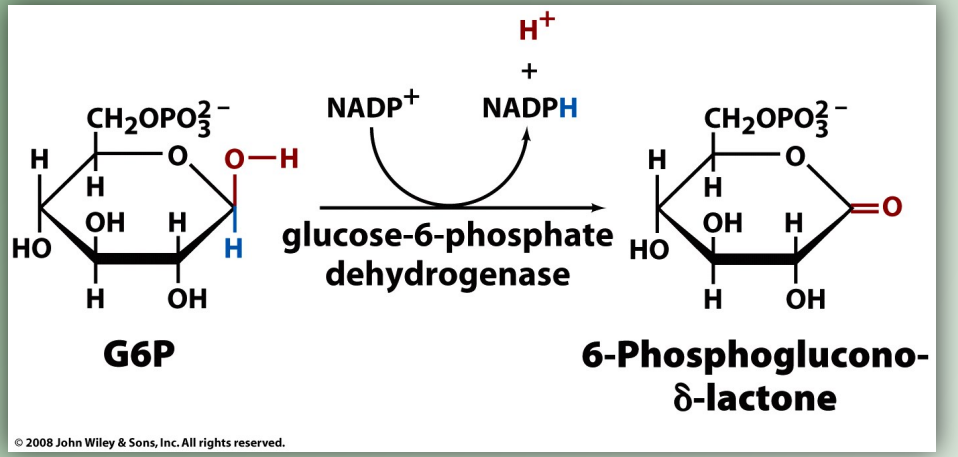
Production of NADPH; reducing equivalents that drive biosynthesis in the cytosol

Production of pentose phosphates for the synthesis of RNA and DNA



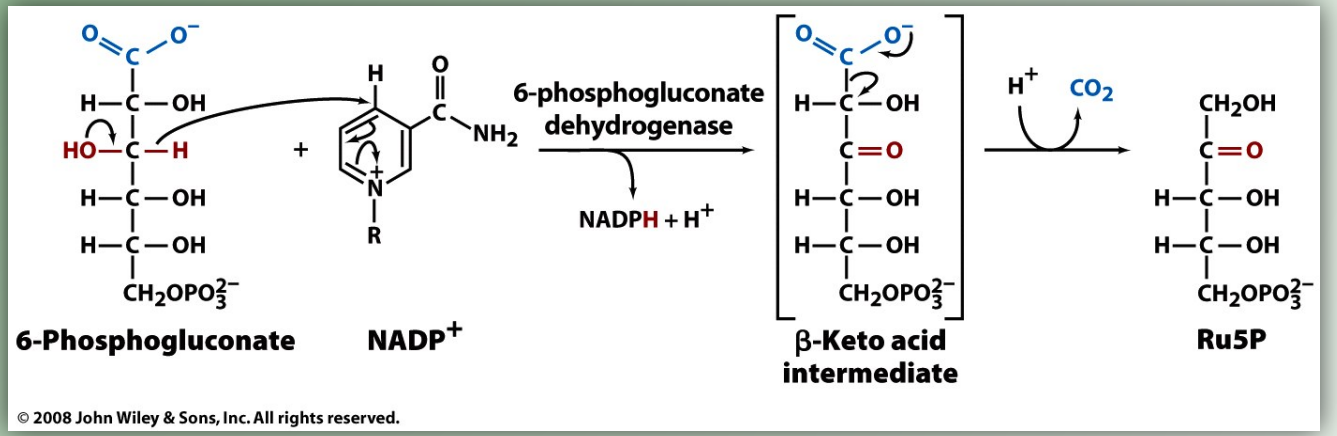
Overview of the pentose phosphate pathway

G6P dehydrogenase

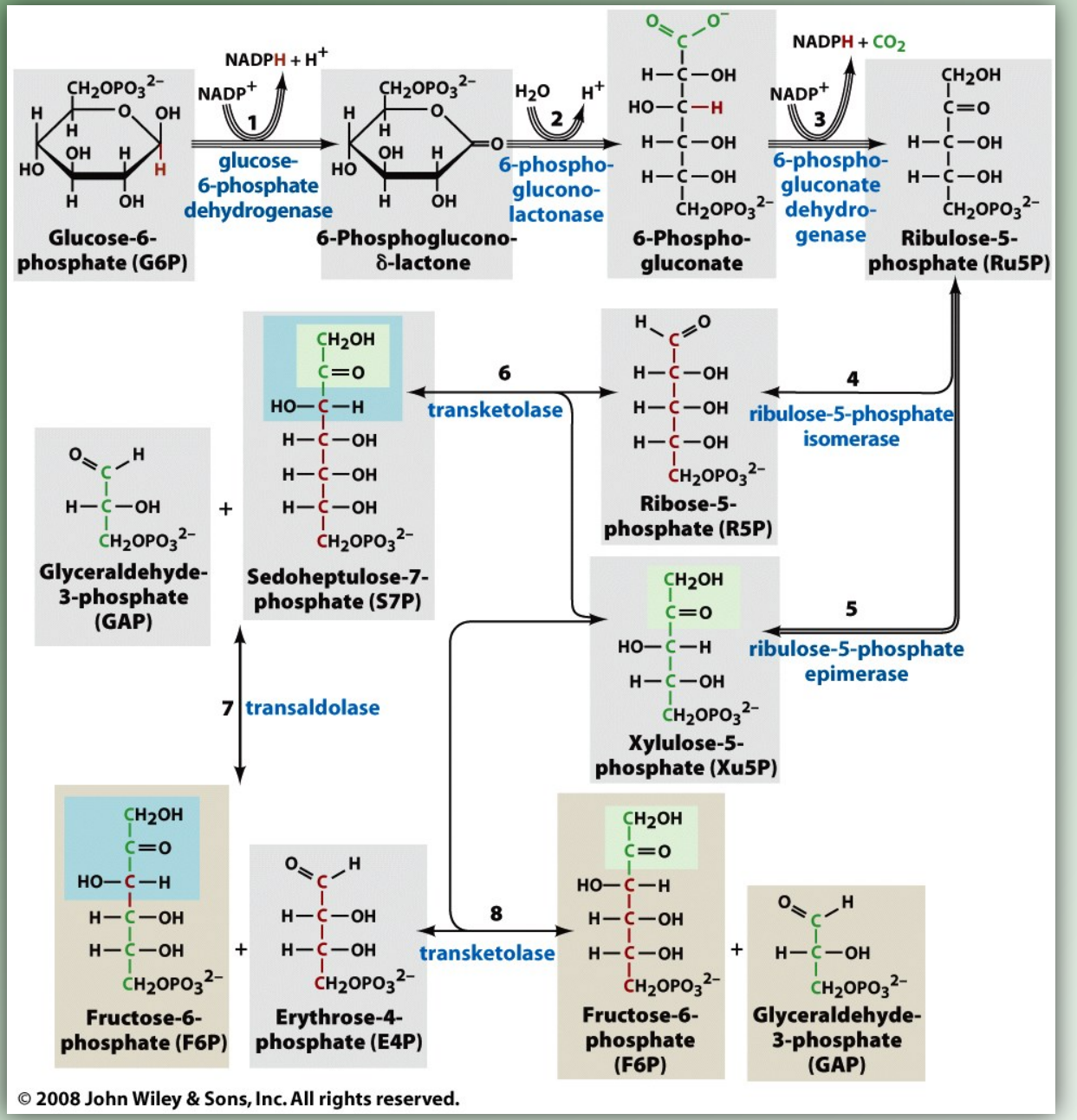


The lactone product needs to be hydrolyzed to the aldonate salt by 6-phosphogluconolactonase before the pathway can continue.

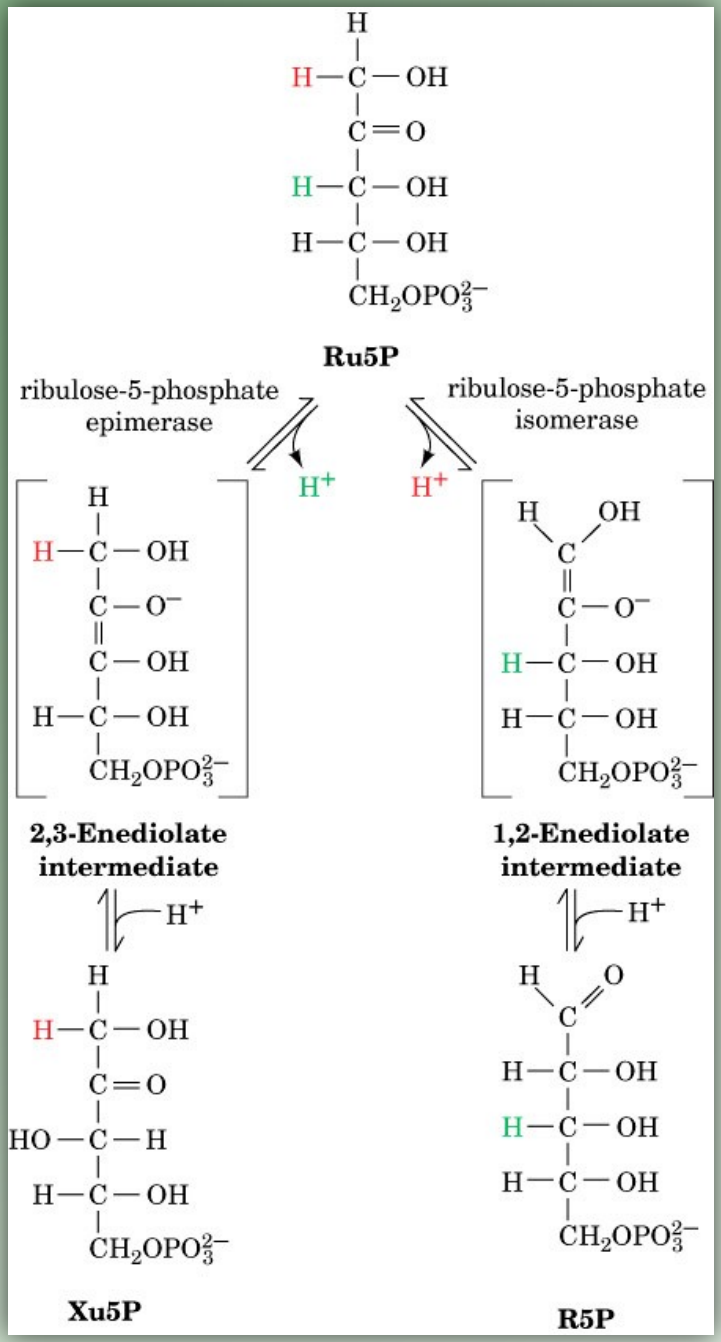
6-Phosphogluconate dehydrogenase



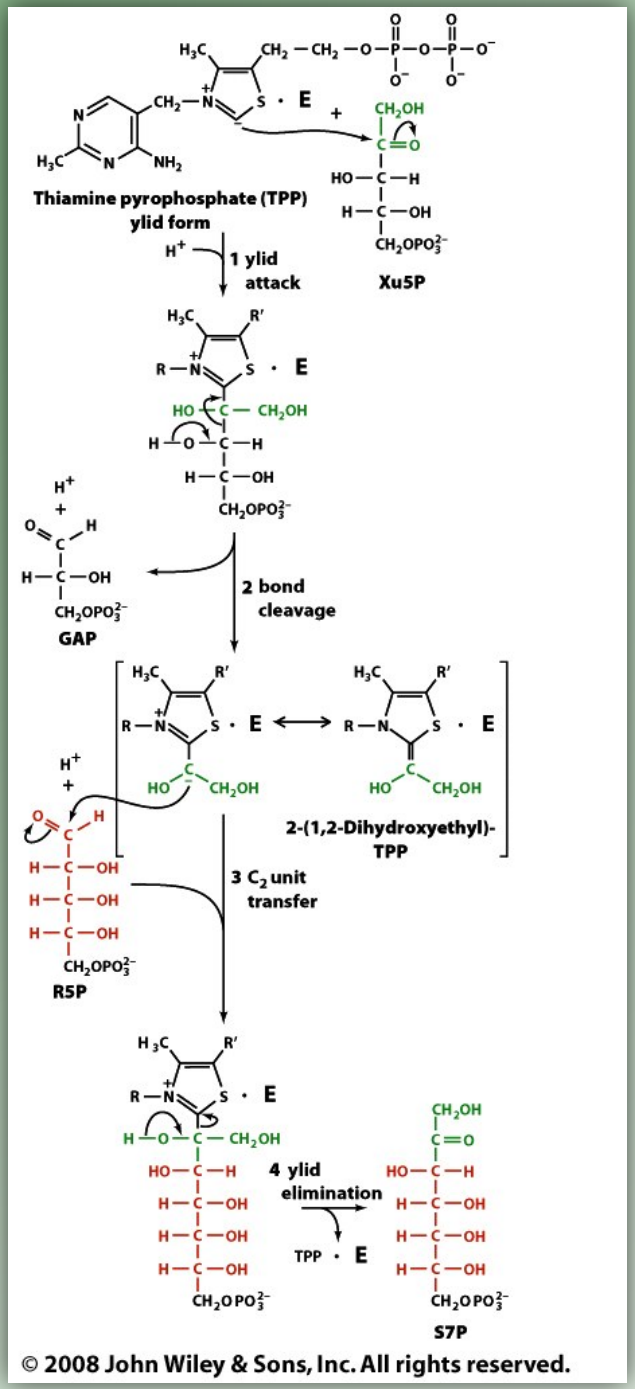
Oxidation at C3 to give the intermediate β-ketoacid, which undergoes subsequent decarboxylation.



Overview of the pentose phosphate pathway



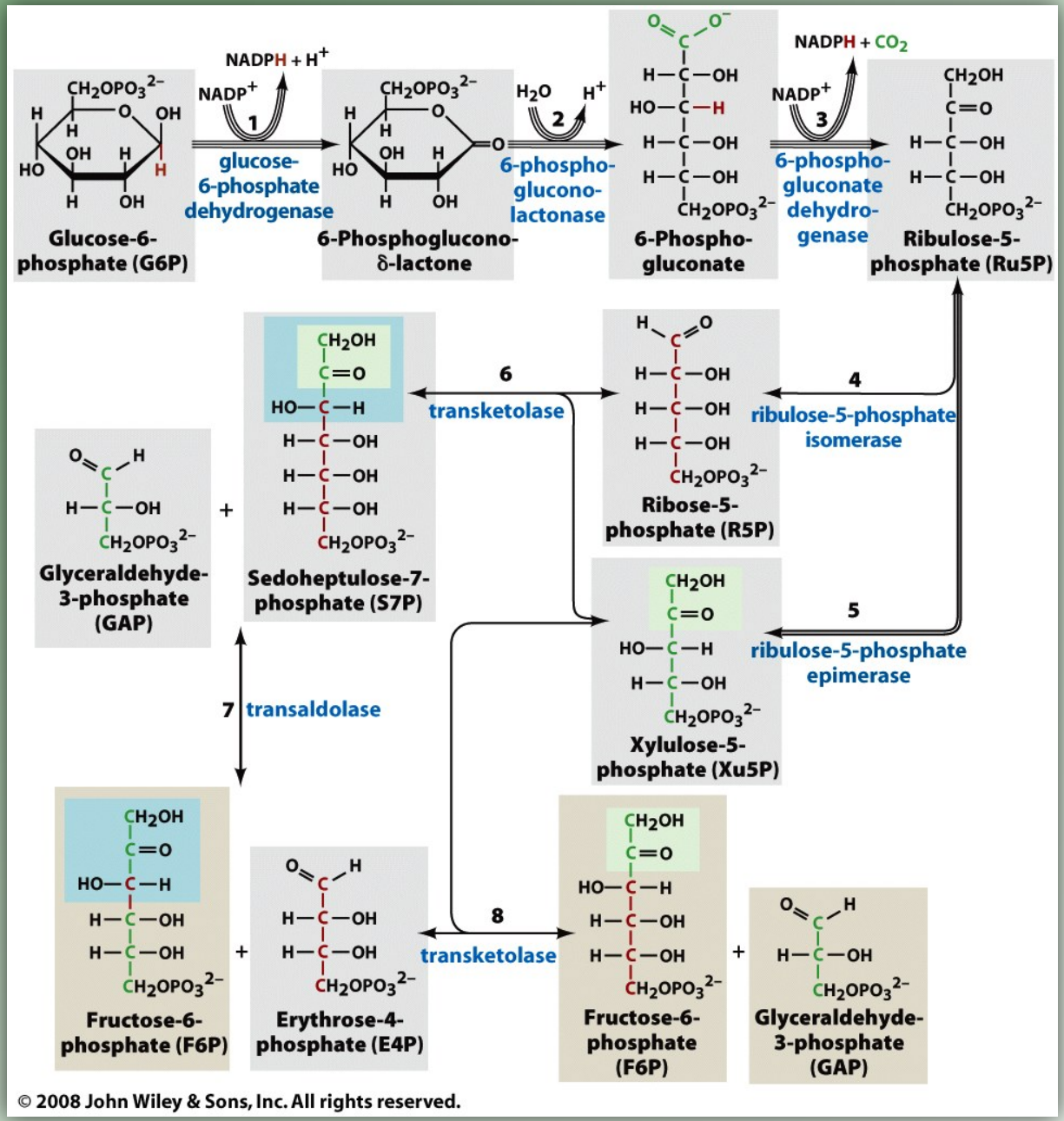
ribulose-5-phosphate isomerase and ribulose-5-phosphate epimerase



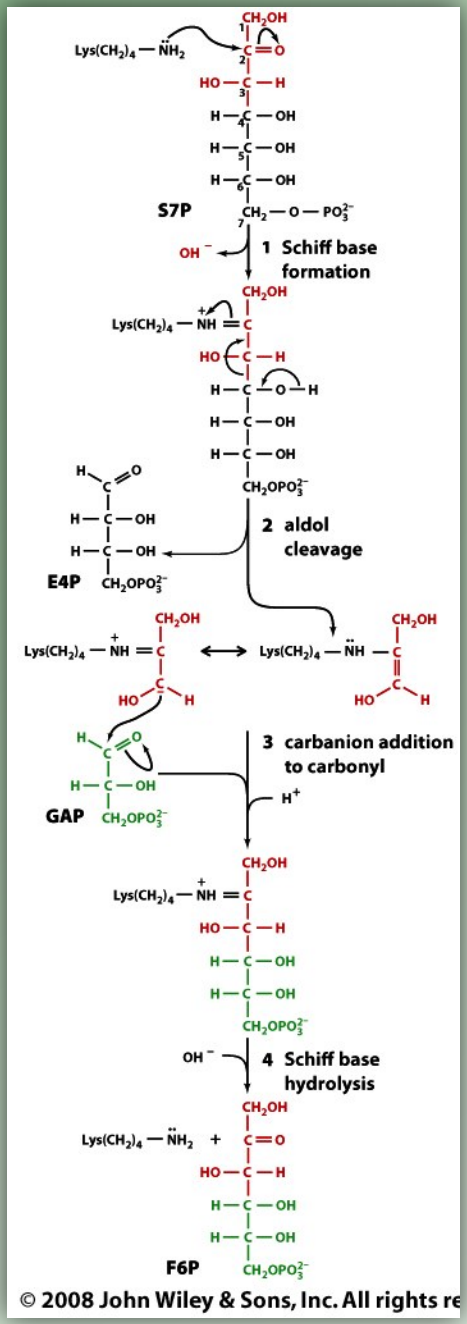
Transketolase reaction 1

(reaction of R5P and Xu5P to give G3P and S7P)

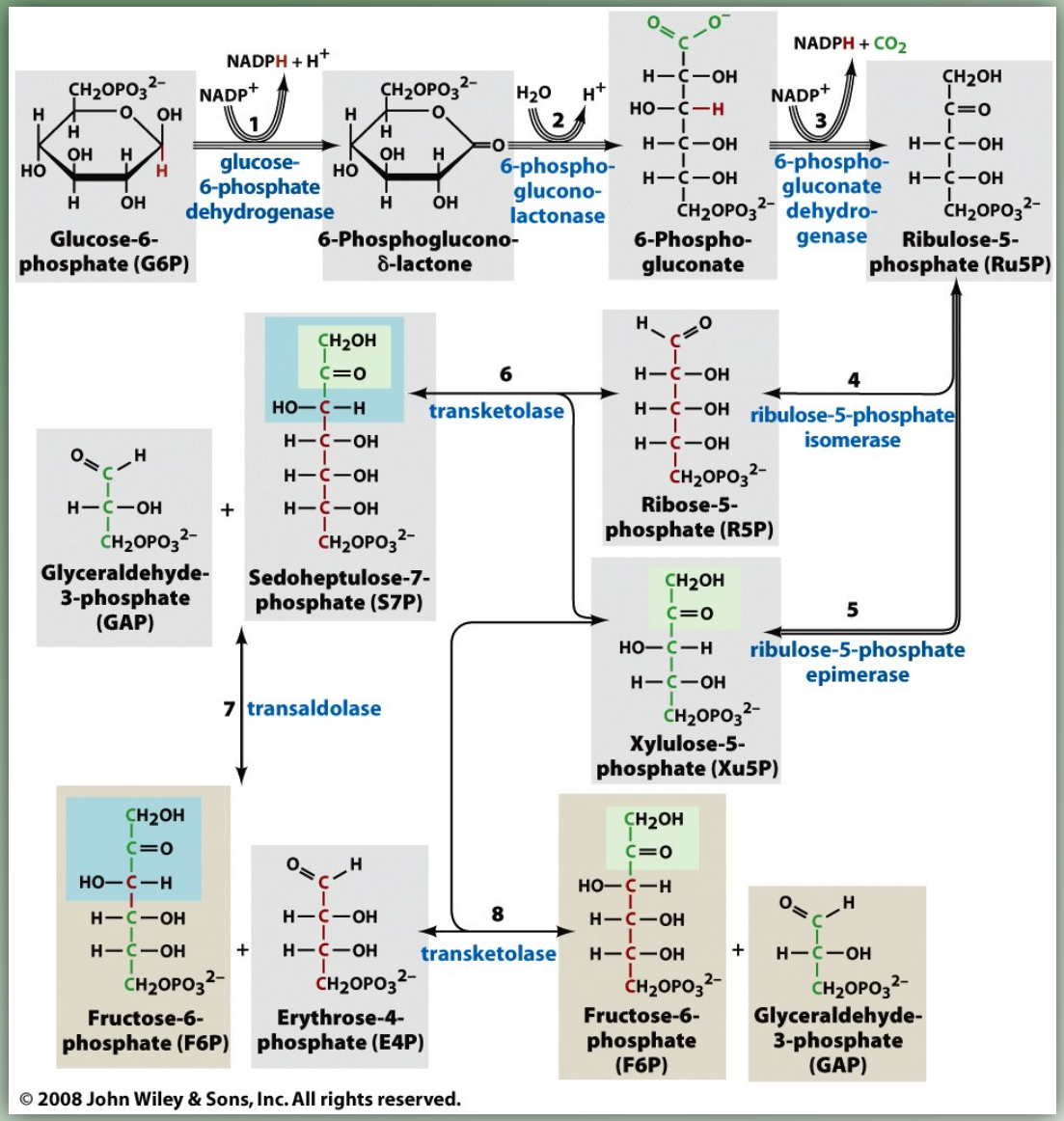
A TPP-requiring enzyme



Overview of the pentose phosphate pathway



The transaldolase reaction (reaction of G3P and S7P to give E4P and F6P)



Overview of the pentose phosphate pathway

Transketolase reaction 2 (reaction of E4P and Xu5P to give F6P and G3P)

A TPP-requiring enzyme

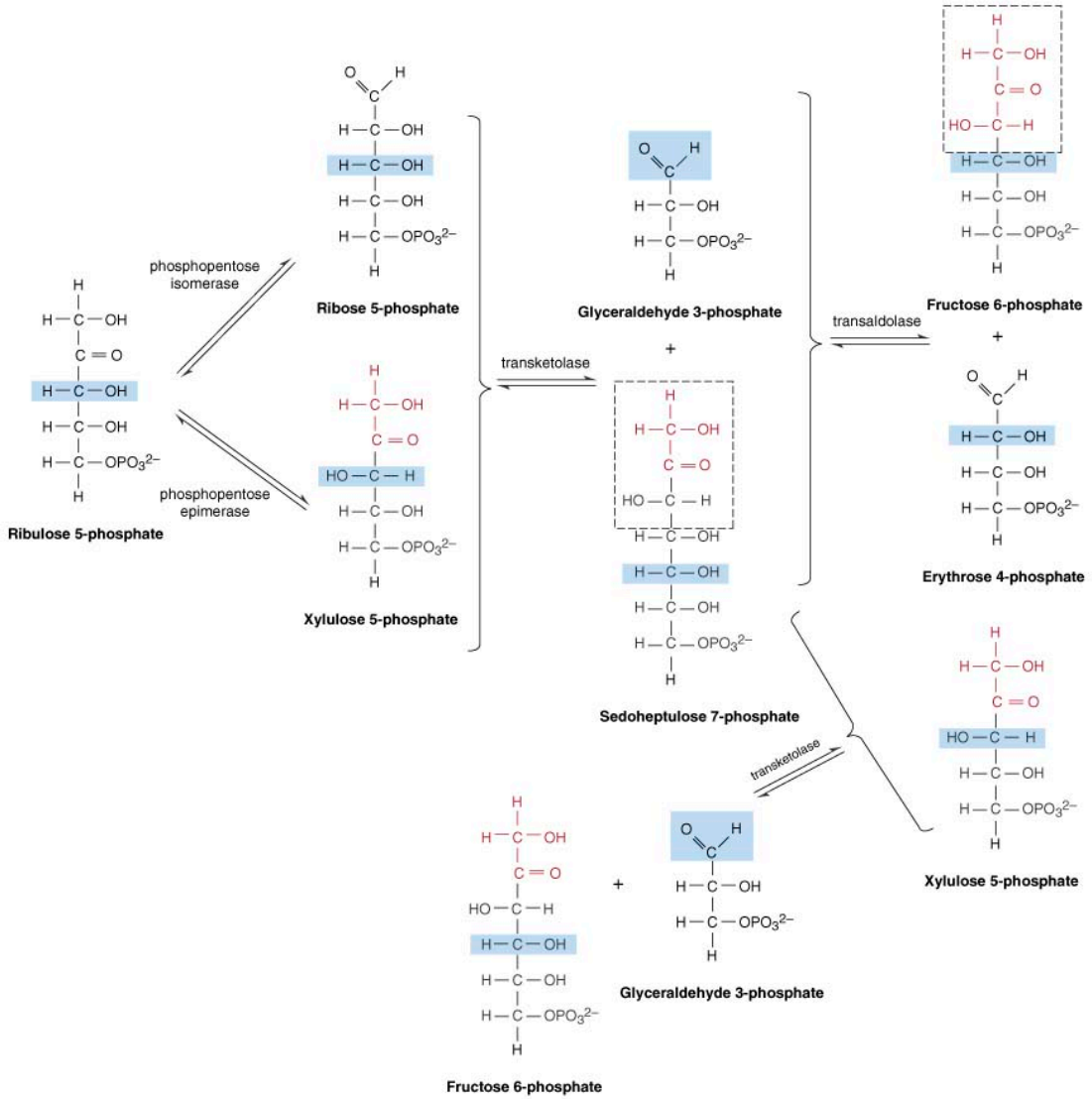
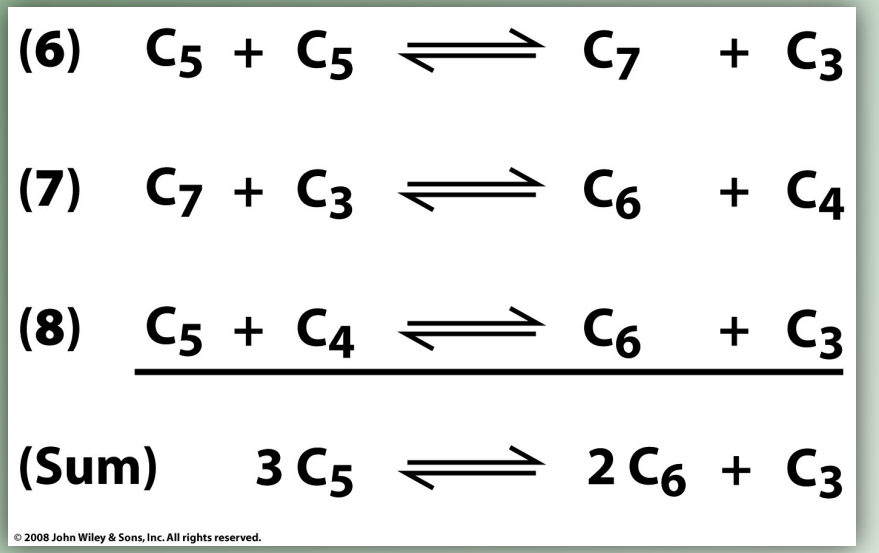
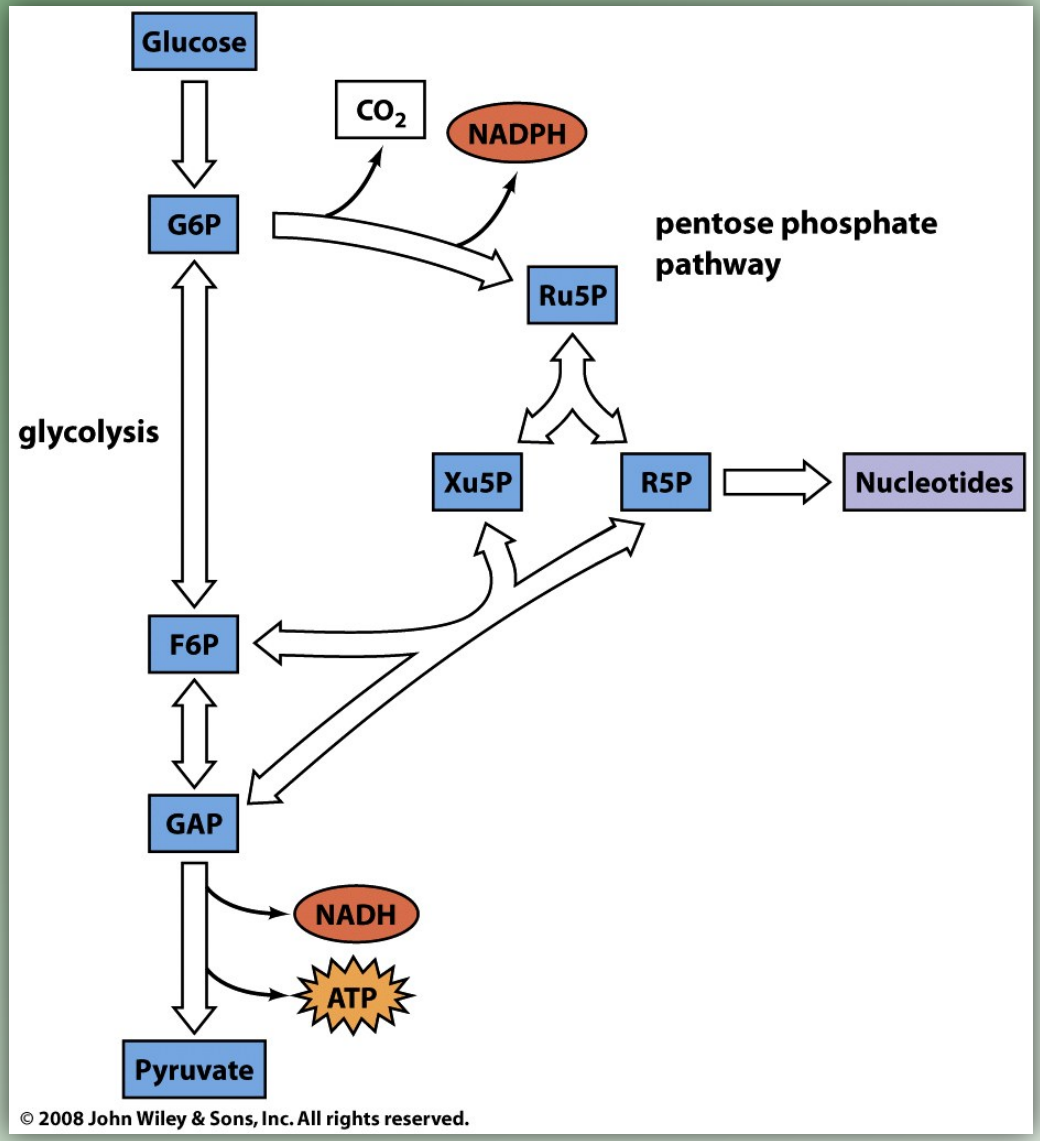


Figure 16.2. Nonoxidative reactions of the pentose phosphate pathway: Interconversions of pentose phosphates.

Summary of carbon skeleton rearrangements from reactions 6-8 in the PPP

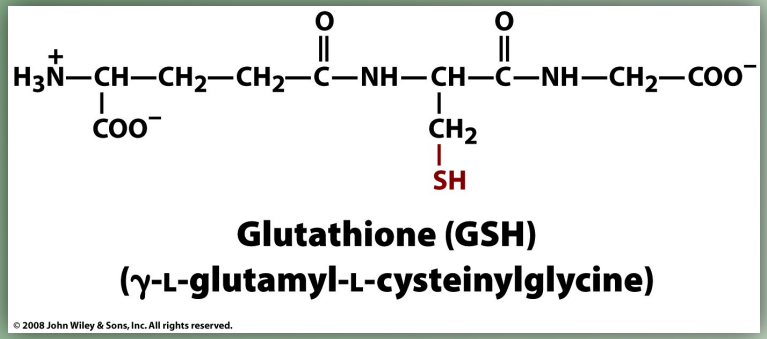


Three C_5 fragments are converted into two C_6 fragments (F6P) and one C_3 fragment (G3P). The F6P and G3P enter glycolysis for subsequent degradation.

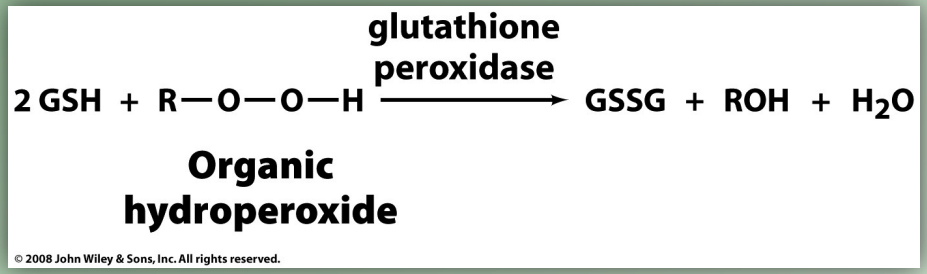


Relationship between glycolysis and the PPP

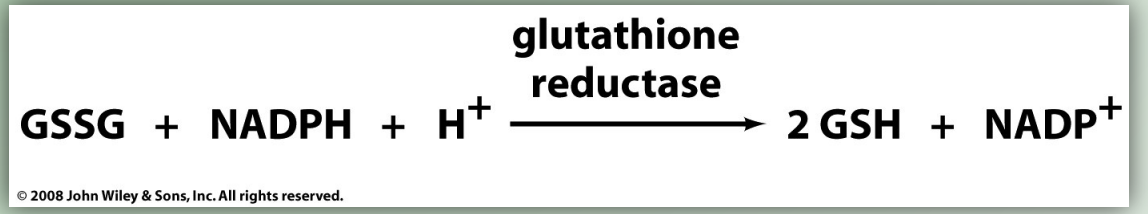
Erythrocyte biochemistry:



GSH is very abundant in erythrocytes.



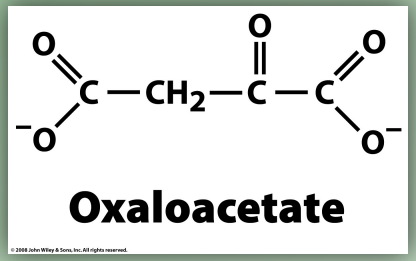
GSH-mediated removal of ROS, which damage Hb and lipids and cause cell lysis



GSSG is converted back to GSH with NADPH.

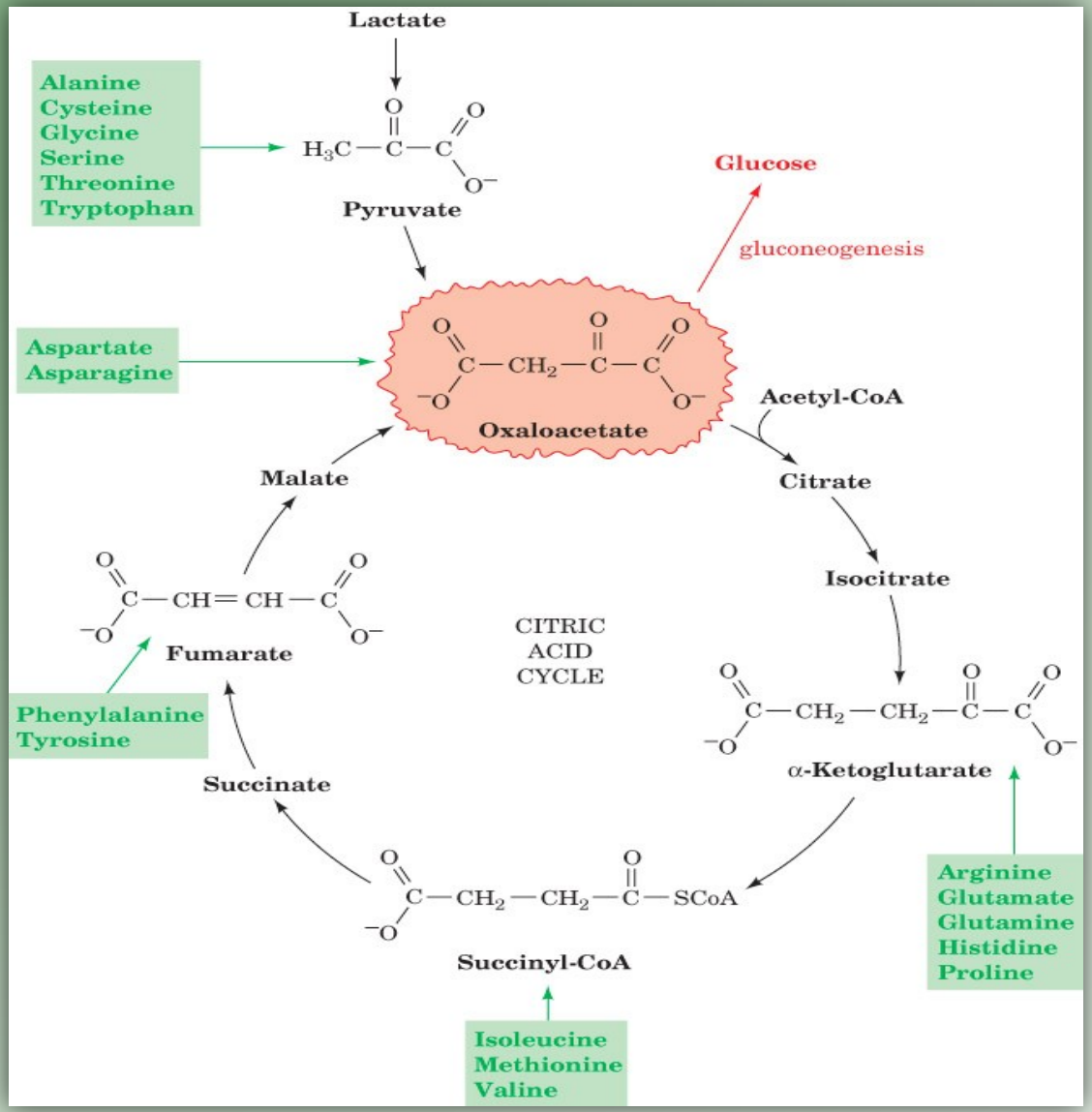
Liver Gluconeogenesis

Gluconeogenesis: the metabolic process through which non-carbohydrate precursors such as lactate, pyruvate, glycerol, and amino acids are converted into glucose.



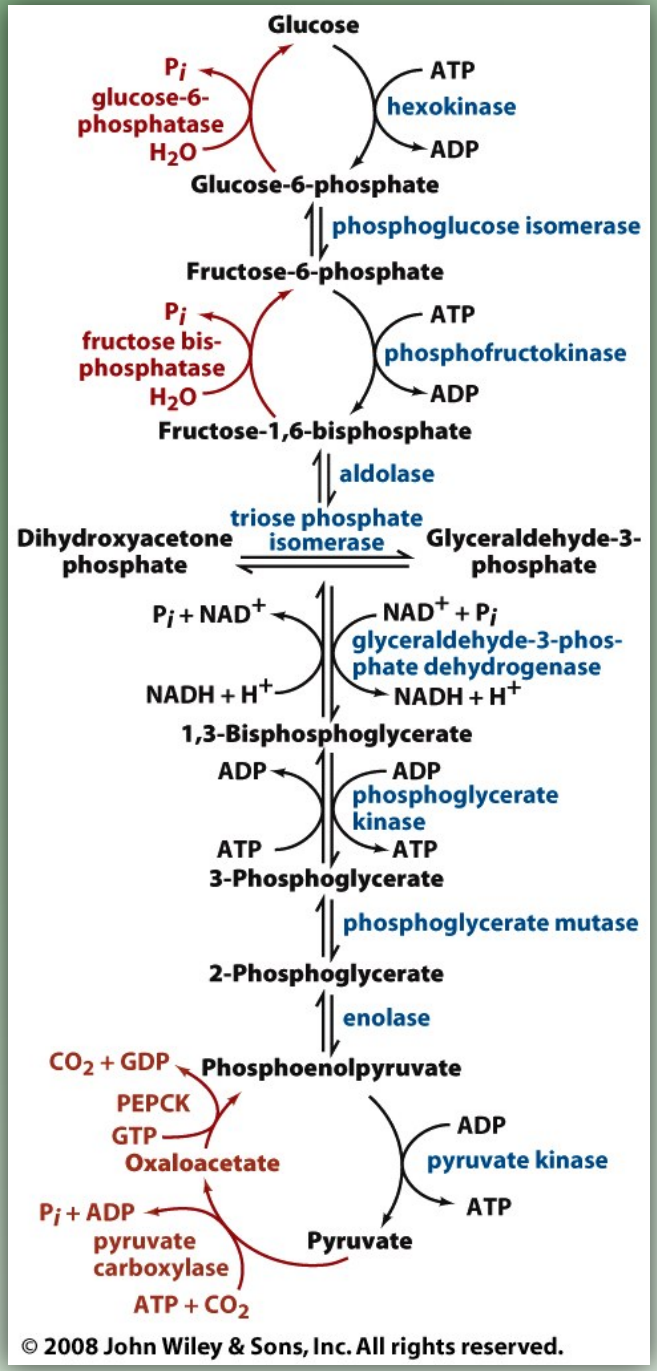
Oxaloacetic acid (OAA), a TCA intermediate, is the starting material for gluconeogenesis; all other precursors need to be converted into it; gluconeogenesis occurs primarily, if not exclusively, in liver.

Brain cells and erythrocytes are heavily dependent on glucose as an energy source.



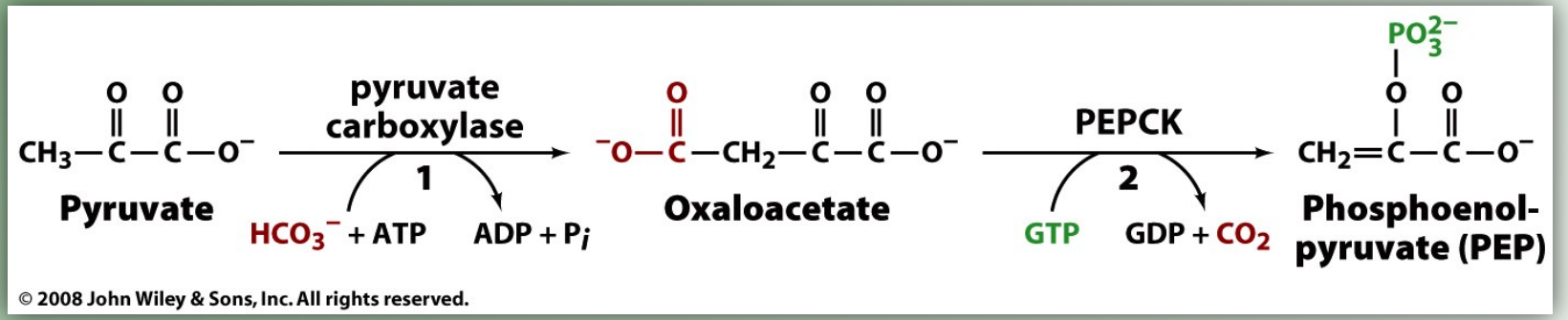
Pathways converting lactate, pyruvate, and citric acid cycle intermediates to oxaloacetate

All of the amino acids shown in green are *glucogenic*; only leucine and lysine are not convertible to OAA, but rather are converted to acetyl CoA (they are *ketogenic*).



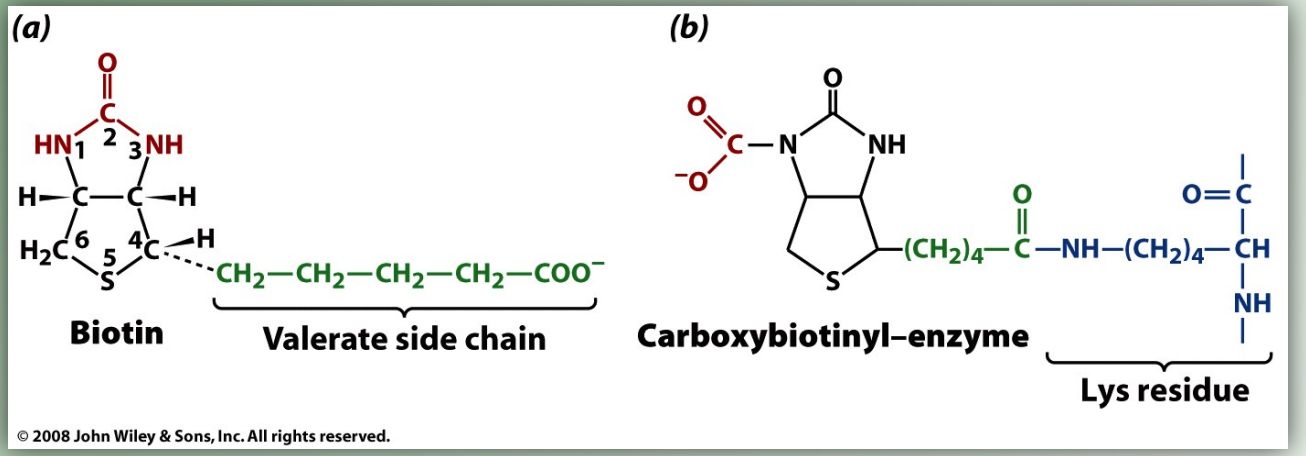
Gluconeogenesis does not occur by strict reversal of glycolysis. This is because the three regulatory enzymes of glycolysis (HK, PFK,and PK) are essentially irreversible *in vivo*. Gluconeogenesis can only occur through specific enzymes that allow for the reversal of these three glycolytic steps. These enabling enzymes are pyruvate carboxylase, PEP carboxykinase, FBP phosphatase, and G6P phosphatase.

Converting pyruvate to PEP via OAA: pyruvate carboxylase and PEPCK

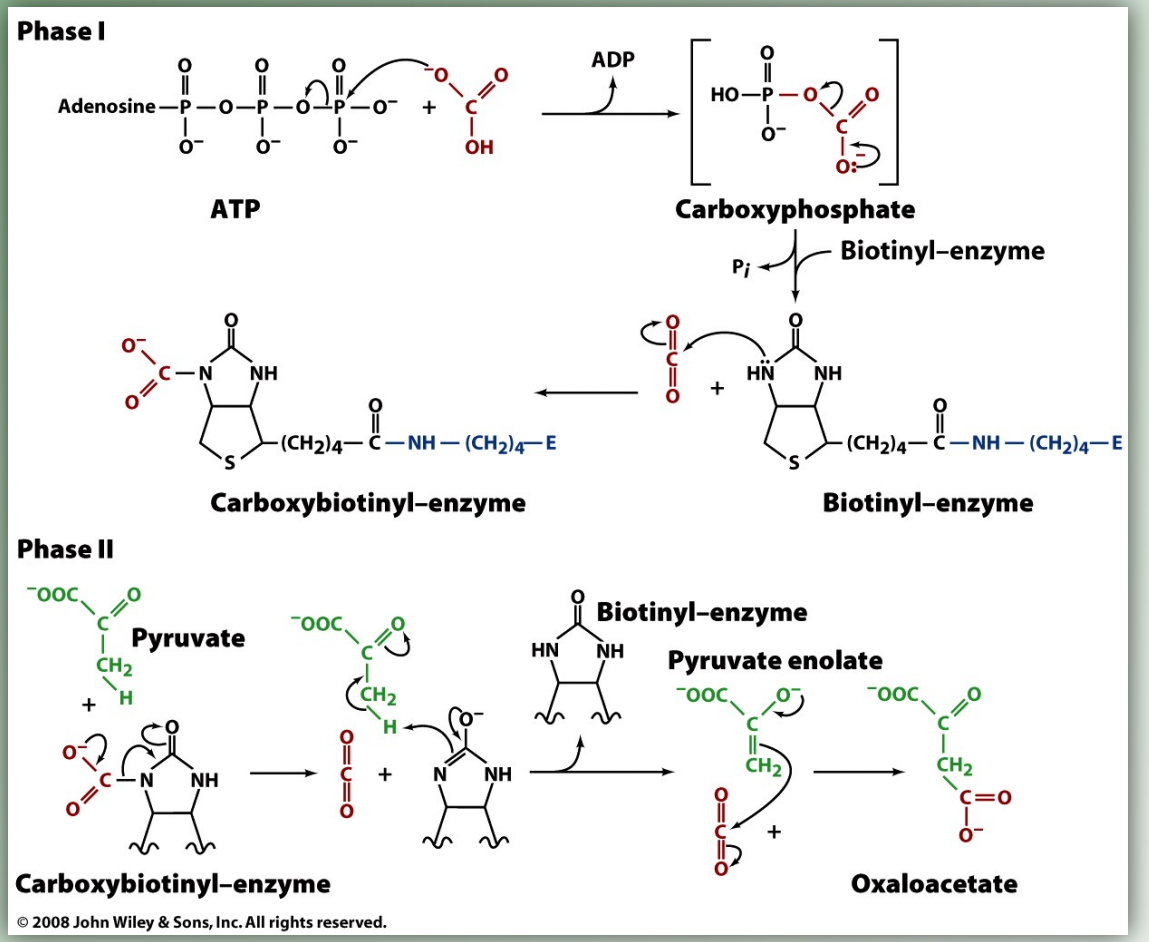


The conversion of pyruvate to OAA occurs in *mitochondria*. PEPCK is found either in the *cytosol* and/or *mitochondria*, depending on the species. This means that pyruvate, PEP and/or OAA need to be transported between the cytosol and mitochondria to support gluconeogenesis.

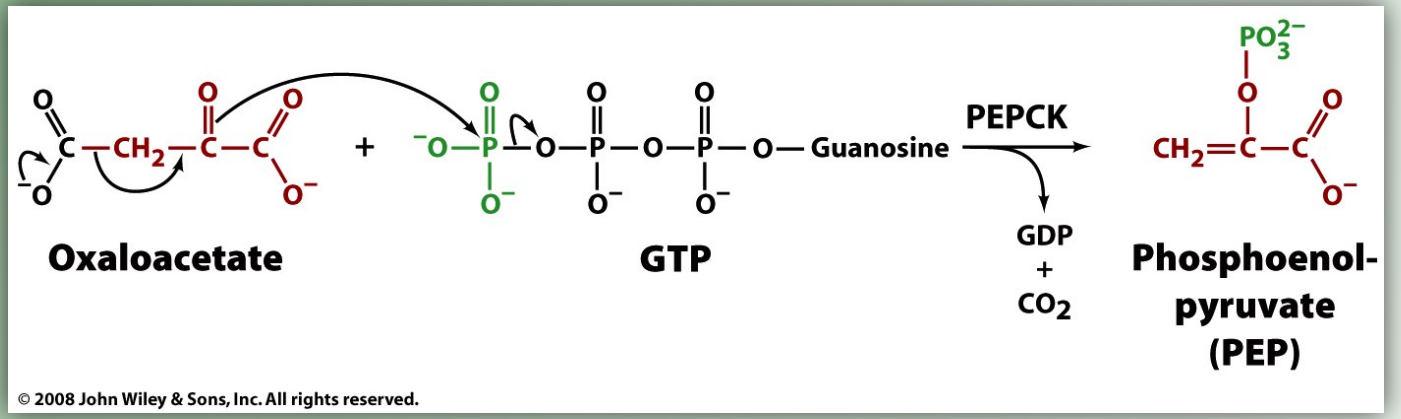
Pyrivate carboxylase is a carboxylating enzyme that requires biotin as a coenzyme.

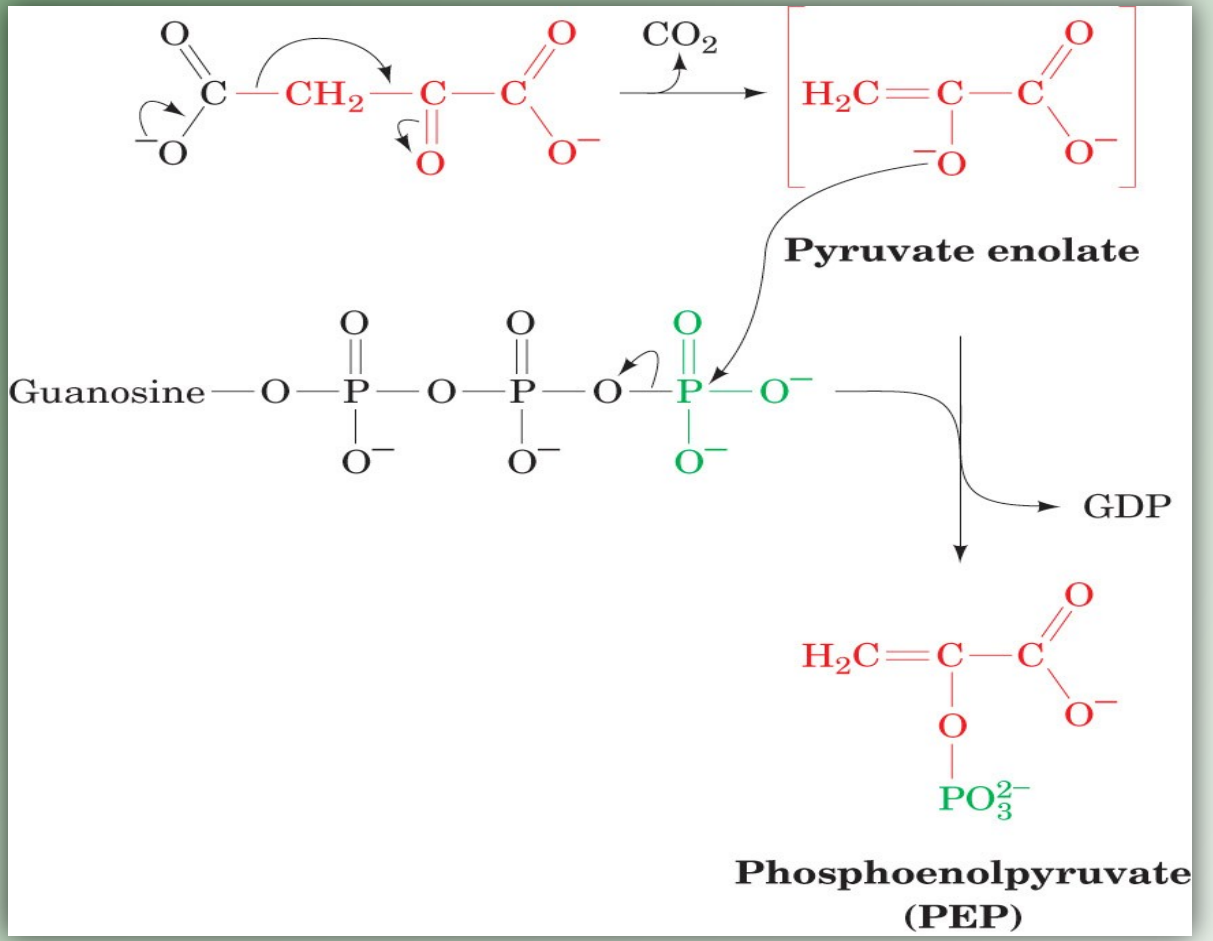


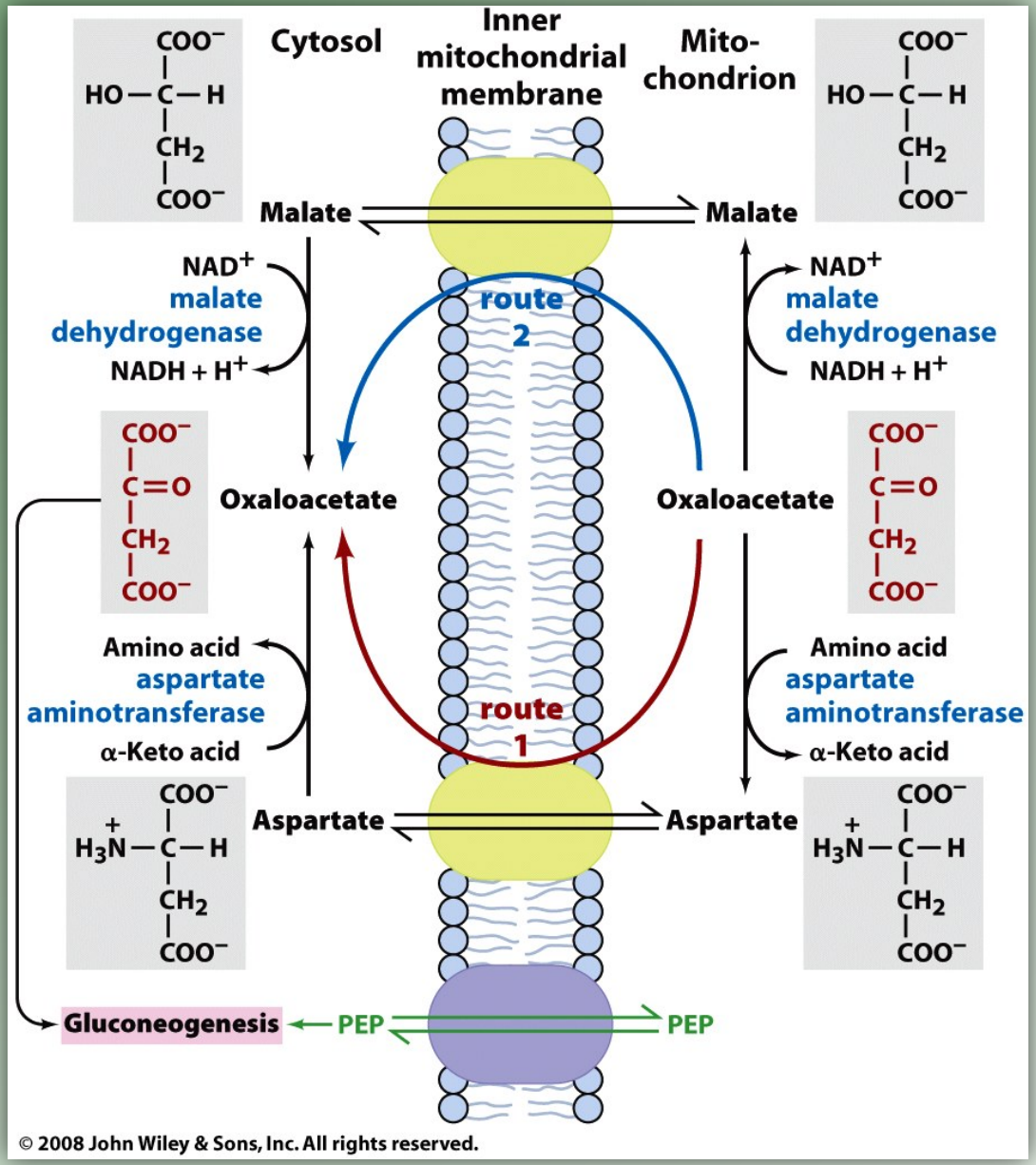
Proposed mechanism of PC



Converting OAA to PEP: PEPCK




CO2
Pyruvate enolate
Guanosine
GDP
PO3 2−
Phosphoenolpyruvate
(PEP)



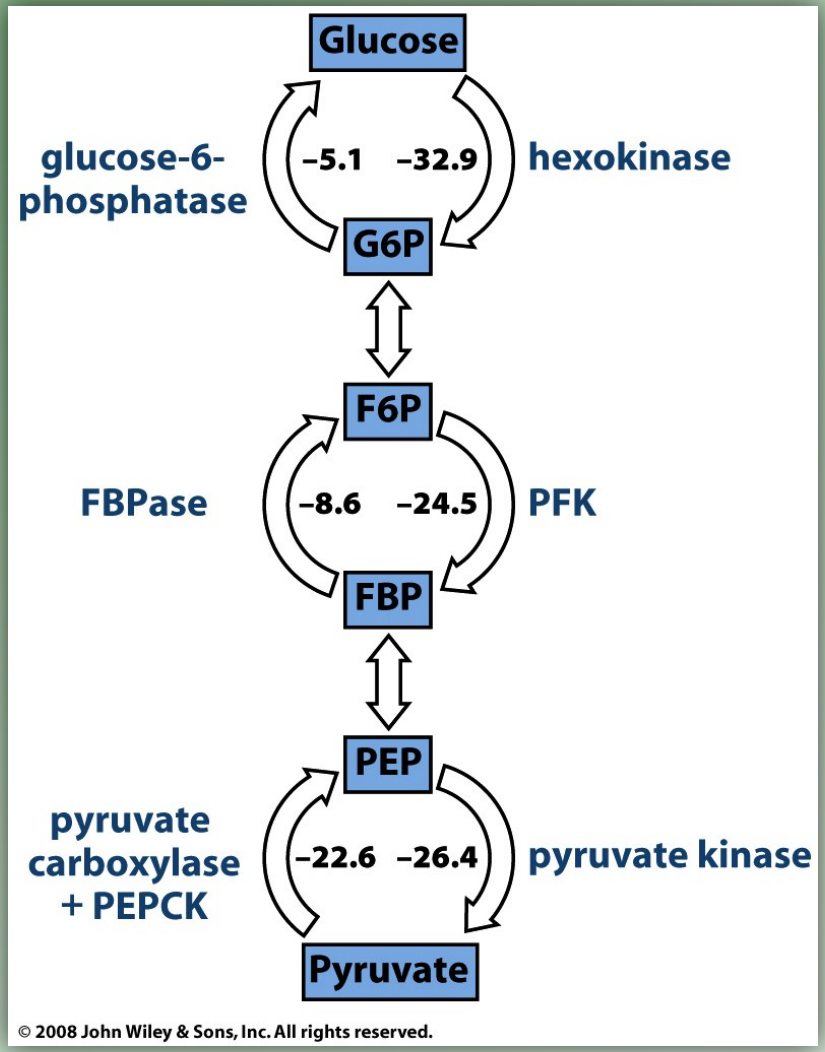
Transport of PEP and OAA between the cytosol and mitochondria: The malate-aspartate shuttle

Pyruvate transport occurs via a specific H^+-ion mediated symport transporter.

The same shuttle is used to transport cytosolic NADH into mitochondria.

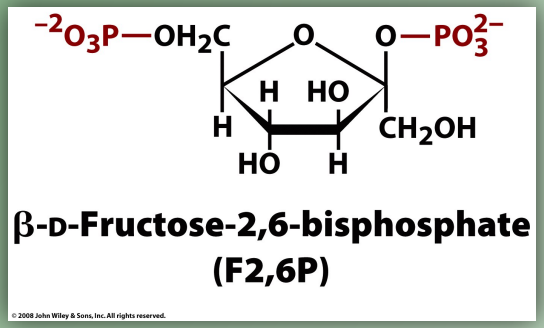
Regulators of gluconeogenic enzyme activity

Enzyme	Allosteric Inhibitors	Allosteric Activators	Enzyme Phosphorylation	Protein Synthesis
PFK	ATP, citrate	AMP, F2,6P		
FBPase	AMP, F2,6P			
Pyruvate kinase	Alanine	F1,6P	Inactivates	
Pyruvate carboxylase		Acetyl-CoA		
PEPCK				Stimulated by glucagon, thyroid hormone, and glucocorticoids, and inhibited by insulin
PFK-2	Citrate	AMP, F6P, P_i	Inactivates	
FBPase-2	F6P	Glycerol-3-P	Activates	



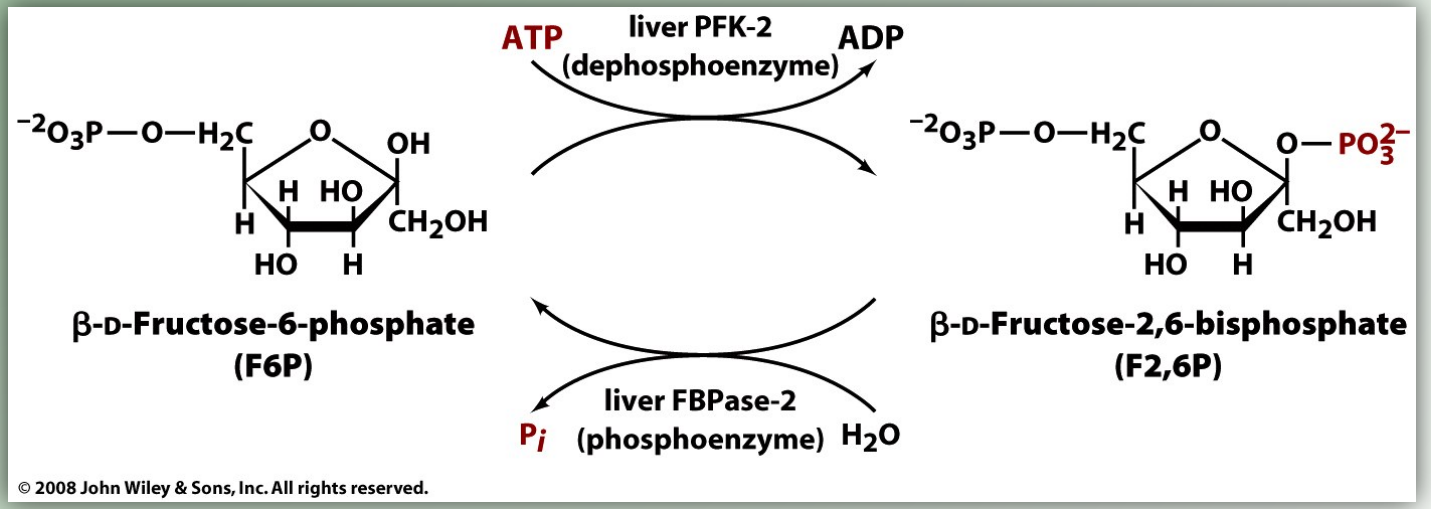
Substrate cycles in glucose metabolism

Glycolysis and gluconeogenesis are regulated independently (the ΔG values shown are for the corresponding reactions in liver; in kJ/mol). All six reactions are exergonic.



F2,6BP activates PFK-1 and inhibits FBPase-1.

The formation and degradation of F2,6BP in liver

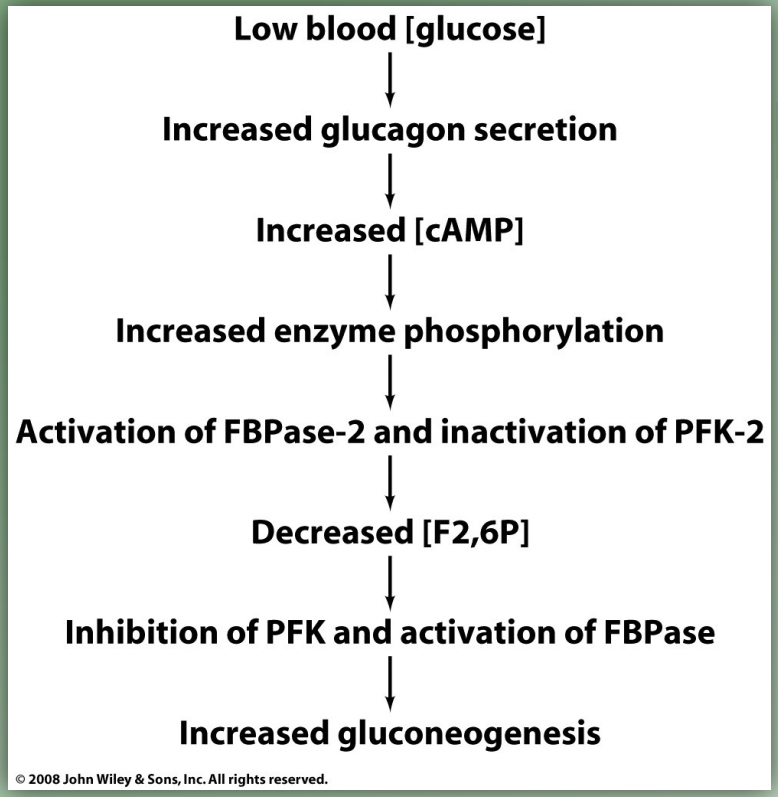


Cellular [F2,6BP] depends on the balance between its rates of synthesis and degradation by *PFK-2* (phosphofructokinase-2) and *FBPase-2* (fructose bisphosphatase-2).

These activities are located on different domains of the same homodimeric protein (a bifunctional enzyme).

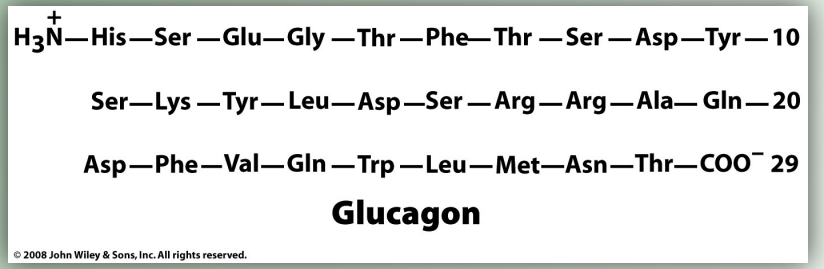
The bifunctional enzyme is regulated by allosteric effectors and by phosphorylation/dephosphorylation catalyzed by *PKA* (protein kinase A) and a phosphoprotein phosphatase.

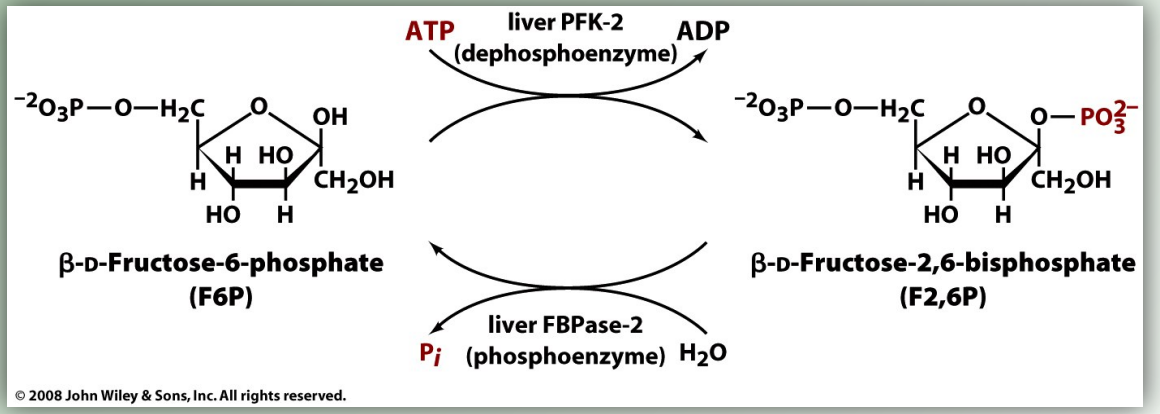
Metabolic events linking low blood [glucose] to gluconeogenesis in liver



F2,6BP activates PFK-1 and inhibits FBPase-1.

When blood [glucose] is high, cAMP levels decrease, and [F2,6BP] rises, promoting glycolysis.





The F2,6BP control system in muscle differs from that in liver.

Hormones that stimulate glycogen breakdown in *heart muscle* lead to phosphorylation of the bifunctional enzyme that stimulates rather than inhibits PFK-2. The increasing [F2,6BP] stimulates glycolysis so that glycogen breakdown and glycolysis are coordinated.

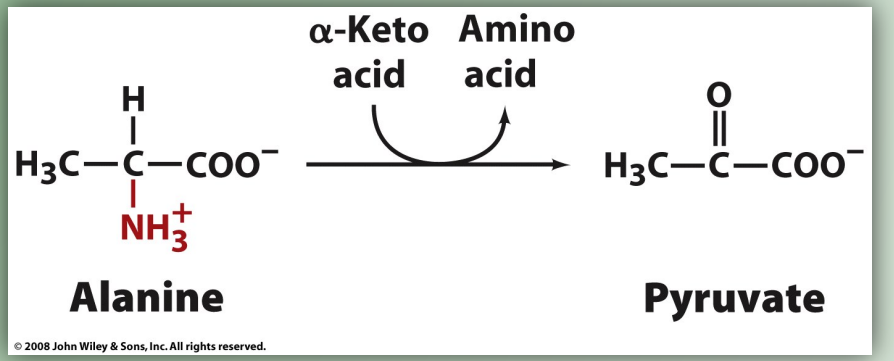
The skeletal muscle PFK-2/PBPase-2 isozyme lacks a phosphorylation site and is thus not subject to cAMP-dependent control.

Regulators of gluconeogenic enzyme activity

Enzyme	Allosteric Inhibitors	Allosteric Activators	Enzyme Phosphorylation	Protein Synthesis
PFK	ATP, citrate	AMP, F2,6P		
FBPase	AMP, F2,6P			
Pyruvate kinase	Alanine	F1,6P	Inactivates	
Pyruvate carboxylase		Acetyl-CoA		
PEPCK				Stimulated by glucagon, thyroid hormone, and glucocorticoids, and inhibited by insulin
PFK-2	Citrate	AMP, F6P, P_i	Inactivates	
FBPase-2	F6P	Glycerol-3-P	Activates	

Alanine inhibits pyruvate kinase.

Alanine, a major gluconeogenic precursor, inhibits PK.



Liver PK is also inactivated by phosphorylation. Phosphorylation activates glycogen phosphorylase and FBPase-2: thus the pathways of gluconeogenesis and glycogen breakdown both flow towards G6P, which is converted to glucose for export from the liver.

Hexokinase/glucokinase and G6Pase activities are also controlled.

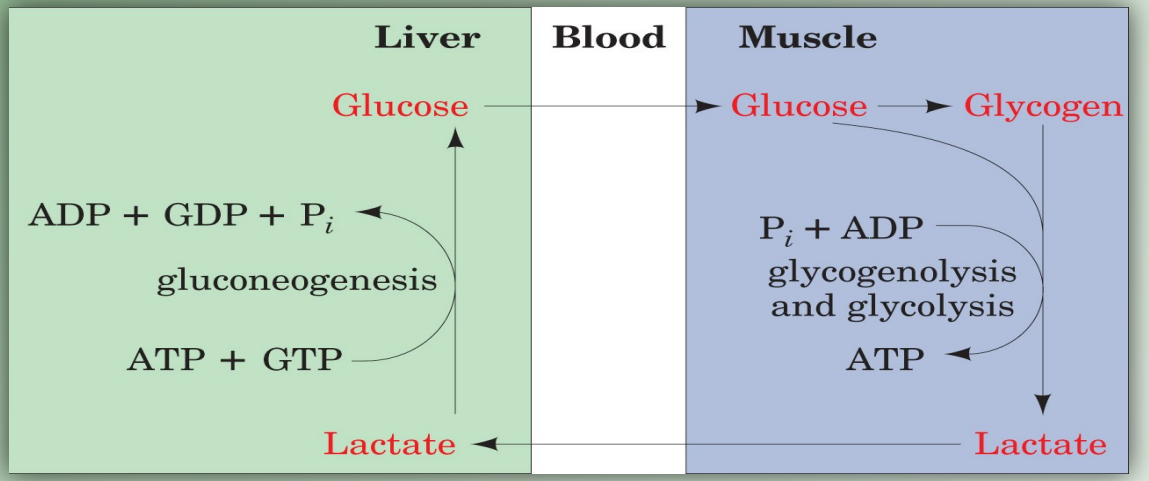
Other control factors

Glucose metabolism is regulated by long-term changes in the *amounts of enzymes* synthesized.

Rates of transcription and mRNA stabilities encoding regulatory enzymes are influenced by hormones.

Insulin (high blood glucose) inhibits transcription of the gene for PEPCK; high [cAMP] (low blood glucose) promotes transcription of the genes for PEPCK, FBPase, and G6Pase (gluconeogenic enzymes), and represses transcription of the genes for glucokinase, PFK (glycolytic enzymes) and PFK-2/FBPase-2.

The Cori cycle: transport of muscle-generated L-lactate to the liver for conversion to glucose



Lactate produced by muscle glycolysis (anaerobic) is transported by the bloodstream to the liver, where it is converted to glucose by gluconeogenesis.

Metabolic interrelationships between brain, adipose tissue, muscle, liver and kidney in humans