GLUCONEOGENESIS

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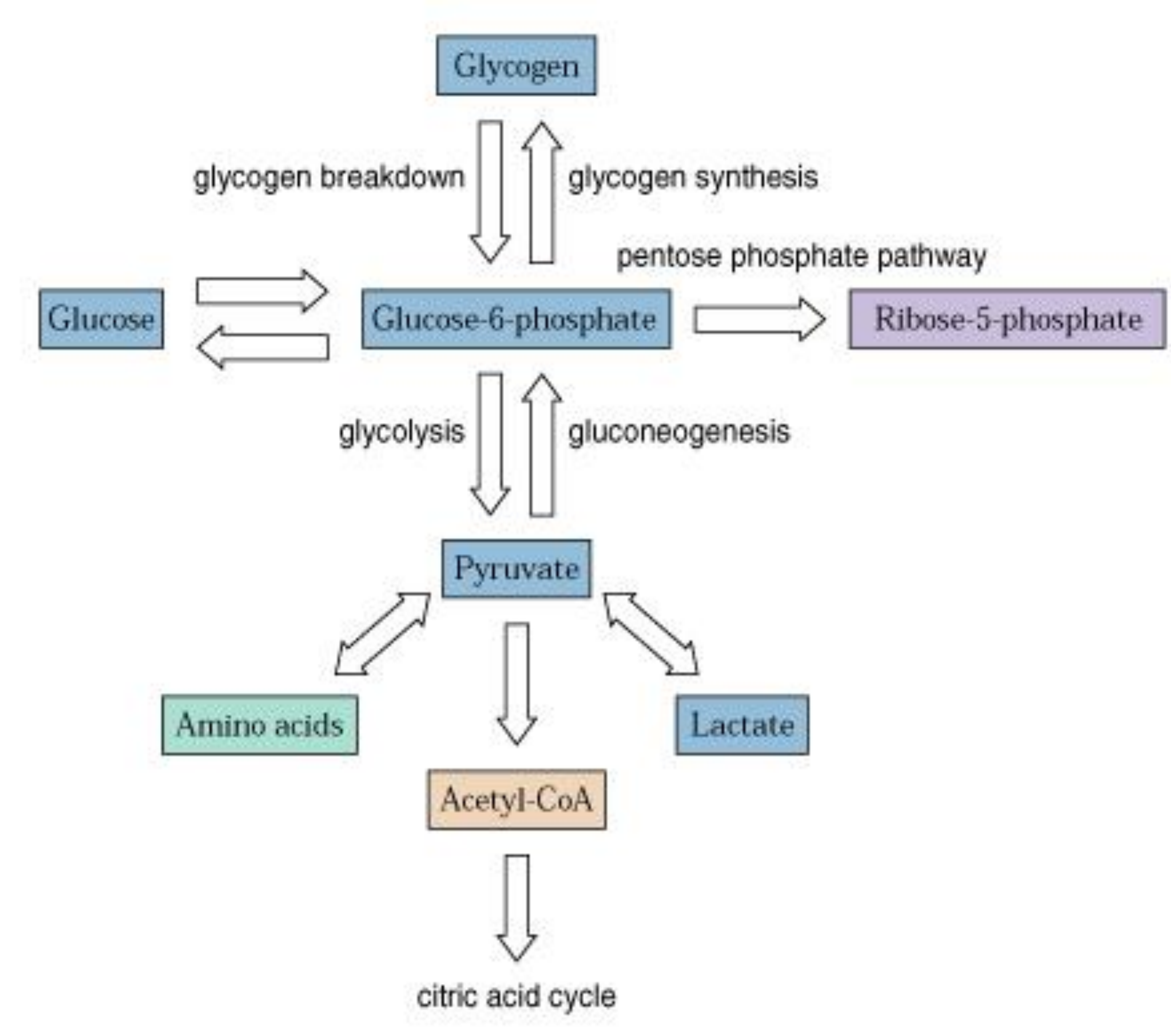
Overview of Glucose Metabolism



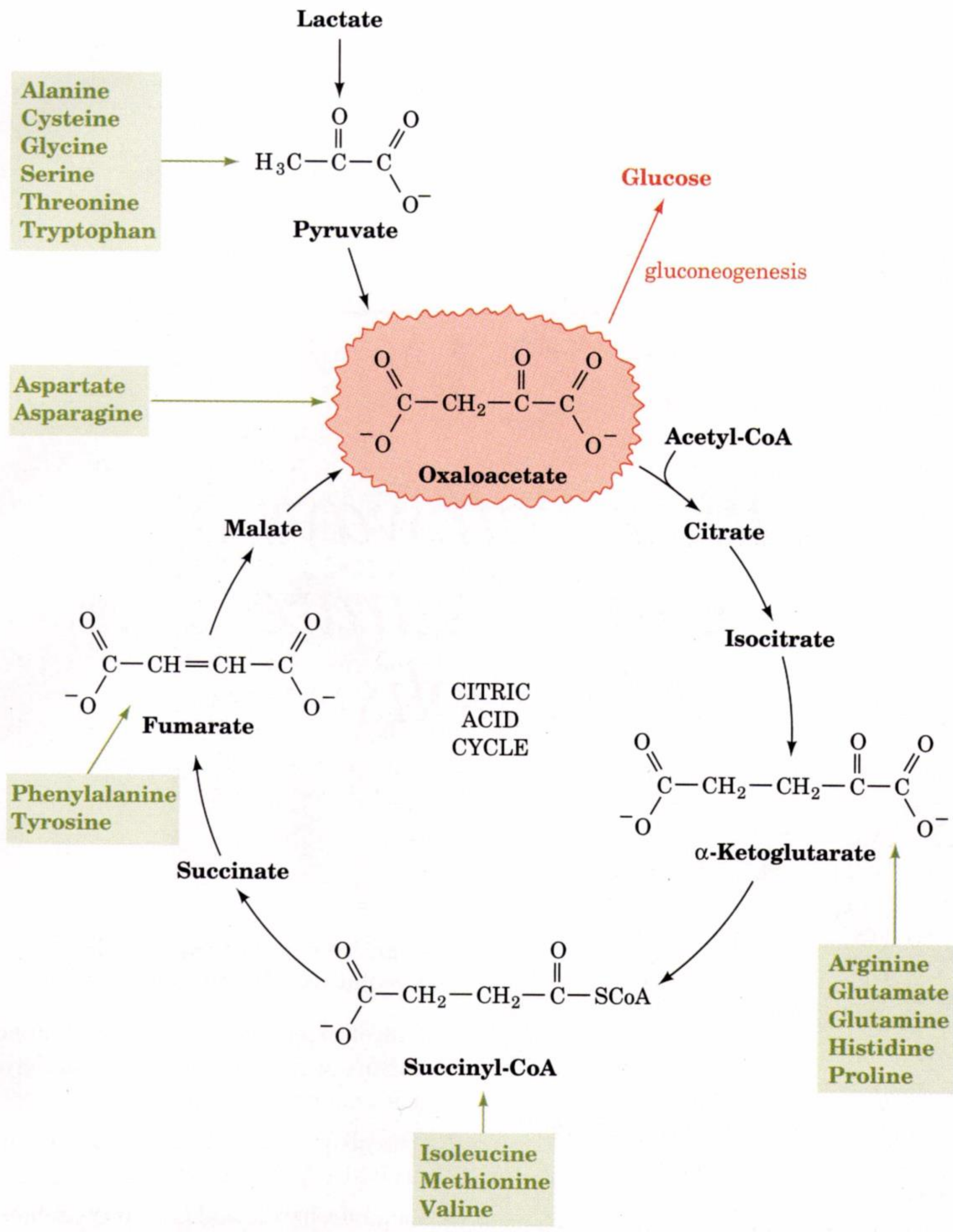
Gluconeogenesis

Gluconeogenesis is the process whereby precursors such as lactate, pyruvate, glycerol, and amino acids are converted to glucose.

Fasting requires all the glucose to be synthesized from these non-carbohydrate precursors.

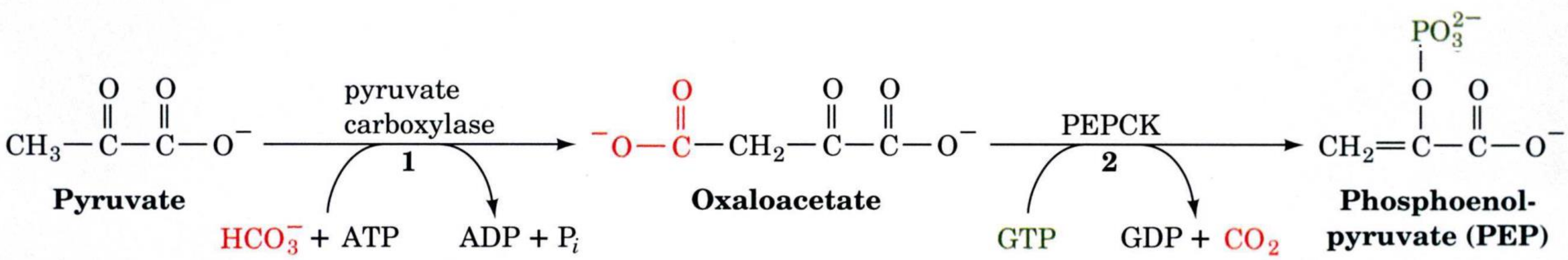
Most precursors must enter the Krebs cycle at some point to be converted to oxaloacetate.

Oxaloacetate is the starting material for gluconeogenesis



Lactate
Alanine
Cysteine
Glycine
Serine
Threonine
Tryptophan
Pyruvate
Glucose
gluconeogenesis
Aspartate
Asparagine
Oxaloacetate
Acetyl-CoA
Citrate
Malate
Isocitrate
Fumarate
CITRIC
ACID
CYCLE
Phenylalanine
Tyrosine
α-Ketoglutarate
Succinate
Arginine
Glutamate
Glutamine
Histidine
Proline
Succinyl-CoA
Isoleucine
Methionine
Valine

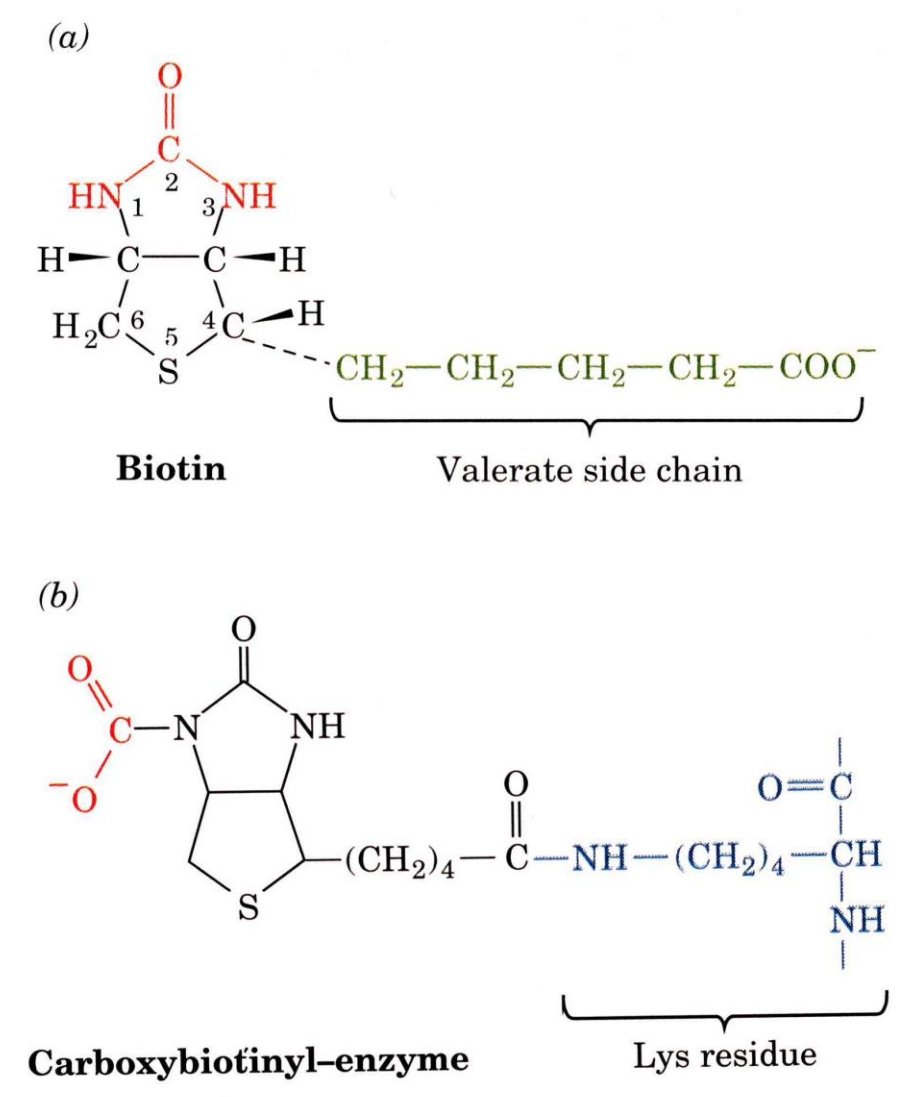
Pyruvate is converted to oxaloacetate before being changed to Phosphoenolpyruvate



1. Pyruvate carboxylase catalyses the ATP-driven formation of oxaloacetate from pyruvate and CO_2

2. PEP carboxykinase (PEPCK) concerts oxaloacetate to PEP that uses GTP as a phosphorylating agent.

Pyruvate carboxylase requires biotin as a cofactor



Gluconeogenesis is not just the reverse of glycolysis

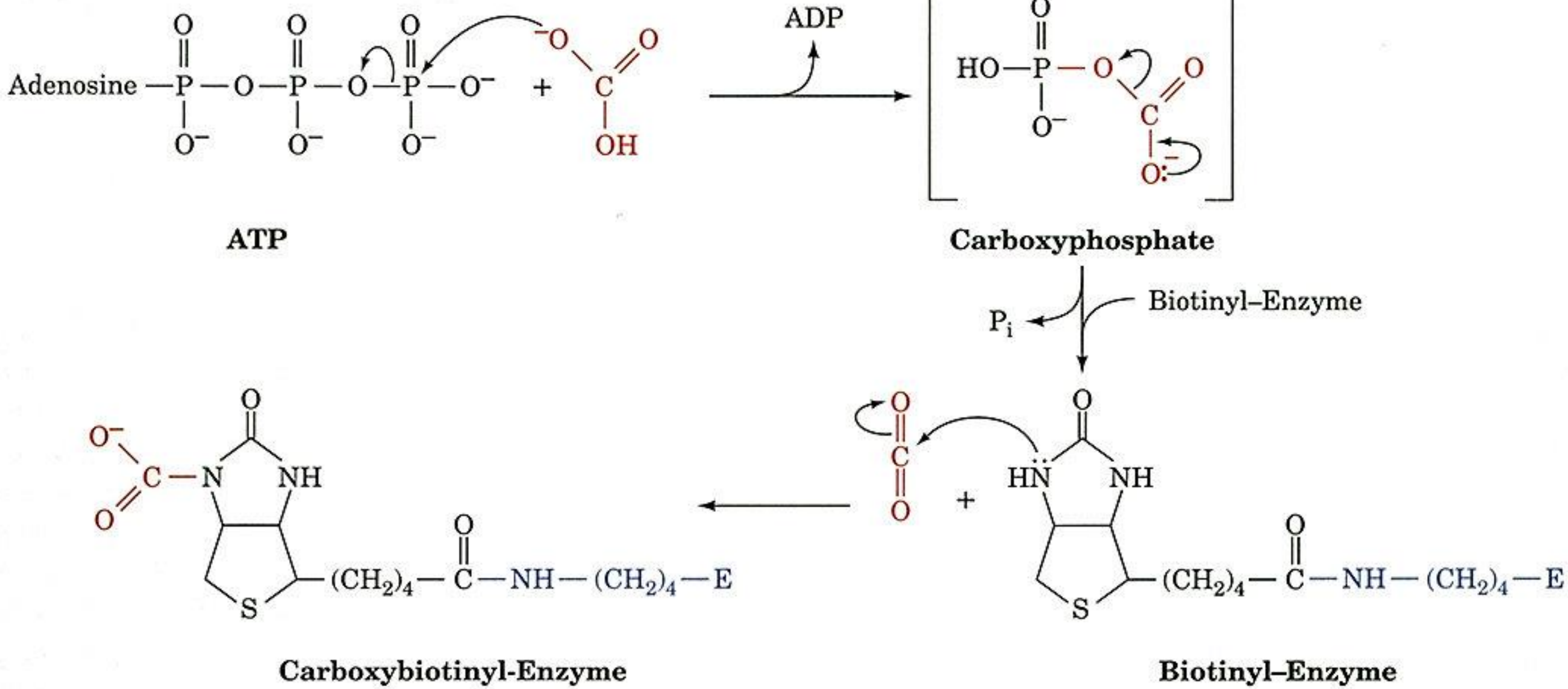
Several steps are different so that control of one pathway does not inactivate the other. However many steps are the same. Three steps are different from glycolysis.

1 Pyruvate to PEP

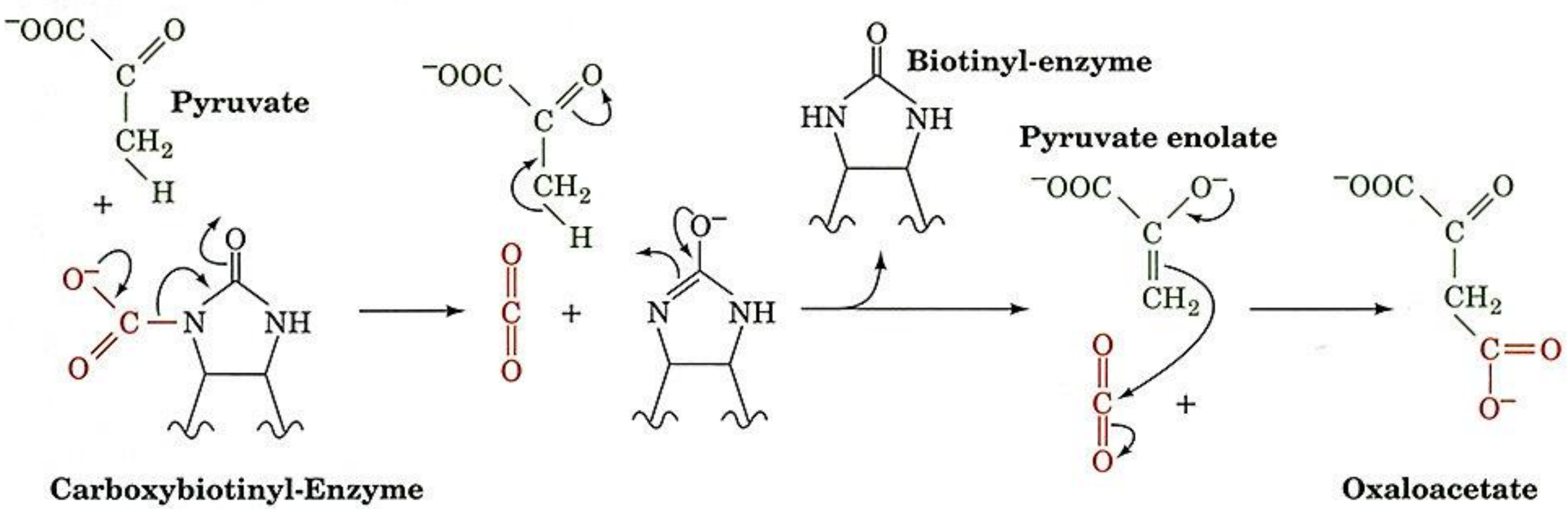
2 Fructose 1,6- bisphosphate to Fructose-6-phosphate

3 Glucose-6-Phosphate to Glucose

Phase I



Phase II



Biotin is an essential nutrient

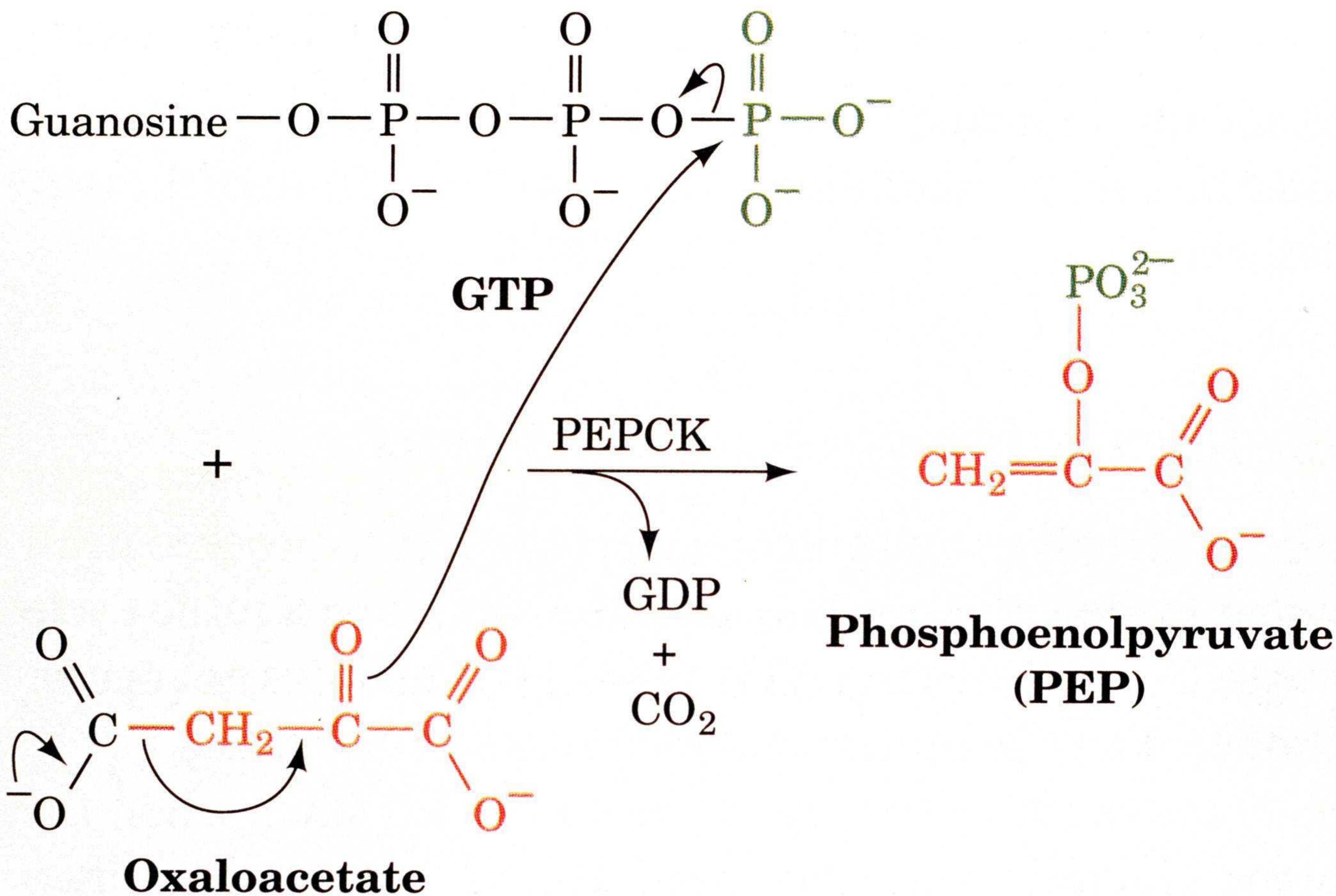
There is hardly any deficiencies for biotin because it is abundant and bacteria in the large intestine also make it.

However, deficiencies have been seen and are nearly always linked to the consumption of raw eggs.

Raw eggs contain Avidin a protein that binds biotin with a $K_d = 10^{-15}$ (that is one tight binding reaction!)

It is thought that Avidin protects eggs from bacterial invasion by binding bioitin and killing bacteria.

PEP carboxykinase

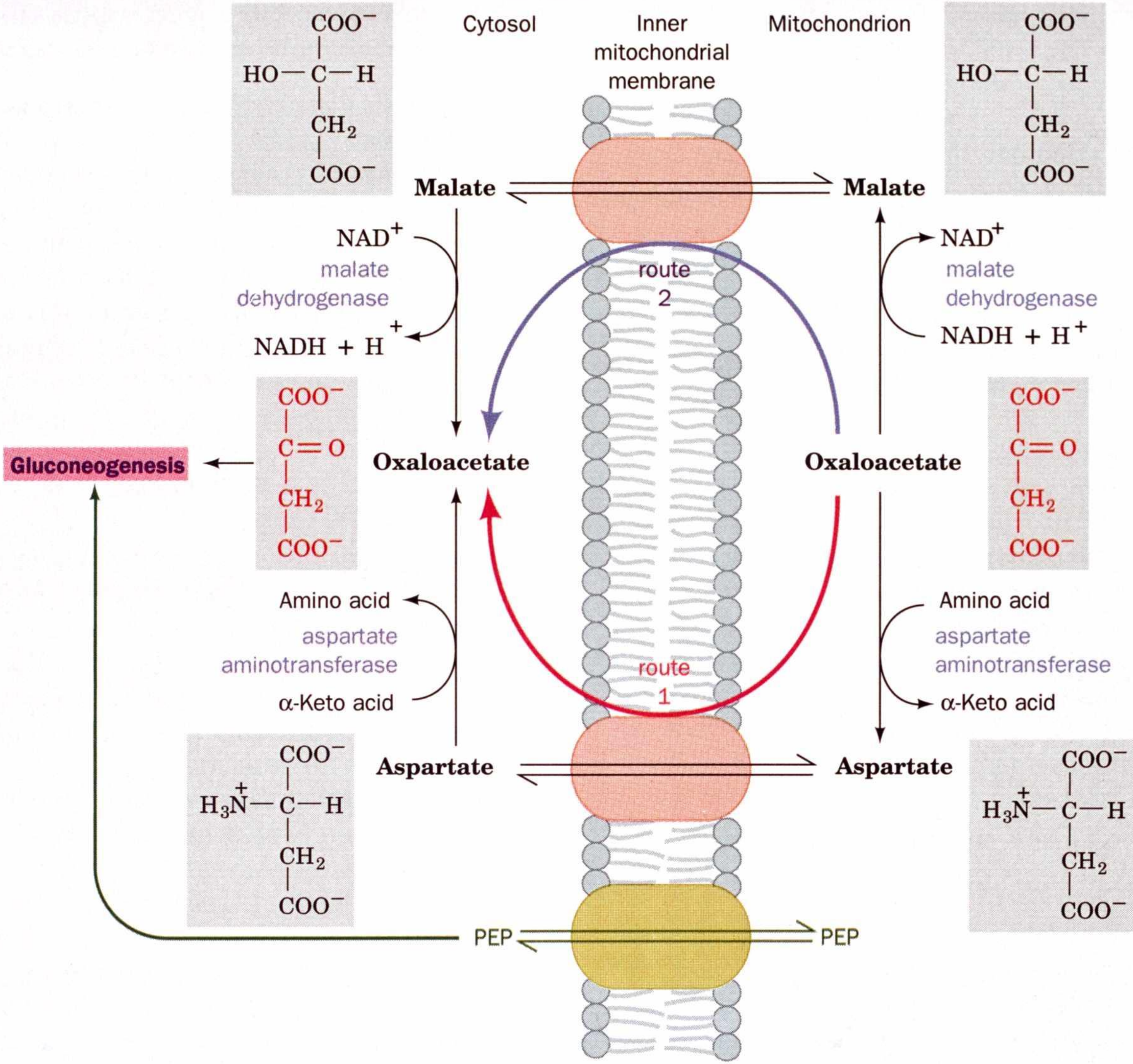


Acetyl-CoA regulates pyruvate carboxylase

Increases in oxaloacetate concentrations increase the activity of the Krebs cycle and acetyl-CoA is a allosteric activator of the carboxylase. However when ATP and NADH concentrations are high and the Krebs cycle is inhibited, oxaloacetate goes to glucose.

Transport between the mitochondria and the cytosol

Generation of oxaloacetate occurs in the mito-chondria only, but, gluconeogenesis occurs in the cytosol. PEPCK is distributed between both compartments in humans, while in mice, it is only found in the cytosol. In rabbits, it is found in the mitochondria. Either PEP must be transported across the membranes or oxaloacetate has to be transported. PEP transport systems are seen in the mitochondria but oxaloacetate can not be trans-ported directly in or out of the mitochondria.



Cytosol
Inner mitochondrial membrane
Mitochondrion
Malate
Malate
NAD+
malate dehydrogenase
NADH + H+
NAD+
malate dehydrogenase
NADH + H+
route 2
Gluconeogenesis
Oxaloacetate
Oxaloacetate
Amino acid
aspartate aminotransferase
α-Keto acid
Amino acid
aspartate aminotransferase
α-Keto acid
route 1
Aspartate
Aspartate
PEP
PEP

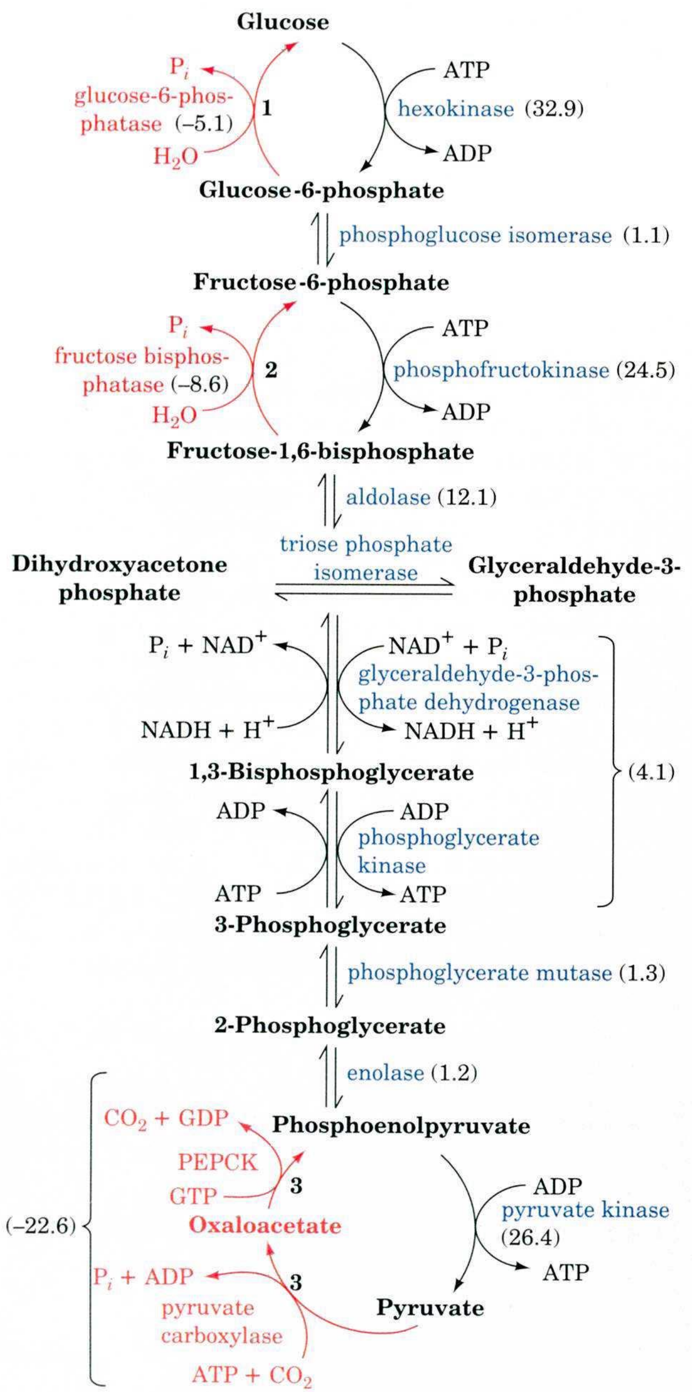
Hydrolytic reactions bypass PFK and Hexokinase

The hydrolysis of fructose-1,6-phosphate and glucose-6- phosphate are separate enzymes from glycolysis. Glucose-6-phosphatase is only found in the liver and kidney. The liver is the primary organ for gluconeogenesis.

$$\text{Glucose} + 2NAD^+ + 2ADP + 2Pi \longrightarrow 2\text{Pyruvate} + 2NADH + 4H^+ + 2ATP + 2H_2O$$

$$2\text{Pyruvate} + 2NADH + 4H^+ + 4ATP + 2GTP + 6H_2O \longrightarrow \text{glucose} + 2NAD^+ + 4ATP + 2GDP + 4Pi$$

$$2ATP + 2GTP + 4H_2O \longrightarrow 2ADP + 2GTP + 4Pi$$



Glucose
P_i
glucose-6-phos-
phatase (–5.1)
1
H_2O
ATP
hexokinase (32.9)
ADP
Glucose-6-phosphate
phosphoglucose isomerase (1.1)
Fructose-6-phosphate
P_i
fructose bisphos-
phatase (–8.6)
2
H_2O
ATP
phosphofructokinase (24.5)
ADP
Fructose-1,6-bisphosphate
aldolase (12.1)
triose phosphate
isomerase
Dihydroxyacetone
phosphate
Glyceraldehyde-3-
phosphate
$P_i + NAD^+$
$NAD^+ + P_i$
glyceraldehyde-3-phos-
phate dehydrogenase
$NADH + H^+$
$NADH + H^+$
1,3-Bisphosphoglycerate
(4.1)
ADP
ADP
phosphoglycerate
kinase
ATP
ATP
3-Phosphoglycerate
phosphoglycerate mutase (1.3)
2-Phosphoglycerate
enolase (1.2)
CO_2 + GDP
Phosphoenolpyruvate
PEPCK
3
GTP
Oxaloacetate
(–22.6)
ADP
pyruvate kinase
(26.4)
ATP
P_i + ADP
3
pyruvate
carboxylase
Pyruvate
ATP + CO_2

Regulators of gluconeogenic enzyme activity

Enzyme	**Allosteric Inhibitors**	**Allosteric Activators**	**Enzyme Phosphorylation**	**Protein Synthesis**
PFK	ATP, citrate	AMP, F2-6P		
FBPase	AMP, F2-6P			
PK	Alanine	F1-6P	Inactivates	
Pyr. Carb.		AcetylCoA		
PEPCK				Glucogon
PFK-2	Citrate	AMP, F6P, Pi	Inactivates	
FBPase-2	F6P	Glycerol-3-P	Activates	

Low blood [glucose]

↓

Increased glucagon secretion

↓

Increased [cAMP]

↓

Increased enzyme phosphorylation

↓

Activation of FBPase-2 and inactivation of PFK-2

↓

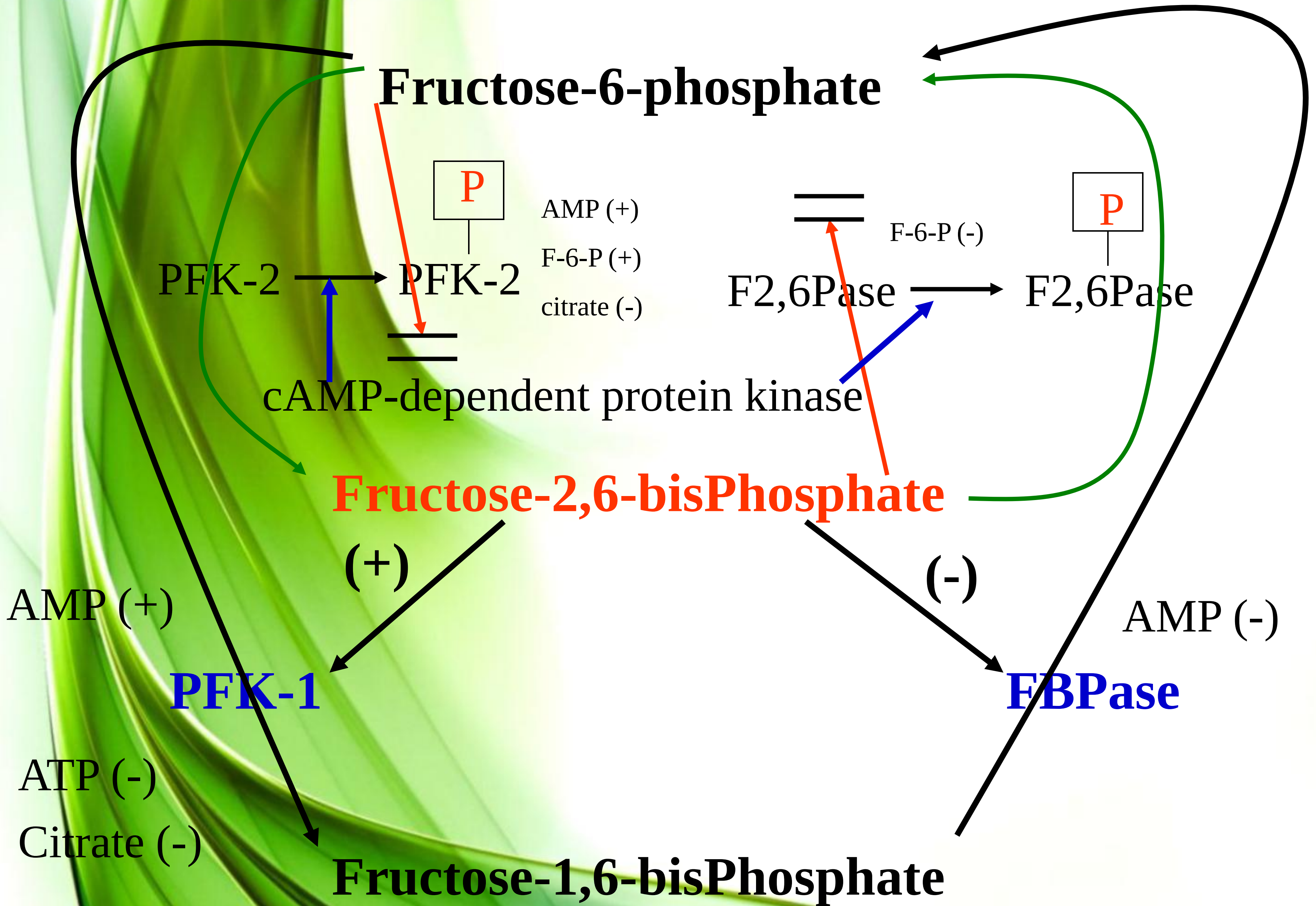
Decreased [F2,6P]

↓

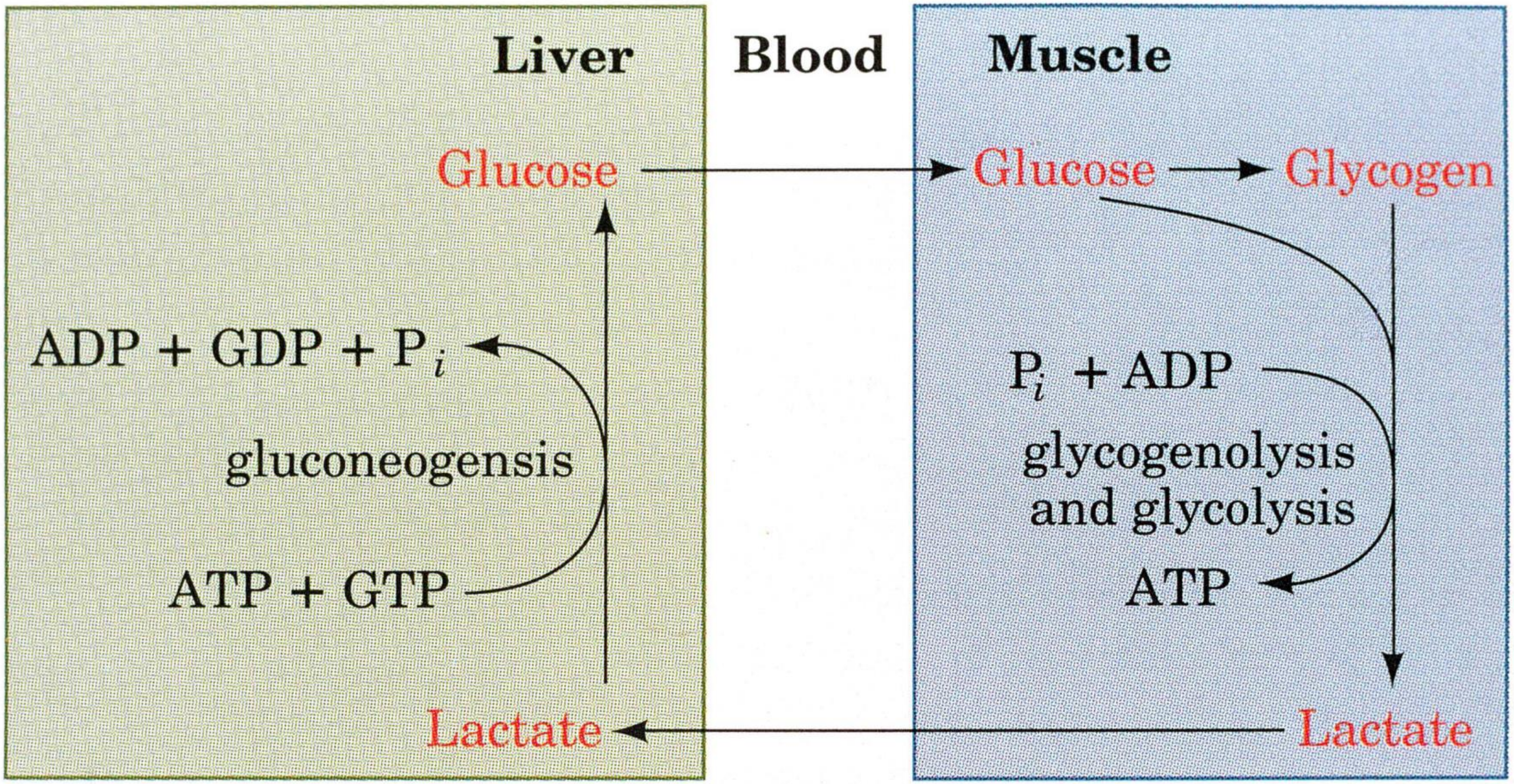
Inhibition of PFK and activation of FBPase

↓

Increased gluconeogenesis



Hormonal control of glycolysis and gluconeogenesis


Liver
Blood
Muscle
Glucose
Glucose
Glycogen
ADP + GDP + P_i
gluconeogensis
ATP + GTP
P_i + ADP
glycogenolysis
and glycolysis
ATP
Lactate
Lactate

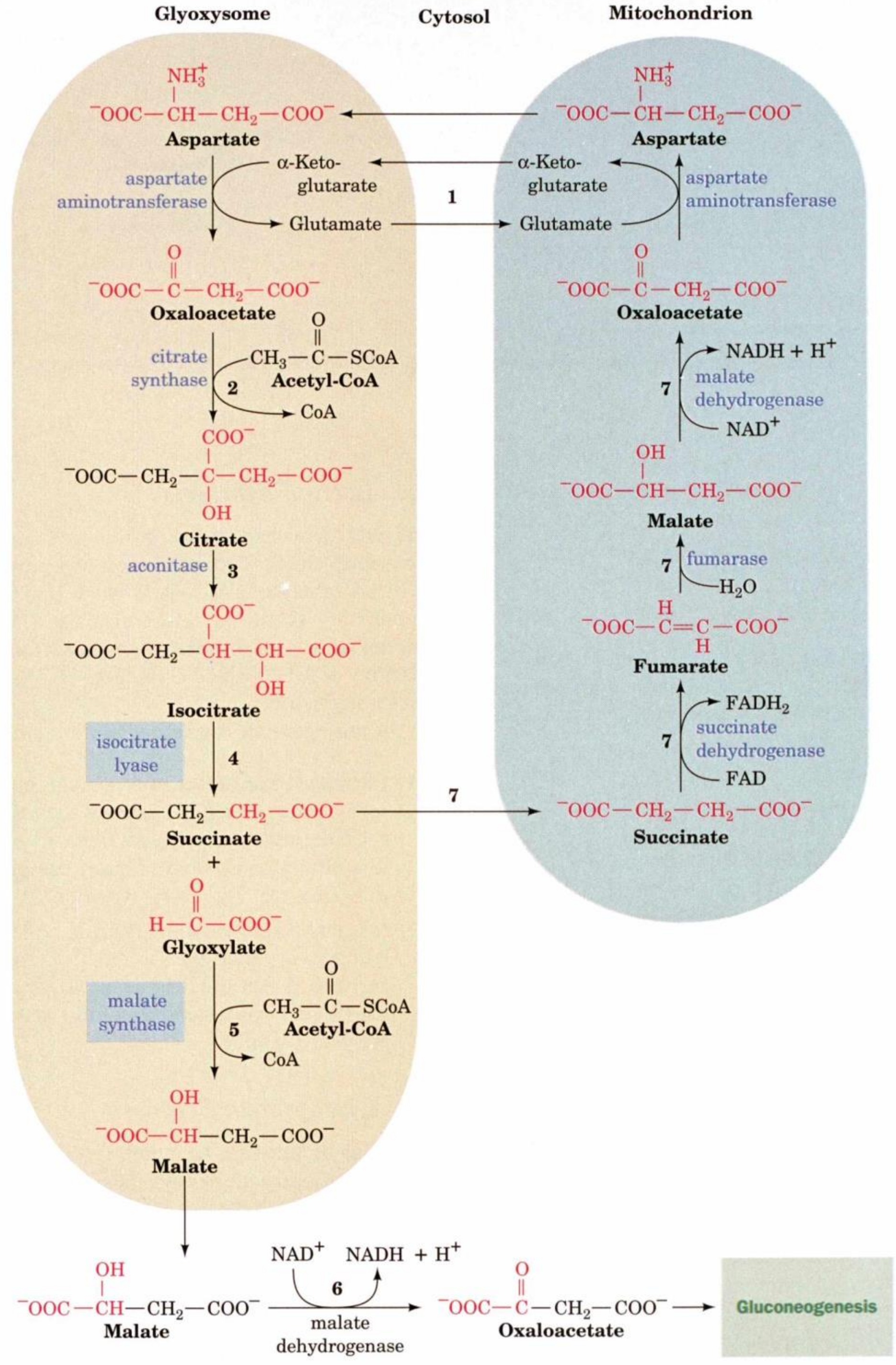
The glyoxylate pathway

Only plants have the ability to convert acetyl-CoA to Oxaloacetate directly without producing reducing equilivents of NADH. This is done in the glyoxyzome, separate from the mitochondria and allows a replenishment of oxaloacetate.

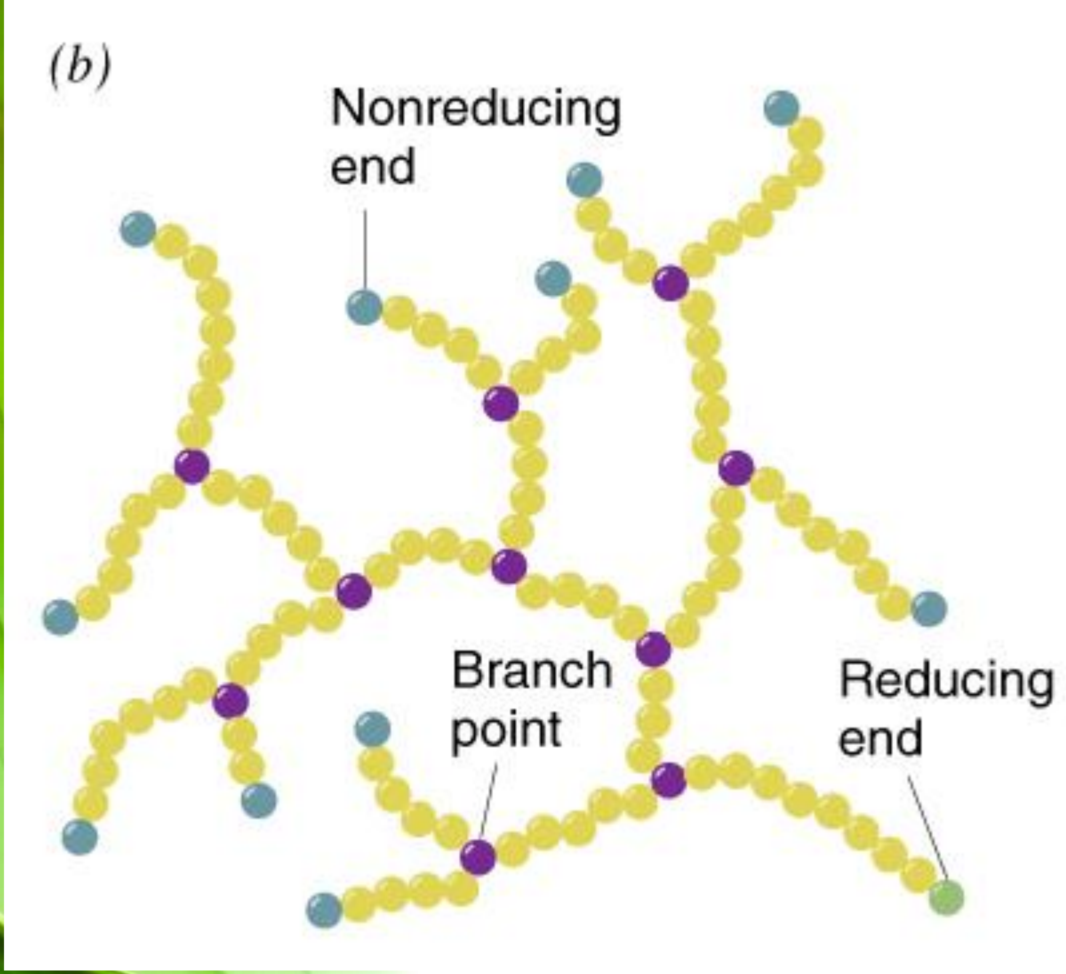
Isocitrate lyase - cleaves isocitrate into succinate and glyoxylate. The succinate goes to the mitochondria

Malate synthase makes malate from glyoxylate and Acetyl-CoA.

The Oxaloacetate can go directly to carbohydrate synthesis.

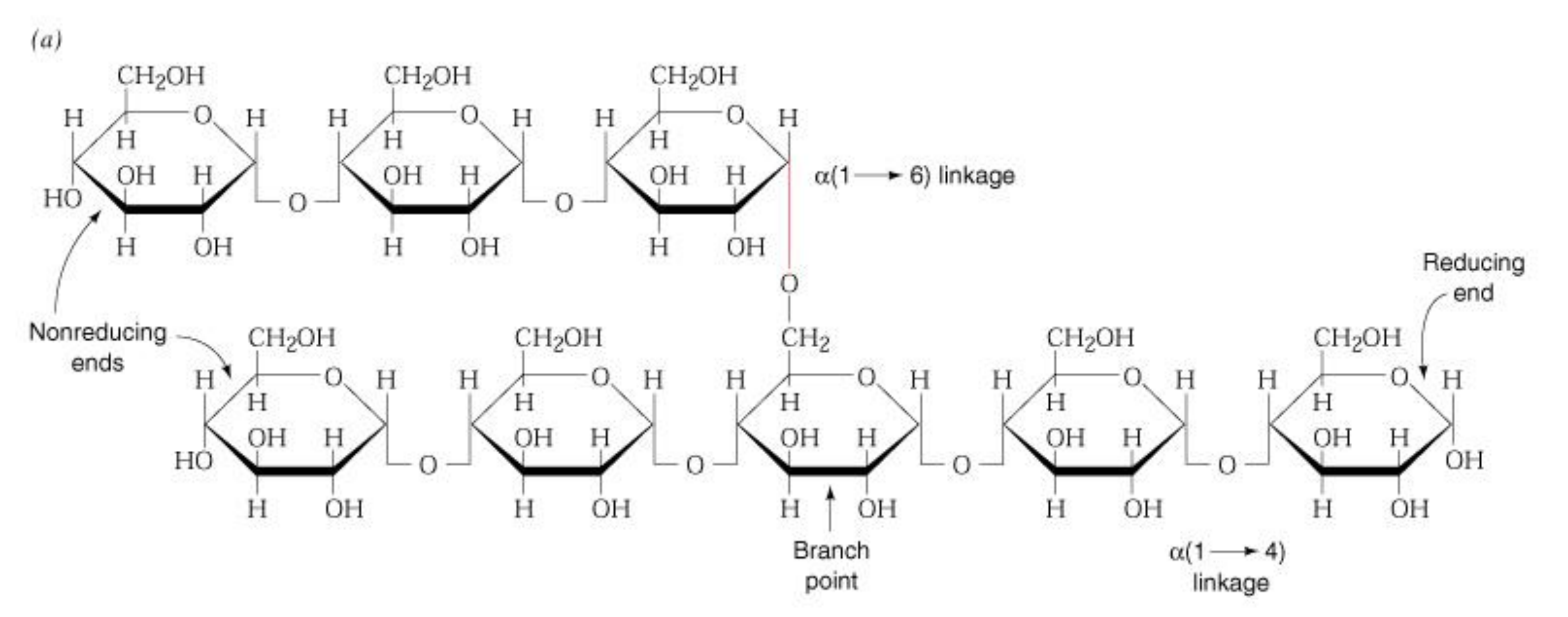


Glyoxysome
Cytosol
Mitochondrion
Aspartate
α-Ketoglutarate
Glutamate
aspartate aminotransferase
1
Oxaloacetate
citrate synthase
2
Acetyl-CoA
CoA
Citrate
aconitase
3
Isocitrate
isocitrate lyase
4
Succinate
+
Glyoxylate
malate synthase
5
Malate
7
NADH + H+
malate dehydrogenase
NAD+
fumarase
H2O
Fumarate
FADH2
succinate dehydrogenase
FAD
6
Gluconeogenesis


(b)
Nonreducing end
Branch point
Reducing end

Glycogen Storage

- Glycogen is a D-glucose polymer
- $\alpha(1\rightarrow4)$ linkages
- $\alpha(1\rightarrow6)$ linked branches every 8-14 residues



Glycogen Breakdown or Glycogenolysis

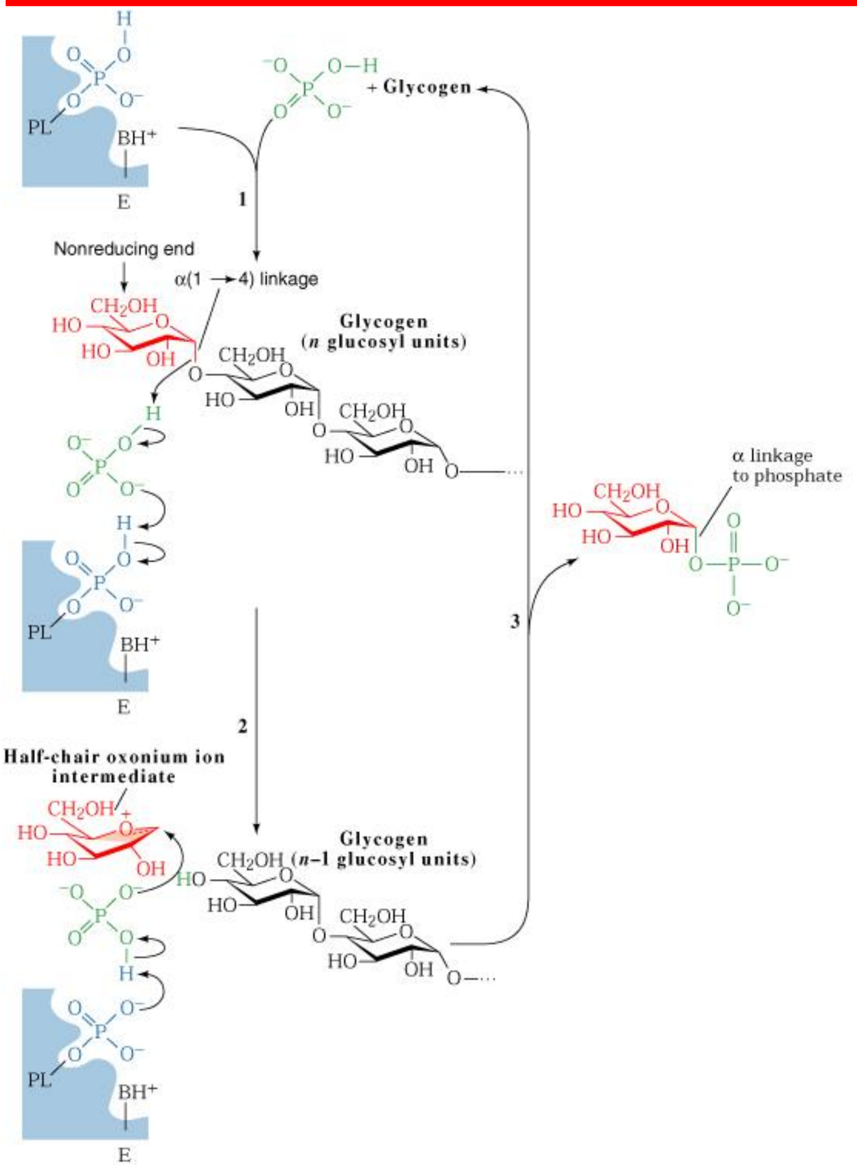
- Three steps
  - Glycogen phosphorylase

    Glycogen + Pi <-> glycogen + G1P

    (n residues)   (n-1 residues)

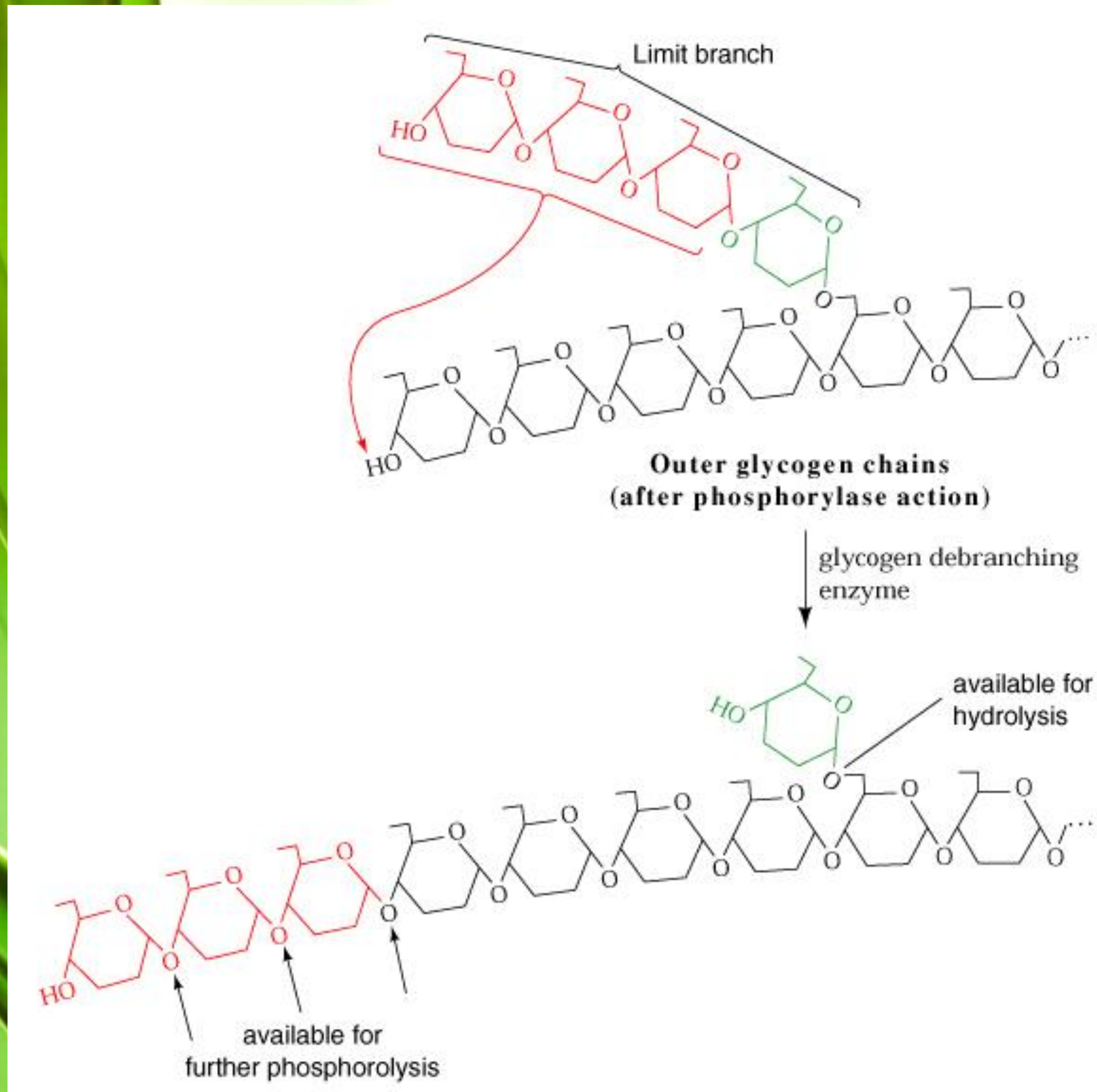
  - Glycogen debranching
  - Phosphofructomutase

Glycogen Phosphorylase

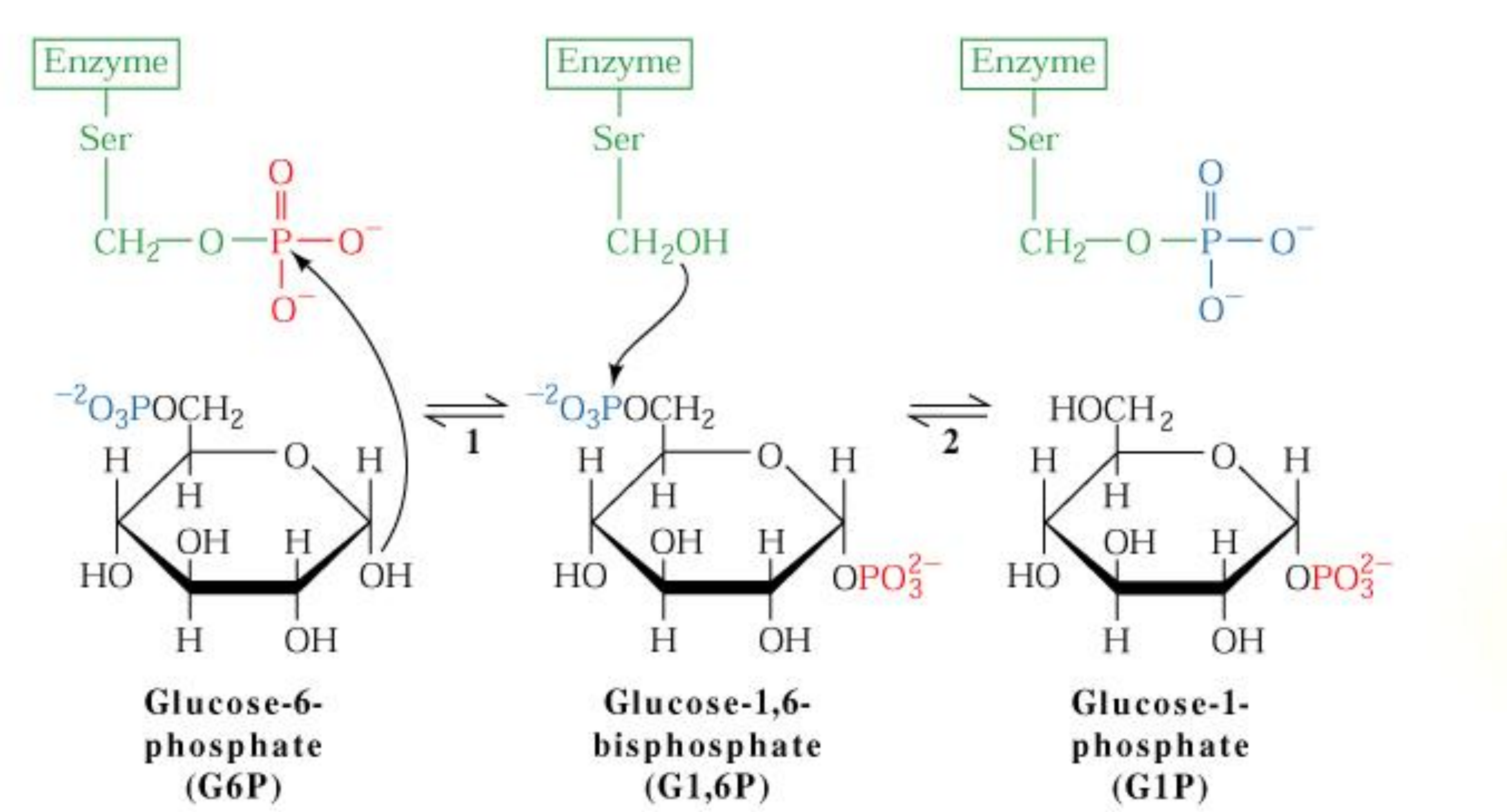


Requires
Pyridoxal-5’-phosphate
PLP

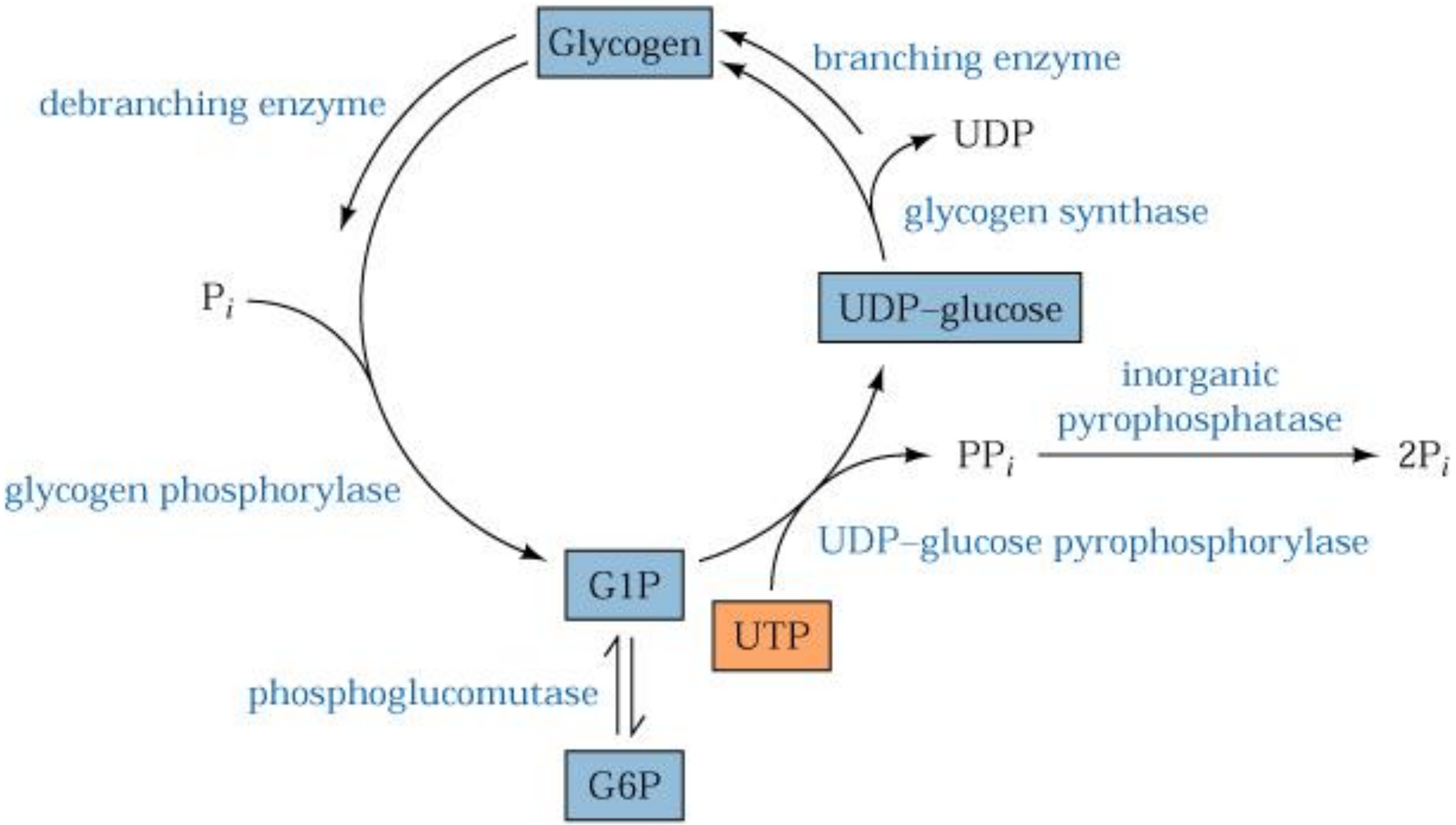
Glycogen Debranching Enzyme



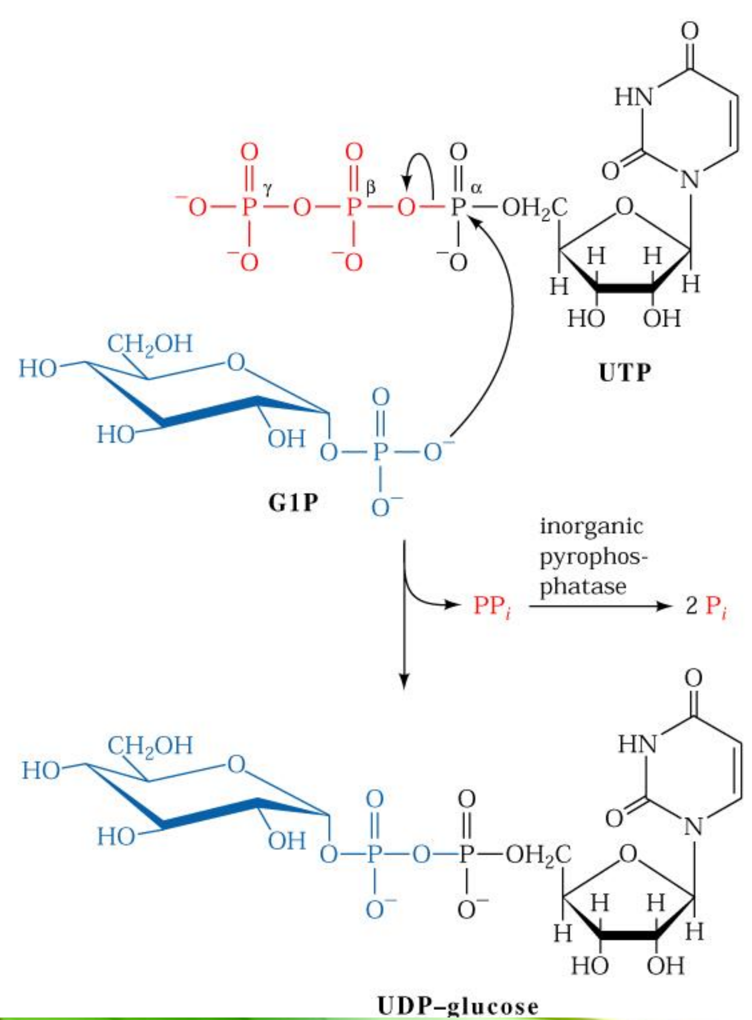
Phosphofructomutase



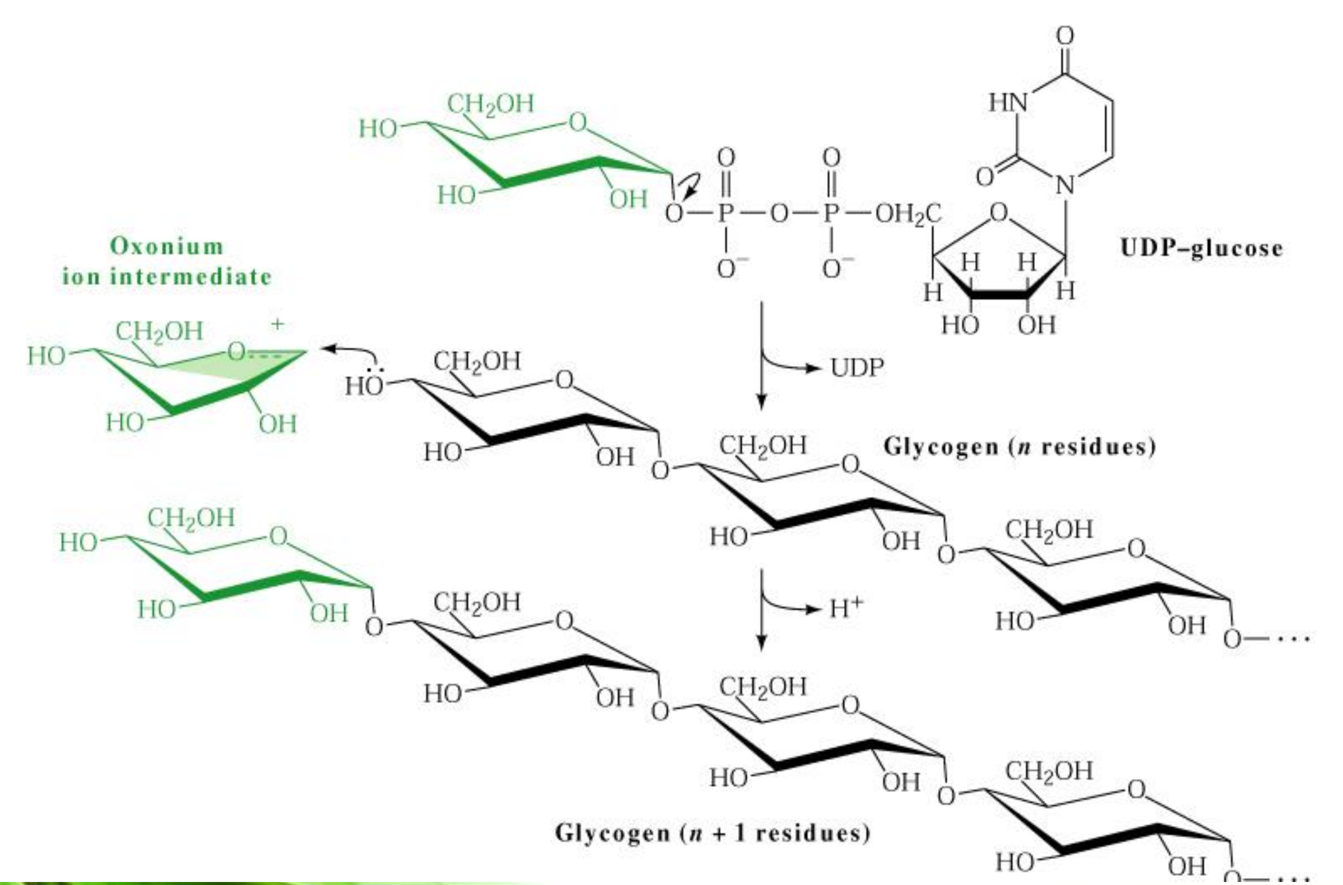
Glycogen Synthesis



UDP-glucose Pyrophorylase



Glycogen Synthase



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