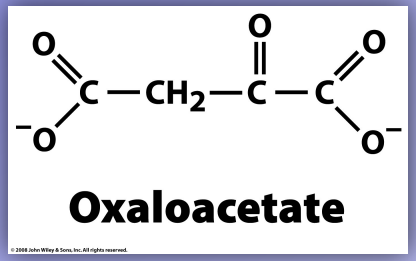
CHEM 539

Molecular Metabolism: Pathways and Regulation

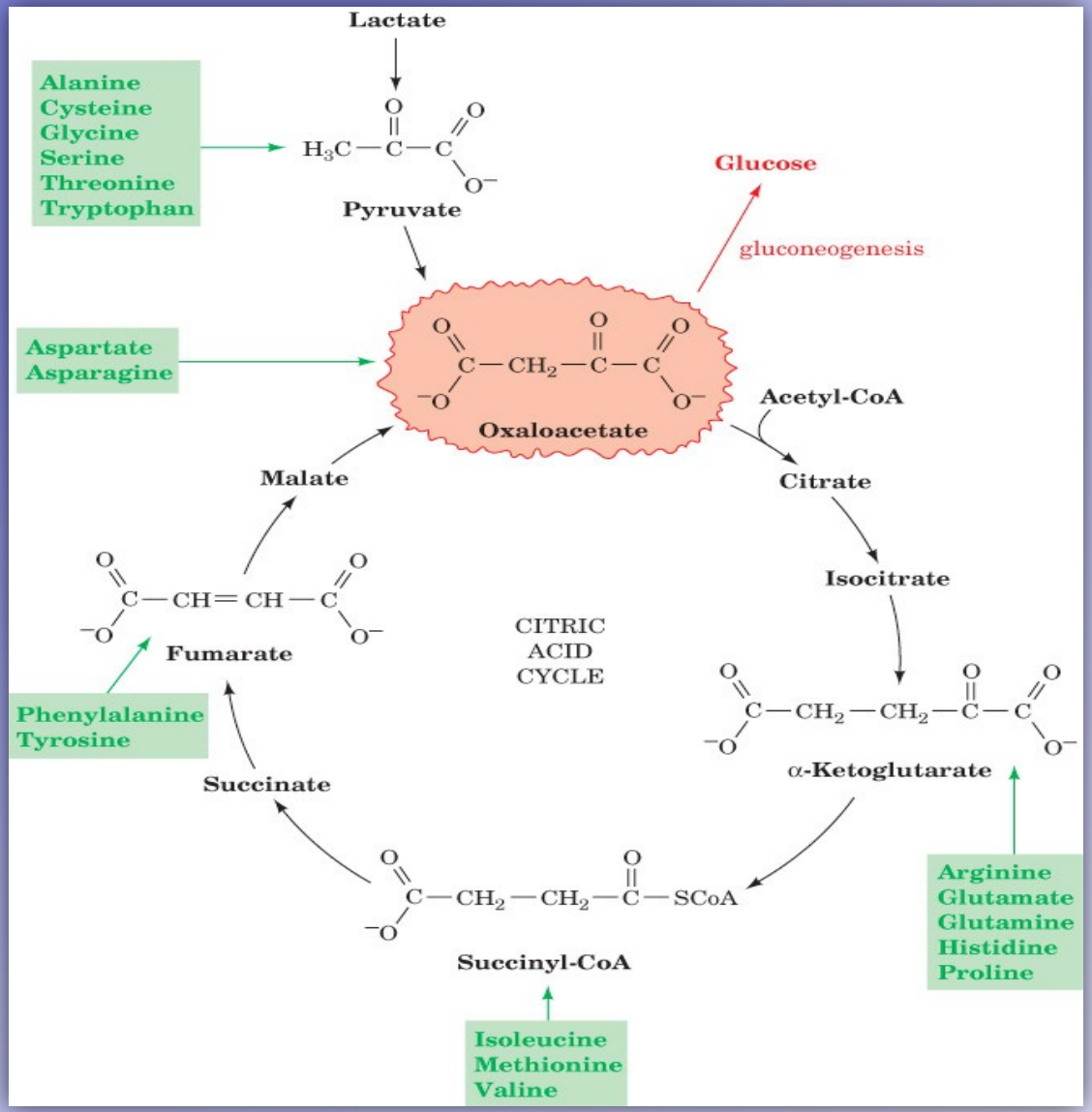
PPT Set 5: Liver Gluconeogenesis (Part A)

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



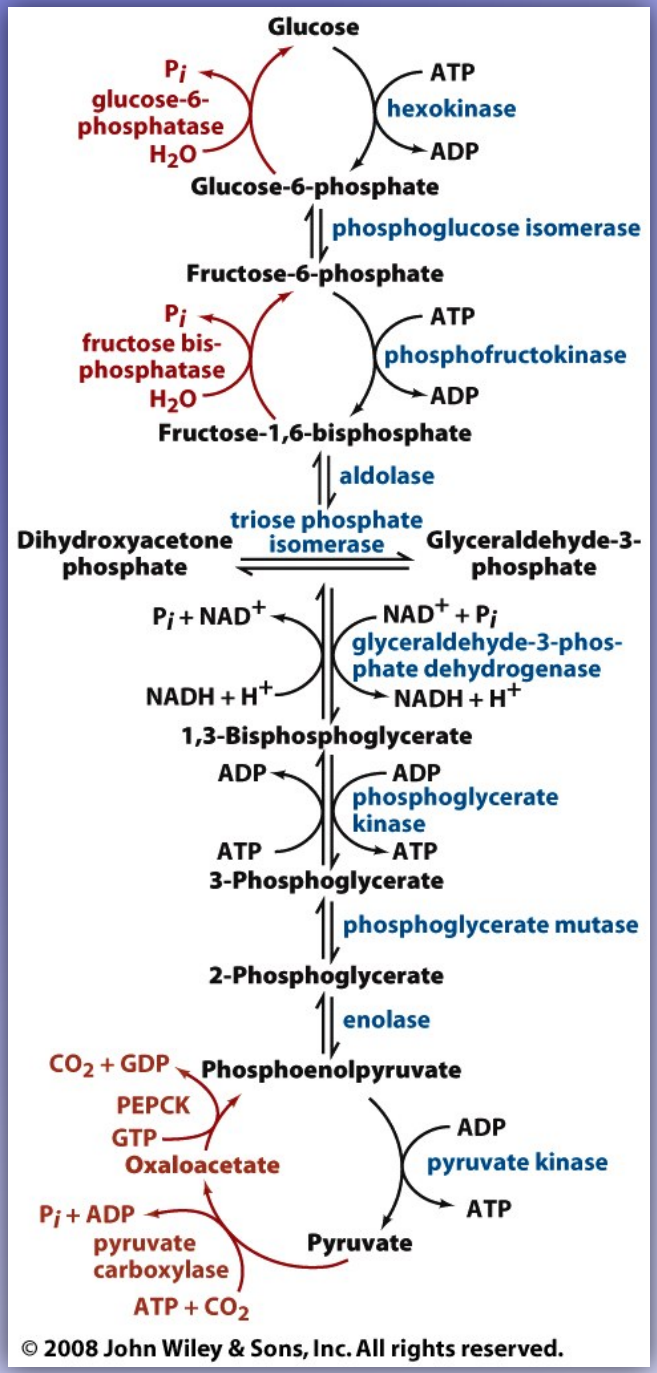
Oxaloacetic acid (OAA), a TCA intermediate, is the starting material for gluconeogenesis; all other precursors need to be converted into it; gluconeogenesis occurs primarily, if not exclusively, in liver.

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



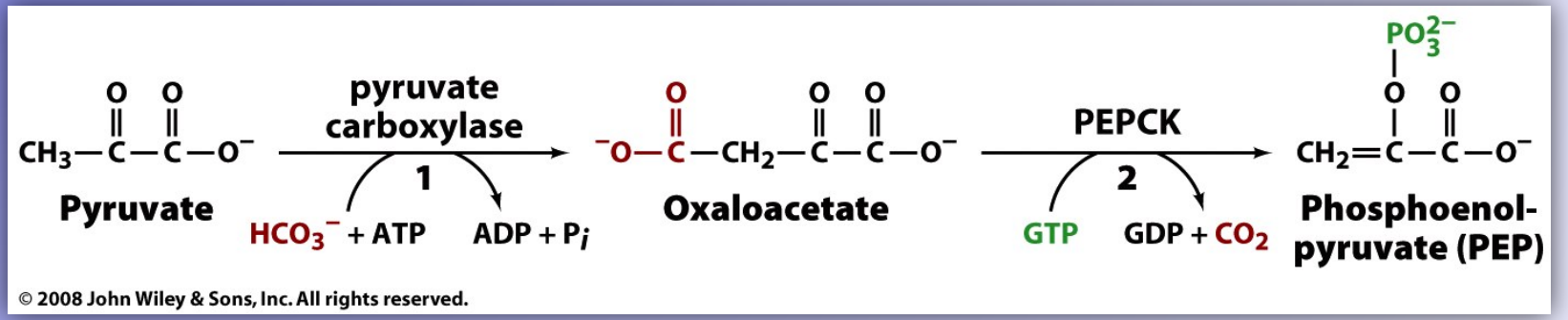
Pathways converting lactate, pyruvate, and citric acid cycle intermediates to oxaloacetate

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*).



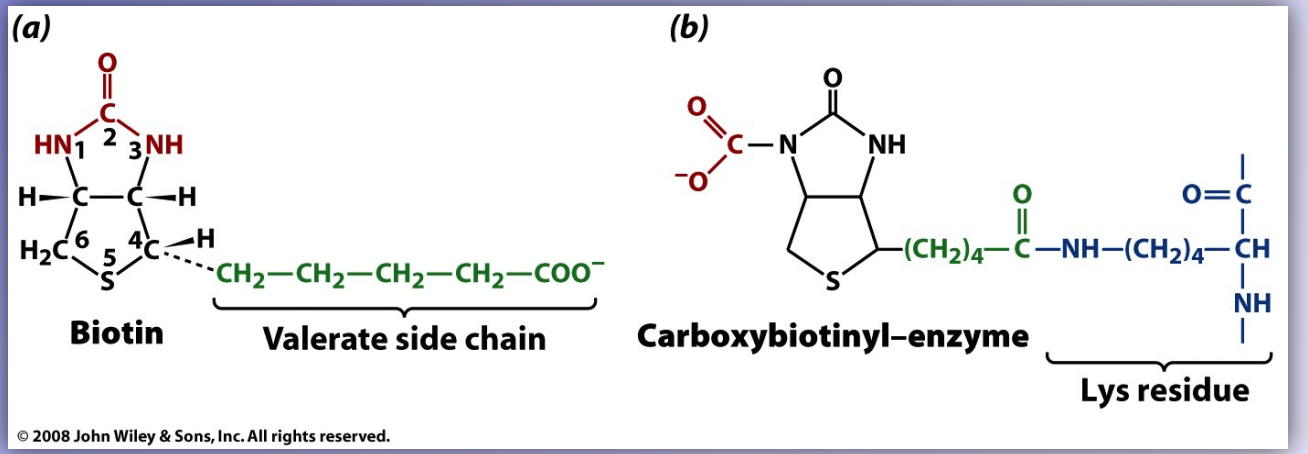
Gluconeogenesis does not occur by strict reversal of glycolysis. This is because the three regulatory enzymes of glycolysis (HK, PFK,and PK) are essentially irreversible *in vivo*. Gluconeogenesis can only occur through specific enzymes that allow for the reversal of these three glycolytic steps. These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

Converting pyruvate to PEP via OAA: pyruvate carboxylase and PEPCK

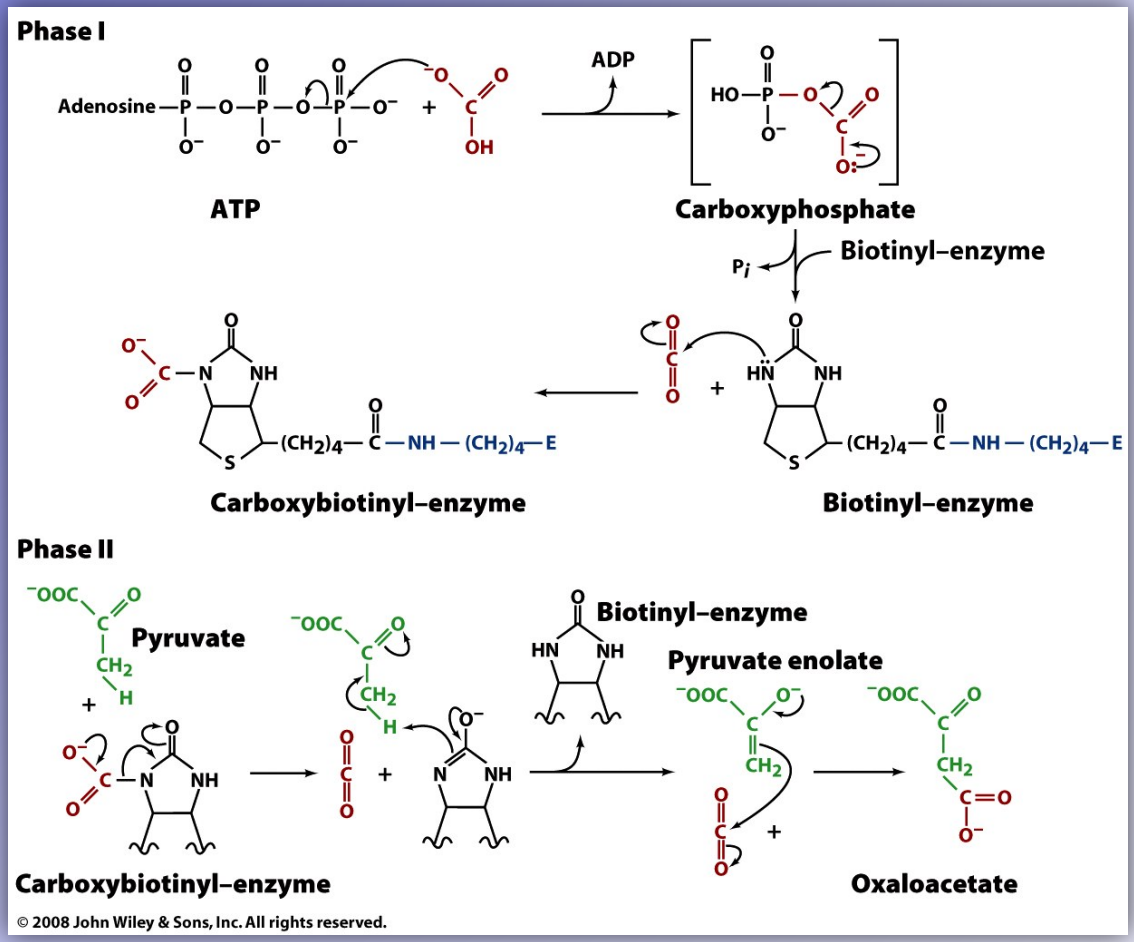


The conversion of pyruvate to OAA occurs in *mitochondria*. PEPCK is found either in the *cytosol* and/or *mitochondria*, depending on the species. This means that pyruvate, PEP and/or OAA need to be transported between the cytosol and mitochondria to support gluconeogenesis.

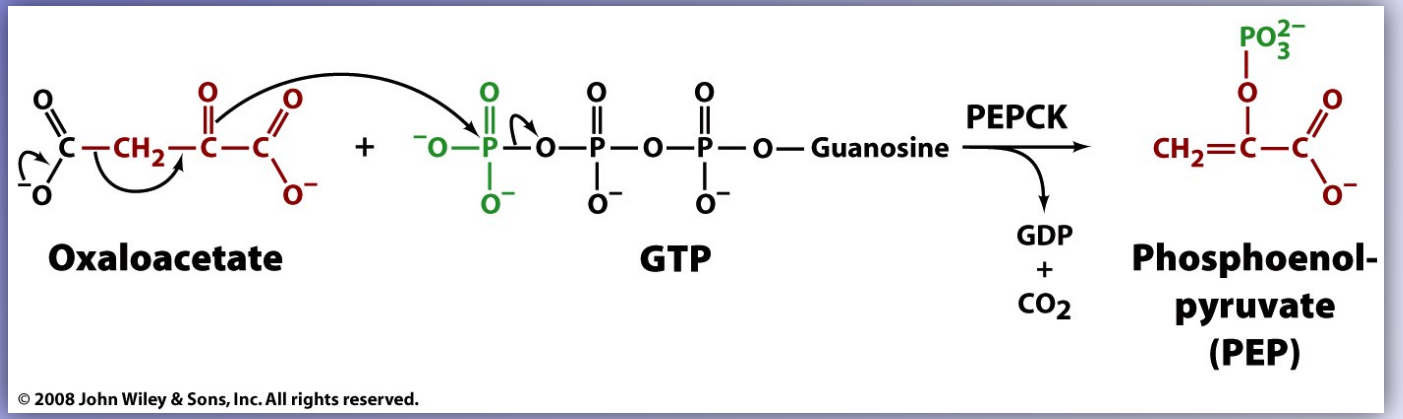
Pyrivate carboxylase is a carboxylating enzyme that requires biotin as a coenzyme.

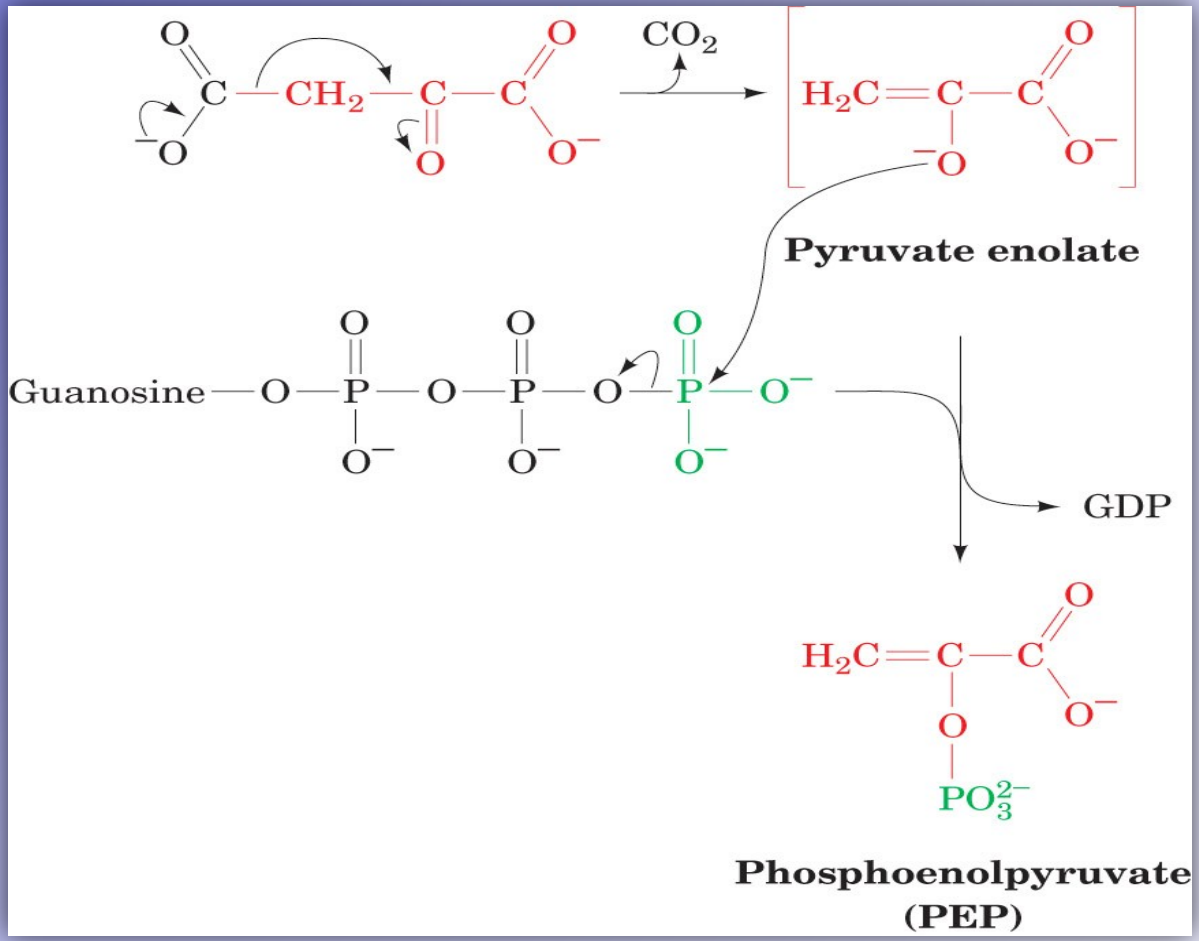


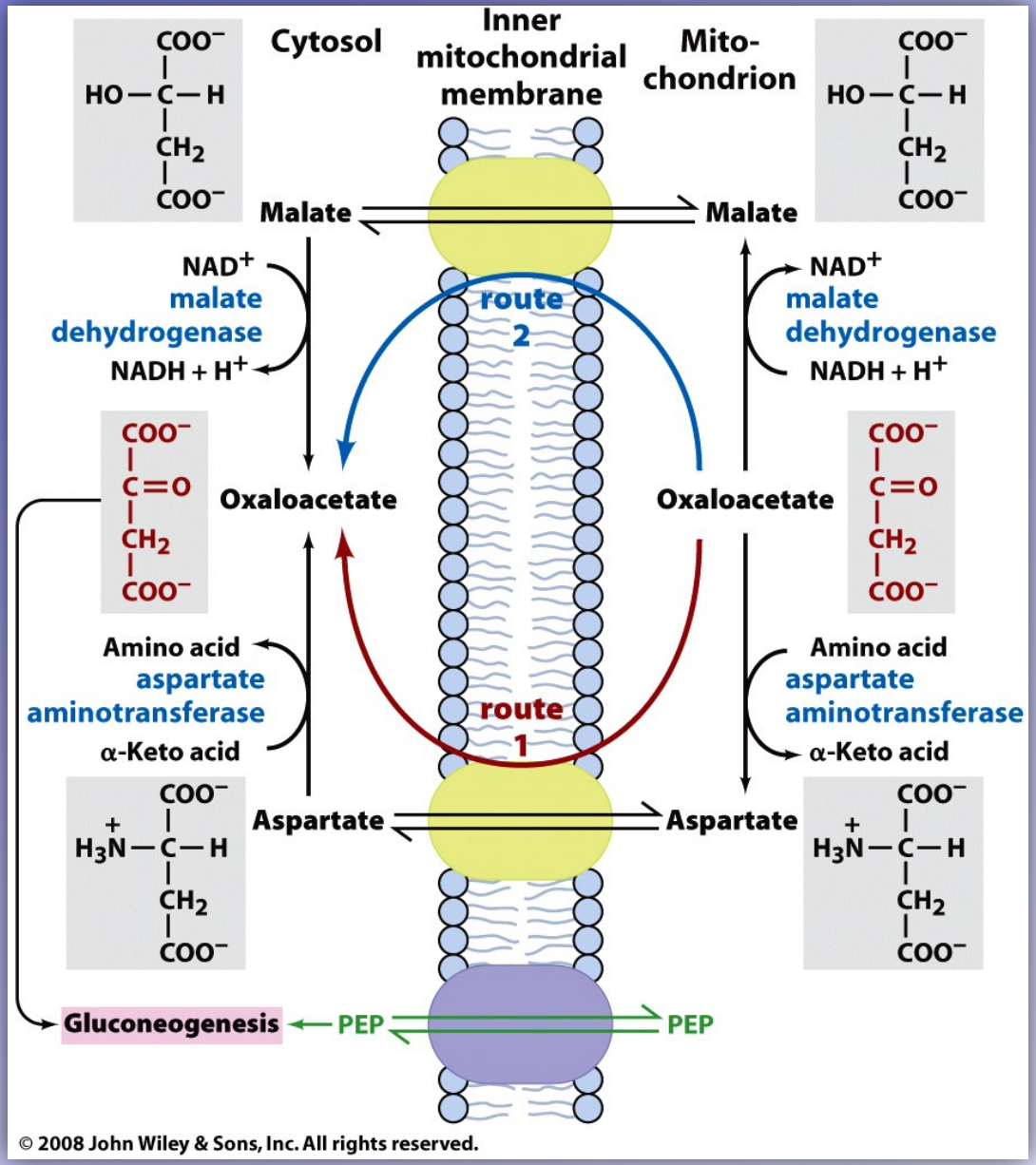
Proposed mechanism of PC



Converting OAA to PEP: PEPCK




CO2
Pyruvate enolate
Guanosine
GDP
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.