Definition

the denovo synthesis of glucose, requires both mitochondrial and cytosolic enzymes
Substrates: Glycerol, Lactate, amino acids
4 unique reactions in gluconeogenesis to overcome irreversible reactions in glycolysis
Gluconeogenesis is regulated by glucagon, substrate availability, acetyl-CoA and AMP

Substrates

Glycerol	released during TAG hydrolysis, converted to G3P by Glycerol kinase, then to DHAP by G3P DH, DHAP can then enter gluconeogenesis
Lactate	released by excreting skeletal muscles and nonmitochondriated cells, used via cori cycle where lactate is oxidized to pyruvate
Amino Acids	hydrolysis of tissue proteins lead to production of α-KG, which can then form OAA via the TCA cycle. Gives rise to ketone bodies.

Regulation

Glucagon (stimulant)	changes allosteric effectors (lower hepatic F2,6BP), covalent modification of enzyme activity (GPCR, cAMP, CDK-A; diverts PEP to gluconeogenesis), increase PEPCK transcription.
Substrate availability	more substrate = increased rate, decreased insulin leads to mobilization of AA to provide carbon skeletons, ATP and NADH is provided by FA[O]
Acetyl-CoA (allos.)	increases TAG hydrolysis in adipose, increasing FA above β-[O], Acetly-CoA accumulates and activates PC. Diverts pyruvate toward gluconeogenesis.
AMP inhibition (allos.)	F1,6BP inhibited, reciprocal reguation of glycolysis and gluconeogenesis

Reactions

Pyruvate Carboxylase	Pyruvate carboxylated to OAA, then to PEP by carboxykinase. PC require biotin as a coenzyme. PC has two functions: produce PEP and replenish OAA in the TCA cycle. PC is allosterically activated by Acetyl-CoA.
Reducation of OAA to malate	OAA can't transfer through mito membrane, so must be reduced to malate first by Malate DH. Once on the other side, MDH will reoxidize it to OAA. NADH is used throughout this process.
PEP carboxykinase	OAA converted to PEP, this is performed by coupling of PC to PEPCK. PEP can then continue through reverse glycolysis reactions until F1,6BP.
F1,6BPase	Key regulatory step, inhibited by high AMP:ATP ratio and by F2,6BP.
G6P DP	G6P DP hydrolyses G6P, bypassing glucokinase. Primarily takes place in the liver, requires G6P translocase to transport G6P through ER membrane.

By **BTNR**
cheatography.com/btnr/

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