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# Gluconeogenesis

Tuesday, January 08, 2008  
10:00 AM

12. What are the major carbon sources for gluconeogenesis? Where does gluconeogenesis begin? How does the TCA cycle function to coordinate the flow of precursors into gluconeogenesis?
  - a. Major carbon sources: AA, lactate, fructose, galactose, glycerol from triglyceride breakdown
  - b. Occurs in liver and lesser extent in kidney, begins in mitochondria with production of oxaloacetate from pyruvate
  - c. TCA cycle intermediates are usually the eventual destination of amino acids that will be used to make glucose; most AA flow through TCA cycle to become OAA or pyruvate
13. How is oxaloacetate formed from pyruvate? What regulated the reaction? What is the required cofactor and what vitamin is involved?
  - a. Pyruvate crosses mitochondrial membrane
  - b. Pyruvate carboxylase:  $\text{Pyruvate} + \text{CO}_2 + \text{ATP} \rightarrow \text{oxaloacetate} + \text{ADP} + \text{P}_i$ ; requires biotin cofactor (vit B7/H)
  - c. Reaction is stimulated by Acetyl CoA
14. What are the reactions involved in the conversion of pyruvate to phosphoenolpyruvate? How are the carbons from aspartate and glutamate transferred from mitochondria to cytosol? Does CO<sub>2</sub> become incorporated into glucose?
  - a. Malate Dehydrogenase:  $\text{OAA} + \text{NADH} + \text{H}^+ \rightarrow \text{Malate} + \text{NAD}^+$
  - b. Malate is exported to cytosol
  - c. Malate Dehydrogenase reverse rxn
  - d. PEP Carboxykinase:  $\text{OAA} + \text{GTP} \rightarrow \text{PEP} + \text{CO}_2 + \text{GDP}$
  - e. Thus the CO<sub>2</sub> that was used to make the oxaloacetate in the pyruvate carboxylase rxn is not incorporated into glucose
  - f. The entire pathway from Pyr  $\rightarrow$  PEP requires 2 ATP
  - g.  $\text{PEP} \rightarrow \rightarrow 3\text{PG} + \text{ATP} \rightarrow 1,3\text{DPG} + \text{NADH} \rightarrow \text{G3P} + \text{NAD}^+$ 
    - i. The reducing equivalent that was produced in the cytosol is used
    - ii. The net is that a reducing equivalent was transferred from the mitochondria to the cytosol and used
15. How does the malate shuttle operate? What is the significance of the shuttle in terms of transfer of reducing equivalents? What precursors would need the malate shuttle?
  - a. Malate shuttles operates to transfer a malate from the mitochondria to the cytosol
  - b. It transfers one reducing equivalent
  - c. Malate shuttle is required for pyruvate and any amino acids that are converted to pyruvate or malate
16. How does the aspartate / alpha-ketoglutarate shuttle operate? Under what conditions would this shuttle function?
  - a. Lactate is converted to pyruvate in the cytosol
    - i. Pyruvate is exchanged w/ alpha-KG in the mito
    - ii. Pyruvate is converted to OAA
    - iii. Transaminase:  $\text{OAA} + \text{Glu} \rightarrow \text{alpha-KG} + \text{Asp}$
    - iv. Asp-Glu transporter sends Asp to cytosol and Glu into mito
    - v. Transaminase:  $\text{alpha-KG} + \text{Asp} \rightarrow \text{OAA} + \text{Glu}$
    - vi.  $\text{OAA} \rightarrow \text{PEP} \rightarrow \text{G3P} \rightarrow$
  - b. This would function in anaerobic conditions, because effectively the pyruvate has been transported out of the mitochondria w/o transporting a reducing equivalent with it
17. How are lactate and alanine converted to glucose? Under what conditions would PEP transfer from mitochondria to cytosol be involved?
  - a. Alanine-glucose cycle
    - i. Alanine travels in bloodstream to liver
    - ii. Aminotransferase:  $\text{Ala} + \text{alpha-KG} \rightarrow \text{Pyr} + \text{Glu}$

- iii. Pyr --> Glucose via gluconeogenesis
  - b. Lactate
    - i. Via the asp/alpha-KG shuttle
    - ii. Mitochondrial
      - 1) Mito. PEP Carboxykinase:  $\text{OAA} + \text{GTP} \rightarrow \text{PEP} + \text{GDP} + \text{CO}_2$
      - 2) Once again under conditions where lactate is produced (reducing equivalents can't be transferred out of mitochondria)
18. How is phosphoenolpyruvate converted to glucose-6-P?
- a. Essentially reverse of glycolysis
  - b.  $\text{PEP} \leftrightarrow 2\text{PG}$
  - c.  $2\text{PG} \leftrightarrow 3\text{PG}$
  - d.  $3\text{PG} + \text{ATP} \leftrightarrow 1,3\text{DPG} + \text{ADP}$
  - e.  $1,3\text{DPG} + \text{NADH} + \text{H}^+ \leftrightarrow \text{G3P} + \text{NAD}^+ + \text{Pi}$
  - f.  $\text{G3P} \leftrightarrow \text{DHAP}$
  - g.  $\text{G3P} + \text{DHAP} \rightarrow \text{F-1,6-BP}$
  - h.  $\text{F-1,6-BP} \rightarrow \text{F6P} + \text{Pi}$
  - i.  $\text{F6P} \leftrightarrow \text{G6P}$
  - j.  $\text{G6P} \rightarrow \text{Glucose} + \text{Pi}$