Cellular Metabolism

Part 4 - Cell Physiology

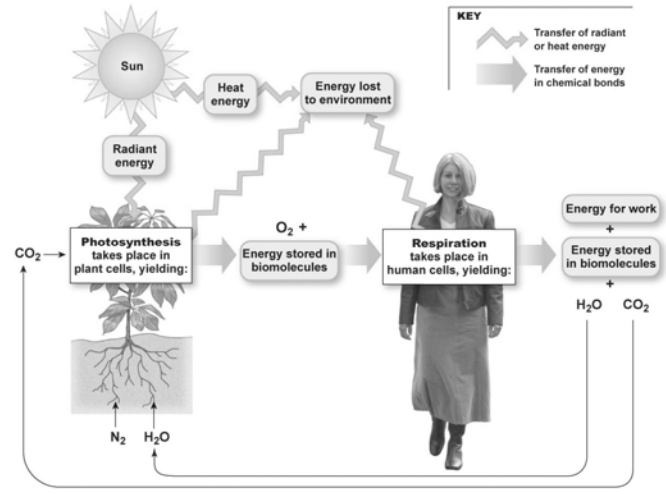
Lecture Outline

- Energy Systems & Flow
- Metabolism Basics
- Cellular Respiration
  - Glycolysis
  - Citric Acid Cycle
  - Electron Transport Chain & Oxidative Phosphorylation
- Substitutes – what can be used besides glucose & how?

Energy Systems & Flow

- Energy is stored in two macro systems
  - Plants & Animals
    - Both flora and fauna are composed of additional subsystems with both storage and flows
- Energy flows between these two storages when consumption occurs
- Entropy increases at each level of consumption (trophic level)
- We are concerned with chemical energy use and conversion to ATP = cellular respiration
  - $C_6H_{12}0_6 + 6O_2 = 6CO_2 + 6H_2O + 36ATP$

Energy Systems and Flow



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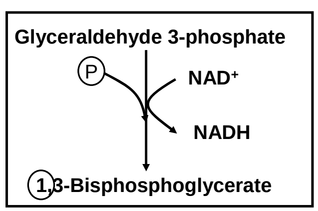
Metabolism Basics

- Metabolism:
  – The sum of all chemical reactions that occur in the body
  – Require the use of enzymes and coenzymes
- General Classification of chemical reactions
  – Anabolic
    - Those that create larger molecules
      – Ex. glycogenesis
  – Catabolic
    - Those that breakdown larger molecules into smaller molecules
      – Ex. glycogenolysis

Metabolism Basics

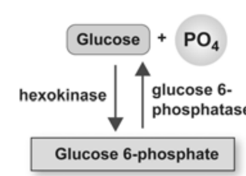
- Special types of metabolic reactions
  1. **Oxidation – Reduction**
     - A **coupled** reaction in which electrons are transferred from one molecule to another
     - This is a MAJOR player in the ATP production pathway
     - Mediated by oxioreductase class of enzymes
     - Oxidation
       – Transfers electrons from a molecule to oxygen (removes e^-)
       – Removes H^+
         » A catabolic pathway
     - Reduction
       – The gain of electrons from a molecule
         » An anabolic pathway



       – Example: Glyceraldehyde 3-phosphate is oxidized (and phosphorylated) to 1,3-Bisphosphoglycerate

Metabolism Basics

- Special types of metabolic reactions
  2. **dehydration-hydrolysis**
     - Uses hydrolase class of enzymes
     - Removing water to create larger molecules
     - Adding water to split larger molecules into smaller molecules
  3. **addition-subtraction-exchange**
     - Transferases – mediate exchanges
     - Lyases – mediate addition/removal
     - The addition, removal or exchange of chemical groups between molecules
       – Carboxylation – Decarboxylation
       – Phosphorylation – dephosphorylation



Metabolism Basics

- Special types of metabolic reactions

4. Ligation Reactions

- – Molecular groups are joined using energy
- – Uses ligase class of enzymes
- – Ex. Formation of acetyl CoA, succinyl CoA

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Production of ATP Overview

Recall the overall equation:

$C_6H_{12}0_6 + 6O_2 = 6CO_2 + 6H_2O + 36ATP$

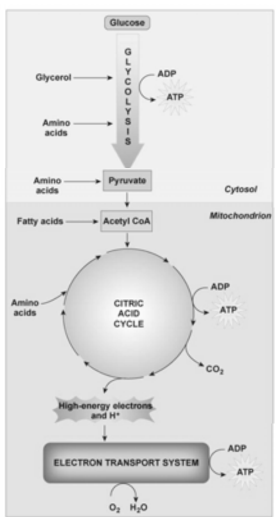
To accomplish this requires different processes at different places within the cell

Step 1 – Glycolysis
- formation of two pyruvates

Step 2 – Pyruvate oxidative decarboxylation
- formation of two acetyl CoA

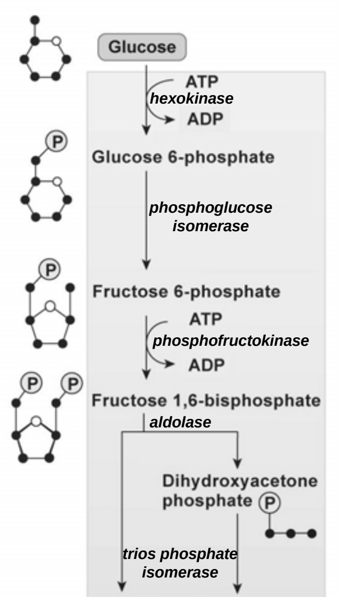
Step 3 – Citric Acid Cycle
- end product (oxaloacetate) combines with acetyl CoA to start, forming the same end product

Step 4 – Electron Transport System
use of high energy protons and electrons (from coenzymes) to power ATP synthesis



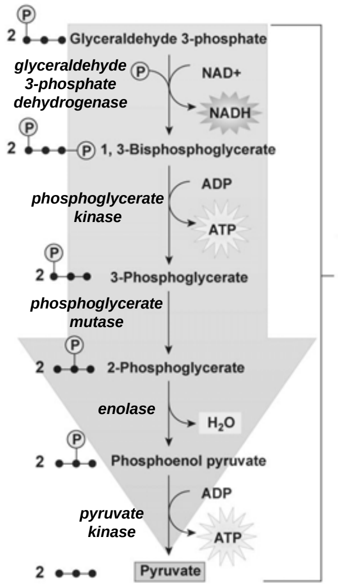
Glycolysis

1. Glucose upon entering the cell is phosphorylated to Glucose 6-phosphate
   - – Additive reaction, enzyme is *hexokinase*, converting ATP to ADP and adding P to 6th carbon of glucose
2. Glucose 6-phosphate is converted to Fructose 6-phosphate by *phosphoglucose isomerase*
3. Additional phosphate group added by *phosphofructokinase* to make Fructose 1,6-bisphosphate
4. Enzyme *aldolase* splits Fructose 1,6-bisphosphate into two dihydroxyacetone phosphate molecules
5. *Trios phosphate isomerase* then converts dihydroxyacetone to glyceraldehyde 3-phosphate



Glycolysis

5. Glyceraldehyde 3-phosphate (G3P) is oxidized (NAD^+ is reduced to NADH) and has phosphate added to third carbon by *glyceraldehyde 3-phosphate dehydrogenase* to make 1,3-bisphosphoglycerate (1,3 BPG)
6. ADP undergoes phosphorylation as 1,3 BPG is dephosphorylated by *phosphoglycerate kinase*, making 3-phosphoglycerate molecules
7. 3-phosphoglycerate is converted to 2-phosphoglycerate by *phosphoglycerate mutase*
8. 2-phosphoglycerate is converted by phosphoenol pyruvate by *enolase*
9. phosphoenol pyruvate is dephosphorylated as ADP is phosphorylated to Pyruvate by *pyruvate kinase*

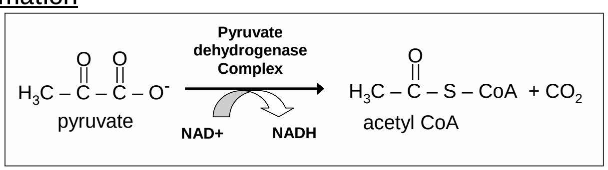


Glycolysis

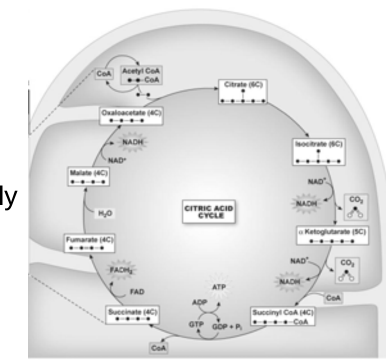
- Animation
- End result:
  - 2 ATP produced
  - 2 NADH produced
  - 2 pyruvate molecules

Pyruvate Oxidative Decarboxylation (Link reaction)

- This is mediated by a large enzyme complex (pyruvate dehydrogenase) that converts pyruvate to Acetyl CoA
- Occurs within the mitochondria
- NAD^+ is reduced to NADH,
- Carbon dioxide is released
  - This leaves a 2 carbon group (acetyl) to which CoA is attached
- Acetyl CoA is formed **Why is this an important step?**
- Animation



Kreb's Cycle

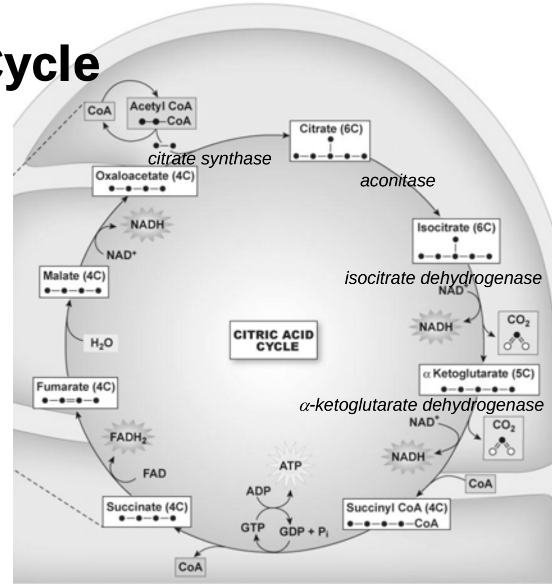


- Goals of Krebs Cycle
  - Combine end product of last cycle with newly formed acetyl CoA
  - Through a series of oxidation/reduction, addition/subtraction, and ligand reactions oxidize pyruvate to carbon dioxide and water AND
    - Make an end product (oxaloacetate) that can start the cycle again
    - Produce GTP (which phosphorylates ADP to ATP)
    - Reduce NAD+ and FAD coenzymes which are to be used in the **Electron Transport System**

Kreb's Cycle

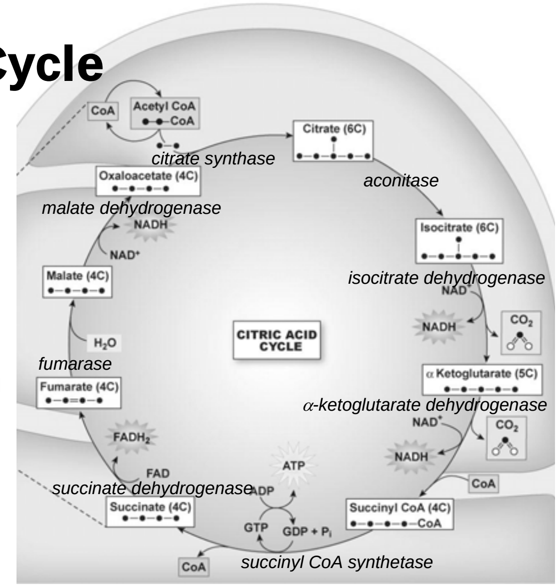
Steps

1. Acetyl CoA combines with oxaloacetate to form Citrate using *citrate synthase*
2. Citrate is converted to Isocitrate by *aconitase*
3. Isocitrate is oxidized and decarboxylated by *isocitrate dehydrogenase* to form α-ketoglutarate
4. α-ketoglutarate is converted into succinyl CoA by *α-ketoglutarate dehydrogenase*



Kreb's Cycle

5. Succinyl CoA is converted into Succinate as CoA is subtracted and GDP is phosphorylated by *succinyl CoA synthetase*
6. Succinate is oxidized to Fumarate by *succinate dehydrogenase*, reducing FAD in the process
7. Fumarate is converted to Malate by *fumarase*, adding water in the process
8. Malate is converted back to oxaloacetate by *malate dehydrogenase* and is further oxidized, and NAD⁺ is reduced.

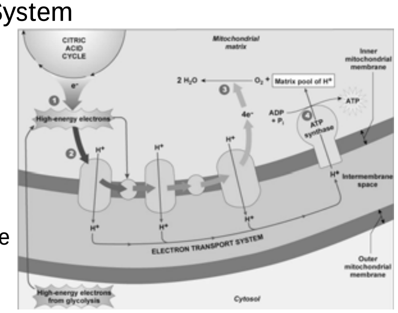


Kreb's Cycle

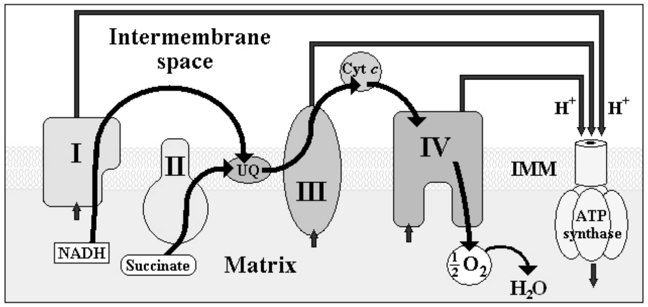
- <u>Animation</u>
- From Kreb's Cycle:
  - Each of the NADH (NADH+H+) is capable of providing the energy to synthesize 2.5 ATP molecules
  - Each of the FADH2 coenzymes is capable of synthesizing 1.5 ATP molecules
    - These energized coenzymes are utilized by mitochondrial membrane components in the electron transport system
  - GTP quickly phosphorylates ADP to ATP

Electron Transport System

- Goal of Electron Transport System
  - Utilize the protons and electrons that the coenzymes (NAD⁺ and FAD) "picked up" during glycolysis (NAD⁺ only) and Kreb's cycle (both NAD⁺ and FAD).
  - The electrons "power" the movement of H⁺ (protons) across the inner membrane space creating a proton motive gradient
  - This gradient is utilized along with oxygen that has entered the mitochondrial matrix to power a rotary ATP synthase transmembrane protein complex
  - The "spent" electrons are picked up by oxygen
    - Oxygen is the final electron acceptor in the process of aerobic cellular respiration – it's why we breathe.

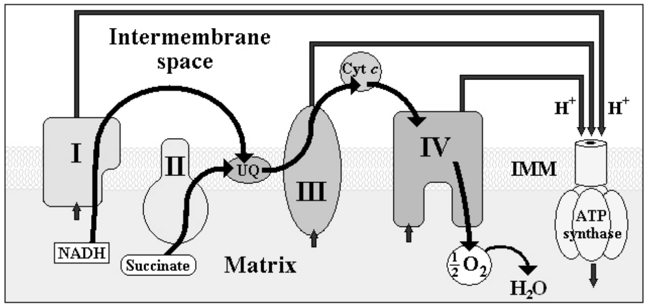


Electron Transport System



1. Membrane complex I enzymatically (*NADH dehydrogenase*) removes the high energy electrons from NADH (oxidizing it) and pumps protons into the intermembrane space.
   - The electrons are picked up by membrane carrier ubiquinone (UQ)
2. Ubiquinone transfers them to membrane complex III which uses the energy to pump additional protons into the intermembrane space.

Electron Transport System

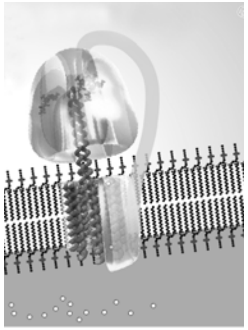


3. Cytochrome c (Cyt c) then transfers them to membrane complex IV, which pumps additional protons to the intermembrane space.

- The "spent" electrons (along with H^+ that return to the matrix) are transferred to their final electron acceptor = oxygen!

Oxidative Phosphorylation

- The continuation of the electron transport system
  - Utilizes the protons potential energy that is stored in the intermembrane space
    - A gradient has been established…
      - High proton concentration in the intermembrane space, low proton concentration in the matrix
      - The only way (besides leaking and or binding with oxygen too early to form free radicals) through the membrane and therefore down the gradient is by the large ATP synthase complex.
      - 3 hydrogen ions power the ATP synthase, which use the energy to reattach Phosphate to ADP making ATP



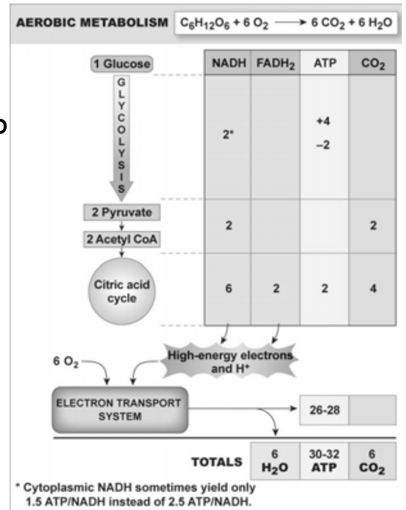
Oxidative Phosphorylation

- Animation

End Result of Aerobic Cellular Respiration

- ATP numbers…
- 8 NADH = 20 ATP
- 2 NADH = 3 ATP
- 2 FADH = 3 ATP
- Glyc/Kreb 4 ATP

30 ATP



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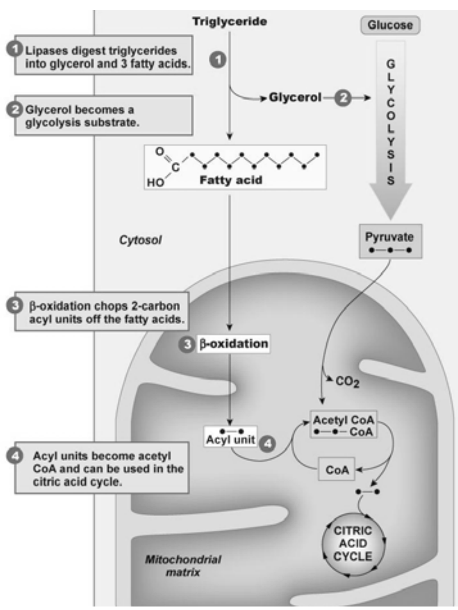
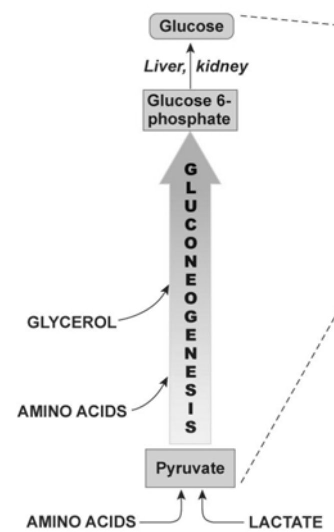
Substitutes

- Triglycerides can be utilized



Substitutes

- Proteins can be utilized:
  - Formation of new glucose from non glucose sources such as amino acids (gluconeogenesis)
  - Carbon backbones of amino acids can be converted into acetyl CoA



Wrap Up

- Eating and breathing provide all the key elements for cellular respiration
  - Metabolic pathways and membrane components take care of the rest of ATP production
  - Without ATP
    - No communication, no movement – anywhere!