Chapter 22
Aerobic Respiration and Energy Production

22.1 The Mitochondria
- Football shaped organelle about the size of a bacterial cell
- Dual membrane structure:
  - Outer mitochondrial membrane
  - Inner mitochondrial membrane:
    - Highly folded membranes = cristae
    - Has electron transport system and ATP synthase
- Space between membranes is the intermembrane space
- Interior is the matrix space containing enzymes
  - Citric acid cycle
  - β-oxidation of fatty acids
  - Degradation of amino acids

Structure and Function
- Outer membranes have many pores for the passage of small molecules
- Folds of the inner membrane create a large surface area with many transport proteins

22.2 Conversion of Pyruvate to Acetyl CoA
- Under aerobic conditions, pyruvate from glycolysis is completely oxidized to CO₂
- Enters the mitochondria and is converted to acetyl CoA
  - Activates the acetyl group for entry into the citric acid cycle
    - Kreb’s cycle
    - Tricarboxylic acid cycle
    - TCA cycle

Structure of Acetyl CoA
- Pyruvate enters the mitochondria
- Converted to a 2-carbon acetyl group
  - For further reactions, acetyl group must be activated
  - Activation occurs when the acetyl group is bonded to the thiol group of coenzyme A in a high-energy bond
    - Coenzyme A is a large thiol derived from ATP and pantothenic acid, a vitamin
Overall Decarboxylation and Oxidation of Pyruvate

- Pyruvate to acetyl CoA
  1. Decarboxylation – loss of a carboxyl group as CO₂
  2. Oxidation by NAD⁺ which accepts the hydride anion
  3. Remaining acetyl group linked to coenzyme A via a high-energy thioester bond

Reactions catalyzed by 3 enzymes and 5 coenzymes bundled together as the pyruvate dehydrogenase complex.

Role of Acetyl CoA in Cellular Metabolism

- Acetyl CoA is central in cellular metabolism
- Major function is to carry the acetyl group to the citric acid cycle
- Also functions in biosynthetic reactions to produce cholesterol and fatty acids
- Permits interconversion of energy sources
  - Fats
  - Proteins
  - Carbohydrates
- Produced by degrading
  - Glucose
  - Fatty acids
  - Some amino acids

Pyruvate Dehydrogenase Complex

- Complex contains:
  - 5 coenzymes (4 which are vitamin derived) and 3 enzymes
  - Thiamine pyrophosphate – thiamine
  - FAD – riboflavin
  - NAD⁺ – niacin
  - Coenzyme A – pantothenic acid
  - Lipoamide

Pyruvate Dehydrogenase Complex

- Pyruvate to acetyl CoA
- Reactions catalyzed by 3 enzymes and 5 coenzymes bundled together as the pyruvate dehydrogenase complex.
- Complex contains:
  - 5 coenzymes (4 which are vitamin derived) and 3 enzymes
  - Thiamine pyrophosphate – thiamine
  - FAD – riboflavin
  - NAD⁺ – niacin
  - Coenzyme A – pantothenic acid
  - Lipoamide

The Citric Acid Cycle

- Citric acid cycle is the final stage in the breakdown of dietary nutrients
- Acetyl CoA and oxaloacetate feed the citric acid cycle
- The acetyl group is oxidized to two molecules of CO₂ and high energy electrons are transferred to NAD⁺ and FAD
- Cycle comprises 8 enzymatic steps several of which are allosterically controlled

Overview: Aerobic Respiration

- Is the oxygen-requiring breakdown of food and production of ATP
- Process is also called oxidative phosphorylation as energy from oxidative reactions is used to phosphorylate ADP making ATP
- Performed by enzymes in the mitochondrial matrix
- Three oxidations transfer hydride to NAD⁺ or FAD
- Electrons passed from NAD⁺ or FAD to the electron transport chain and then O₂
- Protons are transferred to the intermembrane space which leads to the synthesis of ATP as protons return to the mitochondrial matrix
Reaction 1
A condensation reaction between the acetyl group of acetyl CoA and oxaloacetate
- Aldol condensation reaction
- Catalyzed by citrate synthase
- Product is citrate

Reaction 2
A dehydration reaction of citrate followed by hydration to isocitrate
1. Dehydration reaction releasing H₂O
2. Hydration of cis-aconitate to isocitrate
   - Catalyzed by aconitase
   - Intermediate is cis-aconitate
   - Final product is isocitrate

Reaction 3
- First oxidative step of the citric acid cycle
- Complex 3-step reaction
  - Hydroxyl group of isocitrate is oxidized to a ketone
  - Carbon dioxide is released in a decarboxylation
  - NAD⁺ is reduced to NADH
- Catalyzed by isocitrate dehydrogenase
- Product is α-ketoglutarate

Reaction 4
Coenzyme A attaches to the α-ketoglutarate in a 3-step reaction similar to that of the pyruvate dehydrogenase complex
- Enzyme involved is α-ketoglutarate dehydrogenase complex
  1. First, α-ketoglutarate loses a carboxylate group as CO₂
  2. Then, α-ketoglutarate is oxidized with NAD⁺ reduced to NADH
     - Coenzyme A combines with succinate to form succinyl CoA
       - Bond between succinate and coenzyme A is high-energy

Reaction 5
A very chemically involved step where succinyl CoA is converted to succinate by the enzyme succinyl CoA synthase
- The high-energy thioester bond is hydrolyzed adding an inorganic phosphate group to GDP making GTP
Reaction 5 also

A second enzyme, dinucleotide diphosphokinase, catalyzes transfer of the inorganic phosphate group from GTP to ATP.

\[
\text{GDP} + \text{ATP} \xrightarrow{\text{diphosphokinase}} \text{GTP} + \text{ADP}
\]

---

Reaction 6

- **Succinate** is oxidized by succinate dehydrogenase to form fumarate.
- Oxidizing agent, FAD, flavin adenine dinucleotide, is reduced in this step to FADH₂.

\[
\begin{align*}
\text{COO}^- + \text{CH}_2 + \text{FAD} & \xrightarrow{\text{dehydrogenase}} \text{C} = \text{H} + \text{FADH}_2 \\
\text{COO}^- + \text{F} \text{H}_2 \text{O} & \xrightarrow{\text{hydration or addition reaction}} \text{C} = \text{H} + \text{HO} - \text{C} = \text{H} + \text{COO}^- \\
\text{Succinate} & \xrightarrow{\text{hydration or addition reaction}} \text{Fumarate} \\
\end{align*}
\]

---

Reaction 7

- Reducing the double bond of **fumarate** by the hydration or addition reaction of H₂O produces **malate**.
- Reaction is catalyzed by **fumarase**.

\[
\begin{align*}
\text{COO}^- + \text{CH} = \text{H} + \text{HO} - \text{C} = \text{H} + \text{COO}^- \\
\text{Fumarate} & \xrightarrow{\text{hydration or addition reaction}} \text{Malate} \\
\end{align*}
\]

---

Reaction 8

- Final reaction step uses **malate dehydrogenase** to:
  - Reduce NAD⁺ to NADH.
  - Oxidize **malate** to oxaloacetate.
  - Cycle begins as an acetyl group is added to oxaloacetate, bring a full turn of the cycle.

\[
\begin{align*}
\text{COO}^- + \text{HO} - \text{C} = \text{H} + \text{NAD}^+ & \xrightarrow{\text{malate dehydrogenase}} \text{C} = \text{O} + \text{NADH} \\
\text{CH}_2 & \xrightarrow{\text{Oxidation}} \text{CH}_2 \\
\text{COO}^- & \xrightarrow{\text{Oxidation}} \text{COO}^- \\
\text{Malate} & \xrightarrow{\text{Oxidation}} \text{Oxaloacetate} \\
\end{align*}
\]

---

Summary of the Reactions of the Citric Acid Cycle

\[
\begin{align*}
\text{GTP} + \text{ADP} & \xrightarrow{\text{diphosphokinase}} \text{GTP} + \text{ADP} \\
\text{COO}^- + \text{CH} = \text{H} + \text{HO} - \text{C} = \text{H} + \text{COO}^- & \xrightarrow{\text{Malate dehydrogenase}} \text{C} = \text{O} + \text{NADH} \\
\end{align*}
\]
22.5 Control of the Citric Acid Cycle

- As with glycolysis, citric acid cycle responds to the energy needs of the cell
- Pathway speeds up when greater demand for energy
- Four enzymes/enzyme complexes are allosterically regulated
  - Several regulated steps demonstrate the importance of precise control

### Allosterically Regulated Reactions

1. Conversion of pyruvate to acetyl CoA
   - Inhibited by high concentrations of:
     - ATP
     - Acetyl CoA
     - NADH

2. Synthesis of citrate from oxaloacetate and acetyl CoA
   - Negative effector is high levels of ATP

3. Oxidation and decarboxylation of isocitrate to α-ketoglutarate
   - Positive effector, ADP controls this enzyme
   - Inhibited by high levels of NADH and ATP

4. Conversion of α-ketoglutarate to succinyl CoA
   - Inhibited by high concentrations of:
     - ATP
     - Succinyl CoA
     - NADH
22.6 Oxidative Phosphorylation

• The respiratory electron transport system is made up of a series of electron carriers embedded in the inner mitochondrial membrane.

• At three sites in the electron transport system, protons, $H^+$, can be pumped from the matrix to the intermembrane space:
  - NADH provides three ATP molecules.
  - FADH$_2$ provides two ATP molecules.

• ATP synthesis occurs at the ATP synthase.
ATP Synthase and the Production of ATP

NADH carries electrons (original source glucose) to the first carrier of the electron transport system, NADH dehydrogenase
- NADH is oxidized to NAD⁺ which returns to citric acid cycle
- Pair of electrons passed to the next electron carrier and H⁺ are pumped to the intermembrane compartment
- These electrons are passed through the electron transport system
  - With each transfer the electrons lose some energy
  - This energy is used to transport H⁺ across the inner membrane

Energy Yield from One Glucose

- Glycolysis
  - Substrate-level phosphorylation: 2 ATP
  - 2 NADH X 2 ATP (cytoplasm): 4 ATP
- Two Pyruvate to two Ac-CoA
  - 2 NADH X 3 ATP/NADH: 6 ATP
- Citric Acid Cycle (Two turns)
  - 2 GTP X 1 ATP/GTP: 2 ATP
  - 6 NADH X 3 ATP/NADH: 18 ATP
  - 2 FADH₂ X 2 ATP/FADH₂: 4 ATP
- NET: 36 ATP

22.7 The Degradation of Amino Acids

- When the body has depleted glycogen (starving), it can use amino acids for fuel
- Degradation takes place in the liver in two stages
  1. Removal of the α-amino group
     - Typically excreted in the urine
  2. Degradation of the carbon skeleton leads to conversion into a variety of compounds
     - Pyruvate
     - Acetyl CoA

Removal of α-Amino Groups: Transamination

- Transaminase catalyzes the transfer of the α-amino group from an α-amino acid to an α-keto acid
- The α-keto acid is often α-ketoglutarate
- Transfer process appears simple, but actually very complex
  - Transaminase binds the amino acid in its active site
  - Transfer amino group to pyridoxal phosphate
  - Next move the amino group to a keto acid

\[
\begin{align*}
\text{NH}_2 & \quad \begin{array}{c}	ext{O} \\
\text{R} \end{array} \quad \text{Transaminase} \\
\begin{array}{c}	ext{C} - \text{COOH} \quad \text{C} - \text{COOH} \\
\text{R'} \quad \text{R'} \end{array} & \quad \begin{array}{c}	ext{O} \\
\text{R} \end{array} \quad \text{NH}_2 \\
\text{Donor amino acid} & \quad \text{Acceptor keto acid} & \quad \text{α-Keto acid of amino acid} & \quad \text{New amino acid}
\end{align*}
\]
Pyridoxal Phosphate and Pyridoxine
- Pyridoxal phosphate is the coenzyme required for all transamination reactions
  - Over 50 discovered, all use this coenzyme
- Pyridoxine is also known as vitamin B₆, which is the source of pyridoxal phosphate

Aspartate Transaminase
- This particular transaminase catalyzes the transfer of the α-amino acid of aspartate to α-ketoglutarate
- Produces oxaloacetate and glutamate

Alanine Transaminase
- This transaminase catalyzes transfer of the α-amino group of alanine to α-ketoglutarate
- Produces pyruvate and glutamate
- Transaminases producing glutamate are called transglutaminases
  - Produce a citric acid cycle intermediate
  - Provide a direct link between amino acid degradation and the citric acid cycle

Mechanism of Transamination
- Oxidative deamination is an oxidation-reduction process in which
  - NAD⁺ is reduced to NADH
  - Amino acid is deaminated (amino group removed)

Removal of α-Amino Groups: Oxidative Deamination
- Ammonium ion is liberated from the glutamate formed by the transaminase
- Glutamate breakdown is catalyzed by glutamate dehydrogenase

Deamination of an α-Amino Acid and the Fate of Ammonium Ion
22.8 The Urea Cycle

- Oxidative deamination produces large amounts of ammonium ion
- As ammonium ion is toxic, it must be removed quickly from the body regardless of the energy required
  - Eliminate ammonium ion via the urea cycle. Urea is excreted in the urine
- Failure of enzymes in the urea cycle can be genetic and leads to hyperammonemia
  - Severe cases lead to early death from toxic ammonium ion buildup
  - Also leads to:
    - Retardation
    - Convulsions
    - Vomiting

Step 1

- First step combines CO₂ and NH₄⁺ to form carbamoyl phosphate
  - Reaction requires ATP and H₂O
  - Takes place in the mitochondria
  - Catalyzed by carbamoyl phosphate synthase
Step 2

- Carbamoyl phosphate condenses with the amino acid ornithine to produce the amino acid citrulline
  - Occurs in the mitochondria
  - Catalyzed by ornithine transcarbamoylase

Step 3

- Citrulline is transported to the cytoplasm
  - Condensed with aspartate to produce argininosuccinate
  - Catalyzed by argininosuccinate synthase
  - Requires energy released by ATP hydrolysis

Step 4

- Argininosuccinate cleaved to produce the amino acid arginine and fumarate of the citric acid cycle
  - Reaction catalyzed by argininosuccinate lyase

Step 5

- Final reaction hydrolyzes arginine to generate urea – the reaction product that is excreted
  - Reaction also regenerates ornithine, the original reactant in the cycle
  - Reaction is catalyzed by arginase

22.9 Overview of Anabolism: The Citric Acid Cycle as a Source of Biosynthetic Intermediates

- The citric acid cycle functions as:
  - An energy-harvesting mechanism
  - Anabolism = biosynthesis

- Just as amino acids can be converted to citric acid cycle intermediate, these intermediates can also be used to make amino acids
  - Oxaloacetate is used to make aspartate
  - Asparagine is made from aspartate in an amination reaction
  - Glutamate is made from α-ketoglutarate

- Glutamine, proline, and arginine are made from glutamate
22.9 Overview of Anabolism

Schematic of the Urea Cycle