Continued Education Program

Biology

I-Biological Macromolecules

B-Lipids

Presented by:

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B. Lipids

- **Structure:** Greasy or oily nonpolar compounds
- **Functions:**
  - Energy storage
  - Membrane structure
  - Protecting against desiccation (drying out).
  - Insulating against cold.
  - Absorbing shocks.
  - Regulating cell activities by hormone actions.
Lipids are non-polar (hydrophobic) compounds, soluble in organic solvents.

Most membrane lipids are amphipathic, having a non-polar end and a polar end.

Fatty acids consist of a hydrocarbon chain with a carboxylic acid at one end.
1. Structure of Fatty Acids

- Long chains of mostly carbon and hydrogen atoms with a -COOH group at one end.
- When they are part of lipids, the fatty acids resemble long flexible tails.
Saturated and Unsaturated Fats

- Unsaturated fats:
  - liquid at room temp
  - one or more double bonds between carbons in the fatty acids allows for “kinks” in the tails
  - most plant fats

- Saturated fats:
  - have only single C-C bonds in fatty acid tails
  - solid at room temp
  - most animal fats
Saturated fatty acid
Saturated fatty acid

Unsaturated fatty acid
2. Structure of Triglycerides

- Glycerol + 3 fatty acids
- 3 ester linkages are formed between a hydroxyl group of the glycerol and a carboxyl group of the fatty acid.
3. Phospholipids

- **Structure**: Glycerol + 2 fatty acids + phosphate group.
- **Function**: Main structural component of membranes, where they arrange in bilayers.
Phospholipids in Water

(a) Micelle

(b) Phospholipid bilayer
Amphipathic lipids in association with water form complexes in which polar regions are in contact with water and hydrophobic regions away from water.

Depending on the lipid, possible molecular arrangements:

Various **micelle** structures. E.g., a spherical micelle is a stable configuration for amphipathic lipids with a **conical** shape, such as **fatty acids**.

A **bilayer**. This is the most stable configuration for amphipathic lipids with a **cylindrical** shape, such as **phospholipids**.
In the **liquid crystal state**, hydrocarbon chains of phospholipids are disordered and in constant motion.

At **lower temperature**, a membrane containing a single phospholipid type undergoes transition to a **crystalline state** in which fatty acid tails are fully extended, packing is highly ordered, & van der Waals interactions between adjacent chains are maximal.

**Kinks** in fatty acid chains, due to **cis double bonds**, interfere with packing in the crystalline state, and **lower the phase transition temperature**.
Cholesterol, an important constituent of cell membranes, has a **rigid** ring system and a short branched hydrocarbon tail.

Cholesterol is largely **hydrophobic**.

But it has one polar group, a **hydroxyl**, making it **amphipathic**.
**Cholesterol** inserts into bilayer membranes with its hydroxyl group oriented toward the aqueous phase & its hydrophobic ring system adjacent to fatty acid chains of phospholipids.

The **OH** group of cholesterol forms hydrogen bonds with polar phospholipid head groups.
Interaction with the relatively **rigid cholesterol** decreases the mobility of hydrocarbon tails of phospholipids.

But the presence of **cholesterol** in a phospholipid membrane interferes with close packing of fatty acid tails in the crystalline state, and thus **inhibits transition** to the crystal state.

Phospholipid membranes with a high concentration of cholesterol have a **fluidity intermediate** between the liquid crystal and crystal states.
Two strategies by which phase changes of membrane lipids are avoided:

- **Cholesterol** is abundant in membranes, such as plasma membranes, that include many lipids with long-chain saturated fatty acids.

  In the absence of cholesterol, such membranes would crystallize at physiological temperatures.

- The inner mitochondrial membrane lacks cholesterol, but includes many phospholipids whose fatty acids have one or more **double bonds**, which lower the melting point to below physiological temperature.
Lateral mobility of a lipid, within the plane of a membrane.

High speed tracking of individual lipid molecules has shown that lateral movements are constrained within small membrane domains.

Hopping from one domain to another occurs less frequently than rapid movements within a domain.

The apparent constraints on lateral movements of lipids (and proteins) has been attributed to integral membrane proteins, anchored to the cytoskeleton, functioning as a picket fence. See the website of the Kusumi laboratory.
**Flip-flop** of lipids (from one half of a bilayer to the other) is normally very slow.

Flip-flop would require the polar head-group of a lipid to traverse the hydrophobic core of the membrane.

The **two leaflets** of a bilayer membrane tend to **differ** in their lipid composition.

**Flippases** catalyze flip-flop in membranes where lipid synthesis occurs.

Some membranes contain enzymes that **actively transport** particular lipids from one monolayer to the other.
Peripheral proteins are on the membrane surface. They are water-soluble, with mostly hydrophilic surfaces. Often peripheral proteins can be dislodged by conditions that disrupt ionic & H-bond interactions, e.g., extraction with solutions containing high concentrations of salts, change of pH, and/or chelators that bind divalent cations.
Many proteins have a modular design, with different segments of the primary structure folding into domains with different functions.

Some cytosolic proteins have domains that bind to polar head groups of lipids that transiently exist in a membrane.

The enzymes that create or degrade these lipids are subject to signal-mediated regulation, providing a mechanism for modulating affinity of a protein for a membrane surface.
4. Waxes

• Function:
• Lipids that serve as coatings for plant parts and as animal coverings.
5. Steroids

- **Structure**: Four carbon rings with no fatty acid tails
- **Functions**:
  - Component of animal cell membranes
  - Modified to form sex hormones
Digestion of **Triacylglycerols**

- **Small intestine**
  - $H_2C \rightarrow$ Fatty acid
  - $HC \rightarrow$ Fatty acid + $2H_2O$ 
  - $H_2C \rightarrow$ Fatty acid

  - **Pancreatic lipase**
  - $HC \rightarrow$ Fatty acid + $2$ Fatty acids
  - $H_2C \rightarrow$ OH

- **Triacylglycerol**
- **Monoacylglycerol**

**Intestinal wall (epithelial cells)**
- **Monoacylglycerols + 2 Fatty acids** $\rightarrow$ **Triacylglycerols**

**Protein**

- **Lipoproteins**
- **Chylomicrons**

**Lymphatic system**

**Bloodstream**

**Cells**

- **Glycerol + Fatty acids**
6 Steps of Digestion and absorption of lipids

- **Minor digestion** of triacylglycerols in mouth and stomach by lingual lipase
- **Major digestion** of all lipids in the lumen of the duodenum/jejunum by Pancreatic lipases
- **Bile acid** facilitated formation of mixed micelles that present the lipolytic products to the mucosal surface, followed later by enterohepatic bile acid recycling
- **Passive absorption** of the lipolytic products from the mixed micelle into the intestinal epithelial cell, Glycerol & FAs < 12 carbons in length pass thru the cell into the blood without modification. 2-monacylglycerols and FAs > 12 carbons in length are re-synthesized into TGs in the endoplasmic reticulum TGs then form large lipid globules in the ER called nascent chylomicrons”. Several apolipoproteins are required
- **Re-esterification** of 2-monoacylglycerol, lysolecithin, and cholesterol with free fatty acids inside the intestinal enterocyte
- **Assembly and export** from intestinal cells to the lymphatics of chylomicrons coated with Apo B48 and containing triacylglycerols, cholesterol esters and phospholipids
Metabolism of TAG

1. Synthesis of TAG
2. Catabolism of TAG
   - Fatty acid beta oxidation
     - Ketogenesis and Ketone Bodies
3. Lipogenesis: Fatty Acid Synthesis
4. Some poly-unsaturated FA ramification
The synthesis of TAG

1. **Mono-acylglycerol pathway (MAG pathway)**
   (for dietary fat digestion and absorption)

![Diagram showing the synthesis of TAG]

- **TAG** → **MAG** → **DAG** → **FA**
- **Pancreatic lipase** acts on **TAG** to form **MAG**.
- **MAG** is then converted to **DAG**.
- **DAG** is further hydrolyzed to form **FA**.
- **FA** and **CoA** are used to form **acyl CoA**.
- **Intestinal epithelium** absorbs **acyl CoA** and forms **MAG**.
- **MAG** is transported through **lymphatic vessels** to **adipose tissue**.
- **Chylomicrons** are secreted from the **intestinal lumen**.
2. **Diacylglycerol pathway (DAG pathway)**
(for TAG synthesis of in adipose tissue, liver and kidney)

![Diagram of the Diacylglycerol pathway](image)
CATABOLISM OF TAG
Mobilization of triacylglycerols:

in the adipose tissue, breaks down triacylglycerols to free fatty acids and glycerol (fatty acids are hydrolyzed initially from C1 or C3 of the fat)

hormone sensitive lipase cleave a fatty acid from a triglyceride, then other lipase complete the process of lipolysis, and fatty acid are released into the blood by serum albumin
• The glycerol is absorbed by the liver and converted to glycolytic intermediates
FATTY ACID BATA OXIDATION
Overview of fatty acid degradation

FA = fatty acid
LPL = lipoprotein lipase
FABP = fatty acid binding protein
ACS = acyl CoA synthetase
Steps in Beta Oxidation

- Fatty Acid Activation by esterification with CoASH
- Membrane Transport of Fatty Acyl CoA Esters
- **Carbon Backbone Reaction Sequence**
  - Dehydrogenation
  - Hydration
  - Dehydrogenation
  - Thiolase Reaction *(Carbon-Carbon Cleavage)*
1. Activation of Fatty Acids

- Acyl CoA synthetase reaction occurs on the **mitochondrial membrane**

\[ \text{Fatty acid} + \text{ATP} \rightleftharpoons \text{Acyl adenylate} + \text{PP}_i \]  

(1)

\[ \text{Acyl adenylate} + \text{HS-CoA} \rightleftharpoons \text{Acyl CoA} + \text{AMP} \]  

(2)
2. Transport intoMitochondrial Matrix

- Carnitine carries long-chain activated fatty acids into the mitochondrial matrix
- Carnitine carries long-chain activated fatty acids into the mitochondrial matrix

\[
\text{Acyl CoA} + \text{Carnitine} \rightleftharpoons \text{Acyl carnitine} + \text{HS-CoA}
\]
Each round in fatty acid degradation involves four reactions

1. **oxidation** to *trans*-Δ²-Enoly-CoA
   - Removes H atoms from the α and β carbons
   - Forms a trans C==C bond
   - Reduces FAD to FADH₂
2. **Hydration to L–3–Hydroxylacyl CoA**

- Adds water across the trans C=C bond
- Forms a hydroxyl group (—OH) on the β carbon
3. Oxidation to
- 3–Ketoacyl CoA
- Oxidizes the hydroxyl group
- Forms a keto group on the β carbon
4. Thiolysis to produce Acetyl–CoA

- acetyl CoA is cleaved: By splitting the bond between the α and β carbons.
- To form a shortened fatty acyl CoA that repeats steps 1 - 4 of β-oxidation
**β-Oxidation of Myristic (C14) Acid**

**Reaction 1 Oxidation (dehydrogenation)**

Matrix

\[
\text{CH}_3-(\text{CH}_2)_9-\text{CH}_2-\text{CH}_2-C-\text{CoA} \quad \text{FAD} \\
\text{CH}_3-(\text{CH}_2)_9-\text{CH}==\text{CH}-C-\text{CoA} \quad \text{FADH}_2
\]

**Reaction 2 Hydration**

\[
\text{CH}_3-(\text{CH}_2)_9-\text{CH}==\text{CH}-C-\text{CoA} \quad \text{H}_2\text{O}
\]

**Reaction 3 Oxidation (dehydrogenation)**

\[
\text{CH}_3-(\text{CH}_2)_9-\text{CH}-\text{CH}_2-C-\text{CoA} \quad \text{NAD}^+ \\
\text{CH}_3-(\text{CH}_2)_9-\text{CH}-\text{CH}_2-C-\text{CoA} \quad \text{NADH} + \text{H}^+
\]

**Reaction 4 Cleavage**
β-Oxidation of Myristic (C14) Acid

- Reaction 4 Cleavage
- 6 cycles
- 7 Acetyl CoA
Cycles of β-Oxidation

The length of a fatty acid
Determines the number of oxidations and the total number of acetyl CoA groups

<table>
<thead>
<tr>
<th>β-Oxidation</th>
<th>Acetyl CoA</th>
<th>Carbons in Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C/2 −1)</td>
<td>(C/2)</td>
<td>Fatty Acid</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>
β-Oxidation and ATP

Activation of a fatty acid requires:

\[ 2 \text{ ATP} \]

One cycle of oxidation of a fatty acid produces:

\[ 1 \text{ NADH} \quad \rightarrow \quad 3 \text{ ATP} \]
\[ 1 \text{ FADH}_2 \quad \rightarrow \quad 2 \text{ ATP} \]

Acetyl CoA entering the citric acid cycle produces:

\[ 1 \text{ Acetyl CoA} \quad 12 \text{ ATP} \]
Odd Carbon Fatty Acids

CH₃CH₂CH₂-CH₂CH₂-CH₂CH₂-CH₂CH₂-CH₂COSCoA

5 Cycles

5 CH₃COSCoA + CH₃CH₂COSCoA

Propionyl CoA

TCA Cycle

HO₂CCH₂CH₂COSCoA
Succinyl CoA

Mutase

Vit. B₁₂

Epimerase

L-Methylmalonyl CoA
D-Methylmalonyl CoA

Propionyl CoA Carboxylase
ATP/CO₂
Ketogenesis (Ketosis): formation of **Ketone Bodies**

2 CH$_3$COSCoA $\overset{\text{Thiolase}}{\longrightarrow}$ CH$_3$COCH$_2$COSCoA $\overset{\text{HMG CoA Synthase}}{\longrightarrow}$ CH$_3$COSCoA

Acetoacetyl CoA

Several steps $\overset{\text{Ketogenesis}}{\longrightarrow}$ HO$_2$C-CH$_2$-C-CH$_2$COSCoA

OH

CH$_3$

Cholesterol (in cytosol)

(in liver: mitochondrial matrix)
Ketogenesis: formation of Ketone Bodies

Ketone bodies are important sources of energy, especially in starvation.
Oxidation of ketone bodies in brain, muscle, kidney, and intestine

\[ \beta\text{-Hydroxybutyrate} \rightarrow \beta\text{-Hydroxybutyrate dehydrogenase} \rightarrow \text{Acetoacetate} \rightarrow \text{Succinyl CoA} \rightarrow \text{Succinate} \rightarrow \text{Citric Acid Cycle} \]

\[ \text{NAD}^+ \rightarrow \text{NADH} \]

\[ \text{CoA transferase} \]

\[ \text{Thiolase} \]

\[ \text{Succinyl CoA synthetase} = \text{loss of GTP} \]

\[ 2 \text{ Acetyl CoA} \rightarrow \text{Acetoacetyl CoA} \]
The significance of ketogenesis and ketogenolysis

- **Ketone bodies are water soluble**, they are convenient to transport in blood, and readily **taken up by non-hepatic tissues**

  In the early stages of fasting, the use of ketone bodies by heart, skeletal muscle conserves glucose for support of central nervous system. With more prolonged starvation, brain can take up more ketone bodies to spare glucose consumption

- High concentration of ketone bodies can induce **ketonemia and ketonuria, and even ketosis and acidosis**

  When carbohydrate catabolism is blocked by a disease of diabetes mellitus or defect of sugar source, the blood concentration of ketone bodies may increase, the patient may suffer from ketosis and acidosis
Overview Catabolism of TAG

TAG → FFAs → acetyl CoA → CO₂ + H₂O + energy

Not in adipose tissue and muscle

Glycerol

Glycolysis

Acetylation

Ketone bodies

Extrahepatic tissues

TCA
Lipogenesis:

Fatty Acid Synthesis

• Fatty acid are synthesized and degraded by different pathways
  • from acetyl CoA
  • in the cytosol
  • intermediates are attached to the acyl carrier protein (ACP)
  • the activated donor is malonyl–ACP
  • reduction uses NADPH + H^+
  • stops at C_{16} (palmitic acid)
The intermediates (acetyl-ACP and malonyl-ACP) in fatty acid synthesis are covalently linked to the acyl carrier protein (ACP).
In bacteria the enzymes that are involved in elongation are separate proteins.

In higher organisms the activities all reside on the same polypeptide.

- To start an elongation cycle, Acetyl–CoA and Malonyl–CoA are each transferred to an acyl carrier protein.

\[
\begin{align*}
\text{Acetyl–ACP} & : \text{CH}_3\text{C–S–ACP} \\
\text{Malonyl–ACP} & : \text{-O–C–CH}_2\text{C–S–ACP}
\end{align*}
\]
Condensation and Reduction

In reactions 1 and 2 of fatty acid synthesis:

- **Condensation** by a synthase combines acetyl-ACP with malonyl-ACP to form acetoacetyl-ACP (4C) and CO₂ (reaction 1)

- **Reduction** converts a ketone to an alcohol using NADPH (reaction 2)
Dehydration and Reduction

In reactions 3 and 4 of fatty acid synthesis:

- **Dehydration** forms a trans double bond (reaction 3)
- **Reduction** converts the double bond to a single bond using NADPH (Reaction 4)
Lipogenesis Cycle Repeats

Fatty acid synthesis continues:

- Malonyl-ACP combines with the four-carbon butyryl-ACP to form a six-carbon-ACP.
- The carbon chain lengthens by two carbons each cycle.
Lipogenesis Cycle Completed

• Fatty acid synthesis is completed when palmitoyl ACP reacts with water to give palmitate ($C_{16}$) and free ACP.
Elongation and Unsaturation

- Endoplasmic reticulum systems introduce double bonds into long chain acyl–CoA's
  - Reaction combines both NADH and the acyl–CoA's to reduce $\text{O}_2$ to $\text{H}_2\text{O}$

convert palmitoyl–CoA to other fatty acids

Reactions occur on the cytosolic face of the endoplasmic reticulum.

Malonyl–CoA is the donor in elongation reactions
### β Oxidation and Fatty Acid Synthesis

<table>
<thead>
<tr>
<th></th>
<th>β Oxidation</th>
<th>Fatty Acid Synthesis (lipogenesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td>Mitochondrial matrix</td>
<td>Cytosol</td>
</tr>
<tr>
<td><strong>Activated by</strong></td>
<td>Glucagon</td>
<td>Insulin</td>
</tr>
<tr>
<td></td>
<td>Low blood glucose</td>
<td>High blood glucose</td>
</tr>
<tr>
<td><strong>Activator</strong></td>
<td>Coenzyme A (CoA)</td>
<td>Acyl carrier protein (ACP)</td>
</tr>
<tr>
<td><strong>Initial substrate</strong></td>
<td>Fatty acid</td>
<td>Acetyl CoA → Malonyl CoA</td>
</tr>
<tr>
<td><strong>Coenzymes</strong></td>
<td>FAD, NAD⁺</td>
<td>NADPH, NADP⁺</td>
</tr>
<tr>
<td><strong>Types of Reaction</strong></td>
<td>Oxidation, Hydration, Cleavage</td>
<td>Reduction, Dehydration, Condensation</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Cleaves two-carbon acyl group</td>
<td>Adds two-carbon acyl group</td>
</tr>
<tr>
<td><strong>Final product</strong></td>
<td>Acetyl CoA units</td>
<td>Palmitate (C₁₆) and other fatty acids</td>
</tr>
</tbody>
</table>
Fatty Acid Formation

- Shorter fatty acids undergo fewer cycles
- Longer fatty acids are produced from palmitate using special enzymes
- Unsaturated cis bonds are incorporated into a 10-carbon fatty acid that is elongated further
- When blood glucose is high, insulin stimulates glycolysis and pyruvate oxidation to obtain acetyl CoA to form fatty acids
Stoichiometry of FA synthesis

- The stoichiometry of palmitate synthesis:
  - Synthesis of palmitate from Malonyl–CoA

\[
\text{Acetyl-CoA} + 7 \text{malonyl-CoA} + 14 \text{NADPH} + 20 H^+ \longrightarrow \]

\[
\text{palmitate} + 7 \text{CO}_2 + 14 \text{NADP}^+ + 8 \text{CoA} + 6 \text{H}_2\text{O}
\]

- Synthesis of Malonyl–CoA from Acetyl–CoA

\[
7\ \text{Acetyl-CoA} + 7 \text{CO}_2 + 7 \text{ATP} \longrightarrow \]

\[
7\ \text{Malonyl-CoA} + 7 \text{ADP} + 7 \text{P}_i + 14 H^+
\]

- Overall synthesis

\[
\text{Acetyl-CoA} + 7 \text{ATP} + 14 \text{NADPH} + 6 H^+ \longrightarrow \]

\[
\text{palmitate} + 14 \text{NADP}^+ + 8 \text{CoA} + 6 \text{H}_2\text{O} + 7 \text{ADP} + 7 \text{P}_i
\]
Sources of NADPH

- The malate dehydrogenase and NADP$^+$–linked malate enzyme reactions of the citrate shuttle exchange NADH for NADPH.
Citrate Shuttle

- Acetyl-CoA is synthesized in the **mitochondrial matrix**, whereas fatty acids are synthesized in the **cytosol**
- Acetyl-CoA units are shuttled out of the mitochondrial matrix as citrate:
Regulation of Fatty Acid Synthesis

• Regulation of Acetyl carboxylase
  • Global
  (+) insulin
  (-) glucagon
  (-) epinephrine
  • Local
  (+) Citrate
  (-) Palmitoyl–CoA
  (-) AMP
Eicosanoid Hormones

- Eicosanoid horomones are synthesized from arachadonic acid
  - Prostaglandins
    - 20-carbon fatty acid containing 5-carbon ring
    - Prostacyclins
    - Thromboxanes
  - Leukotrienes
    - contain three conjugated double bonds
Eicosanoid Hormones

- Leukotrienes
- Lipoxygenases
- DG lipase
- Diacylglycerols

Phospholipids → PLA$_2$ → Arachidonate → Leukotrienes

Arachidonate → Lipoxygenases → Prostaglandin H$_2$ (PGH$_2$)

- Prostacyclin synthase → Prostacyclin
- Thromboxane synthases → Thromboxanes
- Other prostaglandins
Eicosanoid Hormones

- **Prostaglandin A₂**
- **Prostacyclin (PGI₂)**
- **Thromboxane A₂ (TXA₂)**
- **Leukotriene B₄**
Phospholipids

- **Structure**
  - Glycerol + 2 fatty acids + phosphate group

- **Functions**
  - Component of cell membranes
  - Lipid transport as part of lipoproteins

- **Food sources**
  - Egg yolks, liver, soybeans, peanuts
Phospholipids

- Phospholipids are intermediates in the biosynthesis of triacylglycerols
- The starting materials are glycerol 3-phosphate and the appropriate acyl coenzyme A molecules
Structure of Cholesterol

Fundamental framework of steroids

Structure of Cholesterol
Cholesterol Biosynthesis

1. Formation of Mevalonate

Liver is primary site of cholesterol biosynthesis

\[
2 \text{CH}_3\text{COSCoA} \rightarrow \text{CH}_3\text{COCH}_2\text{COSCoA}
\]

Thiolase

\[
\text{CH}_3\text{COSCoA} \rightarrow \text{Acetoacetyl CoA}
\]

HMG CoA Synthase

\[
\text{HO}_2\text{C-CH}_2\text{C-CH}_2\text{CH}_2\text{OH} \rightarrow \text{HO}_2\text{C-CH}_2\text{C-CH}_2\text{COSCoA}
\]

HMGCoA reductase

\[
\square-\text{Hydroxy-buta-methyl-glutaryl CoA (HMG CoA)}
\]

3\(R\)-Mevalonic acid

Key control step
Cholesterol Biosynthesis

2. processing of Squalene

\[ \text{Mevalonate} \]

\[ \text{Dimethylallyl pyrophosphate} \]

\[ \text{Isopentenyl pyrophosphate} \]

\[ \text{5-Pyrophosphomevalonate} \]

\[ \text{CO}_2 \]

\[ \text{H}_2\text{O} \]
Isoprenoid Condensation

- Dimethylallyl pyrophosphate

- Isopentenyl pyrophosphate (IPP)

- Geranyl pyrophosphate (GPP)

- Farnesyl pyrophosphate (FPP)

Head to tail condensation of IPP and GPP

Tail to tail condensation of 2 FPPs

Squalene

Isoprenes
3. Conversion of Squalene to Cholesterol

Squalene monooxygenase

Squalene

2,3-Oxidosqualene: lanosterol cyclase

Lanosterol

20 Steps

Squalene-2,3-epoxide

Oxygen

2,3-Oxidosqualene

Cholesterol

Oxygen
Transformations of Cholesterol

Cholesterol is the biosynthetic precursor to a large number of important steroids:

- Bile acids
  - Vitamin D3
  - Corticosteroids
  - Sex hormones
LIPOPROTEINS
METABOLISM
General Features of Lipoproteins

- **Apolipoproteins**: specific lipid-binding proteins that attach to the surface intracellular recognition for exocytosis of the nascent particle after synthesis activation of lipid-processing enzymes in the bloodstream, binding to cell surface receptors for endocytosis and clearance.

- **Main lipid components**: triacylglycerols, cholesterol esters, phospholipids.

- **Major lipoproteins**:
  - chylomicrons
  - very low density lipoproteins (VLDL)
  - low density lipoproteins (LDL)
  - high density lipoproteins (HDL)

- **Subfraction**: intermediate density lipoproteins (IDL)

- **Electrophoretic mobility** (charge):
  - HDLs = \( \alpha \) lipoproteins
  - LDLs = \( \beta \) lipoproteins
  - VLDLs = pre-\( \beta \) lipoproteins (intermediate between \( \alpha \) and \( \beta \) mobility)
Model of low density lipoprotein. Other lipoproteins have a similar structure differing in the core content of lipid and the type of apoproteins on the surface of the molecule.
# Functions of apolipoproteins

<table>
<thead>
<tr>
<th>Protein (Enzyme)</th>
<th>Site of Action</th>
<th>Activator</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL (Enzyme)</td>
<td>capillary walls</td>
<td>apo CII</td>
<td>excises FFA from TAGs in chylomicrons and VLDLs for adipose and muscle</td>
</tr>
<tr>
<td>CERP</td>
<td>plasma membrane</td>
<td>apo A1 (choles. Induced)</td>
<td>flips cholesterol (and lecithin) to outer layer of lipid bilayer for LCAT action in blood</td>
</tr>
<tr>
<td>Apo A1</td>
<td>blood, plasma membrane</td>
<td>none</td>
<td>activates LCAT and CERP; binds to apo A1 receptors on cells requiring cholesterol extraction</td>
</tr>
<tr>
<td>Apo B48</td>
<td>Gut</td>
<td>none</td>
<td>export of chylomicrons from intestinal cells</td>
</tr>
<tr>
<td>Apo B100</td>
<td>Various cells</td>
<td>none</td>
<td>ligand for LDL receptor; export of liver VLDL</td>
</tr>
<tr>
<td>Apo CII</td>
<td>capillary walls</td>
<td>none</td>
<td>activates lipoprotein lipase</td>
</tr>
<tr>
<td>Apo E</td>
<td>liver</td>
<td>none</td>
<td>receptor ligand - clears remnants, IDL, and HDL</td>
</tr>
</tbody>
</table>
## Composition of Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein Classes</th>
<th>Total Protein (%</th>
<th>Total Lipids (%)</th>
<th>Percent Composition of Lipid Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PL</td>
</tr>
<tr>
<td>CM</td>
<td>1.5-2.5</td>
<td>97-99</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(B,C-III,II,I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>5-10</td>
<td>90-95</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>(B,C-III,II,I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>20-25</td>
<td>75-80</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>(B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>40-45</td>
<td>55</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>(A-I)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ApoB48 aids with chylomicron assembly

Lymph system:
Chylomicrons to capillaries via lymph

Nascent chylomicrons acquire apo CII (C) and E (E) from HDL

Chylomicron interacts with lipoprotein lipase removing FFA

Chylomicrons carry dietary fatty acids to tissues
Lipoprotein lipase action on chylomicron triacylglycerol
(an identical reaction occurs with VLDL)
Exogenous pathway of lipid transport
Chylomicrons carry dietary fatty acids to tissues and the remnants take cholesterol to the liver
B100 (B) helps assemble and export nascent VLDL. Nascent VLDL acquires apo CII (C) and apo E (E) from HDL. LPL hydrolyze TAGs; FFA uptake; LDL circulate to tissues. CII and E release to HDL. apo B100 on LDL bind to receptor. LDL taken into the cell to deliver cholesterol. HDL scavenge cholesterol. The liver-directed endogenous pathway of lipoprotein metabolism.
**Chylomicrons: Exogenous Pathway**

- **Nascent Chylomicron**: Assembly in Gut Mediated by B48
- **Mature Chylomicron**: Apo E and CII added from HDL, CII activates LPL
- **Chylomicron Remnant**: from mature chylomicron, apo CII returned to HDL

**Chylomicron Processing and Interface with HDL**

- Lipoprotein Lipase
  - Capillary walls
  - Hydrolyzes TAG
  - Delivers FFA into adipose/muscle

**HDL: Both Pathways**

- **Nascent HDL**: Assembled in liver, Loans apo E/ apo CII to nascent chylomicrons
- **Mature HDL**: CE from peripheral cells, activated by apo A1, Apo CII returned by chylomicrons

**Key Components**

- Triacylglycerol
- Cholesterol ester
- Phospholipid
VLDL/LDL Processing and Interface with HDL

HDL: Both Pathways

Lipoprotein Lipase
- capillary walls
- hydrolyzes TAG
- deliver FFA into adipose/muscle

VLDL/LDL: Endogenous Pathway
- Nascent VLDL
  - Assembly in Liver
  - Mediated by B100

Mature VLDL
- Apo E and CII added from HDL
- CII activates LPL

Mature HDL
- Apo CII/E returned by VLDL

FFA

apo CII + E

adipose & muscle

apo CII & E from VLDL
Clearance of Cholesterol by Liver from Chylomicron Remnants, HDL and LDL

Chylomicron Remnant

Mature HDL

Bile acids

CE Metabolism

E Receptor

LDL

B100 receptor

B100

B100

B100

LDL

B100

B100

LDL

B100

B100

LDL

B100

B100

LDL
Consequence of Oxidized LDL Formation

1. Uptake by "scavenger receptors" on macrophages that invade artery walls; become foam cells
2. Elicits CE deposition in artery walls

Oxidation of LDL

Oxidized LDL

Atherosclerosis
# Lipoprotein classes

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Source</th>
<th>Apo Proteins</th>
<th>Protein:Lipid/Major (minor) Lipid Transported</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>gut</td>
<td>B48, CII*, E*</td>
<td>1:49 triacylglycerol (CE)</td>
<td>Dietary: FFA → Adipose/muscle CE → Liver via remnants</td>
</tr>
<tr>
<td>VLDL</td>
<td>liver</td>
<td>B100, CII*, E*</td>
<td>1:9 triacylglycerol (CE)</td>
<td>Synthesized: FFA → adipose/muscle CE → LDL</td>
</tr>
<tr>
<td>LDL</td>
<td>blood</td>
<td>B100</td>
<td>1:3 cholesterol ester</td>
<td>CE to liver (70%) and peripheral cells (30%)</td>
</tr>
<tr>
<td>HDL</td>
<td>liver</td>
<td>A1, CII, E(&quot;ACE&quot;)</td>
<td>1:1 cholesterol ester</td>
<td>supplies apo CII, E to chylomicrons and VLDL; mediates reverse cholesterol transport</td>
</tr>
</tbody>
</table>
hypercholesterolemia
Guidelines for Appropriate Intake of Fat

• reduce fat in diet to <30%
• avoid saturated fat (animal fat)
• avoid margarine, baked goods, fried food
• mono/polyunsaturated cooking oils are best (olive, corn)
• eat foods rich in ω-3 polyunsaturated fatty acids
  (e.g., soybean, salmon)
LIPID METABOLIC DISORDERS
Impaired Lipid Digestion or Absorption

- Pancreatic disorders
- Liver disorders
- Small intestinal problems
- Causes steatorrhea
  - Excessive fat in feces (grey color, greasy appearance)
    - Most frequently seen in companion animals
Metabolic Disorders

• Impairment of liver function can alter lipid metabolism
  • Infectious disease, genetic disorders
  • Other drugs or compounds
• Large number of metabolic disorders associated with lipid metabolism
  • Genetic: usually appear at birth, fatal
    • Tay-Sachs is ONE example
Tay-Sachs

- Autosomal recessive trait
- Accumulation of gangliosides (fatty acid derivatives) in CNS neurons
  - Lack enzyme that breaks down lipids
  - Gangliosides accumulate, destroy function of neurons, and eventually destroy neurons themselves
Infantile Tay-Sachs

- Most common variant
- Appear normal at first, but by 6 months of age affected infants become blind, deaf, unable to swallow, muscles atrophy and eventually become paralyzed
- Death before age 4 in most cases
- Juvenile onset and adult onset variants also exist
Metabolic Disorder – Fatty Liver

Negative energy balance

Rapid mobilization of adipose tissue

Liver can not efficiently utilize fats

Liver stores fat, produces ketones
Hyperlipemia

- Horses and ponies, llamas and alpacas
- Similar to ketosis in cattle
  - Mobilization of body fats and incomplete oxidation leading to excess ketones in blood
- Occurs with poor feed intake in conjunction with high energy demand (pregnancy, lactation, stress)
- Higher frequency in obese animals
Fatty Liver

• Consequences
  • Impaired liver function
  • Increased incidence of disease
  • Decreased fertility

• Prevention
  • Increase diet energy density prior to parturition
  • Do not over-condition animals prior to parturition
Ketosis/Pregnancy Toxemia

- Adipose response to low blood glucose

1. Low blood glucose
2. Fat reserves mobilized
3. Free fatty acids (FFA) released
4. Partial oxidation of FFA to ketone bodies
5. Liver uptake of FFA
Ketosis

- Dairy cows
  - Occurs most often following calving
  - Increased glucose demands to support lactation
  - Body fat is mobilized to meet energy demands, but TCA cycle ‘backs up’
  - Over conditioned cows

- Pregnant ewes
  - Last third of gestation
  - Fetus takes up space and reduces capacity of intestine
  - Caused by inadequate energy intake
  - Mortality can be as high as 80%
  - Twin lamb disease
Thank you!