

WHERE CLASSICAL WISDOM MEETS INTELLIGENT LEARNING

iii. Lipid chemistry and metabolism...

iii. Lipid chemistry and metabolism, Disorders associated with lipid metabolism, Lipidomics

Lipid Chemistry

Classification and Structure

1. Fatty Acids (FAs)

- **Definition**: Long-chain carboxylic acids, typically with an even number of carbons (4–24). May be saturated (no double bonds) or unsaturated (one or more double bonds).
- Nomenclature: Numbering from carboxyl (COOH) end (e.g., 16:0 palmitic acid, 18:1 oleic acid). Omega nomenclature counts from the methyl (CH₃) end (e.g., ω-3, ω-6).

2. Triacylglycerols (TAGs) / Triglycerides

- **Definition**: Three FAs esterified to glycerol.
- Function: Main storage form of energy in adipose tissue.

3. Phospholipids

- **Glycerophospholipids**: Glycerol backbone, two FA tails, phosphate head (often with an additional polar group). Major constituents of biological membranes.
- o Sphingophospholipids (e.g., sphingomyelin): Sphingosine backbone, phosphocholine head group.

4. Glycolipids

• **Glycosphingolipids**: Sphingosine-based lipids with one or more sugar residues, crucial in cell membranes (e.g., cerebrosides, gangliosides).

5. Sterols (Steroids)

- Cholesterol: Characteristic four-fused ring structure, modulates membrane fluidity, precursor to bile acids, steroid hormones, and vitamin D.
- **Steroid Hormones**: Cortisol, aldosterone, sex steroids (testosterone, estrogen, progesterone).

6. Other Lipids

- **Waxes**: Esters of long-chain FAs with long-chain alcohols.
- \circ **Eicosanoids**: Signaling molecules (prostaglandins, thromboxanes, leukotrienes) derived from arachidonic acid (20:4 ω -6).

Lipid Metabolism

Digestion and Absorption

1. Dietary Lipids

- o Mostly TAGs, phospholipids, cholesterol, and fat-soluble vitamins.
- o **Emulsification** in the small intestine by bile salts (synthesized in the liver, stored in the gallbladder).
- Pancreatic Lipases hydrolyze TAGs to monoacylglycerol and free FAs.
- Mixed micelles deliver lipids to enterocytes → re-esterification into TAGs → packaging into chylomicrons for transport via the lymphatic system.

2. Lipoproteins

- Chylomicrons: Transport dietary TAGs and cholesterol from intestine to peripheral tissues.
- VLDL: Export TAGs synthesized in the liver to tissues, becomes IDL → LDL upon TAG removal.
- **LDL** (Low-Density Lipoprotein): Delivers cholesterol to peripheral cells. High LDL levels linked to atherosclerosis.
- HDL (High-Density Lipoprotein): Participates in reverse cholesterol transport from tissues back to the liver.

Fatty Acid Synthesis and Oxidation

1. Fatty Acid Synthesis (Lipogenesis)

- **Location**: Cytosol of liver, adipose tissue.
- Key Enzyme: Acetyl-CoA Carboxylase (ACC) converts acetyl-CoA → malonyl-CoA. Fatty Acid Synthase
 extends the chain two carbons at a time.

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Regulation: Stimulated by insulin, inhibited by glucagon/epinephrine. Excess carbohydrate intake drives FA synthesis → TAG storage.

2. Beta-Oxidation

- **Location**: Mitochondrial matrix (long-chain FAs first activated to acyl-CoA, then transported via carnitine shuttle).
- Process: Seguential removal of two-carbon units as acetyl-CoA, generating NADH and FADH2.
- Regulation: Inhibited by malonyl-CoA (prevents simultaneous synthesis and degradation).

3. Ketone Body Metabolism

- Produced in the liver (mitochondria) from excess acetyl-CoA when carbohydrate availability is low (fasting, diabetes).
- **Ketone Bodies**: Acetoacetate, β-hydroxybutyrate, acetone. Provide alternative fuel for brain, muscle.
- Excess production → ketoacidosis (seen in uncontrolled Type 1 diabetes).

Cholesterol Synthesis and Transport

1. Biosynthesis

- Acetyl-CoA → HMG-CoA → Mevalonate via HMG-CoA Reductase (rate-limiting step).
- o Location: Cytosol and ER of hepatocytes.
- Highly regulated by intracellular cholesterol levels, hormones, statin drugs inhibit HMG-CoA reductase.

2. Excretion

o Cholesterol converted to bile acids in the liver, aids fat digestion and excretion.

3. Regulation

- LDL Receptor-mediated endocytosis controls plasma LDL levels.
- SREBP (Sterol Regulatory Element-Binding Protein) transcription factor regulates expression of LDL receptors and enzymes for cholesterol synthesis.

Disorders Associated with Lipid Metabolism

Hyperlipidemias (Dyslipidemias)

1. Familial Hypercholesterolemia (Type IIa)

- Genetic defects in the LDL receptor or ApoB-100 → elevated LDL levels, early atherosclerosis, tendon xanthomas.
- o Treatments: Statins, PCSK9 inhibitors, LDL apheresis.

2. Hypertriglyceridemia

- Elevated VLDL or chylomicrons; associated with pancreatitis risk, metabolic syndrome.
- o Often managed with fibrates, omega-3 fatty acids, lifestyle changes.

3. Metabolic Syndrome

o Cluster of obesity, insulin resistance, hyperlipidemia, hypertension; increases risk of cardiovascular disease.

Fatty Liver Diseases

1. Non-Alcoholic Fatty Liver Disease (NAFLD)

- Excess fat accumulation in hepatocytes linked to obesity, insulin resistance.
- o Can progress to **Non-Alcoholic Steatohepatitis (NASH)**, fibrosis, cirrhosis, hepatocellular carcinoma.

2. Alcoholic Liver Disease

High alcohol intake → impaired lipid metabolism in liver → steatosis, hepatitis, cirrhosis.

Lipid Storage Disorders (Sphingolipidoses)

1. Gaucher Disease

 Glucocerebrosidase deficiency → accumulation of glucocerebrosides, causing hepatosplenomegaly, bone lesions.

2. Niemann-Pick Disease

Sphingomyelinase deficiency → sphingomyelin build-up. Neurological decline, organomegaly.

3. Tay-Sachs Disease

Hexosaminidase A deficiency → GM2 ganglioside accumulation in neurons, progressive

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neurodegeneration.

Obesity and Associated Dysregulation

- Chronic positive energy balance → adipocyte hypertrophy/hyperplasia, chronic inflammation, insulin resistance.
- Vicious cycle of elevated FFA flux from adipose tissue impairing metabolic regulation.

Lipidomics

Definition and Scope

- **Lipidomics**: A branch of metabolomics focusing on the comprehensive characterization and quantification of lipids within cells, tissues, or organisms.
- Applies advanced mass spectrometry (MS) and chromatography techniques to identify lipid species, modifications, dynamics.

Biological and Clinical Relevance

1. Biomarker Discovery

 Specific lipid profiles can indicate early disease states (e.g., changes in phospholipids in neurodegenerative disorders).

2. Mechanistic Insights

 Lipidomics reveals signaling lipids (e.g., eicosanoids, ceramides) and how metabolic pathways adapt under stress, diet, or pharmacological intervention.

3. Precision Medicine

 Tailoring interventions based on individual lipidomic signatures, improving disease prediction, prevention, and treatment strategies.

Methodological Approaches

- LC-MS (Liquid Chromatography-Mass Spectrometry), GC-MS (Gas Chromatography-MS), Shotgun Lipidomics (direct infusion MS).
- Bioinformatics for data processing, lipid identification (MS/MS spectra), and pathway analysis.

Concluding Remarks

Lipids encompass a broad class of structurally diverse molecules fulfilling critical **energy storage** (TAGs), **membrane structure** (phospholipids, cholesterol), **signaling** (steroid hormones, eicosanoids), and **protective** (myelin sheaths, waxes) roles. Their **metabolism**—including absorption, transport via lipoproteins, beta-oxidation, and biosynthesis—is intricately regulated by **hormonal** and **nutritional** signals.

Disorders of lipid metabolism can manifest as **atherosclerosis**, **hyperlipidemias**, **fatty liver diseases**, **sphingolipidoses**, and **obesity-associated pathologies**, often with far-reaching consequences for cardiovascular, hepatic, and neurological health. Finally, **lipidomics** is revolutionizing our capacity to dissect the lipid milieu, shedding new light on disease mechanisms, identifying novel biomarkers, and guiding next-generation therapies and precision nutrition interventions.

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