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 (CH_3) 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.
   - **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.
   - **Eicosanoids**: Signaling molecules (prostaglandins, thromboxanes, leukotrienes) derived from arachidonic acid (20:4 ω-6).

Lipid Metabolism

Digestion and Absorption

1. **Dietary Lipids**
   - Mostly TAGs, phospholipids, cholesterol, and fat-soluble vitamins.
   - **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.

- **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**: Sequential removal of two-carbon units as acetyl-CoA, generating NADH and $FADH_2$.
   - **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).
   - Location: Cytosol and ER of hepatocytes.
   - Highly regulated by intracellular cholesterol levels, hormones, statin drugs inhibit HMG-CoA reductase.
2. **Excretion**
   - 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.
   - Treatments: Statins, PCSK9 inhibitors, LDL apheresis.
2. **Hypertriglyceridemia**
   - Elevated VLDL or chylomicrons; associated with pancreatitis risk, metabolic syndrome.
   - Often managed with fibrates, omega-3 fatty acids, lifestyle changes.
3. **Metabolic Syndrome**
   - 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.
   - 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

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.