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The Impact of Lipid Metabolism on Human Health and Disease

Alber Fares[1]*, George Fares[2] and Beshoy Fares[3]

[1]*Professor of Medical Biochemistry and Genetics, Orlando, FL, USA*

[2]*Intern Pharmacist, Advent Health, East Orlando, Florida, USA*

[3]*Anesthesiologist Assistant's Candidate, Orlando, Florida, USA*

***Corresponding author:** Alber Fares, Professor of Medical Biochemistry and Genetics, Orlando, FL, USA

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ABSTRACT

Lipids are hydrophobic organic molecules. Due to their insolubility in water, they are compartmentalized in membranes or transported in plasma with proteins. They serve as a major energy source, create hydrophobic barriers for cells, and have regulatory roles through fat-soluble vitamins and hormones. Imbalances in lipid metabolism can lead to clinical issues like atherosclerosis and obesity. This review provides an overview of the critical roles' lipids play in cellular processes, including signal transduction, membrane structure, and energy regulation. The review highlights recent advances in lipid metabolism research, emphasizing catabolism, synthesis, and signaling pathways. By synthesizing current knowledge, this work aims to delineate the distinct physiological effects of various lipid species, offering insights into potential therapeutic targets for metabolic disorders.

Keywords: Lipid; Fat; Fatty Acids; Triacylglycerol; Metabolism; Lipotoxicity

Abbreviations: TAG: Triacylglycerol; FAs: Fatty Acids; GPLs: Glycerophospholipids; TCA: Tricarboxylic Acid; LCFA: Long- Chain Fatty Acids; FFAs: Effectively Directing Free Fatty Acids; LDs: Lipid Droplets; ER: Endoplasmic Reticulum; DAGs: Diacylglycerols; FAO: FA Oxidation; FAT: FA Translocase; FABPpm: Plasma Membrane FA-Binding Protein; FABPc: Cytoplasmic FABP; mAspAt: Mitochondrial Aspartate Aminotransferase; CoA: Acyl-Coenzyme A; PUFAs: Polyunsaturated FAs; FASN: The Multifunctional Enzyme FA Synthase; TCA: Citric Acid Cycle; ACLY: ATP Citrate Lyase; ACCs: Ac-CoA Carboxylases; MCD: Malonyl-CoA Decarboxylase; ELOVL5: Elongated By Fatty Acid Elongase 5; SCD: Stearoyl-CoA Desaturase; FADS2: Fatty Acid Desaturase 2; DGAT: Diglyceride Acyltransferase; SREBP-1: Sterol Regulatory Element-Binding Protein 1; GIs: Genetic Interactions; LCFA: Long-Chain Fatty Acid; PtdCho: Phosphatidylcholine; PtdIns: Phosphatidylinositol; PLP: Pyridoxal 5'-Phosphate; SPT: Serine Palmitoyltransferase; 3KS: 3-Ketosphinganine; UPR: Unfolded Protein Response; MALDI-MS/MS (Liquid Chromatography-Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry); MAGL: Monoacylglycerol Lipase; PHD3: Prolyl-Hydroxylase 3 Protein; WAT: White Adipose Tissue; BAT: Brown Adipose Tissue; PAHSAs: Palmitic Acid Hydroxystearic Acids; LDL: Low-Density Lipoprotein; ASCVD: Atherosclerotic Cardiovascular Diseases; PI: Phosphatidylinositol; PUFAs: Omega-3 Polyunsaturated Fatty Acids

Introduction

The average U.S. adult consumes about 81 g of lipids daily, with over 90% being triacylglycerol (TAG, formerly called triglyceride). The rest includes cholesterol, cholesteryl esters, phospholipids, and free fatty acids [1]. The digestion of lipids initiates in the stomach, facilitated by an acid- stable lipase known as lingual lipase, which is produced by glands located at the back of the tongue. This enzyme primarily targets triacylglycerol (TAG) molecules, especially those containing short- or medium-chain fatty acids (fewer than 12 carbons), such as those found in milk fat [1]. In addition to lingual lipase, a separate gastric lipase secreted by the gastric mucosa also degrades these TAGs. Both enzymes exhibit relative acid stability, functioning optimally between pH 4 and pH 6 [1]. These "acid lipases" are particularly crucial for lipid digestion in neonates, who rely heavily on milk fat as their main source of calories. They also serve as vital digestive aids for individuals with pancreatic insufficiency, such as those with cystic fibrosis. In these cases, lingual and gastric lipases assist in breaking down TAG molecules, particularly those with short- to medium-chain fatty acids, even when pancreatic lipase is absent or significantly reduced, represented in Figure 1 [1].

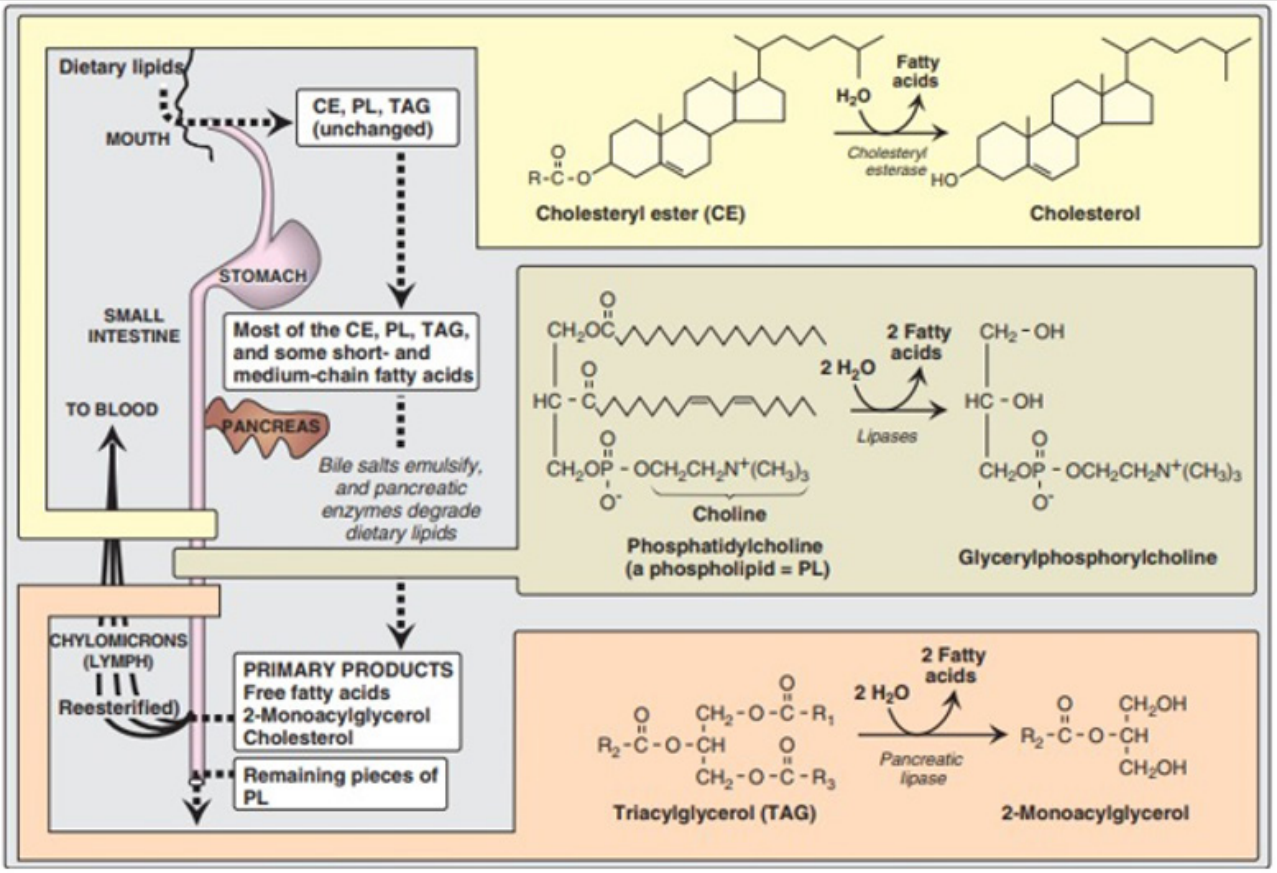


Figure 1: Overview of lipid digestion [1].

Regulation of Lipid Digestion

The hormonal control of lipid digestion involves the pancreatic secretion of hydrolytic enzymes that break down dietary lipids in the small intestine (see Figure 2). When lipids and partially digested proteins enter the lower duodenum and jejunum, cells in the mucosa produce a small peptide hormone known as cholecystokinin (CCK) [1].

Functions of CCK

- **Gallbladder Action:** CCK prompts the gallbladder to contract and release bile, which consists of bile salts, phospholipids, and free cholesterol.
- **Pancreatic Stimulation:** It also stimulates the exocrine cells of the pancreas to secrete digestive enzymes.
- **Gastric Motility:** CCK reduces gastric motility, leading to a slower release of gastric contents into the small intestine. Additionally, other intestinal cells secrete another small peptide hormone called secretin in response of the chyme entering the intestine. Secretin prompts the pancreas and liver to release a bicarbonate-rich solution that neutralizes the pH of the intestinal contents, creating the optimal environment for pancreatic enzyme activity [1]. In Summery digestion of dietary lipids begins in the stomach and continues in the small intestine. Due to their hydrophobic nature, lipids, especially those with long-chain fatty acids (LCFA), must be emulsified for effective breakdown. Short- to medium-chain fatty acids in milk triacylglycerols (TAG) are degraded in the stomach by acid lipases. In the small intestine, pancreatic lipase and other enzymes break down cholesteryl esters, phospholipids, and TAG with LCFAs. Emulsification occurs via peristaltic action and bile salts. Enzymatic degradation produces 2- monoacylglycerol, unesterified cholesterol, and free fatty acids, which form mixed micelles for absorption by intestinal cells (enterocytes). These cells resynthesize TAG, cholesteryl esters, and phospholipids, assembling them into chylomicrons that enter the lymph and then the blood. Short- and medium-chain fatty acids directly enter the blood. Issues with fat absorption can lead to steatorrhea, and deficiencies in degrading chylomicron components can cause their accumulation in the blood [1].

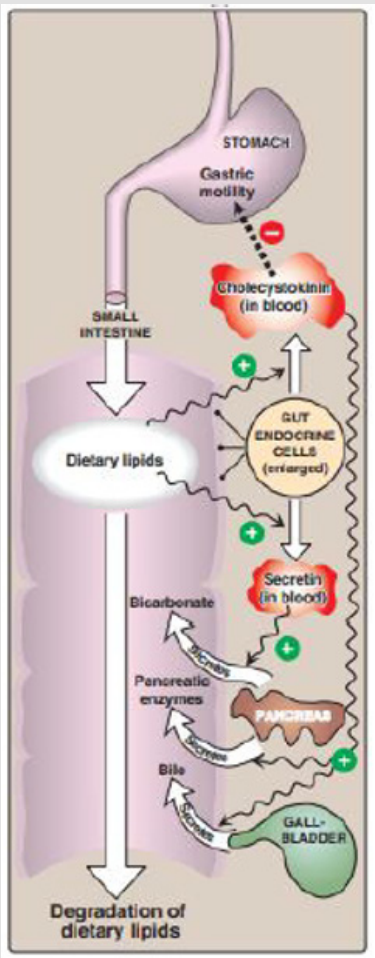


Figure 2: Hormonal Regulation of Lipid Digestion in the Small Intestine [1].

Cellular lipids comprise a wide array of individual molecular components, resulting in an extensive variety of lipid species, collectively referred to as the lipidome [2]. Lipid metabolism plays a vital role in numerous cellular processes essential for maintaining homeostasis, such as membrane synthesis and utilizing lipids (e.g., triacylglycerol "TAG") as energy reserves. Fatty acids (FAs) are crucial lipids that form the primary structural elements of membrane lipids (including glycerophospholipids "GPLs" and sphingolipids) and function as a significant energy source through mitochondrial β-oxidation and the catabolism of the tricarboxylic acid (TCA) cycle (citric acid cycle) [3]. Excessive amounts of circulating lipids have been associated with metabolic diseases [4,5] and cancer [6]. The adverse effects resulting from prolonged exposure to high lipid levels are termed "lipotoxicity" [7,8]. This term was first introduced by Roger Unger (1924 – 2020) and his team to describe the inhibition of pancreatic β-cell function and the onset of type 2 diabetes in rats with lipid overload in their pancreatic islets [9]. The molecular mechanisms that contribute to lipotoxicity encompass endoplasmic reticulum (ER) stress, oxidative stress, mitochondrial dysfunction, impaired autophagy, and inflammation [7]. Metabolic disorders characterized by an imbalance between the uptake or synthesis and consumption of fatty acids (FAs) lead to the accumulation of lipid intermediates within cells, causing dysfunction and cell death in various tissues, including the kidneys, brain, skeletal muscle, and heart.

According to [10] effectively directing free fatty acids (FFAs) towards structural lipids, lipid droplets (LDs), or mitochondria for β-oxidation can help alleviate the detrimental effects of lipid accumulation. This raises important questions:

1. How do imbalances in lipid uptake or synthesis, and their consumption or breakdown, impact downstream signaling pathways?
2. In what ways does the intracellular buildup of lipid intermediates lead to cellular dysfunction?

In this review, we emphasize the critical roles of lipids across various cell types, aiming to establish a framework for comprehending the mechanisms that connect excess lipids and lipotoxicity to dysfunction in metabolic disorders such as chronic kidney disease, fatty liver, heart failure, obesity, neurodegeneration, and cancer [3]. Gaining insight into the processes that regulate lipid fate within cells will shed light on the finely tuned mechanisms of homeostasis. This research explores the processes of fatty acid synthesis, uptake, degradation, and signaling in both homeostatic and disease contexts (see Figure 3).

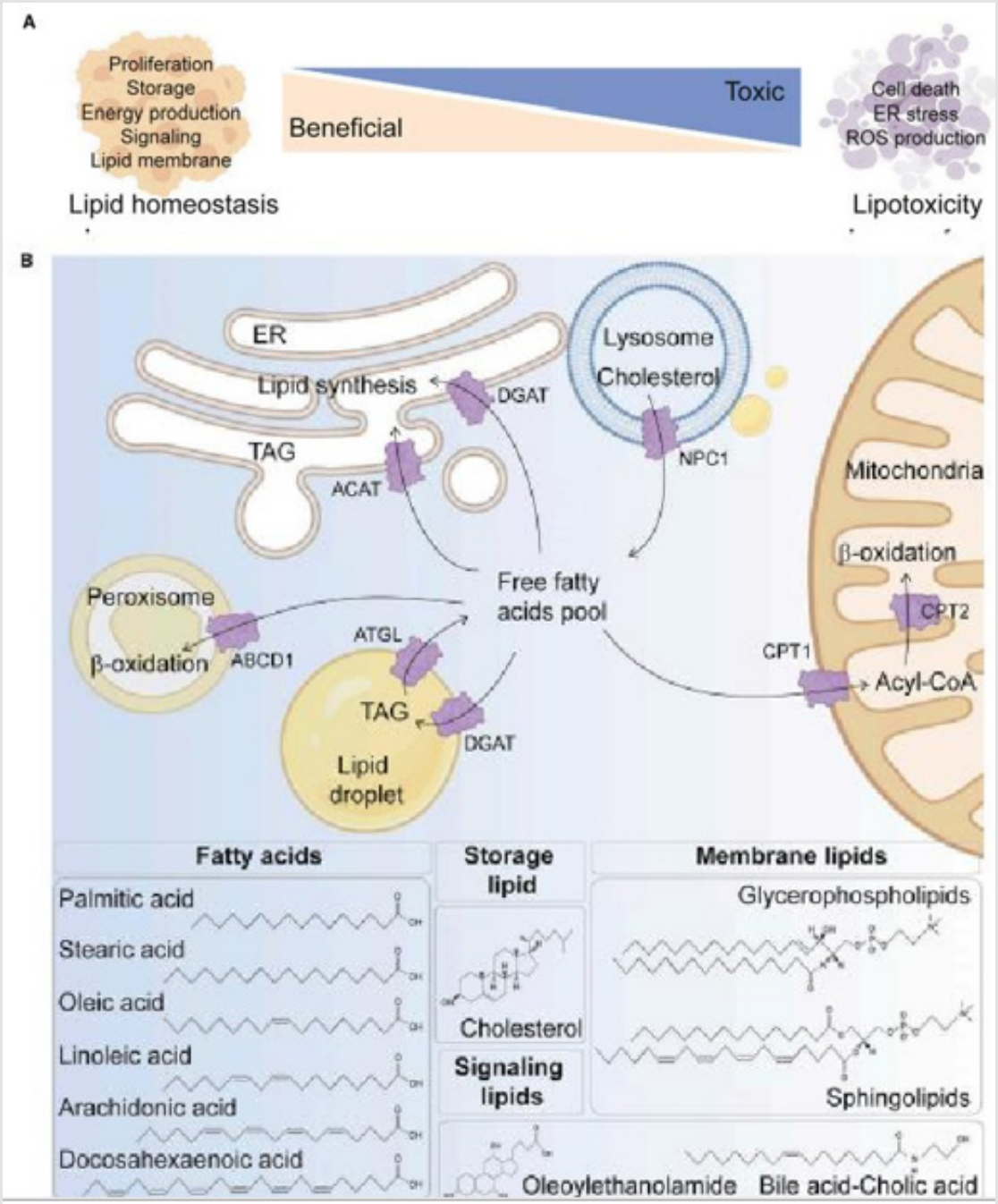


Figure 3: Outlines lipid metabolism, highlighting the need for a systematic approach to differentiate between beneficial and lipotoxic lipids. Bioactive lipids regulate functions like proliferation, storage, and energy production, while lipotoxic lipids can cause cell death and metabolic disorders. Understanding these roles is crucial for maintaining metabolic homeostasis [3].

The Roles of Lipids in Cell Biology and Physiology

Over 40,000 lipids have been identified across various kingdoms of life, yet our comprehension of the functions many of these lipids serve in cell biology and physiology remains incomplete [3]. Lipids are complex molecules formed from simpler components through enzymatic processes. Typically, each lipid features a head group with a distinct chemical makeup, esterified to hydrophobic tails made of fatty acyl chains or sphingoid bases [11]. The biological roles of different lipid classes are influenced by their head groups. Fatty acids (FAs) play diverse and crucial roles, including:

- Serving as building blocks in cells
- Acting as vital biochemical intermediates
- Determining membrane properties
- Modulating cellular signaling pathways
- Functioning as a fuel source

Classification of Lipids

A membrane lipid consists of fundamental components:

Fatty Acids

Fatty acids are made up of long chains of carbon atoms, featuring a carboxylic acid (COOH) group at the first carbon and a methyl (CH_3) group at the end of the chain. The carboxylic acid group plays a crucial role in bonding the fatty acid to other lipid components. In humans, fatty acids typically range from 12 to 24 carbons in length, with most having an even number of carbon atoms. They can contain: Single bonds (C—C), Double bonds (C=C) and Triple bonds (C≡C). Saturated fatty acids only possess single carbon–carbon bonds and are fully bonded to the maximum number of hydrogen atoms. Unsaturated fatty acids contain at least one double bond, allowing for additional hydrogen bonding possibilities along the carbon chain. If more than one double bond is present, the term polyunsaturated is applicable. Double bonds may be in a "kinked" cis configuration or a more linear trans configuration [12].

Glycerol

Glycerol is a simple three-carbon molecule, with hydroxyl groups attached to each carbon. These hydroxyl groups are where fatty acids and other lipid components bond to form diacylglycerol and triacylglycerol molecules. The number and type of double bonds in a lipid's fatty acid influence how it interacts with other fatty acids, affecting the melting temperature of the lipid. Saturated fatty acids have melting points between 44°C and 77°C. In contrast, unsaturated fatty acids exhibit much lower melting points, ranging from 13°C to −50°C, which decrease as the number of double bonds increases. The "kinked" cis double bonds create more disorganization in fatty acid packing, lowering the melting temperature further. This difference is evident when comparing the melting temperatures of butter (highly saturated lipids) and margarine (unsaturated lipids). The linear structure of trans fatty acids resembles that of saturated fatty acids, complicating their metabolism and leading to longer circulation times, which may contribute to arterial deposits and the development of coronary heart disease. Generally, unsaturated fats are considered healthier for the body, so dieticians and clinicians recommend consuming fats primarily composed of cis double-bonded, polyunsaturated fats to help prevent heart disease and other health issues [12].

Essential Fatty Acids

Like essential amino acids, certain fatty acids are considered essential. Notably, two essential fatty acids, linoleate and linolenate, contain double bonds at the sixth and third carbon atoms from the methyl end of their chains, respectively, and are necessary for producing specific 20-carbon fatty acids with double bonds. These are known as omega-6 (ω-6) and omega-3 (ω-3) fatty acids. Humans cannot produce double bonds at these positions, so these essential fatty acids must be obtained from dietary sources, particularly vegetable oils. Arachidonate, a 20-carbon chain with four cis double bonds, is also an essential fatty acid involved in various biological functions. Recently, longer-chain ω-3 fatty acids have been linked to a reduced risk of heart attacks and strokes; thus, supplements and certain food products containing these fatty acids are now available. Interestingly, excessive intake of ω-6 fatty acids has been associated with an increased risk of heart attacks, strokes, some cancers, and even depression [12].

Head Group

The final component of a lipid molecule varies among different lipid types and, along with the two specific fatty acids, defines each lipid. This third part is often referred to as the "head group," aptly named if one imagines the end methyl group of the fatty acid chains as the tail of the lipid molecule. Most biological membrane lipids contain a phosphate group (PO_4^{3-}) attached to the third glycerol carbon, categorizing them as phospholipids. Often, an additional molecule (several common examples found in humans is attached to the phosphate group, creating the final head group of the lipid molecule. This head group is typically charged, making it hydrophilic and drawn to water—a critical quality for forming biological membranes and for various lipid functions [12]. Fatty acids (FAs) are the foundational components of all lipids, act as precursors for synthesizing other lipid types, including glycerolipids, glycerophospholipids (GPLs), sphingolipids, sterols, and saccharolipids [13]. Imbalances between fatty acid (FA) uptake and oxidation can result in the buildup of long-chain fatty acids. These fatty acids are then incorporated into triglycerides (TAGs), phospholipids, and various other lipid species [10]. Ceramides, diacylglycerols (DAGs), and acyl-carnitines, which regulate intracellular signaling cascades and metabolism [14,15] are generally regarded as toxic signaling lipids [10]. Additionally, defective mitochondrial FA oxidation (FAO) results in an increase of medium-chain acyl-carnitines, another toxic species [16]. Exploring the varied roles

of lipids, particularly regarding metabolic diseases and cancer, provides a pathway to understanding lipid-mediated toxicity.

Fatty Acid and Triacylglycerol Metabolism

Generally, Fatty acids, linear hydrocarbons with a terminal carboxyl group, can be saturated or unsaturated. Essential fatty acids like linoleic and α-linolenic acids must be obtained through diet. In the liver, fatty acids are synthesized from excess carbohydrates and proteins using acetyl CoA, ATP, and NADPH. The process begins with acetyl CoA carboxylase, which is regulated by citrate and long-chain fatty acyl CoA, and is influenced by insulin and AMPK [1]. Fatty acid synthase further produces palmitoyl CoA from acetyl CoA and malonyl CoA. Degradation of stored triacylglycerol for energy is initiated by hormone-sensitive lipase in adipose cells. Fatty acids are transported via serum albumin to the liver and tissues for oxidation, providing energy, while glycerol serves as a gluconeogenic precursor [1]. β-oxidation of fatty acids occurs in mitochondria, requiring the carnitine shuttle for long-chain fatty acids, with malonyl CoA inhibiting transport. The oxidation process yields acetyl CoA, NADH, and FADH2. Medium-chain fatty acyl CoA dehydrogenase deficiency can lead to metabolic issues. Odd-chain fatty acids produce propionyl CoA, which is converted to succinyl CoA, necessary for gluconeogenesis [1]. Fatty acid oxidation also occurs in peroxisomes and the ER, with liver mitochondria converting acetyl CoA into ketone bodies for energy during fasting, particularly when fatty acids are unavailable. Ketoacidosis can occur in uncontrolled type 1 diabetes due to excessive ketone body production [1]. Figure 4 illustrates the metabolic pathways of fatty acid synthesis and degradation, and their relationship to carbohydrate metabolism.

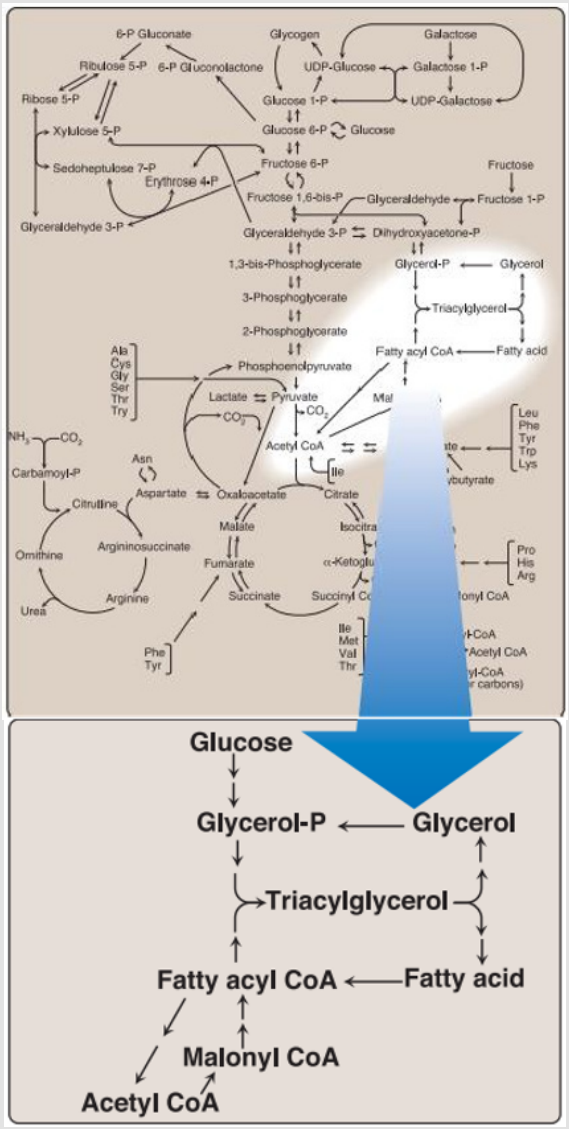


Figure 4: The metabolic pathways of fatty acid synthesis and degradation [1].

Complex Lipid Metabolism

[1] Concluded phospholipids are polar compounds (Figure 5) formed from an alcohol and either diacylglycerol or sphingosine, with key types including sphingomyelin, crucial for cell membranes. They play roles in lung surfactants, with dipalmitoyl phosphatidylcholine being a major component. Phosphatidylinositol (PI) serves as a reservoir for arachidonic acid, which, when phosphorylated, produces PIP2 that mediates intracellular calcium mobilization. Glycolipids, derived from ceramides, are vital in brain membranes and are antigenic. Prostaglandins, thromboxane's, and leukotrienes act as inflammatory mediators, derived from linoleic acid and arachidonic acid. Their synthesis involves enzymes like COX, with NSAIDs inhibiting their production.

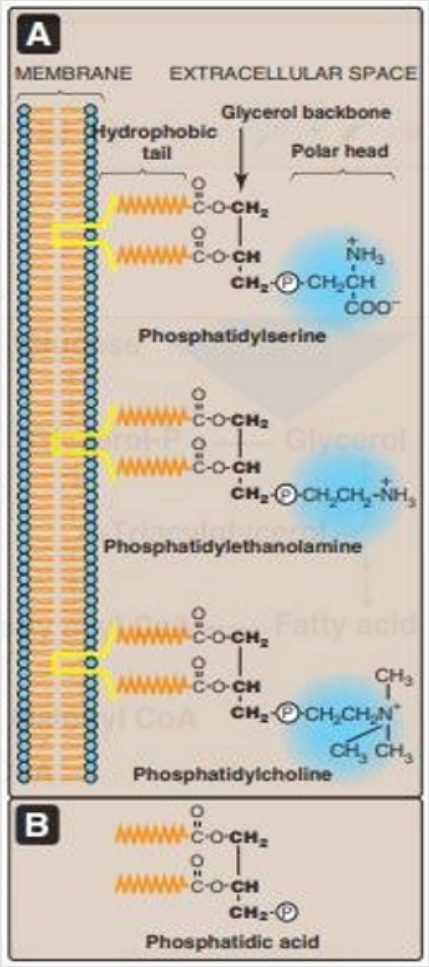


Figure 5:
A. Structures of some glycerophospholipids,
B. Phosphatidic acid,
P in circle= phosphate, PO41- [1].

Cholesterol and Steroid Metabolism

[1] Cholesterol is a hydrophobic compound vital for human health, synthesized mainly in the liver, intestine, and adrenal cortex, with its production driven by acetate and NADPH. The key regulatory enzyme, HMG CoA reductase, is influenced by various factors such as insulin and glucagon levels. Statins inhibit this enzyme to lower plasma cholesterol. Cholesterol is eliminated through bile salts, which are produced from cholesterol and help emulsify fats. Bile acids are reabsorbed in the intestine and returned to the liver. Lipoproteins, such as chylomicrons and VLDL, transport lipids throughout the body, while HDL plays roles in cholesterol transport and metabolism. Cholesterol serves as a precursor for steroid hormones, which interact with specific receptors to regulate gene expression (See Figure 6) [1].

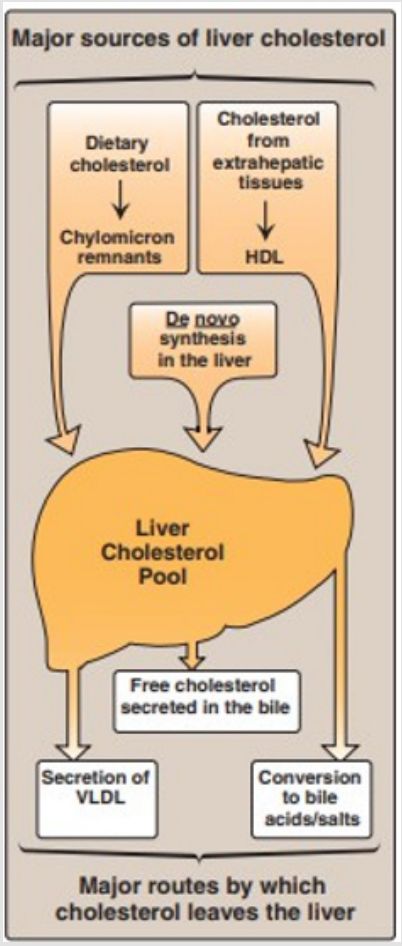


Figure 6: Summarizes the main sources of liver cholesterol and its exit routes from the liver [1].

Cellular Uptake of Fatty Acids

[17-20] The cellular uptake of fatty acids (FAs) is crucial for metabolic regulation. Although FAs can naturally diffuse through phospholipid bilayers, the majority of FA uptake in mammalian cells is supported by integral or membrane- associated proteins. Various transporters from multiple classes mediate cellular FA uptake, including:

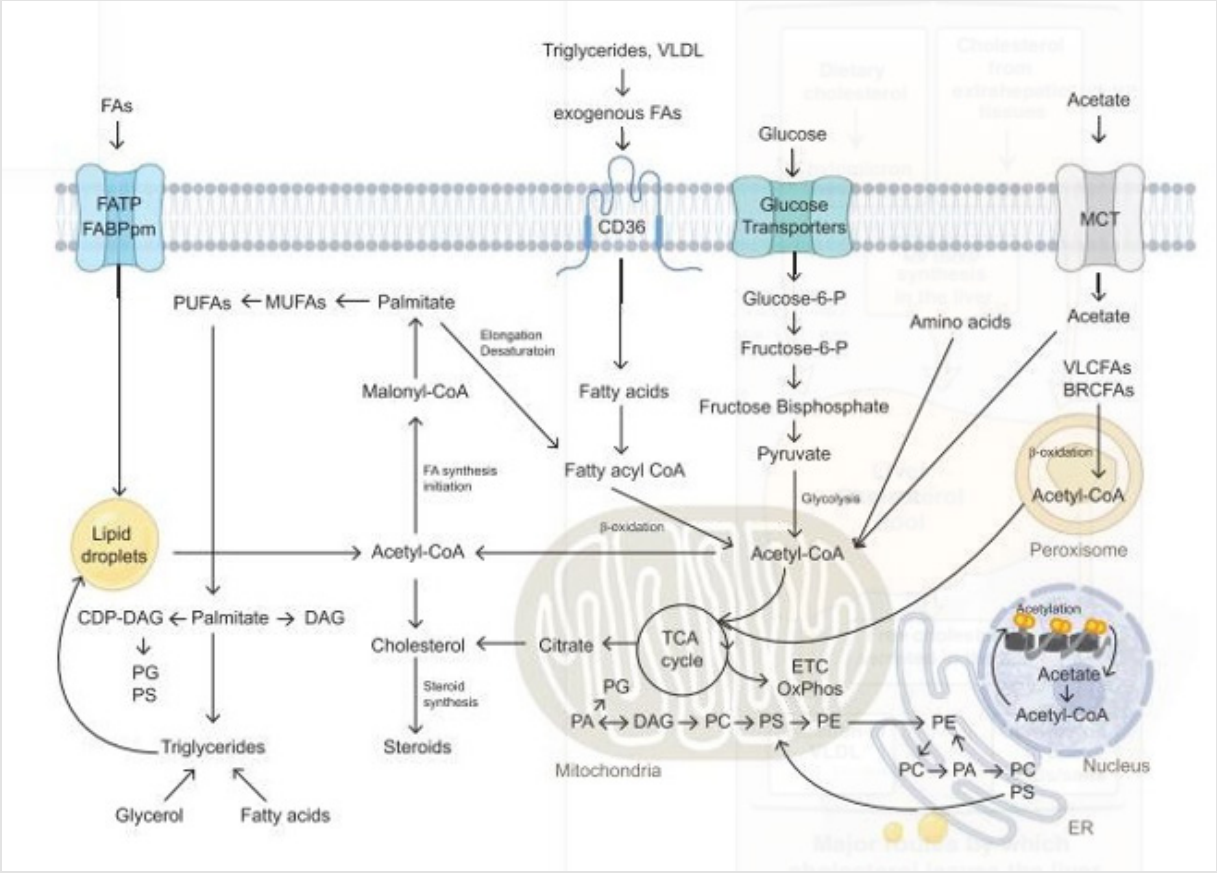
- Scavenger receptor CD36 (FA translocase "FAT")
- Plasma membrane FA-binding protein (FABPpm)
- Six FA transport proteins (FATPs; solute carrier family SLC27A1–6)

Once FAs reach the inner side of the membrane, they bind to cytoplasmic FABP (FABPc) before entering various metabolic or signaling pathways. Interestingly, research has revealed that FABPpm and mitochondrial aspartate aminotransferase (mAspAt) are the same proteins involved in amino acid metabolism [21,22]. Moreover, FAs are activated by a group of acyl-coenzyme A (CoA) synthetase (ACS) enzymes that catalyze the conversion of free fatty acids (FFAs) into CoA esters [23]. This CoA conjugation helps maintain the concentration gradient by actively drawing FAs into the cell. Additionally, FATPs are a family of membrane proteins that facilitate the import of long-chain FAs (LCFAs) and leverage ACS activity to regulate intracellular polyunsaturated FAs (PUFAs) [24]. Among the six FATP/SLC27A family members, the overexpression of FATP1 in 3T3-L1 cells—a mouse embryonic fibroblast cell line capable of differentiating into adipocyte-like cells—leads to the uptake of palmitic acid, oleic acid, and arachidonic acid without any specific preference for these FAs [25]. Subcellular fractionation studies indicate that FATP is situated in the plasma membrane, facilitating the transport of LCFAs into the cell for energy substrate utilization [3].

Fatty Acids Synthesis

FA synthesis is an anabolic process responsible for creating a variety of lipid species. The multifunctional enzyme FA synthase (FASN) plays a crucial role by converting dietary carbohydrates into long-chain saturated fatty acids (FAs), primarily focusing on the 16-carbon

palmitate. This conversion utilizes acetyl-CoA (Ac-CoA) as a primer (see Figure 7). FASN contributes to the supply of additional lipids, which support membrane structure and facilitate cytosolic signaling. Several metabolic enzymes participate in transforming carbon from citrate within the citric acid cycle (TCA) into bioactive FAs. ATP citrate lyase (ACLY) converts citrate generated in the mitochondrial TCA cycle into Ac- CoA in the cytosol, serving as a precursor for FA synthesis [26]. Other key molecular components include Ac-CoA carboxylases (ACCs), which produce malonyl-CoA. Additionally, malonyl-CoA decarboxylase (MCD) transforms malonyl-CoA back into Ac-CoA, effectively reversing the ACC-catalyzed reaction [27]. Through a series of condensations involving seven malonyl- CoA molecules and one priming Ac-CoA, FASN generates palmitate, the primary product of FA synthesis. This 16- carbon saturated fatty acid (16:0) is subsequently activated by acyl-CoA synthetase (ACS), elongated by fatty acid elongase 5 (ELOVL5), and desaturated by stearoyl-CoA desaturase (SCD) and fatty acid desaturase 2 (FADS2), resulting in a range of molecules with varying lengths and degrees of saturation [28,29]. The synthesized fats are stored as triglycerides (TGs) within cells.



Note:

Fatty acid transport into mitochondria for oxidation, producing acetyl-CoA for ATP.

Glucose entering the TCA cycle through pyruvate and acetyl- CoA.

Acetate uptake via MCT, increasing cytosolic acetyl-CoA.

Acetyl-CoA affecting histone and protein acetylation for epigenetic changes.

VLCFAs and BRCFAs oxidized in peroxisomes, supporting TCA metabolism.

Citrate from the TCA cycle exported for de novo lipogenesis, leading to fatty acid and cholesterol synthesis.

Fatty acids synthesized from malonyl-CoA, producing palmitate, convertible to MUFAs and PUFAs.

Long-chain fatty acids stored as triglycerides, with palmitate transforming into CDP-DAG and diacylglycerol for phospholipid synthesis, crucial for cell membranes.

In summary, lipid metabolism pathways coordinate to regulate cellular metabolic states [3].

Figure 7: Lipid metabolism involves both catabolic and anabolic processes, including: Uptake of lipids via transport proteins.

Diglyceride acyltransferase (DGAT) is integral to the TG synthesis pathway, converting diacylglycerol (DAG) into triacylglycerols (TAGs). DGAT enzymes catalyze the final step in the known TG synthesis pathways. Although the two DGAT enzymes differ in protein sequences, they both utilize fatty acyl-CoA substrates [30]. The TGs produced by DGAT enzymes are stored in cytosolic lipid droplets or in organs like the liver and small intestine, where they are released as components of lipoproteins. Both DGAT enzymes are expressed ubiquitously across tissues and are especially prevalent in organs involved in triglyceride metabolism, including adipose tissue and the liver [31]. Fatty acid (FA) synthesis enzymes are governed at the transcriptional level by sterol regulatory element-binding protein 1 (SREBP-1) transcription factors [32]. A recent genome-wide CRISPR screen systematically identified genetic interactions (GIs) in human HAP1 cells, a near- haploid cell line derived from chronic myelogenous leukemia (CML), to explore how cells adapt to the absence of de novo FA synthesis [33]. Cells with a loss-of-function mutation in FASN, the enzyme responsible for long-chain fatty acid (LCFA) formation, demonstrate a significant reliance on lipid uptake, evidenced by negative GIs with genes associated with the low- density lipoprotein receptor signaling pathway [33]. Notably, a previously unrecognized role for C12orf49 has emerged in regulating exogenous lipid uptake via the sterol regulatory element-binding protein SREBF2.

This study illustrates how pooled genome-wide CRISPR screens can identify novel metabolic targets in human cells. While most normal cells favor extracellular lipids for synthesizing new structural lipids, cancer cells increase de novo FA synthesis to support proliferation in lipid-poor environments lacking extracellular lipids [34]. SREBP enhances the synthesis of phospholipids, triglycerides (TAG), and cholesterol, thereby promoting the survival and growth of cancer cells [35,36]. Cancer progression is further accelerated by SREBP-1 signaling, with the RNA- binding protein LIN-28 speeding up de novo FA synthesis and facilitating the conversion from saturated to unsaturated fatty acids [37]. Together with essential fatty acids like linolenic acid obtained from the diet, they create a complex array of substrates for synthesizing FA-containing lipids. FASN, along with membrane receptor tyrosine kinases (RTKs) and the serine/threonine kinase mTOR, plays a crucial role in regulating survival signaling by providing second messenger signaling lipids [34]. Consequently, de novo FA synthesis leads to the production of diverse lipids that play critical roles in cellular signaling and lipid homeostasis. For a more in-depth exploration of FA dysregulation in cancer cells, we recommend a recent comprehensive review on the topic [38].

The Importance of Fatty Acids in Metabolism

Fatty acids (FAs) engage with various metabolic enzymes to integrate into complex lipid species, such as diacylglycerols (DAGs) and triacylglycerols (TAGs), or to be transformed into phosphoglycerides like phosphatidic acid (PA), phosphatidylethanolamine (PE), and phosphatidylserine (PS) [39,40] (Figure 4).

Diversity of Phospholipids

The acyl groups of fatty acids, especially the stearoyl groups present in mammalian cells, play a significant role in shaping the diversity of phosphatidylcholine (PtdCho) and phosphatidylinositol (PtdIns) [41,42]. PtdIns are recognized as some of the most well-studied secondary messengers in signal transduction pathways [43]. Through phosphorylation, PtdIns can be converted into various phosphoinositide species, including PtdIns 4,5-bisphosphate and PtdIns (3,4,5)-trisphosphate (PIP2/3) [43]. PIP3 activates AKT, which triggers pro-tumorigenic signaling via phosphoinositide-dependent kinase 1 (PDK1), tuberous sclerosis complex (TSC) 1/2, and mTORC2 [40].

Ceramide Synthesis and ER Stress

Additionally, FAs can be utilized for the de novo synthesis of ceramide in the endoplasmic reticulum (ER). The

process begins with the condensation of the activated C16 FA palmitoyl-CoA and the amino acid L-serine, catalyzed by pyridoxal 5'-phosphate (PLP)-dependent serine palmitoyltransferase (SPT). This reaction yields 3- ketosphinganine (3KS), which can be quickly reduced to sphinganine (dihydrosphingosine [d18:0 Sph]) by 3KS reductase (KDSR) in a NADPH-dependent reaction [44]. FA synthesis is stimulated by hypoxia-inducible factor (HIF) signaling [45]. HIF represses carnitine palmitoyltransferase 1 (CPT1), which decreases FA transport into mitochondria and redirects FAs toward lipid droplets (LDs) for storage [46]. Both HIF-1α and HIF-2α are upregulated in response to ER stress [47] which promotes the formation of LDs to mitigate cytotoxic ER stress responses [48].

Lipotoxicity and Metabolic Regulation

An increase in LDs within cells is often linked to lipotoxicity and metabolic alterations that lead to cellular dysfunction. The composition and catabolism of LDs serve as crucial regulatory points that integrate physiological inputs, such as dietary lipids and lipolytic signals, to synchronize cellular signaling and metabolism. LDs help maintain lipid homeostasis, prevent lipotoxicity, and generate ATP by degrading stored lipids during metabolic stress [49]. Furthermore, the inhibition of SREBP or restriction of fatty acid synthase (FASN) can activate the HIF-1α signaling pathway and the unfolded protein response (UPR) [35]. In situations of energy deficiency-mediated stress, HIF signaling pathways work in conjunction with AMP-activated protein kinase (AMPK) and mTOR to compensate for FASN limitations and activate lipid metabolism, thus alleviating lipid-mediated ER stress.

FASN Antagonists as a Cancer Treatment

FASN antagonists are gaining attention as a potential therapeutic strategy for cancer treatment. Advanced techniques like MALDI-MS/MS (liquid chromatography-matrix-assisted laser desorption/ionization mass spectrometry) ease enhanced proteome analysis [50]. Mass spectrometry applications show that FASN inhibitors, such as

C75 and G28UCM, increase PUFAs while decreasing signaling lipids like DAG and PIP3 in ovarian cancer cell lines [45]. [45,51-53] FASN inhibition affects several downstream targets, indicating that a deeper understanding of pathway interactions could improve drug target efficacy by impacting multiple pathways. Specifically, FASN inhibition influences ERBB-PI3K-mTORC1 activity by:

- Blocking phosphorylation of the EGF receptor/ERBB/HER
- Inhibiting GRB2-EGF receptor recruitment
- Suppressing PI3K-AKT signaling

Furthermore, fatty acid synthesis is heightened in metastatic breast cancer, particularly in the brain [54]. This phenomenon arises as an adaptation to the lower lipid availability in the brain compared to other tissues, leading to a specific reliance on fatty acid synthesis for breast tumors developing in the brain. FASN inhibition notably reduces the growth of human EGF receptor 2-positive breast tumors in the brain, highlighting the potential for new cancer targets based on different nutrient availability across metastatic sites [54]. FABP5 serves as an intracellular chaperone that transports cytosolic fatty acids to nuclear receptors, promoting metastasis. Both FASN and monoacylglycerol lipase (MAGL) are crucial for activating nuclear receptors, and prostate cancer metastasis significantly relies on the co-expression of FABP5 [55]. Additionally, the expression level of FASN influences PI3K/AKT signaling through phosphatase and tensing homolog deleted on chromosome 10 (PTEN) [56]. According to [57] greater insight into these intersecting pathways will enhance the design of effective FASN inhibitors that manage multiple interconnected targets. Besides HIF-dependent pathways, fatty acid synthesis is also regulated by various metabolic enzymes. Lipid biosynthesis and oxidation are governed by a master regulator of fatty acid metabolism, ACC, which converts Ac-CoA to malonyl-CoA. This conversion serves as a precursor for fat synthesis while inhibiting fatty acid oxidation.

- ACC1 is found in the cytosol and promotes fatty acid production.
- ACC2, located in the mitochondrial outer membrane, generates malonyl-CoA to inhibit FATP CPT1 Cellular stress has a direct impact on enzymatic activities related to ACC and regulates fatty acid metabolism. Under energy stress conditions, AMPK activates both fatty acid synthesis and catabolism by inhibiting both ACCs [58]. Conversely, in nutrient-rich conditions, AMPK is downregulated and ceases to repress ACC1 and ACC2. Additionally, ACC2 is influenced by post-translational modifications; for instance, prolyl-hydroxylase 3 protein (PHD3) creates a metabolic barrier to fatty acid utilization by hydroxylating and activating ACC2 [56,59]. Thus, ACC acts as a signaling hub that senses nutrient levels and adjusts anabolic versus catabolic fatty acid metabolism accordingly. In acute myeloid leukemia, decreased PHD3 levels lead to a reliance on fats, which can be targeted by fatty acid oxidation inhibitors. Beyond AML, many cancer cells utilize fatty acid synthesis to promote proliferation [3].

Lipotoxicity Across Diverse Organ Systems

[60] concluded that impairments in fatty acid (FA) metabolism significantly impact on various human diseases. Recent advancements using CRISPR-based genetic screens and unbiased lipidomics have unveiled new ways to investigate the enzymes that manage how FAs integrate into membrane and storage glycerolipids. The accumulation of lipids within tissues is increasingly acknowledged as a factor contributing to cellular dysfunction. Many cells across different organ systems struggle to cope with excess lipid loads, and the mechanisms through which surplus lipids induce cellular injury, or lipotoxicity, are being explored in the kidney, liver, heart, skeletal muscle, bone, pancreas, and brain (see Figure 8). Saturated FAs are believed to be particularly detrimental, triggering a variety of harmful cellular responses such as:

- Apoptosis
- Inflammation
- Ceramide formation
- Reactive oxygen species (ROS)
- Small nucleolar RNAs
- Endoplasmic reticulum (ER) stress

A key focus in this field is identifying bioactive lipid species that influence the lipotoxic cellular response [60].

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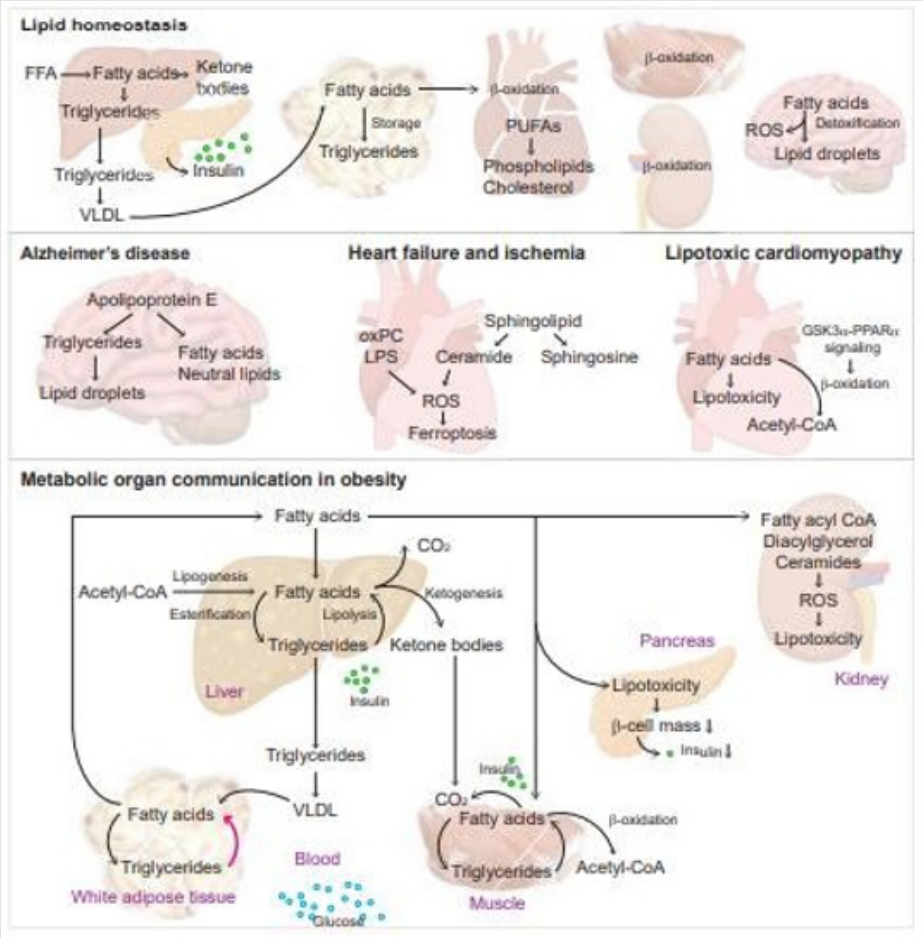

Figure 8: Under excess nutrient conditions, lipolysis decreases, promoting triglyceride storage in adipose tissue, while glucose oxidation rises in muscle cells. In fasting, lipolysis and fatty acid oxidation increase for energy in adipose and muscle cells, respectively. Metabolic changes also occur in the brain, heart, liver, pancreas, kidney, and adipose tissue [3].

Lipid Accumulation in Adipose Tissue

[61] Adipose tissue plays a crucial role in regulating energy homeostasis, and its dysfunction leads to energy imbalances due to inappropriate lipid loads in peripheral tissues. Adipocytes serve as energy reservoirs, sensing energy demands and releasing paracrine factors to regulate other metabolic tissues. Mammals possess two types of adipose tissue:

- White adipose tissue (WAT), which stores excess energy.
- Brown adipose tissue (BAT), which expends excess energy as heat.

A primary function of WAT is to release non-esterified fatty acids (NEFAs) into the bloodstream during times of energy need. Recent research has focused on the byproducts of lipid metabolism that affect adipocyte function. Short-chain fatty acids (SCFAs) and TCA cycle metabolites are emerging as key players that link lipogenesis to WAT energy balance [61]. SCFAs such as acetate, butyrate, and propionate inhibit lipolysis and promote adipogenesis in WAT, while also providing substrates for glucose and lipid synthesis. They act on G protein-coupled receptors (GPR41 and GPR43) to reduce lipolysis and lower plasma levels of free fatty acids (FFAs) [61]. Using extremely sensitive mass spectrometry-based proteomics on human adipocytes, researchers identified 471 secreted proteins, including hormones, growth factors, and extracellular matrix proteins, that are differentially regulated between BAT and WAT [62]. Notably, brown and white adipocytes exhibit distinct secretory profiles and metabolic functions. The mammalian ependymin-related protein 1 (EPDR1) is selectively secreted by brown adipocytes and is essential for promoting the development of functional thermogenic adipocytes by activating UCP1 expression [3]. This recent analysis of the secretome in mature white and brown adipocytes has highlighted crucial regulators of human metabolism. However, questions remain regarding the dynamic regulation of lipid metabolism and secretome throughout the differentiation process.

Future studies examining various stages of differentiation in adipocytes could provide deeper insight into the mechanisms that preserve metabolic health in individuals with obesity, severe insulin resistance, and type 2 diabetes [3].

Lipid Accumulation in the Kidney

Extensive research in animal models has established a connection between kidney dysfunction and lipid accumulation in various metabolic diseases, such as obesity, metabolic syndrome, diabetes mellitus, chronic kidney disease, and acute kidney injury [63-65]. Human clinical studies have also reported lipid accumulation and kidney dysfunction associated with conditions such as focal segmental glomerulosclerosis (FSGS), minimal change disease, Fabry's disease, and lipoprotein glomerulopathy [66]. The kidney utilizes multiple substrates for energy, depending on their availability [67-69]. Substrate utilization varies across different kidney regions based on energy demands [66]. The proximal tubules, which have a high energy requirement—second only to cardiac myocytes—exhibit limited glycolytic capacity. Instead, they predominantly rely on mitochondrial β-oxidation of free fatty acids (FFAs) for optimal ATP production [70-72]. Recent findings suggest that in diabetic kidney disease, the proximal tubule expresses kidney injury molecule (KIM)- 1, which facilitates the uptake of palmitate (PA) and leads to increased tubule injury characterized by DNA damage, interstitial inflammation, and fibrosis [73]. The small-molecule inhibitor of KIM-1, TW-37, has demonstrated the ability to alleviate kidney inflammation and fibrosis. These studies underline the potential of targeting small molecules upstream of fatty acid oxidation (FAO) as a novel therapeutic strategy for kidney injury.

[3] states that the kidney responds to lipid toxicity by upregulating regulators involved in lipid peroxidation and accumulating toxic metabolites like fatty acyl-CoA, diacylglycerol (DAG), and ceramides. Lipotoxic cellular dysfunction results in the production of reactive oxygen species (ROS), organelle damage, disruption of intracellular signaling pathways, and the release of pro-inflammatory and pro-fibrotic factors, ultimately leading to lipid-induced apoptosis. Lipid peroxidation occurs when oxidants, such as free radicals, attack lipids containing carbon-carbon double bonds, particularly polyunsaturated fatty acids (PUFAs). Although numerous studies indicate that PUFAs can reduce kidney disease by lowering triglycerides (TGs) and inflammation, it is theorized that PUFAs may be converted into oxidized lipids by lipoxygenases (LOX), cyclooxygenases (COX), and cytochrome P450 enzymes (CYP) [74]. The kidney is particularly vulnerable to changes in the gene expression of sterol regulatory element-binding proteins (SREBPs) induced by diabetes. This leads to triglyceride accumulation, mesangial expansion, and glomerulosclerosis [75]. This suggests that the activation of renal SREBP-1 leads to changes in renal lipid metabolism, indicating that renal lipid accumulation plays a significant role in the pathogenesis of diabetic nephropathy [3]. Lipid accumulation is a major factor contributing to diabetic kidney disease, which is currently the fastest-growing cause of kidney failure globally [76].

Podocytes, essential components of the kidney filter, are highly specialized epithelial cells that are particularly vulnerable to lipid accumulation and toxicity [77]. Coenzyme Q10 (CoQ), a lipid found in all cellular membranes, offers protection against PUFA-mediated lipid peroxidation [78]. In the context of mitochondrial dysfunction, the lack of protection from lipid peroxidation makes cells more susceptible to death [79]. Increased lipid peroxidation, indicated by elevated glutathione peroxidase 4 (GPX4), has been observed in podocytes of CoQ-deficient mice [78]. Furthermore, the loss of GPX4 can trigger ferroptosis in the kidney, contributing to renal degeneration [80]. Recent research efforts to explore the connection between kidney disease, PUFAs, and dysregulated pathways in podocytes have utilized single-nucleus RNA sequencing (sNuc-Seq) along with integrated metabolomics and transcriptomics to identify a therapeutically relevant Braf/MAPK pathway [78]. Additionally, junctional adhesion molecule-like protein (JAML) is expressed in podocytes and is induced under diabetic conditions [81]. Deleting JAML specifically in podocytes has been shown to reduce podocyte injury and proteinuria in two different models of diabetic mice [81]. Junctional adhesion molecules, part of an immunoglobulin subfamily, are increasingly recognized for their role in lipid metabolism. For instance, Jam-A knockout mice fed a high-saturated fat, fructose, and cholesterol diet (HFCD) develop severe non-alcoholic steatohepatitis [82].

Utilizing LC/MS-based lipidomics analysis revealed that JAML deletion in podocytes lowers levels of lipids, including FFAs, cholesteryl esters, and phosphatidylcholines (PtdChos) [81]. JAML regulates podocyte lipid metabolism through SIRT1-mediated SREBP-1 signaling and is found at elevated levels in the glomeruli of patients with kidney disease. In the future, clinical studies focused on preventing lipid accumulation and preserving glomerular function may present promising therapeutic targets for diabetic kidney disease and other proteinuric kidney diseases [3].

The Roles of the Liver, Bone, and Skeletal Muscle in Lipotoxicity According to [3] fatty acids (FAs) are transported to the liver via the bloodstream following the lipolysis of triglycerides (TGs) in adipose tissue. In the liver, FAs bind to FABP1 and undergo mitochondrial β-oxidation. Conditions such as obesity and type 2 diabetes often led to excessive fat accumulation in the liver, commonly referred to as non-alcoholic fatty liver disease (NAFLD). The primary genetic factors associated with NAFLD include PNPLA3, HSD17B13, and TM6SF2, with liver steatosis arising from the dysregulation of pathways that govern de novo lipogenesis and fat catabolism. Recent findings indicate that a decrease in the activity of lysosomal acid lipase (LAL), a crucial enzyme for intracellular fat breakdown, is clinically significant for NAFLD patients [83]. Advances in high-throughput sequencing technology have revealed potential gene candidates influencing fat deposition.

- FABP1 is a liver-specific fatty acid-binding protein that plays vital roles in the liver's lipid metabolism. Its knockdown prevents lipid accumulation in hepatocytes [84]. FABP1 regulates fat deposition through PPAR signaling and fatty acid biosynthesis [85].

- Palmitic acid hydroxystearic acids (PAHSAs) are endogenous lipids known for their anti-diabetic and anti- inflammatory properties. Chronic PAHSA treatment enhances insulin-stimulated glucose uptake in glycolytic muscle and heart tissues of high-fat diet-fed mice by improving hepatic insulin sensitivity and reducing lipolysis in adipose tissue [86]. Furthermore, PAHSAs activate GPR40 receptors, which help regulate glucose tolerance and insulin sensitivity [87]. Beyond metabolic systems, bones also play a significant role in eliminating circulating lipoproteins and non-esterified fatty acids (NEFAs) [88]. Notably, long-chain fatty acid oxidation influences postnatal bone development by modifying fatty acid utilization. Eicosapentaenoic acid (EPA; a long-chain polyunsaturated n-3 fatty acid) alters substrate cycling in human skeletal muscle cells by affecting the lipolysis rate of intracellular TAG and enhancing the re-esterification of fatty acids, thereby increasing fatty acid turnover [89].

Lipids and Cardiovascular Function

The heart has the highest caloric demand and performs extensive oxidation of fatty acids [10], efficiently acquiring lipids from circulating NEFAs and esterified fatty acids bound to lipoproteins. Lipid energy metabolism is critical for heart health, particularly concerning diseases like heart failure and ischemia. Strong clinical evidence links lipid oxidation and inflammatory responses to cardiovascular diseases. Polyunsaturated fatty acids (PUFAs) influence the levels of phospholipids and cholesterol esters in lipoproteins during atherosclerosis development [90]. Free radical lipids and altered lipoproteins produced from oxidized lipid peroxidation are crucial in influencing inflammatory responses [91,92]. Increased lipid availability exacerbates ischemia-induced cardiac dysfunction and reduces myocardial mitochondrial efficiency. This condition leads to greater myocardial FA-linked respiration and oxidative stress, while mitochondrial efficiency declines, heightening susceptibility to ischemia-related cardiac dysfunction [93]. Cell death occurs through various mechanisms, with ferroptosis—a programmed iron-dependent cell death—being driven by lipid membrane damage in ischemia/reperfusion-induced cardiomyopathy, alongside lipid peroxidation. Recent studies suggest that free iron accumulation in mitochondria can induce oxidative stress and ferroptosis, contributing to heart damage [94]. During myocardial infarction (MI), the glutathione metabolic pathway and reactive oxygen species (ROS) pathway are significantly downregulated [95].

Notably, GPX4, which protects against ferroptosis, is also downregulated during MI. Moreover, oxidized phospholipids promote inflammation in global myocardial ischemia/reperfusion injury. The cytokine IL-10 serves an anti-inflammatory function and regulates the production of oxidized phosphatidylcholines in cardiomyocytes, helping to reduce inflammation and cell death [96]. Lipid levels and composition in patient blood during MI can predict complication risks [97]. Sphingolipids serve as biomarkers for recurrence and mortality following MI [98]. Ceramides, a type of simple membrane sphingolipid that forms the backbone of complex sphingolipids, can trigger programmed cell death when present at high cellular levels [99]. Research indicates that ceramide levels are elevated in human heart tissues during acute MI [98]. Within 24 hours post-MI, 30% of genes involved in sphingolipid metabolism are significantly upregulated, resulting in increased levels of C16-ceramide, C20-ceramide, C20:1-ceramide, and C24-ceramide [98]. In hypoxic conditions resembling MI, several inhibitors can limit ceramide degradation, including the pan-ceramidase inhibitor B13 and the acid ceramidase-specific inhibitor ARN14974Additionally, a pan-sphingosine kinase inhibitor (SK1-II) notably increases the levels of cardiomyocyte cell death [98]. Alterations in sphingolipid metabolism by ceramidase, which hydrolyzes pro-apoptotic ceramide and generates sphingosine, are essential for managing ceramide levels and cell survival in ischemic heart disease [98].

Transcriptomic and protein analyses reveal that modifying ceramide metabolism through chemical inhibitors of sphingolipid metabolism can confer cardio protection following MI. Furthermore, the expression of microsomal TG transport protein (MTTP) is linked to structural and perfusion abnormalities in patients with ischemic heart disease, indicating that TGs are crucial for cardiac function in relation to ischemic events [100]. Decreased levels of fatty acid oxidation are commonly associated with heart failure [101]. Genetic overexpression of PPARα in the heart replicates the characteristics of lipotoxic cardiomyopathy [102], while knockdown diminishes this phenotype [102]. Emerging questions regarding PPARα activity include:

- How is endogenous PPARα regulated within the context of diabetes and obesity?

- How does this modification contribute to lipotoxicity?

PPARα is a nuclear receptor transcription factor that regulates the expression of genes involved in fatty acid metabolism, including uptake, storage, and oxidation. Different fatty acids, such as saturated FAs (including palmitic acid), monounsaturated FAs (like oleic acid), and polyunsaturated FAs (such as linoleic acid), have distinct effects on metabolic diseases [103]. Current research focuses on the influence of various FAs on the GSK-3α-PPARα signaling pathways. Notably, palmitic acid enhances PPARα activity, but knocking down GSK-3α negates this increase [104]. The functional role of PPARα phosphorylation impacts energy metabolism; specifically, PPARα-S280D increases the expression of genes related to fatty acid uptake and pyruvate dehydrogenase kinase 4 (PDK4), which inactivates the PDH complex and inhibits glucose oxidation. [3] Overall, this study suggests that fatty acid exposure boosts GSK-3α activity, forming a feedforward loop with PPARα that contributes to lipotoxic cardiomy-

opathy in obesity. Importantly, constitutively active GSK-3α and GSK-3β exhibit opposing effects on genes involved in fatty acid uptake and transport. Therefore, the therapeutic potential of GSK-3α inhibitors will rely on isoform-specific small-molecule inhibitors, as beneficial outcomes from GSK-3α inhibition might be undermined by unintended GSK-3β inhibition.

Lipid-Immune Interactions

Different fatty acids (FAs) and lipids have varying effects on immune cell subsets. Omega-3 polyunsaturated fatty acids (PUFAs) exhibit strong immunomodulatory properties, playing a significant role in the regulation of inflammatory and autoimmune diseases such as arthritis, Crohn's disease, ulcerative colitis, and lupus erythematosus [105].

- PUFAs are known to suppress the production of interleukin-1 (IL-1) and the expression of COX-2 mRNA, which is induced by IL-1.
- Additionally, alpha-linolenic acid (ALA), a precursor to omega-3 compounds, increases the secretion of pro-inflammatory cytokines (IL-1, IL-2, and tumor necrosis factor-alpha).
- Alongside these pro-inflammatory mediators, ALA has been recognized for its ability to suppress prostaglandins and leukotrienes while promoting anti-inflammatory and resolving functions [105-107]. PUFAs and related fatty acids hold promise as potential targets for treating inflammatory diseases. [108] The immune system plays a pivotal role in eliminating cancerous cells. The interaction between immune cells and cancer is highlighted by how tumor-infiltrating T lymphocytes (TILs) adapt to the metabolic challenges within the tumor microenvironment (TME), providing a pathway to combat tumor progression.
- T cells exhibit a degree of metabolic flexibility.
- CD36, located in the plasma membrane, is crucial for facilitating the uptake of exogenous fatty acids. The upregulation of CD36 in intratumoral regulatory T (Treg) cells significantly influences tumor progression and T cell function.
- In TMEs with low glucose levels, CD8+ T cells enhance PPAR-alpha signaling and fatty acid catabolism under hypoglycemic and hypoxic conditions to partially maintain effector functions [108]. Notably, the metabolic reprogramming of T cells using a PPAR-alpha agonist has been shown to inhibit tumor growth, an effect that is further amplified in conjunction with PD-1 inhibition [109]. Given that fatty acid oxidation (FAO) is essential for the differentiation of Treg cells, inhibiting FAO could hinder the buildup of this immunosuppressive T cell population [110]. These findings suggest that lipid metabolism offers exciting opportunities to influence the TME and specific immune cell populations. Metabolic rewiring has been associated with a protumor phenotype in tumor-associated macrophages, extending beyond T cells. The alternative (M2) activation of macrophages relies on fat oxidation. Triacylglycerol (TAG) substrates are absorbed via the scavenger receptor CD36, and their lipolysis by lysosomal acid lipase (LAL) results in prolonged survival and M2 activation in ovarian cancer. This indicates that inhibiting CD36 could be a crucial approach in cancer treatment [111]. Furthermore, the production of α-ketoglutarate (α-KG) through glutaminolysis enhances fatty acid oxidation (FAO) and epigenetic activation in the alternative (M2) activation of macrophages [112].

Impact of Fatty Acid Metabolism on Macrophage Responses It is suggested that the responses of macrophages are precisely regulated by fatty acid metabolism and epigenetic reprogramming. Metabolic adaptations in both tumor and immune cells within the tumor microenvironment (TME) likely arise due to changes in local nutrient availability. We will explore how these lipid metabolic processes affect cancer biology [3].

Lipid Metabolism in Cancer

Different lipid species exhibit contrasting effects on cancer growth and cell death, necessitating thorough mechanistic exploration. Cellular proliferation is a hallmark of all cancers, as fatty acids (FAs) are essential for synthesizing membranes and signaling molecules. Tumor cells accumulate significant lipids to support rapid

growth; however, they manage to evade toxicity from this apparent surplus of FAs. In fact, highly proliferative cancer cells often upregulate enzymes responsible for lipid and cholesterol biosynthesis, contributing to increased aggressiveness in certain cancers [113].

Emerging Insights into Cancer Fat Metabolism

Understanding how cancer metabolizes fats is a developing field of research. Many tumors prefer fatty acid oxidation (FAO) over glucose and glutamine. In various tissues, FAs are not the primary energy source; they are typically reserved for stressful conditions or nutrient scarcity, helping to restore metabolic balance. Notable metabolic rewiring in FA metabolism has been observed in mouse hepatocellular carcinomas, primary human liver, and lung carcinomas. Cancer cells convert palmitate into the unusual fatty acid sapienate to aid in membrane biosynthesis [114]. Moreover, plasma membrane remodeling is crucial for oncogenic signaling. Lipids form the fundamental building blocks of cellular membranes and are vital for establishing barriers between subcellular compartments. Even minor alterations in the structure, composition, and interactions of lipids within cellular membranes can significantly impact biological functions. Advances in lipidomics have revealed the lipid species that constitute mammalian membranes, with major membrane lipids including glycerophospholipids (GPLs), sphingolipids, and sterols [115]. The composition of membrane lipids, their saturation levels, and their distribution within

cells are often overlooked areas that are essential for maintaining organelle homeostasis, facilitating cell signaling, and managing nutrient and oxidative stress [34,116]. Additionally, Lysphosphatidylcholine acyltransferase 1 (LPCAT1) increases the saturated phosphatidylcholine content in the plasma membrane, further promoting tumor growth by activating oncogenic signals [117].

Interestingly, elevated levels of monounsaturated fatty acids (MUFAs) inhibit ferroptosis by competing with polyunsaturated fatty acids (PUFAs) for incorporation into the membrane [115]. This specific lipid composition at the membrane plays a role in reducing reactive oxygen species (ROS) and lowers the amounts of oxidizable PUFA-containing phospholipids. This effect necessitates the activation of MUFAs by the long-chain family member of acyl- CoA synthetase (ACSL) 3 [118]. In a comparable manner, lysophosphatidylcholine acyltransferase 3 (LPCAT3) plays an essential role in incorporating polyunsaturated fatty acids (PUFAs) into phospholipids. A lack of LPCAT3 leads to considerable alterations in the composition of membrane phospholipids, especially marked by a significant decrease in arachidonic acid (AA), a PUFA present in these lipids [119]. ACSL4 is also involved in the localized release of AA within mitochondria, as it catalyzes the conversion of long- chain fatty acids (LCFAs) into their active form, acyl-CoA, which is essential for lipid synthesis [120]. By producing arachidonoyl-CoA, ACSL4 mitigates the cytotoxic effects associated with elevated levels of unesterified AA, thereby raising the apoptotic threshold and enhancing the survival of castration-resistant prostate cancer cells [120].

This suggests that the localized accumulation of PUFAs in mitochondria could result in membrane depolarization and the uncoupling of the electron transport chain (ETC), ultimately leading to heightened ROS production. Consequently, certain fatty acids may trigger ROS generation, endoplasmic reticulum (ER) stress, and ferroptosis. This highlights the importance of further research to clarify the influence of lipid properties on cancer (Figure 9).

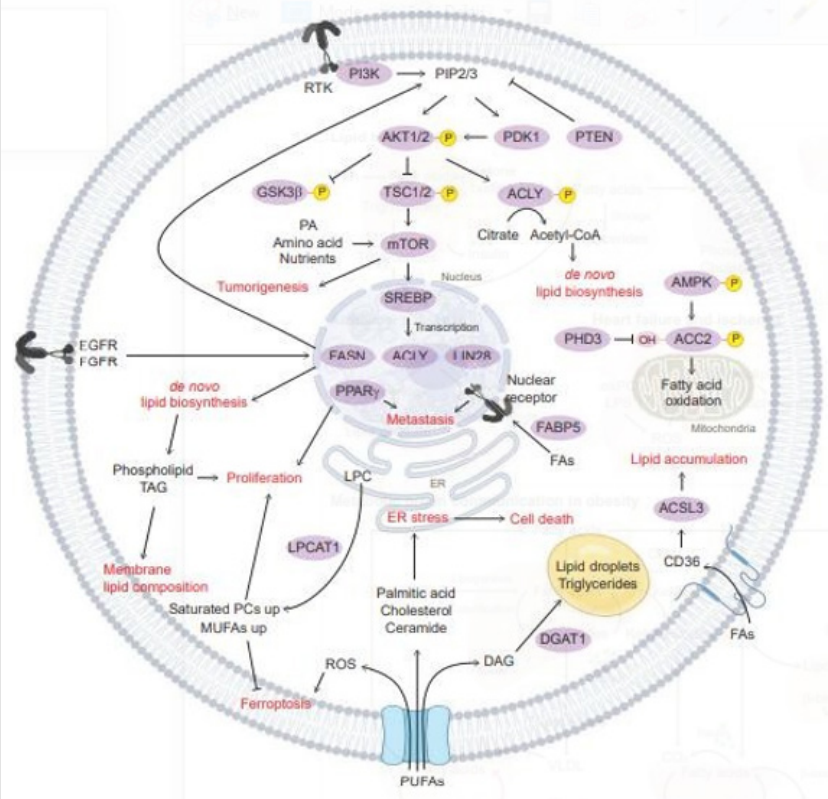

Figure 9: Lipid metabolism significantly influences cancer signaling, primarily through AKT phosphorylation, which starts lipid biosynthesis via ACLY. This process enhances tumorigenesis by coordinating with PA, amino acids, and mTOR signaling, leading to increased fatty acid synthesis and SREBP transcription. De novo biosynthesis produces phospholipids and TAGs that promote cell proliferation and alter membrane lipid composition. Fatty acids entering the nucleus can activate cancer metastasis through nuclear receptors and PPAR. PUFAs can also trigger ROS-dependent ferroptosis. Different lipid signaling pathways in cancer may lead to either survival or cell death [3].

Lipid Toxicity in Cancer and Immune Cells

Tumors exploit pathways that typically protect normal cells from lipotoxicity as a strategy to navigate the challenging tumor microenvironment (TME). Cancer cells utilize autophagy to prevent the buildup of toxic cellular lipids and waste products by targeting intracellular components and organelles for degradation in the lysosomal compartment [121]. For instance, palmitate and other saturated fatty acids (FAs) can induce apoptosis in breast cancer cells, while unsaturated FAs, like oleate, remain non-toxic to these cancer cells [122]. Additionally, cancer cells mitigate lipid toxicity by converting potentially harmful lipids—including FAs, diacylglycerol (DAG), cholesterol, and ceramide—into triglycerides (TGs), cholesterol esters, and acylceramides that can be stored in lipid droplets (LDs) [123]. The enzyme DGAT1 plays a role in this process by converting excess FAs into TGs and LDs, thereby shielding glioblastoma cells from oxidative damage (Cheng, et al. 2020). Consequently, inhibiting DGAT1 leads to an influx of FAs into mitochondria for oxidation, causing an increase in reactive oxygen species (ROS), mitochondrial damage, cytochrome c release, and ultimately, apoptosis. Furthermore, blocking DGAT1 may redirect FAs into phospholipids, enhancing ferroptosis [124].

Ferroptosis in Cancer Cells

Ferroptosis [125], which also occurs in cancer cells, results from the lipid peroxidation of polyunsaturated fatty acids (PUFAs) found in phospholipids, generating various lipid hydroperoxides [126]. In gastric cancer cells, the expression of ELOVL5 and fatty acid desaturase 1 (FADS1) is upregulated, leading to increased sensitivity to ferroptosis. Notably, arachidonic acid (AA) supplementation can restore sensitivity to ferroptosis in these cells [127]. The enzyme GPX4 serves as a key regulator of ferroptosis, offering cellular protection by neutralizing lipid peroxides. The suppression of ferroptosis-by-ferroptosis suppressor protein 1 (FSP1) decreases coenzyme Q (CoQ), a lipophilic radical-trapping antioxidant that inhibits the spread of lipid peroxides in various cancer cells [128]. Recent research indicates that immunotherapy-activated CD8+ T cells boost ferroptosis-specific lipid peroxidation in tumor cells, suggesting that increased ferroptosis enhances the anti-tumor effectiveness of immunotherapy [85]. Thus, targeting biosynthetic and peroxisomal oxidation pathways may reveal new avenues for ferroptosis-mediated cancer therapies.

Summary

We explore the multifaceted world of lipids and their crucial roles in biological systems. Starting with the regulation of lipid digestion, the study highlights the pivotal functions of cholecystokinin (CCK) in stimulating digestive enzymes and bile secretion. It then delves into the diverse roles lipids play in cell biology and physiology, emphasizing their structural, signaling, and energy-storage functions. The classification of lipids sets the foundation, detailing the various types, including fatty acids, glycerol-based lipids, and complex lipids with distinct head groups. Understanding fatty acid and triacylglycerol metabolism is essential, as these processes are central to energy balance and cellular function. The metabolism of complex lipids, cholesterol, and steroids further illustrates their influence on cellular processes and hormonal regulation. Key discussions include the cellular uptake and synthesis of fatty acids, pivotal for maintaining metabolic homeostasis. The diversity of phospholipids and their roles in membrane dynamics are also explored, alongside ceramide synthesis and its association with endoplasmic reticulum (ER) stress. The research addresses lipotoxicity, examining how excess lipid accumulation impacts organ systems such as adipose tissue, kidneys, liver, bone, and skeletal muscle, and its implications for metabolic regulation. The potential of fatty acid synthase (FASN) antagonists in cancer treatment is highlighted, offering insights into targeting lipid metabolism in oncological contexts. Lipid interactions with the immune system and their significance in cardiovascular health are discussed, underlining the complexity of lipid roles across physiological systems. The study concludes by examining emerging insights into cancer fat metabolism and the intriguing phenomenon of ferroptosis in cancer cells, providing a window into future therapeutic strategies.

Conclusion

In conclusion, this research provides a comprehensive overview of the intricate roles that lipids play in various biological processes and their profound impact on health and disease. From the fundamental aspects of lipid digestion and metabolism to their involvement in cell signaling and structural integrity, lipids are indispensable for maintaining physiological balance. The exploration of lipid metabolism reveals critical insights into energy homeostasis and the intricate mechanisms by which lipids influence hormonal and cellular regulation. The study further sheds light on the pathological consequences of lipid dysregulation, such as lipotoxicity and its effects on organ function, emphasizing the need for targeted approaches to manage metabolic disorders. The potential therapeutic applications of modulating lipid pathways are particularly promising in the context of cancer treatment and immune regulation. By targeting specific enzymes and pathways, such as fatty acid synthase, new strategies could emerge to combat cancer and other lipid-related diseases. Overall, this research underscores the necessity of continued investigation into lipid biology, as understanding these complex molecules offers valuable opportunities for the development of innovative therapeutic interventions. As research progresses, the evolving landscape of lipid science promises to unveil even more profound insights into the vital role's lipids play in health and disease.

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