Journal of Frontiers in Multidisciplinary Research

# Targeting Lipid Metabolism and Lipid Droplets for Effective Cancer Treatment

**Ajao Ebenezer Taiwo [1*], Sandra Oparah [2], Opeoluwa Oluwanifemi Akomolafe [3], Tolulope Bolarinwa [4], Irene Sagay [5]**
[1] Independent Researcher, Indiana, USA
[2] Independent Researcher, Maryland, USA
[3] Independent Researcher, UK
[4] Indepenent Researcher, Indiana, USA
[5] Marley Neck Health and Rehabilitation, Maryland, USA

* Corresponding Author: **Ajao Ebenezer Taiwo**

## Article Info

**E-ISSN:** 3050-9726
**P-ISSN:** 3050-9718
**Volume:** 05
**Issue:** 01
**January-June 2024**
**Received:** 05-04-2024
**Accepted:** 06-05-2024
**Published:** 07-06-2024
**Page No:** 289-295

**Abstract**
The intricate relationship between lipid metabolism and cancer progression presents a promising target for novel therapeutic strategies. This review explores the critical roles of lipid metabolism and lipid droplets in cancer cells, highlighting how these pathways support tumor growth, survival, and metastasis. Preclinical models have made significant strides by inhibiting key enzymes and disrupting lipid droplet dynamics. However, translating these findings into clinical applications poses substantial challenges, including potential side effects and toxicity. This review also identifies future research directions to refine these therapeutic strategies, enhance their efficacy, and mitigate adverse effects, ultimately aiming to improve patient outcomes in cancer treatment.

**DOI:** https://doi.org/10.54660/.JFMR.2024.5.1.289-295

**Keywords:** Lipid Metabolism, Lipid Droplets, Cancer Therapy, FASN Inhibitors, Chemoresistance, Clinical Translation

## Introduction

Cancer remains one of the most formidable challenges in modern medicine. Despite significant advancements in detection and treatment, it continues to be a leading cause of death worldwide (Johariya, Joshi, Malviya, & Malviya, 2024; Tanabe & Sahara, 2020). Traditional cancer therapies, including surgery, chemotherapy, and radiation, have extended survival and improved outcomes for many patients. However, these treatments often come with severe side effects and limitations. Chemotherapy, for instance, targets rapidly dividing cells but lacks specificity, leading to damage in healthy tissues and resulting in adverse effects such as hair loss, nausea, and immunosuppression. Radiation therapy, while more localized, can still harm surrounding healthy tissues and is not effective against all cancer types. Furthermore, many cancers develop resistance to these conventional treatments, necessitating the exploration of novel therapeutic approaches (Zeman, Schreiber, & Tepper, 2020).

In recent years, the understanding of cancer has shifted from viewing it solely as a genetic disease to recognizing the critical role of metabolic reprogramming in tumor development and progression. One aspect of this metabolic reprogramming that has garnered increasing attention is lipid metabolism. Lipids are essential components of cell membranes and serve as energy sources and signaling molecules (Koundouros & Poulogiannis, 2020; M. Zhang, Wei, Zhang, & Guo, 2022). Cancer cells often exhibit altered lipid metabolism, characterized by increased lipid synthesis, uptake, and storage. These changes support rapid cell proliferation, survival under stress conditions, and metastasis. Understanding the nuances of lipid metabolism in cancer cells opens new avenues for therapeutic intervention.

The significance of targeting lipid metabolism and lipid droplets in cancer treatment lies in the potential to disrupt the metabolic adaptations cancer cells rely on for growth and survival. Lipid droplets, intracellular organelles that store neutral lipids, are pivotal in maintaining lipid homeostasis. In cancer cells, lipid droplets are not merely passive storage sites but are actively involved in regulating lipid availability, energy production, and signaling pathways that promote tumorigenesis.

By targeting the enzymes and pathways involved in lipid metabolism and lipid droplet dynamics, it may be possible to selectively impair cancer cell viability while sparing normal cells, thereby reducing the side effects commonly associated with conventional therapies.

One promising area of research involves inhibiting key enzymes in lipid metabolism. For example, fatty acid synthase (FASN), an enzyme overexpressed in many cancers, is crucial for the de novo synthesis of fatty acids. Inhibitors of FASN have shown potential in preclinical models by inducing cancer cell apoptosis and reducing tumor growth. Similarly, targeting other enzymes involved in lipid synthesis, such as acetyl-CoA carboxylase (ACC) and stearoyl-CoA desaturase (SCD), could disrupt the lipid biosynthesis pathway essential for cancer cell survival (Fhu & Ali, 2020; Raeisi *et al*., 2022).

Another intriguing target is the process of lipid droplet formation and utilization. Cancer cells often exhibit increased lipid droplets, which provide a reservoir of fatty acids that can be mobilized for energy production and membrane synthesis. Inhibiting the formation of lipid droplets or promoting their degradation can deprive cancer cells of these vital resources. For instance, disrupting the function of proteins involved in lipid droplet biogenesis, such as adipose triglyceride lipase (ATGL) and perilipin, could impair the ability of cancer cells to store and utilize lipids effectively (Cruz, Barreto, Fazolini, Viola, & Bozza, 2020; Luo *et al*., 2022).

Moreover, combining lipid metabolism-targeting therapies with existing treatments could enhance their efficacy. For example, combining FASN inhibitors with chemotherapeutic agents has demonstrated synergistic effects in reducing tumor growth in preclinical studies. This approach could potentially overcome resistance mechanisms and improve patient outcomes. However, translating these promising preclinical findings into clinical practice presents several challenges (Almeida *et al*., 2023). One major hurdle is the potential for toxicity, as lipid metabolism is essential for normal cell function. Therefore, it is crucial to develop strategies that selectively target cancer cells while minimizing harm to healthy tissues. Additionally, understanding the heterogeneity of lipid metabolism across different cancer types and individual tumors will be vital in designing personalized treatment strategies.

## 1. Lipid Metabolism in Cancer Cells

### 1.1. Role of Lipids

Lipids play a multifaceted role in cancer cell biology, contributing significantly to cell proliferation, survival, and metastasis. As fundamental components of cell membranes, lipids are crucial for maintaining the structural integrity of cells and enabling various cellular functions (Fernández, Gomez de Cedron, & Ramirez de Molina, 2020). The demand for lipids is markedly elevated in cancer cells due to the rapid cell division and growth rate. This heightened lipid requirement supports the synthesis of new cellular membranes necessary to form daughter cells during mitosis. Additionally, lipids serve as key signaling molecules that modulate pathways involved in cell proliferation, differentiation, and survival. For instance, phospholipids and sphingolipids can act as second messengers in signaling cascades that promote oncogenic activities (Cheng *et al*., 2022; Fu *et al*., 2021).

Lipids also play a vital role in cancer cell survival, particularly under conditions of metabolic stress. Cancer cells often face challenging environments characterized by hypoxia and nutrient deprivation. In such settings, lipid droplets, which store neutral lipids like triglycerides and cholesterol esters, provide an essential energy reservoir. These stored lipids can be mobilized through lipolysis to generate free fatty acids, which are then oxidized in the mitochondria to produce ATP. This process helps cancer cells to sustain energy production and survive even under adverse conditions (Kloska, Węsierska, Malinowska, Gabig-Cimińska, & Jakóbkiewicz-Banecka, 2020).

Moreover, lipids contribute to cancer metastasis, the process by which cancer cells spread from the primary tumor site to distant organs. Metastasis involves a complex series of steps, including local invasion, intravasation into the bloodstream, survival in the circulatory system, extravasation into new tissues, and colonization of distant organs. Lipid metabolism is intricately involved in several of these steps. For example, fatty acids are necessary for synthesizing phospholipids, which are critical for forming cell membranes and invadopodia—actin-rich protrusions that facilitate tissue invasion. Additionally, the remodeling of lipid membranes can influence the fluidity and deformability of cancer cells, aiding their passage through the extracellular matrix and blood vessels (Durán-Saenz *et al*., 2022).

### 1.2. Altered Lipid Metabolism

Cancer cells exhibit profound alterations in lipid metabolism, a phenomenon often called "lipid metabolic reprogramming." This reprogramming is driven by oncogenic signaling pathways and the unique metabolic demands of rapidly proliferating tumor cells. One of the hallmarks of altered lipid metabolism in cancer is the upregulation of lipid biosynthesis. Many cancer cells show increased expression and activity of enzymes involved in de novo lipogenesis, synthesizing fatty acids from acetyl-CoA. This pathway is typically upregulated by oncogenes such as MYC and AKT and by loss of tumor suppressors like PTEN. Enhanced lipogenesis provides cancer cells the necessary lipids for membrane biogenesis and energy storage (Simeone *et al*., 2021).

In addition to increased lipogenesis, cancer cells often exhibit elevated uptake of exogenous lipids. This is mediated by upregulation of lipid transporters, such as CD36 and fatty acid transport protein 1 (FATP1), which facilitate the import of fatty acids from the extracellular environment. The heightened lipid uptake supports the energy and biosynthetic needs of cancer cells and can also provide a survival advantage under conditions of metabolic stress (Acharya & Shetty, 2023; Q. He, Chen, Wang, He, & Yu, 2023).

Another significant alteration in lipid metabolism observed in cancer is the accumulation of lipid droplets. Traditionally viewed as inert storage sites, these organelles have emerged as dynamic entities involved in cancer cell metabolism and signaling. The increase in lipid droplet formation in cancer cells is often associated with enhanced expression of proteins involved in lipid droplet biogenesis, such as perilipin-2 (PLIN2) and diacylglycerol O-acyltransferase 1 (DGAT1). Lipid droplets serve as reservoirs of fatty acids that can be mobilized during energy demand or nutrient scarcity, thereby supporting cancer cell survival and growth (Y. Li, 2020).

Furthermore, alterations in cholesterol metabolism are frequently observed in cancer cells. Cholesterol is a critical component of cell membranes and is involved in forming

lipid rafts—specialized membrane microdomains that facilitate signal transduction. Cancer cells often show increased cholesterol synthesis and uptake, driven by upregulation of enzymes such as HMG-CoA reductase (HMGCR) and the low-density lipoprotein receptor (LDLR). Elevated cholesterol levels can enhance cell membrane fluidity and stability, promoting cell proliferation and resistance to apoptosis (Matés, Campos-Sandoval, de Los Santos-Jiménez, & Márquez, 2020; Mayengbam, Singh, Pillai, & Bhat, 2021; Škara *et al*., 2021).

### 1.3. Key Enzymes and Pathways

Several key enzymes and metabolic pathways are involved in the lipid metabolism of cancer cells, each playing a crucial role in supporting tumor growth and survival. Fatty acid synthase (FASN) is one of the most prominent enzymes in de novo lipogenesis. FASN catalyzes the synthesis of palmitate, a 16-carbon saturated fatty acid, from acetyl-CoA and malonyl-CoA. Overexpression of FASN is observed in many types of cancer and is associated with poor prognosis. Inhibition of FASN has been shown to induce apoptosis and reduce tumor growth in preclinical models, highlighting its potential as a therapeutic target (Singh, Karthikeyan, & Moorthy, 2020).

Acetyl-CoA carboxylase (ACC) is another key enzyme in lipid biosynthesis, responsible for the carboxylation of acetyl-CoA to malonyl-CoA, the first committed step in fatty acid synthesis. ACC exists in two isoforms: ACC1, which is involved in lipogenesis, and ACC2, which regulates fatty acid oxidation. Inhibition of ACC1 can disrupt lipid synthesis, thereby impairing cancer cell proliferation.Stearoyl-CoA desaturase (SCD) is involved in desaturating saturated fatty acids to monounsaturated fatty acids, critical components of membrane phospholipids and signaling molecules. Overexpression of SCD has been linked to cancer cell survival and resistance to chemotherapy. Targeting SCD can alter the lipid composition of cancer cell membranes, affecting their fluidity and signaling properties (Kubota & Espenshade, 2022).

In lipid droplet metabolism, adipose triglyceride lipase (ATGL) plays a pivotal role in lipolysis, breaking triglycerides into free fatty acids. Cancer cells with high lipolytic activity can mobilize stored lipids to meet their energy demands (Grabner, Xie, Schweiger, & Zechner, 2021). Inhibiting ATGL can reduce the availability of free fatty acids, thereby impairing cancer cell metabolism and growth.Additionally, the mevalonate pathway, which is responsible for cholesterol synthesis, is often upregulated in cancer. HMG-CoA reductase (HMGCR), the rate-limiting enzyme in this pathway, is a critical target for cholesterol-lowering drugs such as statins. There is growing interest in repurposing statins for cancer therapy, given their potential to inhibit cholesterol synthesis and disrupt cancer cell proliferation (Gesto, Pereira, Cerqueira, & Sousa, 2020).

In summary, lipid metabolism in cancer cells involves a complex interplay of biosynthesis, uptake, and storage pathways, each contributing to the malignant phenotype. By targeting key enzymes and pathways involved in lipid metabolism, it may be possible to develop novel therapeutic strategies that selectively impair cancer cell viability while sparing normal cells. This approach holds promise for improving the efficacy and reducing the toxicity of cancer treatments.

## 2. Lipid Droplets in Cancer Cells

### 2.1. Formation and Function

Lipid droplets are dynamic organelles that play a crucial role in cellular lipid homeostasis. They comprise a core of neutral lipids, mainly triglycerides and cholesterol esters, surrounded by a phospholipid monolayer embedded with specific proteins (Seebacher, Zeigerer, Kory, & Krahmer, 2020). Lipid droplet formation begins in the endoplasmic reticulum (ER), where enzymes involved in lipid synthesis catalyze the esterification of fatty acids to produce neutral lipids. These neutral lipids accumulate between the leaflets of the ER membrane, forming an oil lens that eventually buds off into the cytoplasm as a nascent lipid droplet. Several proteins, including seipin, facilitate this process, which is essential for the initial steps of lipid droplet formation (Wang, Liu, Miao, Pan, & Cao, 2021).

Once formed, lipid droplets serve multiple functions in cellular physiology. Primarily, they act as storage depots for excess lipids, safeguarding cells from lipotoxicity that can arise from the accumulation of free fatty acids. By sequestering these fatty acids as triglycerides, lipid droplets prevent the disruption of cellular membranes and organelles. Lipid droplets also play a vital role in energy metabolism (W. Zhang *et al*., 2021). During energy demand or nutrient scarcity periods, lipids stored in lipid droplets can be mobilized through lipolysis, a process mediated by enzymes such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). The released fatty acids are then transported to mitochondria for β-oxidation, generating ATP to fuel cellular processes (Bosch, Parton, & Pol, 2020).

In addition to their roles in storage and energy metabolism, lipid droplets are involved in various cellular signaling pathways. They serve as platforms for the localization and activity of signaling proteins, influencing processes such as autophagy, inflammation, and lipid signaling. Lipid droplets also interact with other organelles, including mitochondria and peroxisomes, facilitating the exchange of lipids and metabolic intermediates. This dynamic interplay underscores the integral role of lipid droplets in maintaining cellular homeostasis (Mashek, 2021).

### 2.2. Lipid Droplets in Cancer

In cancer cells, the accumulation of lipid droplets is a common feature that has significant implications for tumor progression. Cancer cells often exhibit more lipid droplets than their normal counterparts, reflecting malignancy's altered lipid metabolism characteristic. Several factors, including the enhanced uptake of exogenous lipids, upregulation of lipid biosynthesis pathways, and metabolic adaptations to the tumor microenvironment drive this accumulation (Srivastava *et al*., 2022).

Lipid droplets in cancer cells are closely linked to their metabolic flexibility and ability to adapt to changing conditions. Lipid droplets provide a reservoir of energy-rich lipids that can be mobilized to support rapid cell proliferation and survival under stress. For instance, during hypoxia or nutrient deprivation, cancer cells can hydrolyze stored triglycerides to release fatty acids, which are then oxidized to generate ATP. This metabolic adaptation helps cancer cells to withstand adverse conditions and continue proliferating.Moreover, lipid droplets play a role in protecting cancer cells from oxidative stress and apoptosis. The storage of fatty acids in lipid droplets reduces the levels of free fatty acids in the cytoplasm, thereby minimizing

lipotoxicity and the production of reactive oxygen species (ROS) (Danielli, Perne, Jarc Jovičić, & Petan, 2023). Elevated ROS levels can damage cellular components and induce cell death. By sequestering fatty acids, lipid droplets help to mitigate oxidative stress and enhance cell survival. Additionally, lipid droplets can influence the tumor microenvironment by modulating lipid signaling and inflammatory responses, further promoting tumor growth and metastasis (Srivastava *et al*., 2022).

The accumulation of lipid droplets in cancer cells also has implications for chemoresistance. Lipid droplets can sequester lipophilic drugs, reducing their availability and efficacy within cancer cells. This sequestration can contribute to developing resistance to chemotherapy, presenting a significant challenge in cancer treatment. Understanding the role of lipid droplets in drug sequestration and resistance mechanisms is crucial for developing strategies to overcome chemoresistance and improve therapeutic outcomes.

### 2.3. Molecular Mechanisms

The formation and utilization of lipid droplets in cancer cells are regulated by intricate molecular mechanisms involving various proteins and signaling pathways. One key regulator is the sterol regulatory element-binding protein (SREBP) family of transcription factors, which control the expression of genes involved in lipid biosynthesis and uptake. SREBPs are activated in response to cellular lipid demand and promote the synthesis of fatty acids, triglycerides, and cholesterol, contributing to lipid droplet formation. In cancer cells, the activation of SREBPs is often driven by oncogenic signaling pathways, such as the PI3K/AKT/mTOR pathway, leading to increased lipid synthesis and storage (C. Li, Zhang, Qiu, Deng, & Wang, 2022; Triki *et al*., 2020).

Perilipins, a family of lipid droplet-associated proteins, play a crucial role in regulating lipid droplet dynamics. Perilipin 1 (PLIN1) is primarily expressed in adipocytes, while perilipin 2 (PLIN2) and perilipin 3 (PLIN3) are more ubiquitously expressed and are commonly found in cancer cells (Bombarda-Rocha *et al*., 2023). These proteins coat the surface of lipid droplets and regulate access to lipases, controlling the balance between lipid storage and mobilization. PLIN2, for example, stabilizes lipid droplets and protects them from lipolysis, promoting lipid accumulation in cancer cells. Conversely, the phosphorylation of perilipins by protein kinase A (PKA) can promote lipolysis by allowing lipases to access stored lipids (Edwards & Mohiuddin, 2020).

Another important regulator of lipid droplet metabolism in cancer is ATGL, the enzyme responsible for initiating the breakdown of triglycerides into free fatty acids and glycerol. The activity of ATGL is modulated by various factors, including comparative gene identification-58 (CGI-58), which acts as a coactivator, and G0/G1 switch gene 2 (G0S2), which functions as an inhibitor. The precise regulation of ATGL activity is essential for maintaining lipid homeostasis and supporting the metabolic needs of cancer cells (T. Li, Guo, & Zhou, 2021).

Autophagy, a cellular process involved in the degradation and recycling of cellular components, also intersects with lipid droplet metabolism. Lipophagy, a selective form of autophagy targeting lipid droplets, contributes to the mobilization of stored lipids. During lipophagy, lipid droplets are sequestered into autophagosomes and delivered to lysosomes for degradation, releasing free fatty acids that can be used for energy production. The regulation of lipophagy involves various autophagy-related proteins, such as microtubule-associated proteins 1A/1B light chain 3 (LC3) and autophagy-related protein 14 (ATG14), which coordinate the formation and maturation of autophagosomes (Robichaud *et al*., 2021; Soto-Avellaneda & Morrison, 2020).

## 3. Therapeutic Strategies Targeting Lipid Metabolism and Lipid Droplets

### 3.1. Inhibitors of Lipid Metabolism

Inhibiting lipid metabolism presents a promising approach for cancer therapy, targeting the metabolic adaptations essential for tumor growth and survival. Several drugs and compounds have been developed to inhibit key enzymes and pathways involved in lipid metabolism, offering potential therapeutic benefits.One of the most extensively studied targets is fatty acid synthase (FASN), an enzyme overexpressed in many cancers and involved in de novo lipogenesis. FASN catalyzes the synthesis of palmitate, a crucial fatty acid for membrane biogenesis and energy storage. Inhibitors of FASN, such as orlistat and TVB-2640, have demonstrated efficacy in preclinical models by inducing apoptosis and reducing tumor growth. Originally an anti-obesity drug, Orlistatcan inhibit FASN activity and induce cell death in various cancer cell lines. TVB-2640, a more specific FASN inhibitor, has entered clinical trials and has shown promising results in reducing tumor size and enhancing the efficacy of other treatments (Falchook *et al*., 2021; Singh, Karthikeyan, & Moorthy, 2024).

Another key enzyme in lipid metabolism is acetyl-CoA carboxylase (ACC), which catalyzes the carboxylation of acetyl-CoA to malonyl-CoA, the first committed step in fatty acid synthesis. Inhibition of ACC can disrupt lipid biosynthesis, thereby impairing cancer cell proliferation. TOFA (5-tetradecyloxy-2-furoic acid) is an ACC inhibitor that has been shown to reduce lipid synthesis and inhibit tumor growth in preclinical models. Additionally, a newer class of ACC inhibitors, including drugs like ND-646, is being explored for their potential to selectively target cancer cells with minimal toxicity to normal tissues (Cronan, 2021; Harwood, 2020).

Stearoyl-CoA desaturase (SCD) is another enzyme involved in lipid metabolism that has garnered attention as a therapeutic target. SCD catalyzes the desaturation of saturated fatty acids to monounsaturated fatty acids, which are critical components of membrane phospholipids and signaling molecules. Inhibitors of SCD, such as CAY10566, have shown the ability to induce cancer cell death and reduce tumor growth. By altering the lipid composition of cancer cell membranes, SCD inhibitors can affect membrane fluidity and signaling properties, disrupting processes essential for tumor progression.The mevalonate pathway, responsible for cholesterol synthesis, is also a significant target in cancer therapy. HMG-CoA reductase (HMGCR), the rate-limiting enzyme in this pathway, is targeted by statins, widely used cholesterol-lowering drugs. Statins, such as atorvastatin and simvastatin, have demonstrated anti-cancer effects by inhibiting cholesterol synthesis and inducing apoptosis in cancer cells. There is growing interest in repurposing statins for cancer therapy, given their potential to disrupt cancer cell proliferation and enhance the efficacy of other treatments

(Paul *et al*., 2021; Yin *et al*., 2022).

### 3.2. Targeting Lipid Droplets

Disrupting lipid droplet formation and function is another promising strategy for cancer therapy. Cancer cells often exhibit increased lipid droplet accumulation, which supports their metabolic flexibility and survival. Targeting the proteins and pathways involved in lipid droplet dynamics can impair the ability of cancer cells to store and utilize lipids, thereby reducing their growth and viability.

One approach involves inhibiting the proteins responsible for lipid droplet biogenesis. For example, targeting diacylglycerol O-acyltransferase 1 (DGAT1), an enzyme that catalyzes the final step in triglyceride synthesis, can reduce lipid droplet formation and impair cancer cell survival. DGAT1 inhibitors, such as A922500, canminimise lipid droplet accumulation and induce apoptosis in cancer cells. Similarly, inhibiting the activity of perilipins, proteins that coat the surface of lipid droplets and regulate lipolysis, can disrupt lipid droplet dynamics and impair cancer cell metabolism (Hernandez-Corbacho & Canals, 2024).

Autophagy, a cellular process involved in the degradation and recycling of cellular components, also intersects with lipid droplet metabolism. Targeting autophagy-related proteins involved in lipophagy, the selective autophagy of lipid droplets, can disrupt the mobilization of stored lipids and reduce the availability of free fatty acids for energy production. For instance, inhibiting the activity of ATG14, a protein involved in the formation of autophagosomes, can impair lipophagy and reduce the survival of cancer cells (Abate *et al*., 2020; Aquila *et al*., 2020).

Furthermore, strategies that promote the degradation of lipid droplets can also be effective in cancer therapy. The protein PNPLA2, also known as adipose triglyceride lipase (ATGL), is involved in the breakdown of triglycerides stored in lipid droplets. Enhancing the activity of ATGL can increase lipolysis and deplete the lipid reserves of cancer cells, thereby impairing their growth and survival. Compounds that activate ATGL or mimic its activity are being explored as potential therapeutic agents (Bononi, Tuccinardi, Rizzolio, & Granchi, 2021).

### 3.3. Combination Therapies

Combining lipid metabolism-targeting drugs with other cancer treatments offers the potential for enhanced efficacy and overcoming resistance mechanisms. Cancer cells often develop resistance to single-agent therapies by activating compensatory pathways or altering their metabolic state. By targeting multiple aspects of cancer cell metabolism and signaling, combination therapies can reduce the likelihood of resistance and improve treatment outcomes (Germain *et al*., 2020).

One promising combination involves FASN inhibitors and chemotherapeutic agents. FASN inhibitors, by disrupting lipid biosynthesis, can sensitize cancer cells to chemotherapy-induced apoptosis. For example, combining TVB-2640 with paclitaxel, a common chemotherapeutic drug, has shown synergistic effects in preclinical models, reducing tumor growth more effectively than either agent alone. This combination approach can enhance the efficacy of chemotherapy while potentially reducing the required dose and associated side effects. Another combination strategy involves targeting both lipid biosynthesis and lipid uptake pathways. Inhibitors of ACC, which disrupt lipid biosynthesis, can be combined with inhibitors of lipid transporters, such as CD36, to reduce the availability of lipids for cancer cells. This dual targeting approach can impair the metabolic flexibility of cancer cells and enhance the anti-tumor effects (Devereux, Bayliss, Keenan, Montgomery, & Watt, 2023; Z. He *et al*., 2022).

Combining lipid metabolism-targeting drugs with inhibitors of other metabolic pathways, such as glycolysis or oxidative phosphorylation, is also being explored. Cancer cells rely on multiple metabolic pathways to meet their energy and biosynthetic needs. By simultaneously targeting lipid metabolism and other key metabolic pathways, it may be possible to induce metabolic stress and selectively kill cancer cells. For example, combining FASN inhibitors with glycolysis inhibitors, such as 2-deoxyglucose, has shown promise in preclinical studies by inducing energy deprivation and apoptosis in cancer cells (Icard *et al*., 2021).

Furthermore, combining lipid metabolism-targeting drugs with immunotherapies is an emerging area of research. Cancer cells can evade immune surveillance by modulating lipid metabolism and creating an immunosuppressive microenvironment. Targeting lipid metabolism may enhance the efficacy of immunotherapies and promote anti-tumor immune responses. For instance, inhibiting SCD with immune checkpoint inhibitors, such as anti-PD-1 antibodies, has synergistic effects in enhancing anti-tumor immunity in preclinical models (Bleve, Durante, Sica, & Consonni, 2020).

## 4. Challenges and Future Directions

### 4.1. Clinical Translation

One of the primary challenges in translating preclinical findings to clinical applications is the complexity of cancer biology. While many inhibitors of lipid metabolism have shown promise in preclinical models, their efficacy in human patients can be inconsistent. This discrepancy often arises due to differences in tumor microenvironments, genetic heterogeneity among patients, and variations in lipid metabolism across different cancer types. Furthermore, the pharmacokinetics and pharmacodynamics of these inhibitors can differ significantly between animal models and humans, complicating the prediction of effective dosages and therapeutic windows. Addressing these challenges requires robust clinical trials that can account for the diversity of human cancers and validate the efficacy of lipid metabolism-targeting therapies in a clinical setting.

### 4.2. Potential Side Effects

Targeting lipid metabolism in cancer treatment raises concerns about potential side effects and toxicity. Lipid metabolism is essential for the normal function of healthy cells, and inhibiting key enzymes or pathways could inadvertently affect non-cancerous tissues. For instance, inhibitors of fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC) could disrupt lipid biosynthesis in healthy cells, leading to adverse effects such as liver toxicity, lipid dysregulation, and metabolic disorders. Additionally, long-term inhibition of lipid metabolism could impair energy homeostasis and immune function. Therefore, it is crucial to develop strategies that selectively target cancer cells while sparing normal tissues, such as using targeted delivery systems or developing inhibitors with higher specificity for cancer-associated isoforms of metabolic enzymes.

### 4.3. Future Research

Future research targeting lipid metabolism and lipid droplets for cancer therapy should focus on several key areas. First, understanding the molecular mechanisms underlying lipid metabolism reprogramming in cancer cells will be essential for identifying novel therapeutic targets and developing more selective inhibitors. This includes exploring the role of lipid signaling, lipid-protein interactions, and the regulation of lipid droplets in different cancer types.

Second, the development of combination therapies holds significant promise. Combining lipid metabolism-targeting drugs with other treatments, such as chemotherapy, immunotherapy, or inhibitors of other metabolic pathways, could enhance therapeutic efficacy and overcome resistance mechanisms. Research should focus on identifying synergistic combinations and optimizing treatment regimens.

Third, personalized medicine approaches should be integrated into the development of lipid metabolism-targeting therapies. By utilizing genomic, transcriptomic, and metabolomic profiling, it is possible to identify biomarkers that predict response to these therapies and tailor treatments to individual patients.Finally, further research is needed to address these therapies' potential side effects and toxicity. This includes developing targeted delivery systems, such as nanoparticles, to enhance the specificity of drug delivery to cancer cells and reduce off-target effects. Additionally, investigating the long-term effects of lipid metabolism inhibition on systemic metabolism and immune function will be crucial for ensuring the safety and efficacy of these therapies in clinical practice.

### References


1. Abate M, Festa A, Falco M, Lombardi A, Luce A, Grimaldi A, *et al*. Mitochondria as playmakers of apoptosis, autophagy and senescence. Semin Cell Dev Biol. 2020; [Seminar presentation].
2. Acharya R, Shetty SS. Fatty acid transport proteins (FATPs) in cancer. Chem Phys Lipids. 2023;250:105269.
3. Almeida LYd, Moreira FDS, Santos GASd, Zelaya FJMC, Ortiz CA, Agostini M, *et al*. FASN inhibition sensitizes metastatic OSCC cells to cisplatin and paclitaxel by downregulating cyclin B1. Oral Dis. 2023;29(2):649-60.
4. Aquila S, Santoro M, Caputo A, Panno ML, Pezzi V, De Amicis F. The tumor suppressor PTEN as molecular switch node regulating cell metabolism and autophagy: implications in immune system and tumor microenvironment. Cells. 2020;9(7):1725.
5. Bleve A, Durante B, Sica A, Consonni FM. Lipid metabolism and cancer immunotherapy: immunosuppressive myeloid cells at the crossroad. Int J Mol Sci. 2020;21(16):5845.
6. Bombarda-Rocha V, Silva D, Badr-Eddine A, Nogueira P, Gonçalves J, Fresco P. Challenges in pharmacological intervention in perilipins (PLINs) to modulate lipid droplet dynamics in obesity and cancer. Cancers. 2023;15(15):4013.
7. Bononi G, Tuccinardi T, Rizzolio F, Granchi C. α/β-Hydrolase domain (ABHD) inhibitors as new potential therapeutic options against lipid-related diseases. J Med Chem. 2021;64(14):9759-85.
8. Bosch M, Parton RG, Pol A. Lipid droplets, bioenergetic fluxes, and metabolic flexibility. Semin Cell Dev Biol. 2020; [Seminar presentation].
9. Cheng H, Wang M, Su J, Li Y, Long J, Chu J, *et al*. Lipid metabolism and cancer. Life. 2022;12(6):784.
10. Cronan JE. The classical, yet controversial, first enzyme of lipid synthesis: Escherichia coli acetyl-CoA carboxylase. Microbiol Mol Biol Rev. 2021;85(3):e00032-21.
11. Cruz AL, Barreto EdA, Fazolini NP, Viola JP, Bozza PT. Lipid droplets: platforms with multiple functions in cancer hallmarks. Cell Death Dis. 2020;11(2):105.
12. Danielli M, Perne L, Jovičić EJ, Petan T. Lipid droplets and polyunsaturated fatty acid trafficking: Balancing life and death. Front Cell Dev Biol. 2023;11:1104725.
13. Devereux CJ, Bayliss J, Keenan SN, Montgomery MK, Watt MJ. Investigating dual inhibition of ACC and CD36 for the treatment of nonalcoholic fatty liver disease in mice. Am J Physiol Endocrinol Metab. 2023;324(2):E187-E198.
14. Durán-Saenz NZ, Serrano-Puente A, Gallegos-Flores PI, Mendoza-Almanza BD, Esparza-Ibarra EL, Godina-González S, *et al*. Platelet membrane: an outstanding factor in cancer metastasis. Membranes. 2022;12(2):182.
15. Edwards M, Mohiuddin SS. Biochemistry, lipolysis. StatPearls [Internet]. 2020.
16. Falchook G, Infante J, Arkenau H-T, Patel MR, Dean E, Borazanci E, *et al*. First-in-human study of the safety, pharmacokinetics, and pharmacodynamics of first-in-class fatty acid synthase inhibitor TVB-2640 alone and with a taxane in advanced tumors. EClinicalMedicine. 2021;34:100797.
17. Fernández LP, Gomez de Cedron M, Ramirez de Molina A. Alterations of lipid metabolism in cancer: implications in prognosis and treatment. Front Oncol. 2020;10:577420.
18. Fhu CW, Ali A. Fatty acid synthase: an emerging target in cancer. Molecules. 2020;25(17):3935.
19. Fu Y, Zou T, Shen X, Nelson PJ, Li J, Wu C, *et al*. Lipid metabolism in cancer progression and therapeutic strategies. MedComm. 2021;2(1):27-59.
20. Germain N, Dhayer M, Boileau M, Fovez Q, Kluza J, Marchetti P. Lipid metabolism and resistance to anticancer treatment. Biology. 2020;9(12):474.
21. Gesto DS, Pereira CM, Cerqueira NM, Sousa SF. An atomic-level perspective of HMG-CoA-reductase: The target enzyme to treat hypercholesterolemia. Molecules. 2020;25(17):3891.
22. Grabner GF, Xie H, Schweiger M, Zechner R. Lipolysis: cellular mechanisms for lipid mobilization from fat stores. Nat Metab. 2021;3(11):1445-65.
23. Harwood JL. Fatty acid biosynthesis. In: Harwood JL, editor. Plant lipids. Blackwell; 2020. p. 27-66.
24. He Q, Chen Y, Wang Z, He H, Yu P. Cellular uptake, metabolism and sensing of long-chain fatty acids. Front Biosci (Landmark Ed). 2023;28(1):10.
25. He Z, Guo T, Cui Z, Xu J, Wu Z, Yang X, *et al*. New understanding of Angelica sinensis polysaccharide improving fatty liver: The dual inhibition of lipid synthesis and CD36-mediated lipid uptake and the regulation of alcohol metabolism. Int J Biol Macromol. 2022;207:813-25.
26. Hernandez-Corbacho M, Canals D. Drug targeting of acyltransferases in the Triacylglyceride and 1-O-AcylCeramide biosynthetic pathways. Mol Pharmacol. 2024;105(3):166-78.

27. Icard P, Loi M, Wu Z, Ginguay A, Lincet H, Robin E, *et al*. Metabolic strategies for inhibiting cancer development. Adv Nutr. 2021;12(4):1461-80.
28. Johariya V, Joshi A, Malviya N, Malviya S. Introduction to Cancer. In: Johariya V, Joshi A, Malviya N, Malviya S, editors. Medicinal Plants and Cancer Chemoprevention. CRC Press; 2024. p. 1-28.
29. Kloska A, Węsierska M, Malinowska M, Gabig-Cimińska M, Jakóbkiewicz-Banecka J. Lipophagy and lipolysis status in lipid storage and lipid metabolism diseases. Int J Mol Sci. 2020;21(17):6113.
30. Koundouros N, Poulogiannis G. Reprogramming of fatty acid metabolism in cancer. Br J Cancer. 2020;122(1):4-22.
31. Kubota CS, Espenshade PJ. Targeting stearoyl-CoA desaturase in solid tumors. Cancer Res. 2022;82(9):1682-8.
32. Li C, Zhang L, Qiu Z, Deng W, Wang W. Key molecules of fatty acid metabolism in gastric cancer. Biomolecules. 2022;12(5):706.
33. Li T, Guo W, Zhou Z. Adipose triglyceride lipase in hepatic physiology and pathophysiology. Biomolecules. 2021;12(1):57.
34. Li Y. Perilipins: Protectors of lipid reservoirs: Regulation of lipid droplets and lipid flux by Plin2 and Plin5. [Doctoral dissertation]. 2020.
35. Luo W, Wang H, Ren L, Lu Z, Zheng Q, Ding L, *et al*. Adding fuel to the fire: The lipid droplet and its associated proteins in cancer progression. Int J Biol Sci. 2022;18(16):6020.
36. Mashek DG. Hepatic lipid droplets: A balancing act between energy storage and metabolic dysfunction in NAFLD. Mol Metab. 2021;50:101115.
37. Matés JM, Campos-Sandoval JA, de Los Santos-Jiménez J, Márquez J. Glutaminases regulate glutathione and oxidative stress in cancer. Arch Toxicol. 2020;94(8):2603-23.
38. Mayengbam SS, Singh A, Pillai AD, Bhat MK. Influence of cholesterol on cancer progression and therapy. Transl Oncol. 2021;14(6):101043.
39. Paul S, Vázquez LAB, Uribe SP, Cárdenas LAM, Aguilar MFR, Chakraborty S, *et al*. Roles of microRNAs in carbohydrate and lipid metabolism disorders and their therapeutic potential. Biochimie. 2021;187:83-93.
40. Raeisi M, Hassanbeigi L, Khalili F, Kharrati-Shishavan H, Yousefi M, Mehdizadeh A. Stearoyl-CoA desaturase 1 as a therapeutic target for cancer: A focus on hepatocellular carcinoma. Mol Biol Rep. 2022;49(9):8871-82.
41. Robichaud S, Fairman G, Vijithakumar V, Mak E, Cook DP, Pelletier AR, *et al*. Identification of novel lipid droplet factors that regulate lipophagy and cholesterol efflux in macrophage foam cells. Autophagy. 2021;17(11):3671-89.
42. Seebacher F, Zeigerer A, Kory N, Krahmer N. Hepatic lipid droplet homeostasis and fatty liver disease. Semin Cell Dev Biol. 2020; [Seminar presentation].
43. Simeone P, Tacconi S, Longo S, Lanuti P, Bravaccini S, Pirini F, *et al*. Expanding roles of de novo lipogenesis in breast cancer. Int J Environ Res Public Health. 2021;18(7):3575.
44. Singh S, Karthikeyan C, Moorthy NHN. Recent advances in the development of fatty acid synthase inhibitors as anticancer agents. Mini Rev Med Chem. 2020;20(18):1820-37.
45. Singh S, Karthikeyan C, Moorthy NSHN. Fatty acid synthase (FASN): A patent review since 2016-present. Recent Pat Anticancer Drug Discov. 2024;19(1):37-56.
46. Škara L, Turković AH, Pezelj I, Vrtarić A, Sinčić N, Krušlin B, *et al*. Prostate cancer—Focus on cholesterol. Cancers. 2021;13(18):4696.
47. Soto-Avellaneda A, Morrison BE. Signaling and other functions of lipids in autophagy: a review. Lipids Health Dis. 2020;19(1):214.
48. Srivastava A, Srivastava P, Mathur S, Abbas S, Rai N, Tiwari S, *et al*. Lipid metabolism and mitochondria: Cross talk in cancer. Curr Drug Targets. 2022;23(6):606-27.
49. Tanabe A, Sahara H. The metabolic heterogeneity and flexibility of cancer stem cells. Cancers. 2020;12(10):2780.
50. Triki M, Rinaldi G, Planque M, Broekaert D, Winkelkotte AM, Maier CR, *et al*. mTOR signaling and SREBP activity increase FADS2 expression and can activate sapienate biosynthesis. Cell Rep. 2020;31(12):107703.
51. Wang L, Liu J, Miao Z, Pan Q, Cao W. Lipid droplets and their interactions with other organelles in liver diseases. Int J Biochem Cell Biol. 2021;133:105937.
52. Bitragunta SL. Intelligent Power Feedback Control for Motor-Generator Pairs: A Machine Learning-Based Approach. Int J Lead Res Publ. 2024;5(12).
53. Yin X, Xu R, Song J, Ruze R, Chen Y, Wang C, *et al*. Lipid metabolism in pancreatic cancer: emerging roles and potential targets. Cancer Commun. 2022;42(12):1234-56.
54. Zeman EM, Schreiber EC, Tepper JE. Basics of radiation therapy. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, editors. Abeloff's Clinical Oncology. 6th ed. Elsevier; 2020. p. 431-60.
55. Zhang M, Wei T, Zhang X, Guo D. Targeting lipid metabolism reprogramming of immunocytes in response to the tumor microenvironment stressor: A potential approach for tumor therapy. Front Immunol. 2022;13:937406.
56. Zhang W, Xu L, Zhu L, Liu Y, Yang S, Zhao M. Lipid droplets, the central hub integrating cell metabolism and the immune system. Front Physiol. 2021;12:746749.