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Novel Therapeutic Strategies for Targeting Lipid Droplets in Cancer

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Abstract
Lipid droplets (LDs) have emerged as pivotal organelles in cancer biology, influencing cell proliferation, survival, and metabolic reprogramming. This review explores the multifaceted roles of LDs in cancer, encompassing their structure, function, and interactions within the tumor microenvironment. LDs serve as reservoirs for neutral lipids and bioactive molecules, supporting cancer cell energetics, membrane biosynthesis, and signaling pathways crucial for tumor progression. Evidence linking LD accumulation to aggressive tumor phenotypes underscores their clinical relevance as diagnostic and prognostic biomarkers. Current therapeutic strategies targeting LD metabolism and function, including inhibition of LD formation and modulation of lipid metabolism pathways, are discussed. Challenges such as tumor heterogeneity and therapy resistance are examined, alongside emerging approaches leveraging nanotechnology and personalized medicine to enhance LD-targeted therapies. Future directions highlight the potential for innovative strategies and combination therapies to exploit LD vulnerabilities, offering new avenues for improving cancer treatment outcomes.

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Introduction

Cancer is a multifaceted and formidable disease characterized by uncontrolled cell growth, invasion of surrounding tissues, and metastasis to distant organs. The complexity of cancer is amplified by its ability to undergo metabolic reprogramming, a process that enables cancer cells to sustain rapid proliferation and survive in hostile environments (Acharya & Shetty, 2023; Butler, van der Meer, & van Leeuwen, 2021). One of the hallmark features of this metabolic reprogramming is the alteration of lipid metabolism. Lipids, which include fats, oils, and certain vitamins and hormones, play a crucial role in energy storage, cell membrane structure, and signaling pathways. In cancer, lipid metabolism is often dysregulated, accumulating lipid droplets (LDs) within cells. These LDs serve as reservoirs of neutral lipids and have emerged as significant players in cancer biology (Cruz, Barreto, Fazolini, Viola, & Bozza, 2020; Danielli, Perne, Jarc Jovičić, & Petan, 2023).

Lipid metabolism is essential for cancer progression due to its involvement in various cellular processes. Cancer cells exhibit a high demand for lipids to support rapid cell division, membrane synthesis, and energy production. The enhanced lipid biosynthesis and uptake in cancer cells facilitate the formation of LDs, which are dynamic organelles of a neutral lipid core surrounded by a phospholipid monolayer. LDs are not merely passive storage sites; they actively participate in cellular metabolism and signaling. The reprogramming of lipid metabolism in cancer involves increased fatty acid synthesis, uptake, and storage, contributing to tumor growth and survival (Bartolacci, Andreani, El-Gammal, & Scaglioni, 2021; Bleve, Durante, Sica, & Consonni, 2020; Cheng *et al*., 2022). The role of LDs in cancer has garnered significant attention in recent years. LDs are found in abundance in various types of cancer cells, including breast, prostate, liver, and ovarian cancers.

These droplets are involved in multiple aspects of cancer cell biology, such as energy homeostasis, protection against oxidative stress, and modulation of signaling pathways. LDs provide a readily accessible energy source that can be mobilized during periods of nutrient scarcity or metabolic stress, thereby supporting the high metabolic demands of cancer cells. Additionally, LDs play a role in the storage and detoxification of lipophilic compounds, protecting cancer cells from lipotoxicity and oxidative damage (Jin, Tan, Wu, & Ren, 2023; Z. Li, Liu, & Luo, 2020).

The presence of LDs in cancer cells is not merely a byproduct of metabolic reprogramming; it also has functional implications for tumor progression and therapy resistance. Studies have shown that LDs can influence cancer cell behavior, including proliferation, migration, and invasion. Moreover, LDs have been implicated in regulatingsignaling pathways involved in cancer progression, such as the PI3K/Akt and mTOR pathways. The dynamic nature of LDs allows them to interact with various cellular organelles, including mitochondria and endoplasmic reticulum, further highlighting their importance in cellular metabolism and signaling (Z. Li *et al*., 2020; Petan, 2020; L. Wang, Liu, Miao, Pan, & Cao, 2021).

Given the critical role of LDs in cancer biology, targeting these organelles presents a novel and promising therapeutic strategy. The objective of targeting LDs in cancer therapy is to disrupt the metabolic dependencies of cancer cells, thereby inhibiting tumor growth and progression. This approach involves pharmacological agents that interfere with LD formation, lipid metabolism, and signaling pathways associated with LDs. Several strategies have been proposed, including inhibiting enzymes involved in lipid biosynthesis, blocking fatty acid uptake, and promoting lipid oxidation. By targeting LDs, it is possible to reduce cancer cells' energy supply and metabolic flexibility, making them more susceptible to existing treatments and reducing the likelihood of therapy resistance.

The significance of targeting LDs in cancer therapy extends beyond metabolic reprogramming. LDs are also involved in the interaction between cancer cells and the tumor microenvironment. They contribute to the secretion of pro-tumorigenic factors, immune modulation, and angiogenesis. Therefore, targeting LDs could have a multifaceted impact on tumor biology, affecting the cancer cells and the surrounding stromal and immune cells. This holistic approach could enhance the efficacy of cancer therapies and improve patient outcomes.

1. Lipid Droplets: Structure and Function

1.1. Description of Lipid Droplets and Their Composition

Lipid droplets are intracellular organelles that are the primary storage sites for neutral lipids such as triglycerides and cholesteryl esters. These droplets are ubiquitous in eukaryotic cells and are especially abundant in adipocytes, the specialized cells responsible for fat storage. Structurally, LDs are characterized by a hydrophobic core of neutral lipids encased in a phospholipid monolayer. Unlike other organelles bounded by bilayers, the unique monolayer of LDs is embedded with a variety of proteins that play crucial roles in lipid metabolism and droplet dynamics (Cruz *et al*., 2020; Danielli *et al*., 2023).

The composition of LDs is dynamic and varies depending on the cellular context and metabolic state. The lipid core primarily consists of triglycerides and cholesteryl esters, but it can also contain other neutral lipids such as retinyl esters and sterol esters. The surrounding phospholipid monolayer is composed mainly of phosphatidylcholine and phosphatidylethanolamine. Embedded in this monolayer are numerous proteins, including perilipins essential for LD stability and function, and enzymes involved in lipid metabolism, such as lipases and acyltransferases. LDs' specific lipid and protein composition can be modulated in response to cellular signals, making LDs highly adaptable organelles (He *et al*., 2022; Y. Li, 2020).

1.2. Biological Functions of Lipid Droplets in Normal and Cancer Cells

In normal cells, LDs play several critical biological roles, primarily related to lipid storage and mobilization. They act as reservoirs of metabolic energy, storing excess lipids during periods of nutrient abundance and releasing them when energy demand increases. This ability to store and mobilize lipids is crucial for maintaining cellular energy homeostasis. LDs also contribute to membrane biosynthesis by supplying lipid precursors necessary for forming and maintaining cellular membranes. Additionally, LDs participate in lipid signaling pathways by sequestering and releasing bioactive lipids that regulate various cellular processes (Soto-Avellaneda & Morrison, 2020; Yue *et al*., 2022).

In cancer cells, the functions of LDs are amplified and often altered to support the unique metabolic needs of rapidly proliferating tumor cells. Cancer cells exhibit increased lipid synthesis and uptake, leading to the accumulation of LDs. These organelles provide a readily accessible energy source that can be rapidly mobilized to fuel cell division and growth. Beyond energy storage, LDs in cancer cells protect cells from lipotoxicity and oxidative stress by sequestering excess fatty acids and reactive oxygen species. Moreover, LDs have been implicated in modulating signaling pathways that promote cancer cell survival, proliferation, and metastasis. For example, LDs can influence the activity of key signaling molecules such as Akt and mTOR, which are involved in cell growth and survival (Mashek, 2021; Paul *et al*., 2021).

1.3. Mechanisms of Lipid Droplet Formation and Regulation

The formation of LDs, known as lipogenesis, is a highly regulated process that begins in the endoplasmic reticulum (ER). Lipid synthesis enzymes located in the ER membrane catalyze the production of neutral lipids, which then accumulate between the two leaflets of the ER membrane, forming a lens-like structure. As more lipids accumulate, this structure grows and eventually buds off the ER, forming a nascent LD. The surface of the newly formed LD is coated with proteins that regulate its growth, stability, and interactions with other cellular structures (Ischebeck, Krawczyk, Mullen, Dyer, & Chapman, 2020).

Several factors, including nutrient availability, hormonal signals, and cellular energy status, control LD formation and size regulation. Key regulatory proteins involved in LD dynamics include the aforementioned perilipins, which protect LDs from premature degradation by lipases, and seipin, a protein that facilitates LD budding and growth. Enzymes such as diacylglycerol acyltransferase (DGAT) are critical for the final steps of triglyceride synthesis and LD enlargement. Additionally, signaling pathways like the AMP-activated protein kinase (AMPK) pathway can influence LD formation by regulating lipid metabolism and energy balance

(Bosch, Parton, & Pol, 2020; Cheng *et al*., 2022; Cruz *et al*., 2020).

1.4. Role of Lipid Droplets in Cellular Energy Storage and Membrane Biosynthesis

Lipid droplets play a central role in cellular energy storage. By storing triglycerides and other neutral lipids, LDs act as energy depots that cells can draw upon during periods of increased energy demand or nutrient scarcity. Lipases can hydrolyze the stored lipids to release fatty acids, which are then oxidized in the mitochondria to generate ATP. This process, known as lipolysis, is tightly regulated to ensure that energy supply meets cellular demands without causing lipotoxicity.

In addition to their role in energy storage, LDs are essential for membrane biosynthesis. The lipids stored in LDs serve as precursors for synthesizing phospholipids, the primary components of cellular membranes. During membrane biogenesis, especially in rapidly growing cells such as cancer cells, the demand for phospholipids increases significantly. LDs can supply the necessary lipids to support the formation of new membranes and the expansion of existing ones. This function is particularly important in cancer cells requiring extensive membrane remodeling to support rapid proliferation and invasion.

Overall, lipid droplets are versatile organelles that play critical roles in both normal and cancer cell biology. Their ability to store and mobilize lipids, regulate lipid metabolism, and interact with key signaling pathways are important in cellular homeostasis and disease progression. Understanding the structure and function of LDs provides valuable insights into their role in cancer and highlights the potential for targeting LDs as a therapeutic strategy in cancer treatment.

2. Lipid Droplets in Cancer Biology

2.1. Evidence Linking LDs to Cancer Cell Proliferation and Survival

Lipid droplets (LDs) have emerged as crucial organelles in cancer biology, contributing significantly to cell proliferation and survival. Numerous studies have provided compelling evidence linking LDs to the aggressive phenotype of cancer cells. One of the key findings is the observation of increased LD accumulation in various types of cancer, including breast, prostate, and liver cancers. This accumulation is often associated with poor prognosis and treatment resistance. LDs in cancer cells serve as reservoirs of lipids, primarily triglycerides and cholesteryl esters, which can be mobilized to support the high metabolic demands of proliferating cells (Mashek, 2021; Tirinato *et al*., 2020).

LDs play a dual role in cancer cell survival by providing energy through lipid oxidation and protecting cells from lipotoxicity and oxidative stress. The stored lipids can be hydrolyzed into fatty acids, which are then used as substrates for mitochondrial oxidative phosphorylation to generate ATP. This process meets the energy demands of rapidly dividing cancer cells and supports their survival under conditions of metabolic stress. Additionally, LDs act as buffers against lipotoxicity by sequestering excess fatty acids and lipid intermediates that could otherwise induce cellular damage and apoptosis (Bartolacci *et al*., 2021; Bombarda-Rocha *et al*., 2023).

2.2. Influence of LDs on Cancer Cell Metabolism and Signaling Pathways

LDs profoundly affect cancer cell metabolism and signaling pathways, contributing to tumor growth and progression. Beyond their role in energy storage, LDs participate in lipid metabolism pathways that are dysregulated in cancer cells. For instance, LDs can modulate the activity of key signaling molecules such as Akt and mTOR, critical regulators of cell growth, survival, and metabolism. The interaction between LDs and these signaling pathways promotes the reprogramming of cancer cell metabolism towards aerobic glycolysis (the Warburg effect) and lipid biosynthesis, facilitating rapid cell proliferation and biomass accumulation (Jacquet & Stéphanou, 2022; Jaworska *et al*., 2023).

Moreover, LDs are involved in synthesizing and releasing lipid-derived signaling molecules, such as prostaglandins and leukotrienes, which regulate inflammation, immune responses, and cell signaling within the tumor microenvironment. By influencing these pathways, LDs contribute to the complex network of interactions between cancer cells and their surrounding stroma, promoting tumor progression, angiogenesis, and metastasis (Urbano, 2021; Vaupel & Multhoff, 2021).

2.3. Interaction Between LDs and Tumor Microenvironment

The interaction between LDs and the tumor microenvironment (TME) is crucial in cancer progression and therapy resistance. LDs contribute to the metabolic crosstalk between cancer cells and stromal cells within the TME. For example, LDs in cancer-associated fibroblasts (CAFs) can transfer lipids to adjacent cancer cells, providing essential nutrients and promoting their survival and proliferation. This lipid transfer supports the metabolic adaptation of cancer cells to the nutrient-poor and hypoxic conditions characteristic of the TME (Keerthana *et al*., 2023; Shriwas *et al*., 2021).

Furthermore, LDs influence the immune response within the TME by modulating lipid-mediated signaling pathways that regulate immune cell function and polarization. LDs in cancer cells can alter the expression of immune checkpoint proteins and cytokines, thereby promoting immune evasion and facilitating tumor immune escape. LDs in the TME are associated with immunosuppressive phenotypes, which contribute to tumor progression and resistance to immunotherapy (Aquila *et al*., 2020; Asl *et al*., 2021).

2.4. Clinical Relevance of LDs in Cancer Diagnosis and Prognosis

The clinical relevance of LDs in cancer extends beyond their role in tumor biology to their potential utility as diagnostic and prognostic biomarkers. Imaging techniques such as coherent anti-Stokes Raman scattering (CARS) microscopy and magnetic resonance spectroscopy (MRS) have enabled the visualization and quantification of LDs in live tissues and clinical samples. Elevated LD levels detected by these techniques have been correlated with aggressive tumor phenotypes, poor prognosis, and reduced overall survival in cancer patients (Abate *et al*., 2020; Alam, Mukherjee, & Krishnakumar, 2022).Moreover, LDs have been implicated in the development of resistance to chemotherapy and targeted therapies. The ability of LDs to sequester and detoxify chemotherapeutic agents contributes to treatment failure and disease recurrence. Understanding the mechanisms underlying LD-mediated therapy resistance could lead to developing strategies to overcome this obstacle

and improve treatment outcomes for cancer patients (Abate *et al*., 2020; Fernández, Gomez de Cedron, & Ramirez de Molina, 2020).

3. Current Therapeutic Approaches Targeting Lipid Droplets

3.1. Overview of Existing Therapies Targeting Lipid Metabolism in Cancer

Therapeutic strategies targeting lipid metabolism in cancer have gained significant attention due to the crucial role of lipids in sustaining cancer cell proliferation and survival. One approach involves inhibiting key enzymes involved in lipid biosynthesis pathways, such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC). These enzymes are essential for de novo lipid synthesis, and their inhibition can disrupt the production of lipids necessary for tumor growth. Several inhibitors targeting FASN and ACC have shown promise in preclinical studies and early-phase clinical trials, highlighting their potential as novel anticancer agents (Menendez *et al*., 2024).

Another strategy focuses on targeting pathways that regulate fatty acid uptake and storage in cancer cells. For instance, inhibitors of fatty acid transport proteins (FATPs) and fatty acid binding proteins (FABPs) have been developed to block exogenous fatty acids' uptake and intracellular transport. By reducing the availability of fatty acids for lipid droplet (LD) formation and metabolism, these inhibitors aim to inhibit cancer cell proliferation and induce cell death. However, the clinical efficacy of these agents in cancer therapy remains to be fully validated (Acharya & Shetty, 2023; Danielli *et al*., 2023; Devereux, Bayliss, Keenan, Montgomery, & Watt, 2023).

3.2. Specific Strategies Aimed at Disrupting LD Formation and Function

Targeting lipid droplets directly represents a promising therapeutic approach in cancer treatment. One strategy involves inhibiting proteins that regulate LD biogenesis and dynamics, such as perilipins and seipins. Perilipins stabilize and protect LDs from lipolysis, while seipins facilitate LD formation and growth. Inhibitors targeting these proteins could disrupt LD stability and function, thereby sensitizing cancer cells to metabolic stress and apoptosis. Preclinical studies have shown that genetic or pharmacological inhibition of perilipins can reduce LD accumulation and inhibit tumor growth in animal models.

Modulating lipases involved in LD breakdown is another strategy to target LDs in cancer cells. Lipases such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) catalyze the hydrolysis of triglycerides stored in LDs, releasing free fatty acids for energy production and cellular metabolism. Inhibitors targeting these lipases can impair lipid mobilization from LDs, leading to lipid accumulation and metabolic stress in cancer cells. However, the clinical development of lipase inhibitors faces challenges related to specificity, efficacy, and off-target effects (T. Li, Guo, & Zhou, 2021).

Several pharmacological agents targeting LD metabolism and function have been investigated for their anticancer potential. For example, inhibitors of diacylglycerol O-acyltransferase 1 (DGAT1), a key enzyme in triglyceride synthesis and LD formation, have shown efficacy in preclinical cancer models. DGAT1 inhibitors reduce LD accumulation and impair cancer cell proliferation by disrupting lipid homeostasis and inducing metabolic stress. Furthermore, DGAT1 inhibition sensitizes cancer cells to chemotherapy and radiation therapy, highlighting its potential as a therapeutic adjunct in cancer treatment (Futatsugi *et al*., 2022; Kou, Geng, & Guo, 2022).

Another example includes fatty acid oxidation (FAO) inhibitors, such as etomoxir and perhexiline. These agents block the transport of fatty acids into mitochondria for oxidation, thereby promoting the accumulation of fatty acids in LDs and impairing cancer cell metabolism. Inhibition of FAO reduces ATP production and induces oxidative stress, leading to cytotoxic effects in cancer cells dependent on fatty acid oxidation for survival. Clinical trials evaluating FAO inhibitors in combination with standard therapies are ongoing to assess their efficacy and safety in cancer treatment (Ma *et al*., 2020; J. Wang, Xiang, Lu, Wu, & Ji, 2021).

3.3. Challenges and Limitations of Current LD-Targeting Therapies

Despite the promising preclinical data, several challenges and limitations hinder the clinical translation of LD-targeting therapies in cancer treatment. One major challenge is the complexity of lipid metabolism and the redundancy of lipid pathways in cancer cells. Cancer cells can adapt to metabolic stress by rewiring lipid metabolism, circumventing single-target inhibitors' effects. Combinatorial approaches targeting multiple nodes in lipid metabolism may be necessary to achieve sustained therapeutic efficacy.Moreover, the specificity and toxicity of LD-targeting agents pose significant concerns in clinical applications. Many inhibitors of LD formation or function exhibit off-target effects on normal tissues, leading to dose-limiting toxicities and adverse side effects. Strategies to enhance the specificity of LD-targeting therapies while minimizing systemic toxicity are actively being pursued through drug formulation and delivery innovations (Antunes, Cruz, Barbosa, Bonifácio, & Pinto, 2022; Cruz *et al*., 2020).

Another limitation is the heterogeneity of lipid droplets within tumors and among different cancer types. Variations in LD composition, size, and function can influence the response to LD-targeting therapies and contribute to treatment resistance. Personalized approaches that account for tumor-specific metabolic profiles and LD characteristics may improve therapeutic outcomes and patient responses (Petan, 2020).

4. Future Directions and Emerging Strategies

4.1. Innovative Approaches and Potential Targets for LD-Focused Therapies

The future of targeting lipid droplets (LDs) in cancer therapy holds promise with innovative approaches to exploit LDs' metabolic vulnerabilities. One emerging strategy involves targeting LD-associated proteins and regulatory pathways that control LD formation and function. For instance, inhibitors of seipin, a protein critical for LD biogenesis, could potentially disrupt LD formation and sensitize cancer cells to metabolic stress and apoptosis. Additionally, targeting proteins involved in LD dynamics and lipid metabolism pathways, such as perilipins and enzymes like diacylglycerol O-acyltransferase (DGAT), represents a fertile area for drug development.

Furthermore, recent research has identified novel molecular targets within LDs that are essential for cancer cell survival and proliferation. For example, lipid metabolism enzymes

involved in specialized lipid biosynthesis pathways, such as sphingolipids and ether lipids, have been implicated in promoting oncogenic signaling and therapy resistance. Targeting these specific lipid species and their biosynthetic enzymes could offer new avenues for selectively disrupting LD-dependent pathways in cancer cells while sparing normal tissues.

4.2. Role of Nanotechnology and Drug Delivery Systems

Nanotechnology and advanced drug delivery systems present promising opportunities for targeting LDs with enhanced specificity and efficacy. Nanoparticles can be engineered to encapsulate LD-targeting agents, such as small molecule inhibitors and siRNAs targeting LD-associated proteins. These nanoparticles can exploit tumours' enhanced permeability and retention effect to selectively deliver therapeutic payloads to cancer cells with elevated LD levels. Moreover, surface modifications of nanoparticles with targeting ligands can enhance their specificity for LD-rich cancer cells, thereby minimizing off-target effects and systemic toxicity.

In addition to nanoparticles, lipid-based drug delivery systems, such as liposomes and lipid nanoparticles, offer unique advantages for LD-targeted therapies. Lipid carriers can encapsulate hydrophobic drugs and siRNAs, facilitating their delivery to LDs and enhancing intracellular uptake. Lipid-based formulations can also stabilize therapeutic agents in biological fluids and improve their pharmacokinetic profiles, thereby optimizing drug efficacy and bioavailability in cancer treatment.

4.3. Combination Therapies and Their Potential to Enhance Efficacy

Combination therapies that target multiple nodes in LD metabolism and signaling pathways represent a promising approach to enhancing therapeutic efficacy in cancer treatment. Combining therapies can exert synergistic effects on cancer cells by simultaneously inhibiting LD formation, disrupting lipid metabolism, and targeting LD-associated proteins while minimizing the risk of resistance development. For example, combining inhibitors of DGAT and fatty acid oxidation pathways with conventional chemotherapy or targeted therapies could overcome metabolic adaptations and enhance treatment responses in refractory cancers.

Moreover, combining immunotherapy with LD-targeted therapies can enhance antitumor immune responses and overcome immune evasion mechanisms mediated by LDs in the tumor microenvironment. Strategies that modulate lipid-mediated signaling pathways, such as immune checkpoint inhibitors and lipid metabolism inhibitors, could synergistically enhance the efficacy of immunotherapy and improve clinical outcomes for cancer patients.

4.4. Prospects of Personalized Medicine in Targeting LDs in Cancer Treatment

Personalized medicine approaches offer exciting prospects for tailoring LD-targeted therapies to individual patient profiles and tumor characteristics. Advances in genomic and metabolomic profiling have identified specific molecular alterations and metabolic dependencies associated with LD metabolism in cancer cells. Biomarker-driven strategies can stratify patients based on LD levels, lipid metabolism gene expression signatures, and metabolic phenotypes, allowing for the selection of optimal LD-targeting therapies and predictive biomarkers of treatment response.

Furthermore, the development of patient-derived xenograft models and organoid cultures has facilitated the preclinical evaluation of LD-targeted therapies in tumor models that recapitulate patient-specific tumor heterogeneity and metabolic profiles. These model systems provide valuable platforms for testing novel LD-targeting agents, assessing treatment responses, and predicting clinical outcomes in a more representative context.

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