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Lipid droplets in cancer: A review of their implications for tumor biology and treatment

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Abstract

Lipid droplets (LDs) are intracellular organelles traditionally known for their role in lipid storage and energy homeostasis. Recent research has unveiled their significant involvement in cancer biology, revealing them as dynamic structures that contribute to various aspects of tumor development and progression. This review delves into the multifaceted roles of LDs in cancer, highlighting their implications for tumor biology and potential therapeutic strategies. LDs are increasingly recognised for their ability to modulate cellular metabolism, signaling pathways, and stress responses in cancer cells. Their accumulation is often observed in various tumor types, correlating with aggressive phenotypes and poor prognosis. LDs support rapid cell proliferation by providing essential lipids for membrane synthesis and energy production, enabling cancer cells to thrive under metabolic stress. Furthermore, LDs serve as hubs for lipid signaling molecules, influencing key oncogenic pathways such as the PI3K/Akt/mTOR and Wnt/β-catenin pathways, thereby promoting tumorigenesis and metastasis. Beyond their metabolic functions, LDs contribute to the oxidative stress response and lipid peroxidation, mechanisms that can either facilitate cancer cell survival or lead to cell death, depending on the context. The dual role of LDs in regulating reactive oxygen species (ROS) levels underscores their complexity in cancer biology. Importantly, LDs have emerged as potential targets for cancer therapy. Strategies to disrupt LD formation, enhance lipid catabolism, or modulate lipid signaling are being explored to impair tumor growth and sensitize cancer cells to treatment. Pharmacological agents targeting LD-associated proteins, such as perilipins and diacylglycerol acyltransferase (DGAT) inhibitors, are showing promise in preclinical models. LDs play a critical and versatile role in cancer biology, influencing tumor metabolism, signaling, and stress responses. Understanding the intricate functions of LDs in cancer can pave the way for novel therapeutic approaches, offering hope for more effective treatments in oncology. This review underscores the need for further research to fully elucidate the therapeutic potential of targeting LDs in cancer.

Keywords: Lipid droplets; Cancer; Tumor Treatment

1. Introduction

Lipid droplets (LDs) are dynamic organelles found ubiquitously in cells, serving as the primary storage sites for neutral lipids such as triacylglycerols and sterol esters (Olzmann and Carvalho, 2019). Initially perceived merely as fat storage depots, LDs are now recognized as complex and multifunctional structures involved in various cellular processes. Structurally, LDs consist of a hydrophobic core encased by a phospholipid monolayer embedded with diverse proteins (Renne *et al.*, 2020). This unique architecture allows them to interact with other organelles, participate in lipid metabolism, and play crucial roles in cellular homeostasis. LDs are essential for energy storage, membrane synthesis, and the sequestration of toxic lipids (Mashek, 2021). Additionally, they are involved in intracellular signaling pathways

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and the regulation of lipid and protein trafficking. The versatility and dynamic nature of LDs highlight their significance beyond mere lipid storage, positioning them as central players in cellular physiology (Ischebeck *et al*., 2020).

The study of lipid droplets has gained considerable attention in cancer research due to their emerging role in tumor biology. Cancer cells exhibit profound alterations in lipid metabolism, often characterized by increased lipid droplet formation (Yi *et al*., 2018). These changes are believed to support the rapid proliferation and survival of malignant cells. LDs provide a reservoir of lipids that can be mobilized to meet the high energy and biosynthetic demands of cancer cells. Furthermore, they are implicated in the modulation of signaling pathways associated with cell growth, apoptosis, and stress responses. The accumulation of LDs in cancer cells is also linked to the development of resistance to chemotherapy and radiotherapy, posing significant challenges in cancer treatment (Shyu Jr *et al*., 2018; Maha *et al*., 2024). By understanding the mechanisms regulating LD formation and function in cancer, researchers can identify novel therapeutic targets and develop strategies to overcome treatment resistance. The intersection of lipid metabolism and cancer biology thus represents a promising avenue for advancing cancer diagnostics and therapeutics.

This review aims to provide a comprehensive overview of the current understanding of lipid droplets, with a specific focus on their role in cancer. We will explore the molecular mechanisms underlying lipid droplet biogenesis and regulation, highlighting the key proteins and signaling pathways involved. The review will also examine the functional significance of lipid droplets in cancer cells, discussing how they contribute to tumor progression, metastasis, and therapy resistance. By synthesizing the latest research findings, we aim to elucidate the complex interplay between lipid droplets and cancer, offering insights into potential therapeutic interventions. This review seeks to underscore the importance of lipid droplets as critical organelles in cancer biology and to inspire further research into their potential as diagnostic and therapeutic targets. Ultimately, a deeper understanding of lipid droplets in cancer could pave the way for novel strategies to combat this devastating disease. Lipid droplets are multifunctional organelles with significant implications in cellular physiology and disease. Their role in cancer, marked by altered lipid metabolism and increased formation, underscores the importance of studying these organelles in the context of tumor biology (Luo *et al*., 2022). This review aims to consolidate current knowledge on lipid droplets, shedding light on their contribution to cancer progression and highlighting their potential as targets for therapeutic intervention.

2. Biology of Lipid Droplets

Lipid droplet (LD) biogenesis is a highly regulated process that begins in the endoplasmic reticulum (ER) (Maha *et al*., 2022). The initial step involves the synthesis of neutral lipids, primarily triacylglycerols (TAG) and sterol esters, which are generated by acyl-CoA:diacylglycerol acyltransferase (DGAT) enzymes. As these neutral lipids accumulate between the leaflets of the ER membrane, they form a lipid lens or oil phase (Renne *et al*., 2020). This nascent lipid droplet grows by budding off from the ER, enveloped by a phospholipid monolayer derived from the ER membrane. This phospholipid monolayer is crucial as it provides a boundary that separates the hydrophobic core from the aqueous cytosol and contains various proteins that regulate LD function (Abdul *et al*., 2024). The budding process is facilitated by specific proteins such as seipin, which localizes to ER–lipid droplet junctions and ensures the correct formation and release of LDs from the ER. The composition of lipid droplets is complex and diverse, reflecting their multifaceted roles in cellular physiology (Henne e al., 2018). The hydrophobic core primarily consists of TAG and sterol esters, serving as a reservoir of energy-rich molecules that can be mobilized during periods of nutrient scarcity. The surrounding phospholipid monolayer contains a variety of proteins, including enzymes involved in lipid metabolism, structural proteins, and regulatory proteins that mediate interactions with other organelles (Wang *et al*., 2021; Abdul *et al*., 2024). These proteins play critical roles in lipid droplet growth, trafficking, and degradation. Lipid droplets are not merely static storage depots; they are dynamic organelles involved in numerous cellular processes. They participate in lipid metabolism by storing and releasing fatty acids and sterols as needed. LDs also play a role in cellular homeostasis by sequestering excess or toxic lipids, thus protecting cells from lipotoxicity (Mashek, 2021). Additionally, they are involved in intracellular signaling pathways and can interact with other organelles, such as mitochondria and peroxisomes, to regulate lipid exchange and energy metabolism. The ability of LDs to respond to cellular metabolic needs underscores their importance in maintaining cellular health and function (Yoon *et al*., 2021).

The formation and turnover of lipid droplets are tightly regulated by a network of enzymes. Key enzymes involved in lipid droplet biogenesis include DGAT1 and DGAT2, which catalyze the final step in TAG synthesis (Dejgaard and Presley, 2021). These enzymes are critical for the initiation and growth of lipid droplets. Another important enzyme is acyl-CoA:cholesterol acyltransferase (ACAT), which is involved in the synthesis of sterol esters. The degradation of lipid droplets is primarily mediated by lipases such as adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and lysosomal acid lipase (LAL), which hydrolyze TAG and sterol esters to release free fatty acids and cholesterol (Fader Kaiser *et al*., 2022; Abdul *et al*., 2024). The activity of these enzymes is regulated by various factors, including phosphorylation, interactions with co-activators and inhibitors, and localization within the cell. For instance, ATGL

activity is enhanced by its co-activator comparative gene identification-58 (CGI-58), while HSL activity is regulated by phosphorylation in response to hormonal signals (Han *et al*., 2021). These enzymatic controls ensure that lipid droplet formation and breakdown are precisely coordinated with cellular metabolic demands. The regulation of lipid droplets is also influenced by multiple signaling pathways. One of the key pathways is the mammalian target of rapamycin (mTOR) pathway, which senses nutrient availability and regulates lipid metabolism accordingly (Querfurth and Lee, 2021). When nutrients are abundant, mTOR signaling promotes lipid synthesis and storage in lipid droplets. Conversely, during nutrient deprivation, mTOR activity decreases, leading to the mobilization of stored lipids to meet cellular energy requirements. Another important pathway is the AMP-activated protein kinase (AMPK) pathway, which is activated under conditions of low energy and promotes the catabolism of stored lipids to generate ATP (Fang *et al*., 2022). AMPK activation enhances the activity of lipolytic enzymes and inhibits lipid synthesis, thus facilitating the breakdown of lipid droplets. Additionally, hormonal signals such as insulin and glucagon play crucial roles in lipid droplet regulation. Insulin promotes lipid storage by activating lipogenic enzymes and inhibiting lipolysis, while glucagon triggers lipid mobilization by activating lipolytic pathways (Morigny *et al*., 2021). Other signaling molecules, including peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element-binding proteins (SREBPs), also contribute to the regulation of lipid droplet dynamics by modulating the expression of genes involved in lipid metabolism.

Lipid droplets are dynamic organelles formed through a regulated process of lipid accumulation and budding from the ER (Seebacher *et al*., 2020). They play essential roles in cellular energy storage, lipid metabolism, and homeostasis. The regulation of lipid droplets involves a complex interplay of enzymatic control and signaling pathways, ensuring that lipid storage and mobilization are tightly coordinated with cellular metabolic needs. Understanding these regulatory mechanisms is crucial for elucidating the roles of lipid droplets in health and disease.

2.1. Lipid Droplets in Cancer Biology

Lipid droplets (LDs) have been observed to accumulate in a wide range of cancer types, highlighting their significance in tumor biology (Antunes *et al*., 2022). For instance, increased LD content has been reported in prostate, breast, ovarian, and colorectal cancers, among others. Studies using various imaging techniques, such as electron microscopy and fluorescence microscopy, have demonstrated the presence of abundant LDs in cancer cells compared to their normal counterparts. In addition to histological evidence, biochemical analyses have confirmed elevated levels of neutral lipids, including triacylglycerols and sterol esters, in tumor tissues. The ubiquitous presence of LDs in different cancer types underscores their potential role in supporting malignancy. The accumulation of LDs in cancer cells is driven by several mechanisms, often linked to alterations in lipid metabolism (Cheng *et al*., 2022). One key mechanism is the upregulation of enzymes involved in lipid synthesis, such as acyl-CoA:diacylglycerol acyltransferase (DGAT) and fatty acid synthase (FASN) (Kou *et al*., 2022). These enzymes catalyze the formation of triacylglycerols and other neutral lipids, promoting LD formation. Cancer cells also exhibit increased uptake of exogenous lipids from the extracellular environment, facilitated by the overexpression of lipid transporters like CD36 and fatty acid-binding proteins (FABPs). Moreover, oncogenic signaling pathways, such as those mediated by MYC and PI3K-AKT, drive lipid biosynthesis and storage. Hypoxia, a common feature of the tumor microenvironment, further induces lipid accumulation by activating hypoxia-inducible factor (HIF) pathways, which enhance the expression of lipid storage genes (Seo *et al*., 2022; Abdul *et al*., 2024).

Lipid droplets serve as crucial energy reservoirs for cancer cells, providing a readily accessible source of energy to support rapid proliferation. The stored triacylglycerols within LDs can be hydrolyzed by lipases, such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), to release free fatty acids (FFAs) (Tardelli *et al*., 2020). These FFAs are then oxidized through β-oxidation in mitochondria, generating ATP and other metabolites necessary for cellular growth and survival. The ability to store and mobilize lipids allows cancer cells to adapt to fluctuating energy demands and maintain metabolic flexibility. Cancer cells rewire their lipid metabolism pathways to support LD accumulation and utilization. Key pathways involved include the de novo lipogenesis pathway, driven by enzymes like FASN and acetyl-CoA carboxylase (ACC), which synthesizes fatty acids from acetyl-CoA. Additionally, the uptake and incorporation of exogenous lipids are enhanced through upregulation of lipid transporters and scavenger receptors. The sterol regulatory element-binding proteins (SREBPs) play a pivotal role in regulating the expression of genes involved in lipid synthesis and uptake (Jiang *et al*., 2020). These pathways collectively ensure a continuous supply of lipids for storage in LDs and subsequent mobilization for energy production.

The ability to efficiently store and utilize lipids gives cancer cells a significant growth advantage. LDs provide a sustained source of energy, enabling cancer cells to proliferate even under conditions of nutrient deprivation (Cruz *et al*., 2020). The release of FFAs from LDs supports mitochondrial β-oxidation and ATP production, fueling various biosynthetic processes required for cell division. This metabolic reprogramming towards lipid utilization is often termed "lipid addiction," highlighting the dependence of cancer cells on lipid metabolism for sustained growth and survival. Lipid

droplets also play a protective role in cancer cells by mitigating lipotoxicity and oxidative stress. The sequestration of excess or toxic lipids into LDs prevents the accumulation of harmful lipid intermediates, such as ceramides and diacylglycerols, which can induce apoptosis. Furthermore, LDs contribute to the detoxification of reactive oxygen species (ROS) by housing antioxidant enzymes and providing a buffer against lipid peroxidation (Soto *et al*., 2020). This protective function is particularly important in the hypoxic and oxidative stress-rich tumor microenvironment, where cancer cells are constantly exposed to ROS. By safeguarding cellular integrity and preventing lipid-induced damage, LDs enhance the survival and resilience of cancer cells. The accumulation and utilization of LDs support the energetic and biosynthetic demands of rapidly proliferating cancer cells while providing resilience against lipotoxicity and oxidative stress. Understanding the mechanisms underlying LD regulation and function in cancer cells offers promising avenues for developing novel therapeutic strategies targeting lipid metabolism in cancer.

2.2. Lipid Droplets and Tumor Microenvironment

Lipid droplets (LDs) are not only pivotal for the metabolic needs of cancer cells but also play a significant role in the interaction with the tumor stroma, the supportive tissue surrounding tumor cells (Shang *et al*., 2020). The tumor stroma comprises various cell types, including fibroblasts, endothelial cells, and immune cells, which interact dynamically with cancer cells. Cancer-associated fibroblasts (CAFs) are a major component of the tumor stroma and have been shown to influence lipid metabolism in cancer cells. CAFs can secrete cytokines and growth factors that stimulate lipid droplet formation in cancer cells. Additionally, cancer cells can induce lipid accumulation in CAFs, creating a reciprocal relationship that supports tumor growth and survival (Jena *et al*., 2020). Stromal cells can also transfer lipids to cancer cells via lipid transport proteins or extracellular vesicles, facilitating the formation of lipid droplets within cancer cells. This lipid exchange not only supplies energy but also contributes to the biosynthesis of membrane lipids and signaling molecules, thereby promoting tumor progression. The crosstalk between cancer cells and stromal cells through lipid droplets underscores the complexity of tumor-stroma interactions and the integral role of lipid metabolism in the tumor microenvironment. Lipid droplets significantly influence the tumor microenvironment by modulating the metabolic and signaling landscape. The accumulation of lipid droplets in cancer cells and stromal cells alters the availability of lipids and metabolic intermediates, which can impact various cellular functions and signaling pathways. For instance, the release of free fatty acids (FFAs) from lipid droplets can activate nuclear receptors such as peroxisome proliferator-activated receptors (PPARs), leading to the transcriptional activation of genes involved in lipid metabolism and inflammation (Dixon *et al*., 2021). Furthermore, lipid droplets can affect the extracellular matrix (ECM) composition and remodeling, processes that are crucial for tumor invasion and metastasis. The lipids stored in droplets can be used for the synthesis of ECM components or serve as signaling molecules that regulate ECM-modifying enzymes. By influencing the ECM and other aspects of the tumor microenvironment, lipid droplets play a vital role in creating a supportive niche for tumor growth and metastasis.

Lipid droplets are increasingly recognized for their role in modulating immune cell function within the tumor microenvironment. Tumor-associated macrophages (TAMs) and other immune cells can accumulate lipid droplets, which can alter their phenotype and function (Siddiqui and Glauben, 2022). For example, lipid-laden TAMs often exhibit an immunosuppressive phenotype, characterized by the production of anti-inflammatory cytokines and the suppression of anti-tumor immune responses. The accumulation of lipids in TAMs is associated with the inhibition of their phagocytic activity and the promotion of tumor growth. In addition, lipid droplets can modulate the function of dendritic cells (DCs) and T cells, crucial players in the immune response against tumors. Lipid accumulation in DCs can impair their ability to present antigens and activate T cells, leading to a weakened immune response (Currivan *et al*., 2022). Similarly, lipid-laden T cells may have reduced proliferative capacity and effector functions, further contributing to immune evasion by cancer cells. The impact of lipid droplets on immune cell function has significant implications for immune surveillance and tumor immune evasion. By altering the phenotype and function of immune cells, lipid droplets can create an immunosuppressive tumor microenvironment that allows cancer cells to escape detection and destruction by the immune system. This immune evasion is a critical challenge in cancer therapy, particularly in the context of immunotherapies that rely on the activation of anti-tumor immune responses. Moreover, the metabolic reprogramming associated with lipid droplet accumulation can lead to the production of immunosuppressive metabolites, such as prostaglandins and eicosanoids, which further inhibit immune cell function and promote tumor growth (Bleve *et al*., 2020). Understanding the mechanisms by which lipid droplets modulate immune cell function and contribute to immune evasion is essential for developing strategies to enhance immune surveillance and improve the efficacy of immunotherapies.

Lipid droplets play a multifaceted role in the tumor microenvironment by mediating interactions with stromal cells, influencing ECM remodeling, and modulating immune cell function. These interactions contribute to tumor growth, metastasis, and immune evasion, highlighting the importance of lipid metabolism in cancer biology and therapy.

2.3. Lipid Droplets and Cancer Progression

Lipid droplets (LDs) are increasingly recognized for their role in metastasis, the spread of cancer cells from the primary tumor to distant sites (Yin *et al*., 2022). Metastatic cells often exhibit enhanced lipid droplet formation and dynamic regulation compared to non-metastatic cells. These droplets serve as reservoirs of energy and signaling molecules that support the unique metabolic and functional requirements of metastatic cells. The high energy demand associated with detachment, migration, invasion, and colonization of new tissues necessitates efficient lipid storage and mobilization. Enzymes involved in lipid metabolism, such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), are often upregulated in metastatic cells, facilitating the rapid hydrolysis of stored lipids to meet energetic needs. Additionally, metastatic cells may alter their lipid uptake and synthesis pathways to increase the availability of fatty acids and other lipids for droplet formation. These adaptations provide metabolic flexibility and ensure that metastatic cells have a steady supply of lipids for energy production, membrane synthesis, and signaling purposes. The ability to dynamically regulate lipid droplet formation and utilization is thus crucial for the metastatic potential of cancer cells. Lipid droplets contribute significantly to the metastatic potential of cancer cells through various mechanisms. The stored lipids within these droplets can be mobilized to produce energy via β-oxidation, a process critical for sustaining the high metabolic demands of migrating and invading cells (Petan, 2020). Furthermore, the breakdown of lipid droplets releases fatty acids that can activate signaling pathways promoting cell survival, migration, and invasion. For example, fatty acids can activate peroxisome proliferator-activated receptors (PPARs), which regulate genes involved in lipid metabolism, inflammation, and cell proliferation. Lipid droplets also play a role in protecting metastatic cells from environmental stresses encountered during metastasis. The sequestration of excess or toxic lipids in droplets prevents lipotoxicity and mitigates oxidative stress, enhancing the survival of metastatic cells in the bloodstream and at secondary sites. Additionally, lipid droplets can modulate the rigidity and deformability of cancer cells, facilitating their passage through narrow capillaries and enhancing their ability to colonize distant tissues. Overall, lipid droplets provide metabolic and functional advantages that enhance the metastatic potential of cancer cells.

Angiogenesis, the formation of new blood vessels, is a critical process in tumor progression, enabling tumors to obtain the necessary nutrients and oxygen for continued growth (Al-Ostoot *et al*., 2021). Endothelial cells, which line blood vessels, are key players in angiogenesis, and their function is influenced by lipid metabolism and lipid droplet dynamics. Endothelial cells can form lipid droplets in response to metabolic cues and environmental signals, and these droplets play important roles in energy storage and lipid signaling.

Lipid droplets in endothelial cells serve as reservoirs of fatty acids and other lipids that can be mobilized to support the energetic and biosynthetic needs of angiogenesis (Heravi, *et al*., 2022). The dynamic regulation of lipid droplet formation and utilization in endothelial cells is crucial for their proliferation, migration, and tube formation during angiogenesis. Moreover, the breakdown of lipid droplets releases signaling molecules that can activate angiogenic pathways and promote the vascularization of tumors. Lipid droplets contribute to the promotion of tumor angiogenesis by supplying energy and signaling molecules necessary for the proliferation and migration of endothelial cells. The release of fatty acids from lipid droplets provides a readily available energy source for endothelial cells, supporting their rapid proliferation and migration during blood vessel formation. Additionally, lipid-derived signaling molecules, such as prostaglandins and eicosanoids, can activate angiogenic pathways and enhance the expression of pro-angiogenic factors like vascular endothelial growth factor (VEGF). The interaction between cancer cells and endothelial cells further promotes angiogenesis. Cancer cells can secrete factors that induce lipid droplet formation in endothelial cells, enhancing their angiogenic capacity. The newly formed blood vessels supply the growing tumor with oxygen and nutrients, facilitating further tumor growth and metastasis. Thus, lipid droplets in endothelial cells play a vital role in the promotion of tumor angiogenesis, contributing to cancer progression and the establishment of a supportive tumor microenvironment (Corn *et al*., 2020). Lipid droplets are integral to cancer progression, influencing both metastasis and angiogenesis. Their dynamic regulation and diverse functions support the metabolic and signaling needs of metastatic and endothelial cells, promoting tumor growth, invasion, and vascularization. Understanding the role of lipid droplets in these processes offers potential avenues for therapeutic intervention in cancer.

2.4. Lipid Droplets as Therapeutic Targets

Targeting lipid droplet (LD) formation presents a promising therapeutic strategy in cancer treatment (Chen *et al*., 2020). LDs play a crucial role in cancer cell metabolism and survival, making them attractive targets for intervention. Inhibitors of enzymes involved in LD formation, such as acyl-CoA:diacylglycerol acyltransferase (DGAT) and fatty acid synthase (FASN), have shown potential in reducing LD accumulation in cancer cells. DGAT inhibitors, by preventing the esterification of diacylglycerol to triacylglycerol, can effectively reduce the lipid storage capacity of cancer cells, impairing their energy supply and growth. Similarly, FASN inhibitors, which block the synthesis of fatty acids, can decrease lipid availability, thereby limiting the formation of LDs and inducing metabolic stress in cancer cells. Beyond direct inhibition of LD formation, modulating lipid metabolism as a whole can also be an effective strategy. This includes

targeting pathways involved in lipid uptake, synthesis, and degradation. For example, inhibitors of sterol regulatory element-binding proteins (SREBPs), which regulate the expression of genes involved in lipid biosynthesis, can reduce lipid accumulation in cancer cells. Additionally, activators of lipolytic enzymes, such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), can promote the breakdown of stored lipids in LDs, leading to increased fatty acid oxidation and reduced energy reserves for cancer cells (Kulminskaya and Oberer, 2020). These approaches aim to disrupt the lipid homeostasis in cancer cells, thereby inhibiting their growth and survival.

A variety of small molecules and natural compounds have been identified as potential therapeutic agents targeting lipid metabolism in cancer. Small molecule inhibitors, such as orlistat (a FASN inhibitor) and GSK2194069 (a DGAT inhibitor), have shown efficacy in preclinical studies by reducing LD accumulation and impairing cancer cell growth (Matsushita *et al*., 2021). Natural compounds, including curcumin, resveratrol, and epigallocatechin gallate (EGCG), have also demonstrated lipid-lowering effects in cancer cells. These compounds can modulate lipid metabolism through various mechanisms, including inhibition of lipid biosynthesis enzymes, activation of lipolytic pathways, and alteration of lipid signaling pathways. Their natural origin and multi-target effects make them attractive candidates for further development. The development of novel drug delivery systems can enhance the efficacy and specificity of lipid-targeting therapies. Nanoparticles, liposomes, and other nanocarriers can be designed to deliver lipid-modulating agents directly to tumor cells, minimizing off-target effects and improving therapeutic outcomes (Huang *et al*., 2024). For instance, lipid-based nanoparticles can encapsulate lipid metabolism inhibitors, ensuring their stability and targeted delivery. Additionally, these systems can be engineered to respond to specific tumor microenvironmental cues, such as pH or enzyme activity, ensuring the controlled release of therapeutic agents at the tumor site (Zhou *et al*., 202o). Such advanced delivery systems hold promise for improving the clinical application of lipid-targeting therapies.

One of the main challenges in targeting lipid metabolism in cancer is achieving specificity without causing toxicity to normal cells. Lipid metabolism is fundamental to all cells, and broad inhibition can lead to adverse effects on normal tissues (Lee *et al*., 2021). Therefore, it is crucial to develop strategies that selectively target cancer cells with minimal impact on healthy cells. This can be achieved through the identification of cancer-specific metabolic dependencies and the design of targeted delivery systems that preferentially accumulate in tumors. Understanding the differential regulation of lipid metabolism in cancer versus normal cells is essential for the development of specific and safe therapeutic agents. Combination therapies offer a promising approach to overcoming the limitations of single-agent treatments. By combining lipid metabolism inhibitors with other therapeutic agents, such as chemotherapy, immunotherapy, or targeted therapies, it is possible to enhance anti-tumor efficacy and overcome resistance mechanisms. Clinical trials are essential to evaluate the safety and effectiveness of these combination strategies. For instance, combining FASN inhibitors with immune checkpoint inhibitors could potentially improve immune responses against tumors by disrupting the metabolic adaptations that facilitate immune evasion (Luby and Alves-Guerra, 2021). Ongoing and future clinical trials will provide critical insights into the therapeutic potential and optimal use of lipid-targeting agents in cancer treatment. Targeting lipid droplets and lipid metabolism in cancer represents a promising therapeutic strategy with the potential to disrupt critical metabolic pathways in cancer cells (Fu *et al*., 2021). The development of specific inhibitors, advanced drug delivery systems, and combination therapies offers new avenues for improving cancer treatment outcomes. Addressing the challenges of specificity and toxicity through targeted approaches and rigorous clinical evaluation will be key to realizing the full potential of lipid-targeting therapies in cancer.

2.5. Future Directions and Research Opportunities

Despite significant advancements in understanding lipid droplet (LD) biology, many questions remain unanswered. One critical area of inquiry is the precise mechanisms governing LD biogenesis, particularly the roles of various proteins and signaling pathways in the initial stages of LD formation (Sanchez and Ganfornina, 2021). Additionally, the specific functions of LDs in different types of cells and tissues, beyond their role in energy storage, are not fully elucidated. For example, the interplay between LDs and cellular stress responses, such as autophagy and oxidative stress, requires further investigation. Understanding the diversity of LD functions and their regulation in various physiological and pathological contexts is essential for developing targeted therapies.

Technological advancements in imaging and analytical techniques are poised to significantly enhance our understanding of LD biology (Hickey *et al*., 2021). High-resolution microscopy methods, such as super-resolution microscopy and cryo-electron microscopy, allow for detailed visualization of LD structure and dynamics at the nanoscale level. These techniques can reveal insights into the spatial organization and interactions of LDs with other cellular organelles. Furthermore, advances in mass spectrometry-based lipidomics enable comprehensive profiling of LD-associated lipids and proteins, providing a deeper understanding of their composition and functional roles. Single-

cell imaging and omics approaches can also uncover cell-to-cell variability in LD biology, shedding light on heterogeneity within tissues and tumors.

Integrating LD studies with omics approaches offers a holistic view of LD biology and its implications in health and disease. Combining lipidomics with genomics, transcriptomics, and proteomics can identify key regulatory networks and pathways involved in LD metabolism and function (Blencowe *et al*., 2021). For instance, integrating lipidomics data with gene expression profiles can reveal how genetic and epigenetic alterations affect LD dynamics in cancer cells. Similarly, proteomics can identify LD-associated proteins and their post-translational modifications, providing insights into the regulation of LD biogenesis and degradation. Multi-omics approaches can also help identify biomarkers for LD-related diseases and potential therapeutic targets, paving the way for personalized medicine.

Translational research is crucial for bridging the gap between basic LD biology and clinical applications. Understanding the role of LDs in various diseases, including cancer, metabolic disorders, and neurodegenerative diseases, can inform the development of targeted therapies. For example, identifying specific LD-associated proteins or pathways that are dysregulated in cancer can lead to the design of novel inhibitors or modulators. Clinical trials are needed to evaluate the safety and efficacy of these therapeutic agents in patients. Furthermore, LD-related biomarkers could be developed for early diagnosis, prognosis, and monitoring of treatment responses in various diseases (Pinto e Vairo *et al*., 2020). Integrating LD studies with clinical research can ultimately improve patient outcomes and advance precision medicine.

Future research should focus on elucidating the molecular mechanisms of LD regulation and their diverse functions in different cell types and diseases. Leveraging advances in imaging and analytical techniques will provide detailed insights into LD biology at the cellular and molecular levels (Watson *et al*., 2022). Integrating omics approaches will help uncover comprehensive regulatory networks and identify potential therapeutic targets. Translational research efforts should prioritize the development and clinical evaluation of LD-targeting therapies, as well as the identification of LD-related biomarkers for precision medicine (Ding *et al*., 2023). By addressing these research opportunities, we can enhance our understanding of LD biology and its implications for human health, ultimately leading to innovative treatments and improved clinical outcomes.

3. Conclusion

Lipid droplets (LDs) play a multifaceted role in cancer biology, impacting tumor progression through mechanisms such as metastasis and angiogenesis. They serve as crucial energy reservoirs and modulators of cellular metabolism, influencing the survival and proliferation of cancer cells. Advances in understanding LD formation, regulation, and interaction with the tumor microenvironment have highlighted their significance in supporting cancer cell metabolic demands, protecting against oxidative stress, and aiding immune evasion. Moreover, targeting LD metabolism presents promising therapeutic strategies, with potential agents ranging from small molecules to natural compounds and novel drug delivery systems.

The insights into LD dynamics and their regulatory mechanisms have profound implications for cancer biology and treatment. By elucidating the roles of LDs in cancer cell metabolism, metastasis, and angiogenesis, researchers can identify novel therapeutic targets and develop strategies to disrupt these processes. Targeting lipid metabolism in cancer cells can potentially impair their growth and metastatic potential, offering a new avenue for cancer therapy. Additionally, the integration of LD studies with omics approaches can lead to the identification of biomarkers for early diagnosis and treatment monitoring, enhancing personalized medicine approaches.

Despite significant progress, many aspects of LD biology remain unexplored. A call to action for continued research and collaboration is essential to fully unravel the complexities of LD function and regulation in cancer and other diseases. Advancing imaging and analytical techniques, coupled with multi-omics approaches, will provide deeper insights into LD dynamics and their roles in various pathological contexts. Collaborative efforts between basic researchers, clinicians, and pharmaceutical developers are crucial to translate these findings into effective therapies and clinical applications. By fostering interdisciplinary collaboration and sustained research efforts, we can harness the potential of targeting LDs to improve cancer treatment outcomes and advance our understanding of cellular metabolism in disease.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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