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Lipid Droplet Accumulation in Cancer: Targeting Lipophagy as a Therapeutic Strategy

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ABSTRACT

Lipid droplets (LDs) are dynamic organelles involved in cellular lipid storage, trafficking, and metabolic regulation. Recent studies highlight their altered accumulation in various cancer types, correlating with tumorigenesis, progression, and metastasis. The accumulation of LDs in cancer cells contributes to oncogenic lipid metabolism, which promotes cell proliferation, resistance to apoptosis, and adaptation to tumor microenvironment stresses, including hypoxia and nutrient deprivation. Lipophagy, a specialized form of autophagy responsible for the selective degradation of LDs, has emerged as a potential target for cancer therapy due to its role in modulating cellular lipid reserves and maintaining energy balance. This review explores the molecular mechanisms underlying LD accumulation in cancer and the regulation of lipophagy, examining the implications of lipid storage modulation on cancer cell survival and metabolic adaptation. We also discuss therapeutic strategies aimed at targeting lipophagy pathways, such as inhibition of key lipophagic regulators and combination approaches with established chemotherapies, to improve cancer treatment efficacy. Understanding the intersection of lipid metabolism, LD biogenesis, and lipophagy may offer novel therapeutic avenues, providing more personalized and effective interventions for lipid-metabolism-driven cancers.

Keywords: Lipid droplets**;** Lipophagy**;** Cancer metabolism**;** Autophagy**;** Lipid metabolism**;** Therapeutic targets in cancer**;** Lipid accumulation in tumors

INTRODUCTION

Lipid droplets (LDs) are cellular organelles involved in lipid storage and metabolism, traditionally viewed as inert lipid reservoirs but now recognized as dynamic entities integral to various cellular processes. In cancer, metabolic reprogramming is a hallmark that supports rapid cell growth and adaptation to hostile microenvironments. Notably, cancer cells exhibit heightened LD accumulation, serving as both an energy source and a buffer against metabolic stress[1–3]. Furthermore, accumulating evidence suggests that LDs influence signaling pathways related to cancer progression, aggressiveness, and resistance to therapy. Lipophagy, a selective form of autophagy, enables cells to regulate lipid turnover by degrading LDs through lysosomal pathways[4]. Given the metabolic flexibility it imparts, lipophagy has garnered significant interest in oncology. Targeting lipophagy may offer new therapeutic strategies to disrupt cancer cells' metabolic adaptations, potentially overcoming resistance mechanisms and improving outcomes. This review examines the regulatory mechanisms driving LD accumulation in cancer, the role of lipophagy in lipid turnover, and the potential of targeting lipophagy in cancer therapy[5].

Lipid droplets

Lipid droplets (LDs) are dynamic organelles that play a crucial role in maintaining cellular functions and supporting tumor growth, survival, and metastasis. In cancer, the upregulation of LDs is observed across many tumor types and is closely linked to metabolic reprogramming essential for tumor growth, survival, and metastasis. LD accumulation is often driven by increased lipid uptake and synthesis in cancer cells, a phenomenon tied to their unique metabolic demands[6]. LDs in cancer cells support several oncogenic processes through various mechanisms. They serve as energy reservoirs, buffering oxidative stress, modulating signaling pathways, and supporting metabolic flexibility. Cancer cells often face fluctuating nutrient availability in the tumor microenvironment, which LDs act as accessible reservoirs of energy-dense

molecules. When needed, these lipids are hydrolyzed by lipases to generate free fatty acids, which enter β-oxidation, producing ATP and other metabolic intermediates[7]. This process not only meets the high energy demands of rapidly proliferating cancer cells but also provides building blocks for membrane synthesis and other biosynthetic needs critical for cell division.

LDs also help mitigate oxidative stress due to high rates of reactive oxygen species (ROS) production, which is exacerbated under hypoxic and nutrient-deprived conditions within the tumor microenvironment. They sequester excess free fatty acids, which are highly susceptible to peroxidation and can be cytotoxic in free form, and serve as a platform for antioxidant enzymes, contributing to ROS detoxification and enhancing cancer cell resilience against oxidative damage[8]. Targeting LDs in cancer presents a promising target for cancer therapy, with strategies aimed at disrupting LD formation, inhibiting lipid storage, or promoting lipotoxicity being under investigation. Targeting enzymes involved in lipid synthesis or LD-associated proteins could reduce LD accumulation, compromising the tumor's energy reserves and resilience to oxidative stress. Drugs that induce lipid peroxidation, such as ferroptosis inducers, are being explored for their ability to overcome therapy resistance by exploiting the cancer cells' dependency on LDs for oxidative stress protection [9].

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Molecular Mechanisms Driving Lipid Droplet Biogenesis in Cancer

Lipid droplet (LD) formation is a finely tuned process driven primarily by the activity of lipogenic enzymes, such as diacylglycerol O-acyltransferase 1 (DGAT1) and stearoyl-CoA desaturase (SCD). These enzymes are central to the synthesis and storage of neutral lipids within the cellular environment. DGAT1 catalyzes the final step of triglyceride synthesis, converting diacylglycerol into triacylglycerol, while SCD introduces a double bond into saturated fatty acyl-CoAs, forming monounsaturated fatty acids that are crucial components of triglycerides and phospholipids. Together, these enzymes contribute to the formation and expansion of LDs, which serve as reservoirs of stored lipids[4, 15].

In cancer cells, there is an upregulation of these enzymes, accompanied by increased uptake of exogenous fatty acids, which is facilitated by membrane fatty acid transporters such as CD36 and fatty acid-binding proteins (FABPs). This combination of enhanced lipogenesis and fatty acid uptake leads to a substantial accumulation of LDs within the cytoplasm. Elevated LD formation in cancer cells supports rapid growth and survival by providing essential lipids for membrane synthesis, energy production, and signaling molecules[15].

Oncogenic signaling pathways, particularly the PI3K-AKT and AMPK-mTOR axes, further drive this lipogenic shift by upregulating genes involved in lipid synthesis. The PI3K-AKT pathway enhances the expression of key lipogenic transcription factors, such as sterol regulatory element-binding protein 1 (SREBP1), which subsequently activates downstream genes involved in fatty acid and triglyceride synthesis. Concurrently, the AMPK-mTOR pathway plays a dual role, responding to energy availability and cellular stress while promoting lipogenic gene expression under certain conditions. This coordinated upregulation of lipogenic pathways in cancer cells fuels LD biogenesis and expands intracellular lipid reserves, creating a metabolic advantage that supports tumor growth, resistance to apoptosis, and adaptation to the tumor microenvironment[16].

Lipophagy: A Specialized Autophagic Process

Mechanism of Lipophagy

Lipophagy involves the selective degradation of LDs via autophagic machinery. This process begins with the sequestration of LDs into autophagosomes, which then fuse with lysosomes for lipid degradation. Key proteins such as autophagy-related gene 7 (ATG7) and microtubule-associated protein 1A/1B-light chain 3 (LC3) are essential for autophagosome formation and lipid degradation [17].

Regulation of Lipophagy in Cancer

Lipophagy regulation in cancer is influenced by metabolic stressors and signaling pathways responsive to nutrient availability. For instance, AMP-activated protein kinase (AMPK) activation in low-nutrient conditions enhances lipophagy, allowing cancer cells to mobilize lipid stores. Conversely, mTOR signaling can inhibit autophagy, reducing lipid turnover. The balance between these pathways determines cancer cells' ability to adapt to metabolic challenges, influencing survival and progression[17, 18].

Implications of Lipid Droplet Accumulation and Lipophagy in Cancer

Lipid Droplets and Cancer Cell Survival: In tumors, LDs facilitate cell survival by providing a continuous energy supply and mediating adaptive responses to metabolic stress. Increased LD accumulation is often associated with aggressive phenotypes, chemotherapy resistance, and poor prognosis [18, 19].

Lipophagy as a Modulator of Metabolic Plasticity: Lipophagy enables cancer cells to maintain metabolic flexibility, allowing dynamic adaptation to nutrient fluctuations. By modulating lipid turnover, lipophagy can sustain ATP production, support biosynthetic pathways, and buffer against lipotoxic stress. However, excessive lipophagy can also lead to lipid depletion, sensitizing cells to apoptosis. Thus, targeting lipophagy holds therapeutic potential, particularly for tumors with high lipid metabolic reliance.

Targeting Lipophagy as a Therapeutic Strategy

Pharmacological Inhibition of Lipophagy

Pharmacological inhibitors targeting lipophagy-associated proteins like ATG7 or lysosomal function could disrupt LD turnover in cancer cells, depleting lipid reserves essential for survival. For instance, chloroquine and hydroxychloroquine have been tested in clinical trials to inhibit autophagic processes and show potential for combinatorial use with chemotherapy.

Dual Targeting Approaches

Combining lipophagy inhibitors with metabolic inhibitors (e.g., fatty acid synthesis inhibitors) may enhance therapeutic efficacy by inducing metabolic stress, promoting cancer cell apoptosis. Additionally, targeting LD biogenesis alongside lipophagy inhibition could further compromise cancer cell metabolic resilience, offering a synergistic approach to cancer treatment.

Future Therapeutic Perspectives

Future studies should explore selective lipophagy modulation in cancer, developing inhibitors that target cancer-specific autophagic adaptations. Nanotechnology-based delivery systems may enhance therapeutic precision, ensuring that lipophagy inhibitors target tumor cells while minimizing off-target effects. Investigating the interplay between lipophagy and tumor immunity could also uncover new approaches for integrating immunotherapy with metabolic interventions.

Challenges and Future Directions

While targeting lipophagy presents a promising approach, challenges such as cancer-specific autophagic dependencies and potential off-target effects remain. Additionally, understanding inter-tumor heterogeneity in lipophagic regulation and lipid metabolism will be crucial for developing personalized therapies. Advances in lipidomics and autophagy research will likely yield new insights, aiding in the development of selective lipophagy modulators and combination therapies tailored to individual metabolic profiles.

CONCLUSION

Lipid droplet accumulation and lipophagy play pivotal roles in cancer cell metabolism, adaptation, and survival. By enabling dynamic regulation of lipid storage and turnover, lipophagy provides metabolic flexibility essential for tumor progression. Targeting lipophagy holds potential as a therapeutic strategy, disrupting lipid metabolism in cancer cells and sensitizing them to existing treatments. Further research is necessary to fully elucidate lipophagy's role in cancer and translate these insights into clinical therapies that capitalize on the metabolic vulnerabilities of lipid-driven cancers.

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