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Intervening in Lipid Droplet-Mediated Metastasis: Recent Advances and Approaches

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Abstract
Lipid droplets (LDs) have emerged as pivotal organelles implicated in cancer metastasis, offering novel therapeutic targets for intervention. This review comprehensively examines the mechanisms by which LDs contribute to metastasis, focusing on their biogenesis, interaction with metastatic pathways, and influence on the tumor microenvironment. Recent advances in LD-targeted therapies, including pharmacological interventions, genetic and molecular approaches, and nanotechnology-based delivery systems, are discussed. Challenges such as biological complexity, therapeutic delivery barriers, and potential resistance mechanisms are also addressed. Future directions highlight emerging technologies, opportunities for translational research, and the importance of interdisciplinary collaborations in advancing LD research. By elucidating these aspects, this review aims to contribute to the development of effective strategies to disrupt LD-mediated metastasis and improve cancer treatment outcomes.

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Introduction

Cancer metastasis remains a formidable challenge in oncology, accounting for the majority of cancer-related deaths. The metastatic process involves complex steps where cancer cells detach from the primary tumor, invade surrounding tissues, enter the bloodstream or lymphatic system, and colonize distant organs (Cheng *et al*., 2022; Johariya, Joshi, Malviya, & Malviya, 2024). This multi-stage journey is influenced by various cellular and molecular mechanisms that enable cancer cells to survive and proliferate in foreign microenvironments. Understanding these mechanisms is crucial for developing effective interventions to prevent or mitigate metastasis.

One of the emerging areas of interest in cancer research is the role of lipid droplets (LDs) in metastasis. Lipid droplets are dynamic organelles that store neutral lipids, primarily triglycerides and cholesterol esters, and are traditionally known for their role in energy metabolism. However, recent studies have revealed that LDs are not merely inert storage sites but play active roles in various cellular processes, including signaling, membrane trafficking, and the regulation of lipid metabolism. In the context of cancer, LDs have been implicated in promoting tumor progression and metastasis through several mechanisms (Antunes, Cruz, Barbosa, Bonifácio, & Pinto, 2022; Bombarda-Rocha *et al*., 2023).

Lipid droplets contribute to cancer metastasis by providing a readily accessible energy source that supports the high metabolic demands of rapidly proliferating cancer cells. During metastasis, cancer cells often encounter hostile environments with limited nutrient availability.

LDs can be mobilized to release fatty acids through lipolysis, supplying energy and building blocks for membrane synthesis and signaling molecules that facilitate cell survival, migration, and invasion. Additionally, LDs have been shown to interact with key signaling pathways that drive metastasis, such as the PI3K/AKT/mTOR pathway, enhancing the metastatic potential of cancer cells (Cruz, Barreto, Fazolini, Viola, & Bozza, 2020; Danielli, Perne, Jarc Jovičić, & Petan, 2023).Furthermore, lipid droplets play a critical role in modulating the tumor microenvironment, which is crucial for successful metastasis. The tumor microenvironment comprises various cellular and non-cellular components, including immune cells, fibroblasts, extracellular matrix, and signaling molecules. LDs can influence the tumor microenvironment by affecting the secretion of pro-inflammatory cytokines and chemokines, promoting an immunosuppressive environment that supports tumor growth and dissemination. Moreover, LDs have been implicated in forming pre-metastatic niches, which are conducive environments in distant organs that facilitate colonizing and developing metastatic cancer cells (Deng *et al*., 2021; Jin, Tan, Wu, & Ren, 2023).

Given the multifaceted roles of lipid droplets in cancer metastasis, targeting these organelles presents a novel therapeutic strategy. Traditional cancer therapies primarily focus on targeting proliferating cancer cells; however, these approaches often fall short of addressing the metabolic adaptations and survival mechanisms that support metastasis. By intervening in lipid droplet-mediated pathways, it may be possible to disrupt the energy supply and signaling networks that cancer cells rely on for metastasis, thereby improving therapeutic outcomes (Ischebeck, Krawczyk, Mullen, Dyer, & Chapman, 2020; Li, 2020).

Targeting lipid droplets in cancer therapy can be approached through various strategies. Pharmacological interventions that inhibit lipid droplet formation or promote their degradation have shown promise in preclinical studies. For instance, inhibitors of enzymes involved in lipid droplet biogenesis, such as DGAT1 and ACSL3, have been demonstrated to reduce lipid droplet accumulation and impair metastatic progression in cancer models. Additionally, compounds that enhance lipophagy, a process where lipid droplets are degraded by autophagy, have been explored as potential anti-metastatic agents (Edwards & Mohiuddin, 2020; Kloska, Węsierska, Malinowska, Gabig-Cimińska, & Jakóbkiewicz-Banecka, 2020; Robichaud *et al*., 2021). By promoting the breakdown of lipid droplets, these compounds can deplete the energy reserves of cancer cells, making them more susceptible to other therapeutic interventions.Another promising approach involves targeting the molecular interactions between lipid droplets and metastatic signaling pathways. For example, inhibiting the PI3K/AKT/mTOR pathway, often hyperactivated in metastatic cancer cells and associated with lipid droplet accumulation, can attenuate metastasis. Combining such targeted therapies with existing treatments may provide synergistic effects, enhancing the overall efficacy of cancer therapy (Ahmed *et al*., 2022; Devereux, Bayliss, Keenan, Montgomery, & Watt, 2023; Icard *et al*., 2021).

This research paper aims to explore and elucidate the recent advances and approaches in intervening in lipid droplet-mediated metastasis. The paper aims to:

- Provide a comprehensive overview of how lipid droplets contribute to cancer metastasis, detailing the mechanisms by which they support tumor progression and dissemination.
- Summarize the latest research findings and technological developments in targeting lipid droplets for therapeutic intervention, including pharmacological, genetic, molecular, and nanotechnological approaches.
- Discuss the biological, delivery, and resistance-related challenges associated with targeting lipid droplets in metastatic cancer therapy.
- Suggest potential future research directions, emerging technologies, and collaborative efforts that could enhance the understanding and treatment of lipid droplet-mediated metastasis.

In summary, lipid droplets are emerging as critical players in cancer metastasis, offering new avenues for therapeutic intervention. By understanding the complex roles of lipid droplets in supporting the metastatic process, researchers can develop innovative strategies to disrupt these pathways and improve the management of metastatic cancer. As research in this field progresses, it holds the potential to transform the landscape of cancer therapy, offering hope for more effective treatments against one of the deadliest aspects of cancer.

1. Mechanisms of Lipid Droplet-Mediated Metastasis

The metastasis of cancer cells is a complex and multi-step process that involves the spread of cancer cells from the primary tumor site to distant organs, leading to the formation of secondary tumors. Lipid droplets (LDs) have emerged as significant players, influencing various aspects of cancer cell behavior and the tumor microenvironment. Understanding the mechanisms by which LDs mediate metastasis is crucial for developing targeted therapies to combat metastatic cancer.

1.1. Lipid Droplet Biogenesis and Dynamics

Lipid droplets are intracellular organelles that store neutral lipids such as triglycerides and cholesterol esters. They are formed in the endoplasmic reticulum (ER) when excess lipids are synthesized or taken up by the cell. The biogenesis of LDs begins with the accumulation of neutral lipids between the leaflets of the ER membrane, leading to the budding of these lipid-rich domains into the cytoplasm, encapsulated by a phospholipid monolayer. Several key proteins are involved in LD formation, including diacylglycerol O-acyltransferase (DGAT) enzymes that catalyze the final step in triglyceride synthesis, and perilipins that coat the surface of LDs, protecting them from premature degradation (Bombarda-Rocha *et al*., 2023; Bononi, Tuccinardi, Rizzolio, & Granchi, 2021).

The regulation of LD dynamics is tightly controlled and involves a balance between lipogenesis (the synthesis of new lipids) and lipolysis (the breakdown of stored lipids). Enzymes such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) play crucial roles in lipolysis, releasing fatty acids from LDs for cellular energy production and other metabolic processes. In cancer cells, alterations in lipid metabolism often lead to increased LD accumulation, providing a reservoir of energy and lipid signaling molecules that can be mobilized to support rapid cell proliferation and survival.

1.2. Interaction with Metastatic Pathways

Lipid droplets interact with several key signaling pathways

that drive metastasis. One of the primary pathways influenced by LDs is the PI3K/AKT/mTOR pathway, which is often dysregulated in cancer. This pathway promotes cell growth, survival, and motility, and its activation is associated with increased lipid synthesis and LD accumulation. By providing a source of lipids for membrane synthesis and signaling molecules, LDs can enhance the activity of the PI3K/AKT/mTOR pathway, thereby promoting metastatic behavior (Danielli *et al*., 2023; Fernández, Gomez de Cedron, & Ramirez de Molina, 2020).

Another critical interaction involves the hypoxia-inducible factor (HIF) pathway. Tumor hypoxia, a common feature of rapidly growing tumors, leads to the stabilization and activation of HIFs, which in turn upregulate genes involved in lipid metabolism and LD formation. Hypoxic conditions also drive angiogenesis and the expression of genes that promote cell invasion and metastasis. LDs support these processes by supplying energy and lipid mediators that facilitate the adaptive responses of cancer cells to hypoxia (Akman *et al*., 2021; Hapke & Haake, 2020).

Moreover, LDs are involved in the epithelial-mesenchymal transition (EMT), a process by which cancer cells acquire migratory and invasive properties. During EMT, changes in cellular metabolism, including increased lipid synthesis and LD formation, are essential for reprogramming cancer cells. LDs provide the necessary lipids for membrane remodeling and the production of signaling lipids such as lysophosphatidic acid (LPA), which can promote cell migration and invasion (Lee, Golinska, & Griffiths, 2021; Pan, Liu, Mou, & Cai, 2023).

1.3. Impact on Tumor Microenvironment

The tumor microenvironment (TME) is a complex and dynamic network of various cell types, extracellular matrix components, and signaling molecules that collectively influence tumor progression and metastasis. Lipid droplets significantly impact the TME by modulating the behavior of both cancer cells and stromal cells, such as immune cells and fibroblasts (El Hassouni *et al*., 2020; Han, 2021).

LDs contribute to the creation of a pro-tumorigenic microenvironment by affecting the secretion of cytokines and chemokines. For instance, cancer cells with high LD content can secrete pro-inflammatory cytokines that recruit immune cells, such as macrophages, to the tumor site. These tumor-associated macrophages (TAMs) often adopt an immunosuppressive phenotype that supports tumor growth and metastasis by producing growth factors and matrix-remodeling enzymes. LDs also provide fatty acids that TAMs use for energy, further enhancing their pro-tumorigenic functions. Additionally, LDs play a role in forming pre-metastatic niches, which are conducive environments in distant organs that facilitate the colonization and growth of metastatic cancer cells. Cancer cells can release extracellular vesicles (EVs) enriched with lipids and proteins that prime distant tissues to become receptive to metastatic cells. These EVs can modulate the local immune environment, promote angiogenesis, and alter the extracellular matrix, making it easier for circulating tumor cells to establish secondary tumors (Aquila *et al*., 2020; Liu, Zhao, Wu, Liu, & Liu, 2022; Mi, 2020).

LDs also interact with cancer-associated fibroblasts (CAFs) in the TME. CAFs support tumor growth and metastasis by remodeling the extracellular matrix and secreting growth factors. LDs can influence the lipid metabolism of CAFs, enhancing their ability to support tumor progression. For example, CAFs can take up fatty acids released from LDs in cancer cells, fueling their metabolic activities and contributing to a supportive TME (Fernández *et al*., 2020; Germain *et al*., 2020).

2. Recent Advances in Targeting Lipid Droplets

The understanding of lipid droplets (LDs) in cancer metastasis has significantly evolved, highlighting their potential as therapeutic targets. Researchers have developed various innovative approaches to target LDs, aiming to disrupt their formation and function, ultimately inhibiting cancer progression. This section delves into recent advances in pharmacological interventions, genetic and molecular approaches, and the application of nanotechnology in targeting LDs.

2.1. Pharmacological Interventions

Pharmacological strategies to target LDs focus on disrupting their biogenesis, mobilization, and the metabolic pathways that sustain them. One promising approach involves using inhibitors that target enzymes crucial for LD formation. Diacylglycerol O-acyltransferase (DGAT) enzymes, specifically DGAT1 and DGAT2, are key players in triglyceride synthesis, a major component of LDs. Inhibitors of these enzymes, such as A922500 (DGAT1 inhibitor) and PF-06424439 (DGAT2 inhibitor), have shown potential in reducing LD accumulation in cancer cells. By limiting LD formation, these inhibitors can decrease the energy reserves of cancer cells, making them more vulnerable to other treatments (Futatsugi *et al*., 2022; Gomes *et al*., 2021).

Another promising area of pharmacological intervention involves the inhibition of lipolysis, the process by which stored lipids in LDs are broken down into free fatty acids. Adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) are critical enzymes in this process. Inhibiting these enzymes can prevent cancer cells from accessing the energy stored in LDs. Research has shown that inhibitors of ATGL, such as Atglistatin, can reduce the availability of fatty acids necessary for the survival and proliferation of metastatic cancer cells (Bosc *et al*., 2021; Devereux *et al*., 2023).Additionally, compounds that induce lipophagy and the autophagic degradation of LDs have garnered interest. Lipophagy promotes the breakdown of LDs within lysosomes, reducing the lipid reserves of cancer cells. Agents that enhance lipophagy, such as the natural compound spermidine, have been explored for their potential to deplete LDs and inhibit cancer cell growth. By promoting the degradation of LDs, these compounds can impair the metabolic flexibility of cancer cells, hindering their ability to adapt to the energetic demands of metastasis (Fhu & Ali, 2020; Harwood, 2020).

2.2. Genetic and Molecular Approaches

Advances in genetic and molecular techniques have provided new avenues for targeting LDs in cancer therapy. Gene editing technologies, particularly CRISPR-Cas9, have been employed to disrupt genes involved in LD biogenesis and metabolism. For instance, knocking out genes encoding DGAT1 or DGAT2 in cancer cell lines has reduced LD accumulation and impaired cell proliferation. These genetic modifications highlight the critical role of LDs in supporting cancer cells' metabolic needs and underscore gene editing's potential as a therapeutic strategy (Thakur *et al*., 2020;

Wanniarachchi, 2023).

RNA interference (RNAi) is another powerful tool for targeting LD-related genes. Small interfering RNAs (siRNAs) can be designed to specifically degrade mRNA transcripts of key enzymes involved in LD formation and metabolism. For example, siRNAs targeting DGAT1, DGAT2, or ATGL can effectively reduce the expression of these enzymes, leading to decreased LD content in cancer cells. RNAi-based therapies offer a precise approach to disrupt the pathways that support LD-mediated metastasis. Moreover, molecular approaches such as the use of small molecule inhibitors targeting specific protein-protein interactions involved in LD dynamics have shown promise. For instance, targeting the interaction between perilipins (proteins that coat LDs and regulate their metabolism) and other metabolic enzymes can disrupt LD stability and function. Inhibitors that prevent these interactions can promote LD degradation and limit the availability of lipids necessary for cancer cell survival and metastasis (Bandesh, Masih, Bhattacharyya, & Bharadwaj, 2021; Sparmann & Vogel, 2023).

2.3. Nanotechnology and Lipid Droplets

Nanotechnology has emerged as a cutting-edge approach to deliver therapies targeting LDs with high precision and efficiency. Nanoparticles can be engineered to encapsulate drugs or genetic material, providing targeted delivery to cancer cells while minimizing off-target effects. This targeted delivery is particularly advantageous for therapies that aim to disrupt LDs, as it ensures that therapeutic agents reach the specific cellular compartments where LDs are located (McClements & Öztürk, 2021; Tu, Gao, Sun, Shi, & Huang, 2022).

One example of nanotechnology application is the use of liposomes, which are lipid-based nanoparticles capable of encapsulating hydrophobic drugs. Liposomes can be designed to carry inhibitors of LD formation or metabolism, enhancing their delivery to cancer cells. By incorporating targeting ligands on their surface, liposomes can selectively bind to cancer cells, facilitating the localized release of therapeutic agents. This targeted approach increases the efficacy of LD-targeting drugs while reducing systemic toxicity (Antunes *et al*., 2022).

Another innovative application involves the use of nanocarriers for RNAi delivery. Nanoparticles can protect siRNAs from degradation in the bloodstream and facilitate their uptake by cancer cells. Lipid-based nanoparticles, such as lipid nanoparticles (LNPs), have successfully delivered siRNAs targeting LD-related genes in preclinical models. These LNPs can efficiently deliver siRNAs to cancer cells, silencing key genes involved in LD biogenesis and metabolism, and thereby inhibiting tumor growth and metastasis. Moreover, gold nanoparticles (AuNPs) have been explored for their potential to disrupt LDs through photothermal therapy. AuNPs can be designed to accumulate in cancer cells and, upon exposure to near-infrared light, generate heat that induces LD degradation. This localized thermal effect can reduce LD content and impair the metabolic adaptability of cancer cells, offering a novel approach to target LDs in metastatic cancer (Zhao *et al*., 2022).

3. Challenges and Limitations in Targeting Lipid Droplets

Despite the promising advances in targeting lipid droplets (LDs) for cancer therapy, several challenges and limitations must be addressed to optimize their clinical utility. This paper explores the biological complexity of LDs, challenges in therapeutic delivery, and potential issues related to resistance and side effects.

3.1. Biological Complexity

The biology of lipid droplets is inherently complex, posing challenges to understanding their precise roles in cancer biology and developing effective therapeutic strategies. LDs are dynamic organelles that undergo constant size, number, and composition changes in response to cellular metabolic status and environmental cues. The regulation of LD biogenesis, lipolysis, and lipid trafficking involves a network of proteins and lipids, many of which have multifaceted roles in cellular physiology beyond lipid storage. Moreover, LDs interact intricately with various cellular pathways involved in cancer progression and metastasis. Their roles extend beyond energy storage to include signaling molecule production, membrane dynamics, and modulation of cellular stress responses. Deciphering these complex interactions and their implications for cancer therapy requires comprehensive experimental approaches and interdisciplinary collaborations (Cruz *et al*., 2020; Danielli *et al*., 2023).

3.2. Therapeutic Delivery

Effectively delivering LD-targeted therapies to metastatic sites presents significant challenges due to the unique characteristics of LDs and the tumor microenvironment. LDs are heterogeneous in size and distribution within cancer cells, complicating targeted drug delivery strategies. Therapeutic agents must penetrate cell membranes and accumulate specifically within LD-rich compartments to exert their intended effects.

Furthermore, the tumor microenvironment poses additional barriers to drug delivery. Tumors exhibit abnormal vasculature, increased interstitial pressure, and altered pH conditions, which can hinder the distribution and efficacy of therapeutic agents targeting LDs. Nanotechnology-based approaches, such as liposomes and nanoparticles, have shown promise in enhancing drug delivery to cancer cells; however, optimizing their design and ensuring sufficient drug release at LD sites remain ongoing challenges.

3.3. Resistance and Side Effects

Resistance to LD-targeting therapies and potential side effects represent critical concerns in clinical applications. Cancer cells can develop mechanisms to bypass LD inhibition by upregulating alternative metabolic pathways or acquiring mutations that confer resistance to therapeutic agents. For example, tumors may switch to alternative lipid sources or enhance lipogenesis pathways to compensate for reduced LD availability. Understanding these adaptive mechanisms and developing combination therapies targeting multiple metabolic vulnerabilities are essential strategies for overcoming resistance (Vasseur & Guillaumond, 2022).

Moreover, LD-targeting therapies may exhibit unintended side effects due to their impact on normal cellular processes. LDs play essential roles in cellular homeostasis beyond cancer metabolism, including hormone secretion, membrane trafficking, and stress responses. Disrupting LD function

indiscriminately could potentially affect non-cancerous cells and tissues, leading to systemic toxicity and adverse effects. Careful consideration of dosage, administration schedules, and patient-specific factors is crucial to minimize side effects while maximizing therapeutic efficacy. Preclinical and clinical studies are essential to assess the safety profile of LD-targeting therapies and identify biomarkers that predict treatment response and toxicity (Miao, Zang, Cui, & Zhang, 2020; Zhang, Su, Xu, Zhang, & Guan, 2022).

In conclusion, while targeting lipid droplets holds promise as a novel approach to inhibit cancer metastasis, several challenges and limitations must be addressed to translate these strategies into clinical practice effectively. The biological complexity of LDs necessitates a comprehensive understanding of their roles in cancer biology and metastasis. Overcoming challenges in therapeutic delivery, including optimizing drug formulations and navigating the tumor microenvironment, is essential for achieving targeted and effective LD inhibition. Additionally, addressing resistance mechanisms and minimizing potential side effects are critical for ensuring safety and long-term efficacy of LD-targeting therapies. Researchers, clinicians, and industry stakeholders must collaborate to overcome these challenges and advance LD-targeted strategies toward clinical applications. By addressing these challenges with innovative approaches and rigorous scientific investigation, the field holds promise for transforming cancer therapy and improving outcomes for patients with metastatic disease.

4. Future Directions and Opportunities in Lipid Droplet Research

The future of lipid droplet (LD) research holds promising avenues that could revolutionize cancer therapy and our understanding of cellular metabolism. This paper explores emerging technologies, opportunities for translational research, and the importance of collaborative efforts in advancing LD research.

4.1. Emerging Technologies

Advancements in technology offer new tools and approaches to deepen our understanding of LD biology and develop targeted therapies. High-resolution imaging techniques, such as super-resolution microscopy and live-cell imaging, enable researchers to visualize LD dynamics in real-time and study their interactions with cellular components. These technologies provide valuable insights into LD formation, metabolism, and their roles in cancer progression.

Furthermore, omics technologies, including lipidomics and proteomics, allow comprehensive profiling of LD composition and protein interactions. Integrating multi-omics data provides a holistic view of LD function in cancer cells and identifies potential therapeutic targets. Emerging techniques such as single-cell analysis and spatial transcriptomics offer opportunities to dissect heterogeneity in LD distribution within tumors and understand its implications for metastasis.

Nanotechnology continues to drive innovation in LD-targeted therapies. Advanced nanoparticle platforms, such as multifunctional liposomes and lipid-based nanoparticles, enhance drug delivery specificity to LD-rich cancer cells while minimizing systemic toxicity. Additionally, nanoscale imaging probes enable non-invasive monitoring of LD dynamics *in vivo*, facilitating early detection and assessment of treatment responses.

4.2. Translational Research

Translating basic research findings into clinical applications is crucial for realizing the therapeutic potential of LD-targeting strategies. Preclinical studies have demonstrated the efficacy of LD inhibitors and modulators in suppressing tumor growth and metastasis. Clinical trials are needed to validate these findings and evaluate the safety and effectiveness of LD-targeted therapies in patients.

Personalized medicine approaches offer opportunities to tailor LD-targeting therapies based on individual tumor characteristics and metabolic profiles. Biomarker discovery and molecular profiling technologies enable the stratification of patients likely to benefit from LD inhibition. Integrating clinical data with experimental models facilitates identifying predictive biomarkers and optimizing treatment strategies. Moreover, combination therapies that target LDs in conjunction with conventional treatments, such as chemotherapy and immunotherapy, hold promise for synergistic effects and overcoming treatment resistance. Collaborative efforts between academia, industry, and healthcare providers are essential for designing and conducting robust clinical trials validating LD-targeting therapies and translating research findings into clinical practice.

4.3. Collaborative Efforts

Interdisciplinary collaborations are pivotal in advancing LD research and addressing complex challenges. Integration of expertise from oncologists, biochemists, computational biologists, and engineers accelerates innovation in LD-targeted therapies. Collaborative networks facilitate data sharing, standardization of experimental protocols, and the development of novel technologies.

Furthermore, partnerships with pharmaceutical companies and regulatory agencies are essential for navigating the drug development pipeline and obtaining regulatory approval for LD-targeting therapies. Industry collaborations facilitate nanomedicines' scale-up production, drug formulation optimization, and innovative LD inhibitors' commercialization. International consortia and research networks promote global collaboration in LD research, fostering knowledge exchange and accelerating scientific discoveries. Shared resources, such as databases of LD-associated proteins and therapeutic targets, enhance research reproducibility and facilitate the development of next-generation LD-targeting therapies.

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