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Addressing Lipid Droplet-Mediated Stress Responses in Cancer Cells

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Abstract

Lipid droplets (LDs) play crucial roles in cellular metabolism and stress responses, particularly in cancer cells, contributing significantly to survival, growth, and therapeutic resistance. This review explores the multifaceted involvement of LDs in cancer biology, focusing on their biogenesis, molecular regulation, and impact on cellular metabolism under stress conditions. LDs are dynamic organelles that store and mobilize lipids, essential for energy homeostasis and membrane synthesis in rapidly proliferating cancer cells. Mechanistically, LD formation is regulated by signaling pathways such as mTOR and AMPK, which integrate metabolic cues and stress signals to modulate lipid metabolism. Interactions between LDs and other organelles, including mitochondria and the endoplasmic reticulum, further influence cellular metabolism and stress responses in cancer. Importantly, LD-mediated stress adaptations enable cancer cells to survive hostile tumor microenvironments characterized by oxidative stress, hypoxia, and nutrient deprivation. These adaptations contribute to therapeutic resistance and disease progression, highlighting LDs as potential targets for novel cancer therapies. Future research should focus on elucidating specific molecular mechanisms governing LD dynamics in cancer, exploring their heterogeneity within tumors, and leveraging interdisciplinary approaches to translate findings into clinical applications.

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1. Introduction

1.1. Background and Significance

Cancer remains one of the most formidable challenges in modern medicine, characterized by its complex pathophysiology and the diverse mechanisms by which it evades therapeutic interventions. One such mechanism involves lipid droplets, cellular organelles traditionally associated with energy storage in the form of neutral lipids (Bombarda-Rocha *et al.*, 2023; Bosch, Parton, & Pol, 2020). However, emerging research indicates lipid droplets play a more dynamic role, particularly in cellular stress responses and metabolic reprogramming in cancer cells. Understanding the multifaceted roles of lipid droplets in cancer can open new avenues for therapeutic interventions.

Lipid droplets are ubiquitous in eukaryotic cells, where they serve as reservoirs for neutral lipids, such as triglycerides and sterol esters, surrounded by a phospholipid monolayer. These organelles regulate lipid metabolism, energy homeostasis, and membrane trafficking (Cruz, Barreto, Fazolini, Viola, & Bozza, 2020). Beyond their metabolic functions, lipid droplets have been implicated in regulating various cellular processes, including protein storage and degradation, signaling pathways, and the cellular stress response. In cancer cells, lipid droplets are not merely passive storage sites but active participants in cellular adaptation to the tumor microenvironment (Danielli, Perne, Jarc Jovičić, & Petan, 2023).

1.2. Overview of Lipid Droplets and Their Role in Cellular Metabolism

Lipid droplets play a crucial role in cellular metabolism by managing the storage and release of energy-rich lipids. Under conditions of nutrient excess, cells synthesize and store lipids within these droplets. Conversely, lipids are mobilized from the droplets during nutrient scarcity and metabolized to meet the cell's energy demands. This dynamic storage and mobilization mechanism is vital for cellular energy balance and metabolic flexibility (Y. Li, 2020; Luo *et al.*, 2022). Moreover, lipid droplets interact closely with other organelles, such as mitochondria and the endoplasmic reticulum, to regulate lipid metabolism and cellular homeostasis. For instance, lipid droplets supply fatty acids for mitochondrial β -oxidation, a critical process for energy production. They also detoxify excess free fatty acids, which can be toxic at high concentrations. Through these interactions, lipid droplets help maintain cellular lipid equilibrium and prevent lipotoxicity, a condition often associated with metabolic disorders and cancer (Y. Li, 2020; Mashek, 2021).

1.3. Importance of Lipid Droplets in Cancer Biology

In cancer cells, the role of lipid droplets extends beyond mere energy storage to include modulation of various cellular stress responses. Tumor cells frequently encounter stress conditions such as hypoxia, nutrient deprivation, and oxidative stress, which challenge their survival and proliferation. Lipid droplets confer a survival advantage by serving as buffers against these stresses. For example, under hypoxic conditions, lipid droplets can sequester excess fatty acids, reducing oxidative stress and preventing damage to cellular components (Robichaud *et al.*, 2021; Seebacher, Zeigerer, Kory, & Krahmer, 2020).

Cancer cells often exhibit altered lipid metabolism, characterized by increased lipogenesis and accumulation of lipid droplets. This metabolic reprogramming supports rapid cell division and growth by providing essential lipids for membrane synthesis and signaling molecules for growth pathways. The increased lipid droplet content in cancer cells is also associated with resistance to chemotherapy and radiotherapy, further underscoring their importance in cancer biology (L. Wang, Liu, Miao, Pan, & Cao, 2021).

1.4. Research Objective

The primary objective of studying lipid droplet-mediated stress responses in cancer cells is to elucidate the mechanisms by which these organelles contribute to tumorigenesis and cancer progression. By understanding how lipid droplets regulate cellular stress responses and metabolic reprogramming, researchers aim to identify novel targets for cancer therapy.

One key area of interest is the signaling pathways that regulate lipid droplet formation and turnover in cancer cells. These pathways include well-known oncogenic and metabolic regulators such as mTOR, AMPK, and SREBP. Investigating how these pathways are modulated in response to stress can provide insights into the adaptive mechanisms employed by cancer cells. Additionally, the interaction between lipid droplets and other cellular structures, such as mitochondria and the endoplasmic reticulum, is critical for understanding the integrative role of lipid droplets in cellular homeostasis and stress adaptation.

1.5. Potential Impact on Cancer Treatment and Therapy

The implications of lipid droplet research in cancer therapy are profound. Targeting lipid droplet formation and function represents a novel therapeutic strategy that could complement existing treatments. For example, inhibiting key enzymes involved in lipid droplet biogenesis or promoting the degradation of lipid droplets could sensitize cancer cells to chemotherapy and radiotherapy by disrupting their metabolic flexibility and stress response mechanisms.

Furthermore, understanding lipid droplet-mediated signaling pathways can lead to the development of targeted therapies that specifically disrupt the survival mechanisms of cancer cells. For instance, small molecule inhibitors that block the interaction between lipid droplets and stress response proteins could impair the ability of cancer cells to withstand adverse conditions, thereby enhancing the efficacy of conventional treatments (Zhang *et al.*, 2021).

2. Lipid Droplets and Cellular Stress Responses

2.1. Lipid Droplet Formation and Function

Lipid droplets (LDs) are intracellular organelles that emerge from the endoplasmic reticulum (ER) (L. Wang *et al.*, 2021). Their biogenesis begins with the accumulation of neutral lipids, such as triglycerides and sterol esters, within the bilayer of the ER membrane. As these lipids accumulate, they coalesce to form a lens-shaped structure that eventually buds off, encased in a phospholipid monolayer derived from the ER membrane. The surface of lipid droplets is decorated with specific proteins, including perilipins, which play crucial roles in regulating their dynamics and interactions with other cellular organelles. This biogenesis process is tightly controlled and responds to the cellular lipid status, ensuring that cells can adapt to lipid availability and demand fluctuations (Cheng *et al.*, 2022).

Lipid droplets are central to cellular energy homeostasis. They serve as reservoirs for excess lipids, storing them during periods of nutrient surplus and releasing them during times of energy demand. This storage and mobilization process is critical for maintaining energy balance within the cell. In conditions of nutrient deprivation, lipids stored in lipid droplets are hydrolyzed by lipases, releasing fatty acids that are transported to mitochondria for β -oxidation, a process that generates ATP. By managing lipid reserves, lipid droplets help cells cope with metabolic stress and prevent lipotoxicity, which can occur when free fatty acids accumulate to toxic levels (Jin, Tan, Wu, & Ren, 2023).

2.2. Types of Cellular Stress

Cancer cells frequently encounter various forms of cellular stress, significantly impacting their survival and proliferation. Among these, oxidative, ER, and hypoxic stress are particularly notable. Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and the cell's ability to detoxify these harmful molecules. High levels of ROS can damage proteins, lipids, and DNA, leading to cellular dysfunction and death (Oakes, 2020). However, cancer cells often exhibit enhanced antioxidant defenses that allow them to manage elevated ROS levels and use them to promote cell signaling and proliferation. ER stress occurs when the protein-folding capacity of the endoplasmic reticulum is overwhelmed, leading to the accumulation of misfolded or unfolded proteins. This triggers the unfolded protein response (UPR), a cellular stress response to restore ER homeostasis. The UPR

can lead to cell survival or apoptosis, depending on the severity and duration of the stress. Cancer cells frequently exploit the UPR to adapt to the stressful tumor microenvironment and sustain their growth (Akman *et al.*, 2021).

Hypoxic stress results from inadequate oxygen supply, a common feature of solid tumors due to their rapid growth and poor vascularization. Hypoxia induces a range of adaptive responses in cancer cells, primarily mediated by hypoxia-inducible factors (HIFs). These responses include metabolic reprogramming, angiogenesis, and resistance to cell death, all of which contribute to tumor progression and therapy resistance (Sebestyén, Kopper, Dankó, & Tímár, 2021).

Oxidative, ER, and hypoxic stresses are integral to the cancer cell's survival and proliferation in a hostile environment. Oxidative stress can promote genetic mutations and genomic instability, driving cancer progression. ER stress and the UPR enable cancer cells to adapt to the high protein synthesis demand and hypoxic conditions commonly found in tumors. Through the activation of HIFs, hypoxia supports metabolic changes that favor anaerobic glycolysis (the Warburg effect), angiogenesis, and survival under low oxygen conditions. Together, these stress responses help cancer cells maintain their malignant phenotype and resist therapeutic interventions (Jacquet & Stéphanou, 2022; Jaworska *et al.*, 2023; Majidpoor & Mortezaee, 2021).

2.3. Lipid Droplets in Stress Response

Lipid droplets mediate cellular stress responses, particularly in cancer cells. Their involvement extends beyond lipid storage and metabolism, encompassing various mechanisms that help cells manage and survive under stress conditions.

Lipid droplets can sequester excess fatty acids, preventing their peroxidation and reducing oxidative stress. By storing these fatty acids, lipid droplets help maintain cellular redox balance and protect against ROS-induced damage. This protective mechanism is particularly important in cancer cells, which often exhibit high levels of oxidative stress. They interact closely with the ER, and their formation can be induced as part of the unfolded protein response. By buffering lipids that would otherwise accumulate in the ER membrane, lipid droplets help alleviate ER stress and restore ER function. This interaction is vital for cancer cells, which must manage high protein synthesis demand and associated stress.

Under hypoxic conditions, lipid droplets provide a ready source of fatty acids for β -oxidation, enabling continued ATP production despite limited oxygen availability. This energy supply is critical for cancer cell survival and proliferation in poorly vascularized tumor regions. Lipid droplets serve as platforms for various signaling molecules and pathways. They are involved in regulating lipid metabolism, inflammation, and stress responses. For instance, lipid droplets can influence the activation of AMPK, a key energy sensor, and modulate the mTOR pathway, which controls cell growth and metabolism. These signaling functions are crucial for cancer cells to adapt and thrive under stress (Hsu, Peng, Cai, & Lin, 2022; Keerthana *et al.*, 2023).

Hypoxia is a well-documented trigger for lipid droplet formation in cancer cells. Under low oxygen conditions, cancer cells upregulate lipid synthesis pathways and accumulate lipid droplets to store fatty acids. This adaptation helps cells manage energy stress and supports their survival in hypoxic tumor regions (Cozene *et al.*, 2020; Gesto, Pereira,

Cerqueira, & Sousa, 2020). When nutrients are scarce, cancer cells increase lipid droplet formation to store energy reserves that can be mobilized. This is particularly important for maintaining cellular functions and survival during periods of metabolic stress. Elevated ROS levels can induce lipid droplet formation as a protective response. By sequestering fatty acids and reducing their availability for peroxidation, lipid droplets help mitigate oxidative damage and support cell survival. Conditions that induce ER stress, such as the accumulation of misfolded proteins, also promote lipid droplet formation. This response helps alleviate the stress on the ER by buffering excess lipids and supporting the unfolded protein response (Akman *et al.*, 2021; Chen, Han, Du, Shi, & Zhou, 2023).

In conclusion, lipid droplets are integral to the cellular stress responses that cancer cells rely on for survival and proliferation. Their ability to buffer lipids, support energy homeostasis, and modulate stress signaling pathways highlights their importance in cancer biology. Understanding the mechanisms by which lipid droplets mediate stress responses in cancer cells can reveal novel therapeutic targets, offering new strategies to disrupt the adaptive capabilities of cancer cells and improve treatment outcomes.

3. Mechanistic Insights into Lipid Droplet-Mediated Stress Responses

Understanding the mechanisms behind lipid droplet-mediated stress responses in cancer cells requires a detailed exploration of the molecular pathways involved, the interaction of lipid droplets with other cellular organelles, the regulation of lipid droplet dynamics, and the consequent impact on cancer cell metabolism. These aspects are pivotal in comprehending how lipid droplets contribute to cancer cell survival, growth, and metastasis.

3.1. Molecular Pathways Involved

The formation and regulation of lipid droplets in cells are controlled by intricate signaling pathways, with the mTOR (mechanistic target of rapamycin) and AMPK (AMP-activated protein kinase) pathways being particularly significant. The mTOR pathway, a critical regulator of cell growth and metabolism, promotes lipid biosynthesis and storage by activating sterol regulatory element-binding proteins (SREBPs). These proteins enhance the transcription of genes involved in fatty acid and triglyceride synthesis, leading to increased lipid droplet formation. In cancer cells, the mTOR pathway is often hyperactivated, driving anabolic processes that support rapid proliferation and growth (Glaviano *et al.*, 2023; Goul, Peruzzo, & Zoncu, 2023).

Conversely, the AMPK pathway functions as a cellular energy sensor, activated under low energy conditions (high AMP/ATP ratio). AMPK activation inhibits mTOR signaling, reducing anabolic processes and promoting catabolic pathways that generate ATP. In lipid metabolism, AMPK activation can lead to the phosphorylation and inhibition of acetyl-CoA carboxylase (ACC), reducing lipid synthesis. However, AMPK also promotes lipid droplet formation by facilitating the storage of fatty acids during metabolic stress, providing an energy reservoir that can be mobilized when needed (Ahmed *et al.*, 2022; Bartolacci, Andreani, El-Gammal, & Scaglioni, 2021; Devereux, Bayliss, Keenan, Montgomery, & Watt, 2023).

Lipid droplets do not function in isolation; they interact dynamically with other organelles, such as mitochondria and

the endoplasmic reticulum (ER), to coordinate cellular metabolic responses. The physical and functional interactions between lipid droplets and mitochondria are crucial for the regulation of lipid metabolism and energy production. Lipid droplets supply fatty acids to mitochondria for β -oxidation, which generates ATP. This interaction is vital for maintaining energy homeostasis, especially under conditions of metabolic stress, such as hypoxia or nutrient deprivation, which are common in the tumor microenvironment (L. Wang *et al.*, 2021).

The relationship between lipid droplets and the ER is also significant. The ER is the site of lipid synthesis and the origin of lipid droplets. During ER stress, lipid droplets help alleviate the burden on the ER by sequestering excess lipids, thus preventing lipotoxicity and maintaining ER function. This interaction supports the unfolded protein response (UPR), a critical adaptive mechanism in cancer cells that enables them to cope with the high demand for protein synthesis and the associated stress (Huang *et al.*, 2021).

3.2. Regulation of Lipid Droplet Dynamics

Various factors, including specific proteins such as perilipins and lipases tightly regulate the size, number, and distribution of lipid droplets within cells. Perilipins are a family of proteins that coat the surface of lipid droplets, protecting them from lipolysis and regulating their interaction with lipases. Different perilipin isoforms have distinct roles; for instance, perilipin-1 is primarily involved in the storage and mobilization of triglycerides in adipocytes, while perilipin-2 is more ubiquitous and plays a role in lipid droplet formation and stability in various cell types, including cancer cells (Deng *et al.*, 2021).

Lipases, such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), are enzymes that hydrolyze stored triglycerides into free fatty acids and glycerol. Various signaling pathways and post-translational modifications regulate the activity of these lipases. In cancer cells, the regulation of lipase activity and lipid droplet turnover is crucial for maintaining a balance between lipid storage and mobilization, ensuring a steady supply of fatty acids for energy production and membrane synthesis (T. Li, Guo, & Zhou, 2021; Yue *et al.*, 2022).

3.3. Impact on Cancer Cell Metabolism

Lipid droplet-mediated stress responses significantly alter cancer cell metabolism, contributing to the adaptability and aggressiveness of cancer cells. The accumulation of lipid droplets in cancer cells is often associated with metabolic reprogramming, a hallmark of cancer. This reprogramming involves a shift towards increased lipogenesis and lipid storage, providing a reservoir of energy and biosynthetic precursors necessary for rapid cell proliferation.

Lipid droplets also play a role in protecting cancer cells from metabolic stress and oxidative damage. By sequestering excess fatty acids, lipid droplets prevent lipotoxicity and reduce the generation of reactive oxygen species (ROS), which can damage cellular components. This protective mechanism enhances cancer cell survival under stressful conditions, such as hypoxia and nutrient deprivation, commonly found in the tumor microenvironment (Danielli *et al.*, 2023; Petan, 2020).

The interplay between lipid droplets and other metabolic pathways further supports cancer cell growth and metastasis. For instance, the lipolysis of stored triglycerides in lipid

droplets provides free fatty acids that can be oxidized in mitochondria to generate ATP, supporting energy-intensive processes such as cell migration and invasion. Additionally, lipid droplets supply lipids for membrane synthesis and the production of signaling molecules, facilitating cancer cell communication and adaptation. The ability of cancer cells to regulate lipid droplet dynamics and mediate stress responses has profound implications for their survival, growth, and metastasis. By managing energy storage and release, lipid droplets help cancer cells maintain metabolic flexibility, allowing them to adapt to the fluctuating availability of nutrients and oxygen. This adaptability is critical for cancer cell survival in the hostile tumor microenvironment and during metastatic dissemination (Acharya & Shetty, 2023; Hincă *et al.*, 2021; Mashek, 2021).

Moreover, lipid droplets contribute to the resistance of cancer cells to therapeutic interventions. The enhanced storage and utilization of lipids in lipid droplets can support the survival of cancer cells under treatment-induced stress, such as chemotherapy and radiotherapy, which often induce oxidative and metabolic stress. The ability to buffer and mobilize lipids provides cancer cells with a means to endure and recover from such treatments, leading to therapy resistance and disease recurrence (Germain *et al.*, 2020; Tirinato *et al.*, 2020).

4. Therapeutic Implications

Lipid droplets have emerged as promising targets for novel therapeutic strategies in cancer treatment, given their integral role in cellular stress responses and metabolism. Efforts to exploit lipid droplet biology for therapeutic purposes encompass inhibiting lipid droplet formation, modulating stress response pathways influenced by lipid droplets, and integrating these approaches with conventional cancer treatments.

4.1. Targeting Lipid Droplet Formation

Inhibiting lipid droplet formation represents a direct approach to disrupting the metabolic and survival advantages conferred by these organelles in cancer cells. One potential strategy involves targeting enzymes involved in lipid synthesis and droplet biogenesis. For instance, acetyl-CoA carboxylase (ACC) inhibitors, a key enzyme in fatty acid synthesis, have shown promise in preclinical studies by reducing lipid droplet accumulation and impairing cancer cell proliferation. Similarly, drugs targeting diacylglycerol O-acyltransferase (DGAT), which catalyzes the final step in triglyceride synthesis, can inhibit lipid droplet formation and sensitize cancer cells to chemotherapy-induced cell death (Alcolado, 2022; Z. Li, Liu, & Luo, 2020).

Small molecules that interfere with lipid droplet-associated pathways are also being explored. These molecules often target proteins involved in lipid droplet stabilization and turnover, such as perilipins and adipose triglyceride lipase (ATGL). By disrupting the interaction between perilipins and lipid droplets or enhancing lipase activity, these compounds promote lipolysis and reduce lipid droplet accumulation in cancer cells. Such strategies aim to deplete the energy reserves stored in lipid droplets, thereby compromising cancer cell survival and growth (T. Li *et al.*, 2021).

4.2. Modulating Lipid Droplet-Mediated Stress Responses

Beyond inhibiting lipid droplet formation, therapeutic

approaches focus on modulating the stress response pathways influenced by lipid droplets. These pathways are critical for cancer cell adaptation to the tumor microenvironment and resistance to therapeutic interventions. For instance, targeting the mTOR pathway, which regulates lipid droplet biogenesis and growth signaling in cancer cells, can disrupt metabolic reprogramming and sensitize tumors to treatment. Combination therapies that integrate mTOR inhibitors with conventional chemotherapeutic agents have shown synergistic effects in preclinical models, highlighting the therapeutic potential of targeting lipid droplet-mediated stress responses.

Additionally, modulating AMPK activity represents another strategy to manipulate lipid droplet metabolism and stress responses in cancer cells. Activators of AMPK, such as metformin, inhibit lipid synthesis and promote lipolysis and mitochondrial biogenesis, leading to metabolic reprogramming and reduced cancer cell proliferation. These effects are particularly relevant in tumors characterized by high metabolic demand and resistance to apoptosis. AMPK activation can induce metabolic stress and sensitize cancer cells to apoptosis-inducing therapies (Y. Wang, Pan, Guo, & Wang, 2021).

The integration of lipid droplet-targeted therapies with conventional cancer treatments holds significant promise for enhancing therapeutic efficacy and overcoming treatment resistance. By disrupting lipid droplet-mediated survival mechanisms, these therapies can complement the cytotoxic effects of chemotherapy and radiotherapy. For example, combining lipid droplet inhibitors with agents that induce oxidative stress or disrupt mitochondrial function can synergistically induce apoptosis in cancer cells (Zhao, Zhang, An, Zhang, & Liu, 2023). Furthermore, lipid droplet-targeted therapies may mitigate the adverse effects of conventional treatments by reducing their doses or enhancing tumor-specific responses. This approach improves treatment outcomes, reduces systemic toxicity, and improves patient quality of life. Clinical trials evaluating combination therapies are underway to assess their safety, efficacy, and potential for overcoming resistance mechanisms in various cancer types (Lu *et al.*, 2023).

4.3. Clinical Relevance

The translational potential of lipid droplet-targeted therapies in cancer treatment is underscored by their ability to address critical challenges in current oncology practice. These therapies offer novel avenues for targeting metabolic vulnerabilities specific to cancer cells while sparing normal tissues. However, several challenges must be addressed to realize their clinical application fully.

Current challenges include the development of selective and potent inhibitors that specifically target lipid droplet-associated pathways without affecting essential cellular functions in non-cancerous tissues. Moreover, the heterogeneity of cancer cells within tumors poses a challenge to achieving uniform therapeutic responses across patient populations. Personalized medicine approaches, such as biomarker-driven selection of patients likely to benefit from lipid droplet-targeted therapies, may enhance treatment efficacy and patient outcomes.

Future prospects in clinical applications of lipid droplet-targeted therapies include exploring combination strategies with immunotherapy and precision medicine approaches. Immunomodulatory effects of lipid droplet inhibition and

their impact on tumor microenvironment immune responses warrant investigation. Additionally, advancements in imaging technologies and biomarker identification will facilitate monitoring treatment responses and guiding therapeutic decisions in real-time clinical settings.

5. Conclusion

5.1. Summary of Key Findings

Throughout this paper, we have explored the intricate role of lipid droplets (LDs) in mediating stress responses within cancer cells and their profound implications for cancer biology and therapy. Initially considered as mere lipid storage organelles, LDs are now recognized as dynamic structures that actively participate in cellular metabolism, stress adaptation, and signaling pathways crucial for cancer cell survival and proliferation.

We began by elucidating the biogenesis and function of LDs, highlighting their role in cellular energy homeostasis through the storage and mobilization of lipids. This function is particularly significant in cancer cells, where LDs help mitigate metabolic stressors such as oxidative stress, endoplasmic reticulum (ER) stress, and hypoxia. These stress conditions, prevalent in the tumor microenvironment, trigger the formation and utilization of LDs as adaptive responses that support tumor growth and resistance to therapy.

Moreover, we explored the molecular pathways that regulate LD dynamics, including the mTOR and AMPK pathways, which govern lipid synthesis, storage, and turnover. The interaction between LDs and other organelles, such as mitochondria and the ER, further underscores their role in maintaining cellular homeostasis under stress. This interaction influences lipid metabolism and impacts broader cellular functions essential for cancer cell survival and progression.

The impact of LD-mediated stress responses on cancer cell metabolism was another focal point, revealing how LDs contribute to metabolic reprogramming in cancer cells. By providing energy substrates and signaling molecules, LDs support the high metabolic demands of proliferating cancer cells and promote their survival in adverse tumor conditions. This metabolic plasticity is a hallmark of cancer cells and a critical determinant of therapeutic resistance and disease progression.

5.2. Future Directions

Looking ahead, several avenues for future research on LD-mediated stress responses in cancer emerge. First and foremost is the need to deepen our understanding of the specific molecular mechanisms that regulate LD dynamics and stress responses in different cancer types. This includes identifying novel LD biogenesis and turnover regulators that could serve as therapeutic intervention targets. Additionally, exploring the heterogeneity of LDs within tumors and their differential roles in cancer progression could provide insights into tumor biology and therapeutic responses. Advanced imaging techniques and single-cell analysis will be instrumental in deciphering the spatial and temporal dynamics of LDs in the complex tumor microenvironment. Furthermore, interdisciplinary approaches integrating biology, biochemistry, imaging, and computational modeling will be essential in advancing our understanding of LDs in cancer biology. Collaborations between researchers with expertise in lipid metabolism, cancer biology, and clinical oncology will facilitate the translation of basic science

discoveries into clinical applications. These efforts are crucial for developing targeted therapies that exploit LD vulnerabilities in cancer cells while minimizing off-target effects on normal tissues.

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