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A New Target for the Treatment of Cancer: Lipid Droplets

Kanser Tedavisinde Yeni Bir Hedef: Lipit Damlacıkları

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Abstract
Cancer is characterized by the uncontrolled proliferation of cells and their ability to spread to distant tissues. Metabolic reprogramming is a hallmark of cancer, and dysregulation of lipid metabolism represents one of the most prominent metabolic alterations in tumor cells. In this context, lipid droplets (LDs) play a key role by supporting energy production and redox homeostasis, regulating autophagy, directing membrane synthesis, and modulating membrane composition. Through these functions, LDs help tumor cells minimize metabolic stress and facilitate tumor progression. LDs are dynamic organelles present in eukaryotic cells, consisting of a hydrophobic core of neutral lipids surrounded by a phospholipid monolayer. By regulating lipid storage and mobilization, LDs directly influence essential cellular processes required for survival, growth, and proliferation, including energy metabolism, membrane and organelle biogenesis, cell signaling, and gene transcription. This review addresses the composition and synthesis of LDs and examines their critical roles in cancer development, focusing particularly on selected cancer types.
Keywords: Cancer, lipid droplet, lipid energy metabolism

Öz
Kanser, hücrelerin kontrolsüz çoğalması ve uzak dokulara yayılma yeteneği ile karakterize edilir. Metabolik yeniden programlama, kanserin ayırt edici özelliklerinden biridir ve lipit metabolizmasının düzensizliği, tümör hücrelerindeki en belirgin metabolik değişikliklerden birini temsil etmektedir. Bu bağlamda, lipit damlacıkları (LD'ler), enerji üretimini ve redoks homeostazını destekleyerek, otofajiyi düzenleyerek, membran sentezini yönlendirerek ve membran bileşimini modüle ederek önemli bir rol oynar. Bu işlevler aracılığıyla LD'ler, tümör hücrelerinin metabolik stresi en aza indirmesine ve tümör ilerlemesini kolaylaştırmasına yardımcı olur. LD'ler, ökaryotik hücrelerde bulunan, nötr lipitlerden oluşan hidrofobik bir çekirdek ve etrafını saran bir fosfolipid tek tabakasından oluşan dinamik organellerdir. Lipit depolama ve mobilizasyonunu düzenleyerek, LD'ler, enerji metabolizması, membran ve organel biyogenezi, hücre sinyalleşmesi ve gen transkripsiyonu dahil olmak üzere hayatta kalma, büyüme ve çoğalma için gerekli olan temel hücresel süreçleri doğrudan etkiler. Bu derlemede, LD'lerin bileşimi ve sentezi ele alınmakta ve özellikle seçilmiş kanser türlerine odaklanarak, kanser oluşumundaki kritik rolleri incelenmektedir.
Anahtar Kelimeler: Kanser, lipit damlacığı, lipit enerji metabolizması

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INTRODUCTION

Cancer is a disease characterized by abnormal cell growth in tissues or organs resulting from the disruption of regulatory mechanisms controlling growth and development, and it remains one of the most common causes of death worldwide.[1,2] The seminal studies by Hanahan and Weinberg, Hallmarks of Cancer, categorized cancer according to its fundamental biological features, among which metabolic reprogramming represents a key hallmark of malignancy. However, the marked metabolic heterogeneity observed among human tumors poses a significant challenge to the development of effective metabolism-targeted therapeutic strategies.[3,4] In 2022, Hanahan further refined this framework by re-schematizing the distinctive features of tumor cells and introducing additional hallmarks of cancer (Figure 1).[5]

Although tumor cells predominantly rely on glycolysis for energy production, glycolytic inhibitors such as 2-deoxyglucose have shown limited efficacy in suppressing tumor growth. Consequently, alternative metabolic pathways, particularly lipid metabolism, are increasingly recognized as critical for tumor cell survival.[6] Tumor cells exploit lipid metabolism to satisfy their energy demands, synthesize biological membrane components, and generate signaling molecules required for proliferation, survival, metastasis, and adaptation to the tumor microenvironment and therapeutic stress. Accumulating evidence indicates that upregulation of lipid metabolism substantially enhances the capacity of tumors to survive and proliferate. Accordingly, tumor cells reprogram lipid metabolism to fulfill energy requirements, support membrane biosynthesis, and sustain signal transduction.[6,7]

Dysregulation of lipid metabolism in cancer is characterized by metabolic adaptations, including increased glycolysis, enhanced lipogenesis, and the accumulation of lipid droplets (LDs).[8] The unlimited proliferative capacity of tumor cells requires an increased supply of fatty acids (FAs) and enhanced LD metabolism.[6] In recent years, LDs have gained increasing attention due to their central role in tumor cell metabolism. LDs participate in essential cellular functions, including energy storage, membrane biogenesis, and signal transduction. Reprogramming of LD metabolism in tumor cells has been shown to contribute to tumor growth, metastasis, and resistance to anticancer therapies.[9]

In this review, we examine current advances in the regulation of lipid and LD metabolism in tumor cells and discuss their association with LD-rich tumor cells and the tumor microenvironment. This study is a review article; ethics committee approval is not required.

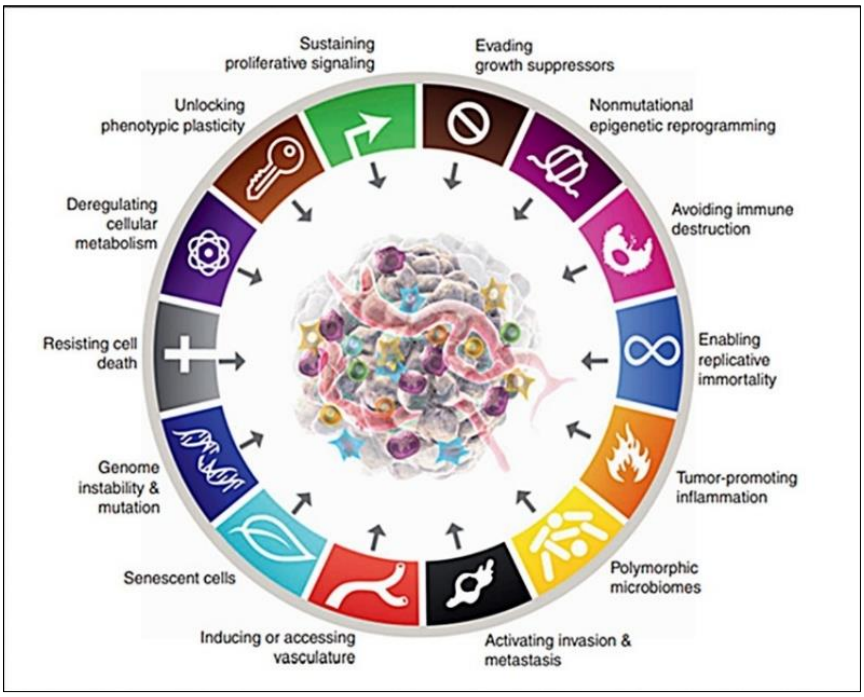

Figure 1. Hallmarks of cancer.[5]

METABOLIC REPROGRAMMING IN CANCER

Tumor cells undergo metabolic reprogramming of their energy metabolism to support growth, survival, and proliferation, particularly under nutrient-poor conditions. Accordingly, metabolic reprogramming is recognized as a hallmark of malignancy. The metabolic requirements, characteristics, and preferences of tumor cells dynamically change during cancer progression, and in advanced stages of carcinogenesis, tumors increasingly depend on alternative metabolic pathways that facilitate metastasis and resistance to therapy.[1,10]

Due to their rapid proliferation, tumor cells require a greater supply of nutrients than normal cells and therefore adapt their metabolism according to nutrient availability. Metabolic reprogramming in cancer involves a shift from oxidative phosphorylation to glycolysis, alterations in nutrient uptake pathways, and increased lipid biosynthesis. The major metabolic pathways reprogrammed in cancer include glucose, amino acid, nucleotide, and lipid metabolism.[1] Accumulating evidence indicates that glycolytic pathways are extensively altered in tumor cells.[11] Notably, even under normoxic conditions, tumor cells preferentially utilize glycolysis for adenosine triphosphate (ATP) production, and they further adjust their metabolic pathways in response to varying stress conditions.[12]

Recent studies indicate that aberrant lipid metabolic signaling contributes to cancer initiation, progression, metastasis, recurrence, and poor therapeutic response by reprogramming both tumor cells and non-tumor cells within the tumor microenvironment (TME). Consequently, key features of tumor cells include the coordinated reprogramming of glucose and lipid metabolism—most notably the upregulation of glycolysis and lipogenesis—along with the accumulation of LDs in tumor cells and their surrounding microenvironment.[13,14]

LIPID METABOLISM

One of the defining hallmarks of cancer is abnormal tumor metabolism, and dysregulated and enhanced lipid metabolism has been documented across many cancer types. Lipids not only serve as essential structural components of biological membranes but also form hydrophobic barriers that separate the intracellular and extracellular environments. In addition, lipids preserve membrane protein function and support tumor cell proliferation by supplying energy and metabolic substrates. The major lipid classes involved in these processes include fatty acids, cholesterol, and phospholipids.[15,16]

Reprogramming of lipid metabolism in cancer is closely associated with the activation of oncogenic signaling pathways and interactions within the TME. This metabolic activity supports tumor cell survival and proliferation under the harsh and fluctuating conditions characteristic of the TME. Accordingly, lipid metabolism is highly active in tumor cells residing in the TME, as reflected by the elevated expression of receptors and key enzymes involved in lipid uptake, synthesis, storage, and degradation. Concurrently, tumor cells exploit lipid metabolism to sustain rapid proliferation, migration, invasion, and metastasis in environments where nutrient availability continually changes during tumor progression.[17] Tumor cells may differentially acquire lipids to enhance their survival and proliferative capacity, thereby contributing to cancer progression. In cancer, cells can increase de novo lipogenesis, FA uptake, and fatty acid oxidation (FAO) to support energy production and lipid accumulation (Figure 2).[18,19]

De novo lipogenesis is the process of endogenous lipid synthesis, classically occurring in adipocytes and hepatocytes, in which carbon atoms derived from carbohydrates such as glucose and amino acids such as glutamine are converted into fatty acids.[19,20] Despite the availability of exogenous lipid sources, tumor cells frequently activate lipogenesis in response to their elevated metabolic demands or lipid scarcity within the TME.[17] Accordingly, de novo lipogenesis is markedly upregulated in human cancers to meet the increased requirements for membrane biogenesis, while lipid uptake and storage are also enhanced in malignant cells.[21]

Cytoplasmic acetyl-CoA represents the principal substrate for lipid synthesis and can be generated from citrate via ATP-citrate lyase (ACLY) or from acetate through acetyl-CoA synthetase (ACSS). Carbon atoms derived from glucose and glutamine contribute to citrate production through pyruvate oxidation in the tricarboxylic acid (TCA) cycle or via reductive carboxylation, respectively.[7] Under metabolic stress conditions, such as hypoxia or lipid deprivation, tumor cells further upregulate acetyl-CoA synthetase 2 (ACSS2) to generate acetyl-CoA from acetate. Citrate-derived acetyl-CoA is subsequently converted to malonyl-CoA by acetyl-CoA carboxylases (ACCs), with the irreversible carboxylation of acetyl-CoA to malonyl-CoA constituting the rate-limiting step of de novo lipogenesis.[20] Notably, inhibition of key lipogenic enzymes has been shown to reduce tumor cell proliferation and tumor growth.

In healthy cells, growth factor stimulation activates phosphatidylinositol 3-kinase (PI3K) and its downstream effectors AKT and the mammalian target of rapamycin (mTOR), thereby promoting an anabolic program

characterized by increased glycolytic flux and fatty acid synthesis through activation of hypoxia-inducible factor-1 (HIF-1) and sterol regulatory element-binding proteins (SREBPs), respectively. In contrast, tumor cells frequently harbor genetic alterations that enable sustained activation of the PI3K-AKT-mTOR signaling network with minimal dependence on exogenous growth factor stimulation. Many well-characterized oncogenes and tumor suppressors converge on this pathway, and its aberrant activation represents one of the most common molecular alterations observed across diverse cancer types.[22]

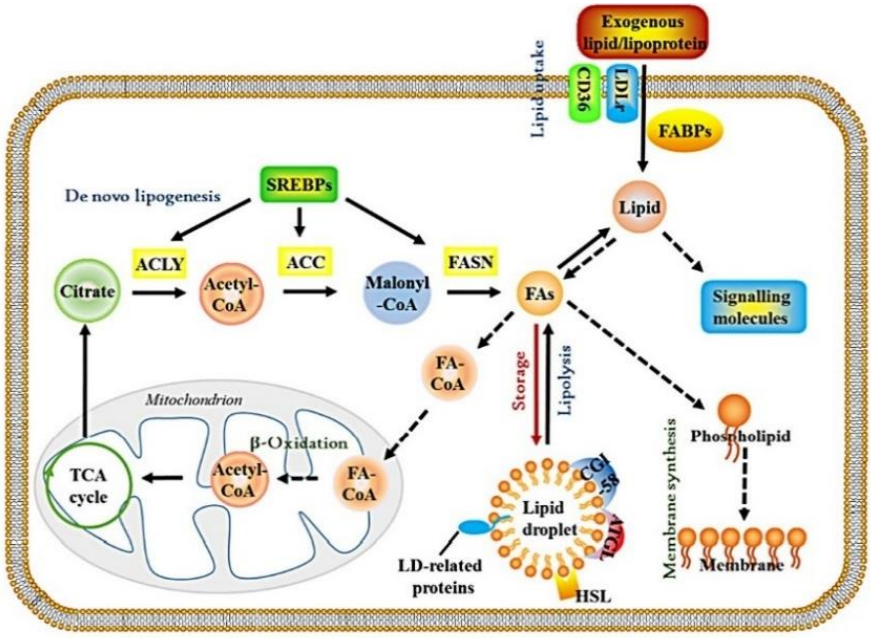

Figure 2. Lipid metabolic pathways altered in cancer.[18]

SREBPs comprise a family of endoplasmic reticulum (ER)-localized, membrane-bound transcription factors that regulate the expression of genes involved in lipid synthesis and uptake, thereby playing a central role in lipid metabolism under both physiological and pathological conditions. Accumulating evidence indicates that SREBPs are highly upregulated in multiple cancers and actively promote tumor growth. SREBP cleavage-activating protein is essential for the transport and activation of SREBPs and functions as a critical glucose sensor, thereby linking glucose metabolism with *de novo* lipid synthesis.[21]

As a consequence of dysregulated lipid metabolism, excessive LD formation is a prominent feature of tumor cells. Increased LD accumulation contributes to tumor metastasis and resistance to cell death, highlighting LD biogenesis as a promising therapeutic target. Accordingly, pioneering studies aimed at disrupting LD formation offer potential strategies for the development of novel anticancer therapies.

LIPID DROPLETS

LDs are intracellular organelles composed of a hydrophobic core of neutral lipids surrounded by a single phospholipid monolayer decorated with a variety of associated proteins.[23] The neutral lipid core primarily consists of triacylglycerols (TAGs) and sterol esters (SEs) (Figure 3).[24] LDs perform multiple essential functions, including the reduction of oxidative stress, membrane biogenesis, and signal transduction.[23]

In tumor cells, LD biogenesis originates from the ER, where enzymes responsible for neutral lipid synthesis are localized, and is induced in response to conditions such as ER stress, hypoxia, and energy deprivation.[25] LDs are coated with proteins of the PAT family (perilipin, adipophilin, and TIP47), including perilipin (PLIN)-1 and PLIN2. In addition to lipid composition, several protein families-including seipins, PLINs, fat storage–inducing

transmembrane (FIT) proteins, and ER-shaping proteins-play critical roles in LD biogenesis and structural organization.[26]

Although LDs were first observed in the late 1890s, their molecular architecture gained significant attention only a century later following the identification of key LD-associated proteins such as PLINs and oleosins. Subsequent studies have established LDs as highly dynamic organelles that influence multiple aspects of cellular physiology. Beyond their classical role in energy storage, LDs are essential for alleviating various forms of cellular stress, including lipotoxic stress, ER stress, oxidative stress, and nutrient deprivation.[25]

The neutral lipid core of LDs stores lipids predominantly in esterified forms, including fatty acids as TAGs, cholesterol and other sterols as sterol esters, retinoic acids as retinyl esters, and ceramides as acyl ceramides. By regulating the storage and mobilization of these lipid species, LDs directly modulate processes essential for cell survival, growth, and proliferation, such as energy production, membrane and organelle biogenesis, cell signaling, and gene transcription.[23] Notably, increased LD abundance has also been associated with enhanced invasive and metastatic potential of tumor cells. Regulation of enzymes involved in lipid biosynthesis is therefore critical for meeting the energetic demands of tumor cells, with enzyme expression levels dynamically adapting to changing metabolic requirements.

Initial evidence linking LD metabolism to cancer emerged from studies demonstrating the involvement of LDs in prostaglandin E2 (PGE2) synthesis and tumor cell proliferation in colon cancer cells. Since then, particularly over the past decade, substantial progress has been made in elucidating the mechanisms governing LD formation and function in cancer. Accumulating evidence indicates that LDs participate in virtually all stages of cancer development, including tumor initiation and progression.[26]

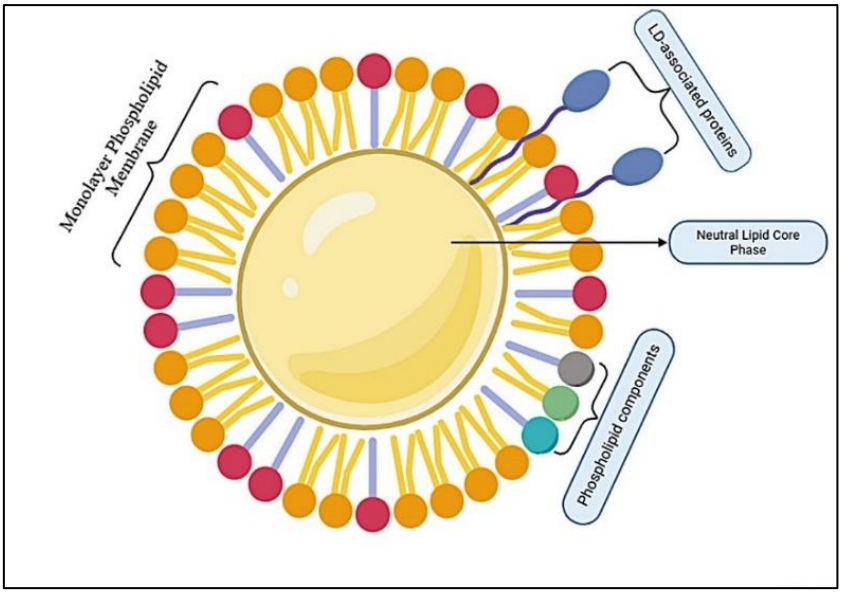

Figure 3. Schematic illustration of lipid droplet components.

Lipid metabolism and signaling involve a wide range of proteins associated with redox metabolism, autophagy, gene transcription, ubiquitination, membrane trafficking, and immune regulation. Although the functions of many LD-associated proteins remain unclear, several have been shown to participate directly in lipid- or LD-related processes. Likewise, the functional significance of protein localization to LDs is not yet fully understood. In certain contexts, the sequestration of proteins at the LD surface represents a regulatory mechanism that controls their availability for processes occurring at other cellular sites. For example, LDs can influence gene transcription, protein quality control, and immune cell function by sequestering histones, transcription factors such as NFAT5, and molecular chaperones including Hsc70 and calreticulin.[23] Collectively, these observations suggest that LDs and their associated metabolic pathways represent promising targets for cancer therapy. Pharmacological inhibition of LD biosynthesis or degradation may disrupt tumor cell energy homeostasis, thereby limiting tumor growth and dissemination. Ongoing and future studies will be essential to further clarify the efficacy and clinical applicability of LD-targeted strategies. Targeting LD biosynthesis may induce tumor cell death by restricting the energetic

capacity of cancer cells, and such approaches could be combined with conventional treatment modalities, including chemotherapy and radiotherapy, to enhance therapeutic outcomes.

LIPID DROPLETS UTILIZED BY CERTAIN CANCER TYPES

LD–associated proteins, which play a critical role in regulating LD metabolism, are increasingly recognized as potential diagnostic biomarkers and therapeutic targets in cancer. Consistent with this evidence, the functional versatility of LDs in cancer progression has been demonstrated, underscoring their contribution to tumor cell adaptation and survival within heterogeneous and dynamic microenvironments.[27] Accordingly, a more comprehensive understanding of the roles of LDs in cancer biology may facilitate the development of novel therapeutic strategies. Targeting genes involved in LD metabolism has been suggested to suppress tumor cell proliferation and may provide new treatment options for cancer.

In this review, we examine the most common cancer types that exploit LD metabolism worldwide and in Türkiye. These cancer types include bladder, breast, colorectal, endometrial, glioblastoma, liver, lung, pancreatic, prostate, renal cell carcinoma, and thyroid cancers (Table 1).

Table 1. High rates of accumulation of LDs and this metabolic adaptation play a critical role in some types of cancer.

Cancer Type	Description
Bladder Cancer (BCa)	Bladder cancer (BCa) is the most common malignant tumor of the urinary tract with a high mortality rate in men worldwide.[28,29] LDs are lipid-rich cytoplasmic organelles that have diverse functions in the development and progression of cancer and have been associated with poor prognosis. Moreover, one published study has shown that the accumulation of LD is regulated throughout the cell cycle in mouse fibroblasts.[28] Pagliari et al. showed a positive correlation between the radiation resistance of tumor cells and increasing LDs on bladder cell lines. It is known that cancer cells show varying levels of radiosensitivity throughout the cell cycle, with cells in S phase revealing the highest radioresistance. This study showed that LD accumulation may contribute to the ability of tumor cells to better withstand X-ray radiation while in the S phase.[28] Therefore, LDs may represent new players in the radioresistance processes associated with cancer metabolism.
Breast Cancer (BC)	Breast cancer (BC) is the most common malignancy in women and the leading cause of cancer deaths. Breast cancer cells use LDs to have their energy needs and to produce membrane components. In aggressive subtypes such as triple negative breast cancer (TNBC), lipid biosynthesis processes are activated, which increases the rate of cell proliferation. LD accumulation allows storage of essential fatty acids for cell membrane synthesis and energy production. This process may also contribute to chemotherapy resistance.[7,30] Lipid metabolism is often dysregulated in breast cancer, and significant differences in lipid synthesis, loading, storage, and utilization are seen among breast cancers with different biology, invasiveness, response to treatment, and prognosis.[30] Despite the abundance of exogenous lipids in the tumor microenvironment, most tumor cell types utilize *de novo* lipogenesis. Genes involved in the fatty acid synthesis (FAS) pathway, such as SREBP-1, fatty acid synthase (FASN), acetyl-coA carboxylase 1 (ACC1), and ATP citrate lyase (ACLY), which are essential for breast cancer cell survival, have been reported to be over-expressed in breast tumor tissues.[31] Genes related to FA biosynthesis and lipid metabolism, such as SREBP-1, FASN, ACC1 and ACLY, show a positive correlation, suggesting that increased glycolysis may also contribute to increased citrate production in the TCA cycle, thereby promoting new lipid production and utilization.[30]
Colorectal Cancer (CRC)	Colorectal cancer (CRC) is among the five most common types of cancer worldwide and the second leading cause of cancer-related death.[32,33] LD accumulation has been demonstrated by Raman spectroscopy to be a feature of CRC stem cells. This suggests a role for LD biogenesis in CRC recurrence and is used as a potential biomarker.[34] Tirinato et al. reported that the number of LDs in CRC CSCs was associated with tumor formation. The higher the amount of LD, the stronger the tumor formation.[32] There is a positive correlation between the number of LD and tumor formation. The energy provided by tumor cells through FAs promotes tumor growth and metastasis. Li et al. suggested that overproduction of LD facilitates CRC cell metastasis, suggesting its potential use as a prognostic biomarker for CRC recurrence and survival. Zhang et al. have shown that regenerative gene 4 (REG4), known to be carcinogenic in cancer types such as CRC, plays a role in LD accumulation and chemoresistance.[35] LD formation in tumor cells increases cancer aggressiveness and drug resistance. Genes and proteins involved in LD metabolism may serve as biomarkers depending on the type of cancer and provide a warning for treatment.
Endometrial Cancer (EC)	Endometrial cancer (EC) is the fourth most common type of cancer in women.[36] Metabolic reprogramming, particularly FA metabolism, is associated with carcinogenesis and progression of endometrial cancer (EC).[37] Neutral lipid synthesis is upregulated in EC and LD accumulation is associated with cancer progression.[38] Zhao et al. showed in their study that palmitic acid increased the intracellular formation of LDs in a time and dose-dependent manner.[36] Lactamase β (LACTB) inhibits the metastasis and progression of malignant tumors. Zhou et al. reported in another study that LACTB suppresses EC cell proliferation and metastasis and reprograms lipid metabolism by attenuating the ubiquitination and degradation of p53.[39] This suggests a new LD-related pathway that can be targeted for EC treatment.

Continuation of **Table 1.**

Glioblastoma Multiforme (GBM)	Glioblastoma Multiforme (GBM) is the most deadly primary brain tumor and requires excess lipids for rapid growth. Reprogramming of lipid metabolism is a hallmark of GBM. GBM cells require abundant lipids for rapid growth. Increased intracellular lipid levels, especially free fatty acids and cholesterol accumulation, may cause lipotoxicity. However, this is different for GBM cells; in GBM cells, lipotoxicity is prevented and excess lipids are dynamically stored as LDs, sustaining tumor growth.[40] Inhibition of DGAT1, an important enzyme involved in this storage, disrupts this process.[41] Drugs targeting lipid metabolism pathways such as *de novo* synthesis, uptake, storage and catabolism are now being actively developed for cancer treatment, including therapy based on LD metabolism.[40] Analysis of brain tissues from GBM patients shows that LDs are highly enriched in tumor tissues but undetectable in normal brain tissues. Monounsaturated FAs promote GBM proliferation via triglyceride metabolism, suggesting a novel LD-mediated pathway that could be targeted for GBM therapy.[42]
Hepatocellular Carcinoma (HCC)	Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide. More than 90% of HCCs develop due to chronic liver injury and inflammation. HCC shows marked alterations in lipid metabolism. In this type of cancer, LDs function not only as an energy source but also as a regulatory system for cellular stress responses. Increased lipid storage capacity increases the liver's ability to cope with lipidic stress. Furthermore, the presence of these droplets reduces oxidative damage and promotes cell survival under hypoxia conditions. HCC shows metabolic reprogramming for lipid in various aspects of carcinogenesis, such as adapting to a hypoxic environment and supporting the self-renewal ability of cancer stem cells (CSCs) and treatment resistance.[43] Wu et al. showed that LD metabolism dependent on aldo-keto reductase family 1 member C3 (AKR1C3) effectively reduces cellular lipotoxicity and ROS production, thus supporting HCC cell survival. Excess intracellular FAs that cannot be broken down in mitochondria are transferred to LDs via AKR1C3 activity.[44] They may support tumor cell survival and growth by participating in the regulation of both energy metabolism and cellular stress responses. Therefore, understanding the role of LDs in HCC may contribute to the development of new treatment strategies.
Lung Cancer (LC)	Lung cancer (LC) is one of the most common types of cancer and the leading cause of cancer-related deaths worldwide, with approximately 85% being non-small cell lung cancer (NSCLC). Lung cancer is one of the most common types of cancer in the world. There is increased lipid uptake and synthesis in tumor cells compared to healthy cells. The expression of lipid-associated proteins such as adipophilin has been shown to be higher in lung adenocarcinoma compared to normal lung tissues. This increased expression is associated with a poor prognosis for patients with lung adenocarcinoma.[45] Furthermore, large amounts of LD have been shown to accumulate in lung cancer cells resistant to high-dose radiation, and the more resistant tumor cells are to radiation, the more LD accumulates in their cytoplasm.[46] There is also a relationship between LD and resistance to radiotherapy. LDs participate in various biological processes, particularly in the regulation of energy metabolism, cell proliferation, stress resistance and immune response.[45] Therefore, the role of LDs deserves attention when searching for new treatments for cancer.
Pancreatic Cancer (PC)	Pancreatic cancer (PC) is one of the leading causes of cancer death worldwide, with an overall 5-year survival rate of ~10%.[47,48] Cancer metabolism, and particularly lipid metabolism, plays an important role in pancreatic cancer progression and metastasis. Normal lipid synthesis and reprogrammed lipid metabolism are also associated with the development and progression of pancreatic cancer. The importance of LD accumulation in pancreatic cancer progression remains obscure under chemotherapeutic conditions. However, LDs have been suggested to mediate proliferation, invasion, metastasis and chemotherapy resistance in pancreatic cancer. Oncogenic KRAS, involved in pancreatic cancer development, controls the storage and utilization of LDs, which promotes reprogramming of tumor cell metabolism, invasion and migration. LD-associated proteins play an important role in LD dynamics, and expression of LD-associated genes is associated with survival in pancreatic cancer patients.[47] Identifying LD-associated factors can increase knowledge about their cancer-specific roles, which may enable the development of more specific and personalized treatments for pancreatic cancer patients in the future.
Prostate Cancer (PCa)	Prostate cancer (PCa) is a hormone-dependent cancer that exhibits oncogenic modulated metabolic programming that utilizes lipid oxidation for energy.[49] PCa cells have metabolic characteristics such as higher expression of several enzymes associated with FA uptake, β-oxidation, and *de novo* lipogenesis. PCa cells utilize lipid metabolism for growth, treatment resistance, and survival in harsh environmental conditions. Hypoxic tumors such as PCa accumulate higher lipids through a combination of metabolic changes including

	increased glutamine and FA uptake.[50] These lipids are stored in LDs or converted into phospholipids, which are the main components of the cell membrane.[51] Atakol et al. compared the levels of proteins involved in LD metabolism in DU145 and PC3 PCa cells in 2023. The levels of proteins involved in LD metabolism are positively correlated with poor cancer prognosis.[52] Hadjmimoune et al. also targeted proteins involved in LD metabolism in PCa with Thymoquinone (TQ) in their study. They suggested that TQ may have a suppressive effect on LD and that it may be a useful molecule for PCa treatment with further research.[53] In their study, Sahin et al. aimed to reduce the levels of PLA2G7, UCP2 and NEDD4L proteins involved in LD metabolism in PCa with MDA19 and showed that MDA19 may have a suppressive effect on LD.[49]

Continuation of **Table 1.**

Renal Cell Carcinoma (RCC)	Renal cell carcinoma (RCC) is the most common pathological type of kidney cancer and one of the most common malignancies of the urinary system.[54] Clear cell renal cell carcinoma (ccRCC), a common subtype of kidney cancer, has specific alterations in multiple metabolic pathways, including the accumulation of LDs[55] and is a type of cancer resistant to cytotoxic chemotherapy.[54] LD accumulation, which is a key feature in metabolic reprogramming, is of critical importance during ccRCC tumorigenesis. Analysis of ccRCC tissue and healthy kidney control samples indicated HILPDA, which is involved in LD metabolism, as a specific ccRCC biomarker.[56] Together with this result, it may constitute an approach for the development of alternative therapeutic interventions for the treatment of this type of kidney cancer.
Thyroid Cancer (TC)	Thyroid cancer (TC) is the most common endocrine cancer. Follicular neoplasms of the thyroid include follicular thyroid carcinoma (FTC) and follicular thyroid adenoma (FTA). FTC is an important type of primary thyroid cancer. Hayakawa et al. evaluated the accumulation of LDs and the expression of adipophilin, a known LD marker, in FTC and FTA cells. They showed that FTC cells contained increased numbers of LDs and higher levels of adipophilin, and that adipophilin expression in FTC cells from resected human thyroid tissues was higher than in FTA cells.[57] This result suggests that immunohistochemical assessment of adipophilin can be used to distinguish FTC from FTA. In conclusion, it is thought that LDs can be used as a potential marker among thyroid cancer types. With further studies in this area, current personalized treatment approaches for thyroid cancer patients can be detailed.

DISCUSSION AND CONCLUSION

Our understanding of the concept and biological roles of LDs has advanced substantially since their initial description. As dynamic organelles, LDs have gained increasing attention due to their functional diversity and critical roles in cellular homeostasis. While LD formation is generally considered protective under physiological and acute stress conditions, its long-term accumulation and uncontrolled expansion in chronic diseases, including cancer, may exacerbate disease progression.[25]

In cancer, metabolic reprogramming extends beyond dysregulated glucose metabolism and involves profound alterations in lipid metabolism, amino acid metabolism, mitochondrial biogenesis,[11] and nucleotide metabolism pathways.[1] Elucidating these metabolic adaptations is essential for defining the molecular basis of malignancy and for identifying novel diagnostic and therapeutic opportunities.

In conclusion, cancer-associated lipid metabolism represents a key feature of metabolic reprogramming that supports tumor growth, survival, and progression. In this context, LDs contribute to tumor development through multiple mechanisms, including regulating cellular stress responses, enhancing tumor cell survival, and modulating immune function across different cancer types. Therefore, a deeper understanding of LD biology in cancer may facilitate the development of innovative therapeutic strategies. Targeting lipid metabolism, LD-associated genes and proteins, and related cell death pathways holds significant promise for the design of more effective and combinatorial cancer treatment approaches.

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