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Review Article

Lipid droplet and its implication in cancer progression

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Abstract: Lipid droplets (LDs) are a kind of organelle that is commonly found in eukaryotic cells to store lipids, which encompass a hydrophobic core composed of a single layer of phospholipids and neutral lipids (mainly including triacylglycerol (TAG) and cholesterol ester (CE)) as well as a small amount of proteins. LD accumulation is gradually recognized as a prominent characteristic in a variety of cancers and attracts increasing attention on this field. In this article, we not only summarize the composition, synthesis and decomposition of LD, but also highlight its role in carcinogenesis and malignant development of cancers.

Keywords: Lipid droplet, lipid metabolism, cancer, metastasis, chemotherapy resistance

Introduction

Lipid droplets (LDs), existing in most eukaryotic cells and some prokaryotes and first observed by van Leeuwenhoek in 1674 [1, 2], are independent organelles whose main function is to store lipids in cells. LDs act as important metabolic organelles in most cell types and play an essential role in maintaining the stability of the intracellular environment. In addition to being a fat storage compartment, LDs also perform a variety of functions, such as serving as a platform for certain protein turnover and playing an important role in cellular stress [3].

Here, we not only summarize the composition, synthesis and decomposition of LD, but also highlight its role in carcinogenesis and malignant development of cancers.

The composition, biogenesis and degradation of LD

The composition of LD

Lipid droplets are composed of a monolayer of phospholipids and a hydrophobic core consisting of neutral lipids (mainly including triacylglycerols (TAG) and cholesterol esters (CEs)). The phospholipid monolayer together with bound proteins shields hydrophobic lipid esters from the aqueous cytosolic milieu [4]. According to proteomic analyses, there are more than 200 proteins isolated from LDs, which are mainly divided into four categories as structural proteins, membrane transport proteins, enzymes and other lipid droplet proteins.

Structural proteins, which are located on the surface of LDs, play an important role in maintaining the structure, morphology and function of LDs. For example, members of the perilipin-ADRP-TIP47 (PAT) family [5] and the cell death-inducing DNA fragmentation factor 45-like effector (CIDE) family are both classified into the structural protein. The PAT family consists of five members, perilipin1-5 (PLIN1-5) [5-7]. PLIN1 and PLIN2 are mainly located in LDs, while PLIN3, PLIN4 and PLIN5 may also be enriched in cytoplasm or endoplasmic reticulum (ER) [8, 9]. CIDE is another important family of LD coat proteins, including CIDEA, CIDEB and CIDEC, which is related to the control of the formation, growth and lipolysis of LDs [10-12].

Membrane transport proteins encompass but not limited to Arf1, soluble NSF attachment protein receptor (SNARE), Rab10, Rab18, Rab32.

These proteins seem to be involved in the transport and segregation of proteins and lipid mobilization in LDs to allocate them to different cell compartments, modulate their levels or prevent them from binding to targets [13, 14].

Enzymes associated with lipid synthesis, such as diacylglycerol acyltransferase 2 (DGAT2) and lipolysis, such as ATGL and hormone-sensitive lipase (HSL) have been shown expressed in LDs [15]. In addition, other proteins such as histones [13], ribosomal proteins [16] and signaling molecules [17] have been enriched within LDs.

One of the main components of the hydrophobic core of LDs is TAG, which consists of three FAs and one glycerol linkage in ER. CE, another major component of LDs, is derived from the esterification of acyl-CoA with cholesterol (CH) [18]. Lipidomic analyses have shown that LDs contain more than 100 types of neutral lipids [3] and most lipids in the core of LDs are identified to be triglycerides and sterol esters with a range of different FA side chains.

Biogenesis and degradation of LD

Lipid droplets are dynamic organelles. The biogenesis and degradation of the main components of LDs including TAG, CE and membrane phospholipids are tightly regulated by a series of lipid metabolic enzymes in response to cellular metabolic stress.

Owing to the potential toxicity of fatty acids (FA) to cells, excess FA and cholesterol (CH) are esterified and stored as neutral molecules (such as TAG or sterol ester) in LD (**Figure 1**). Extracellular FAs pass through the cell membrane under the promotion of cluster of differentiation 36 (CD36) and FATP [1]. The synthesis process of TAG is successively catalyzed by fatty acyl-CoA synthetase (ACS), glycerol-3-phosphate acyltransferase (GPAT), 1-acylglycerol-3-phosphate acyltransferase (AGPAT), phosphatidic acid phosphatase (PAP) and diacylglycerol acyltransferase 1 and 2 (DGAT1 and DGAT2) [18-20]. CEs, the other core constituent of LDs, are produced by acyl-CoA: cholesterol acyltransferases (ACAT) catalyzing the esterification reaction between FA-CoA and free CH [18, 21]. Once enough neutral lipids are formed, nascent LDs are germinated from the ER membrane and released into the cytoplasm [2, 22, 23].

The monolayer of LDs is mainly composed of phosphatidylcholine (PC) and a series of related proteins [24]. PC synthesis is mainly achieved through two different pathways: the Kennedy pathway to support *de novo* PC synthesis and the Lands cycle involved in phospholipid remodeling through deacylation/reacylation steps. PC remodeling is catalyzed by lysophosphatidylcholine acyltransferases (LPCATs) in the Lands cycle that re-acylate lysophosphatidylcholine (LPC) [25, 26].

Cellular energy requirements can drive the degradation of LD mainly mediated by the process of lipolysis [27, 28] or lipophagy [1, 29]. In the former approach, ATGL, HSL and monoacylglycerol lipase (MGL) sequentially hydrolyze TAGs into glycerol and free FAs (FFA). FFAs can be used for energy production via mitochondria or peroxisomal β-oxidation and as substrates for membrane synthesis, reesterification or signaling molecules [20, 30, 31]. During the latter process, LDs are delivered to autophagosomes, which are fused with lysosomes to form autolysosomes [31, 32].

The roles of LD in cancer development

The metabolic disorders of LDs related to multiple metabolic diseases such as obesity, fatty liver, diabetes mellitus and cardiovascular diseases [1, 33-35], have been extensively investigated. LD accumulation in non-adipocytic tissues has represented as a new hallmark of cancer. Compared with healthy cells and tissues, higher LD contents have been reported in cancer cells and cancerous tissues such as colorectal cancer, breast and prostate cancers, hepatocellular carcinoma, renal cell carcinoma and glioblastoma.

Accumulating documents support that oncogenic and lipid metabolic pathways are interacted to modulate LDs homeostasis in cancer cells (**Figure 2**). Among the oncogenic regulatory hubs, loss of PTEN and activation of phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway have shown closely associated with increased LD density [36]. However, FOXO3/Sirtuin6 signaling represents a negative regulator of lipid synthesis [37, 38] and there exists a negative regulatory loop between LDs and FOXO3/Sirtuin6 [36].

Another series of crucial regulator in LD homeostasis mainly contains lipid metabolic enzymes

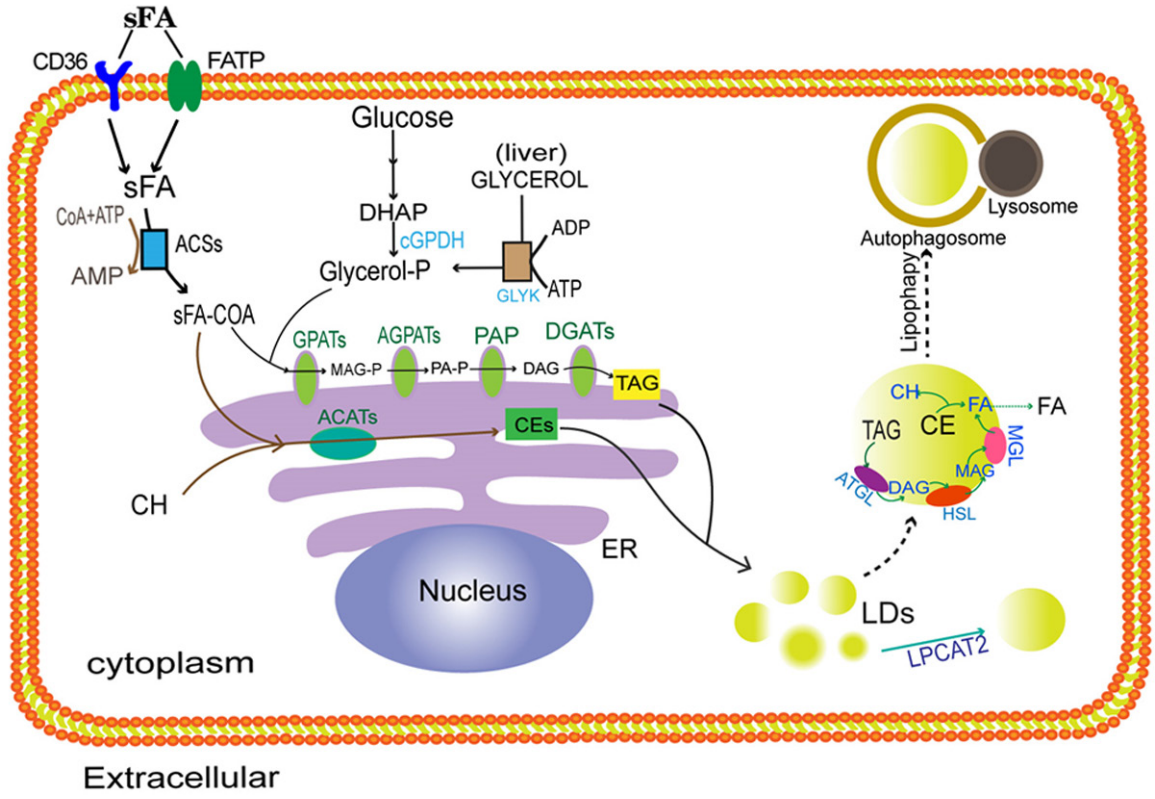

Figure 1. The schematic of synthesis and decomposition of LDs. The synthesis process of TAG is as follows: firstly, ACS converts inert FA to produce active fatty acyl-CoA (FA-CoA) ester; secondly, GPAT is responsible for catalyzing glycerol 3-phosphate and FA-CoA to form MAG-P on the ER. Herein, glycerol 3-phosphate is generated by the action of GLYK on glycerol or is produced by DHAP derived from glycolysis under the action of GPDH. Thirdly, MAG-P sequentially generates TAG under the action of AGPAT, PAP, and DGAT1/2. The decomposition of LD is mainly conducted through lipolysis sequentially catalyzed by ATGL, HSL and MGL or lipophagy. ACATs, acyl-coA: cholesterol acyltransferases; AGPATs, 1-acyl-glycerol-3-phosphate acyltransferases; AMP, adenosine monophosphate; ATGL, adipose tissue triacylglycerol lipase; ATP: adenosine triphosphate; sFA, saturated fat acids; CD36, cluster of differentiation; CEs, cholesteryl esters; CH, cholesterol; cGPDH, cytosolic glycerol-3-phosphate dehydrogenase; DAG, diacylglycerol; DGAT, diacylglycerol acyltransferase; DHAP, dihydroxyacetone phosphate; ER, endoplasmic reticulum; FATP, fatty acid transport protein; GLYK, glycerol kinase; GPATs, glycerol-3-phosphate acyltransferases; HSL, hormone-sensitive lipase; LD, lipid droplet; MAG, 1-acylglycerols; LPCAT2, lysophosphatidylcholine acyltransferase 2; PAP, phosphatidic acid phosphatase; PA-P, phosphatidic acid; MAG-P, 1-acylglycerol-3-phosphate; MGL, monoacylglycerol lipase; TAG, triacylglycerol.

responsible for the synthesis or degradation of LD components, such as LPCAT2, cytosolic phospholipase 2 (cPLA2), sterol O-acyltransferase 1 (SOAT1), squalene epoxidase (SQLE), etc [39-41]. The transcription factor sterol regulatory element-binding protein-1 (SREBP-1) with a central role in lipid anabolism is frequently activated in cancers and has been shown to mediate the accumulation of LDs [42]. In addition, LD coat proteins (Perilipins) [43] and fatty acid-binding proteins (FABPs) [44] are also involved in the regulation of LD formation and trafficking in cancer cells.

As a complex and functional organelle, LD extensively mediates the proliferation, invasion, metastasis and chemotherapy resistance in multiple types of cancers (**Table 1**). Increased storage of lipids in LDs is beneficial for the survival of cancer cells. Intracellular excess fatty acids and cholesterol can be stored in LDs to prevent lipotoxicity and endoplasmic reticulum stress. Increased LD contents could expand the source of lipid substrates and energy to meet the metabolic need of proliferative cancer cells. Especially in the tumor microenvironment (TME), LDs could provide energy reservoir for an aggressive cancer to trigger metastatic cloning. Moreover, LDs accumulation might impair drug-induced apoptosis as well as immunogenic cell death, resulting in the chemotherapy resistance of cancer cells.

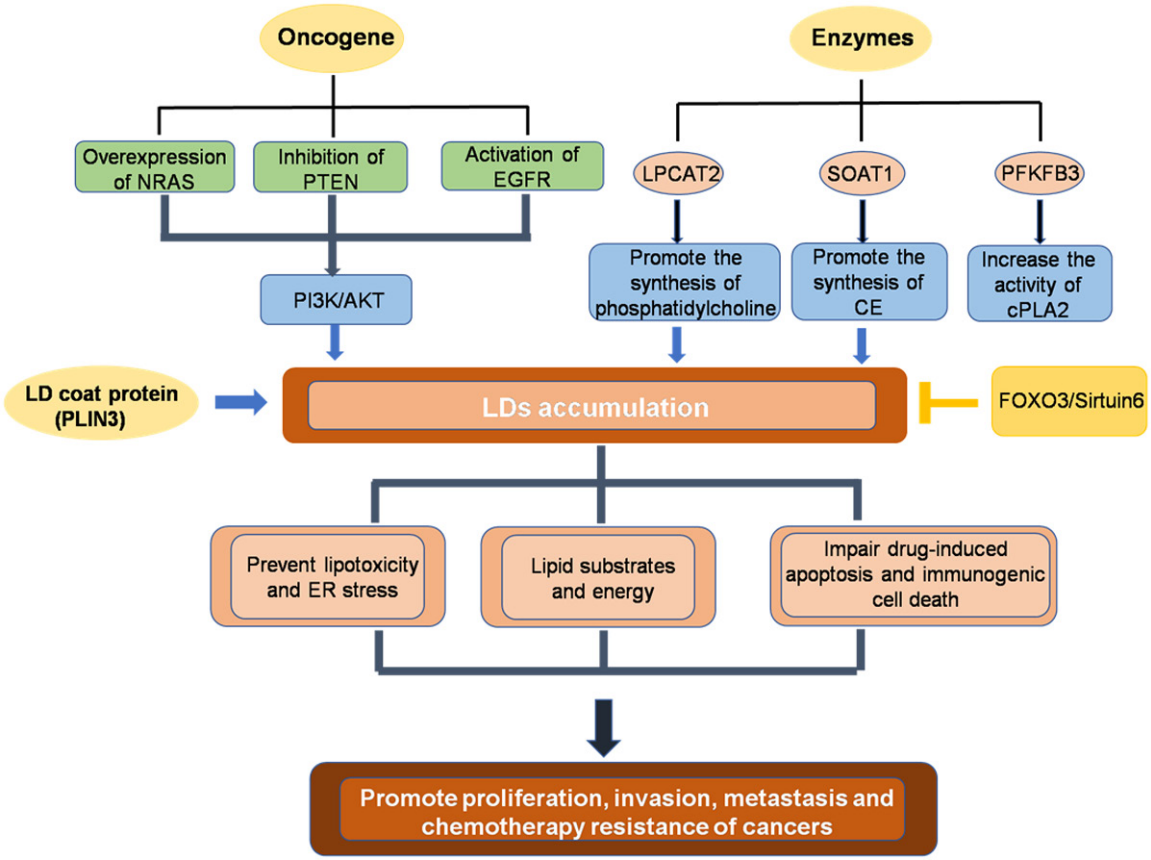

Figure 2. The regulatory mechanism of LDs homeostasis and its function in cancer progression. CE, cholesteryl ester; cPLA2, cytoplasmic phospholipase A2; EGFR, Epidermal growth factor receptor; FOXO3, Fork-head transcription factor 3; LPCAT2, lysophosphatidylcholine acyltransferase 2; NRAS, neuroblastoma RAS; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PLIN3, perilipin 3; PTEN, phosphatase and tension homolog deleted on chromosome 10; STOA1,sterol-O transferase 1.

LDs and colorectal cancer

Colorectal cancer (CRC) is one of the most common forms of cancer in the world [45]. Label-free Raman spectroscopy shows that increased LD intensity is a characteristic of colorectal cancer stem cells and LDs are also abnormally increased in CRC tissues [46, 47].

The proliferation of CRC cells is partly mediated by epidermal growth factor receptor (EGFR) signaling and requires sustained cellular energy levels to meet its high metabolic needs. The binding of the epidermal growth factor (EGF) ligand to the extracellular domain of the receptor leads to its activation, enabling downstream signaling pathways including PI3K/mTOR pathway to stimulate LD biogenesis and cell proliferation [36]. Meanwhile, prostaglandin E2 (PGE2) synthesis is necessary for CRC growth and is interdependent on LD density [48]. Moreover, EGF treatment can stimulate loss of FOXO3/SIRT6 to increase LD density, which is required for CRC cell proliferation [36].

LPCAT2, which is responsible for the Lands circulation of phosphatidylcholine synthesis, is a LD-localized enzyme. Recent study has shown that LPCAT2 can drive the production of LD in colorectal cancer and is positively correlated with the content of LDs in cancer tissues. Moreover, LPCAT2-mediated generation of LDs drives cell-death resistance to 5-fluorouracil and oxaliplatin *in vitro* and *in vivo*. These might attribute to the impairment of chemotherapy-induced ER stress responses, calreticulin membrane translocation as well as reduction in immunogenic cell death and $CD8^+$ T cell infiltration induced by LPCAT2/LD accumulation [39].

Membrane fluidity is an important factor affecting cancer cell invasion and metastasis [49].

Table 1. The regulatory mechanism of LDs and its implications in diversified cancers

Regulator	Regulatory mechanism	Cancer type	Effect on LDs and cancer progression	References
EGFR	EGFR/PI3K/mTOR	Colorectal cancer	LD accumulation	Accioly, M. T (2008)
	PGE2 synthesis		Cell proliferation	Penrose, H et al. (2016)
	FOXO3/Sirtuin6	Colorectal cancer	Reduction in LD density	Penrose, H et al. (2016)
			Cell proliferative inhibition	Wentao, Q et al. (2013)
LPCAT2	Upregulation of phosphatidylcholine synthesis	Colorectal cancer	LD accumulation	Cotte, A. K et al. (2018)
			Promoting cell death resistance to 5-fluorouracil and oxaliplatin	
CASIMO1	Interaction with SQLE to promote cholesterol synthesis	Breast Cancer	LD accumulation	Maria, PS et al. (2018)
			Cell proliferation and cell cycle progression	
V-ATPase↑ PEDF↓	Acidification of the TME	Prostate cancer	LD trafficking	Nardi, F et al. (2019)
			Promoting cell invasion	
NARS↑ PTEN↓	Activation of PI3K/AKT signaling	Hepatocellular carcinoma	LD accumulation	Gao, M et al. (2017)
			Promoting neoplasia and progression of HCC	Boespflug, A et al. (2017) Milella, M et al. (2015)
PFKFB3	Upregulation of cPLA2 activity	Ovarian cancer	Positively correlating with LD biogenesis and chemoresistance	Novellasdemunt, L et al. (2013)
				Mondal, S et al. (2019)
SOAT1	Upregulation of SREBP-1 mediated CE synthesis	Glioblastoma	Promoting LD formation and cell growth	Geng, F et al. (2016) Geng, F et al. (2017)
PLIN3	Upregulation of LD formation and lipid storage	Renal clear cell carcinoma	Correlating with tumor TNM stage and poor prognosis	Wang, K et al. (2018)

ACSL1, acyl-CoA synthetase long-chain family member 1; CASIMO1, cancer-associated amall integral membrane open reading frame 1; cPLA2, cytoplasmic phospholipase A2; FABPs, fatty acid-binding proteins; FOXO3, forkhead transcription factor 3; HSL, hormone-sensitive lipase; LDs, lipid droplets; LPCAT2, lysophosphatidylcholine acyltransferase 2; MAGL, monoacylglycerol lipase; NRAS, neuroblastoma RAS; PEDF, pigment epithelium-derived factor; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PGE2, prostaglandin E2; PLIN3, perilipin 3; PTEN, phosphatase and tension homolog deleted on chromosome 10; SOAT1, sterol O-acyltransferase 1; SQLE, squalene epoxidase; SREBP-1, sterol-regulatory element binding proteins 1.

The lower cholesterol/phospholipid ratio and higher unsaturated phospholipid can increase membrane fluidity. Recently, Mehdizadeh et al. reported metabolic side effects of conventional chemotherapy associated with lipid droplets accumulation and change of fatty acids distribution in gastrointestinal cancer cells. Treatment with doxorubicin and 5-FU produced highly saturated lipid droplets and unsaturated membrane lipids. The change of fatty acids distribution between phospholipids and triglycerides in the cells increased the content of lipid droplets and the fluidity of the membrane, potentially triggering the invasion and metastasis of cancer cells [50], which might partially account for gastrointestinal cancers treatment failure.

Therefore, LD overproduction facilitates cells proliferation, invasion and metastasis and confers CRC cell chemoresistance, which might be a druggable target to recover CRC cell sensitivity. The existence of LD accumulation in CRC stem cells also implicates its potential use as a prognostic biomarker for CRC recurrence and survival.

LDs and breast and prostate cancers

Breast cancer (BC) is the leading cause of cancer-associated death for women and the second most common cancer worldwide [51]. In addition to established risk factors such as age, family history of BC and genetic constellation, dysfunction of adipose tissue is now considered to be a contributing factor to the development and progression of BC [52]. Several studies have identified that aggressive BC cells contain higher numbers of intracellular LDs.

BC cells readily absorb extracellular fatty acids provided by the surrounding environment and store them in LDs. When incubated with adipose tissue-conditioned medium (ACM) derived from obese patients, a significant increase in unsaturation, esterification and lipid to protein ratio in LDs of BC cells was observed compared to that with ACM from overweight donors [53]. Considering that obesity is a known risk factor for BC, this might implicate a link between LD homeostasis disruption of cancer cells and obesity.

Microproteins, also known as sORF-proteins, are defined as a new class of molecules encoded by transcripts from presumed long non-coding RNA (lncRNAs). Recently, a novel microprotein CASIMO1 is implicated in the regulation of lipid homeostasis in BC cells. It interacted with SQLE, a key enzyme in cholesterol synthesis and increased LD clustering, thus impacting cell proliferation and cell cycle progression as well as actin assembly at the extension of membrane protrusions [41].

Prostate cancer (PCa) is the second leading cause of cancer-related deaths in men in Western countries [54]. Emerging evidence suggests that accumulation of intracellular lipids is progressively increased with higher Gleason score (GS) grade of human PCa [55]. LDs utilize microtubules (MTs) to mediate intracellular transport of cargo proteins. The LD density and movement velocity of LDs positively correlate with cancer aggressiveness, thus, expanding nutrient source to meet the metabolic needs of aggressive cells in the TME [55]. Acidification of the TME facilitates LD movement and accelerates velocity in cancer. Moreover, the membrane proton pump V-ATPase and lipolysis regulator pigment epithelium-derived factor (PEDF) are identifies as new modulators of LD trafficking in the TME.

In summary, driven by oncogenic signaling, increased LD contents are profoundly associated with the aggressive phenotype of both human BC and PCa.

LDs and hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common and aggressive cancer of the liver. One of the pathological features of HCC is steatosis. Steatosis usually leads to the accumulation of LDs and the number of LDs changes with cancer progression [56, 57].

PTEN is a classic tumor suppressor gene with lipid and protein phosphatase activity, and also a negative regulator of PI3K/AKT pathway [58]. Neuroblastoma RAS viral oncogene homolog (NRAS) is related to the occurrence and development of HCC after being activated [59]. Studies have shown that knocking down PTEN and overexpressing NRAS synergistically led to the disorder of glucose and lipid metabolism in liver cells, increased LD content and promoted the occurrence of HCC [60]. Hence, LD accumulation induced by activation of oncogenic pathways might contribute to the neoplasia and progression of HCC.

LDs and renal cell carcinoma

Renal cell carcinoma (RCC) is defined as a metabolic disease and is one of the most common malignant tumors in the urinary system [61]. Renal clear cell carcinoma (ccRCC) is the most common RCC subtype characterized by increased lipid droplets, which has a high risk of metastasis and poor response to radiotherapy and chemotherapy [62].

PLIN3, one of the members of the lipid droplet coating protein PAT family, is considered to be involved in the formation of lipid droplets and the storage of lipids in cells. The expression of PLIN3 is elevated in ccRCC patients and is closely correlated with the clinicopathological features, such as TNM stage. Moreover, high expression of PLIN3 suggests a poor clinical prognosis [43]. In that, the expression of PLIN3, which mediates the formation and accumulation of LDs, could serve as a useful evaluation index for clinical diagnosis of ccRCC.

LDs and glioblastoma

Glioblastoma (GBM) is a malignant tumor with dysfunction of lipid metabolism [63, 64]. It is the most aggressive brain cancer, also known as grade IV astrocytoma. Large amounts of LDs are observed in tumor tissues from GBM patients, but are not detectable in low-grade gliomas or normal brain tissues [42]. Thus, LDs might develop as a promising diagnostic biomarker for GBM.

SREBP-1, the central membrane-bound transcription factor in lipid metabolism, represents high avidity in glioblastoma (GBM) [65]. SOAT1 is a key enzyme responsible for cholesterol esterification and storage in LDs. Inhibition of SOAT1 down-regulates SREBP-1, resulting in a decrease in sterol synthesis. Meanwhile, suppression of SOAT1 reduces the synthesis of CE and the formation of LD, and consequently blocks GBM growth [42, 66]. Thereby, considering that cholesterol esterification and LDs formation emerge as novel characteristics of GBM, blocking these pathways may be a novel therapeutic strategy to treat GBM.

LDs and ovarian and cervical cancer

Ovarian cancer (OC) and cervical cancer are the two deadliest gynecological cancers. Although most patients initially respond to chemotherapy, 70% of patients relapse with tumors that are typically resistant to chemotherapy [67].

6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), a key regulator of glycolysis and gluconeogenesis, was reported to positively correlate with LD biogenesis and chemoresistance in gynecological cancer cells [40, 68]. PFK158 is a potent and selective inhibitor of PFKFB3 [69]. The autophagy flux induced by PFK158 treatment led to lipophagy, which down-regulated the activity of lipid droplet-associated protein cytosolic phospholipase 2 (cPLA2) and promoted LDs decomposition. Moreover, PFK158 administration combined with standard chemotherapy significantly alleviated tumor growth and LDs in tumor tissues in a highly metastatic drug-resistant ovarian xenograft model [40]. These effects may ascribe to the dual-targeting of glycolytic and lipogenic pathways by PFK158. In that, inducing lipophagy to decompose LDs might develop as a novel auxiliary strategy to improve standard chemotherapy sensitivity in gynecological cancers.

Conclusion

LDs are ubiquitous cellular organelles in eukaryotic cells. Not limited to lipid storage, LDs also perform diverse functions in different biological contexts, such as membrane biosynthesis, lipid metabolism, cell signaling and inflammation as well as maturation, storage, and turnover of proteins [66, 70-72]. LD accumulation is gradually recognized as a prominent characteristic in a variety of cancers and attracts increasing attention. LDs content has been identified associated with clinicopathological features and prognosis of cancers, which implicates its potential use as a biomarker for diagnosis, recurrence and survival of cancers.

Mechanically, intracellular excess lipid can be stored in LDs to avoid lipotoxicity, which is beneficial for the survival of cancer cells. Moreover, due to the rapidly proliferative state, cancer cells extensively require membrane biogenesis. The intermediate products of LDs metabolism could be converted to different phosphoglycerides, including phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG) and phosphatidylserine (PS), which constitute the biofilm of the main structural components.

LDs also act as regulatory hub of energy homeostasis. In case of nutrient deprivation, fatty acids released from LDs are used for energy production via mitochondria β-oxidation and Kreb's cycle. Thereby, during the aggressive process of cancer cells, LDs can function as energy source to support distant dissemination of cells. Notably, not only LD density but also LD motility is correlated with cancer aggressiveness. What is more, accumulating documents indicate that LDs are closely involved in chemotherapy resistance of cancer cells [39, 40, 73]. Increased LD content leads to the impairment of caspase cascade activation and ER stress responses induced by chemotherapy and is accompanied by a reduction in immunogenic cell death. Therefore, LDs accumulation might be develop as potential predictive index of the responses to conventional neoadjuvant therapies or immunotherapies in advanced stages of cancer patients.

Dysregulation of energy metabolism has been well established as a hallmark of cancer [74-78]. LDs are highly dynamic organelles, the biogenesis and degradation of which are tightly coupled to cell metabolism. Nevertheless, the regulatory mechanism of LDs metabolism by oncogenic signaling is far less understood. How do LD content, lipid/protein distribution in LDs as wells as the interaction between LDs and other organelles such as ER, mitochondrial, nucleus, peroxisomes and Golgi change in response to stress from tumor microenvironment? Therefore, further profound understanding the role of LDs in cancer progression should provide novel and promising strategy for cancer therapy.

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Disclosure of conflict of interest

None.

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