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REVIEW

# Lipid droplets provide metabolic flexibility for cancer progression

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**A hallmark of cancer cells is their remarkable ability to efficiently adapt to favorable and hostile environments. Due to a unique metabolic flexibility, tumor cells can grow even in the absence of extracellular nutrients or in stressful scenarios. To achieve this, cancer cells need large amounts of lipids to build membranes, synthesize lipid-derived molecules, and generate metabolic energy in the absence of other nutrients. Tumor cells potentiate strategies to obtain lipids from other cells, metabolic pathways to synthesize new lipids, and mechanisms for efficient storage, mobilization, and utilization of these lipids. Lipid droplets (LDs) are the organelles that collect and supply lipids in eukaryotes and it is increasingly recognized that the accumulation of LDs is a new hallmark of cancer cells. Furthermore, an active role of LD proteins in processes underlying tumorigenesis has been proposed. Here, by focusing on three major classes of LD-resident proteins (perilipins, lipases, and acyl-CoA synthetases), we provide an overview of the contribution of LDs to cancer progression and discuss the role of LD proteins during the proliferation, invasion, metastasis, apoptosis, and stemness of cancer cells.**

**Keywords:** cancer; invasion; lipid droplets; lipids; metastasis; tumorigenesis

**Abbreviations**

ACSL, acyl-CoA synthetase family; AML, acute myeloid leukemia; AMPK, AMP-activated protein kinase; ATGL, adipose triglyceride lipase; cAMP, 3′,5′-cyclic AMP; Cav-2, caveolin 2; Cdk1, cyclin-dependent kinase 1; CE, cholesterol esters; CES-1, carboxylesterase; CGI-58, comparative gene identification-58; COPI, coat protein complex I; CPT-1A, carnitine palmitoyltransferase 1A; CSCs, cancer stem cells; DGAT, diacylglycerol *O*-acyltransferase; EMT, epithelial-to-mesenchymal transition; ER, endoplasmic reticulum; FABP, FA binding protein; FA-CoA, cholesterol and acyl-CoA; FAO, β-oxidation; FAs, fatty acids; FASN, fatty acid synthase; GLUT, glucose transporters; HBXIP, hepatitis B interaction protein; HER2, human epidermal growth factor receptor 2; HIFs, hypoxia-inducible factors; HIG2, hypoxia-inducible protein 2; HILPDA, hypoxia-inducible lipid droplet associated; HNF-1α, hepatocyte nuclear factor 1α; HSL, hormone-sensitive lipase; IFN-γ, interferon γ; LDs, lipid droplets; LIPG, endothelial lipase; LPS, lipopolysaccharide; LPTAT-1, cardiac phosphatidyl transferase; MAGL, monoacylglycerol lipase; NCEH-1, neutral cholesterol ester hydrolase 1; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; PEDF, pigment epithelium-derived factor; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1alpha; PGE2, prostaglandin E2; PKA, cAMP-dependent protein kinase; PLINs, perilipins; PPP, pentose phosphate pathway; PUFAs, polyunsaturated FAs; ROS, reactive oxygen species; SCD-1, stearoyl coenzyme A desaturase-1; SIRT-1, sirtuin 1; SOAT, sterol *O*-acyltransferase; TAGs, triglycerides; TBK-1, TRAF family member associated with NFκB activator-binding kinase; TME, tumor microenvironment; TNBC, triple-negative breast cancer; TNF, tumor necrosis factor; VEGF-A, vascular endothelial growth factor-A; VHL, Von Hippel–Lindau tumor suppressor.

## The metabolic flexibility of cancer cells

The metabolic reprogramming exhibited by tumor cells was early recognized as a fundamental hallmark of cancer [1,2]. Since then, an avalanche of data has emerged to describe how cancer cells exploit a plethora of metabolic pathways and how this particularity could be used for targeted therapeutics [3,4]. In contrast to the tightly regulated metabolic pathways used by healthy cells, obediently responding to internal and external cues, cancer cells have developed countless strategies to heighten fundamental metabolic circuits involved in the generation of metabolic energy and the production of essential metabolic intermediates. The acquisition of the tumoral phenotype apparently requires a profound reprogramming of cellular metabolism in which tumors hijack well-defined metabolic pathways for their benefit by activating oncogenes or/and inhibiting tumor suppressor genes [5].

The metabolism of aggressive cancer cells is frequently characterized by the consumption of large amounts of glucose, which has been estimated as 20–30 times higher than that of normal cells [6]. Even in the presence of oxygen, cancer cells metabolize glucose into lactate (fermentation) but also into fatty acids (FAs) and nucleic acid-associated carbohydrates [7]. This allocation reflects both the high demands of proliferating cells and a relative reduction of the rates of oxidative phosphorylation when compared to fermentation [6]. Commonly known as the "Warburg effect", this metabolic rewiring was initially described by Otto Warburg as "aerobic glycolysis" [2] and later redefined by him as "aerobic fermentation" [8]. Although still controversial, the relative preference exhibited by cancer cells for aerobic fermentation could reflect a mechanism to avoid the saturation of the metabolic circuits functioning within mitochondria or/and the need of mechanisms to ensure the production of key intermediates of the redox metabolism [9–11].

Furthermore, cancer cells exploit other metabolic circuits including glutaminolysis, the pentose phosphate pathway (PPP), and upregulate the biogenesis of mitochondria [12]. Especially in the harsh tumor microenvironment (TME), often insufficiently vascularized, hypoxic, and acidic, this metabolic flexibility secures cancer cells with continuous bioenergetic fuels and intermediates [3]. Among the hijacked metabolic pathways, a hastened lipid metabolism is increasingly recognized as a fundamental trait of cancer cells and a salvation tactic when confronted the inhospitable TME [13–15]. Phospholipids, glycolipids, sterols or cholesterol esters (CE), and FAs or triglycerides (TAGs) provide cancer cells with raw material for membrane synthesis, to produce signaling molecules, and to generate metabolic energy independently of glucose [15,16]. These lipids, increasingly recognized as key mediators of cancer cell expansion and motility, are generated either intrinsically by *de novo* lipogenesis (from glucose or amino acids) or are extrinsically obtained from neighboring cells such as adipocytes, stromal cells, and immune cells [17].

In eukaryotic cells, intracellular lipids are collected, stored, and supplied to different fates in a timely manner by atypical organelles called lipid droplets (LDs) [18]. Transformed cells often accumulate LDs, a phenotype increasingly recognized as a new hallmark of cancer cells, reflecting a highly dynamic lipid metabolism [19,20] (Fig. 1). Whether LD-lipids and LD proteins actively participate in the establishment of different types of malignancies is still debatable although recent evidence has implicated LDs in different aspects of cancer initiation, progression, and resistance [16,19,21]. Far beyond their functioning as metabolic hubs and their main contribution to nutrient administration [22], LDs are overseeing a variety of intracellular and environmental stresses, most of them likely occurring in tumor cells [23–25].

Here, we delve into the current knowledge of the LD participation in cancer metabolism. We will discuss when and how LD-lipids and LD proteins support proliferation, apoptosis, invasion, metastasis, and stemness of cancer cells. We will focus particularly on the available data about the role of three classes of major LD-resident proteins (perilipins, neutral lipases, and acyl-CoA synthetases), all of them with well-characterized functions on healthy LDs.

## Lipid droplet-lipids

As a major class of biological molecules, lipids are involved in most cellular processes; from essential components of the bilayers (e.g. phospholipids or cholesterol) to influential signaling molecules (e.g. diacylglycerol or ceramides), inflammatory mediators (e.g. prostaglandins and leukotrienes), and protein regulators (e.g., palmitoylation or myristylation) [26]. Furthermore, the FAs esterified in TAG represent the main energy reservoirs of eukaryotic cells, yielding a large amount of energy when oxidized in mitochondria or peroxisomes by β-oxidation (FAO) [27].

However, when lipid concentration exceeds the physiological levels, intracellular lipids display toxic properties, a process known as lipotoxicity [28]. Lipids can act as detergents, change membranes fluidity, affect

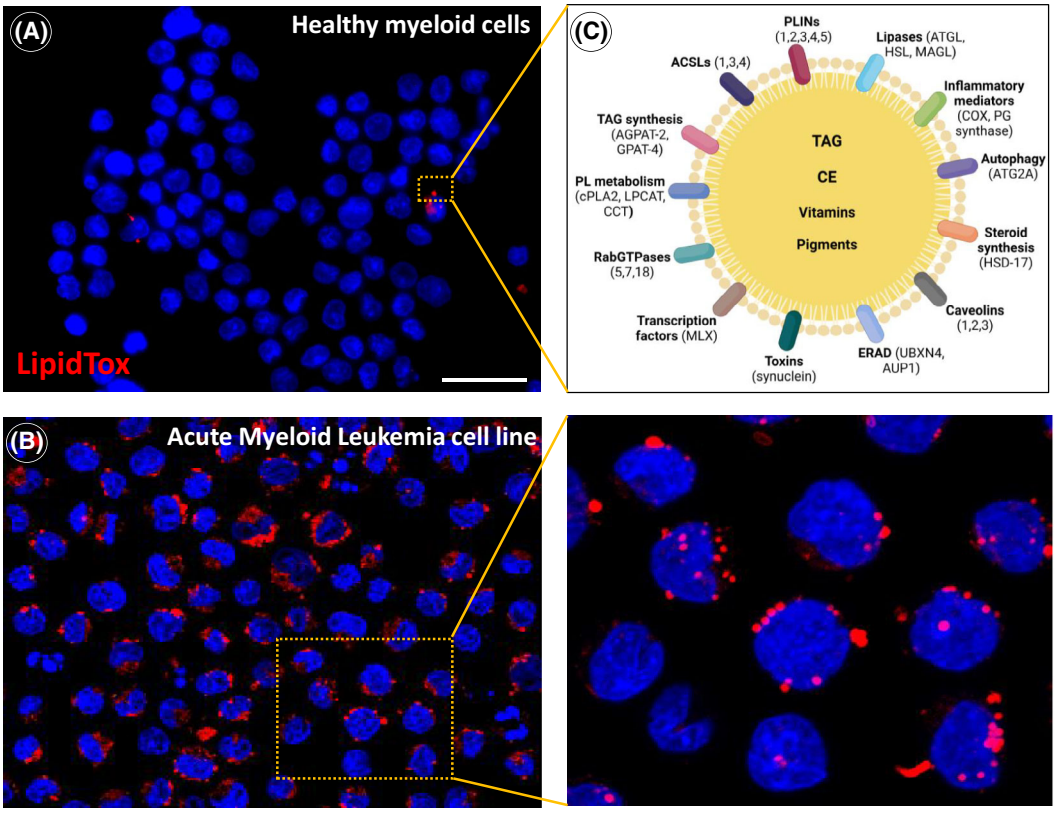


**Fig. 1.** Representative images of LDs in healthy and cancer cells. (A, B) Fluorescent images of LDs content in healthy cells (normal bone marrow myeloid progenitor) and acute myeloid leukemia (AML) cell line. The accumulation of LDs occurring in cancer cells is clearly illustrated in myeloid cells, with low LD levels in healthy cells and high LD levels in AML. (B) High magnification image (Z stack projection) representing LDs heterogeneity in size and number between cancer cells. LDs are stained with Lipid Tox, and nuclei are stained with DAPI. Scale bar, 20 μm. (C) Simplified scheme representing major LD-proteins in healthy cells.

acid–base homeostasis, cause overactivation of signaling pathways, boost the generation of reactive oxygen species (ROS), and can be oxidized into lipid peroxides, all of these toxic processes causing cellular stress and leading to various forms of cell death [29–31].

To deal with the antagonist aspects of intracellular lipids, eukaryotic cells rapidly esterify FAs and cholesterol into neutral TAGs and CE. These neutral lipids are rapidly packed and accumulated within LDs until needed [32]. Thus, LDs prevent lipotoxicity by buffering lipids and provide cells with resources during nutrient scarcity. Indeed, by channeling the surplus of lipids into LDs, cells reduce lipotoxicity and endoplasmic reticulum (ER) stress [33,34], palmitate-induced apoptosis [35,36], accumulation of ceramides [37], or the oxidation of polyunsaturated FAs (PUFAs) leading to ferroptosis [38] (Fig. 2). The overloading or dysregulation of these pathways, caused for example during obesity or by mutations in genes related to LDs, have been associated with disease progression, especially with metabolic disorders such as lipodystrophy, metabolic syndrome, diabetes, fatty liver disease, and atherosclerosis [39].

Fundamental questions about the biogenesis of LDs are still being addressed and the reader can find fascinating details of this remarkable and highly conserved biological process in the excellent reviews of this special issue. Briefly, FAs are esterified into TAG by the sequential action of enzymes residing in the ER [18] (Fig. 3). The last step in neutral lipid synthesis is conducted in the ER by diacylglycerol *O*-acyltransferase (DGAT-1 and -2) converting diacylglycerol into TAG and for sterol *O*-acyltransferase 1 (SOAT-1 and -2) forming CE from cholesterol and acyl-CoA (FA-CoA). Recently, an alternative TAG synthesis pathway was described, whereby the ER-resident acyltransferase DIESL and its regulator TMX1 synthesize TAG at the expense of membrane phospholipids, especially during fluctuations or limitations in nutrient supply [40]. Neutral lipids are gradually accrued into lipid lens that phase separate within the ER bilayer in a process nucleated by seipin and coordinated by proteins

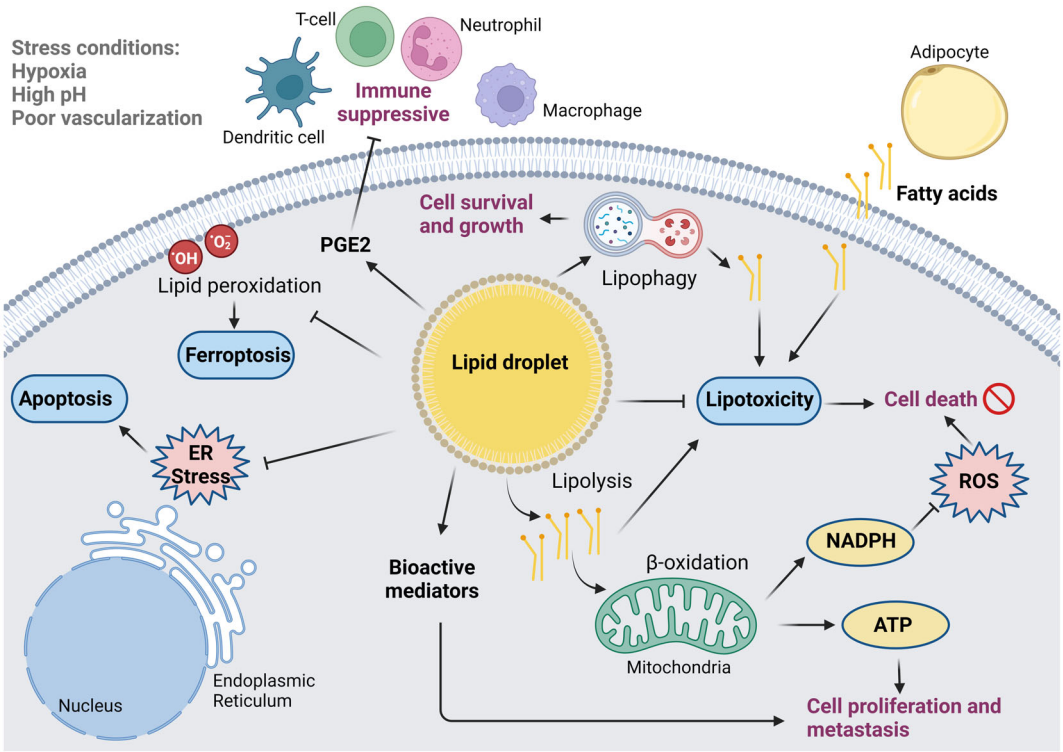


**Fig. 2.** LD functions in healthy and cancer cells. During stress conditions, LDs inhibit ER stress, ROS, lipid peroxidation and impede lipotoxicity by retaining toxic lipids. These processes will prevent cancer cell death. LDs release bioactive mediators (diacylglycerol, ceramides, vitamins, prostaglandins, and leukotrienes) and FAs, fueling cell proliferation and metastasis. LDs secrete PGE2 that enables an immune suppressive microenvironment. LD degradation by lipolysis and lipophagy will provide the building blocks for cancer growth and survival. ATP, adenosine triphosphate; ER, endoplasmic reticulum; NADPH, nicotinamide adenine dinucleotide phosphate; PGE2, prostaglandin E2; ROS, reactive oxygen species.

forming "LD assembly complexes" [41]. As additional lipid arrives, the lens progressively grows into the cytosol to generate a nascent LD and finally a mature LD. Thus, LDs are spherical organelles with a hydrophobic core of TAG, CE, and hydrophobic molecules, such as vitamins or pigments, encircled by a monolayer of phospholipids [18,42].

## Lipid droplet-proteins

The LD surface accommodates a complex proteome that, recruited from the ER or from the cytoplasm [43], administrates the nutrients. High throughput proteomic analyses determined that more than 150 different proteins simultaneously reside on LDs [44,45]. Dynamic competition between LD proteins allows rapid remodeling of the LD proteome to quickly respond to changes in nutritional, metabolic, and stress conditions [46].

Perilipins (PLINs) are the major cytosolic LD-associated proteins [47,48]. The PLIN family is of ancient origin and has expanded to include five mammalian genes (PLIN 1–5). PLINs show differential patterns of gene expression, with PLIN-1 limited to adipose tissues, PLIN-2 and PLIN-3 in the rest of cell types (including preadipocytes), PLIN-4 to adipocytes but also brain, heart, and skeletal muscle, and PLIN-5 restricted to FA oxidizing tissues such as heart, brown adipose tissue, and skeletal muscle [47,49]. In addition to coating hydrophobic lipids in the aqueous environment of the cytosol, a main function of PLINs is regulating the activity of the lipases functioning on LDs (see details below). Further, PLINs could tether LDs to mitochondria [50–54] and, in the case of PLIN-5 translocate into the nucleus to activate sirtuin 1 (SIRT-1) and peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) and promote mitochondrial biogenesis during starvation [55,56].

Neutral lipases are also abundant proteins on LDs. The "canonical" lipolysis is a process accomplished by the consecutive action of at least three lipases: Adipose

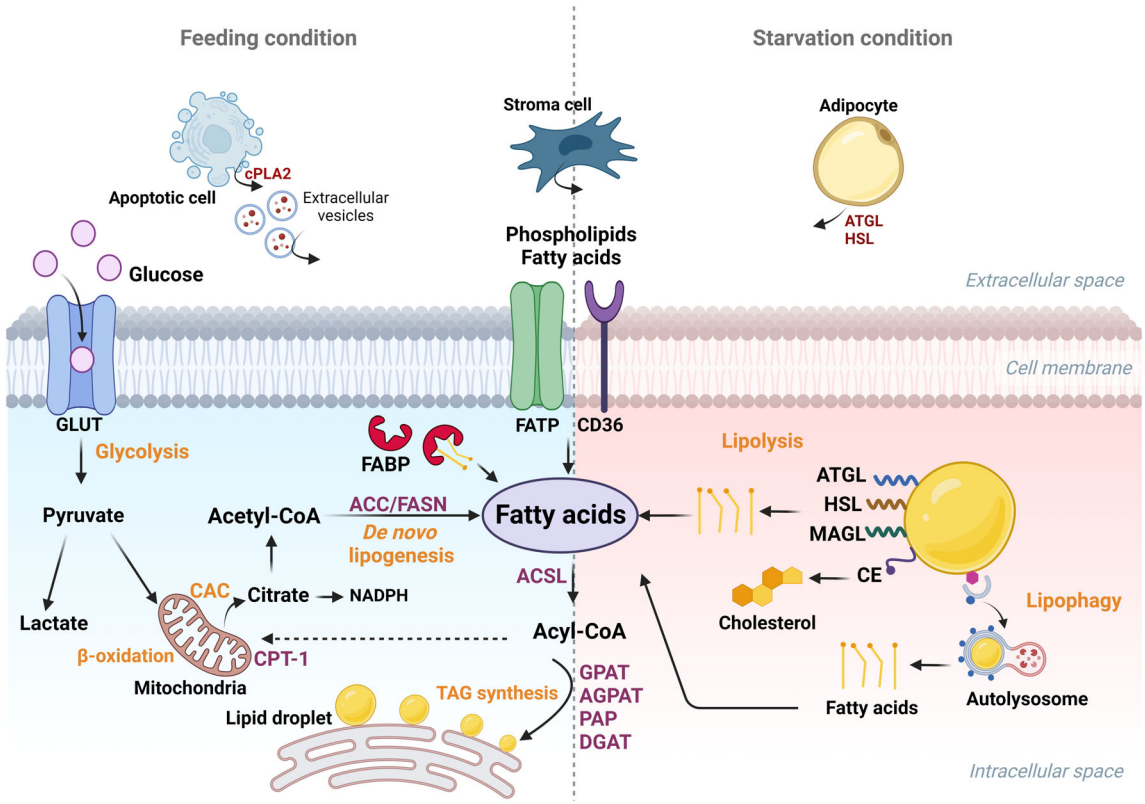


**Fig. 3.** Schematic representation of LDs turnover in cells. In feeding conditions, FAs are supplied from the extracellular space through lipids mobilization from adjacent cells such as adipocytes, stroma cells and apoptotic cells and from the intracellular space through *de novo* lipogenesis, lipolysis, and lipophagy. During starvation, LDs are consumed mainly through lipolysis, including key enzymes ATGL, HSL, MAGL and CE. LDs could also be catabolized through lipophagy. ACC, acetyl-CoA carboxylase; ACSL, long-chain acyl-CoA synthetase; AGPAT, 1-acylglycerol-3-phosphate-*O*-acyltransferase; ATGL, adipose triglyceride lipase; CAC, citric acid cycle; CD36, fatty acid receptor; CE, cholesterol esterase; cPLA2, cytosolic phospholipase A2; CPT-1, carnitine palmitoyltransferase 1; DGAT, diglyceride acyltransferase; FASN, fatty acid synthase; FATP, FABP, fatty acid transporters; GPAT, glycerol-3-phosphate acyltransferase; HSL, hormone-sensitive lipase; MAGL, monoacylglycerol lipase; PAP, phosphatidic acid phosphatase.

triglyceride lipase (ATGL) and its coactivator comparative gene identification-58 (CGI-58 or ABHD-5), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MAGL) [29]. A minor pool of these enzymes is constitutively active to generate a cycle of lipolysis and re-synthesis of TAG and facilitate cellular adjustments in the quality of the stored FAs [57]. However, in response to low glucose or low ATP levels, PLINs and lipases are robustly phosphorylated by the energetic sensors 3′,5′-cyclic AMP (cAMP)-dependent protein kinase (PKA) and AMP-activated protein kinase (AMPK). Phosphorylation reorganizes the LD proteome facilitating recruitment of additional lipases and activating their lipolytic activity to gradually hydrolyze TAGs into three FAs and glycerol [27]. On the other hand, CE is hydrolyzed by HSL, neutral cholesterol ester hydrolase 1 (NCEH-1) and carboxylesterase 1 (CES-1) yielding cholesterol and one FA. Interestingly, the identity of additional "non-canonical" lipases, especially in non-adipose tissues, is being gradually demonstrated, likely suggesting the existence of alternative mechanisms and environmental conditions in which LDs may provide cells with FAs responding to specific needs rather than nutrient scarcity [29].

In addition, especially during periods of prolonged starvation, TAG and CE within LDs are metabolized by different types of lipophagy involving small parts of LDs, the whole organelle, or specific LD proteins [58–61]. Whether produced by lipolysis or/and lipophagy, the potential of LDs for supplying energetic and metabolic substrates to proliferative cells is exemplified by the fact that these organelles provide hepatocytes with the necessary resources to regenerate the liver after a 70% hepatectomy, a compensatory hyperplasia accomplished in just 5/7 days [62].

A third group of major LD proteins includes several members of the acyl-CoA synthetase family (ACSL) [63]. Before use, FAs need to be activated by esterification with coenzyme A to form an acyl-CoA (or FA-CoA), an ATP-dependent two-step reaction catalyzed by ACSLs. The proposed LD-resident ACSL members are ACSL-1, ACSL-3, and ACSL-4 [42,64–69]. Different ACSLs differ in their substrate preference: ACSL-1 has a marked preference for oleate and linoleate, ACSL-3 for myristate, palmitate, arachidonate, and eicosapentaenoate, and ACSL-4 for arachidonate [70]. Although with highly redundant activities, different ACSLs could be targeting FAs to different cellular fates: ACSL-3 has been involved in LD formation [42,66], ACSL-1 in channeling FAs into mitochondria [71,72], and the arachidonate activated by ACSL-4 has been involved in processes such as ferroptosis or inflammation by channeling the activated FAs into phospholipids or prostaglandins [30,73].

In addition to the aforementioned proteins, LDs also recruit proteins involved in TAG synthesis (e.g. AGPAT-2 and GPAT-4), phospholipid metabolism (e.g. LPCAT or CCT), steroid synthesis (e.g. HSD-17), proteins related to autophagy (e.g. ATG2A), and up to 26 Rab GTPases (e.g. Rab5, 7 or 18) [44,45]. Furthermore, likely reflecting additional roles beyond lipid administration, LDs accrue proteins such as histones [74], toxic proteins [75], caveolins [76–78], transcription factors [79,80], proteins of the ubiquitin system [81], components of the ER-associated degradation of proteins [82,83], and immune-related proteins [25,84,85]. Although the function of these proteins on LDs is still poorly characterized, the use of systematic molecular profiling approaches has revealed that these non-intuitive systems could be functional on LDs, clearly increasing the potential functions of LDs in healthy and cancer cells [86].

## Lipid droplets in cancer

Epidemiological evidence suggests that obesity and the associated metabolic syndrome increase the risk of many cancer types [87,88]. Alterations in circulating cholesterol levels are a risk factor for melanoma, non-Hodgkin lymphoma, endometrial, colorectal, prostate, and breast cancers [89–92]. Diabetic patients are more susceptible to developing colorectal, pancreatic, gallbladder, biliary, hepatocellular, gastric, esophageal, oral, breast, endometrial, ovary, kidney, and thyroid cancers as well as leukemias [93]. Indeed, whilst alteration in lipid metabolism could have a direct or indirect role in oncogenicity in cancers such as liposarcoma [94], sebaceous gland carcinoma [20], and hepatocellular carcinoma [95], it is increasingly considered as a risk factor for many other cancer types [96,97]. For instance, LDs correlate negatively with tumor grade and differentiation status in liposarcoma: they are prominently present in dedifferentiated liposarcomas and absent in well-differentiated liposarcomas, lipomas, and normal adipose tissue [98]. In hepatocellular carcinoma, an increase in lipid synthesis and fatty acid desaturation, a reduction in fatty acid oxidation, and a generation of phosphatidylcholine are among the metabolic adaptations occurring in normal hepatocytes when they switch to proliferation [95].

The key contribution of lipid metabolism to cancer progression has been recently explained in excellent reviews [13,14] and thus, here we will focus on the existing data directly involving LDs.

The extent and purpose of the LD accumulation exhibited by cancer cells is highly heterogenous and depends on the cancer subtype and dysregulated metabolic and signaling pathways. Furthermore, LDs may vary in size and number due to the heterogeneity across and within tumors and vary during different stages of cancer progression. However, independently of the causative factors, the presence of LDs in cancer cells often correlates with increased aggressiveness [99–103]. Cancer cells accumulate LDs as the result of a variety of factors such as (a) an overexpression of lipogenic enzymes [104,105], (b) a heightened autophagic flux [99], (c) mechanisms to increase the cellular uptake of FAs [106,107], and (d) by decreasing the consumption of FAs by mitochondria [108]. For example, in hepatocellular adenomas the accumulation of LDs results from the inactivation of the hepatocyte nuclear factor 1α (HNF-1α) leading to an aberrant increase in lipogenesis and accumulation of the LDs typically used as a diagnostic marker of the disease [109]. However, in clear cell renal carcinoma (phenotypically recognized by high lipid and glycogen deposition), the constitutive activation of the hypoxia-induced factor 1 (HIF-1) and HIF-2 by the von Hippel–Lindau tumor suppressor (VHL) leads to the repression of carnitine palmitoyltransferase 1A (CPT-1A), the FA transporter at the mitochondrial outer membrane, reducing FA uptake and FAO and re-driving FAs into LDs [108]. In contrast, glioblastoma cells exploit mitochondria and FAO not only to generate metabolic energy but also metabolic intermediates rendering molecules such as NADPH to counteract oxidative stress [110,111]. Thus, the accumulation of LDs exhibited by cancer cells is caused by diverse factors and serves to different strategies in various cancer types.

In this heterogeneous scenario, cancer LDs could be directly involved in four key features of cancer

progression. First, LDs are rapidly accumulated during apoptosis [112–115]. Indeed, LD formation, determined by nuclear magnetic resonance spectroscopy, is used as an *in vivo* marker of the efficiency of antitumoral pro-apoptotic drugs [116–119]. The apoptosis-induced generation of intramitochondrial ROS leads to the inhibition of FAO and the accumulation of LDs despite of the decreased cell's capacity for lipid synthesis due to p53 activation and mTOR inhibition [115]. Although the precise role of these LDs or whether cancer cells exploit this mechanism more efficiently than healthy cells is still debatable, apoptosis-induced LDs may contribute to reduce free toxic lipid species generated during apoptosis including palmitate, diacylglycerol, ceramides, or polyunsaturated FAs and thus, overall reducing signaling, DNA damage, inflammation, and lipid peroxidation [120–122]. Furthermore, apoptosis-induced LDs could indirectly participate in the resistance of cancer cells to pro-apoptotic drugs by sequestering the toxic and often hydrophobic compounds [123,124]. By reducing formation of apoptosis-induced LDs, cytosolic phospholipase A2 (cPLA2α) inhibitors sensitize glioblastoma multiforme cancer cells to the cell death promoted by anticancer compounds [125].

Second, LDs accumulate in cancer cells when exposed to hypoxic conditions. After uncontrolled proliferation, cancer cells are often subjected to hypoxia due to an aberrant tumor vascularization. In response to low oxygen levels, cells regulate the adaptative response by HIF-1 and HIF-2 [126]. HIF-1 exert their effects on cancer progression by binding to and activating the transcription of target genes involved in angiogenesis, cell survival, genetic instability, immortalization, immune evasion, invasion and metastasis, proliferation, pH regulation, and stem cell maintenance. A key cellular response mediated by HIF-1 is to increase the formation of LDs [108,127,128]. These LDs could be formed by increasing the FA uptake mediated by FA binding proteins (FABP-3 and FABP-7) and FA storage mediated by PLIN-2 [128] or by inhibition of CPT-1A [108]. Accumulated lipids could provide hypoxic cells with a source of metabolic energy and intermediates required to reduce oxidative stress [128], and specifically support growth and invasiveness following reoxygenation [127,128]. The inhibition of LD formation decreased the survival of breast cancer cell lines subjected to hypoxia-reoxygenation and impaired tumorigenesis [128].

Third, the accumulation of LDs seems to be a prerequisite in primary cancer cells prior to metastasis. Cancer cells activate their motility and invasive capacities to degrade the extracellular matrix and extravasate through the local vasculature to colonize secondary sites. In the context of epithelial cancer, this process starts with an epithelial-to-mesenchymal transition (EMT) during which cancer cells lose their epithelial features and acquire mesenchymal traits favoring cell mobility, metastatic potential, and resistance [129]. A lipid-related metabolic signature is associated with EMT where the epithelial phenotype was distinguished by high levels of monounsaturated FAs and increased expression of *de novo* FA synthesis enzymes, while the mesenchymal phenotype was characterized by high levels of polyunsaturated FAs, reduced lipogenesis, and increased expression of genes implicated in TAG synthesis [130]. Cancer cells accumulate LDs following an acidosis-induced TGF-β2 activation, leading to EMT induction, evasion from immunosurveillance and increase in the invasive potential [131]. The high LD content will fuel FAO in primary tumor sites to increase the promigratory potential of cancer cells and enhance metastasis to secondary tumor sites [132]. Metastatic prostate cancer tissues accumulate CE due to a loss of the tumor suppressor PTEN and an activation of the PI3K/AKT/mTOR/SREBP pathway. The inhibition of cholesterol esterification restrained prostate cancer aggressiveness in terms of reducing invasion and *in vivo* tumor growth [100].

Fourth, LDs deliver energy and maintain the survival of cancer stem cells (CSCs) through the activation of cancer stemness pathways. They grant CSCs the privilege of avoiding starvation and death during scarcity conditions. CSCs, also known as tumor-initiating cells, are a subset of therapy-resistant cells found in many tumors which can regenerate the tumor, making them a major source for cancer recurrence. CSCs harbor metabolic plasticity allowing them to dynamically transform their metabolic state to favor glycolysis or oxidative metabolism [133]. Current data indicate that CSCs have higher levels of LDs than differentiated cancer cells [134–136]. In breast CSCs derived from multiple cell lines, LD numbers correlate with stemness capacity [137]. Furthermore, the pool of CSCs was enriched with the population of cells having high LD numbers, highlighting a key role for the lipid metabolism in the maintenance of the breast CSCs [137].

In conclusion, cancer cells acquire mechanisms of lipid storage for surviving to nutrient deprivation or different types of stress. Cancer cells exploit cellular metabolic circuits to consume LDs in favor of their proliferation, metastasis, and stemness. Studies by Raman microspectroscopy showed that LDs are not homogeneous among cancer cells, but rather show different lipid concentration and composition [138].

Therefore, altogether these studies advise that systematically investigating the composition and hijacked circuits governing cancer-LD metabolism could provide valuable information for tailoring selective therapies according to the metabolic profile of LDs, which is reflecting the specific needs of specific types of cancer cells.

## Lipogenic enzymes in cancer

Fatty acid synthase (FASN), stearoyl coenzyme A desaturase-1 (SCD-1), DGAT-1 and 2, and SOAT-1 and 2 are among the enzymes having a pivotal role in lipogenesis and are frequently overexpressed in cancers [139–141]. FASN is the second enzyme of *de novo* lipogenesis catalyzing the synthesis of palmitate using malonyl-CoA and acetyl-CoA as substrates [139]. SCD-1 catalyzes the conversion of the potentially toxic saturated FAs, including palmitate, into Δ9-monounsaturated FAs and renders palmitoleate and oleate [139]. DGATs catalyze the final step of lipogenesis by converting diacylglycerol and acyl-CoA into TAG [142]. SOATs maintain cholesterol homeostasis by catalyzing the synthesis of CE [143].

The upregulation of these lipogenic enzymes together with the plasma membrane FA receptor (CD36) is coupled to cancer proliferation, resistance to cell death, aggressiveness, and stemness. The analysis of tumors from a computational approach showed that despite the heterogeneity of cancer cells, the majority displays an increased TAG content which might be attributable, at least partially, to the activation of lipogenic enzymes [144]. In fact, several cancer cells increase the uptake and storage of lipids in LDs *via* the overexpression of DGAT-1 [140], SOAT-1 [145] and SCD-1 [146]. Moreover, an accumulation of CE was reported in pancreatic cancer patients and cell lines, where SOAT-1 expression correlated with poor patient survival. Inhibition of cholesterol esterification by either SOAT-1 inhibitor or shRNA knockdown reduced cancer cell proliferation and metastasis in an orthotopic mouse model [147]. In ovarian cancer, LD levels and cancer stemness correlated with the activity of SCD-1, where CSCs possessed high levels of unsaturated FAs. Blocking SCD-1 decreased LDs content and impaired cancer stemness and tumor initiation capacity by inactivating the NF-κB (nuclear factor kappa B) pathway [135]. SCD-1 upregulation also contributes to LD formation in response to hormones, such as progestin, in breast cancer [146]. Furthermore, LD accumulation enhances the metastatic potential of cancer cells through the upregulation of FASN expression, which stimulate prostaglandin E2 (PGE2) synthesis [122] and energy production [134], and DGAT-2 which, in a C/EBPα-dependent manner, triggers FAO and resistance to anoikis [131].

Given that cancer metastasis is controlled by factors outside of the tumor cell itself, lipid mobilization from stromal to cancer cells is often required for metastasis and aggressiveness. A well-established metabolic symbiosis between cancer cells and adipocytes has been found in several cancer types. For instance, in ovarian cancer, adipocytes promote homing and metastasis of cancer cells by upregulating adipokines like IL-8 and FABP-4 at the adipocyte-tumor cell interface. A co-culture of adipocytes and cancer cells demonstrated that adipocytes provide FAs for rapid tumor growth *in vitro* and *in vivo* [148]. In the same context, an additional mechanism of FA transfer was reported where adipocytes supply FAs to cancer cells which, in turn, upregulate the CD36 receptor in the plasma membrane increasing FA uptake [149]. When impairing the FA transfer using CD36 inhibitors, monoclonal antibody or shRNA knockdown, LD levels were diminished as well as the tumor burden and dissemination [149]. The expression levels of CD36 are upregulated not only in human metastatic ovarian tumors but also in mouse oral squamous cell carcinomas, melanoma, lung squamous cell cancer, bladder cancer, and luminal A breast cancer, correlating with poor prognosis in all cases [149,150].

## PLIN-2 in cancer

In mammalian cells, PLINs play a vital role not only in LD biogenesis [151,152] but also in regulating lipolysis and lipophagy [153–155]. In contrast to PLIN-1, 4, and 5 that are expressed in specific tissues, PLIN-2 and PLIN-3 are more ubiquitous [156]. The expression of PLIN-2 is understood as an indicator of the cellular LD content in healthy and cancer cells [49,156]. Next, we will explore the implication of PLIN-2 in cancer progression, while the levels and implications of PLIN-3, 4, and 5 are summarized in Table 1.

The upregulation of PLIN-2 protein has been documented in gastric, colorectal, renal, hepatocellular, lung, esophagus, skin, head and neck, and thyroid cancers. In all these cancer types, PLIN-2 levels have been associated with cell proliferation and metastasis, being often correlated with a poor prognosis [157,158]. Most of the studies discussing PLIN-2 in cancer are correlative, linking the presence of PLIN-2 to many carcinogenesis steps, such as proliferation, invasion, and metastasis.

The association between LDs and cell cycle was first suggested by the fact that LDs are polarized before

**Table 1.** Association of selected LD-associated proteins with tumorigenesis. ND, not determined; +, present; −, absence.

| Cancer type | Biological model | LD-associated proteins | Expression +/− | Role in tumorigenesis | References |
|---|---|---|---|---|---|
| Breast cancer | Cell lines: MDA-MB-468, SKBR3, MCF7 and MDA-MB-231 | PLIN-1 | − | Attenuates cell migration | [229,230] |
| | Cancer genomics database: TCGA and other public datasets | | | High expression predicts a longer overall survival | |
| | Cancer genomics database: TCGA and other public datasets | PLIN-2 | − | High expression predicts a poor overall survival | [230] |
| | Clinical tumor tissue samples: mammary apocrine carcinoma | | + | ND | [231,232] |
| | Cancer genomics database: TCGA and other public datasets (luminal B subtype of cancer) | PLIN-3 | + | ND | [230] |
| | Cancer genomics database: TCGA and other public datasets | PLIN-4 | − | High expression in the HER2 (−) subgroups | [230] |
| | Cell line: MDA-MB-436 | | + | High expression in resistant TNBC cells and chemoresistant tumors treated with doxorubicin-based chemotherapy | [233] |
| | Cancer genomics database: TCGA and other public datasets (luminal A subtype of cancer patient) | PLIN-5 | − | High expression in the HER2 (−) subgroups | [230] |
| | Cell line: MCF-7 | DGAT-2 | ND | Promotes cell migration | [234] |
| | Cancer Genome Atlas database: TCGA (Her2-positive patients) | | − | Increases resistance to radiation therapy<br>Relates to HER2 (+) patient prognosis | [235] |
| | Cell lines: MCF-7, MDA-MB-231, T47-D, MDA-MB-436, MDA-MB-134, MDA-MB-175, MDA-MB-330, MDA-MB-361, MDA-MB-468, BT-483, BT-474, BT-20, and BT-549 | HSL/ATGL | + | Stimulates breast cancer cell proliferation and migration | [236] |
| | Cell lines: ZR-75-1, HMT-3522-T4-2, MCF-7, T47D, and MDA-MB-231 | | + | High expression correlates with aggressiveness<br>Increases invasion | [171] |
| | Cancer Genome Atlas database: TCGA | | + | Associates with poor survival | [237] |
| | Bioinformatics analysis: targeted exome sequencing of tumor | ACSL-3 | + | Associates with poor outcome in TNBC patients | [204] |
| | Mice: xenografts Rag2−/− | | | Reduces LDs content | [132] |
| | Cell lines: MDA-MB-231 and MDA-MB-468 | | | Increases metastasis | |
| Prostate cancer | Xenograft: NOD SCID and R2G2 mice | PLIN-3 | + | Increases proliferation, reduces radiosensitization | [238,239] |
| | Cell lines: DU145, PC3 and 22Rv1 | | | High expression predicts poor prognosis | |
| | Cell line: LNCaP | DGAT-1 | + | Increases the growth of prostate cancer cells<br>Inhibition leads to autophagy | [145] |
| | Cell line: LNCaP | ATGL | + | ND | [145] |
| | Cell line: LNCaP | ABHD5 | + | Increases the growth of the prostate cancer cells<br>Inhibition leads to apoptosis | [145] |
| | Cell lines LNCaP, C4-2, and C4-2B | | − | Triggers EMT<br>Increases proliferation and invasion | [189] |

**Table 1.** (Continued).

| Cancer type | Biological model | LD-associated proteins | Expression +/− | Role in tumorigenesis | References |
|---|---|---|---|---|---|
| | Cell lines: LNCaP DU145 and PC3 | ACSL-3 | + | Promotes cell growth of castration-resistant prostate cancer | [209] |
| Ovarian cancer | Cancer Genome Atlas database: TCGA | DGAT-1 | + | Increases proliferation, migration, invasion, colony forming, and tumor growth | [240] |
| | Cell lines: PEO4, PEO1, OVCAR-5, IGROV1, OVCAR-8, ES2, SKOV3, MCAS, and OVCAR3 | | | High expression predicts poor prognosis | |
| | Clinical tumor tissue samples | ATGL | − | Attenuates the growth, migration and invasion | [241] |
| | Cell lines: ES2, A2780, HO8910, and SKOV3 | | | | |
| | Cancer Genome Atlas database: TGCA | | | Associates with poor survival | [237] |
| | Cell lines: highly metastatic and non-metastatic ovarian cancer cells | ACSL-1 | + | Enhances cancer metastasis<br>Associates with poor clinical outcome | [196] |
| | Clinical tumor tissue samples | ACSL-4 | + | Associates with poor prognosis | [213] |
| Cervical cancer | Clinical tumor tissue samples | PLIN-3 | + | High expression in invasive tumors and in lymph node metastasis<br>Potential clinical biomarker? | [242] |
| | Cell line: HeLa | | + | Involved in apoptosis and differentiation | [243] |
| | Cell lines: HeLa and Me-180 | ATGL | ND | Increases proliferation, migration capability and ROS<br>Potential prognostic marker? | [244] |
| Gastric cancer | Cell lines: SGC7901 and MGC803 | PLIN-2 | + | Increases proliferation and decreases apoptosis and ferroptosis<br>Potential diagnostic and therapeutic marker? | [245] |
| | Cancer Genome Atlas database: TGCA | ATGL | − | Associates with poor survival | [237] |
| | Clinical tumor tissue samples | DGAT-2 | + | Promotes lung and peritoneal metastasis<br>Predictor of poor survival | [131] |
| Colorectal cancer | Clinical tumor tissue samples | PLIN-3 | + | Positively correlates with tumor size | [246] |
| | Clinical tumor tissue samples: epithelial neoplasms | PLIN-2 | + | High expression associates with histologic grade and depth of tumor invasion | [247] |
| | Cell lines: HT29, HCT116, and SW620<br>Clinical tumor tissue samples | ATGL | + | Promotes cell migration, growth and cycling cells | [172] |
| | Cell lines: DLD-1 NoORF, HCT116, HT29, CaCo2, LS174T, SW480 DLD-1 x3, SW620, Colo205, LoVo and T84 | ACSL-1 | + | Stimulates invasion<br>Indicates poor prognosis<br>Induces EMT | [217] |
| | | ACSL-4 | | Stimulates proliferation and migration | |
| Renal cell carcinoma | Clinical tumor tissue samples | PLIN-2 | + | Negatively correlates with tumor grade | [246] |
| | Cell lines: 786-O, A498, and RCC4 | | | Suppresses cytotoxic ER stress responses<br>Biomarker of kidney cancers of proximal tubule origin and small renal masses? | [164,248,249] |

**Table 1.** (Continued).

| Cancer type | Biological model | LD-associated proteins | Expression +/− | Role in tumorigenesis | References |
|---|---|---|---|---|---|
| | Cell line: Caki-1, RCC4, RCC10, 789-0 | HIG2 | | Marker of hypoxia-induced LD? | [163] |
| | Clinical tumor tissue samples | PLIN-3 | + | High expression predicts poor disease-free survival and overall survival | [250] |
| | Cell lines: ACHN, 786-O, OSRC-2, A498, Caki-1, and HK-2 | | | Potential diagnostic and prognostic biomarker? | |
| | Cell lines: 786-O, A-498, Caki-1 and OS-RC-2 | | | Decreases sensitivity to chemotherapy drug sunitinib | [251] |
| | Cell lines: RCC4, MDA-RCC-62 | ACSL-3 | + | Increases susceptibility to ferroptosis<br>Increases LDs content<br>Increases cell viability | [252] |
| Hepatocellular carcinoma | Cell lines: PLC-PRF/5, HepG2, Hep3B, and HuH7<br>Clinical tumor tissue samples | PLIN-1 | + | Expression lost during hepatocarcinogenesis | [246] |
| | Cell lines: PLC-PRF/5, HepG2, Hep3B, and HuH7<br>Clinical tumor tissue samples | PLIN-2 | + | Increases proliferation<br>Upregulated during early tumorigenesis | [246] |
| | Cell lines: PLC-PRF/5, HepG2, Hep3B, and HuH7<br>Clinical tumor tissue samples | PLIN-3 | + | ND | [246] |
| | Clinical tumor tissue samples | PLIN-5 | + | ND | [141] |
| | Mice: TRAF2/RIPK1$^{LPC-KO}$, NEMO$^{LPC-KO}$, TAK1$^{LPC-KO}$ | | | | |
| | Mice: Balb/c nude mice<br>Clinical tumor tissue samples | DGAT-2 | − | Downregulates cell cycle-related gene expressions<br>Reduces tumors in mice<br>High expression associates with longer survival | [253] |
| | Mice: C57BL/6 mice<br>Cell lines: HepG2 and Hep3B<br>Clinical tumor tissue samples | ATGL | − | Reduces proliferation<br>Tumor-suppressor function? | [254] |
| | Cell lines: HepG2 and Huh7 | ACSL-1 | + | Increases tumor growth | [255] |
| | Cell lines: H7402 L-O2 and Chang liver cell line<br>Clinical tumor tissue samples | | | Stimulates accumulation of intracellular triglycerides and cholesterol<br>Enhances cell proliferation | [256] |
| Pancreatic cancer | Clinical tumor tissue samples | ATGL | − | ND | [237] |
| | Bioinformatics analysis: GEPIA | DGAT-1/DGAT-2 | + | ND | [257] |
| | | PLIN-2/PLIN-3 | + | ND | |
| | | HILPDA | + | ND | |
| | | CAV-2 | + | Prognostic factor? | |
| | | PLIN-4/PLIN-5 | − | ND | |
| Lung cancer | Cancer Genome Atlas database: TGCA<br>Clinical tumor tissue samples | ATGL | − | Associates with poor survival<br>Potential tumor suppressor function? | [237] |
| | Cell line: A549 | | | Enhances growth of spheroids and facilitates their adaptation to hypoxia | [258] |
| | Cell lines: A549 and HCC827<br>Xenograft tumor mode | | | Promotes cell proliferation, migration, invasion, and inhibits apoptosis | [259] |
| | Cancer Genome Atlas: TCGA-LUAD | DGAT-1 | − | Associates with poor overall survival | [260] |

**Table 1.** (Continued).

| Cancer type | Biological model | LD-associated proteins | Expression +/− | Role in tumorigenesis | References |
|---|---|---|---|---|---|
| | Clinical tumor tissue samples | PLIN-2 | + | High expression associates with poor prognosis | [157] |
| | Serum of lung cancer patients<br>Cell lines: A549 and NCI-H1299<br>Mice: athymic nude mice (BALB/c) | | | Promotes cell proliferation | [261] |
| | Clinical tumor tissue samples<br>Cell lines: CRL 5803, CRL 5872, CRL 5875, CRL 5877, and CRL 5908 | ACSL-3 | + | Potentiates the antiproliferative effects of statins<br>Prognostic biomarker in non-small cell lung cancer? | [262] |
| | Mice: KrasG12D-driven mouse models<br>Cell line: A549 | | | Increases proliferation and anchorage-independent growth | [206] |
| Liposarcoma | Clinical tumor tissue samples | PLIN-1 | + | Diagnostic marker of liposarcoma and differentiates liposarcoma subtypes? | [263] |
| | Clinical tumor tissue samples | PLIN-4 | + | Diagnostic marker of liposarcoma and differentiates liposarcoma subtypes? | [263] |
| Glioblastoma | Mice: athymic nude (NCr-nu/nu) mice | DGAT-1 | + | Decreases levels of ROS and apoptosis | [263] |
| | Cell lines: U251 from Sigma, T98 and U87 | | | Generates tumor *in vivo* | |
| | Clinical tumor tissue samples | | | High expression indicates poor prognosis | |
| | Clinical tumor tissue samples | PLIN-3 | + | High expression inversely correlates with overall survival | [264] |
| Esophagus cancer | Clinical tumor tissue sample | PLIN-2 | + | ND | [265] |
| Head and neck cancer | Clinical tumor tissue samples: Mammary analogue secretory carcinoma and salivary carcinomas<br>AND | PLIN-2 | + | Could be included among immunohistochemical features? | [266] |
| | Sebaceous carcinoma of the tongue | | + | ND | [267] |
| Burkitt lymphoma | Clinical tumor tissue samples | PLIN-2 | + | Marker for Burkitt lymphoma? | [268] |
| Skin cancer | Clinical tumor tissue samples: cutaneous clear cell lesions<br>AND | PLIN-2 | + | ND | [269–273] |
| | Cutaneous melanomas | | | High expression associates with high proliferation, poor metastasis-free survival, and overall survival rates of patients | |
| | Clinical tumor tissue samples: sebaceous gland carcinoma | PLIN-3 | + | ND | [272] |
| | Clinical tumor tissue samples: melanoma | MAGL | + | High expression in metastatic tumors<br>Marker of tumor aggressiveness? | [178] |
| | Mice: melanoma xenograft NSG and C57BL | ACSL-3 | + | Protects from ferroptosis<br>Negatively associates with the overall survival | [211] |
| Thyroid cancer | Clinical tumor tissue samples: papillary thyroid carcinoma | PLIN-2 | + | ND | [274] |

cell division [159,160]. Non-transformed fibroblasts display increased number and dispersed distribution of LDs specifically during S phase. The accumulation of LDs was accentuated in H-RasV12 transformed cells, where positive PLIN-2 staining was strongly linked with highly proliferative Ki-67 areas in human colon adenocarcinoma tissues. However, PLIN-2 overexpression alone was not enough to transform normal cells to cancerous ones [159]. Whether the dynamic behavior of LDs actively participates in cell division indeed deserves further investigation.

During hypoxia, HIF trigger the upregulation of PLIN-2 in human cancer cell lines [161]. HIF also promote the expression of other LD-resident proteins such as HIG-2/HILPDA (Hypoxia-inducible protein 2/hypoxia-inducible lipid droplet associated), to inhibit ATGL in the absence of oxygen [162]. Indeed, HIF-2α promotes PLIN-2 expression with a concomitant lipid storage, proliferation, and viability in renal cancer xenografts [163,164]. Inhibition of HIF-2α reduces LD content and metastatic burden in triple-negative breast cancer (TNBC) cells [165]. In a hypoxic mouse cancer model (glioblastoma multiforme), HIF-1α stimulated LD accumulation *via* an increase in FA uptake and induction of PLIN-2, FABP-3, and FABP-7 proteins [128]. Inhibiting LD formation reduced ATP production and decreased cell survival and tumorigenesis [128].

## Lipases in cancer

The "canonical" lipolysis pathway starts with the activation of LD-resident lipases and their regulatory proteins. As described earlier, lipolysis is achieved by sequential action of ATGL, HSL, and MAGL to generate three FAs to be exported to other tissues in the case of adipocytes or to be locally used as energetic substrates *via* FAO in oxidative cells [166].

Increased activity of LD-lipases promotes cancer cell survival and tumor progression, especially in breast, prostate, and skin cancers (Table 1). Like in the case of PLIN-2, LD-lipases have been involved in the regulation of the S phase of the cell cycle. The major yeast lipase, Tgl4 (functional analog of ATGL) is phosphorylated by cyclin-dependent kinase 1 (Cdk1/Cdc28), contributing to early bud formation in late G1 phase [167]. In renal carcinoma, having a partial defect in lipid-mediated PTEN late G1 checkpoint, cells continued to cycle using FAs derived from LDs as their sole source of lipids [160]. In addition, the ability of breast cancer cells to survive and spread under oxidative stress was partially warranted by the upregulation of the endothelial lipase (LIPG). When *de novo* FA synthesis fails to adapt to the cell's energetic demands, LIPG will activate external lipolysis of circulating lipoproteins leading to LD accumulation favoring tumor progression. Moreover, high LIPG expression was linked to metastasis recurrence and shorter survival in human node-negative untreated breast cancer patients [168].

Cancer cells rely on their lipases but also on the lipases of cells within the TME. In acute myeloid leukemia (AML), it was shown that survival and proliferation are dependent on the transfer of FAs from bone marrow adipocytes after HSL activation [169]. The pro-tumoral environment fostered by adipocytes is impeded when the FABP-4 is knocked down in adipocytes or when CPT-1A is knocked down in cancer cells, preventing AML blast proliferation and improving AML patient-derived xenografts survival [169]. The contribution of lipolysis in adipocytes to leukemic cells expansion was further confirmed in an additional study showing that cancer cells release exosomes to remodel TME and to enhance the expression of ATGL and HSL in adipocytes. The use of ATGL and HSL inhibitors reduced the release of FAs from adipocytes leading to a decrease in AML cellular proliferation [170]. Similarly, Breast cancer cells use adipocyte-derived FAs for FAO, a process dependent of ATGL and correlated with tumor aggressiveness [171].

Lipolysis is also a vital pathway for CSCs expansion. Indeed, colonospheres (spheres derived from colorectal cancer and enriched in CSCs) accumulated and subsequently utilized LDs; their growth was stimulated by oleate and impeded by an ATGL inhibitor [172]. In accordance with this finding, blocking lipolysis in the digestive system of *Drosophila melanogaster*, through inhibiting the coat protein complex I (COPI)-Arf79F complex which is trafficking lipases to LDs, selectively eradicated CSCs and spared differentiated cells [173].

MAGL is highly expressed in aggressive human cancer cells from multiple tissues of origin [174–178]. In hepatocellular and cervical cancers, high MAGL levels are negatively correlated with cancer prognosis and overall survival [175–177]. In melanoma, ovarian, and breast cancer cell lines, MAGL upregulation increases free FAs levels and regulates a lipid network enriched in pro-tumorigenic signaling lipids such as lysophospholipids, phosphatidic acid and PGE2 [174]. Genetic or pharmacological inhibition of MAGL significantly repressed tumor growth, triggered apoptosis, restrained invasion through mechanisms involving PGE2 and phosphatidic acid [176], and inhibited EMT *via* NF-κB-mediated process [175,177]. Similarly, inhibiting MAGL in TNBC, blocked cancer cell adhesion,

colonization into the brain, and the secretion of IL-6, IL-8, and VEGF-A (Vascular endothelial growth factor-A) [179]. In summary, targeting LD-lipases could be beneficial in impeding cancer progression.

Phospholipases on LDs could be also implicated in cancer progression. It has been documented that LDs are sites for eicosanoid synthesis, recruiting enzymes such as PLA2, cyclooxygenases and prostaglandin synthases [122,180,181]. PLA2 are widely known to be overexpressed in various tumors and hold a pro-tumorigenic role in cancer [182]. PLA2 catalyzes the hydrolysis of acyl-ester bonds of the phospholipids present in the cell membrane to generate polyunsaturated FAs -mostly arachidonate- and lysophospholipids [182]. On one side, arachidonate can be further metabolized into prostaglandins, prostacyclins, and leukotrienes that contribute to cellular proliferation and tumor progression [183]. Among the prostaglandins, PGE2 is a highly pro-inflammatory and immunosuppressive molecule participating in cancer immune evasion, tumor growth and resistance to therapies [184–186]. On the other side, lysophospholipids function as extracellular mediators that increase cancer metastases and sustain immunosuppressive TME [187,188].

## ACSL in cancer

In mammals, the ACSL family comprises five members with different intracellular localizations and substrate specificities [189]. Several experimental approaches have determined that ACSL-1, ACSL-3, and ACSL-4 are associated with LDs [42,44,45,64–69]. As key enzymes for FA activation, deregulation of ACSLs alters the distribution and availability of FAs for different fates such as FAO, protein acylation, steroidogenesis, or the production of inflammatory prostaglandins. It has been described that many cancer cells overexpress ACSLs and that these enzymes actively participate in cancer cell proliferation, metastasis, and generation of the tumor inflammatory microenvironment [190]. Hence, ACSLs have been proposed as prognostic factors, biomarkers, and therapeutic targets for various cancers [70,190,191].

ACSL-1 has a marked preference for oleate and linoleate [192]. It is highly expressed in liver, breast, ovarian, and colorectal cancers [190]. ACSL-1 has been traditionally related with the channeling of FAs towards FAO [71,72,193,194]. In colon and ovarian cancers, high levels of ACSL-1 correlate with the enhancement of the invasive capacity and with poor prognosis [195,196]. In ovarian cancer, ACSL-1 is highly expressed, especially in metastatic tumors, where ACSL-1 enhances FAO but also the myristoylation and activation of kinases such as AMPK and Src [196]. Chemical or genetic inhibition of ACSL-1 suppresses ovarian cancer malignancy [196].

Intriguingly, ACSL-1 is not only transcriptionally regulated by transcription factors controlling metabolism but also by pro-inflammatory signals such as lipopolysaccharide (LPS), interferon gamma (IFN-γ), NF-κB, and the Hepatitis B interaction protein (HBXIP) [197,198]. The distribution and function of ACSL-1 is tightly regulated by TBK-1 (TRAF family member associated with NF-κB activator-binding kinase), a key kinase of the pro-inflammatory response triggered by innate immunity [199]. Proposed to facilitate the tumor inflammatory microenvironment, in turn, ACSL-1 positively regulates the activation of key kinases, transcription factors, and production of pro-inflammatory cytokines. Inhibition of ACSL-1 reduces the activation of NF-κB and the expression of TNF (tumor necrosis factor) in intestinal epithelial cells [200]. In TNBC cells, downregulation of ACSL-1 reduces the activation of key pro-inflammatory kinases, such as MAPK and JNK [201], and significantly decreases the pro-inflammatory TNF signaling [202]. Thus, ACSL-1 emerges as a promising target for reducing the inflammation associated with cancer.

ACSL-3 has an affinity for myristate, palmitate, arachidonate, and eicosapentaenoate [203]. In healthy cells, ACSL-3 has been involved in FA uptake (by intracellularly retaining arriving FAs) and LDs biogenesis [42,66]. High expression of ACSL-3 has been detected in a variety of cancers such as melanoma, TNBC, castration-resistant prostate cancer, and non-small cell lung carcinoma cells, being often correlated with metastasis and poor prognosis [190]. Mutations in ACSL-3 correlate with poor outcome in TNBC patients [204], at least partially by boosting metastasis through FAO activation [132]. Similarly, in non-small cell lung carcinoma cells, characterized by the mutant proto-oncogene KRAS, ACSL-3 mediates the enhancement of FA intake and FAO [205]. Suppression of ACSL-3 in lung cancer cells results in depletion of cellular ATP and the death of lung cancer cells [205]. Furthermore, in non-small cell lung carcinoma cells, ACSL-3 participates in prostaglandin synthesis by delivering arachidonate to the cardiac phosphatidyl transferase 1 (LPTAT-1) [206]. ACSL-3 is also abundant in castration-resistant prostate cancer cells where it has been related to intratumoral steroidogenesis [207–210]. In melanoma, ACSL-3 increases the intracellular pools of oleate to protect cancer cells from ferroptosis, increases their metastatic capacity, and reduces the survival of patients [211].

ACSL-4 has an affinity for 20-carbon PUFAs such as arachidonate, eicosapentaenoate, and adrenate. By activating ω-6 PUFAs, ACSL-4 is a crucial regulator of ferroptosis [212]. The role of ACSL-4 in ferroptosis and implications in cancer has been covered recently by excellent reviews [30]. Furthermore, ACSL-4 is upregulated in pancreatic cancer, ovarian, hepatocellular carcinoma, breast, prostate cancer, and glioblastoma in which it is pro-oncogenic and an indicator of a poor outcome [190,213,214]. ACSL-4 expression enhances arachidonate metabolism to promote cell growth of breast cancer cells [215,216], EMT of colorectal cancer cells [217], accumulation of cholesterol in hepatic carcinoma cells [218], and the myristoylation and activation of Src kinase in prostate cancer cells [219]. Downregulation of ACSL-4 reduces tumor progression in hepatic carcinoma cells [220], breast cancer cells [221], and suppresses proliferation, invasion, and xenograft growth in androgen receptor-independent prostate cancer cells [219].

## Concluding remarks and future direction

Lipid droplets were long considered inert reservoirs of neutral lipids until recent studies emerged linking them to metabolic and non-metabolic diseases. The dynamics of biosynthesis and degradation of LDs is an important indication of the cellular metabolic state in different biological contexts. The last decade has witnessed the discovery of many metabolic characteristics of cancer cells, including the accumulation of LDs. To colonize other tissues, tumor cells overcome cell death mechanisms, alter the composition of lipid membranes, and increase lipid catabolism and anabolism to procure energy and shield themselves from oxidative stress. LDs are decisive organelles in this context, responding when lipid mobilization is necessary to trigger a more aggressive cancer phenotype.

Although many studies have linked the accumulation of LDs in cancer cells to pro-tumorigenic properties, their potential use as diagnostic and prognostic markers in clinical practice has not been proven yet in part due to the lack of reliable methods in clinical use. For diagnostic purposes, different approaches have been developed to monitor LDs inside cells, such as Raman microscopy [222], immunohistochemistry of LDs proteins (discussed in Table 1) and fluorescence imaging [223,224]. Despite recent molecular and imaging advances to analyze and quantify LDs *in vivo*, future efforts should focus on the development of reliable assays for LD discrimination in cancer cells as diagnostic and prognostic markers [225]. Alternatively, LD-resident proteins could be good candidates for LD detection inside living cells, especially since they are abundant in clinical tissues and cellular models of several cancers and correlate with tumor stage or prognosis. Most of our knowledge on lipid metabolism and LDs emerges from cancer genomic databases and the use of tumor cell lines, which might not necessarily reflect cancer metabolism of patients *in situ* (Table 1). A large-scale screening of LDs and LD-associated proteins in patients' samples will be beneficial to confirm the clinical value of detecting and quantifying LDs.

Given the fundamental role of reprogrammed lipid metabolism in cancer pathogenesis, new anticancer approaches targeting lipid metabolism are being explored. Three main methodologies could be undertaken: inhibiting lipid synthesis, blocking lipid uptake, and preventing intracellular lipolysis. In line with the first strategy, TVB-2640 is an inhibitor of FASN entering clinical trials as an anticancer drug for solid tumors, particularly in $KRAS^{MUT}$ tumors [226]. To block the lipid uptake, CD36 is a promising target with specific inhibitors (VT1021) undergoing clinical trials in advanced solid tumors [227]. In contrast, conflicting reports about their function have prevented so far, the clinical translation of LD-lipases (e.g. ATGL inhibitors) [228].

In summary, LDs are much more than passive bystanders in cancer progression as they confer resistance to cell death by alleviating lipotoxic stress, maintaining redox homeostasis, delivering signaling molecules, securing energy for proliferation, invasion, and metastasis, and procuring communication between cancer cells and the TME. However, the delicate equilibrium between LD synthesis and consumption seems to open unanswered questions: what are the spatio-temporal dynamics of LDs and the drivers of malignant phenotype on LDs? How could LDs and LD-associated proteins be exploited in designing selective anticancer strategies? Are LDs homogeneous universal organelles in cancer or do they reflect tumor heterogeneity, where sub-populations of LDs could emerge depending on cancer types and TME cues? We are convinced that the fields of LDs and cancer will converge over the next few years and the contribution of LDs to cancer pathogenesis and their potential role as biomarkers for clinical diagnosis and/or prognosis will flourish.

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